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ПРОПЕДЕВТИКА ВНУТРЕННИХ БОЛЕЗНЕЙ

Часть II: Обследование органов систем пищеварения, мочевыделения, желез внутренней секреции, крови и опорно-двигательного аппарата

PROPAEDEUTICS OF INTERNAL DISEASES

Part II: Examination of Digestive, Urinary, Endocrine, Blood and Locomotor Systems

учебное пособие
на английском языке

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Предназначается для студентов 2- и 3-го курсов, изучающих пропедевтику внутренних болезней на английском языке.

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PREFACE

The textbook “Propaedeutics of Internal Diseases, Part II: Examination of Digestive, Urinary, Endocrine, Blood and Locomotor Systems” is designed for 2-d and 3-d year students for training through the mediation of the English language. The textbook contains the following sections of the educational discipline “Propaedeutics of Internal Diseases”: alimentary tract, liver and biliary tract, urinary, endocrine systems and blood examination.

The textbook corresponds to the basic educational thematic parts of Propaedeutics of Internal Diseases, according to the Standard Educational Program of Propaedeutics of Internal Diseases approved by the Ministry of Public Health of the Republic of Belarus of the 4th of September, 2014, registration № ТД-L.399/тип. and the syllabus of the Propaedeutics of Internal Diseases for students of the Medical Faculty approved by Vitebsk State Medical University in 2014.

This textbook can be useful for instructors teachers in preparations for classes in English-language therapeutic disciplines, for undergraduate students, as well as for post-graduates and clinical residents.

The reference sources are selected regarding a modern level of the internal medicine development. We ask to send all critical remarks and wishes to the Chair of Propaedeutics of Internal Diseases of Vitebsk State Medical University.

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List of Main Abbreviations

AKI – acute kidney injury (acute renal failure)
ALT – alanine aminotransferase
ANA – antinuclear antibodies
ANCA – antineutrophil cytoplasmic antibody
anti-HCV – antibody to hepatitis C virus
AP (ALP) – alkaline phosphatase
APTT (PTT) – activated partial thromboplastin time
ASO – anti-streptolysin 0
AST – asparagine aminotransferase
BMI - body mass index
CKD – chronic kidney disease (chronic renal insufficiency)
CPK – creatine phosphokinase
CVA tenderness (CVAT) – costovertebral angle tenderness
DAT – direct antiglobulin test (Coombs test to determine RBC-binding antibody)
DIC – disseminated intravascular coagulation
ERCP – endoscopic retrograde cholangiopancreatography
ESR – erythrocyte sedimentation rate
GERD – gastroesophageal reflux disease
GFR – glomerular filtration rate
GI – gastrointestinal
GTP (GGTP) – gamma glutamyl transpeptidase
HBsAg – hepatitis B surface antigen
Hct – hematocrit
HP – Helicobacter pylori
HVPG – hepatic portal venous pressure gradient
IBS – irritable bowel syndrome
INR – international normalized ratio
LDH – lactate dehydrogenase
PGI – pepsinogen I
PGII – pepsinogen II
PPI – proton pump inhibitors
PTI – prothrombin time index
RBC – red blood cells
RRS – rectoromanoscopy
SIBO – intestinal bacterial overgrowth syndrome
T_3 – tetraiodothyronine
T_4 – thyroxine (tetraiodothyronine)
TRH – thyrotropin-releasing hormone
TSH – thyroid-stimulating hormone
UTI – urinary tract infection
WBC – white blood cells

Unit IV. Gastrointestinal Tract Examination

CHAPTER 14. Subjective and Objective Examination of Patients with Gastrointestinal Diseases

Goals: to enable students to learn –-

1. subjective examination (inquiry) of patients with gastrointestinal diseases and interpretation of the obtained results;
2. technique of general inspection in patients with gastrointestinal diseases and its diagnostic value;
3. technique and diagnostic value of local inspection, percussion and auscultation of the abdomen;
4. differentiation of enlarged abdomen in obesity, meteorism and ascites.

14.1. Subjective examination (inquiry) of the gastrointestinal tract

Complaints of patients with gastrointestinal diseases depend on the organ having the pathological changes.

Detailed elaboration of the pain syndrome includes

- localization of the pain with the statement of the following questions:
- character of the pain sensation;
- periodicity or persistence of it;
- connection with reception of nutrition (or defecation, physical and emotional activity) and its quality; presence or absence of an irradiation;
- a position of the patient at the moment of an attack;
- how relive pains (a vomiting, medicines, a heater).

Symptoms of digestion disorders (dyspepsia) connect with affections of digestion and/or passage of nutrition in definite parts of the gastrointestinal tract.

14.1.1. Subjective examination in diseases of the esophagus

Complaints

Dysphagia (difficult passage of food via the esophagus) is the most frequent symptom of esophageal pathology (Table 14-1). The patient feels difficulty in swallowing (mostly solid food); the food bolus sometimes stops in the esophagus and the patient feels pain and esophageal distention, sensation of a lump in a throat or thorax, sense of pressure in range of an esophagus or difficulty of transit of nutrition.

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. Dysphagia develops immediately in the presence of a foreign body or burns of esophagus. Dysphagia may also develop due to compression from outside by an aortic aneurysm or mediastinal tumour.

Table 14-1. Typical complaints in diseases of esophagus

Complaints	Characteristics	Causes
Dysphagia (difficult passage of food via the esophagus)	*Functional dysphagia* – - paroxysmal, - non-progressive, - when food passes the esophagus, - with greater difficulty in swallowing liquids rather than solids, - associated with neuropsychic factors, sometimes with - aspiration or coughing	spasm or dysmotility of esophagus in central and autonomic nervous system functional disorders, iron-deficiency anemia, diabetes mellitus, thyroid dysfunction
	Organic dysphagia – - develops gradually and progresses, - difficulty in swallowing solids than liquids, - associated with the loss of weight	esophageal carcinoma, benign strictures, systemic sclerosis, achalasia of cardia, more rarely esophageal diverticulum
Esophageal pain and/or odynophagia (pain on swallowing food and fluids)	- pain by projection of esophagus from the neck to the upper epigastrium; - continues minutes - hours; - with and without swallowing; - may radiate into the left side of chest and simulate angina pectoris	esophagitis, achalasia of cardia, hiatus hernia, gastroesophageal reflux disease (GERD)
Heartburn (pyrosis)	burning sensation behind the sternum associated with position changes, the intake of spicy and fatty foods	gastroesophageal reflux disease (GERD)
Esophageal vomiting	- without previous nausea; - preceded by the feeling of food retained behind the sternum; - vomit mass includes unaltered (non-digested) food that was taken a long time ago, - vomitus has a foul odour	food retained for long periods in esophageal diverticulum or cancer
Esophageal hemorrhage	vomitus contains red non-clotted blood	ulcer or erosions of the esophagus, foreign body, degradation of a tumour, dilated esophageal veins in portal hypertension; Mallory-Weiss syndrome

Functional dysphagia is explained by muscular spasms caused by reflex disorders of innervation of the esophageal muscles. 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.

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. ***Odynophagia*** is a pain on swallowing food and fluids.

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 simulate angina pectoris.

Esophageal vomiting occurs in considerable narrowing of the esophagus. Esophageal vomiting differs from gastric vomiting in the following: it occurs without nausea, and the feeling of food retained behind the sternum precedes it. The vomitus includes unaltered (non-digested) food which does not contain acid gastric juice; the vomitus containing food that was taken a long time ago has a foul smell. The taken food retains in the esophagus for long periods in the presence of diverticulum or degrading cancer.

Regurgitation is the return of swallowed food into the mouth due to esophageal obstruction. Regurgitation sometimes occurs in neuropathic patients in whom it becomes a habitual symptom or a result of cardiospasm.

Hypersalivation occurs in esophagitis, cicatricial narrowing of the esophagus or in cancerous stenosis as a result of the esophago-salivary reflex.

Foul breath (halitosis) is a symptom in which a noticeably unpleasant smell presents on the exhaled breath. It may be due to gastroesophageal reflux, a malignant tumour of the esophagus or congestion and decomposition of food in cardiospasm. Halitosis can result from poor dental health habits or dental and oral cavity diseases (gingivitis, oral candidiasis, salivary glands problems) and may be a sign of other health problems in respiratory tract infections such as pneumonia or bronchitis, chronic sinus infections, diabetes mellitus, and liver or kidney diseases.

Heartburn (pyrosis) is a specific burning sensation behind the sternum associated with regurgitation of gastric contents into the inferior portion of the esophagus. This is the cause of the gastro-esophageal reflux.

Esophageal hemorrhage can be due to ulcer of the esophagus, injury to 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 due to small lacerations of the blood vessels in the esophagogastric junction in straining and vomiting (Mallory-Weiss syndrome). The vomit in esophageal bleeding contains non-clotted red blood.

Anamnesis

Functional disorders (*cardiospasm*) are characterized of by exacerbations connected with psychogenic factors, esophagogastric junction that are followed by remissions. The disease has a progressive course in organic affections of the esophagus. Past acid or alkali burns of the esophagus are frequent causes of cicatricial changes. Development of traction diverticula in the esophagus may be due to *bronchoadenitis* (an inflammation of intrathoracic lymph nodes) in the past life history. Pulsion diverticula arise due to esophagospasm.

14.1.2. Subjective examination in diseases of the stomach and duodenum

Complaints

Patients with diseases of the stomach and duodenum complain of poor appetite, perverted taste, regurgitation, heartburn, nausea, vomiting, epigastric pain (or discomfort), and hematemesis. Regurgitation, nausea, vomiting, and the feeling of overfilled stomach after meals are the group of the so-called "dyspeptic" complaints. The specific character of each symptom is important to define during inquiry of the patient (Table 14-2).

Deranged (poor or increased) appetite occurs in infectious diseases, metabolic disorders, etc. Poor appetite or its complete absence (*anorexia*) is usually characteristic of gastric cancer. This symptom is often an early sign of cancer. Appetite often increases in peptic ulcer, especially in duodenal ulcer. Loss of appetite should be differentiated from cases when the patient refuses from food for fear of pain (*citophobia*). This condition often occurs in subjects with gastric ulcer, though their appetite is increased. Increased appetite presents in *bulimia*, a mental illness in which someone eats in an uncontrolled way and in large amounts, then vomits intentionally.

***Perverted appetite* (*pica pereverta*)** that sometimes occurs in patients is characterized by the desire to eat inedible materials such as charcoal, chalk, soil, petrol, etc. *Pica* is caused in many cases by mineral deficiency, such as iron deficiency in the body. Appetite is perverted in pregnant women and in persons suffering from achlorhydria. Some patients with cancer of the stomach or some other organs often feel aversion to meat.

Taste may be perverted due to the presence of an unpleasant taste in the mouth and a partial loss of taste in an individual. It can often be associated with some pathology in the mouth, e.g. caries or chronic tonsillitis. A coated tongue can be another cause of the unpleasant taste in the mouth.

Regurgitation (belching) includes *eructation* (a sudden loud uprise of wind from the stomach or esophagus) and the return of swallowed food into the mouth (sometimes together with air). Regurgitation depends on contraction of the esophageal muscles with the open cardia. Regurgitation may be due to air swallowing (*aerophagy*). It is heard at a distance and occurs in psychoneurosis.

In the presence of motor dysfunction of the stomach, fermentation and putrefaction of food with increased formation of gas occur in the stomach.

Table 14-2. Typical complaints in diseases of stomach and duodenum

Comp-laints	Characteristics	Causes
Epigastric pain and/or discomfort	- localization; the time and periodicity of the onset of the pain; - irradiation; intensity, and character of feeling the pain; - association with food intake (effect of quantity, quality and consistency of food, pain after eating); - provoking factors (food, physical exercises, neuropsychic overstrain); - pain relief by medication, food intake, hot or cold application, vomiting	gastritis, gastroduodenitis, peptic ulcers and erosions, functional dyspepsia, carcinomas, may be in diseases of the liver, gallbladder, pancreas, hernia of the linea alba, and in myocardial infarction
"Dyspeptic" complaints	deranged (poor or increased) appetite, heaviness in epigastrium, nausea, regurgitation (belching), vomiting, with or without epigastric pain	functional dyspepsia, gastritis and duodenitis, peptic ulcers and erosions, malignant tumours
Gastric vomiting	- preceded by nausea and sometimes hypersalivation; - vomitus includes partly digested food; - vomitus may have acid odour and chemical reaction, and greenish colour (in hyperchlorhydria); - neutral (in achylia), or alkaline reaction (in pyloric stenosis, duodenogastric reflux); - foul odour (in pyloric stenosis); - yellow in duodenogastric reflux - - pain less after vomiting	functional dyspepsia, gastritis, gastroduodenitis, peptic ulcers and erosions, carcinomas; pyloric stenosis, duodenogastric reflux
Gastric hemorrhage	- may be manifested by vomiting blood (*hematemesis*) or black tarry stools (*melena*); - vomitus looks like clotted blood or *coffee grounds*	peptic ulcers and erosions, hemorrhagic gastritis, malignant and benign tumours

Belching is characteristic of stenosed pylorus with a great distention of the stomach and significant congestion in it. In decreased secretory function of the stomach (*hypo- anacidity, or achylia*), the eructated air is either odourless or smells of bitter oil, which is due to the presence of butyric, lactic and other organic acids that are produced during fermentation in the stomach. In the presence of abnormal putrefaction, the belched air has the odour of rotten eggs. *Bitter belching* indicates intensive degradation of proteins, a bitterness depends on the bitter taste of peptone. Bitter regurgitation occurs in cases of biliary reflux into the stomach from the duodenum. *Acid regurgitation* is usually associated with hypersecretion of the gastric juice and occurs mostly during pain attacks in the ulcer. However, it can also occur in normal or insufficient secretion of the stomach in the presence of insufficiency of the cardia (when the stomach contents are regurgitated into the esophagus).

Heartburn (pyrosis) is a burning sensation in the epigastric and retrosternal region. Heartburn arises in gastro-esophageal reflux, mostly in the presence of gastric hyperacidity in various diseases (e.g. peptic ulcer, chronic gastritis), hiatus hernia, and sometimes in pregnancy. Heartburn in healthy subjects can be due hypersensitivity to some foods.

Nausea is a reflectory act associated with the irritation of the vagus nerve, indefinite feeling of sickness and sensation of compression in the epigastrium. Nausea is often attended by pallidness of the skin, giddiness, sweating, salivation, fall in the arterial pressure, cold the limbs, and sometimes semisyncopal state. Nausea often (but not necessarily) precedes vomiting. It may be the early sign of stimulation of the cerebral vomiting centre. Nausea may develop without any connection with diseases of the stomach, e.g. in toxemia of pregnancy, renal failure, deranged cerebral circulation, autonomic nervous system dysfunction and sometimes in healthy people in the presence of foul odour (or in remembrance of something unpleasant). Nausea associated with gastric pathology usually occurs after meals, especially after taking some spicy and fat food. Nausea often develops in secretory insufficiency of the stomach (in acute and chronic gastritis, cancer of the stomach).

***Vomiting* (*emesis*)** occurs due to stimulation of the vomiting centre. This is a complicated reflex through the esophagus, larynx and the mouth (sometimes through the nose as well). Vomiting may be caused by ingestion of spoiled food, by seasickness, or irritation arising inside the body (diseases of the gastro-intestinal tract, liver, kidneys, etc.). In most cases, vomiting is preceded by nausea and sometimes hypersalivation. Depending on the cause, there are: (1) *central (nervous) vomiting*; (2) *peripheral (reflex) vomiting* of visceral etiology; and (3) *toxic (hematogenic) vomiting*.

Vomiting of the gastric etiology is caused by stimulation of receptors in the gastric mucosa by inflammatory processes (acute or chronic gastritis) and gastric tumours, in ingestion of strong acids or alkalis, or food acting on the gastric receptors by chemical (spoiled) or physical (overeating or excessively cold food)

routes. Vomiting can be caused by difficult evacuation of the stomach due to spasms or stenosed pylorus.

If a patient complains of a vomiting, the physician should inquire

- the time when the vomiting occurred,
- possible connections with meals,
- association with a pain,
- volume and character of the vomited material.

Morning vomiting (on fasting stomach) with expulsion of much mucus is characteristic of chronic gastritis, especially in alcohol abuse. *Acid vomiting* in the morning indicates nocturnal hypersecretion of the stomach. Vomiting occurring 10-15 minutes after meals suggests ulcer or cancer of the stomach cardia, or acute gastritis. If vomiting occurs 2-3 hours after meals (during intense digestion), it may indicate peptic ulcer or cancer of the stomach body. In the presence of the ulcer of the pylorus or duodenum, vomiting occurs 4-6 hours after meal. Expulsion of food taken a day or two before is characteristic of *pyloric stenosis*. Patients with the stomach or duodenal *peptic ulcer* often have vomit at the height of pain thus removing it, which is typical of the disease.

The smell of the vomit is usually acid, but it can often be putrefactive (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).

The vomited material may have an acid reaction due to the presence of hydrochloric acid (in *hyperchlorhydria*), neutral (in *achylia*), or alkaline (in the presence of ammonia compounds, in pyloric stenosis, uremia, and in regurgitation of the duodenal contents into the stomach). Vomitus may contain materials of great diagnostic importance, e.g. blood, mucus (in chronic gastritis), ample bile (narrowing of the duodenum, gastric achylia), and fecal matter.

Epigastric pain is the leading symptom in diseases of the stomach. Epigastric pain is not obligatory connected with diseases of the stomach. Epigastric pain may be due to diseases of the liver, the pancreas, and of the *linea alba* hernia. Epigastric pain may develop in diseases of other abdominal organs (and sometimes of organs outside of abdomen) (acute appendicitis, myocardial infarction, affection of the diaphragmatic pleura, etc).

In order to locate correctly the source of the pain, a physician should ask the patient:

- to show exactly the site of the pain;
- to characterize the pain which may be periodical or paroxysmal (at certain time of the day); permanent or seasonal (in spring or autumn);
- to describe the connection (if any) between pain and meal, the quality of food and its consistency;
- to indicate possible radiation of the pain (into the back, shoulder blade, behind the sternum, left hypochondrium);

- to describe conditions under which pain lessens (after vomiting, after taking food or baking soda, after applying hot-water bottle or taking spasmolytics);
- to describe possible connections between pain and physical strain (weight lifting, traffic jolting, etc.), or strong emotions.
- intensity and character of the pain are also important diagnostically. The pain may be dull, stabbing, cutting, etc.

Pain in hollow organs with smooth muscles (e.g. stomach and duodenum) is provoked by spasms (spastic pain), distension of the organ (distensional pain), and by its motor dysfuncion.

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.

In peptic ulcers of stomach and duodenum, depending on the time of paroxysmal pain (after meals), it may be *early pain o*ccurring 30-40 min after meal (in ulcers of stomach), *late pain* (90-120 min after meal (in ulcers of bulbus of duodenum), *nocturnal pain* and *hunger pain* (which is abated after taking food). If pain occurs after meal stimulating secretion of gastric juice (bitter, spicy, fried or smoked foods), this indicates the leading role of hypersecretion in its etiology. The pain is located in the epigastrium, radiates to the back, and is rather intense; it is abated after vomiting and taking *antacids* (baking soda and other alkaline reaction medicines) or foods that decrease acidity of gastric juice, and also after taking antispastic preparations and applying hot-water bottle (which removes spasms).

Seasonal character of pain, i.e. development of a periodic pain during spring and autumn, is characteristic of the peptic ulcer, especially if the process is localized in the peripyloric region.

Permanent boring pain is usually intensified after meals and is characteristic of exacerbation of chronic gastritis or cancer of the stomach.

Patients may complain of *unpleasant abdominal fullness after light or moderate meal, or early satiety, the inability to eat a full meal (in functional dyspepsia)*.

Gastric hemorrhage may be manifested by vomiting blood (*hematemesis*) or by black tarry stools (*melena*). Gastric hemorrhage is usually manifested by the presence of blood in the vomitus. The colour 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. The vomitus looks like *coffee grounds*. If the blood was in the stomach for a short time, the blood is clotted and red. If hemorrhage is profuse (affection of a large vessel), the vomitus contains much scarlet (unaltered) blood. 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 (due to portal hypertension in liver cirrhosis). *Melena* (black

tarry stools) is not an obligatory and later (12-24 hours after bleeding) sign of gastric hemorrhage.

Anamnesis

When collecting *anamnesis***,** the patient should be asked about his/her nutrition, because irregular food intake is an important factor in the etiology of gastric diseases. Food quality is as important as its amount taken during one meal. Chewing 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. It is very important to find out if the patient's condition has undergone some changes during recent time (e.g. loss of weight, anemia, blood vomiting, or tarry stools). Gastrointestinal diseases of the past, surgical intervention on the abdominal organs, long medicines intake with preparations irritating the stomach mucosa (acetylsalicylic acid, steroid hormones, potassium chloride, etc.) are also very important.

14.1.3. Subjective examination in diseases of intestines

Complaints

The main complaints with intestinal diseases are pain, meteorism (inflation of the abdomen), motor dysfunction of the intestine (constipation and diarrhea), and intestinal hemorrhage.

Intestinal pain. If the patient complains of pain in the abdomen, the following should be regarded: the location of the pain, its radiation, intensity, character, duration, and means by which it is lessened (Table 14-3).

The general signs by which the intestinal pain may be differentiated from the gastric one are:

- absence of regular dependence of pain on food taking; the only exception is inflammation in the transverse colon (*transversitis*) - pain develops immediately after meal; the pathogenesis of this pain is connected with reflex peristaltic contractions of the transverse colon when food enters the stomach;
- close association of pain with defecation - pain occurs before, during, and (rarely) after defecation;
- pain relief after defecation or passage of gas.

Pain may be boring and spasmodic (*intestinal colic*). Colicky pain is characterized by short repeated attacks that arise and disappear quite of a sudden. Pain may quickly change its location, the main site being round the navel. Sometimes pain may arise in other areas of the abdomen.

Appendicular colic first localizes round the navel and the epigastrium but in several hours (or even on the next day) it descends to the right iliac region where it intensifies gradually. Sometimes the pain arises straight in the right iliac region. Boring pain is sometimes permanent; it intensifies during cough, especially if the mesenterium or peritoneum is involved.

Table 14-3. Typical complaints in diseases of intestines

Comp-laints	Characteristics	Causes
Intestinal pain	- localization of pain depending on the affected department of intestine; - absence of regular dependence of pain on food taking; - close association of pain with defecation: pain occurs before, during, and (rarely) after defecation; - relief after defecation or passage of gas	inflammatory diseases of intestines (enteritis, colitis), infectious and parasitic diseases of intestines, intestinal tumours, intestinal diverticulum; irritable bowel syndrome (IBS); arsenic or lead poisoning
Meteorism	the patient feels flatulence, inflation, and boring distension of the abdomen	enteritis, colitis, excess of carbohydrate food, food intolerance an allergy, intestinal tumours, diverticulosis; IBS
Diarrhea	frequent (>2-3 times a day) and liquid stool	enteritis, colitis, IBS, intestinal infections, excess of carbohydrate food, food intolerance and allergy, endogenous intoxications (diabetes mellitus, uremia, hyperthyroidism), arsenic poisoning
Constipation	- infrequent stool (<3 times per week); - difficulty during defecation; - the sensation of incomplete bowel evacuation	*Organic constipation* – intestinal tumours, adhesions, intestinal abnormalities - megacolon, dolichosigmoid, diverticula); *Functional constipation* - loss of vegetable fibers in food; psychic depression; poisoning with lead, morphine, or cocaine; endocrine problems (hypothyroidism); lack of physical exercise, IBS
Intestinal hemorrhage	- *melena* in cecum and small intestinal bleeding*;* - black-brown stools in bleeding from the right part of the colon; - bright red blood per rectum in left side colon bleeding	malignant and benign tumours; protozoa and helminthic invasions, acute infections (dysentery), mesenteric thrombosis, non-specific ulcerative colitis

Pain is one of characteristics in inflammatory diseases of the intestine. As inflammation extends onto the peritoneum, the pain is attended by a pronounced

muscular defence. An exact location of the source of the pain is very important (Fig. 14-1). Pain in the right iliac region occurs in appendicitis, tuberculosis, cancer, or inflammation of the cecum (*typhlitis*). An acute pain in the left lower abdomen occurs in intestinal obstruction and inflammation of the sigmoid (*sigmoiditis*). Pain in the umbilical region occurs in inflammation of small intestine (*enteritis*) and inflammation or cancer of the colon. Pain in the perineal region, and especially during defecation (with the presence of blood in feces), is characteristic of the rectum diseases (*proctitis*, cancer).

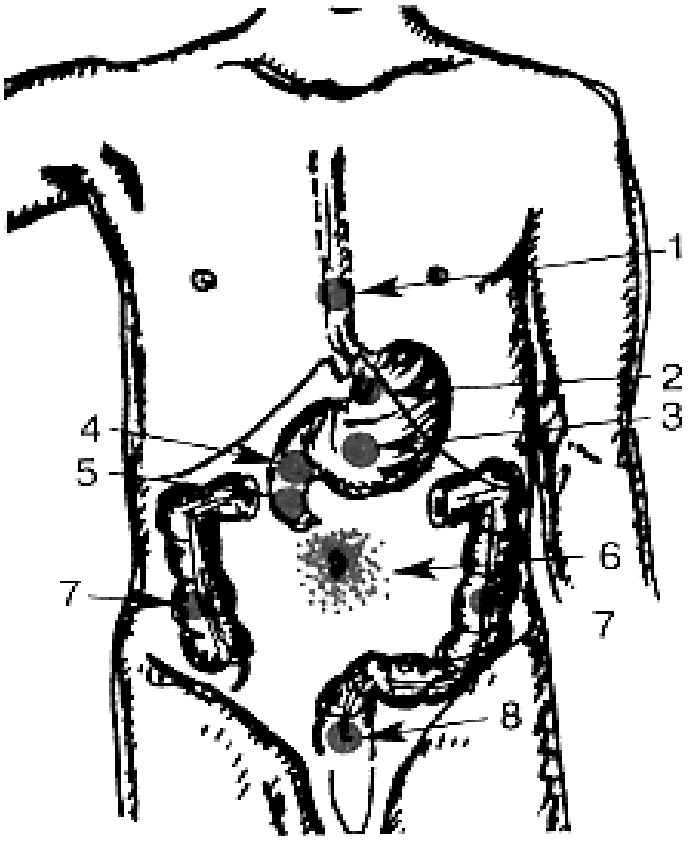


Fig 14-1. Typical localization of the gastrointestinal pain: 1 – esophagus, 2- cardiac part of stomach, 3- body of stomach, 4 – pyloric part of stomach, 5 – duodenum, 6 – small intestines, 7 – large intestines, 8 – rectum.

Pain in intestinal pathology may radiate into the chest; pain associated with affection of the *splenic curvature of the transverse colon* radiates into the left side of the chest (it is sometimes mistaken for pain attacks of angina pectoris); colics of appendicitic origin radiate into the right leg. In acute affection of the left portions of the large intestine, pain radiates into the sacral area. Thermal procedures, spasmolytics, passage of gas, and emptying of the bowels can relieve pain or remove it completely.

Intestinal pain may be caused by obstruction of intestinal patency and upset motor function. Intestinal pain is mostly caused by spasms (spasmodic contraction

of smooth muscles; hence *spastic pain*), or by distension of the intestine by gases. 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 an intestinal obstruction (complete or partial), the colicky pain associates with almost permanent pain in the abdomen. It is characterized by an exact and permanent location (the umbilical region and large intestine). The pain intensifies with intestinal peristalsis.

Pain associated with defecation depends on many factors. 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. It occurs in frequent and painful tenesmus (calls) to defecate and it is associated with spasmodic contractions of the intestine and the sphincter ani. Only clots of mucus passed sometimes instead of actual defecation. Tenesmus occurs in dysentery and other inflammatory or ulcerous diseases of the rectum, and in cancer of the rectum.

Meteorism. The patient feels *flatulence*, inflation, and boring distension of the abdomen. The causes of meteorism are:

- excessive gas formation in the intestine due to ingestion of vegetable cellular tissue and easily fermented food (peas, beans, cabbage, etc.);
- intestinal motor dysfunction due to decreased tone of the intestinal wall or intestinal obstruction;
- lowered absorbtion of gases by the intestinal wall, the process of gas formation being normal;
- *aerophagia*, i.e. excess swallowing of air, with its subsequent propulsion to the stomach and the intestine;
- *hysterical meteorism*: the abdomen is rapidly inflated to the size of the abdomen of a pregnant woman at her last weeks; this nervous mechanism is very complicated.

When inquiring the patient, the physician should ask about the character of his/her nutrition and the site of abdomen inflation (the entire abdomen or only its limited part may be inflated). If an inflation is local, it is necessary to ask the patient whether inflation occurs always at one and the same area. In intestinal obstruction, the patient feels rumbling sounds inside the abdomen, feels movement of liquid in the intestine, and intense peristaltic movements above the point of the obstruction.

Diarrhea. Frequent (three and more times a day) and liquid stool is a common sign of intestinal pathology. Diarrhea occurs in acute and chronic intestinal infections (enteritis, enterocolitis, sigmoiditis, proctitis), in various exogenous intoxications (poisoning with arsenic or mercury), endogenous

intoxications (uremia, diabetes, gout), in endocrine disorders (adrenal dysfunction, thyrotoxicosis), and in hypersensitivity to some food (allergy).

The mechanism of diarrhea is very complicated. Different pathogenic factors may prevail in various pathological conditions:

- *Diarrhea due to rapid transit of stool* through the digestive tract that occurs with motility disorders such as irritable bowel syndrome (IBS).
- *Osmotic diarrhea* occurs when sugars, sugar alcohols and certain minerals in the intestines fail to be absorbed into the bloodstream. These unabsorbed substances draw water into the intestines, resulting in watery stool. Lactose and sorbitol intolerances are among common causes of osmotic diarrhea. Osmotic diarrhea usually goes away once the offending food is excluded from the diet.
- *Secretory diarrhea* happens when the intestines release water and salt into the stool, making it watery. Infections that release toxins are the most common cause of secretory diarrhea. These toxins then cause the intestines to secrete water and salt. Another possible factor stimulating secretions of water and salt by the intestines are carcinoid tumors. Poor absorption of fatty acids and bile acids by the intestines, commonly found in patients with celiac disease or an inflammatory bowel disease, can also lead to secretory diarrhea. Fasting usually does not help improve secretory diarrhea.
- *Exudative diarrhea* occurs when irritation or inflammation of the lining of the colon causes the release of blood and other fluids. It can be caused by a variety of conditions such as inflammatory bowel disease, some cancers or tuberculosis.

Paradoxical diarrhea occurs in prolonged constipation due to mechanical irritation of the intestinal wall by hard fecal masses. Upset equilibrium between the fermentative and putrefactive flora of the intestine (in syndrome of intestinal bacterial overgrowth) is another important factor in the etiology of diarrhea.

Diarrhea occurring in organic affections of the large intestine is mostly of the inflammatory character. It is not abundant, nor does it produce strong negative effect on the patient's general condition (as compared with affections of the small intestine which is attended by profuse diarrhea associated with deranged motor and absorption function of the intestine).

Constipation (obstipation). Constipation includes the following:

- infrequent bowel movements (typically three times or fewer per week);
- difficulty during defecation (straining during bowel movements or a subjective sensation of hard stools; straining a strong effort to push out stool often by holding one's breath and by pushing the respective muscles in the abdominal area hard),
- the sensation of incomplete bowel evacuation.

However, the duration of constipation is only relative, because in many cases it is not the result of pathology but of the living conditions and nutrition. If vegetable food dominates in the diet, the subject may defecate two or three times a day. Stools become rarer if the diet is rich in meat. A radical change in nutrition can remove constipation. Limited mobility of the subject, hunger, and irregular defecations (during the day) may prolong pauses between defecation. The main factor determining defecation is the condition of intestinal motor function. Bowel contents are retained in the large intestine and the rectum in constipation.

There are *organic and functional constipation*. *Organic constipation* is usually associated with mechanical obstruction, such as narrowing of the intestinal lumen due to a tumour, scar, adhesion, and abnormalities in the intestine (megacolon, dolichosigmoid, megasigmoid, diverticulosis).

Functional constipation is subdivided into: (1) alimentary constipation; it occurs due to ingestion of easily assimilable food, which leaves small residue and normally stimulates peristalsis of the intestine by irritating its nervous receptors; (2) neurogenic constipation due to dysfunction of the intramural nervous apparatus or the 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.

Intestinal hemorrhage often occurs in ulcerous affections of the gastrointestinal tract. It develops in the presence of tumour, protozoal and helminthic invasions, acute infections (typhoid fever, bacillary dysentery), in thrombosis of mesenteric vessels, ulcerous non-specific colitis, etc.

Clinical presentation of *intestinal hemorrhage* varies with the anatomical source of the bleeding, as follows:

- melena with cecum and small intestinal bleeding;
- maroon (black-brown) stool with bleeding from the right side of the colon;
- bright red blood per rectum with bleeding from the left side of the colon;
- blood typically covers the stool (a condition known as *hematochezia*). It is on the toilet paper, or drips into the toilet bowl, the stool is usually normally coloured in hemorrhoidal bleeding.

Anamnesis

The patient should be inquired thoroughly about his nutrition since his/her early childhood until the onset of the disease (especially directly before the disease), about poisonings in the past life, and hypersensitivity to some feeds. It

is necessary to find out if the patient's meals are regular, if the food is varied, and if the patient smokes or drinks alcohol. Information about past diseases of the intestine (infections, parasitic invasions, inflammatory bowels diseases) and pathology of other organs is sometimes decisive for establishing the cause of the present affection.

Some functional disorders of the intestine can be associated with occupation hazards (lead or arsenic poisoning, constipation due to frequent suppression of calls to defecate).

14.2. General survey of patients in diseases of the gastrointestinal tract

Deranged mental state (obtundation, stupor) may be rarely in gastrointestinal diseases complicated by severe malnutrition, profuse bleeding and anemia. Nevertheless, large spectrum of psychopathological symptoms (anxiety, depression) have been associated with irritable bowel syndrome (IBS) in the absence of other objective etiology. However, such associations are also evident in other chronic diseases with more clearly defined pathogenesis such as peptic ulcers of stomach and duodenum, ulcerative colitis, etc.

Forced recumbent position on the right side with flexed legs and hands pressed to stomach is typical in exacerbation of peptic ulcer of the stomach. *Forced supine recumbent position* with flexed limbs to relieve abdominal tension is typical in acute peritonitis. Pancreatic tumour and chronic pancreatitis are characterized by position on “all fours" the patient leans on the flexed forearms, or *prone recumbent position* with cushion or folded blanket below abdomen (Table 14-4).

General inspection of the patient with dysphagia may suggest an organic affection of the esophagus if the patient is extremely asthenic (*cachexia*, or severe malnutrition). During general inspection of the patient with stomach diseases, a physician may assess poor nutrition of the patient (cachexia) which is characteristic of stomach cancer and untreated benign pyloric stenosis. Patients with uncomplicated peptic ulcer look practically healthy. Severe prolonged affection of the absorptive function of intestines causes grave cachexia.

Pale skin and visible mucosa are observed after gastric and intestinal hemorrhage, and in anemia. Edema is possible in loss of protein with simultaneous retention in the body of water and salt. Inspection of the skin reveals its dryness and paleness; the mucosa is pale due to insufficient absorption of iron and anemia of the patient. Insufficient absorption of vitamins results in the development of fissures of the lips (*cheilosis*), the skin becomes rough, and scaly skin rashes develops.

Facies Hippocratica is associated with collapse in grave diseases of the abdominal organs (diffuse peritonitis, intestinal obstruction, perforated peptic ulcers of the stomach or duodenum, rupture of the gall bladder). The face is characterized by sunken eyes, pinched nose, deadly livid and cyanotic skin, which is sometimes covered with large drops of cold sweat.

Table 14-4. General survey in gastrointestinal diseases

Signs	Characteristics	Causes
Forced position	recumbent position on the right side with flexed legs, and hands pressed to stomach	- exacerbation of peptic ulcer of the stomach
	the patient in bed on his/her back, with his/her limbs flexed to relieve abdominal tension	acute peritonitis
	"on all fours" the patient leans on the flexed forearms, or in prone position with cushion or folded blanket below abdomen	in pancreatic tumour or chronic pancreatitis
Poor nutrition	underweight – body mass index (BMI)=16,0-18,4 kg/m^2	maldigestion and malabsorbtion syndromes
	severe underweight (cachexia) – BMI <16 kg/m^2	malignant tumours, pyloric stenosis
Pale skin and mucosa	- after gastric and intestinal hemorrhage - in chronic anemia associated with gastrointestinal diseases	peptic ulcers and erosions, chronic gastritis, ulcerative colitis, malignant tumours
Peri-pheral edema	possible in loss of serum total protein and albumin	maldigestion and ma-labsorbtion syndromes, malignant tumours
Facies Hippocratica	- sunken eyes, pinched nose, deadly livid and cyanotic skin, which is sometimes covered with large drops of cold sweat; - associated with collapse in grave diseases of the abdominal organs	diffuse peritonitis, intestinal obstruction, perforated ulcer of the stomach or duodenum, rupture of gall bladder
Oral cavity – conditions of oral mucosa, tongue, teeth	pale mucosa	anemias
	hyperemia (redness), aphtae (erosions), tenderness	stomatitis
	smooth tongue with atrophied papillae	atrophic gastritis, cancer of stomach, sprue, B_2– and – iron deficiency
	"geographic" tongue with hypertrophied papillae and fissures (*Hunter glossitis*)	B_{12}–deficiency in atro-phic gastritis and cancer
	white-grey coated tongue with a foul smell	acute gastritis
	glassy, crimson tongue (*cardinal tongue*)	pellagra
	fissures and ulcers in corners of lips (*cheilosis*, or *angular stomatitis*)	B_2 (riboflavin)– and – iron deficiency
	dry tongue	severe diarrhea, vomiting, acute peritonitis
	enlarged tongue	myxedema, acromegaly

14.3. Survey of the oral cavity

When inspecting the mouth, attention should be paid to its shape (symmetry of the angles, permanently open mouth), the colour of the lips, eruption on the lips (*cold sores, herpes labialis*), and the presence of fissures. Fissures in corners of lips (*cheilosis,* or *angular stomatitis*) are typical in vitamin B_2 (riboflavin) – and – iron deficiency.

The oral mucosa should also be inspected (for the presence of aphthae, ulcers, pigmentation, spots, thrush, and hemorrhage) (see up Table 14-4). Marked changes in the gums can be observed in some diseases (such as pyorrhea, acute leukemia, diabetes mellitus, and scurvy) and poisoning (with lead or mercury).

Teeth should be examined for the absence of defective shape, size, or position. The absence of many teeth is very important in the etiology of some gastrointestinal diseases. Absence of many teeth accounts for inadequate disintegration and chewing food in the mouth, while the presence of carious teeth promotes penetration of microbial flora into the stomach.

Tongue is not the "mirror of the stomach" as it was formerly believed. Nevertheless, in some diseases its appearance is informative. Clean and moist tongue is characteristic of uncomplicated peptic ulcer. The tongue with a foul smelling white-grey coating is a characteristic of the acute gastritis. The dry tongue indicates a severe abdominal pathology or acute pancreatitis.

The tongue with atrophied papillae suggests cancer of the stomach, atrophic gastritis with pronounced gastric secretory hypofunction, or vitamin B deficiency. The smooth glossy tongue caused by complete atrophy of the lingual papillae is a characteristic of gastric cancer, pellagra, sprue, and ariboflavinosis.

"Geographic" tongue with hypertrophied papillae and fissures (*Hunter glossitis*) may be due to B_{12}–deficiency in atrophic gastritis and cancer of stomach.

The tongue in intestinal diseases often becomes crimson (*cardinal tongue*) in vitamin PP-deficiency (*pellagra*), its papillae are smoothed down. The gums may be loose and bleeding.

Disordered movement of the tongue may indicate central nervous system affections, grave infections and poisoning.

14.4. Inspection of the abdomen

Inspection of the abdomen should be with the patient in vertical and horizontal position.

Survey of the abdomen in vertical position. Examination of the abdomen in a vertical position begins with survey. Thus the doctor sits on a chair, and the patient faces the doctor, the person to him/her, completely having naked the abdomen.

For an exact delimitation of the localization of the signs revealed by the objective inspection, abdomen is conditionally divided in some regions. Two horizontal lines (the first line bridges the X ribs, the second - superior edges of

the ileac bones) divide the anterior abdominal wall in three regions, locating one under another: *epigastric, mesogastric and hypogastric regions*. Two collateral vertical lines conducted on outside edges of rectus abdominis muscles divide epigastric region into two (right and left) *subcostal (hypochondria) parts* and epigastric part (in the narrow sense) posed in the middle; mesogastric region - in two *lateral (flancs, or flanks)* and *umbilical parts*; hypogastric region – in two *ileac parts* locating on each side and *suprapubic part* (Fig.14-2).

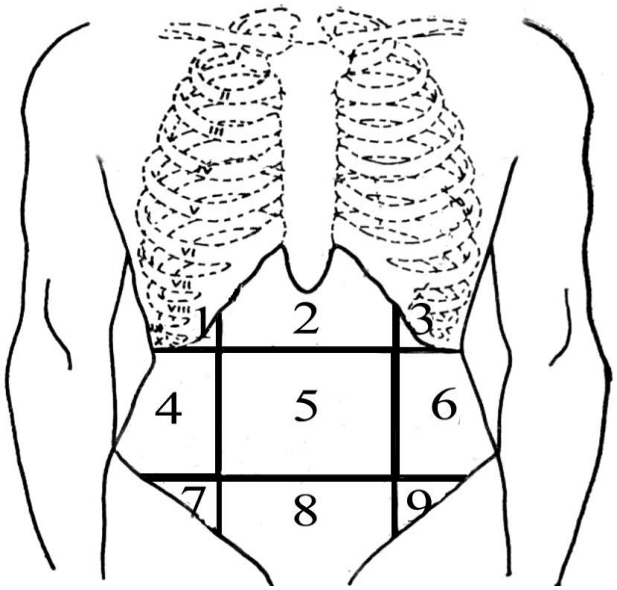


Fig. 14-2. Clinical topography of abdomen:
1, 3 – right and left subcostal (hypochondrium) part;
2 – epigastric part; 4, 6 – right and left lateral parts (flanks); 5 – umbilical part (mesogastrium); 7, 9 – right and left ileac parts; 8 – suprapubic part.

At the beginning of the inspection, the form of the abdomen is defined. In a healthy person, the form of the abdomen is symmetrical, and substantially depends on his/her constitution: normothenic - flat, hypersthenic - slightly bulging, asthenic - slightly concave (Table 14-5). The abdomen can be of a normal shape with a slightly protruding suprapubic region. The enlarged abdomen is possible due to excess subcutaneous fat, and the presence of meteorism or ascites.

Regularity of the abdominal shape should be assessed. An enlarged liver may protrude in the upper of the abdomen; an enlarged uterus causes protrusion in the lower part of the abdomen. Inspection of the abdomen may give information about the contours and peristalsis of the stomach if the patient is cachectic.

In pathological cases (pyloric stenosis, intestinal obstruction), peristalsis motions can be easily seen (ridges raising the abdominal wall). If a physician rubs or taps on the epigastric region peristalsis becomes more distinct. Sometimes, bulging up of abdominal wall can be because of a large tumour.

Table 14-5. Inspection of abdomen

Characteristics	Norm	Alterations
Form and symmetry:	symmetrical – flat, or slightly bulging, or slightly concave (according to the type of thebody-build)	symmetrical increase in the volume - – in meteorism, obesity, ascites
		asymmetric bulging – in hepatomegaly (in the right hypochondrium), splenomegaly (in the left hypochondrium), pathologic mass (tumours, cysts – according to the localization of the affected organ)
		hollow abdomen – in severe malnutrition
Participation of the abdomen in respiratory movements	symmetrical respiratory motions of the anterior abdomi-nal wall	abdomen does not participate in the act of respiration – diffuse peritonitis
		abdomen participates in the act of respiration unevenly – local peritonitis, local pain in abdomen (in acute cholecystitis, appendicitis, perisplenitis, etc.)
Hernias	absent	umbilical, inguinal, linia alba, postoperative hernias
Abdominal wall skin	without skin spots, hemorrhages, visible vascular pattern	- hemorrhagic skin spots (petechiae, ecchymosis) – in hypocoagulation; - widening of the subcutaneous veins surrounding navel (“caput medusae”) – in portal hypertension; - striae – in pregnancy, obesity, hypercorticism (Cushing syndrome); - scars – passed traumas and surgery operations
Umbilicus	normal umbilicus is usually inverted and situated centrally in the abdomen	- eminences of the umbilicus (purple colour may be) with a shift from the vertical line – in malignancy (melanoma, cancer metastasis); - bulging navel may be in ascites, and in meteorism
Visible peristalsis	absent	intestinal obstruction. (scar, tumor, constant spasm), stenosis of pylorus

The patient is asked to breathe "with his/her abdomen" to assess the mobility of the abdominal wall. The patient is unable to take a deep breath in the presence of pain, e.g. in an attack of acute appendicitis or cholecystitis. Divergence of the *rectus abdominis muscles* can be revealed if the patient raises his head. Antiperistalsis movements in the epigastrium or by the course of the intestine can give a hint on the presence of an obstacle to propulsion of food masses in the intestine.

An inflated abdomen presents in obesity, accumulation of liquid, or meteorism. Slight distension of the abdomen may be due to a tumour, encapsulated fluid, or meteorism associated with intestinal stenosis confirmed by visible peristalsis over the constricted portion of the intestine.

The character and localization of postoperative scars enable rather precisely to establish the organ that should be operated. The inspection of an abdomen in a vertical position is completed with the survey of *linia alba*, inguinal and femoral canals where one finds out the hernias producing strong pains in an abdomen. For the detection of hernias it is necessary palpate hernia rings by the index finger which dilating promotes formation of hernias. The outside inguinal ring routinely loosely passes the index finger, intrinsic inguinal ring - only its tip. In a vertical position of the patient, it is possible to distinguish a separation of recti abdominis muscles by a palpation of a white line of the abdomen.

Inspection of the abdomen in horizontal position. During the research a patient should lay on the back with a completely naked abdomen on a bed with a low pillow, the extended legs and hands placed along the trunk. The doctor should sit by the right side from the patient on a chair which level is close to the level of the bed, having a face-to-face contact with the patient.

At the time of the inspection in a horizontal position, attention is paid first of all to a postural change of the abdomen of the patient. In a horizontal position hernias are seen approximately routinely absent.

The abdomen may be enlarged significantly due to the accumulation of the free fluid *(ascites)*, and a pronounced hepato- or splenomegaly. This occurs in liver cirrhosis concurrent with portal hypertension. When the patient with ascites stands erect, his/her abdomen becomes a protruding due to the downward flow of fluid; in the lying position the abdomen is flattened (*"frog belly").* The umbilicus often becomes protruded in ascites when the patient stands. It is due to an increased infra-abdominal pressure. This sign can be used to differentiate between the enlargement of the abdomen in ascites (also large intraabdominal tumours) and pronounced obesity (the umbilicus is retracted) (Table 14-6).

14.5. Percussion of the abdomen

Percussion of the abdomen is only relatively informative. Percussion of the anterior abdominal wall at points of projection of the stomach and intestines gives a tympanic sound of various characters, which depends on the uneven distribution of gaseous, liquid or solid intestinal contents.

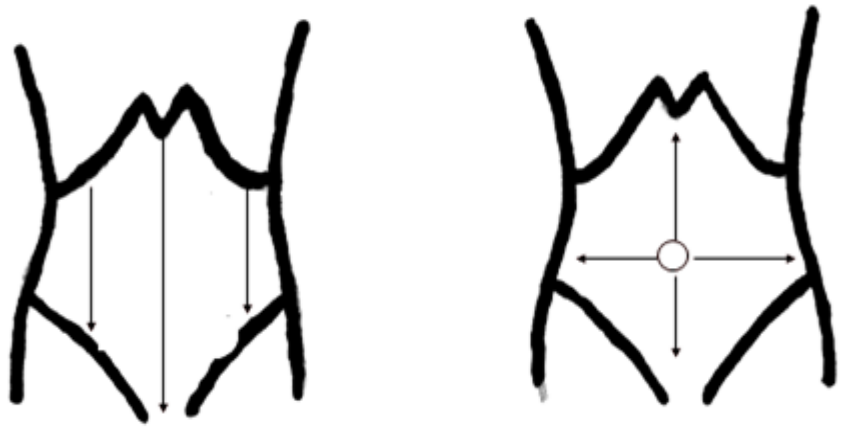
Percussion of abdomen in the vertical position of the patient is used for revealing free fluid in an abdominal cavity and definitions of its level. By percussion on midline and lateral flanks from top to down, it is possible to differentiate the tympanic sound above intestines or the dull sound lower than fluid level (Fig. 14-3, 14-4).

Table 14-6. Differences of enlarged abdomen in ascites, meteorism, and obesity

Characteristics	Ascites	Meteorism	Obesity
Shape of abdomen in vertical position	prominent inferior part	increased evenly	increased evenly, with expressed subcutaneous fat fold (“fatty apron”) inferiorly
Shape of abdomen in horizontal position	“frog belly” protruded sideways and downwards, and flattened in the middle part	increased evenly	increased evenly
Shape of umbilicus	protruding - in the vertical position, flattened – in the horizontal position	protruding	retracted
Percussion in the vertical position	tympanic sound - in the superior part, dull sound - in the inferior part	expressed tympanic sound	tympanic sound, dull sound may be – on expressed subcutaneous fat fold (“fatty apron”) inferiorly
Percussion in the horizontal position	tympanic sound – near umbilicus, dull sound - sideways and downwards, positive sign of the “fluid fluctuation”		

In a horizontal position of the patient percussion of the abdomen is performed from umbilicus on midline to epigastrium and hypogastrium, and from umbilicus - to flanks in lateral directions (Fig. 14-5). With the purpose of differentiation dull sounds originated from free fluid and contents of intestines, the physician can repeat percussion from the umbilicus to flanks in lateral directions in position of the patient on the side of the body. At presence of the

ascites, the level of the dull sound is changed in this position of the patient ("*shifting dullness"*).



(1) **(2)**

Fig. 14-3. Percussion of abdomen:
(1) – percussion in a vertical position; (2) – percussion in a horizontal position.

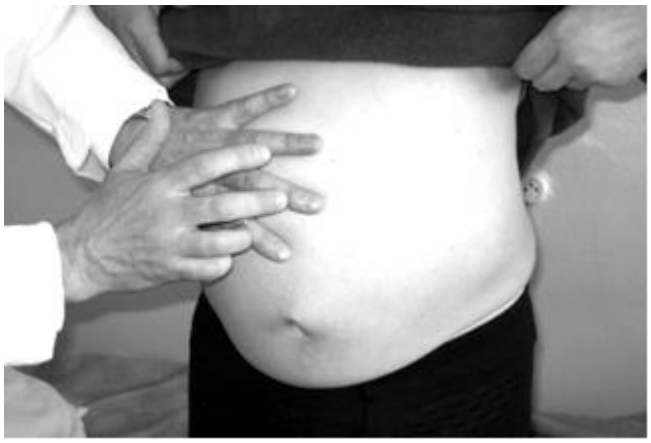


Fig. 14-4. Percussion of abdomen in a vertical position of the patient.

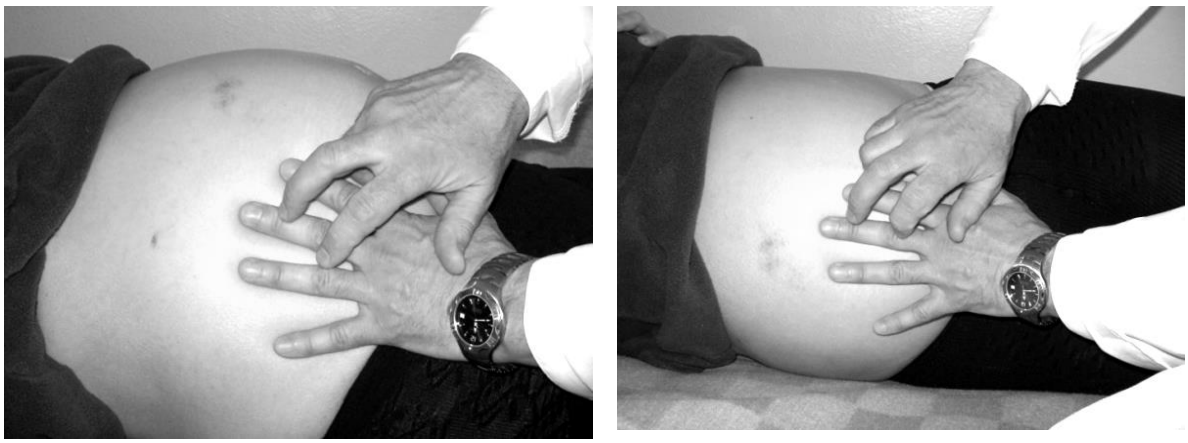
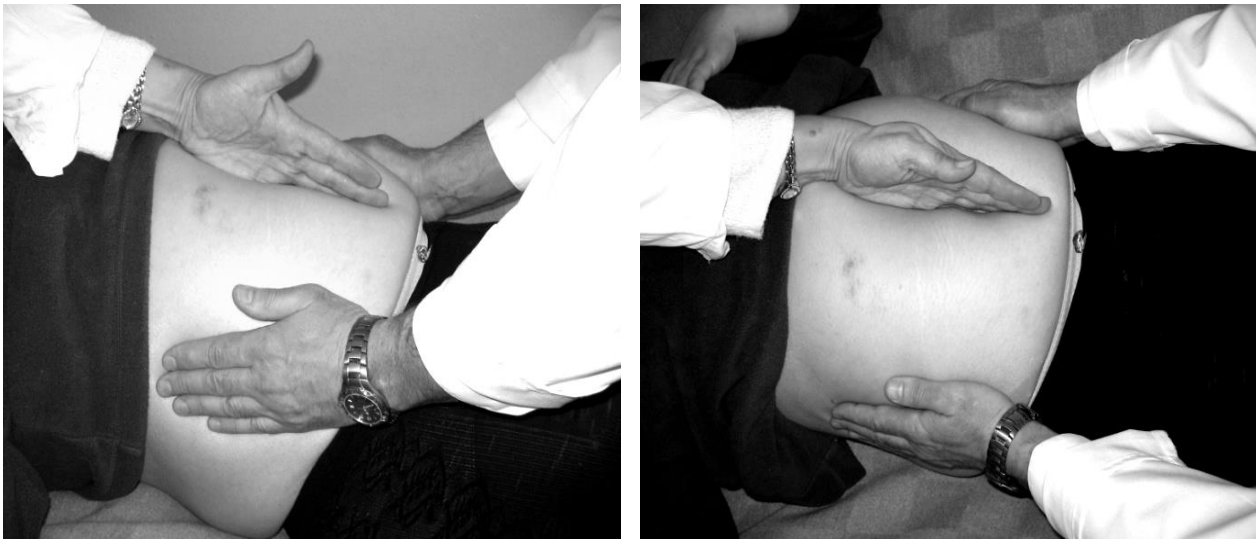


Fig. 14-5. Percussion of abdomen in a horizontal position (on the back and right side) of the patient.

By means of ***percussionary palpation technique***, the "*sign of fluctuation of fluid" ("fluid thrill")* is also defined with a presence of an ascites. For this purpose, the palmar surface of the left arm is placed on the right half of the abdomen in the region with the detection of the dullness (Fig. 14-6). The right arm impacts one-digital percussion (according to Obraztcov method) mild strokes on the left half of the abdomen. At presence of a significant amount of the free fluid in the abdominal cavity, the palm of the left arm clearly accepts fluctuation – a jerky waving of the fluid. To prevent oscillating motions on the anterior abdominal wall, it is possible to put the edge of the arm or a book along the *linia alba* of the abdomen.



(1) (2)

Fig. 14-6. Percussionary palpation method for detection of free fluid in abdominal cavity by "the symptom of fluctuation of fluid" ("fluid thrill"):
(1) side view, (2) top view.

Short strokes of the finger-hammer on the epigastrium (*Mendel sign*) are used to determine involvement of the parietal peritoneum: a pain indicates affection of the peritoneum.

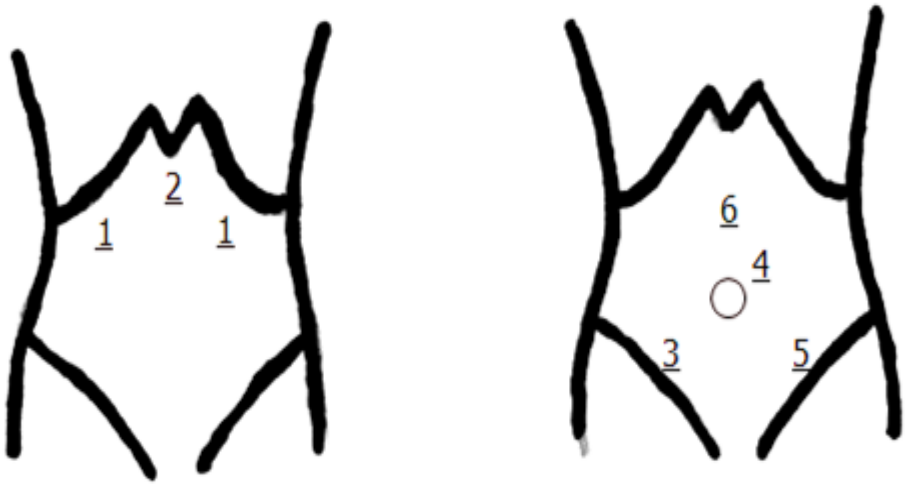
14.6. Auscultation of the abdomen

Auscultation of the abdomen in a vertical position of the patient is performed for the definition of *peritoneum friction murmur* at the right and left hypogastrium in perihepatitis and perisplenitis (Fig. 14-7).

In only rare cases, the peritoneal friction can be heard over the liver and the gall bladder (in perihepatitis or pericholecystitis). This sound resembles pleural friction, and it is a dangerous sign. It indicates deep extension of inflammation

onto all walls of the gall bladder and possible perforation. Peritoneum friction murmur is possibly heard in patients with fibrinous peritonitis during respiratory movements.

Auscultation of esophagus. Listening to the epigastric region below the xiphoid process or above it, at swallowing fluids by the healthy person it is possible to hear two murmurs: the first - at once after swallowing, and 6-9 seconds later the second - connected to the transit of the fluid through the cardia. Delay or absence of the second murmur specifies an interrupting in the inferior third of an esophagus, in cardiac department of the stomach.



Vertical position **Horizontal position**

Fig. 14-7. Locations of auscultation of the abdomen:

(1) right and left hypochondrium (for peritoneum friction murmur);

(2) xiphoid process (for auscultation of esophagus);

(3) right ileac region (for cecum peristalsis);

(4) point of Porges - 2 cm from umbilicus up and to the left (for small intestine peristalsis);

(5) left ileac region (for sigmoid peristalsis);

(6) abdominal aorta - 5-7 cm up from umbilicus (for vascular murmur in the aorta stenosis or aneurism).

Auscultation of the abdomen in a horizontal position

Auscultation of the abdominal aorta is performed on the midline 5-7 cm above the umbilicus. Systolic murmurs can be listened in the abdominal aorta aneurysm, atherosclerosis of the abdominal aorta and its branches, such as renal arteries (Table 14-7). Renal arteries are auscultated on the abdominal wall in points placed 5 cm above umbilicus and 4-5 cm laterally from the anterior midline.

The auscultation of the peristalsis intestinal sounds gives information about the motor function of the intestine. During gastric digestion and movement of the chyme along the small intestine, long periodic rumbling can be heard. Rhythmic intestinal murmurs present in 5-7 hours after meal. The peristalsis intestinal

sounds are listened in the cecum (right ileac region) 2-3 per minute, in the small intestine (above the *point of Porges* – 2 cm from umbilicus in the upper and left direction) up to 3-5 per minute, and in sigmoid (left ileac region) 2-3 per minute. In mechanical obstruction of the intestine, its peristalsis is resonant (in large waves). Peristalsis disappears in a paralytic obstruction of the intestine; the abdomen is absolutely "silent" in perforation of the peptic ulcer with secondary paralysis of the intestine.

Table 14-7. Auscultation of the abdomen

Characteristics	Norm	Alterations
Auscultation of esophagus (below xiphoid)	fluids passage sounds in 6-9 seconds after swallowing	delay more than 14 seconds or absence of in inferior third of esophagus or of stomach cardiac part
Intestinal perisitalsis	rhythmic peristalsis sounds can be heard 2-3 per minute for 5-7 hours after meal	accelerated peristalsis sounds – in diarrhea, meteorism, incomplete ileus
		physiologically accelerated peristalsis sounds – after food and drink intake, physical exercises, deep abdominal palpation
		delayed peristalsis sounds - in constipation
		absence of peristalsis sounds – complete ileus, peritonitis, mesenterial thrombosis
Auscultation of abdominal aorta and renal arteries	vascular murmurs absent	systolic murmur – in stenosis or aneurism of the abdominal aorta (and its branches) and renal arteries
Peritoneum friction murmur	absent	below inferior edge of the costal arches - in fibrinous peritonitis during respiratory movements, and at the right and left hypogastrium - in perihepatitis and perisplenitis
Splashing sound (succussion) in epigastrium	absent	in evacuator dysfunction of the stomach (mostly in pyloric stenosis), and its pronounced gastric hypersecretion
		physiologically – during 1-2 hours after food and drink intake

Auscultation of the stomach

Splashing sound (succussion) from a push can only occur when there is air above the liquid in the stomach. Thanks to this intermediate layer of the air, the anterior wall of the stomach, when struck with fingers, hits the surface of the liquid and a splashing sound is produced. If the anterior wall of the stomach is adjacent to the liquid, a splashing sound cannot be caused.

A splashing sound can be heard if the patient is lying on his/her back, while the examiner pushes the anterior wall of the peritoneum with four flexed fingers of the right hand (Fig. 14-8). A physician presses with the ulnar edge of the left hand on the chest in the region of the xiphoid process, which forces the air in the upper part of the stomach to escape from there and properly distribute over the surface of the liquid. The same result can be obtained by forcing the patient to inflate out the abdomen that contracts the diaphragm, which displaces air from the upper part of the stomach to the lower during its contraction.

The push of the hand is transmitted through the abdominal wall to the liquid and air contained inside the stomach to cause an audible splashing sound, which is inaudible outside the inferior borders of the stomach. This technique for outlining the inferior border of the stomach is effective in cases where the stomach inferior border formed by the greater curvature is at the normal level or lowered. Succussion gives information about the evacuator function of the stomach: the splashing sounds in healthy subjects can be heard only after meal or after intake of not less 200-300 ml of drinks. Splashing sounds heard 7-8 hours after meals suggest an evacuator dysfunction of the stomach (mostly in pyloric stenosis) or its pronounced hypersecretion. Splashing sounds heard to the right of the median line of the abdomen indicate dilatation of the prepyloric part of the stomach (*Vasilenko's sign*).

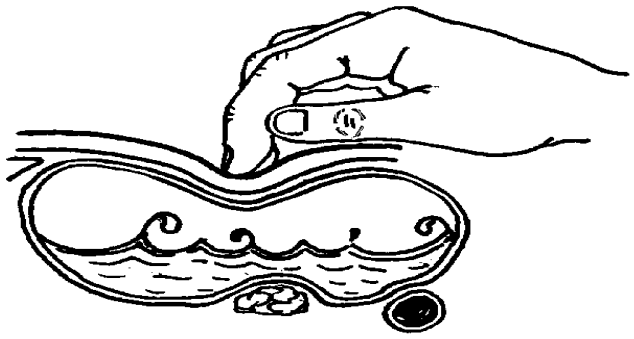


Fig. 14-8. Determining greater curvature of the stomach by a splashing sound.

Auscultative affriction (stethacoustic palpation). Auscultation of the stomach is helpful when used together with palpation of the stomach to outline its greater curvature. *Auscultative affriction* is performed as follows: stethoscope is placed beneath the left costal arch below the xiphoid process (Fig. 14-9). The

examiner rubs the abdominal wall overlying the stomach by the finger of the left arm and gradually moves the finger away from the stethoscope bell. As long as the finger rubs the skin overlying the stomach, the physician hears the friction, but when the finger moves outside the stomach borders, the sound disappears.

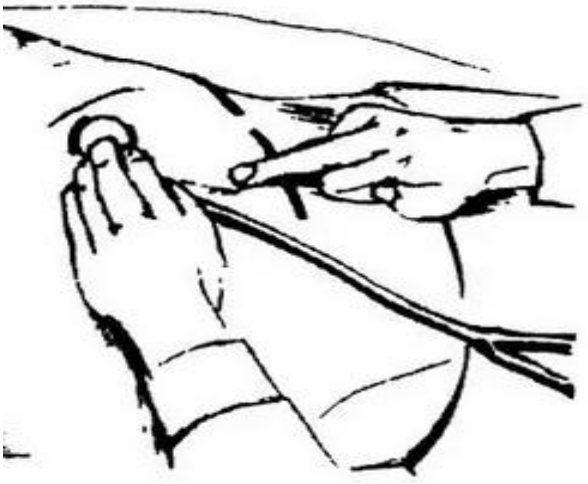


Fig. 14-9. Determining greater curvature of the stomach by an auscultative affriction.

An auscultative affriction of the stomach is a very simple technique but the findings are sometimes inaccurate. In norm, greater curvature of the stomach lies on 3-4 cm above a level of umbilicus in men, in women 1-2 cm higher than umbilicus or at its level.

14.7. The key points of the theme "Subjective and Objective Examination of Patients with Gastrointestinal Tract Diseases"

The main complaints in diseases of esophagus are dysphagia, pain by projection of esophagus from the neck to the upper epigastrium, odynophagia (pain on swallowing food and fluids), heartburn, vomiting with non-digested food, esophageal hemorrhage (when vomitus contains red non-clotted blood).

The main complaints in diseases of the stomach and duodenum **are** epigastric pain and/or discomfort, dyspepsia (deranged appetite, heaviness in epigastrium, nausea, regurgitation, vomiting, with or without epigastric pain), gastric vomiting with partly digested food; gastric hemorrhage manifested by vomiting with clotted blood or *coffee grounds*, or black tarry stools (*melena*).

The main complaints in diseases of intestines are the abdominal pain associated with defecation and/or passage of gas, meteorism, diarrhea, constipation, intestinal hemorrhage manifested by melena (cecum and small intestinal bleeding); brown-red stools (left side colon bleeding) or bright red blood per rectum (rectum bleeding).

General inspection in the gastrointestinal tract diseases can demonstrate a poor nutrition state (underweight, cachexia), pale skin and mucosa, peripheral

edema (in loss of serum total protein), changes in conditions of oral mucosa and tongue, forced recumbent position (in the pain syndrome).

Inspection of the abdomen should be with the patient in the vertical and horizontal position. Inspection of the abdomen enables to assess the form and symmetry of the abdomen, participation of the abdomen in respiratory movements, condition of the abdominal wall skin and umbilicus, to find hernias.

Percussion of the anterior abdominal wall should be with the patient in a vertical and horizontal position. Percussion of the anterior abdominal wall at points of projection of the stomach and intestines givesa tympanic sound of various characters, which depends on the uneven distribution of gaseous, liquid or solid intestinal contents.

Characteristics of an enlarged abdomen in ascites are: (1) in vertical position of the patient - a prominent inferior part, protruding umbilicus, tympanic sound - in superior part, dull sound - in inferior part ; ***2) in horizontal position*** - "frog belly" protruded sideways and downwards, and flattened umbilicus, tympanic sound – near umbilicus, dull sound - side-ways and down-wards, positive sign of "fluctuation of fluid".

Auscultation of the abdomen can be useful for assessment of intestinal peristalsis, esophageal transit, and for provisional diagnosis of stenosis or aneurism of the abdominal aorta (and its branches) and renal arteries by vascular murmurs, local peritonitis – by peritoneum friction murmur.

Auscultation of the stomach can be useful for outlining the inferior border of the stomach by the techniques of *auscultative affriction and splashing sound (succussion)*. Splashing sounds heard 7-8 hours after meal suggest an evacuator dysfunction of the stomach (in pyloric stenosis) or its pronounced hypersecretion.

14.8. Assessment tests on the theme "Subjective and Objective Examination of Patients with Gastrointestinal Tract Diseases"

1. Symptom of melena (black tarry-like stool) is typical in:
1. Anal fissure;
2. Stomach bleeding;
3. Small intestines bleeding;
4. Sigmoid colon bleeding;
5. Bleeding hemorrhoids.

2. Dysphagia means:
1. Difficulties at swallowing of food;
2. Eructation by air and eaten food;
3. Diarrhea;
4. Vomiting;
5. Heartburn.

3. Symptoms of gastroduodenal pathology include:

1. Epigastric pain;
2. Nausea;
3. Early satiation;
4. Vomiting;
5. Diarrhea.

4. It is typical for a pain in pathology of the stomach:
1. Epigastric localization;
2. Seasonal prevalence;
3. Association with reception of nutrition;
4. Relief after defecation;
5. Relief after vomiting.

5. It is typically for a pain in pathology of small intestines:
1. Relief after vomiting;
2. Relief after defecation or passages of gas;
3. Association with the act of defecation;
4. Association with reception of nutrition;
5. Mesogastrium localization.

6. Abdominal pain while eating is typical for the pathology of:
1. Stomach;
2. Transverse colon;
3. Duodenum;
4. Gall bladder;
5. Intestines.

7. Abdominal pain in 1.5-2 hours after meal is typical for the pathology of:
1. Stomach;
2. Transverse colon;
3. Duodenum;
4. Intestines;
5. Gall bladder.

8. What is the basic clinical symptom of the central origin vomiting?
1. Vomiting does not relieve a state of the patient;
2. Preceding nausea;
3. Abundant volume of vomiting masses (a vomiting "fountain");
4. Signs of the expressed intoxication dominate in a clinical pattern;
5. Vomiting relieves a state of the patient.

9. Specify signs of the gastric bleeding:

1. Dizziness;
2. Thirst;
3. Melena;
4. "Coffee grounds" color of vomiting content;
5. Visible blood in the stool.

10. Signs of gastrointestinal bleeding:
1. Coffee-grounds vomiting;
2. Melena;
3. Blood-streaked stool;
4. Arterial hypotension;
5. Acholia.

11. International Classification of adult underweight, overweight and obesity according to BMI includes:
1. Normal (healthy weight) – 18.5-24.99 kg/m^2;
2. Underweight <18.5 kg/m^2;
3. Obesity≥30.0 kg/m^2;
4. Obesity≥25.0 kg/m^2;
5. Underweight <16.0 kg/m^2.

12. Specify the anterior abdominal wall regions in the epigastric part:
1. Right and left flank;
2. Right and left hypochondrium;
3. Epigastrium;
4. Right and left ileum;
5. Umbilical region.

13. Specify the anterior abdominal wall regions in the mesogastric part:
1. Right and left flank;
2. Right and left hypochondrium;
3. Epigastrium;
4. Right and left ileum;
5. Umbilical region.

14. Specify the anterior abdominal wall regions in the hypogastric part:
1. Right and left flank;
2. Right and left hypochondrium;
3. Epigastrium;
4. Right and left ileum;
5. Suprapubic region.

15. Specify the abdominal wall survey criteria:

1. Shape;
2. Symmetry;
3. Visible intestinal peristalsis;
4. Condition of umbilicus;
5. Conditions of subcutaneous.

16. What kind of sound prevails while percussion of the abdomen ?

1. Dull sound;
2. Clear (resonant) sound;
3. Tympanic sound;
4. Box sound;
5. Dulled sound.

17. What is the direction of an anterior abdominal wall percussion in a vertical position of a patient?

1. From the xiphoid process down by anterior midline;
2. From the right and left costal arch vertically downwards in lateral areas;
3. From the umbilicus up, down and sideways;
4. From the flanks to umbilicus;
5. From the hypogastrium to xiphoid process up.

18. What is the direction of an anterior abdominal wall percussion in a horizontal position of a patient?

1. From xiphoid process down anterior midline;
2. From the right and left costal arch vertically downwards in lateral areas;
3. From the umbilicus up, down and to flanks in lateral directions;
4. From flanks to umbilicus;
5. From the hypogastrium to xiphoid process up.

19. Standard points of the intestinal peristalsis auscultation:

1. Right and left hypochondrium;
2. Xiphoid process;
3. Right ileac region;
4. Point of Porges (2 cm from umbilicus up and to the left);
5. Left ileac region.

20. Normal rate of the intestinal peristalsis on empty stomach in point of Porges:

1. 3-5 per minute;
2. 1-2 per minute;
3. 10-15 per minute;
4. 15-20 per minute;
5. Peristalsis sounds absent on empty stomach.

CHAPTER 15. Palpation of the Abdomen

Goals: to enable students to learn -

1. types of abdominal palpation, their purposes and common rules;
2. rules and diagnostic value of superficial palpation of the abdomen;
3. technique and diagnostic value deep methodical sliding palpation of stomach and intestine (according to V.P. Obraztsov, N.D. Strazhesko, F.O. Gausmann);
4. Criteria of assessment of palpating abdominal organs.

15.1. Palpation of the abdomen: history of the method, rules and purposes

Palpation is the basic method of physical examination in diagnosis of diseases of the abdominal organs. This method was appreciated firstly by the French physician (*F. Glenard*) in 80-years of XIXth century. Later in in the first half of the XXth century, Russian internists (*V.P. Obraztsov, N.D. Strazhesko, F.O. Gausmann* and others) further developed this useful method.

F. Glenard proposed palpation of the abdomen and believed that this method should systematically be used for clinical examination of the abdominal cavity. Having established that the cecum, transverse colon, sigmoid may be palpated sometimes, though he decided erroneously that their palpability indicated their pathology.

Independently of F. Glenard, V.P. Obraztsov developed methods for palpation of the gastro-intestinal tract and proved that some parts of the stomach and the intestine can be palpated in the absence of any pathology. V.P. Obraztsov and his disciples (notedly, F.O. Gausmann, the head of therapeutic clinic of the Minsk Medical Institution in 1924-1941 years) developed in detail palpation techniques for examination of the abdominal cavity.

Common rules of the abdominal palpation:

- The patient should relax in his bed. The bed should not be too soft.
- Patient’s legs should be stretched or bent at the knees, and the arms flexed on the chest or placed along the body.
- The patient's breathing should not be deep; his head should rest against a small firm pillow. This position ensures relaxation of the abdominal muscles.
- The physician takes his place by the right side of the bed, facing the patient. The chair should be firm and level with the patient's bed.
- The ambient temperature should be comfortable for the patient,

- The hands of the doctor should be warm and dry, nails must be short.
- Abdominal palpation is performed only after an auscultation and a percussion of the abdominal cavity.
- The examining movements should be careful and gentle so as not to hurt the patient.

It is necessary that the abdominal cavity should be accessible to palpation, i.e. that its muscles of the anterior abdominal wall be relaxed, and that the examiner should not provoke their straining by his manipulations.

Touching the abdomen roughly with cold hands will cause reflex contraction of the abdominal wall muscles to interfere with palpation of the abdomen. The patient with severe constipation would tale laxative or enema to empty the bowels.

However, some organs or their parts can only be palpated when they hang by gravity with the patient in the *vertical position*. Thus, the left lobe of the liver, the lesser curvature of the stomach, the spleen, the kidneys, the cecum, or tumours can become palpable. The epigastrium and the lateral parts of the abdominal cavity should also be palpated with the patient in the vertical position.

***Purposes of superficial and deep palpation*:**

- ***Superficial (light touch) palpation*** examines condition of the anterior abdominal wall.
- ***Deep palpation*** is used to establish normal topographic relations between the abdominal organs and their normal physical condition; the other object is to detect any possible pathology that changes the morphological condition of the organs and their topographic relations responsible for their dysfunction, to locate the defect, and to determine its nature. In other words, the deep palpation gives information on the topography of the abdominal cavity (***topographic palpation***).

15.2. The superficial (light touch) palpation of the abdomen

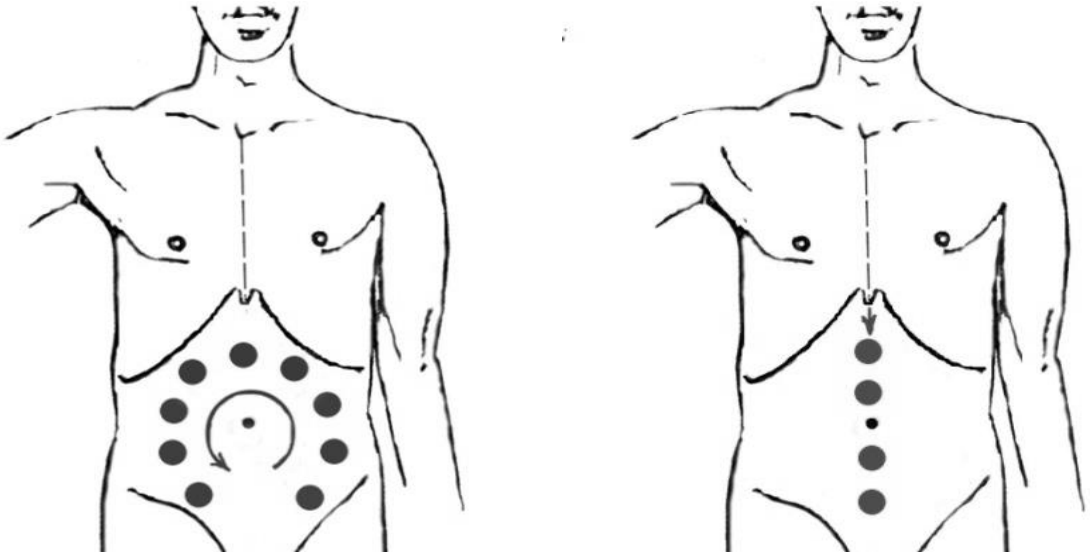
Aims of the superficial (light touch) palpation are research of properties of the anterior abdominal wall:

- location of the painful site;
- resistance and rigidity of anterior abdominal wall or its muscle strain;
- density formed in a wall, hernias, tumours;
- to differentiate a skin puffiness from augmentation of the subcutaneous fatty tissue.

The physician assumes his position by the bedside as described above and places his right hand flat on the abdomen of the patient (the fingers may be slightly flexed) to examine carefully and gradually the entire anterior abdominal wall without trying to penetrate the deep parts of the abdomen. By this examination,

the physician should establish the strain of the abdominal wall, its tenderness, and location of the painful site. The left ileum area should firstly be examined, providing that the patient does not complain of pain in this region.

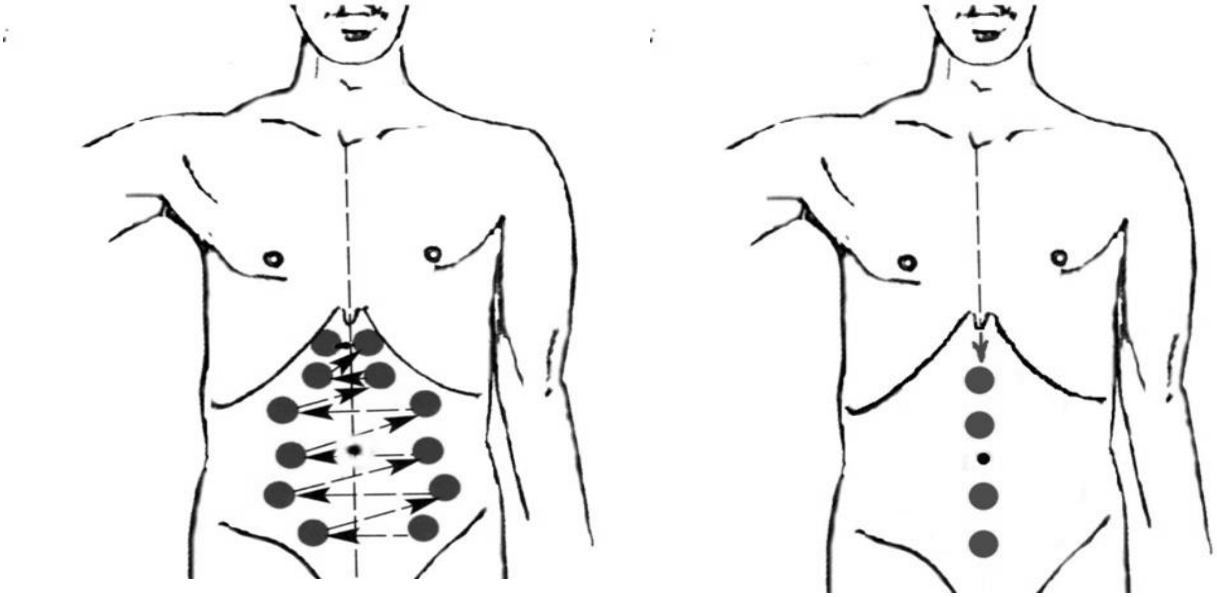
The *superficial (light touch) palpation* of the abdomen is performed in a direction against the hand of a wrist-watch (in an *anticlockwise manner*), i.e. after the left ileum palpation is continued on left flank from below upwards up to the left hypochondrium, then epigastric region, the right hypochondrium and the right flank from top to down to the right ileum. After that, the examiner lays the right arm is on the epigastric region to a superficial palpation of the median zone from the xiphoid process down to suprapubic area (*palpation on the white line, or linia alba*) (Fig. 15-1).



(1) (2)

Fig. 15-1. The sequence of the superficial palpation of the abdomen (basic variant): (1) anticlockwise manner, (2) white line.

It is also a procedure of a superficial palpation of symmetrically areas of an abdomen. In this case, after of the left ileum area palpation is then continued by examining symmetrical points of the abdomen on its left and right sides to end in the epigastric region (Fig. 15-2).



(1) (2)

Fig. 15-2. The sequence of the superficial palpation of the abdomen (second variant): (1) symmetrically areas, (2) white line.

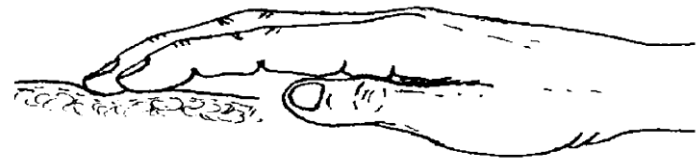
Technique of superficial (light touch) palpation of the abdomen:

1) The examiner puts his right hand flat on the patient's abdomen,

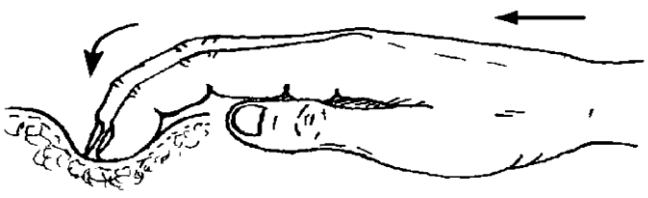
2) slightly flexes the fingers (it is possible to bend the arm and metacarpophalangeal joints, but some) and plunges the fingertips not more 2-3 cm in the abdominal wall without sliding, wherein the base of arm moves in the direction of the fingers, without touching the skin of patient or sliding on it,

3) raises his hand over his stomach and

4) moves in its new position (Fig. 15-3; 15-4).

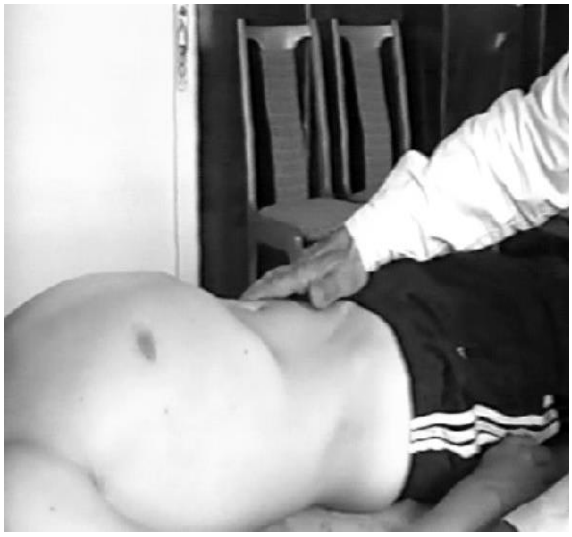


(1) - installation of fingers for superficial palpation.



(2) - the fingers are bent, and their tips are dipped in abdominal wall on 2-3 cm maximally, the arm moves in the direction of the fingers.

Fig. 15-3. Technique of the superficial palpation of the abdomen



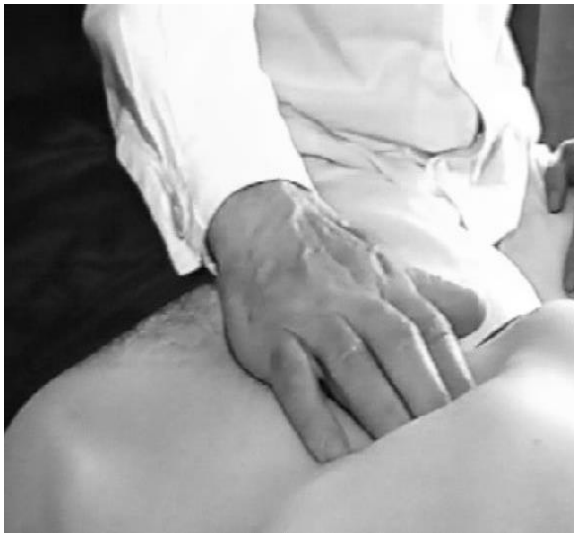


Fig. 15-4. Superficial palpation in the left flank and the median zone.

The superficial palpation of the abdomen reveals presence of tenderness to palpation, resistance of anterior abdominal wall or its muscle strain, *diastasis recti abdominis (a palpable gap of more than 2.5 cm between the two sides of the rectus abdominis muscle),* local densities formed in the wall, hernias, tumours, to distinguish puffiness of skin from an increase in subcutaneous fat. For establishment of tenderness of abdominal wall, before palpation it is necessary to warn the patient that he has told when at him the pain sensation will be maximal, will appear and stop. Pay attention also to a look of the patient.

To confirm *diastasis recti abdominis and midline hernia*, a physician has to palpate abdomen according to *l. mediana anterior* (*white line, or linia alba*) (Fig. 15-5). Palpation along the white line starts at the xiphoid process and goes down to the pubic bone. A longitudinal keel-like protrusion is observed in the diastasis area when the patient is asked to lift (or attempt to lift) the torso and then relax. A vertical defect between the muscles can be palpated with the palm edge. Fingers dipping also indicates the diastasis and allows to palpate the inner edges of the recti abdominis muscles. Examiner should measure width of the muscle gap. Diastasis recti abdominis can be associated with a prolonged abdominal wall distension (ascites, obesity, pregnancy, meteorism), weightlifting, sedentary lifestyle, old age and weakness of the abdominal muscles.

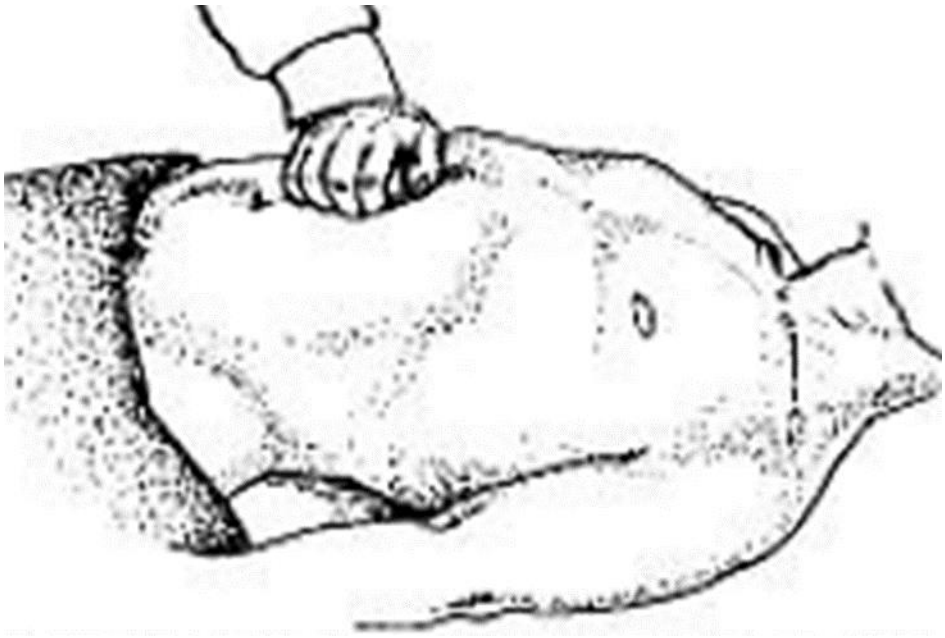


Fig. 15-5. Palpation to detect diastasis recti abdominis and midline hernia.

A physician should simultaneously assess condition of the abdominal skin and subcutaneous tissues, strain of the abdominal wall, superficial and deeper painful areas to locate them accurately. Hernias, separation of muscles and protrusions, and other anatomical changes should be revealed. *Resistance and marked strain of muscles of the abdominal wall* are usually palpated over the organ affected by inflammation, especially so if the peritoneum is involved. In the presence of acute inflammation of the peritoneum (local inflammation included, e.g. in purulent appendicitis, cholecystitis) local pressure causes strong pain but it becomes even more severe when the pressure is released (*Shchetkin-Blumberg sign*). The deep palpation can give information about the condition and topography of the abdominal cavity and its organs.

15.3. The deep (sliding methodical topographic) palpation of the abdomen

Aims of the deep sliding palpation are research of abdominal organs properties, such as:

- localization;
- mobility;
- tenderness;
- consistency;
- diameter;
- condition of the surface (smooth, tubercular);
- absence or presence of rumbling sounds during palpation.

When starting the deep palpation, the examiner should always be aware of the anatomical relations in the abdominal cavity, the shape and physical properties

of the organs, their supporting structures and possible deviations in topographical relations that may depend on the constitution of the patient, his special condition, nutrition, relaxation of the abdominal muscles, etc.

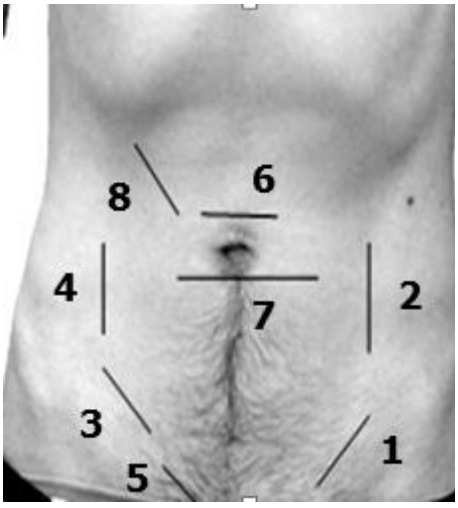
V.P. Obraztsov used the double-checking principle of the examinations. For example, in order to make sure that a given section of the intestine is actually the terminal end of ileum it is necessary to locate the cecum; to determine the size of the stomach, the palpatory findings are checked by *auscultative affriction* and *splashing sound (succussion)* examination of the stomach. Respiratory excursions of the organs should be taken into consideration during palpation according to a strictly predetermined plan, beginning with more readily accessible parts.

Rules and techniques of the deep sliding palpation of the abdomen

The success of the deep sliding palpation of the abdomen depends on strict observation of the rules, convenient position of the patient and the doctor, correct respiration of the first and position and state of arms of the second, rational palpation tactics of investigator and the conforming readiness to a palpation of researched patient.

Necessary condition is the maximal relaxation of muscles, especially anterior abdominal wall. The optimal for palpation of abdomen is the diaphragmatic respiration at which during an inspiration muscles of abdominal wall exert a little, and during an expiration - are as much as possible relaxed. The deep sliding palpation of abdomen provides necessity of palpation of the abdominal organs for fixed sequence and good knowledge of clinical topographical anatomy.

The sequence of the deep palpation: *left ileum area – sigmoid and descending colon; right ileum area – cecum, ascending colon and terminal end of ileum; further the epigastric and umbilical regions - stomach with its parts (greater curvature and pylorus) and transverse colon; the following stage - palpation of liver, spleen and kidneys* (Fig. 15-6).



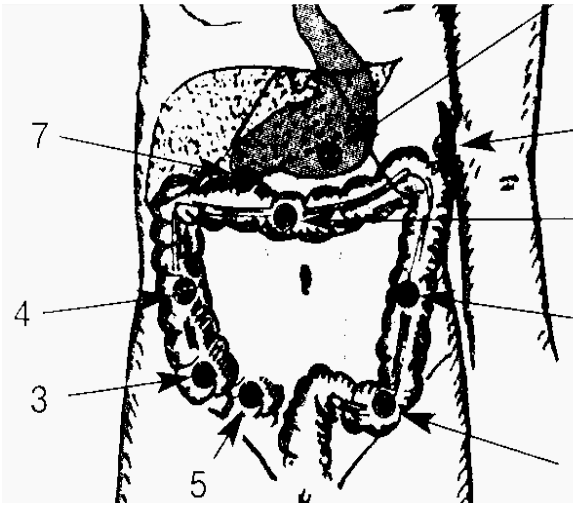


Fig. 15-6. The sequence of the deep palpation of the abdomen and the palpating hands position: 1 – sigmoid, 2 - descending colon, 3 – cecum, 4 – ascending colon, 5 - terminal end of ileum, 6 - greater curvature of stomach, 7 - transverse colon, 8 - pylorus, 9 - liver, spleen and kidneys.

The deep sliding palpation is performed after the superficial palpation of an abdomen. The posture of the patient and the physician should be the same as in surface palpation. The palpation should be carried out by the right hand. In some cases the other hand should be placed on the examining hand to increase pressure. The deep palpation can also be *bimanual (palpation with both hands simultaneously – two-handed deep palpation)*. If only one hand is used, the other hand presses abdominal wall laterally to the palpated zone in order to lessen or overcome resistance of the abdominal wall and hence to promote relaxation in the palpated zone. The other hand can be used to move the palpated organ closer to the examining hand or in order to perform bimanual palpation.

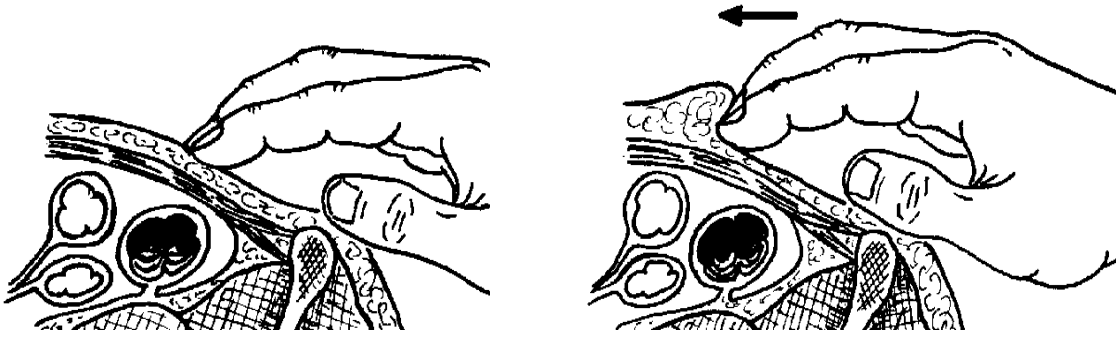
The deep sliding palpation technique includes the following four steps.

I step: proper positioning of the physician's hands. The right hand is placed flat on the anterior abdominal wall collateral to the axis of the examining part or the edge of examining organ (Fig. 15-7).

II step: formation of the skin fold (in direction from examining organ) to facilitate further movements of the examining hand.

III step: moving the hand inside the abdomen. Deep palpation is performed when the fingers are moved gradually with each of expirations, into the abdomen when the abdominal wall is relaxed. The explorative hand thus reaches the posterior wall of the abdomen or the underlying organ.

IV step: sliding movement of the fingertips in the direction perpendicular to the transverse axis of the examining organ. The organ is pressed to the posterior wall of the abdominal cavity, and the explorative fingers continue moving over the examined intestine or the stomach curvature.



I step II step

III step IV step

Fig. 15-7. Technique of deep abdominal palpation:

I step – position of fingers collateral to edge or long axis of examining organ;

II step – formation of skin fold (in direction from examining organ);

III step – dipping the fingers to posterior abdominal wall;

IV step – sliding fingers through the palpating intestine.

Depending on the position of the organ, the sliding movement should be either from inside, in the outward direction (the sigmoid, cecum) or in the downward direction (the stomach, transverse colon); the movements should then be more oblique in accordance with the deviation of the organ from the horizontal or vertical course. The examining hand should always move together with the skin and not over its surface.

15.4. The deep sliding palpation of the gastrointestinal tract departments

Percentage of palpation of abdominal organs in adult humans: sigmoid colon - 92-95%, cecum – 78-80%, terminal end of the ileum - 75-80%, transverse colon - 70%, liver - 80-85% , greater curvature of stomach - 50-60%, pylorus - 20-25%. Spleen, pancreas, kidneys are not palpated in the norm.

By palpating the intestine, physician establishes its localization, mobility, tenderness, consistency, and diameter, the condition of the surface (smooth, tubercular), the absence or presence of rumbling sounds during palpation. All these signs indicate the presence or absence of pathology (table 15-1).

Table 15-1. Diagnostic value of the deep palpation of the gastrointestinal tract

Characteristics	Norm	Pathology
Localization	normal anatomical	abnormal localization – in congenital abnormality
Tenderness at palpation	absent	inflammation, tumour, functional disorders
Passive mobility	≥ 2-3 cm up to 5 cm	restricted passive mobility - commissures due to inflammation or tumour
Consistency	mild or elastic	dense – in tumor, inflammatory infiltration, firm fecal mass, coprostasis
Diameter	according to peri-stalsis stage - 1-2 cm at contraction, ≥2-3 cm at relaxation	- the increase – in tumour, inflammatory infiltration, accumulation of fecal mass, reduced tonicity of muscle layer, - the decrease - in increased tonicity of muscle layer (spasm)
Condition of the surface	smooth	unsmooth, tubercular - in tumour, inflammatory infiltration
Rumbling sounds at palpation	a few may be	intensive - in increased motor function, intestinal dyspepsia

15.4.1. Palpation of the sigmoid and descending colon

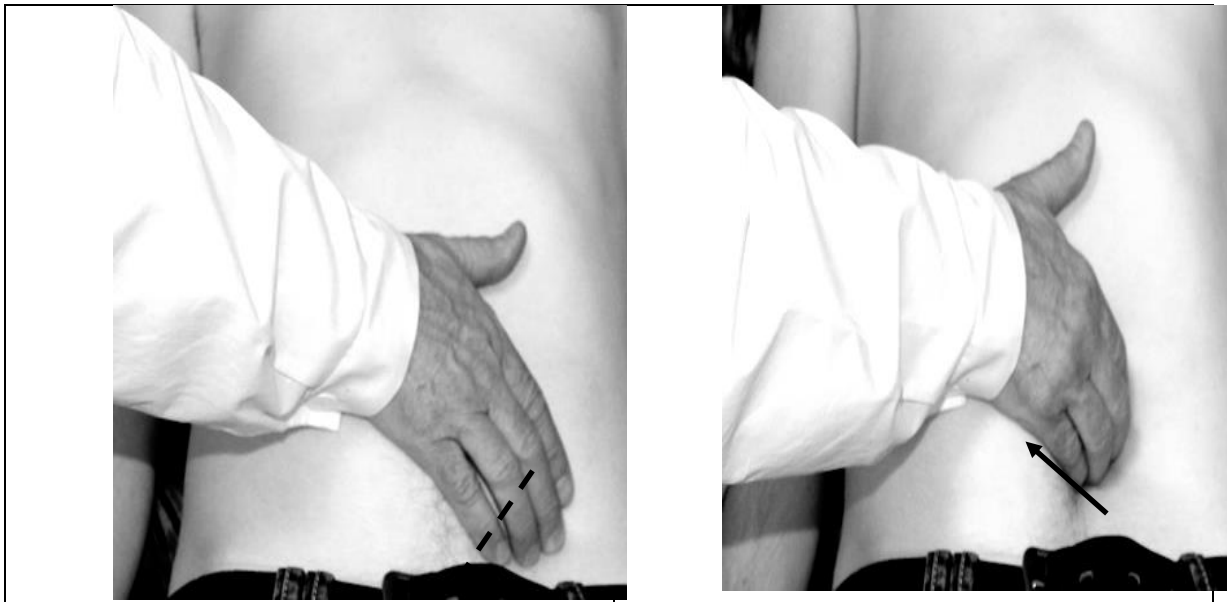
Sigmoid colon is palpated collateral to the axis of the intestine which runs obliquely in the left iliac region at the border of the median and the external third of the *linea umbilico-iliacae* (between umbilicus and *spina iliaca anterior superior*). Palpation is performed by four fingers, placed together and slightly flexed. *I step* - the fingers are placed medially of the expected position of the intestine (collateral to axis of sigmoid) (Fig. 15-6, 15-8). *II step* - formation of skin fold in direction from sigmoid to umbilicus. *III step* - dipping the fingers to posterior abdominal wall during 2-3 expirations. *IV step* - as soon as the posterior wall of the abdomen is reached, the fingers slide along the intestine in the given direction, i.e. laterally and downward.

The intestine is pressed against the posterior wall of abdomen and first slides along it (to the extent allowed by the mesenteric length) but later it slips from under the examining fingers.

Properties of palpated sigmoid colon in norm:

Normally the sigmoid can be palpated over the length of 10-15 cm as a smooth elastic cylinder, its thickness being that of a thumb or an index finger (2-3 cm in diameter); the sigmoid is painless to palpation, it does not produce

rumbling sounds, its peristalsis is rather flaccid and infrequent. The sigmoid can be displaced 3 - 5 cm to either side.



(1) (2)

Fig. 15-8. Palpation of the sigmoid colon: (1) the fingers position for palpation on the linea umbilico-iliacae collateral to the axis of the sigmoid colon (*see dash line*); (2) the skin fold formation from the sigmoid colon to umbilicus (*see arrow*).

Descending colon is palpated immediately after palpation of the sigmoid. The *descending colon* is palpated by two hands. The fingers of the right arm are placed in the left flank collateral to midline, on 3-5 cm above the position of the sigmoid (Fig. 15-5). The left hand is placed under the left lumbar side, while the fingers of the right hand press on the anterior wall of the abdominal cavity until the examiner feels his right and left hands meet. The explorative fingers then slide laterally, perpendicularly to the axis of the intestine.

The descending colon properties are similar in characteristics to the sigmoid colon, the difference consists in relatively slight mobility.

15.4.2. Palpation of the cecum, ascending colon and terminal end of ileum

Cecum is palpated by the same technique like the sigmoid colon, except that the direction is different. Since the cecum is situated at the border of the median and lateral third of the right *linea umbilico-iliacae* (nearly 5 cm by the iliac spine), the palpation is carried along this line (Fig. 15-6, Fig. 15-9).

Properties of the palpated cecum in norm:

The normal *cecum* can be palpated in 80-85 per cent of cases as a moderately strained mild smooth cylinder (widening to the round bottom), 2-3 cm in diameter; when pressed upon it rumbles. Palpation is painless. It reveals a

certain passive mobility of cecum (to 2-3 cm). The lower edge of the cecum is 0.5 cm above the *linea biliaca* in males and 1-1.5 cm below it in females.

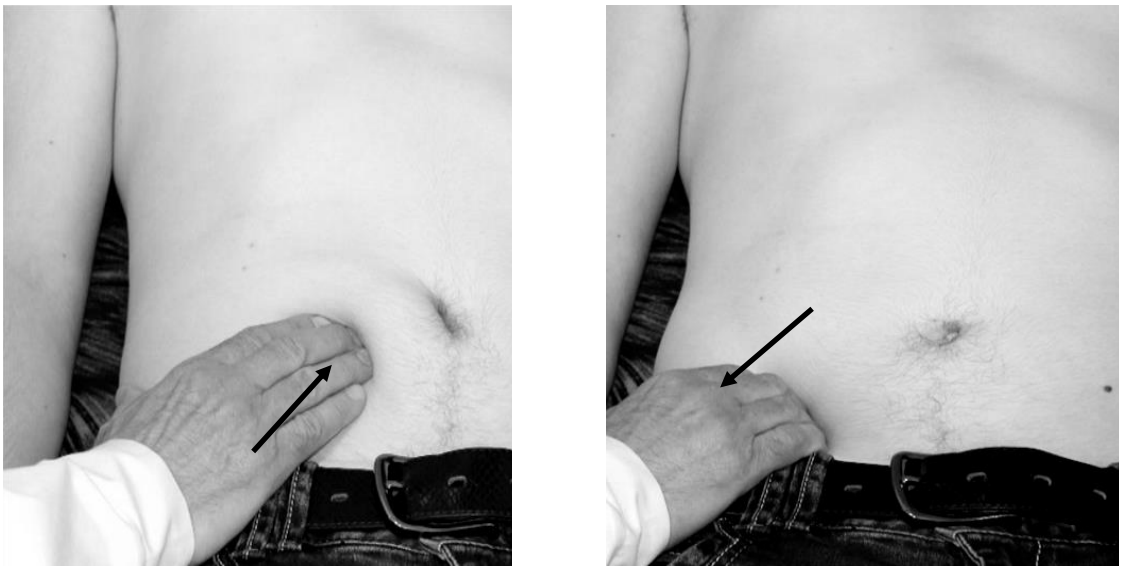


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Fig. 15-9. Palpation of the cecum: (1) the skin fold formation from the cecum to umbilicus (*see arrow*); (2) the fingers slide towards the cecum (*see arrow*).

Ascending colon palpation follows palpation of the cecum. The *ascending colon* is palpated by two hands. The fingers of the right arm are placed in the right flank collateral to midline, on 3-5 cm above the cecum (Fig. 15-6, Fig. 15-10).

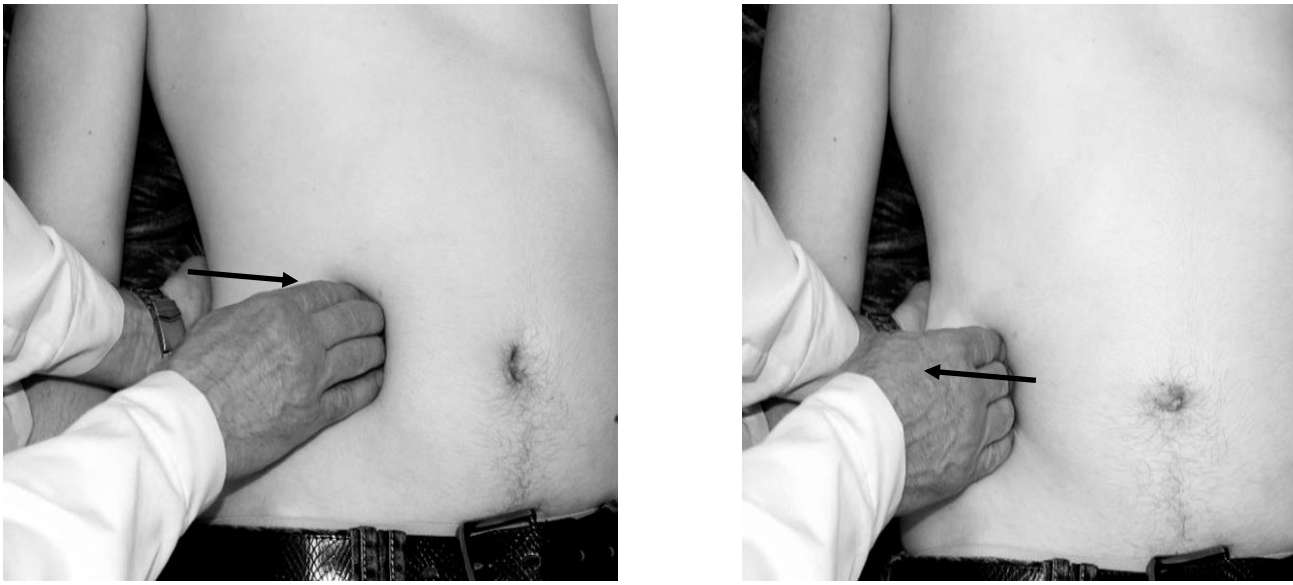

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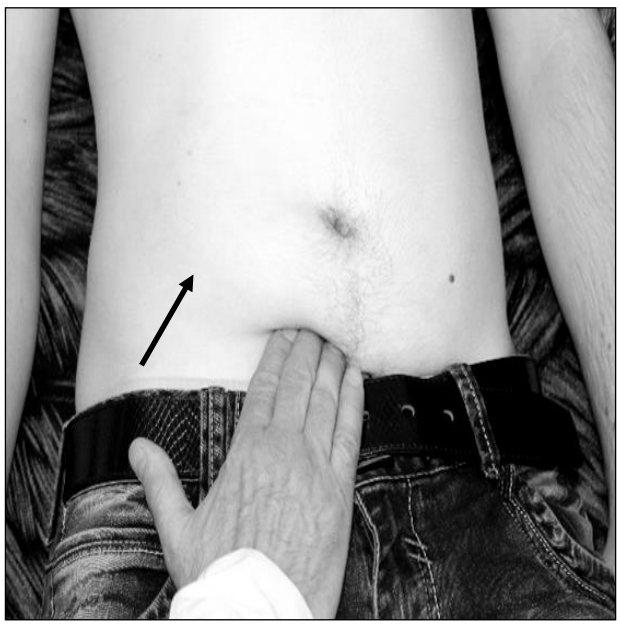
Fig. 15-10. Bimanual palpation of the ascending colon: the skin fold formation towards the umbilicus (*see arrow*); (2) the fingers slide towards the ascending colon (see arrow).

The left arm is placed under the right lumbar area, while the fingers of the right arm form the skin fold in direction to umbilicus. During 2-3 expirations, the fingers of the right hand press on the anterior wall of the abdominal cavity until the examiner feels his right and left hands meet. Then explorative fingers slide laterally, perpendicular to the axis of the intestine. The ascending colon is a similar in characteristics to cecum.

Properties of the palpated ascending colon in norm: smooth elastic cylinder, 3-4 cm in diameter; painless to palpation, a few rumbling sounds may be, it can be displaced 3 - 5 cm to either side.

Terminal end of ileum can be palpated in the depth of the right iliac space (Fig. 15-6, Fig. 15-11).



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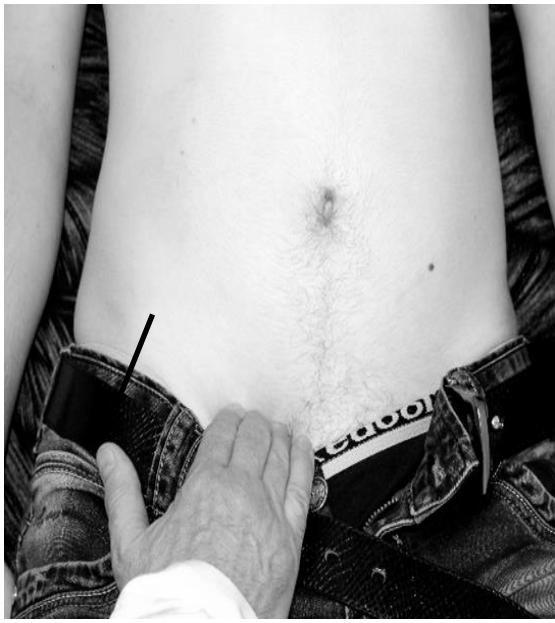


(2)

Fig. 15-11. Palpation of the terminal end of ileum: (1) the skin fold formation towards the umbilicus (*see arrow*); (2) the fingers slide down towards the terminal end of ileum (see arrow).

The terminal end of ileum is palpated by four fingers of the right hand; the fingers should be held together and slightly flexed. Fingers of palpating arm are placed at the border external and medium third of the linea biliaca under the angle 15-20º. If the abdominal muscles are tense, the muscles in the palpation zone can be relaxed by pressing the umbilical area with the radial edge of the left hand.

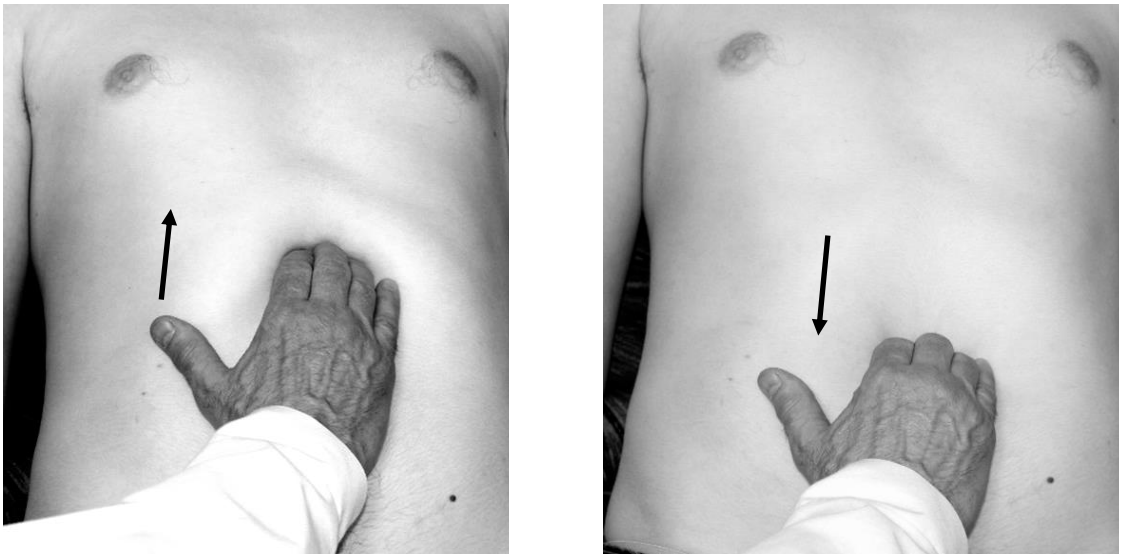
Properties of terminal end of ileum in norm: The terminal end of an ileum is palpated as the sleek elastic cylinder in diameter of 0,5-1,0 cm in stage of reduction of muscle layer of the intestine, or as an impressed thin-walled mild tube of 2-3 cm in diameter, which palpation may be accompanied by a rumbling sound. The palpated part of small bowel is routinely moderately mobile (up to 5-7 cm) and tolerant.

Quite often during palpation, it is possible to establish transferring of the intestine from the weakened state in spasm condition when it as though «plays» near at hand. It slips out from under the examining fingers and rumbles distinctly.

15.4.3. Palpation of the stomach

The deep palpation of the stomach should be carried out according to V.P. Obraztsov. In connection with features of its location, character of the surface and consistence of various departments, the stomach is not entirely palpated. The greater curvature of the stomach and pylorus can be palpated.

*The **deep sliding palpation of the greater curvature of stomach*** begins in the epigastric region from the xiphoid process downward on 3-5 cm (Fig. 15-12). *I step* – to place fingers of the right arm on the anterior midline 3-5 cm below the xiphoid process (see Fig. 15-6).



(1) (2)

Fig. 15-12. Palpation of the greater curvature of stomach:

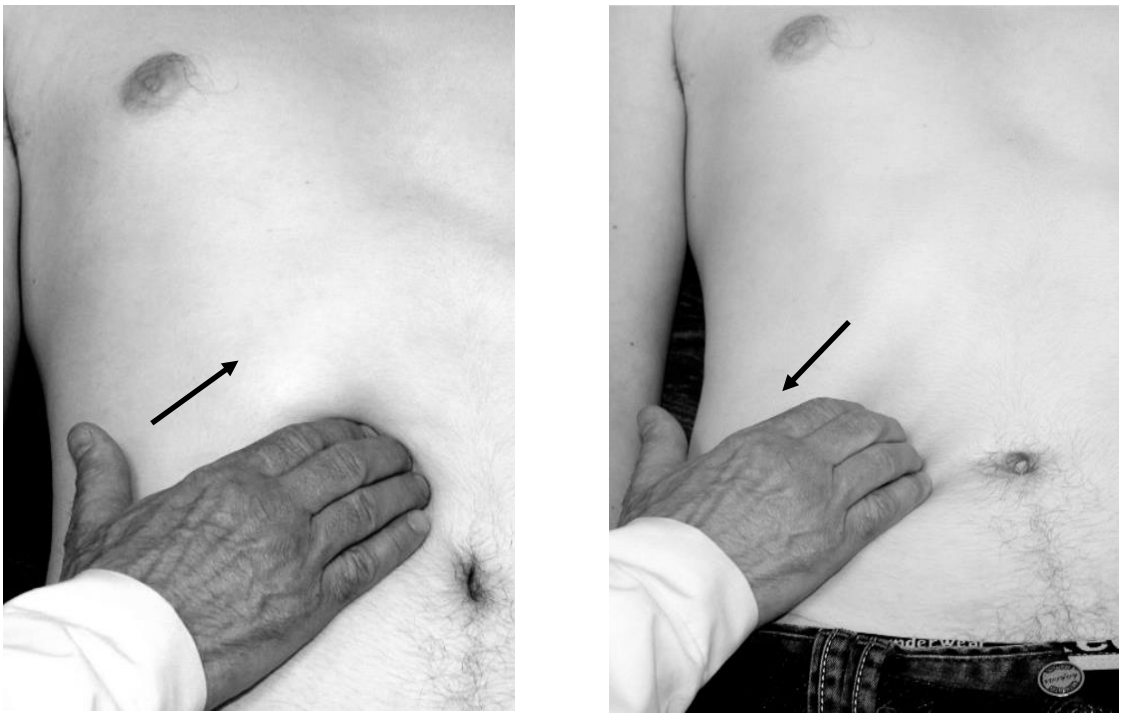
(1) formation of the skin fold towards the xiphoid process (see arrow); (2) the fingers slip down (see arrow) towards the greater curvature of stomach.

II step - formation of skin fold upward in the direction to xiphoid process during expiration (Fig. 15-11). *III step* – dipping fingers to the posterior wall of abdomen during the one expiration. *IV step* – fingers slipping downward. When pressed against the posterior wall of the abdomen, the stomach slips from under the examining fingers. If the first attempt of a palpation appeared unsuccessful, i.e. the sensation of sliding was not, it is necessary to repeat all over again, having established tips of fingers of a right arm is lower on 3-5 sm. The palpating arm is displaced downward to suprapubic region, while the greater curvature will not be palpated.

Properties of the palpated greater curvature of stomach in norm: the greater curvature of the stomach is placed in men on 3-4 cm above the level of

umbilicus, in women - 1-2 cm higher than umbilicus or at its level. The surface of stomach is smooth, and the greater curvature is represented as a painless, elastic, thin, smooth fold, nearly 1-1.5 cm in width.

Palpation of the pylorus. The pylorus is located in the triangle formed by the lower edge of the liver to the right of the median line, by the median line of the body, and the transverse line drawn 3-4 cm above umbilicus, in the region on the right of rectus abdominis muscle. Since the position of the pylorus is the oblique (upwards to the right), the palpating movements should be perpendicular to this direction, i.e. from the left downwards to the right (Fig. 15-6, 15-13).



(1) (2)

Fig. 15-13. Palpation of the pylorus:
(1) formation of the skin fold upward along the right costal arch (see arrow);
(2) the fingers slip down towards the pylorus (see arrow).

I step of pylorus palpation – to place fingers on the bisector of the angle formed by the transverse line 4-5 cm above umbilicus and the anterior median line of the body. *II step* - formation of the skin fold upward along the inferior edge of the right costal arch. *III step* – dipping fingers to the posterior wall of the abdominal cavity during 2-3 expirations. *IV step* - fingers slip down.

Properties of the palpated pylorus in norm: The pylorus is identified by palpation as painless, smooth, elastic cylinder of 1.5-2 cm of width (in case of reduction muscle layer – 40-50 seconds) or as mild band without clear contours 2-3 cm of width (at the time of relaxation – 15-30 seconds). When the pylorus is

palpated by the fingers, a soft rumbling sound may be heard. When contracted spastically (*pylorospasm*), the pylorus remains firm for a long time. Sometimes the spastic pylorus is mistaken for cancer infiltration.

The greater curvature can be examined by deep sliding palpation in 50-60 % and the pylorus in 20-25 % of healthy subjects; the lesser curvature can be palpated in *gastroptosis (*the downward displacement of the stomach*)*. It appears to palpating fingers as a ridge on the vertebral column and by its sides. In cases with *gastroptosis*, the greater curvature can descend below umbilicus. Correctness of determination can be confirmed if the position of the greater curvature coincides with that of the inferior border of the stomach as determined by other techniques - by *splashing sound*, and *auscultative affriction* (see Chapter 14, section 14.6. Auscultation of abdomen).

Palpation of the stomach can reveal tumours of the pylorus and the greater curvature. Palpation of the lesser curvature tumours is possible when the patient in the vertical position. Exact information on their location gives endoscopy and X-ray examination.

15.4.4. Palpation of the transverse colon

Delimitation of the greater curvature of the stomach (by deep sliding palpation, and auscultative affriction) always should precede palpation of the transverse colon.

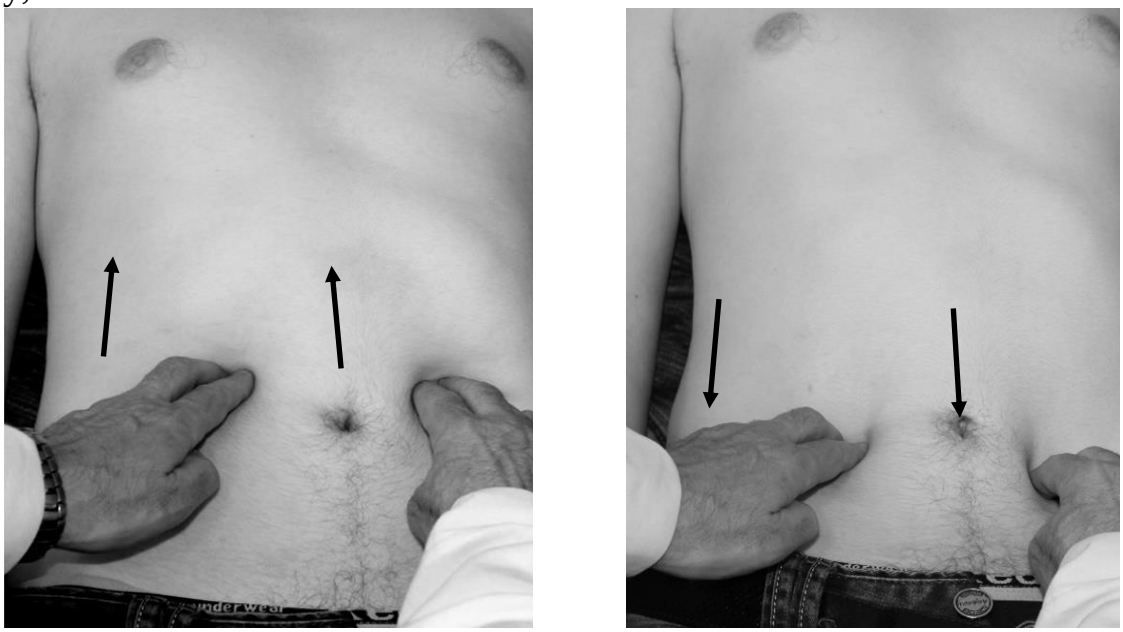
Transverse colon is palpated bimanually by the right and left hand held together on both sides of the *linea alba*. Since the position of the transverse colon is unstable, it is useful first to determine the lower border of the stomach by *auscultative affriction* or by palpation of greater curvature of stomach, and only then to search for the colon some 2-3 cm below this border.

I step of the palpation - the hands are placed on both sides of the *linea alba* 2-3 cm below the greater curvature of stomach. *II step* - formation of the skin fold upward (Fig. 15-6, 15-14). *III step* - dipping fingers to the posterior wall of the abdominal cavity during 2-3 expirations until the posterior wall of the abdomen is felt. *IV step* - the arms slide down to feel the transverse colon.

Having examined transverse colon in the median region, it is necessary to palpate this intestine to the right and to the left outside as far as it is possible. In some cases, following a course of transverse colon, it is possible to reach up to *hepatic* (more often) or *splenic* (less often) *curvatures of the transverse colon*. Normal transverse colon is palpable in 60-70 % of cases.

Properties of the palpated transverse colon in norm: the transverse colon is palpated below the inferior border of the stomach on the both sides of the *linea alba (linea mediana anterior)* - on the level of umbilicus or 1-2 cm above it in men, and 1-2 cm below it - in women. It is an arching (transverse) mild smooth elastic cylinder, width of 2.5-4 cm, easily movable up and down, painless and silent (without rumbling sounds).

The small intestine is usually impalpable because of its deep location, high mobility, and thin walls.



(1) (2)

Fig. 15-14. Bimanual palpation of the transverse colon: (1) formation of the skin fold upward (see arrows); (2) fingers slip down towards the transverse colon (see arrows).

15.5. The key points of the theme "Palpation of the Abdomen"

The ***superficial (light touch) palpation*** examines properties of the anterior abdominal wall: location of the painful site, resistance and rigidity of anterior abdominal wall or its muscle strain, density formed in the wall, hernias, tumours, presence of the abdominal wall edema.

The ***superficial palpation*** is performed in an *anticlockwise manner*, i.e. left *ileum – left flank – left hypochondrium – epigastric region – right hypochondrium – right flank – right ileum*. After that, the examiner palpates the *median zone from the xiphoid process down to suprapubic area*.

The **deep sliding palpation** examines abdominal organs properties, such as: localization, mobility, tenderness, consistency, diameter, condition of the surface (smooth, tubercular presence of rumbling sounds during palpation

The sequence of the deep palpation: *sigmoid colon – descending colon – cecum – ascending colon – terminal end of ileum – stomach with its parts (greater curvature and pylorus) –transverse colon; the following stage - palpation of liver, spleen and kidneys.*

The deep sliding palpation technique includes the following four steps.

I step: positioning the physician's hands collateral to the axis of the examining part or the edge of examining organ. *II step:* formation of the skin fold (in direction opposite the examining organ). *III step:* moving the fingers of the explorative arm gradually into the abdomen with expirations when the abdominal

wall is relaxed. *IV step:* sliding movement of the fingertips in the direction perpendicular to the transverse axis of the examining organ.

Normal characteristics of the gastrointestinal tract parts according to the deep palpation: no pain at palpation, the passive mobility – 2-3 cm or more, soft or elastic consistency, a diameter depending on the phase of peristalsis - from 1-2 cm with contraction to 3-5 cm during relaxation, a smooth surface, possibly a few rumbling sounds during palpation.

Diagnostic value of the gastrointestinal tract deep palpation:

- *abnormal localization* – in the congenital abnormalities;
- *tenderness at palpation* – in an inflammation, tumours, functional disorders;
- *restricted passive mobility* – in commissures due to inflammation or tumours;
- *dense consistency* – in tumours, an inflammatory infiltration, a firm fecal mass;
- *increased diameter* – in tumours, inflammatory infiltration, accumulation of the fecal mass, reduced tonicity of the muscle layer;
- *decreased diameter* – in an increased tonicity of muscle layer (spasm);
- *unsmooth tubercular surface* – in tumours, inflammatory infiltration;
- *intensive rumbling sounds* – in an increased motor function, meteorism, diarrhea.

15.6. Assessment tests on the theme "Palpation of the Abdomen"

1. Superficial palpation of the abdomen reveals:

1. Palpatory tenderness;
2. Defects of the anterior abdominal wall;
3. Muscle strain;
4. Difference between edema of the skin and thickening of the subcutaneous fatty tissue;
5. Position of organs in the abdominal cavity.

2**. Correct directions of the superficial palpation of the abdomen:**

1. in direction by course of a wrist-watch (*clockwise way*) from the right ileum;
2. in direction against a course of a wrist-watch (*anticlockwise way*) from the left ileum;
3. from the xiphoid process down the anterior midline;
4. from the right and left costal arch vertically downwards in the lateral areas;
5. from the umbilicus up, down and sideways.

3. The resistance of the abdominal wall muscles is:

1. Muscle tension of the anterior abdominal wall at palpation;
2. Muscle tension of the anterior abdominal wall with percussion;
3. Muscle tension of the anterior abdominal wall independently of palpation;
4. Painfulness of the anterior abdominal wall muscles to palpation;
5. Presence of an induration in the anterior abdominal wall.

4. The rigidity of the abdominal wall muscles is:

1. Muscle tension of the anterior abdominal wall at palpation;
2. Muscle tension of the anterior abdominal wall with percussion;
3. Muscle tension of the anterior abdominal wall independently of palpation;
4. Painfulness of the anterior abdominal wall muscles to palpation;
5. Presence of an induration in the anterior abdominal wall.

5. How can you differ between an induration of anterior abdominal wall and intra-abdominal formations during the superficial palpation:

1. Ask the patient to strain abdominal wall during palpation;
2. Perform palpation on symmetric fields;
3. Perform palpation in position of the patient on a side;
4. Perform palpation at a pause of respiration;
5. Perform palpation in the vertical and horizontal positions of the patient having compared received results.

6. Deep abdominal palpation reveals:

1. Palpatory tenderness of the abdominal wall;
2. Defects of the anterior abdominal wall;
3. Muscle strain;
4. Tenderness, consistency, surface and size of organs in the abdominal cavity;
5. Position of organs in the abdominal cavity.

7. What characteristics of various parts of bowels can be determined by the deep palpation of the abdomen?

1. Consistence;
2. Diameter;
3. Character of the surface;
4. Depth of locating in abdomen;
5. Shape of a palpated intestine.

8. Procedure of the deep palpation of the abdomen includes:

1. Formation of a skin fold;
2. Dipping fingers of a palpating arm in abdomen;
3. Installation of fingers of the palpating arm;
4. Sliding tips of fingers of the palpating arm on posterior wall of abdominal cavity;
5. Assessment of the abdomen in the act of respiration.

9. Bimanual palpation is used to research of the following departments of the gastrointestinal tract:

1. Greater curvature of stomach;
2. Terminal end of an ileum;
3. Cecum;
4. Ascending colon;
5. Descending colon.

10. Palpation of the greater curvature of the stomach is performed after palpation of:

1. Cecum;
2. Transverse colon;
3. Ascending colon;
4. Pylorus;
5. Terminal end of the ileum.

11. Palpation of the transverse colon is performed after palpation of:

1. Pylorus;
2. The greater curvature of stomach;
3. Terminal end of ileum;
4. Ascending part of colon;
5. Cecum.

12. Palpated characteristics of the sigmoid colon in norm are:

1. Dense immobile cylinder;
2. 2-3 cm in diameter;
3. Painless to palpation;
4. Sigmoid can be displaced 3 - 5 cm to either side;
5. Smooth elastic cylinder.

13. Palpated characteristics of the cecum in norm are:

1. Smooth dense cylinder;
2. 2-3 cm in diameter;
3. Painless to palpation;
4. Cecum can be displaced 3 - 5 cm to either side;
5. Smooth mild cylinder.

14. Palpated characteristics of the terminal end of the ileum in norm are:

1. Smooth elastic cylinder 0.5-1.0 cm in stage of reduction;
2. Smooth mild cylinder 2-3 cm in diameter in stage of relaxation;
3. Painless to palpation;
4. It can be displaced up to 5 7 cm to either side;
5. Dense immobile cylinder;

15. Palpated characteristics of the greater curvature of stomach in norm:

1. In males – on 3-4 cm above umbilicus, in females – 1-2 cm higher than umbilicus;
2. 2-3 cm below umbilicus;
3. Smooth mild cylinder 3-5 cm in diameter;
4. Elastic thin smooth fold, nearly 1-1.5 cm in width;
5. Dense immobile cylinder 2-3 cm in diamete.

16. Palpated characteristics of the descending colon in norm are:

1. Dense immobile cylinder;
2. Smooth elastic cylinder;
3. 2-3 cm in diameter;
4. Painless to palpation;
5. Descending colon can be displaced 3 - 5 cm to either side.

17. Palpated characteristics of ascending colon in the norm are:

1. Smooth elastic cylinder;
2. Dense immobile cylinder;
3. 2-3 cm in diameter;
4. Painless to palpation;
5. Ascending colon can be displaced 2-3 cm to either side.

18. Palpated characteristics of the transverse colon in norm are:

1. Smooth elastic cylinder;
2. 1-2.5 cm in diameter;
3. 2.5-4 cm in diameter;
4. Transverse colon is 2-3 cm below the greater curvature of the stomach;
5. Transverse colon is 5-7 cm below the greater curvature of the stomach.

19. Palpated characteristics of the greater curvature of the stomach in norm are:

1. Smooth elastic cylinder 2-3 cm in diameter;
2. Smooth fold, nearly 1-1.5 cm in width;
3. It is posed in men on 3-4 cm above a level of the umbilicus, in women 1-2 cm higher than the umbilicus or at its level;
4. Greater curvature of the stomach can be displaced 3 - 5 cm to either side;
5. Painless to palpation.

20. Palpated characteristics of the pylorus in norm are:

1. Smooth elastic cylinder;
2. 1.5-3 cm in diameter according to phase of peristalsis;
3. Painless to palpation;
4. Pylorus is located in men on 4-5 cm above a level of the umbilicus, in women 1-2 cm higher than the umbilicus or at its level;
5. Pylorus is located in the triangle formed by the lower edge of the liver to the right of the median line.

CHAPTER 16. Laboratory - Instrumental Examination of the Gastrointestinal Tract

Goals: to enable students to learn –

1. laboratory and instrumental examinations in diseases of the esophagus (X-ray examination, esophagoscopy, esophageal pH- monitoring);
2. laboratory and instrumental examinations in diseases of the stomach and duodenum (gastroduodenoscopy, intragastric pH-metry);
3. Laboratory and instrumental examination in diseases of the intestines (colonoscopy, rectosigmoidoscopy, irrigoscopy, coprology study);

16.1. Laboratory and instrumental studies of the esophagus

X-ray examination of the esophagus can show structural and motor functional disorders, particularly, barium contrast meal aids in detecting anatomic conditions (e.g., *esophageal webs, or membranes; esophagostenosis, peptic ulcers*) and motor disorders (e.g., esophageal spasms, achalasia) (Fig. 16-1).

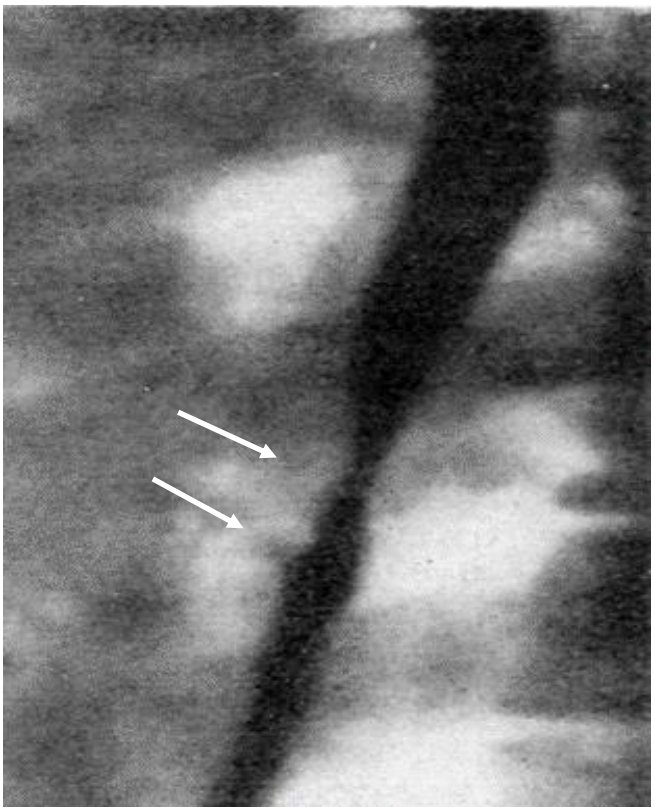


Fig.16-1. Esophagitis in cicatrization stage. Esophagus is narrowed over a large area, spiculated contours of the esophagostenosis (see arrows).

Esophagoscopy (endoscopy study of the esophagus) can be performed diagnostically to evaluate pain or dysphagia, to identify structural abnormalities

(esophagitis, ulcer, tumour) or bleeding sites, or to obtain biopsy specimens (Fig. 16-2).

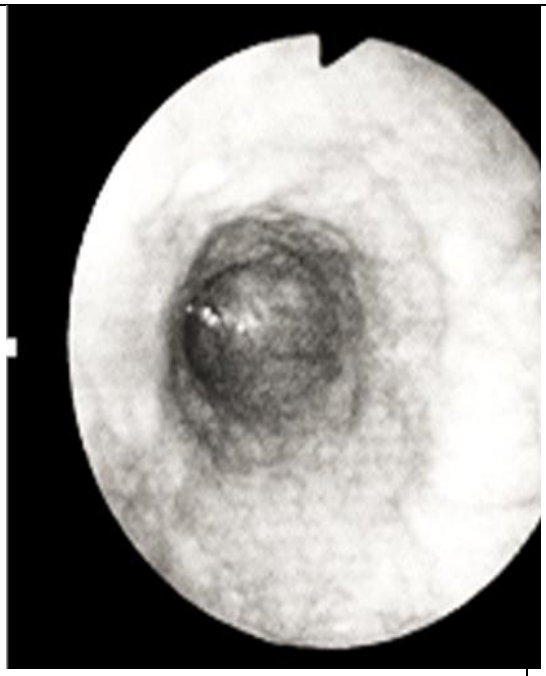


Fig.16-2.1. Normal esophageal mucosa

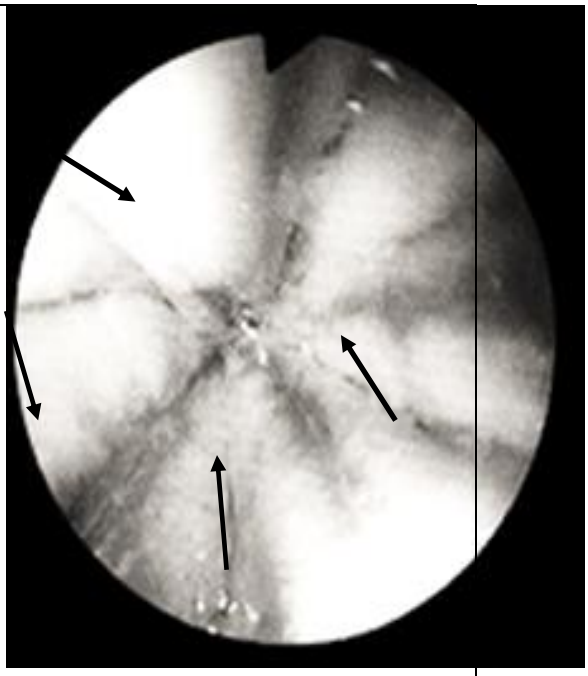


Fig. 16-2.2. Reflux-esophagitis: hyperemic mucosa and confluent erosions in the form of “forks of flame” (see arrows)

Esophageal biopsy can show thinning of the squamous mucosal layer and basilar cell hyperplasia, and malignant cells, even without evidence of the esophagitis or tumour by endoscopy.

Esophageal manometry is used for examination of the 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 be applicable for to diagnose achalasia, diffuse spasm, scleroderma, and lower esophageal sphincter hypo- and hypertension and to evaluate esophageal function for certain therapeutic procedures (e.g., antireflux surgery, pneumatic dilation for achalasia). It is performed by passing a small probe with a sensing device 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 gastroesophageal reflux disease (GERD). The «gold standard» of GERD diagnosis is the diurnal pH-metry of esophagus that allows estimating pH within 24 hours. *Normal esophageal pH is in the range of 5.0-7.0 (Fig. 16-3).*

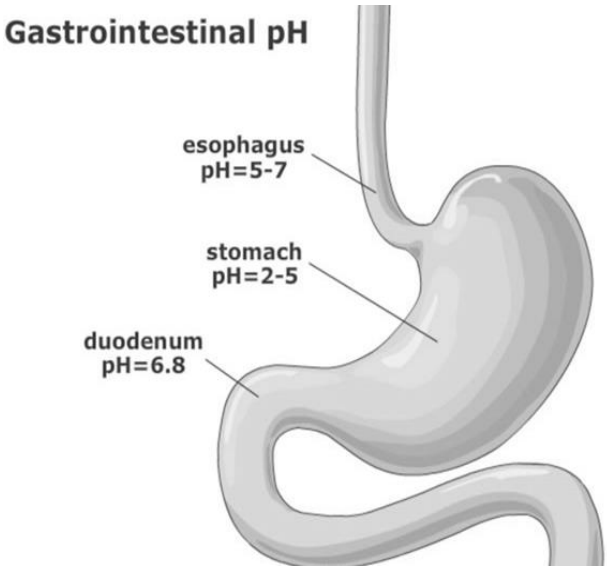


Fig. 16-3. Normal pH of the gastrointestinal tract

The pathological gastroesophageal reflux considers, if esophageal pH is lesser than 4.0 during more than 5 minutes not less than 50 times for a day (24 hours). With GERD, the total time for a decrease in the intraesophageal pH during the day reaches from 4.0 to 14.5 hours (25-60% of the time of day).

16.2. Laboratory-instrumental examination of the stomach and duodenum

16.2.1. Visualization study (endoscopy, X-ray) of the stomach and duodenum

Upper gastrointestinal endoscopy (gastroduodenoscopy) is used to establish the site of the upper GI (gastrointestinal) bleeding, to visually define and biopsy abnormalities seen on upper GI series (gastritis, gastric and duodenal ulcers, tumours), to follow up treated gastric ulcers, and to evaluate stomach and duodenum for infection *Helicobacter pylori (HP)* (Fig. 16-4).

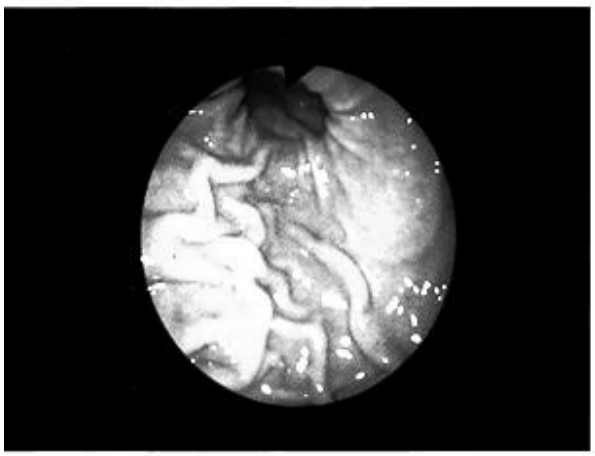


Fig.16-4.1. Normal gastric mucosa.

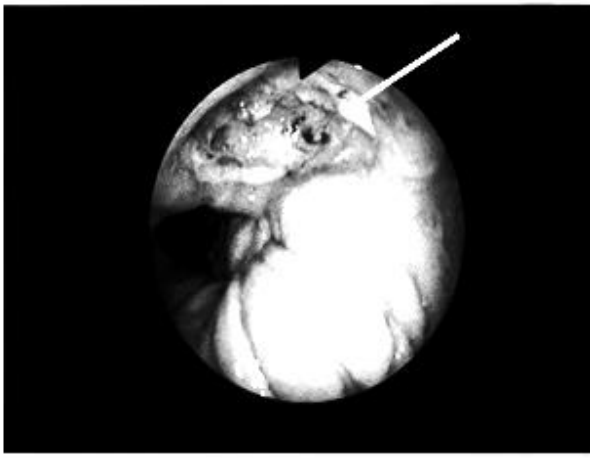
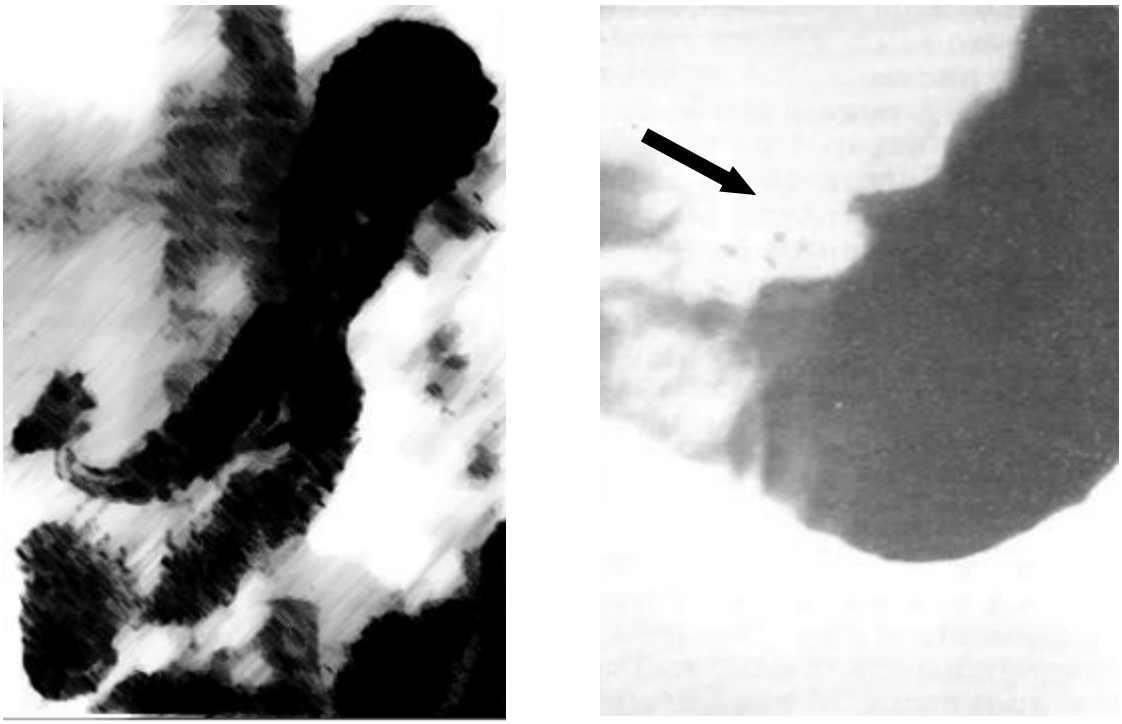


Fig. 16-4.2. Peptic ulcer of the stomach (see arrow.)

Now ***X-ray examination of the stomach and duodenum*** is a complementary (to endoscopy) method for assessing motor disorders and evacuation of the stomach and duodenum (pyloric stenosis, etc.), peptic ulcers, and tumours. A direct radiologic symptom of the peptic ulcer of the stomach and duodenum is a niche on the contour or barium spot on the relief (Fig. 16-5). X-ray signs of the stomach tumours are features of the mucosal pattern distortion, obliteration and narrowing. Delayed images may show barium holdup at the site of the lesion.



(1) (2)

Fig. 16-5. X-ray of the stomach:

(1) contrasted stomach, performed in the horizontal position of the healthy subject on the back; (2) niche (see arrow) on small curvature in the angle of the stomach (by V.B. Antanovich, 1987)

CT (computer tomography) is useful in the diagnosis of a tumour. Esophagogastroduodenoscopy (EGD) is the main test used to find stomach cancer and perform a biopsy, and CT is used to locate the lesion, in staging the gastric cancer and to determine the disease progression.

16.2.2. Study of the gastric secretion

16.2.2.1. Study of the gastric content (juice)

The study (*gastric aspirate analysis*) usually begins with evacuation of the gastric content (juice) from a fasting stomach. Gastric intubation with a thin gastric tube is used to obtain a sample of the gastric contents for an analysis.

The *first portion* (on an empty stomach) - gastric contents extracted after the probe reaches the stomach. *Basal secretion* - gastric contents extracted for a further hour every 15 minutes from the fasting stomach. *Stimulated secretion (submaximal or maximal)* – gastric contents obtained for an hour every 15 minutes after stimulation (a subcutaneous injection of the stimulating agent *Pentagastrin)*. Pentagastrin is an effective and physiological stimulant of the gastric secretion, a synthetic analogue of the hormone gastrin. *It stimulates the secretion of the gastric hydrochloric acid, pepsin, and intrinsic factor of Castle (gastromucoprotein)*.

The gastric aspirate analysis helps to assess the gastric secretion, an acidity of the content, admixtures of the bile and blood. The excess of the free HC1 in the gastric juice in basal and/or stimulation secretion is called a *hyperchlorhydria*. This sign is typical for peptic ulcers of the stomach and duodenum and *chronic gastritis B (HP-associated gastritis).* The low level or absence of the free HC1 in basal and stimulating secretion simultaneously is called respectively a *hypochlorhydria or achlorhydria*. This sign is typical to a chronic atrophic gastritis and cancer of the stomach. The absence of the free HC1 in the gastric juice after giving the maximum dose of the Pentagastrin is called the *refractory achlorhydria*. This sign may suggest an atrophic process in the gastric mucosa.

16.2.2.2. Intragastric pH-metry

The most reliable data on the gastric secretion can be obtained by an *intragastric pH-metry* (Fig. 17-3).

The basic condition of the intragastric pH-metry is a complete emptying of the stomach before a research. The research of the acid-production function of the stomach is provided at the morning on an empty stomach. In presence of the stomach motor (evacuation) dysfunction, its contents are removed with the help of the gastric tube before the research.

Technique of intragastric pH-metry: a pH-probe is introduced through a mouth or nasopharyngeal meatus into the patient's stomach up to conditional labels allowing to judge about a position of the probe. Depending on the aims of the research, the pH-probe can be fixed in the stomach or in duodenum both and in 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 (alkalinizing part of the stomach).*

The first stage of the pH-metry examines a state of the acid-production function in the *basal secretion* (Table 16-1); the research lasts 30 up to 45 minutes. It is necessary to note, that in the basal condition a stomach "secretory device" in a state of the functional rest, and only about 15 % of the parietal cells "work".

Stimulators of the gastric secretion are to apply for definition of the functional activity of the "secretory device" of the stomach. The most frequently used stimulator of the stomach secretion is Pentagastrin. *Stimulated secretion* would be estimated within 45 minutes up to 1 hour.

Diagnostic value of the intragastric pH-metry:

- *hyperacid state (hyperacidity)* is typical for peptic ulcers of the stomach and duodenum, chronic gastritis B (HP-associated gastritis), and in some cases of the epigastric pain syndrome (due to functional dyspepsia) and gastroesophageal reflux disease;

- *hypoacid and anacid state (hypoacidity and anacidity)* is typical for chronic atrophic gastritis and cancer of the stomach;

- *decompensated alkalinization function of the antral part of the stomach* is typical for peptic ulcers of the stomach and duodenum, and chronic gastritis B (HP-associated gastritis).

Table 16-1. Intragastric pH-metry

pH of the body of the stomach		Acid-production function of the stomach
Basal secretion	Stimulated secretion	
<1.5	<1.2	hyperacid state (hyperacidity)
1.6-2.0	1.3-1.7	normacid state (normacidity)
2.1-6.0	1.7-5.0	hypoacid state (hypoacidity)
>6.0	>5.0	anacid state (anacidity)
pH of antral part of the stomach		Alkalinization function of the antral part of the stomach
>6,0	>5,0	compensated alkalinization
3,5-5,9	4,9-2,0	subcompensated alkalinization
<3,5	<2,0	decompensated alkalinization

Endoscopic pH-metry is carried out with the help of a special endoscopic pH-probe introduced through the endoscope instrumental canal. The study is performed during a gastroscopy, extending the usual procedure by about 5 minutes. During this time, the acidity in 9 standard points of the stomach and duodenum is measured under visual control.

When interpreting the results, it is necessary to take into account that the endoscopic research is of itself a factor stimulating the stomach acid secretion.

16.2.2.3. Blood serum tests for assessment of the stomach secretion

Serum gastrin. Gastrin is a peptide hormone that stimulates secretion of the gastric acid (HCl) by the parietal cells of the stomach and aids in gastric motility. It is released by G cells in the pyloric antrum of the stomach and the pancreatic islets of Langerhans.

Measurement of the blood serum gastrin must be made fasting, after quite a long period without the acid-suppression therapy. Normal levels of the serum gastrin – 13 - 115 pg/ml. In Zollinger-Ellison syndrome the level of the gastrin in the blood serum is increased above 100 ng/L. Serum gastrin levels are also increased in autoimmune atrophic gastritis (type A), after vagotomy (a surgical operation that removes part of the *vagus nerve*), and during acid-suppression therapy, and in renal failure, pernicious (vitamin B12-deficiency) anemia. Elevated gastrin levels may be present in chronic gastritis with achlorhydria resulting from Helicobacter pylori infection.

Serum pepsinogens (PG) are used as a marker of the gastric acid secretion. Human pepsinogens I (PGI) and II (PGII) are proenzymes of the pepsin – an proteinase of the gastric juice. They are converted into the active enzyme pepsin by gastric acid. They act between a pH of 1.5 and 5.0 and initiate protein digestion. PGI is secreted mainly by chief cells in the stomach fundus mucosa, whereas PGII is also secreted by the pyloric glands and the proximal duodenal mucosa. Normal serum levels of the PGI > 70 ng/ml.

Serum PGI and PGII concentrations and the ratio between PGI and PGII may be related to the histologic and functional status of the gastric mucosa. *High levels of the PGI and PGII* are found where there is active inflammation of the gastric mucosa such as in antrum HP-associated gastritis (type B) and peptic ulcers of the stomach and duodenum. *Decreased levels of the PGI and PGII, and especially ratio PI/PGII<3.0,* are seen in severe atrophic gastritis with intestinal metaplasia and in gastric cancer. The main use of the measuring serum pepsinogens in clinical practice is to detect subjects with a significant gastric atrophy who are at risk of the gastric cancer.

Antiparietal cells and *intrinsic factor of Castle (IF) antibodies* appear in the blood serum with autoimmune atrophic gastritis (type A).

16.2.3. Diagnosis of the stomach Helicobacter Pylori (HP) infection

There are methods of the HP laboratory diagnosis:

- ***Histological examination of the gastric biopsy with HP special stains*** *is the standard method to assess if the microorganism is the underlying cause of the gastritis*. The histological identification of the HP is the standard approach to identify the infection. False negative results (when the test shows absence of HP, but in fact this bacterium is present) can be at late stages of the diffuse atrophic gastritis, when the number of HP bacteria is significantly reduced because the intestinal metaplasia creates an unfavorable condition for HP.

• ***Urea breath test*** *(with nonradioactive isotope 13C or with radioactive isotope 14C)*

The urea breath test (UBT) is considered the "gold standard" for the noninvasive diagnosis of the HP infection. UBT is based on the ability of the HP to convert urea to ammonia and carbon dioxide (CO_2). The patient swallows urea labeled with an unusual isotope, either radioactive C^{14} or non-radioactive C^{13}. In the following 10-30 minutes, the isotope-labeled CO_2 in the exhaled air indicates the presence of the urease (an enzyme that HP uses to metabolize urea) in the stomach and the presence of HP.

The UBT is recommended for detecting HP before and after treatment: to confirm HP colonization and to monitor its eradication.

A positive UBT result indicates an active HP infection 4 weeks after the end of the antibiotics therapy. At least two weeks should pass before UBT after the end of the proton pump inhibitors (PPI) drugs that reduce the formation of the hydrochloric acid in the stomach. The test should not be performed on the same day as an endoscopic examination (gastroscopy) of the stomach and duodenum with biopsy. It is recommended to avoid taking antacids and H2-histamine receptor blockers 1-2 days before the study.

False positive results (when the test shows that the HP is present but it is not actually present) can be caused by achlorhydria in the marked atrophy of the gastric mucosa (due to presence of other spiral gastric bacteria with urease activity) and violation of the rules of the preparation for the examination and the procedure of the test (conducting UBT earlier than 4 weeks after the end of the HP eradication therapy, or on the same day as an gastroduodenoscopy with biopsy).

Possible causes of the false negative results (when the test shows absence of HP, but in fact this bacterium is present): use of antibiotics, proton pump inhibitors, bismuth drugs in the previous 2 weeks.

• ***Rapid urease test*** *from the gastric biopsy tissue*

The rapid urease test, also known as the Campylobacter-like organism test (CLO test), is a quick diagnostic test to detect HP. The test is based on the ability of the HP to secrete the enzyme urease, which catalyzes the conversion of the urea into ammonia and CO_2.

The CLO test is performed at the time of the gastroscopy. The obtained biopsy sample of the gastric mucosa is placed in a special cell with solutions containing urea and phenol red (as indicator). The rate at which the color of the indicator changes from yellow to bright red depends on the activity of the urease, which in turn depends on the number of bacteria. The method has high sensitivity, accuracy and speed (within several minutes) of obtaining results.

A false negative result is possible in the cases of the low bacterial counts and if coccid forms of the HP appear (e.g., after unsuccessful therapy) without enzymatic urease activity. The result may be false positive in persons whose stomachs are infested with Helicobacter heilmanii.

- ***Bacterial culture*** *of the gastric biopsy specimens*

The culture of HP is performed on the gastric biopsy samples to confirm the HP infection and to determine the antibiotic susceptibility of the HP when the prior treatments have failed. Culturing of the gastric biopsy samples is not a routine method for detecting HP, and it is performed only in specialized laboratories because of its complexity, cost, and time-consuming nature.

- ***Stool antigen test (SAT)*** *for HP-infection noninvasive diagnosis*.

In infected individuals, HP sticks to the gastric epithelial wall, and is excreted in the feces. The test is based on the detection of HP antigens in the stool. There are two types of SATs used for H. pylori detection: enzyme immunoassay (EIA) and immunochromatography assay (ICA) based methods, using either polyclonal antibodies or monoclonal antibodies. The SAT is a quick, easy, and inexpensive test that approaches the accuracy of the UBT. Similar to the UBT, false-negative results occur when the bacterial load is relatively low and due to the use of the antibiotics, bismuth, and proton-pump inhibitors.

- ***serological detection of the anti-HP antibodies***

In this method, antibodies against HP are detected by and *enzyme immunoassays* (EIA). Only the IgG antibody test is reliable, but inferior in accuracy to the UBT. This test involve the use of the blood serum, saliva, or urine.

The serological method is the efficient diagnostic method in gastrointestinal bleeding, gastric carcinoma, MALT lymphoma, and atrophic gastritis.

The IgG antibodies are not reduced during treatment with antibiotics, PPIs, and colloidal bismuth. The IgG antibodies can be found even for the months after treatment and thus provide a positive result after the complete HP eradication. Therefore, IgG antibodies are not suitable for confirming the effectiveness of the HP eradication, but it is useful for epidemiological examinations.

- ***PCR (polymerase chain reaction)-based detection of the HP***

This method has high efficiency of the HP detection. Samples are frequently used in this method including gastric juice and biopsy, saliva, and feces. PCR can detect antibiotic resistance mutations and help in determining the appropriate therapy. However, the technique is expensive and requires a lot of skill and experience.

16.3. Laboratory and instrumental examination of intestines

16.3.1. Visualization study (endoscopy, X-ray) of the intestines

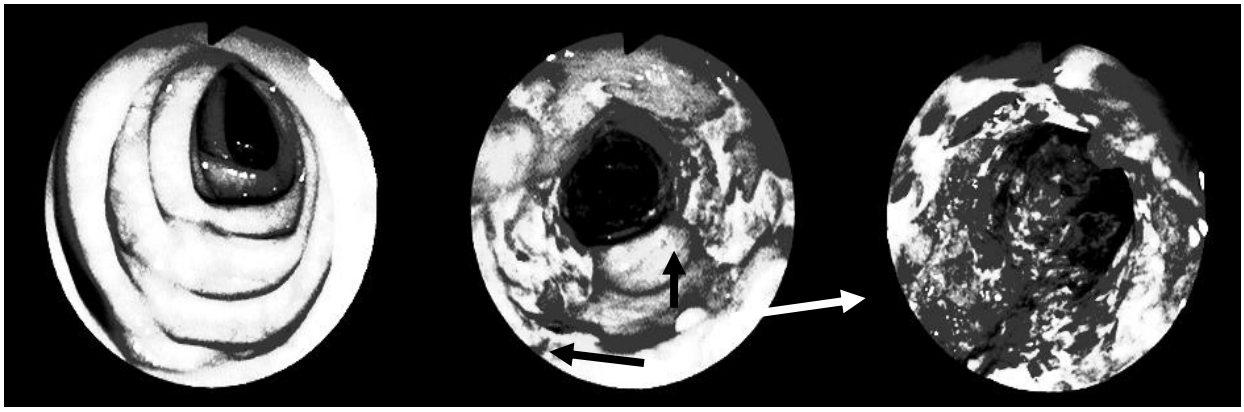
Rectosigmoidoscopy (rectoromanoscopy, RRS) is a direct visualization of the mucosa in the rectum and the sigmoid colon.

Rectosigmoidoscope (rectoromanoscope) 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 (e.g., bright rectal bleeding, protrusions, rectal or/and left ileum pain). The normal intestinal mucosa is smooth, moist, and moderately red. In acute intestinal inflammation, the mucosa is edematous, opaque, and covered with

mucus. Hemorrhage, erosions, ulcers, hemorrhoids, and fissures of the anus are also visible. Rectosigmoidoscopy helps in early diagnosis of the malignant tumours in the rectum and the inferior part 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, whose length is up to 180 cm. Because of the high flexibility, it can be introduced through the anus to any portion of the large intestine and often the terminal end of the ileum, resulting in accurate diagnosis of the inflammatory bowel disease, ulcers and tumours (Fig. 16-6). In addition to visual examination, the instrument can be used to take specimens of the intestinal mucosa for establishing a diagnosis and for polypectomy.

In the ***video capsule endoscopy*** (wireless video endoscopy), patients swallow a disposable capsule containing a camera that transmits images to an external recorder; the capsule does not need to be retrieved. This noninvasive technology provides visualization of the small intestine that is impossible to obtain by the common endoscopy. This procedure is indicated at suspicion on the occult gastrointestinal bleeding and mucosal abnormalities of the small intestine.



(1) (2) (3)

Fig. 16-6. Colonoscopy in intestinal diseases:

(1) Normal colonic mucosa with typical folds; linear, serpiginous, white-based ulcers in the Cronh′s disease (ileocolitis);

(2) diffuse ulceration and bleeding in ulcerative colitis.

Endoscopic tools are not useful in assessing intestinal motility, which can be assessed more accurately by X-ray barium studies.

X-ray study of the intestines

Enterography *is* an X-ray contrast (barium sulphate) study used to determine the morphological and functional properties of the *small intestine.* The patient takes the barium meal, and the barium suspension enters the cecum in 2.5 hours later. Early or delayed entrance of the suspension from the small intestine to the cecum indicates an intestinal motor dysfunction. The relief of the mucosa

in the small intestine has a feather-like pattern, which becomes disfigured in its inflammatory affections (in the *Crohn's disease*) (Fig. 16-7). Shallow horizontal ridges between accumulations of the liquid and gas in the intestinal loops can be seen sometimes 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 a barium contrast is given per os, it reaches the cecum in 2.5-4.0 hours. The ascending colon 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 rentgenological study of the large intestine gives information on its motor function, length, position, shape, tone, and haustration.

Giving the contrast substance per rectum (200 g of the Barium sulphate suspension in 1.5 liters of the water) ensures a more detailed information on possible constrictions, and adhesions in the large intestine, and the relief of its mucosa.

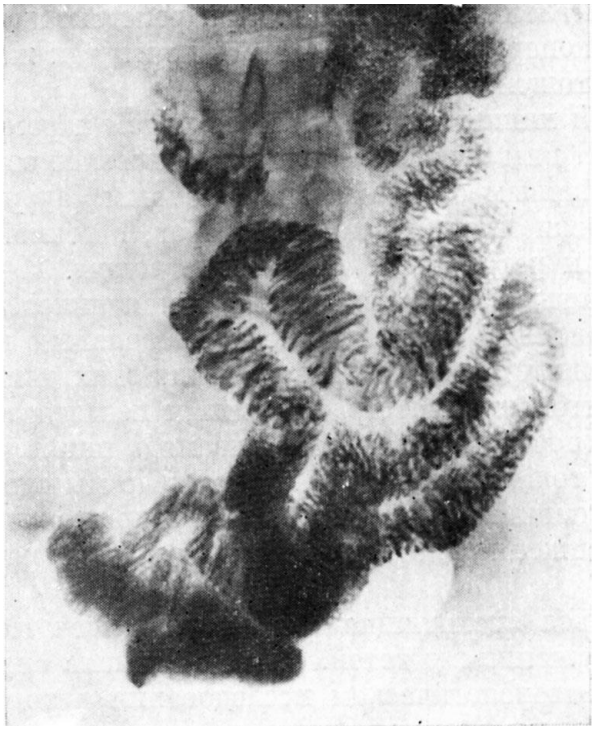


Fig.16-7.1. Normal X-ray of the small intestines. Uniform thin folds form feathery pattern

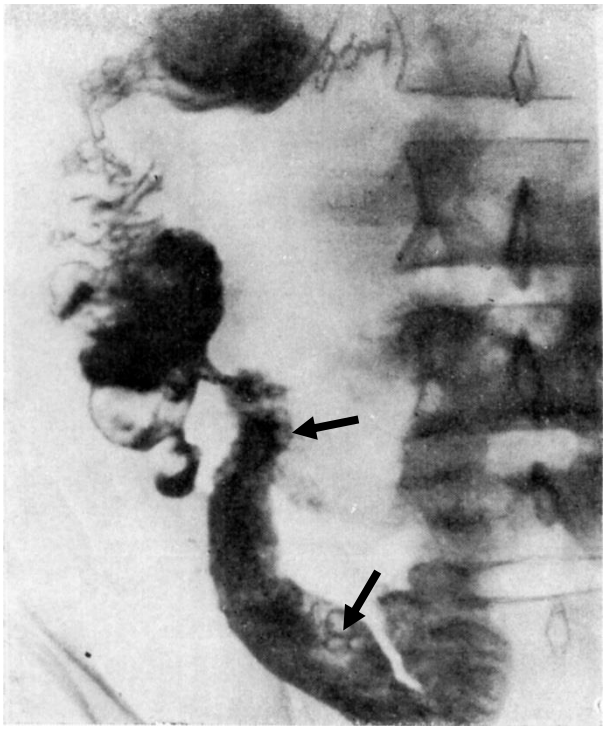


Fig. 16-7.2. Crohn's disease. Relief of the distal ileum loop mucosa as "cobblestones" (polypoid filling defects caused hyperplastic lymph follicles)

CT (computer tomography) "virtual colonoscopy" is a non-endoscopic method of the colon visualizing. It is effective in diagnosis of the inflammatory

masses in patients with Crohn's disease or complications of the diverticular disease.

MRI (magnetic resonance image) may give exquisitely accurate information on the anatomic extent of the invasive rectal cancers and blood flow in patients with vascular disorders.

Radionuclide scans with a radiolabeled technetium can be used to localize a site of the gastrointestinal bleeding.

16.3.2. Coprology studies

Coprology studies means analysis of the feces. Feces of the healthy subject consist of about equal volumes of the undigested food remains, secretions of the alimentary organs and microbes (mainly dead ones).

General clinical analysis of the feces (*coprocytogram, coprogram, or stool test*) includes macroscopy, microscopy, and the occult blood test. Microbiological studies of feces are necessary in cases of the suspected intestinal infections.

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 would be examined for the presence of the protozoa immediately after defecation. When feces are examined for the degree of the 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 the feces

Macroscopy study of the feces includes assessment of the amount of daily excretion, the colour of the feces, their consistency, shape, and smell, presence of the undigested food remains, mucus, blood, pus, and parasites.

Shape of the stool depends mainly on their consistency (Fig 16-8).

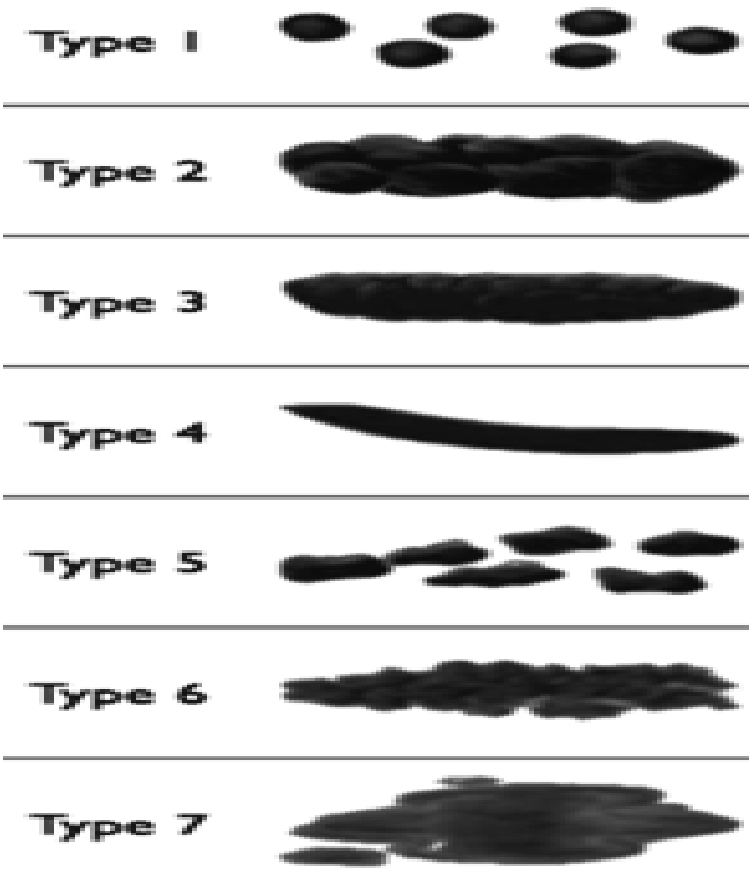


Fig. 16-8. Bristol Stool Chart: types 1-2 – typical in constipation, types 3-4 – in norm, types 5-7 – diarrhea.

The normal *stool mass* (with varied nutrition) is 100-200 g per day. Increased amount (>200 g/ day) of the feces (*polyfecalia)* may be in ample vegetable diet, poor assimilation of a food (in diseases of the pancreas), and intensified peristalsis. Diminished amount (<100 g/ day) of the feces may be observed in protein diet, constipations and hunger.

Normal feces are usually cylindrical and soft (Table 16-2). In constipation, feces are hard, "sheep's-like" ("small nuts"). The consistency of the feces depends on absorption of the water in the intestine. Feces are pasty when it is rich in fat (in *steatorrhea*).

Normal *colour* of the feces is brown due to the presence of the bilirubin derivatives (*stercobilin*). *Feces are golden-yellow or yellow-green* in diarrhea and during antibiotic therapy, because a bilirubin is not reduced. Feces are *greyish-white, clayish, or sandy* (*acholic feces*) in cases with upset a bile excretory function.

The *fatty feces (steatorrhea)* are white-grey as well, loose foamy foul-smelling stool (in exocrine pancreatic insufficiency, celiac disease, and tropical sprue), but they darken on exposure to light and give a positive reaction to stercobilin.

Table 16-2. Coprology studies (stool analysis) in norm

Characteristics	Normal value
Amount of diurnal excretion	100 – 250 g
Consistency	soft and formed
Shape	cylindric
Colour	brown
Smell	slight fecal
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

Black colour of the feces can be due to hemorrhage in the upper portions of the gastro-intestinal tract (formation of sulphur compounds of iron), in constipation due to excess of the meat food, ingested black currants, coffee, sorbent carbon, preparations of the bismuth, iron, etc.

Melena is the passage of the black tarry sticky stool. Melena usually means the upper gastrointestinal (esophagus, stomach, or duodenum), the small intestine and cecum hemorrhage. Melena may develop with as little as 50-60 ml of blood loss from the gastrointestinal tract per day. Melena is indicative of the recent hemorrhage but it does not indicate the presence of the bleeding at the time of the passage. Melena usually appears no earlier than 2 hours after the onset of the bleeding.

Normal smell of the feces is specific slightly fecal. The odour of the feces changes with intensification of the carbohydrates fermentation (acid odour of the organic acids) in *fermentative dyspepsia* and protein putrefaction (putrefactive odor of the ammonia, hydrogen sulphide, skatole, indole, etc.) in the *putrid dyspepsia* and especially in degradation of the large intestine tumours.

Remains of the undigested food are easier detectable in fecal emulsion in a Petri dish placed against a dark background. *Lientery* (the passage of the incompletely digested or undigested food in the feces) presents in the insufficiency of the gastric and/or pancreatic digestion, or in the absence of the

teeth. Remains of the vegetable foods are usually found. Connective tissue remains undigested (in the form of whitish fibrous structures) in the gastric *achylia gastrica*. Ample fat in stools (*steatorrhea*) is characterized by the appearance of the solidified fat coat on the fecal surface.

Pathological components of the feces (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 the *mucus* found on the surface of the feces indicate inflammatory changes in the large intestine.

Appearance of the *blood in feces* is a serious symptom. Dysentery and ulcerative colitis are characterized by blood stained mucus mixed with stools. In anus hemorrhoid bleeding, an unaltered blood is visible on the surface of the stools. *Hematochezia* is the passage of the fresh blood per anus, usually in or with stools. Hematochezia is associated with the lower gastrointestinal bleeding (the left part of the large intestine).

Rectorrhagia (or proctorrhagia) is the rectal bleeding in anal fissures, hemorrhoids, anal cancer, colon polyps. Rectorrhagia should be distinguished from hematochezia. Rectorrhagia is not associated with defecation; it is associated with expulsion of the fresh bright red blood without stools.

Feces contains a *pus* in the ulcerative affections of the large intestine (dysentery, tuberculosis, degrading tumour), or in rupture of the paraproctal abscess. Feces may contain *stones* (gallstones, *coprolites*, pancreatic calculus). *Helminthes* (Ascarides, Acanthocephala, and members of Platyhelminthes) can be found in stools.

Microscopy study of the feces

Microscopy of the feces reveals remains of the food cells, mucus, eggs of the helminthes, and protozoa. Most components of the feces can be found in a native preparation of the fecal emulsion with a small quantity of the sodium chloride isotonic solution.

Detritus is a main component of the feces. This is material whose particles (a dead particulate organic material, decomposed cells and microbes) are difficult to differentiate.

Muscle fibers are yellow cylinders with a transverse striated pattern which remains unchanged after cooking of the meat but which disappears under the action of the pepsin (digestive enzyme of the gastric juice). Feces of a healthy individual on a meat diet can contain a few separate muscle fibers without their striated pattern.

Creatorrhea is an abundance of the muscle fibers in feces. The presence of the muscle fibers with preserved striated pattern indicates insufficiency of the stomach digestion of proteins (in achlorhydria, atrophic gastritis). A lot of muscle fibers without striated pattern in feces indicate insufficiency of the pancreas digestion of proteins (in chronic pancreatitis) or accelerated transport speed of the intestinal contents.

Steatorrhea is a high fat content in stools. Steatorrhea indicates cessation of the bile excretion into the intestines, dysfunction of the pancreas (deficiency of the pancreas lipase), impaired absorption of fats. If bile is not present in the proper quantity, fatty acids are found in feces. From 90 to 98 per cent of the neutral fat is assimilated in norm. The remaining fat is excreted mainly as soaps.

Connective tissue in feces indicates inadequate gastric digestion.

Starch and *vegetable cellular fibers (cellulose)* can be identified among remains of the carbohydrate food. Plant cells are easily identifiable by thick coats, and vegetable fibers by thick intercellular partitions. The amount of the cellulose depends on the character of the food and the time of its passage through the large intestine, where it is partly destroyed by microbes.

In order to reveal a starch, a drop of the Lugol's solution is added to the fecal emulsion. Starch grains are stained blue or violet. Normal feces contain the starch in a very small quantity or do not contain.

Amylorrhea is an excessive starch content in feces. Amylorrhea can be observed in dysfunction of the pancreas (deficiency of the pancreas amylase) or accelerated passage of the food through the small intestines (starch remains unsplit due to accelerated peristalsis).

The following microscopic elements are originated from the 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 inflammation and ulcerative affections of the large intestine (dysentery, tuberculosis, ulcerative colitis, cancer). Neutrophils prevail among leucocytes.

Erythrocytes occur in feces of the patients with ulcerative affections of the large intestine, fissures of the anus, and hemorrhoids. If the lesion stands higher in the intestine, erythrocytes are decomposed before they reach the colon. That is why the presence of the blood in feces should be determined by chemical analysis.

Single cells of the *intestinal columnar epithelium* can occur in normal feces. Their large accumulations in mucus suggest colitis (a large intestine inflammation).

Cells of the malignant tumours can be found in the presence of the malignant tumours at the distal end of the large intestine.

Helminthes ova are be found in native preparations if they are numerous. Their concentration can be increased by precipitation of the feces emulsion. *Acanthocephala ova* are detected in the material scraped from the perianal folds.

Protozoa are detected in freshly defecated material. *Amoeba, Lamblia, and Balantidia* are important pathogenic factors for diarrhea and constipation or inflammation of the colon.

Chemical study of the feces

Normal feces medium reacts weakly alkaline or neutral. This reaction depends on the vital activity of the intestinal flora, which is either fermentative or putrid.

Feces become acid in the fermentative dyspepsia when carbohydrate assimilation is insufficient, and the fermentative flora is activated.

Feces become markedly alkaline due to formation of the ammonia due to poor assimilation of proteins *in gastric or pancreatic achylia*, when putrid flora becomes more active (*putrid dyspepsia*), and also in the presence of an inflammation in the large intestine with exudation of the protein.

Stercobilin gives the normal brown colour of the feces. Feces are decoloured if the bile secretion into the intestine has stopped or decreased.

Presence of the *blood* in feces is of the great diagnostic importance since it indicates ulcer or tumours of the gastrointestinal tract. The colour of the feces changes only in a profuse hemorrhage (the blood loss>50-60 ml per day.). The latent hemorrhage (*occult blood*) can be determined by a chemical analysis. It is necessary to rule out other possible sources of the bleeding, e.g. nose, gums, esophagus, hemorrhoids, etc. and foods containing blood (or hem) or iron, e.g. meat, eggs, fish, green vegetables, iron-contained medications, and vitamin C supplements, which should be excluded from the diet three days before the analysis.

Methods of the *occult blood* detection are based on the property of the hemoglobin to catalyze oxidation-reduction reactions. Hydrogen peroxide is an oxidant, and Benzidine is a reductant in the *Gregersen (benzidine) test*. Benzidine changes its colour on oxidation in the presence of the blood. The Gregersen reagent (containing Hydrogen peroxide and Benzidine) is placed in drops on the feces smear. In the presence of the blood, a green or blue colour develops. Brightness of the colour and the speed of the development depend on the amount of the blood.

Immunochemical fecal occult blood test (fecal immunochemical test, FIT) is preferred over the *Gregersen tests* because it is more sensitive. It does not require any dietary restrictions before the sample collection. This test give positive results only in presence of human hemoglobin.

16.3.3. Breath tests

Breath tests *are indicated for diagnosis of the carbohydrate intolerance* and *intestinal bacterial overgrowth, and Helicobacter Pylori infection* (see *urea breath test,* Section 16.2.3). They typically involve ingestion of a substrate metabolized by gastrointestinal bacteria or digestive enzymes. The ingested substrate metabolites are measured in exhaled air of the patient. Breath tests, using *substrates like glucose, lactulose, and xylose*, are noninvasive and easy to do.

Carbohydrate intolerance is examined by *Hydrogen (H_2) breath test.* This test measures the exhaled hydrogen produced by the bacterial degradation of

carbohydrates. In patients with *disaccharidase deficiencies*, enteric bacteria degrade nonabsorbed carbohydrates in the colon, increasing exhaled hydrogen. The *lactose-hydrogen breath test* is useful only to confirm lactase deficiency. For this test, 50 g of lactose is administered orally, and the hydrogen produced by bacterial metabolism of the undigested lactose is measured with a breath meter at 2, 3, and 4 hours after ingestion. Most affected patients have an increase in expired hydrogen of more than 20 times over baseline.

Bacterial overgrowth in the small intestine is examined by *^{14}C-xylose breath test*. ^{14}C-xylose is given orally, and the exhaled $^{14}CO_2$ concentration is measured. Catabolism of the ingested xylose by the intestinal bacterial overgrowth causes $^{14}CO_2$ to appear in exhaled breath.

16.4. The key points of the theme "Laboratory-Instrumental Examination of the Gastrointestinal Tract"

Laboratory and instrumental examinations in diseases of the esophagus

Esophagoscopy is a diagnostic technique to evaluate dysphagia, to identify structural abnormalities of the esophagus or bleeding sites, or to obtain biopsy specimens. *Barium contrast X-ray examination* aids in diagnostics of the anatomic and motor disorders of the esophagus. *Esophageal pH monitoring* provides direct evidence of gastroesophageal reflux disease (GERD), if esophageal pH is lesser than 4.0 during more than 5 minutes not less than 50 times for a day.

Laboratory and instrumental examinations of the stomach and duodenum

Upper gastrointestinal endoscopy is used to establish the site of the upper gastrointestinal bleeding, to visualize and for biopsy sampling abnormalities of the gastroduodenal mucosa (gastritis, ulcers, tumours). *X-ray examination of the stomach and duodenum* is a complementary (to endoscopy) method for assessing gastroduodenal motor and evacuation disorders (pyloric stenosis, etc.), peptic ulcers, and tumours. *Intragastric pH-metry* gives the most reliable data on the gastric secretion. *Histological examination of the gastric biopsy* is the standard diagnostic test in gastritis and Helicobacter Pylori (HP)-infection.

Laboratory and instrumental examinations in diseases of the intestines

Rectosigmoidoscopy (RRS) and colonoscopy are direct visualization of the large intestine mucosa. Endoscopy is indicated at suspicion on the occult gastrointestinal bleeding and of the mucosal abnormalities of the intestine (e.g., colitis, diverticula, tumours). *X-ray contrast studies such as enterography and irrigoscopy* are used in assessing intestinal motility and to determine the morphological changes of intestines. *Coprology studies* allow to find laboratory signs of the *maldigestion syndrome (creatorrhea, steatorrhea, amylorrhea),* presence of the occult blood and parasites in feces.

Breath tests are indicated for diagnosis of the carbohydrate intolerance and intestinal bacterial overgrowth, and Helicobacter Pylori infection.

16.5 Assessment tests on the theme "Laboratory-Instrumental Examination of the Gastrointestinal Tract"

1. What method is the «gold standard» of the gastroesophageal reflux disease (GERD) diagnosis?

1. Esophagogastroduodenoscopy;
2. Esophageal manometry;
3. Bernstein (acid perfusion) test;
4. X-ray examination of the esophagus;
5. Esophageal pH-monitoring.

2. What method is the most informative to diagnosis of the peptic ulcer of the stomach and duodenum?

1. Gastro-intestinal endoscopy;
2. Common blood count;
3. Occult blood analysis of the feces (fecal immunochemical test);
4. Radiological study;
5. Study of the stomach secretion.

3. Specify the normal pH of the esophagus:

1. 2.1 – 3.0;
2. 5.0- 7.0;
3. 1.6-2.0;
4. <1.6;
5. 3.0-4.9.

4. Specify the pH criteria of the pathological gastroesophageal reflux:

1. 2.0 – 4.9;
2. < 4.0 during more than 5 minutes not less than 50 times for a day;
3. 1.5-1.9 after eating;
4. <1.5 on an empty stomach;
5. >6.0.

5. What is true about the assessment of the stomach body pH?

1. normacidity if pH is 6.0 – 7.0;
2. anacidity if pH >6.0;
3. hypoacidity if pH >1.5;
4. hyperacidity if pH <1.5 in basal secretion;
5. normacidity if pH is in the range of 2.1-6.0 in basal secretion;
6. hyperacidity if pH >5.0.

6. What is true about the assessment of the pH in antral part of the stomach?

1. normal pH is in the range of 2.1 – 6.0;
2. compensated alkalinization if pH> 6.0 in basal secretion;
3. normal pH <1.5 in basal secretion;
4. decompensated alkalinization if pH< 3.5 in basal secretion;
5. compensated alkalinization if pH <1.2;
6. decompensated alkalinization if pH>6.0.

7. Anacid and hypoacid state (achlorhydria and hypochlorhydria) of the stomach acid-production function is typical for:

1. chronic atrophic gastritis;
2. peptic ulcer of the stomach;
3. cancer of the stomach;
4. chronic gastritis B (HP-associated gastritis);
5. gastroesophageal reflux disease.

8. Hyperacid state (hyperchlorhydria) of the stomach acid-production function is typical for:

1. peptic ulcer of the duodenum;
2. chronic gastritis B (HP-associated gastritis);
3. chronic atrophic gastritis;
4. cancer of the stomach;
5. gastroesophageal reflux disease.

9. Decompensated alkalinization function of the antral part of the stomach is typical for:

1. chronic atrophic gastritis;
2. peptic ulcers of the stomach and duodenum;
3. chronic gastritis B;
4. cancer of the stomach;
5. functional dyspepsia.

10. Remains of the undigested food in feces:

1. steatorrhea;
2. dysentery;
3. creatorrhea;
4. amylorrhea;
5. lientery.

11. What method is used to definition of the occult blood in feces:

1. assay with benzidine (reaction of Gregersen);
2. assay of Florens;
3. assay of Bogomolov;
4. fecal immunochemical test;

5. assay of Rivalt.

12. Breath tests are indicated for diagnosis of the:
1. carbohydrate intolerance;
2. intestinal bacterial overgrowth;
3. Helicobacter Pylori infection;
4. acid-production function of the stomach;
5. alkalinization function of the antral part of the stomach.

13. Blood serum tests for assessment of the stomach secretion:
1. pH-metry of the stomach;
2. serum pepsinogens;
3. serum bilirubin;
4. bile acids concentration;
5. serum gastrin.

14. Diagnostic methods of the stomach Helicobacter Pylori (HP):
1. histological examination of the gastric biopsy specimen;
2. urea breath test;
3. Hydrogen (H2) breath test;
4. bacterial culture of the gastric biopsy specimens;
5. stool antigen test for HP-infection noninvasive diagnosis;

15. What is a correct characteristic of the steatorrhea?
1. black tarry-like stool;
2. high fat content in stool;
3. muscle fibers in feces;
4. excessive starch content in feces;
5. undigested vegetable fibers in feces.

16. What is a correct characteristic of the creatorrhea?
1. muscle fibers in feces;
2. high fat content in pasty feces;
3. connective tissue in feces;
4. excessive starch content in feces;
5. undigested vegetable fibers in feces.

17. What is a correct characteristic of the amylorrhea?
1. excessive starch content in feces;
2. high fat content in stool;
3. connective tissue in feces;
4. mucus in stool;
5. undigested vegetable fibers in feces.

18. Erythrocytes occur in microcopy of the feces in the patients with:
1. ulcers of the large intestine;
2. peptic ulcers of the stomach;
3. hemorrhoids;
4. celiac enteropathy;
5. reflux-esopahgitis.

19. Hematochezia is:
1. the black tarry sticky stool;
2. occult blood in stool;
3. pasty feces with fat in stools;
4. passage of the fresh blood per anus;
5. stool with coprolites.

20. According to Bristol Stool Chart, normal types of the stool:
1. types 1-2;
2. types 3-4;
3. types 5-6;
4. type 7;
5. types 2-3.

CHAPTER 17. Clinical-laboratory Syndromes of the Gastrointestinal Tract Diseases

Goals: to enable students to learn –

1. clinical symptoms and laboratory-instrumental signs of the most common syndromes in the gastrointestinal tract pathology such as abdominal pain, and gastrointestinal bleeding;

2. clinical syndromes of the gastrointestinal tract dysfunction – dysphagia, rumination syndrome, dyspepsia, syndromes of the inadequate digestion and absorption (maldigestion and malabsorption***)***, syndrome of the slow evacuation of intestinal contents (constipation), syndrome of the accelerated evacuation of intestinal contents (diarrhea).

17.1. Abdominal pain syndrome

Abdominal pain is one of the most common non-specific symptoms of many diseases. Abdominal pain can be acute and chronic. The term "*acute abdomen*" refers to such severe abdominal symptoms when the possibility of surgical intervention is considered.

Causes:

1. Diseases of the abdominal organs - acute and chronic inflammatory and infectious diseases, cholelithiasis, tumours; gastrointestinal tract obstruction, diverticula, ulcers, impaired motor-evacuation function, functional disorders, perforations and ruptures; ischemic and vascular disorders (embolism, thrombosis), abdominal organs traumas, hernias.

2. Systemic diseases and conditions with severe intoxication – heart and vascular failure, renal failure with hyperazotaemia, decompensated endocrine pathology (ketoacidosis in diabetes mellitus, thyrotoxicosis, hyperparathyroidism), acute and chronic poisoning (lead, arsenic, mushrooms, etc.), allergy, systemic vasculitis, blood system diseases (sicle cell crisis, hemoblastosis), etc.

3. Radiating pain in diseases of organs localized outside the abdominal cavity (so-called *pseudoabdominal pain*) – cardiovascular system (myocardial infarction, pericarditis, aortic aneurism dissection), lungs (pleurisy, lower lobe pneumonia), esophagus, kidneys and urinary tract (urolithiasis, pyelonephritis, renal colic), reproductive system, vertebral column and peripheral nervous system pathology.

Clinical picture: The principal symptom is an abdominal pain.

Localization of the pain in the main depends on the affected organ position (Table 17-1, and see Chapter 14. Fig 14-1): epigastric region - stomach and cardiac part of the esophagus; epigastrium and right hypochondrium - duodenum, liver, gall bladder; epigastrium and left hypochondrium - pancreas; left

hypochondrium – spleen; projection areas of the intestine departments (left ileum - sigmoid colon, left flank - descending colon, right ileum – cecum, appendix and terminal end of the ileum, right flank – ascending colon, umbilical region – jejunum, mesogastrium – transverse colon; suprapubic and perineum region - rectum.

Table 17-1. Localization of the abdominal pain

Parts of the anterior abdominal wall	Pathology of the digestive system organs	Pathology of other organs and systems of the body
Epigastrium	Stomach, duodenum, esophagus, gall bladder and biliary tract, pancreas	Cardiovascular system (myocardial infarction, abdominal aortic aneurism)
Right hypochondrium	Stomach, duodenum, liver, gall bladder and biliary tract, pancreas, hepatic curvature of the transverse colon	Respiratory system (right inferior lobar pneumonia, pleurisy), heart failure (congested liver), kidney (renal colic), intercostal neuralgia
Left hypochondrium	Pancreas, spleen, splenic curvature of the transverse colon	Respiratory system (left inferior lobar pneumonia, pleurisy), kidney (renal colic), intercostal neuralgia
Mesogastrium (umbilical part)	Jejunum, transverse colon, stomach, pancreas	Abdominal aorta (aneurism)
Right flank	Ascending colon	Kidney (renal colic, pyelonephritis, tumours)
Left flank	Descending colon	
Hypogastrium	Rectum	Urinary bladder, uterus
Right ileum	Cecum, terminal end of ileum, vermiform appendix	Uterine adnexa, ureter, sacrum
Left ileum	Sigmoid colon	
Diffuse abdominal localization	Gastrointestinal tract (gastroenteritis, colitis, ileus, intestinal obstruction, irritable bowel syndrome), peritonitis	Urinary infections, autonomic nervous system dysfunction, and neuropathy, metabolic and endocrine disorders (diabetic ketoacidosis, uremia, thyrotoxicosis), poisoning (lead, arsenicum, etc.)

Patterns of abdominal pains:

(1) ***Visceral pain*** comes from the abdominal visceral organs innervated by autonomic nerves. The pain presents mainly due to distention and contraction

of hollow organs such as gastrointestinal tract departments, less often if stretching capsules of the enlarged solid organs (e.g. liver, spleen) or in ischemia of abdominal organs. Visceral pains are commonly variable in character (dull, barning, aching, etc.) and vaguely localized. Usually the pain is palpable near the midline at levels of the affected structures.

(2) ***Somatic (parietal) pain*** comes from the parietal peritoneum innervated by somatic nerves. The pain arises from parietal pleura irritating by infectious, chemical, or other inflammatory processes. Somatic pains are usually sharp, steady, more severe and precisely localized. The pains are growing stronger at movements and coughing. Positive *Mendel sign with abdominal wall percussion* and positive *Shchetkin-Blumberg sign with palpation* confirm involvement of the parietal peritoneum. *Resistance and marked strain of muscles of the abdominal wall* are usually palpated over the organ affected by inflammation, especially so if the peritoneum is involved.

(3) ***Referred pain*** is felt at sites on a distance from its source and corresponds to the same spinal cord levels innervation that is affected organ, and the pain can spreading by the phrenic, obturator, and genitofemoral nerves. Samples of the referred pain are the back or shoulder pain due to biliary colic, inguinal pain in renal colic, shoulder pain due to irritation of the diaphragm by inflammation. The pain is well localized and irradiated from the initially affected organ, which can be confirmed by superficial and deep palpation.

Accompanying symptoms can be nausea, vomiting, meteorism, diarrhea, constipation, hyperthermia, jaundice, gastrointestinal bleeding, changes of the stool and urine.

Physical examination includes general survey with assessment skin and visible mucosa for jaundice, taking body temperature; percussion and auscultation of lungs; examination of the cardiovascular system (taking blood pressure, pulse, heart auscultation); abdominal examination – intestinal peristalsis auscultation, percussion and palpation of the abdomen for masses, tenderness, and peritoneal signs (*Mendel sign and Shchetkin-Blumberg signs* in combination with resistance and marked strain of muscles of the abdominal wall), rectal examination; and gynecological examination for females with pains in the inferior parts of the abdomen.

*Warning signs of the "acute abdomen" are s*evere pain, fever, signs of the shock (tachycardia, filiform pulse, arterial hypotension, mental confusion), abdominal distention, absence or weakness intestinal peristalsis sounds, signs of the peritoneal involvement (positive Mendel and Shchetkin-Blumberg signs), leukocytosis. If symptoms of the "acute abdomen" present the patient should be consulted by a surgeon.

Laboratory and instrumental examination

Standard laboratory tests include clinical blood analysis with leucocyte formula, biochemical blood tests (bilirubin, urea, creatinine, glucose, electrolytes – K, Na, Cl), urinalysis, ECG.

Subsequent tests depend on the primary diagnosis and the need for differential diagnosis: blood serum levels of the amylase and lipase (in suspected pancreatitis), CPK-MB or cardiac troponin (in suspected myocardial infarction), AST, ALT, GGT and ALP (in suspected hepatobiliary pathology); analysis of the feces for the presence of the occult blood, pregnancy test for females of the childbearing age (with lower abdominal pain for exception the extrauterine pregnancy).

*Primary methods of the diagnostic imaging: ultrasonograph*y can find a free fluid in the abdominal cavity, kidney and gallstones, abdominal aortic aneurism, and *plain abdominal radiography* reveals an air in the abdominal cavity, fluid levels in intestinal loops, and kidney stones.

Subsequent instrumental studies can include chest X-ray (for exception inferior lobar pneumonia and pleurisy), contrast X-ray study of the intestines, gastrointestinal endoscopy, and in severe abdominal pain – CT with intravenous contrast and laparoscopy.

17.2. Syndrome of the gastrointestinal bleeding

Gastrointestinal (GI) bleeding can originate from any part of the gastrointestinal tract. Clinical manifestations of the GI bleeding depend on the site, rate and volume of the blood loss. GI bleeding may be acute and chronic, evident and occult.

Causes: ulcer or erosions of the esophagus, esophageal varicose veins (varices) dilatation in portal hypertension; Mallory-Weiss syndrome, gastroduodenal peptic ulcers and erosions, hemorrhagic gastritis; malignant and benign tumours, diverticula; intestinal protozoa and helminthic invasions, acute infections (dysentery), mesenteric thrombosis, non-specific ulcerative colitis, anal fissures and hemorrhoids.

Clinical picture:

Common clinical features of the blood loss*:* complaints on dizziness, weakness, episodes of the syncope may be; pallor and cold sweat on general inspection; arterial hypotension, tachycardia, filiform pulse.

Clinical manifestations of the gastroduodenal bleeding

Esophageal hemorrhage manifests by vomitus contains red non-clotted blood (Fig. 17-1).

Gastric hemorrhage can be manifested by vomiting blood (*hematemesis*) or black tarry stools (*melena*); a vomitus looks like clotted blood or coffee grounds. *Melena* is not an obligatory and later (12-24 hours after bleeding) sign of gastric hemorrhage.

Intestinal hemorrhage manifests by *melena* in cecum and small intestinal bleeding; black-brown stools - in bleeding from the right part of the colon. Bright red blood is mixed the stools in the left side colon bleeding, and the blood typically covers the stool (*hematochezia*), it is on the toilet paper, or drips into the toilet bowl. The stool is usually of the normal color in *hemorrhoidal bleeding*.

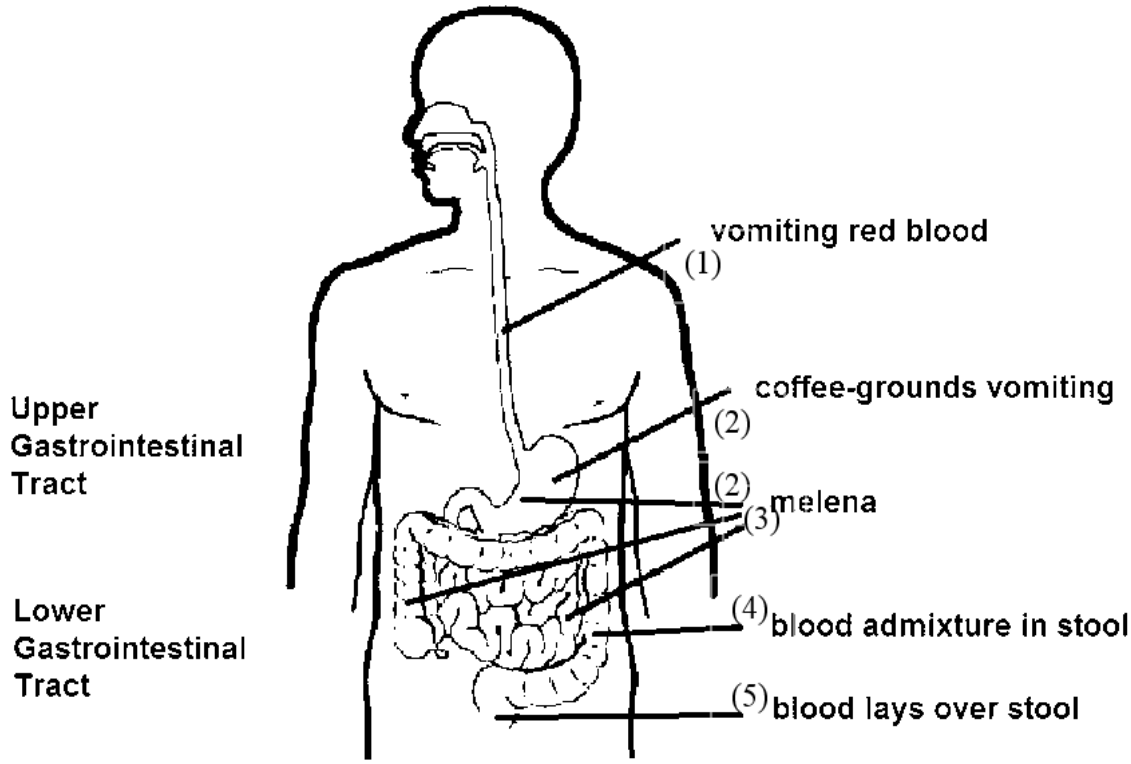


Fig. 17-1. Localization and manifestations of the gastrointestinal bleeding: upper gastrointestinal tract – (1) esophagus, (2) stomach and duodenum; lower gastrointestinal tract – (3) small intestine (jejunum, ileum) and proximal large intestine, (4) descending and sigmoid colon, (5) rectum.

Laboratory-instrumental examination includes complete blood count (to detect anemia), fecal occult blood analysis (for suspected occult GI bleeding). Endoscopy studies (esophagogastroduodenoscopy for suspected upper GI bleeding and colonoscopy for lower GI bleeding) are indicated in case of the positive fecal occult blood test.

Subsequent instrumental studies are recommended if esophagogastroduodenoscopy and colonoscopy do not reveal the bleeding points: X-ray enterography or CT-enterography, abdominal angiography and video capsule endoscopy.

Subsequent laboratory studies are coagulation tests (platelet count, prothrombin time, fibrinogen, partial thromboplastin time) and liver biochemical tests (bilirubin, albumin, AST, ALT, AP, GTP) for suspected hypocoagulation state and liver pathology. Hemoglobin and hematocrit are repeated every 6 hours in prolonged bleeding.

Principles of emergency medical care in gastrointestinal bleeding:

- Transportation on stretchers to surgery department or intensive care unit;
- Consultation of surgeon is recommended;
- Strict bed regimen;

- Ice-bag on abdominal wall;
- Intravenous (IV) fluid resuscitation;
- Hemostatics IV: Sol. Vitamin K (phytomenadione) 1%-2-3 ml, Sol. Calcium chloride 10%-10 ml, Sol. Acidi Amicapronici 5%-100-200 ml;
- Blood transfusion is considered if severe and repeating blood loss ;
- Endoscopic hemostasis (hemoclip, injection and thermo-coagulation methods) by gastroscopy (in gastric bleeding) or colonoscopy (in bowel bleeding);
- *Blakemore-Sengstaken tube* is a double-balloon tamponade system indicated in esophageal varices bleeding.

17.3. Dysphagia

Definition: Dysphagia is a progressive or intermittent difficulty in the transit of the solid food and/or liquids from the oral cavity to the stomach.

Classification and causes:

(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 the dysphagia -

a. Intermittent dysphagia,

b. Progressive dysphagia.

Preesophageal (oropharyngeal) dysphagia is a difficulty emptying bolus material from the oral and pharynx into the esophagus.

Preesophageal dysphagia causes are

(1) *neurologic or muscular disorders* that affect muscles (e.g., dermatomyositis, myasthenia gravis, muscular dystrophy, Parkinson's disease, amyotrophic lateral sclerosis, bulbar poliomyelitis, other central nervous lesions;

(2) *pathology of the oral cavity and pharynx*, such as an inflammation (stomatitis, pharyngitis, tonsillitis, abscess, syphilis), tumors of the pharynx, tongue, and floor of the mouth; compression by the surrounding structures (goiter, lymphadenopathy), or foreign bodies.

Esophageal dysphagia is a difficulty passing food bolus through the esophagus to the stomach due to obstructive or motor disorders. *Esophageal dysphagia* can be due to *organic or functional* narrowing lumen of the esophagus.

Organic dysphagia originates from structural abnormalities that result in stenosis or external compression of the esophageal lumen.

Functional dysphagia is due to muscular spasms caused by autonomic innervation disorders of the esophageal muscles.

Causes of the esophageal dysphagia *are*

1) *esophageal stenosis in* esophageal cancer, cicatricial stenosis after burns, radiation therapy, erosive esophagitis and ulcers of the esophagus in GERD; foreign body, esophageal diverticula, congenital esophageal webs and rings;

2) *extrinsic compression* of the esophagus by an aortic aneurysm, an aberrant subclavian artery, cervical osteophytes, an enlarged left atrium, a substernal thyroid gland or a mediastinal tumour;

3) motility disorders of the esophagus in achalasia, diffuse or segmentary esophageal spasm due to autonomic nervous system dysfunction, diabetic autonomic neuropathy, megaesophagus in chronic *Chagas disease (American trypanosomiasis)*, systemic sclerosis, eosinophilic esophagitis, Plummer–Vinson syndrome (sideropenic dysphagia in iron-deficiency anemia).

Clinical picture

Preesophageal (oropharyngeal) dysphagia is characterized by difficult swallowing with nasal regurgitation and/or coughing due to tracheal aspiration. The patient usually has a feeling *alimentary bolus* in the throat or pharynx. Preesophageal dysphagia can be associated with of the oral and pharyngeal dysfunction symptoms such as the pain in oral cavity and throat during swallowing, hypersalivation, wooly voice and dysphonia (disordered phonation), dry cough.

Esophageal dysphagia is manifested by a feeling alimentary bolus in projection of the esophagus at the level of suprasternal notch or retrosternal level in few seconds after swallowing. Accompanying symptoms can be distension or pressure in the chest, odynophagia (esophageal pain after swallowing), vomiting with indigested food, cough.

Organic dysphagia develops gradually and progresses. *Dysphagia progresses* rapidly over weeks to months (e.g., from esophageal cancer), or progresses over years (e.g., from peptic stricture). 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.

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.

Functional dysphagia diagnostic criteria must include all of the following:

1. Sense of the solid and/or liquid foods sticking, lodging, or passing abnormally through the esophagus;

2. Absence of the evidence that esophageal mucosal or structural abnormality is the cause of the symptom;

3. Absence of the evidence that gastroesophageal reflux or eosinophilic esophagitis is the cause of the symptom;

4. Absence of major esophageal motor disorders.

Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis with a frequency of at least once a week.

Complications of the progressive dysphagia can be a weight loss, malnutrition, aspiration pneumonia, and an esophageal perforation can develop in severe cases.

Diagnosis of the dysphagia is based on clinical picture confirmed by data of barium contrast X-ray examination and esophagoscopy. Esophageal manometry, pH-metry monitoring and impedancemetry can detect esophageal motility disorders and gastroesophageal reflux.

Dysphagia should not be confused with *globus sensation* (*globus hystericus*), a feeling of having a lump in the throat, which is unrelated to a difficult swallowing and occurs without impaired food passage via esophagus. Often noted in association with anxiety or grief, globus sensation is mainly emotional in origin. Specialized medical consultations of the neurologist, otorhinolaryngologist, and stomatologist are considered in case of the preesophageal dysphagia.

17.4 Rumination syndrome of adults

Definition: Rumination is a repeated effortless regurgitation of the food after eating.

Causes: Rumination syndrome is a functional gastrointestinal disorder without known exact causes. This syndrome can be in some patients with emotional problems and stress situations.

Mechanisms of the rumination are an increase in abdominal pressure due to unperceived contraction of the abdominal wall muscles and a relaxation of the lower esophageal sphincter that results in the stomach contents regurgitation.

Clinical picture *Rumination is evident as the voluntary or involuntary regurgitation of the partially digested food after eating. The food may be reswallowed or spit out. Rechewing the food can be before reswallowing.* Regurgitation typically presents at the daytime several times a week. A belching can precede this regurgitation. It is typically not associated with a nausea and vomiting. Patients who spit out the regurgitated food or who limit their food intake can lose some weight.

Clinical diagnosis

Diagnosis of the rumination syndrome is based on a medical history and physical examination. The following criteria of the diagnosis rumination syndrome (first two criteria are necessary):

- Repeated regurgitation of the recently ingested food into the mouth over a period of at least 3 months. Regurgitated food may be rechewed, reswallowed or spit up;
- Regurgitation is not preceded by retching;
- Repeated regurgitation is not due to a gastrointestinal or other medical condition (for example, *gastroesophageal reflux, pyloric stenosis*)

- The eating disorder must not occur only in the presence of *anorexia nervosa, bulimia nervosa, binge eating disorder or avoidant/restrictive food intake disorder*.
- If the eating disorder occurs together with another mental disorder (for example, *intellectual disability*), symptoms must be severe enough and be the main reason for seeking medical care.

Supportive criteria:

- Effortless regurgitation events are usually not preceded by nausea
- Regurgitant contains recognizable food which may have a pleasant taste
- The process tends to cease when the regurgitated material becomes acidic

Laboratory and instrumental tests are indicated to rule out other medical problems: Upper gastrointestinal endoscopy and barium contrast X-ray study for examination the motor and evacuation function of the esophagus and stomach.

Complications associated with rumination syndrome are usually a weight loss and nutritional deficiencies. Other complications include aspiration of the food, pneumonia, asphyxia.

17.5. Dyspepsia

Definition: ***Dyspepsia*** includes chronic and recurrent sensations of the epigastric pains or burning, early satiety and postprandial fullness in the upper abdomen referable mostly to gastroduodenal disorders.

Causes. There are *organic dyspepsia* (due to structural abnormalities of upper abdominal organs), *functional dyspepsia* (due to functional gastroduodenal disorders), and *undiagnosed dyspepsia* (if organic and functional causes of the dyspepsia are not identified by laboratory and instrumental studies).

Organic dyspepsia can develop because of the peptic ulcers and erosions of the stomach and duodenum; diseases of the liver and biliary system (hepatitis; cholelithiasis, cholecystitis); diseases of the pancreas (pancreatitis, pancreatic pseudocysts); malignant tumours of the stomach, pancreas, and intestines; vascular pathology (intestinal ischemia, abdominal aortic aneurysm); gastroesophageal reflux disease (GERD).

Additional categories of the dyspepsia:

Drug-induced dyspepsia due to gastroduodenal mucosal injury by acetylsalicylic acid and other nonsteroidal anti-inflammatory drugs (NSAID). Some other medications (such as oral antibiotics (mainly doxycycline, erythromycin, ampicillin), digitalis, theophylline, iron or potassium salts, calcium channel blockers, nitrates, glucocorticoids, and bisphosphonates) can cause dyspepsia.

H. pylori infection-associated dyspepsia is confirmed by the fact that successful H. pylori eradication therapy leads to a remission of the sustained symptoms.

Clinical picture. *Complaints.* The patient complains of the persistent or recurrent *epigastric pain or burning, early satiety and/or epigastric discomfort described as postprandial fullness* (feeling a food retention in the stomach after eating).

Other symptoms such as bloating, nausea, or belching can be associated with dyspepsia. Heartburn is irrelevant to dyspepsia, occasionally it can present with dyspepsia.

Symptoms of the dyspepsia are not relieved and associated with bowel movements and stool characteristics (changes in the frequency and the appearance of the stool that are features of the irritable bowel syndrome).

General inspection typically does not find changes of the skin and visible mucosa (paleness, jaundice), and a noticeable weight loss. Vital signs (pulse and respiratory rate, blood pressure, body temperature) should note a distinct abnormality.

Abdominal palpation can detect an epigastric pain, and in organic dyspepsia - abdominal masses or enlarged organs (e.g. a hepatomegaly). Rectal examination is performed to find occult gastrointestinal bleeding.

Warning signs ("alarm symptoms") in dyspepsia are severe pain that awakes the patient, fever, weight loss, jaundice, paleness, diaphoresis (sweating), signs of the gastrointestinal bleeding, dysphagia, recurrent vomiting, palpated epigastric mass, hepatomegaly, anemia, and leukocytosis.

If these symptoms and present, the patient should be examined by proper laboratory-instrumental studies and be consulted by surgeon for exception "acute abdomen".

Laboratory and instrumental examination is performed to *confirm or exclude an organic dyspepsia.*

Standard laboratory tests include complete blood count, blood serum levels of the amylase and lipase (in suspected pancreatitis), bilirubin, AST, ALT, GGT and ALP (in suspected hepatobiliary pathology).

Standard instrumental studies include *abdominal ultrasonography* (for suspected abdominal mass, pathology of the hepatobiliary system and pancreas), and upper gastrointestinal endoscopy (for suspected mucosal pathology of the esophagus, stomach and duodenum).

Screening for H. pylori infection is recommended in absence other specific findings to explain symptoms of the dyspepsia (see Chapter 16. Section 16.2.3 Diagnosis of the stomach Helicobacter Pylori (HP) infection).

Diagnosis of the dyspepsia is founded on the assessed data of taking complaints and anamnesis (presence of the recurrent or chronic epigastric pain or burning, early satiety and/or epigastric discomfort) and laboratory- instrumental studies.

Organic dyspepsia presents if laboratory- instrumental studies detects structural and/or biochemical signs of the underlying disease that generates dyspeptic symptoms.

The functional dyspepsia is confirmed if dyspepsia lasting ≥3 months (with onset of symptoms ≥6 months prior to diagnosis) with no identified organic causes. Diagnostic criteria are following:

1. One or more of the following:
   - Bothersome postprandial fullness (i.e., severe enough to impact on usual activities);
   - Bothersome early satiation(i.e., severe enough to prevent finishing a regular size meal);
   - Bothersome epigastric pain (i.e., severe enough to impact on usual activities);
   - Bothersome epigastric burning (i.e., severe enough to impact on usual activities);
2. No evidence of structural disease (including at upper endoscopy) that is likely to explain the symptoms.

H. pylori infection-associated dyspepsia is confirmed if the patient with dyspeptic symptoms after negative laboratory-instrumental studies except for the positive H. pylori (HP) tests has passed HP eradication therapy succeeded by a sustained symptomatic relief.

17.6. Syndrome of the slow evacuation of the intestinal contents (Constipation)

Definition: Constipation (obstipation) is an infrequent passage of the feces (not more than 3 times a week) with a hardness of the stool or a feeling of the incomplete stool evacuation.

Classification and causes of the constipation

1. *According to causes and pathogenesis –*

a) functional constipation - spastic and atonic constipations;

b) organic constipation.

2. *According to course* - acute (acute onset) and chronic constipation.

Organic constipation *is usually associated with mechanical colonic obstruction*, such as narrowing of the intestinal lumen due to a tumour, scar, adhesion, stricture, and also structural abnormalities in the intestine (megacolon, dolichosigmoid, megasigmoid, diverticulosis, ischemic and inflammatory pathology).

Functional constipation is subdivided into:

- *alimentary constipation* - due to low-fiber and sugar-free diets, which leaves small residue and does not normally stimulate peristalsis of the intestine by irritating its nervous receptors;
- *neurogenic constipation* - due to (1) autonomic neuropathy (dysfunction of the intramural nervous apparatus of the intestines or vagus nerve); (2) pathologic reflexes on the intestinal motor function from the another affected organ (cholecystitis, adnexitis, prostatitis, etc.), (3) organic affections of the central nervous system (brain tumours, encephalitis,

parkinsonism, multiple sclerosis, spinal cord injury, posterior spinal sclerosis, etc.);

- *constipation due to psychiatric disorders* (in depressive syndrome);
- *toxic constipation* due to exogenous (in poisoning by lead, mercury, thallium; nicotine poisoning in smokers) and endogenous intoxication (in uremia);
- *drug-induced constipation* due to intake anticholinergics, cations (iron, aluminum, calcium, barium, bismuth), opioids, calcium channel blockers, general anesthetics, cholestyramine, antidepressants, tranquilizers and sedatives; chronic laxative abuse etc.;
- *constipation due to the endocrine etiology and metabolic disorders* - in thyroid or pituitary hypofunction, diabetes mellitus, hypercalcemia;
- *constipation due to functional intestinal disorders* - irritable bowel syndrome, intestinal motor dysfunction of another affected organ (in gastroduodenal peptic ulcer, cholecystitis, adnexitis, prostatitis, etc.);
- *constipation due to disorders of the rectal evacuation* - pelvic floor dysfunction, descending perineum syndrome, rectal mucosal prolapse, anal sphincter spasm (anal fissure, painful hemorrhoid);
- *constipation due to generalized muscle disease* - progressive systemic sclerosis, generalized myopathy;
- *constipation due to lack of the physical exercise* (in hypodynamia);
- *constipation in pregnancy*;
- *constipation due to flaccidity of the abdominal wall*.

Symptoms of the constipation must exists for the last 3 months with symptom onset at least 6 months prior to diagnosis.

Diagnostic criteria of the functional constipation must include two or more of the following:

- Straining during more than ¼ (25%) of defecations;
- Lumpy or hard stools (Bristol Stool Form Scale 1-2) more than ¼ (25%) of defecations;
- Sensation of incomplete evacuation more than ¼ (25%) of defecations;
- Sensation of the anorectal obstruction/blockage more than ¼ (25%) of defecations;
- Manual maneuvers to facilitate more than ¼ (25%) of defecations (e.g., digital evacuation, support of the pelvic floor);
- Fewer than three SBM per week;
- Loose stools are rarely present without the use of laxatives;
- Insufficient criteria for irritable bowel syndrome.

Acute constipation occurs when a sudden change in bowel habits produces infrequent stools or hard stools that are difficult to pass. Acute constipation

suggests an organic cause, whereas chronic constipation may be organic or functional.

Acute constipation can be due to –

- *mechanical bowel obstruction* (ileus, hernia, adhesions, a fecal impaction) that should be suspected in constipation for only hours or a few days;
- *adynamic ileus* that accompanies acute intra-abdominal disease (e.g., peritonitis, diverticulitis), various traumatic conditions (e.g., head injuries, spinal fractures), major acute diseases (e.g., sepsis), may follow general anesthesia;
- *strict bed regime* especially among the elderly patients;
- *drug-induced constipation* which can be caused by medications that act in the intestinal lumen (aluminum hydroxide, bismuth salts, iron salts, cholestyramine), anticholinergics, opioids, tranquilizers and sedatives.

Chronic constipation is a state when a change of the bowel habit persists for weeks or occurs intermittently with increasing frequency or severity (>4 weeks in duration). *Colonic tumors and other causes of partial obstruction should be suspected*. Chronic constipation is particularly common among the elderly patients because of the age-related decrease intestinal motility, low-fiber diets, lack of the exercise, and use of the constipating medications.

Clinical picture

The most typical *complaints* if constipation:

- straining, hard stools or *scybala* (hard, inspissated "sheep's" stools);
- nonproductive calls ("want to but can not*", tenesmus*);
- infrequent stools, or incomplete evacuation;
- less often than 3 bowel movements (defecations) per week;
- daily stool weight ≤35g/day.

Loose stools are rarely present without use of the laxatives. Fecal impaction is particularly common in the bedridden elderly patients, and after barium X-ray contrast (been given by mouth or enema).

A reduced amount of the stool suggests an obstructive lesion in the distal colon. Local anorectal conditions (e.g., anal fissures) cause a rectal pain or bleeding. 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.

Constipation can be associated with many other 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 the abdomen can sometimes reveal a palpatory tenderness and mass due to neoplasm or solid impact feces. Constipation is accompanied

usually by meteorism. Auscultation of the abdomen may detect diminished rate and loudness or absence of the intestinal peristalsis sounds.

Rectal digital examination should be performed to find local anorectal lesions which can cause a pain or bleeding - anal fissures, strictures, hemorrhoids, or masses (including fecal impaction).

*Warning signs ("alarm symptoms") in constipatio*n are weight loss, bloated tympanic abdomen (a marked meteorism), vomiting, blood in the stool, recent onset or worsening of the severe constipations in elder patients.

If these symptoms and signs present, the patient should be examined by the proper laboratory-instrumental studies and be consulted by surgeon for exception "acute abdomen".

Laboratory instrumental examination

X-ray series with barium sulphate suspensions show 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.

Anorectal manometry by assessing various anorectal pressure relationships can reveal how well the rectum and anal sphincters work together to eliminate a stool.

Diagnosis of the constipation is based on typical complaints and history; data of endoscopy (rectosigmoidoscopy, colonoscopy) and/or X-ray study (barium enema, barium passage), anorectal examinations (digital rectal examination is necessarily), and stool examination for occult blood.

17.7. Syndrome of the accelerated evacuation of the intestinal contents (Diarrhea)

Definition: **Diarrhea** is a passage of the abnormally liquid or unformed stools at an increased frequency (≥3 times a day) and/ or increased weight (≥300 g/day).

Etiology and pathogenesis of the 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.

Causes of the osmotic diarrhea:

- sugar intolerance, including lactose intolerance caused by lactase deficiency;
- intake of the poorly absorbed salts (Mg sulfate and oxide, Na phosphates) as laxatives or antacids;

- ingestion of the large amounts of the hexitols (e.g., sorbitol, mannitol) as sugar substitutes ("dietetic food" or "chewing gum" diarrhea) and too much of the certain sweet fruits and vegetables;
- viral infection, protozoa invasion (Lambliosis).

Secretory diarrhea occurs when the small and large bowel secrete more electrolytes and water than they can absorb.

Causes of the secretory diarrhea:

- intestinal infection with bacterial toxins (e.g., *E.coli, V. cholerea, Clostridium difficile, Salmonellosis, Shigellosis,* etc.) and enteropathogenic viruses;
- bile acids (e.g., after ileum resection);
- unabsorbed dietary fat (e.g., in steatorrhea, malabsorption syndrome),
- some drugs (e.g., anthraquinone cathartics, castor oil, prostaglandins, quinidine, quinine, colchicine, orlistat);
- peptide hormones in various hormone-active tumors of the gastrointestinal tract and pancreas, including *vipomas* (vasoactive intestinal peptide), *gastrinomas* (gastrin), *mastocytosis* (histamine), and *carcinoid tumors* (histamine, serotonin, and polypeptides), and in *medullary carcinoma of the thyroid gland* (calcitonin and prostaglandins);
- microscopic colitis (collagenous or lymphocytic colitis.

Exudative diarrhea occurs in intestinal mucosa inflammation, swelling and ulceration, resulting in exudation of the blood serum, blood proteins, mucins and cellular components. An exudate and mucus increase fecal bulk and fluid content.

Causes of the exudative diarrhea:

- intestinal mucosa diseases (e.g., Crohn's disease, ulcerative colitis, tuberculosis, lymphoma, cancer);
- enteroinvasive infections (*E.coli*, *Shigellosis*, *Yersiniosis*, *Salmonellosis* etc.).

Decreased absorption time diarrhea occurs when intestinal content is not in contact with an absorptive surface of the gastrointestinal tract for ample time.

Causes of the decreased absorption time diarrhea are factors that decrease contact time of the absorption surface with intestinal contents:

- gastrointestinal surgical operations - small- or large-bowel resection, gastric resection, pyloroplasty, vagotomy, surgical bypass of intestinal segments;
- drugs (e.g., Mg-containing antacids, laxatives) or humoral agents (e.g., prostaglandins, serotonin) that accelerate an intestinal transit by the smooth muscle stimulation.

Malabsorption-related diarrhea *is due to osmotic or secretory mechanisms.* The *osmotic mechanism* presents in the carbohydrate malabsorption

if the unabsorbed material is abundant, water-soluble, and of low molecular weight. *Secretory mechanism* presents in the fat malabsorption because fatty acids and bile acids act as secretagogues and produce the secretory diarrhea.

In generalized malabsorption (e.g., *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

1. According to course – *acute dirrhea* if <2 weeks, *persistent diarrhea* if 2 to 4 weeks, and *chronic diarrhea* if >4 weeks in duration.
2. According to etiology - infectious, drug-induced, food-related, postsurgical, inflammatory, transit-related, and psychologic causes diarrhea.
3. According to pathogenesis – osmotic, secretory, exudative, decreased absorption time, malabsoption-related diarrhea.
4. Clinical variants – enteral, colitis, gastric, pancreatic diarrhea.

Clinical picture

The main symptoms of the diarrhea are increased frequency, fluid content, and increased volume of the stool (usually >300 ml per a day).

Associated symptoms are an abdominal pain, abdominal bloating, flatulence, nausea, vomiting, and weight loss may occur. Rectal urgency or tenesmus may be if diarrhea connected with pathology of the sigmoid colon and rectum.

Physical examination may show changes in general state of the patient in case of the severe acute or prolonged diarrhea (loss of the body mass; dry skin and visible mucosa, diminished turgor of the skin due to dehydration). Examination of the abdomen can detect meteorism and a palpatory tenderness. Auscultation reveals an increased rate of the intestinal peristalsis sounds.

The digital rectal examination is important in case of the rectal urgency or tenesmus.

The warning signs ("alarm symptoms") are chronic character of the diarrhea, weight loss, fever, blood or pus in the stool, signs of dehydration (thirst; dryness of the mouth, lips and eyes; oliguria, dark-yellow urine). These symptoms and signs are suspicious for serious course of the disease and organic causes of the diarrhea.

Laboratory-instrumental examination

Patients with prolonged or severe diarrhea should pass a *rectosigmoidoscopy and colonoscopy examination with a biopsy of the rectal mucosa* for histologic examination (in infectious, ulcerative, microscopic colitis).

X-ray series with barium sulphate can show an increased intestinal peristalsis.

Coprology study.

Macroscopy study of stool can show a changed consistency, color and volume of the feces, blood in the stool, an evidence of the steatorrhea (fatty stools with a foul odor), mucus, pus, etc.

Microscopy may find the presence of leucocytes (indicating ulceration or bacterial infection), undigested fat, starch, meat and cellulose fibers, and parasitic infestation (e.g., amebiasis, giardiasis). *Stool pH* (normally > 6.0) is decreased by bacterial fermentation of the unabsorbed carbohydrates and protein in the colon. Alkalinization of the stool can be due to bacterial fermentation of the undigested protein. With large volume, stool electrolytes (sodium, potassium, chloride) can be measured to determine if diarrhea is osmotic or secretory.

Fecal leukocytes and/or fecal calprotectin are tests for intestinal inflammation in patients with IBD (inflammatory bowel diseases).

Studies of the stool may show the laboratory sings of *coprology syndromes* according to the affected organ or department of the digestive system. In diseases of the small intestine, there are voluminous, watery or fatty stools. In colonic diseases, stools are frequent, sometimes small in volume, and possibly accompanied by the blood, mucus, and pus.

Stool culture, Clostridium difficile toxin assay, examination feces to parasites and helminthes ova may reveal etiology of diarrhea.

***Diagnosis of the diarrhea* i**s based on (1) typical complaints and history, (2) data of coprology examination, (3) endoscopy (rectosigmoidoscopy, colonoscopy); and (4) stool culture, examination for occult blood, helminthes, parasites, Clostridium difficile toxin assay.

Clinical-laboratory variants of the diarrhea

Enteral diarrhea is characterized by stool frequency up to 4-6/day, a profuse discharge with remains of the undigested food; steatorrhea may be; paraumbilical pains – often. This is typical for diarrhea related to affection of the small intestine (Table 17-2).

Colitic diarrhea is characterized by stool frequency up to 10-15/day, scanty excrements with admixtures of the 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 the large bowels. Involvement of the rectal mucosa can cause urgency and increased stool frequency because the inflamed rectum is more sensitive to distention.

Gastric diarrhea is characterized by stool frequency up to 4-6/day, fluid excrements with remains of the undigested food and mucus, a putrefactive smell. Melena may be due to gastric hemorrhage. Epigastric pains may be often. This variant of the diarrhea may be in the stomach achlorhydria and achylia (chronic gastritis A, diffuse atrophic gastritis), diffuse tumor of the stomach, after stomach surgery.

Table 17-2. Clinical variants of the diarrhea

Variant	Characteristics
Enteral	Stool frequency – up to 4-6/day. Profuse discharge with remains of undigested food. Steatorrhea. Paraumubilical pains - often
Colitic	Stool frequency – up to 10-15/day. Scanty excrements with admixtures of mucus and blood. Bolus-like feces, scybalous ("sheep's") stool. It is often accompanied by pains along the rectum
Gastric	Stool frequency – up to 4-6/day. Fluid excrements with remains of undigested food and mucus, putrefactive odour. Melena – if gastric hemorrhage. Epigastric pains - often
Pancreatic	Stool frequency – up to 4-6/day. Polyfecalia, liquid or semi-liquid stool, yellow-grey colour, steatorrhea, putrefactive odour. It is often accompanied by belting pains in abdomen, meteorism, weight loss

Pancreatic diarrhea is characterized by stool frequency up to 4-6/day, polyfecalia, liquid or semi-liquid stool of the yellow-grey colour, steatorrhea, putrefactive smell. It is often accompanied by belting pains in abdomen, meteorism, weight loss. This variant of the diarrhea is caused by pancreatic secretory insufficiency (in chronic pancreatitis, cystic fibrosis of the pancreas, tumour of the pancreas body).

Complications of the diarrhea may be dehydration, electrolyte loss (Na, K, Mg, Cl), metabolic acidosis (due to loss of HCO_3^-). Vascular collapse may develop rapidly in patients who are very young or old, or have severe diarrhea (e.g., those with cholera). Electrolyte loss after prolonged diarrhea may cause convulsions.

17.8. Syndromes of the inadequate absorption (maldigestion and malabsorption)

Syndromes of the inadequate absorption (maldigestion and malabsorption) include symptoms and signs resulting from inadequate intestinal assimilation of dietary substances due to defects in digestion, absorption, or transport.

Mechanisms of the inadequate absorption

There are three phases of the digestion and absorption:

(1) *intraluminal hydrolysis of fats, proteins, and carbohydrates by enzymes*. An effective hydrolysis of fats can be in strict presence of bile salts that intensify the fat solubilization;

(2) *digestion by brush border enzymes and end-products absorption into the intestinal mucosa*;

(3) *lymphatic transport of nutrients into circulation*.

The mechanism may be direct impairment of the absorption (*malabsorption*) or abnormalities of the digestion (*maldigestion*) and transport that lead to impaired absorption. Malabsorption and maldigestion may occur for macronutrients (e.g., proteins, carbohydrates, fats) and micronutrients (e.g., vitamins, minerals), or both, or for specific carbohydrates, fats, or micronutrients (for example, calcium, iron, cobalamin, folic acid, etc.). *Malabsorption and maldigestion can be the cause of the chronic diarrhea, gastrointestinal symptoms, and malnutrition.*

Malabsorption and maldigestion are pathophysiological different, hence these processes are interdependent, so that in clinical practice the term ***malabsorption*** is usually applied to cover disorders in either process.

17.8.1. Maldigestion syndrome

Definition: Maldigestion syndrome is a set of symptoms associated with impaired digestion of food components in the gastrointestinal tract due to enzymatic insufficiency or other causes.

Maldigestion is a disordered cleavage of the nutrients (proteins, fats, carbohydrates) to the components necessary for absorption (monoglycerides, fatty acids, amino acids, monosaccharides, etc.). The intestinal digestion proceeds in several stages: cavitary digestion, parietal digestion, and intracellular digestion.

Classification of the maldigestion syndrome

1. *According to causes, the syndrome can be:*

- *congenital (primary) maldigestion* due to primary enzymopathy (e.g. disaccharides insufficiency);
- *acquired (secondary) maldigestion* due to secondary enzymopathy (in the background of acquired diseases of the digestive organs, mainly small intestine, pancreas).

2. *According to pathophysiological mechanisms*, four variants of the maldigestion syndrome are conventionally distinguished (Table 17-3):

- dysfunction of the cavitary digestion due to enzymatic (gastrogenic, pancreatogenic, enterogenic) insufficiency;

Table 17-3. Pathophysiological variants of the maldigestion syndrome

Variants	Mechanisms	Main causes
Dysfunction of the cavitary digestion	enzymatic (gastrogenic, pancreatogenic, enterogenic) insufficiency	chronic atrophic gastritis with secretory insufficiency, gastric cancer, after gastric resection, stomach acid hypersecretion (inactivate pancreatic enzymes), chronic pancreatitis with secretory insufficiency; excessive nutrient consumption
	changes in gastrointestinal transit	gastrointestinal tract stenosis; gastro-intestinal functional disorders, passed surgical operations (e.g., resection of stomach or intestine)
	bile acid deficiency	in liver cirrhosis, hepatitis, cholangitis, and biliary tract obstruction
Disorders of the parietal digestion	reduced breakdown of food substances on the surface of cell membranes of the intestinal epithelium (due to dystrophy or /and necrosis of enterocytes)	Crohn's disease, gluten enteropathy, sarcoidosis; radiation, ischemic (and other) enteritis; diverticular disease
Intracellular digestion deficiency	primary or secondary enzymopathies	congenital or acquired insufficiency of cellular disaccharidases: lactase, saccharase, maltase (sucrase-isomaltase) and tricalase insufficiency
Combined variant of the maldigestion	combination of several mechanisms	diabetes mellitus, giardiasis, hyperthyroidism, hypogamma-globulinemia, amyloidosis, AIDS, intestinal tuberculosis, carcinoid; lymphatic duct obstruction (e.g., in lym-phangiaectasia, lymphoma); intestinal bacterial overgrowth

- dysfunction of the parietal digestion – due to reduced breakdown of food substances on the surface of cell membranes of the intestinal epithelium;
- dysfunction of the intracellular digestion – due to primary or secondary enzymopathies;
- combined maldigestion – the most common because all forms of digestion are closely interrelated.

Clinical picture

The main clinical manifestations in any form of maldigestion syndrome are abdominal distension, feeling of the heaviness in the abdomen, meteorism and flatulence (due to increased gas formation), stomach gurgling, diarrhea, regurgitation, nausea, decreased appetite, poor tolerance of the food, and pain in the abdominal area. These symptoms occur more frequently in the afternoon, as this time is associated with an intensification of digestive processes.

There are an increased volume of liquid stools, a change in their color and smell, fatty feces (steatorrhea).

Some patients complain of the certain foods intolerance, for example, patients with lactase deficiency can not ingest milk foods. They have abdominal pain and severe diarrhea with watery and foamy stools after drinking milk.

Severe maldigestion syndrome leads to a marked deterioration of the general condition. Malabsorption syndrome develops as the incompletely digested substances are poorly absorbed. Patients note weakness, apathy, a significant weight loss, menstrual disorders. Objective examination shows trophic skin changes (dryness, desquamation, hyperpigmentation in some places), brittle hair and nails, hair loss, hypoproteinemic edema, muscle atrophy.

Laboratory-instrumental examination

Coprology studies reveal increased content of undigested food (*steatorrhea, creatorrhea, and amylorrhea*) in the feces. Stool smear staining with Sudan III is a simple and sensitive screening test for stool fat (*steatorrhea*).

Coprology studies can show a set of laboratory signs which are typical to particular pathology of the digestive apparatus (Table 17-4).

Gastrogenic maldigestion is characterized by presence of the undigested muscles fibres (*creatorrhoea*), connective tissue, and vegetable fibres (cellulose). This is typical to stomach and duodenum secretory insufficiency (in chronic gastritis type A, diffuse atrophic gastritis and duodenatis, gastrectomy).

Pancreatogenic maldigestion is characterized by profuse discharge of the liquid excrements, *polyfecalia*, yellow-grey color, ointment-like consistency of the feces, presence of the neutral fat (*steatorrhea*), *creatorrhea*, and starch grains (*amylorrhea*). These findings may be revealed in the pancreatic secretory insufficiency (chronic pancreatitis, cystic fibrosis of the pancreas, tumor of the pancreas body).

Bile deficiency indigestion is characterized by a grey color of the feces, presence of the fatty acids, steatorrhea, and stercobilin negative test. This is

typical to pathology of the liver and biliary tract (in cholecystitis, cholangitis, liver cirrhosis and hepatitis).

Table 17-4. Coprology signs of the maldigestion syndrome

Maldigestion variants	Characteristics of the stool	Cause
Gastrogenic	undigested muscles fibers (*creatorrhoea*), connective tissue	stomach secretory insufficiency
Pancreatogenic	liquid excrements, *polyfecalia*, yellow-grey color, ointment-like consistency of feces, neutral fat (*steatorrhea*), *creatorrhea*, starch grains (*amylorrhea*)	pancreatic secretory insufficiency
Bile deficiency	grey color, fatty acids, *steatorrhe*a, *stercobilin* negative test,	cholecystitis, cholangitis, biliary cirrhosis
Enteral	yellow loose consistency, *polyfecalia*, leucocytes, epithelial cells, fatty acids crystals, soluble proteins	small intestine inflammation (enteritis)
Iliocecal	mucus, foamy stool, acid smell, undigested cellulose, *amylorrhoea*, iodinophil microflora	enterocolitis, syndrome of the intestinal bacterial overgrowth
Colitis	mucus, bolus-like feces, scybalous ("sheep's") stool, undigested cellulose, leucocytes, erythrocytes, epithelial cells	large intestine inflammation (colitis)

Enteral maldigestion is characterized by the feces of the yellow loose consistency, presence in feces of leucocytes, epithelial cells, fatty acids crystals, soluble proteins. These findings may be in small intestines inflammation (enteritis), deficiency of intestinal enzymes (lactase deficiency), gluten enteropathy, sprue, etc.

Iliocecal maldigestion is characterized by the liquid foamy stool with an acid smell, presence of the mucus, undigested cellulose, amylorrhoea, iodinophil flora. This is typical to inflammation and pathological digestion of carbochydrates and cellulose in ileum and cecum (enterocolitis, intestinal bacterial overgrowth).

Colitis coprology findings are characterized by bolus-like feces, or scybalous ("sheep's") stool with mucus, presence of undigested cellulose,

leucocytes, erythrocytes, epithelial cells. This is typical to inflammation of large intestine (colitis).

Measurement of the *fecal elastase* and *chymotrypsin in the stools* helps in diagnosis of the pancreatic exocrine insufficiency. Both of these enzymes are reduced in pancreatogenic maldigestion, while being normal in intestinal causes.

Carbohydrate intolerance is examined by *Hydrogen (H2) breath tests*. The lactose-hydrogen breath test is useful only to confirm *lactase deficiency*. The glucose-hydrogen and lactulose-hydrogen breath tests are most commonly used in patients with *disaccharidase deficiencies.*

Lactose tolerance test can easily diagnose lactose intolerance. Blood glucose levels (*glycemic curve*) are examined on empty stomach and later in 60 and 120 minutes after the oral administration of the 50 g lactose. An increase in the blood glucose less than 1.1 mmol/l compared to the initial level and the development of symptoms (diarrhea, meteorism, etc.) are diagnostic.

Instrumental diagnostic imaging tests (barium X-rays, CT, MRI, ultrasound) identifies some gastrointestinal anatomic and transit abnormalities that predispose to maldigestion (intestinal diverticula, fistulas, surgical anastomoses, ulcerations, stenosis, and strictures). These imaging studies can also detect hepatomegaly, chronic pancreatitis, other pathologies of the liver, pancreas (cysts, tumors), and biliary tract obstruction.

Endoscopy and biopsy reveals mucosal disease of the stomach and intestines. Atrophic changes in the mucosa of the stomach and proximal parts of the small intestine can be found. *Celiac disease* is characterized by absence of villi and elongated crypts, and increased intraepithelial lymphocytes in the lamina propria. *Dilation and ectasia of the intramucosal lymphatics* are typical in the intestinal lymphangiectasia.

Evaluation of the stomach secretory function helps to clarify the causes of gastrogenic maldigestion (see Chapter 16. Subsections 16.2.2.2. Intragastric pH-metry, 16.2.2.3. Blood serum tests for assessment of the stomach secretion).

Decrease in gastric pH >3.5-4.0 (hypoacidity and anacidity) is one of the causes of the gastric enzymatic insufficiency due to impaired conversion of pepsinogen to active pepsin.

Elevated serum gastrin levels in combination with decreased serum pepsinogen PGI and PGII levels are found in severe atrophic gastritis and other conditions (after gastric resection, gastrectomy; stomach cancer; during acid-suppression therapy) characterized by hypoacidity and anacidity, and gastrogenic maldigestion.

Hypersecretion of the gastric acid (*hyperacidity*) can lead to pancreatogenic maldigestion due to inactivation of pancreatic enzymes (e.g., in peptic duodenal ulcer, Zollinger-Ellison syndrome).

Diagnosis of the maldigestion syndrome is based on:

- typical clinical picture (e.g., diarrhea, meteorism, the food intolerance) confirmed by the findings of coprology studies (steatorrhea, creatorrhea, and amylorrhea);
- tests to identify the causes of the maldigestion:

- gastrointestinal endoscopy and biopsy (atrophic changes in the mucosa of the stomach and proximal parts of the small intestine);

- decrease of the fecal elastase and chymotrypsin in pancreatogenic maldigestion;

- hydrogen (H2) breath tests and glycemic curve for disaccharidase (lactase, saccharase, maltase) deficiencies;

- intragastric pH >3.5-4.0 (hypoacidity and anacidity) and decreased serum pepsinogens in gastrogenic maldigestion;

- instrumental imaging tests (barium X-rays, CT, MRI, ultrasound) can identify gastrointestinal anatomic and transit abnormalities, hepatobiliary and pancreas pathology that predispose to maldigestion.

17.8.2. Malabsorption syndrome

Definition: Malabsorption syndrome is a set of symptoms and signs caused by an impaired absorption of food substances from the small intestine. *It is manifested by chronic diarrhea, usually combined with maldigestion syndrome, and it results in severe nutritional and metabolic disorders.*

There are *total malabsorption* with impaired absorption of almost all nutrients (proteins, carbohydrates, fats, vitamins, minerals), and *partial (isolated) malabsorption* with impaired absorption of only certain nutrients.

There is a *primary (hereditary) malabsorption syndrome*, when the congenital deficiency of the specific carriers and enzymes cause malabsorption of the tryptophan, gluten, disaccharidases, etc. *Secondary malabsorption syndrome* occurs against the background of the severe pathology of the digestive system, mainly small intestine.

The *basic pathophysiological mechanisms of the malabsorption syndrome*:

- reduced total absorptive surface of the small intestine;
- decreased absorptive capacity of the small intestine;
- accelerated intestinal motility;
- impaired mesenteric circulation.

Classification of the inadequate absorption (according to causes)

I. Primary (hereditary) malabsorption syndrome: glucose-galactose malabsorption, lactase deficiency, abetalipoproteinemia, cystinuria, Hartnup disease (malabsorption and increased renal excretion of tryptophan and other amino acids); congenital lymphangiectasia, Milroy disease (congenital lymphedema).

II. Secondary malabsorption syndrome:

- *defective intraluminal hydrolysis* – pancreatic insufficiency (chronic pancreatitis, cancer of the pancreas, etc.), stomach acid hypersecretion (due to inactivation of the pancreatic enzymes), stomach achlorhydria (atrophic gastritis, stomach cancer), bile acid insufficiency (in liver and biliary tract diseases);
- *inadequate rapid gastric emptying* – Billroth-II gastric resection, gastrectomy, gastrocolic fistula, gastroenterostomy;
- *small intestines diseases* –

a. intestinal wall diseases – Cronh´s disease, enteritis, amyloidosis;

b. mucosal pathology – gluten enteropathy (celiac disease), tropical sprue, lactase deficiency, immunoglobulin A (IgA) deficiency;

- *inadequate absorption surface* – short bowel syndrome, ileum resection, jejunocolic fistula;
- *lymphatic obstruction* – intestinal lymphoma, tuberculosis, Whipple´s disease, intestinal lymphangiectasia;
- *intestinal bacterial overgrowth* – small intestine diverticula, intestinal bacterial overgrowth syndrome (SIBO), enterocolic fistula, scleroderma;
- *miscellaneous causes* – parasites, drugs (wide-spectrum antibiotics), toxic (alchohol), radiation enteritis, ischemic (mesenteric vascular insufficiency), vasculitis, endocrine (diabetes mellitus, thyrotoxicosis, Addison disease).

Clinical picture

Clinical picture of the severe malabsorption syndrome include *local enteral manifestations* (due to effect of the unabsorbed substances) and *general manifestations* (due to nutritional deficiencies).

*Local enteral manifestation*s are an intolerance to a number of foods, flatulence, an abdominal rumbling, feelings of the heaviness and distension in the abdomen, persistent diarrhea with polyphecalia, signs of the steatorrhea, creatorrhea, and amylorrhea. Patients complain of the spastic and distensional pains, localized mainly around the umbilicus.

General manifestations include all types of metabolic disorders. Disorders of the protein, fat, carbohydrate metabolism cause gradual wasting, general weakness, reduced work capacity, mental disorders, decreased immunological reactivity, multiple endocrine deficiencies (hypocorticism, amenorrhea, impotence, etc.); polyhypovitaminosis, including fat-soluble vitamins (A, D, E, K) (Table 17-5).

There are progressive atrophy of the subcutaneous fat and muscles, dystrophic changes of the skin (dryness, peeling, hyperpigmentation in some places), hair loss, brittle nails, and in the internal organs with their subsequent dysfunction. Hypoproteinemic edema develops in the presence of the hypoproteinemia (below 40-50 g/1) and hypoalbuminemia.

The characteristic manifestations of the mineral malabsorption are osteoporosis (pains in bones, pathologic fractures due to vitamin D and calcium deficiencies) and carpopedal spasm (involuntary muscle contractions in hands and feet due to calcium and magnesium deficiencies), and angular stomatitis (due to iron and/or vitamin B_2 deficiency).

Table 17-5. Clinical-laboratory manifestations of the malabsorption syndrome

Clinical-laboratory manifestations	Malabsorbed nutrients
Diarrhea, including:	
creatorrhea	Muscle fibers
steatorrhea	Fats
amylorrhea	Starch
Body weight loss, including:	
skeletal muscle loss	Protein
subcutaneous tissue	Fats
Failure of the wound healing, immunodeficiency disorder (infectious complications)	Protein, vitamin C, zinc
Anemia (hypochromic, microcytic)	Iron
Anemia (macrocytic)	Vitamin B_{12}, folate
Bleeding, bruising, petechiae	Vitamins K and C
Carpopedal spasm (involuntary muscle contractions in hands and feet)	Calcium, magnesium
Edema	Protein, albumin
Glossitis	Vitamins B_1, B_2, B_3, B_6, and B_{12}, folate, nicotinic acid, and iron
Cheilosis (angular stomatitis)	Vitamins B_2, and iron
Koilonychia (spoon nail)	Iron
Night blindness	Vitamin A
Keratinization of the skin and mucous membranes (dryness, thickening)	Vitamin A
Pain in limbs, bones, pathologic fractures	Potassium, magnesium, calcium, vitamin D
Peripheral neuropathy (numbness, tingling, loss of the sensation in the arms and legs, a burning sensation in the feet or hands, etc.) and central nervous system dysfunction (lethargy; sleepiness, mental depression, psychiatric disturbance)	Vitamins B_1, B_6, B_{12}

Laboratory-instrumental examination

Biochemical analysis of the blood detects hypoproteinemia, hypoalbuminemia; hypocholesterolemia, hypocalcemia, and moderate hypoglycemia in the malabsorption syndrome. Serum iron, vitamin B_{12} and folate levels are examined in case of the anemia.

Complete blood count – hypochromic microcytic anemia (due to predominant iron deficiency). Hyperchromic macrocytic anemia occurs in vitamin B12 and folate malabsorption.

Coprology studies finds steatorrhea, creatorrhea, and amylorrhea.

Fecal elastase and chymotrypsin (both pancreas proteases) levels can be used to distinguish between pancreatogenic and enterogenic malabsorption.

Serologic tests (specific for malabsorption syndrome) – serum antigliadin and anti-endomysial antibodies for the diagnosis of celiac disease; *serum immunoglobulin A (IgA)* to exclude IgA deficiency.

Gastrointestinal endoscopy and biopsy can reveal atrophy of the gastrointestinal mucosa, signs of the celiac disease (absence of villi, elongated crypts, and increased intraepithelial lymphocytes in the lamina propria), and an intestinal lymphangiectasia.

Instrumental diagnostic imaging tests (barium x-rays, CT, MRI, ultrasound) can indicate anatomic and mucosal abnormalities of the digestive system (e.g., gastric and intestinal resections, gastrectomy, gastrocolic fistula, gastroenterostomy, hepatomegaly, biliary tract obstruction, chronic pancreatitis) that predispose to malabsorption syndrome.

Intestinal absorption study includes a determination of the unabsorbed nutrients by the comparative study of the chemical composition of the food and stools during a certain period of the time and *breath tests* (see Chapter 17. Section 17.3.3. Breath tests).

The *Schilling test* uses oral radiolabeled cyanocobalamin to assess malabsorption of the vitamin B_{12}. Its 4 stages determine whether the deficiency results from pernicious anemia, pancreatic exocrine insufficiency, bacterial overgrowth, or ileum disease.

The *selenium-75–labeled homocholic acid taurine (SeHCAT) test* can be done to diagnose bile acid malabsorption, which may occur with diseases of the terminal ileum (e.g., Crohn disease, extensive resection of terminal ileum).

Disaccharides absorption can be assessed by the glycemic curve. The blood glucose concentration is examined before the saccharose (or lactose, or maltose) 50 g intake on an empty stomach and 15, 30 and 60 minutes later. If the glucose level has not increased, there is a deficiency of the corresponding enzyme and malabsorption syndrome.

Diagnosis of the malabsorption syndrome is based on-

- typical clinical picture confirmed by the findings of laboratory-instrumental examinations such as blood biochemical tests

(hypoproteinemia, hypocholesterolemia, hypoglycemia, and other tests due to malabsorption);

- coprology studies (steatorrhea, creatorrhea, and amylorrhea);
- causes of the malabsorption should be found by instrumental imaging tests (barium x-rays, endoscopy and biopsy, CT, MRI, ultrasound), or other tests based on findings of the unabsorbed nutrients.

Course and prognosis of the syndrome depend on the underlying disease, an opportunity of the effective treatment, and severity of complications (malnutrition, hypovitaminosis, mineral metabolism disorders, etc.).

17.9. The key points on the theme "Clinical-laboratory Syndromes of the Gastrointestinal Tract Diseases"

Abdominal pain is a non-specific syndrome of many diseases. There are three groups of the syndrome causes: abdominal organs pathology, systemic diseases and conditions with severe intoxication (e.g., renal failure, decompensated endocrine pathology, cardiovascular failure), and radiating pain in diseases of organs localized outside the abdominal cavity (e.g., myocardial infarction, pleurisy, renal colic, peripheral nervous system pathology).

The pain localization depends on the position of the affected organ. Accompanying symptoms can be nausea, vomiting, meteorism, diarrhea, constipation, hyperthermia, jaundice, gastrointestinal bleeding.

Gastrointestinal (GI) bleeding can originate from any part of the gastrointestinal tract. GI bleeding may be acute and chronic, evident and occult. Clinical manifestations of the GI bleeding depend on the site, rate and volume of the blood loss. *Common clinical features of the blood loss*: dizziness, weakness, syncope, pallor; arterial hypotension, tachycardia, filiform pulse. *Standard laboratory tests* are complete blood count, and fecal occult blood analysis. Endoscopy studies (esophagogastroduodenoscopy, colonoscopy) are indicated in case of the positive fecal occult blood test.

Clinical syndromes of the gastrointestinal tract dysfunction are dysphagia, rumination syndrome, dyspepsia, syndromes of the inadequate digestion and absorption (maldigestion and malabsorption), slow evacuation of intestinal contents (constipation), accelerated evacuation of intestinal contents (diarrhea. Clinical manifestations of these syndromes depend on localization of the affected department and disordered functions of the digestive system.

Upper gastrointestinal syndromes (dysphagia, rumination, dyspepsia) should be evaluated by esophagogastroduodenoscopy and biopsy (for mucosal pathology of the esophagus, stomach and duodenum), screening tests for H. pylori infection, and an abdominal ultrasonography can detect suspected an abdominal mass, pathology of the hepatobiliary system and pancreas. Esophageal manometry, pH-metry monitoring and barium X-ray can detect esophageal motility disorders and gastroesophageal reflux.

Syndromes with predominantly intestinal disorders (maldigestion and malabsorption, constipation, diarrhea) should be confirmed by blood biochemical tests (hypoproteinemia, hypocholesterolemia, hypoglycemia, and other tests due to malabsorption), coprology studies (*steatorrhea, creatorrhea, and amylorrhea*) or other tests based on findings of the unabsorbed nutrients (e.g. breast tests). Instrumental diagnostic imaging tests (barium x-rays, endoscopy and biopsy, CT, MRI, ultrasound) can detect anatomic and mucosal abnormalities of the gastrointestinal tract.

17.10. Assessment tests on the theme "Clinical-laboratory Syndromes of the Gastrointestinal Tract Diseases"

1. Dysphagia means:
1. difficulties at food passage via esophagus;
2. eructation by air and eaten food;
3. diarrhea;
4. vomiting;
5. heartburn.

2. Melena (black tarry-like stool) is typical in:
1. stomach bleeding;
2. small intestines bleeding;
3. bleeding hemorrhoids;
4. sigmoid colon bleeding;
5. cecum hemorrhoids.

3. Specify signs of the gastric bleeding:
1. visible blood in the stool;
2. pallor;
3. melena;
4. "coffee grounds" color of the vomiting content;
5. arterial hypertension.

4. Signs of the gastrointestinal bleeding:
1. coffee-grounds vomiting;
2. melena;
3. blood-streaked stool;
4. arterial hypotension;
5. acholia.

5. Possible localization of the pain in a stomach pathology:
1. epigastric region;
2. left hypochondrium;

3. right hypochondrium;
4. mesogastrium;
5. hypogastrium.

6. Typical localization of the pain in pathology of intestines:
1. transverse colon – hypogastrium;
2. cecum – right flank;
3. jejunum – mesogastrium;
4. sigmoid colon – left ileum;
5. descending colon – left flank.

7. Laboratory and instrumental examination for an abdominal pain evaluation:
1. clinical blood analysis;
2. biochemical blood tests;
3. abdominal ultrasonography;
4. ECG;
5. urinalysis.

8. Organic dysphagia characteristics:
1. gradual and progressive course;
2. nonprogressive course;
3. solid food first passes with difficulty;
4. paroxysmal course;
5. solid food passes more readily than liquids.

9. Diagnosis of the dysphagia is based on:
1. clinical picture;
2. abdominal ultasonography
3. data of barium contrast X-ray examination;
4. esophagoscopy;
5. ECG
6. chest X-ray.

10. Rumination syndrome characteristics:
1. difficulties at food passage via esophagus;
2. repeated effortless regurgitation of the food after eating;
3. coffee-grounds vomiting;
4. air regurgitation;
5. vomiting with indigested food.

11. Symptoms of the dyspepsia include:
1. epigastric pain;

2. postprandial fullness
3. diarrhea;
4. nausea;
5. early satiation.

12. Functional dyspepsia is confirmed by such data as:

1. dyspepsia lasts ≥3 months (with onset of symptoms ≥6 months prior to diagnosis);
2. no identified organic causes;
3. mucosal pathology of the esophagus, stomach and duodenum;
4. heartburn;
5. changes in the frequency and the appearance of the stool.

13. Syndrome of the slow evacuation of the intestinal contents (constipation) characteristics:

1. infrequent passage of the feces (not more than 3 times a week);
2. everyday dense stool;
3. a hardness of the stool;
4. feeling of the incomplete stool evacuation;
5. loose stool without use of the laxatives.

14. Syndrome of the accelerated evacuation of the intestinal contents (diarrhea) characteristics:

1. increased frequency (≥3 times a day) of the unformed stool;
2. increased weight (≥100 g/day) of the stool;
3. unformed stool 1-2 times a day;
4. increased weight (≥300 g/day);
5. feelings of the incomplete stool evacuation.

15. Clinical manifestations of the malabsorption syndrome:

1. weight loss;
2. progressive atrophy of the subcutaneous fat and muscles;
3. persistent diarrhea;
4. weight gain;
5. jaundice.

16. Laboratory manifestations of the malabsorption syndrome:

1. hyperglycemia;
2. hypoalbuminemia;
3. hypocholestrolemia;
4. hyperbilirubinemia;
5. hyperkalemia.

17. Coprology study in the malabsorption syndrome detects:
1. proctorrhea
2. steatorrhea;
3. creatorrhea;
4. amylorrhea;
5. hematochezia;

18. Pancreatogenic maldigestion is characterized by:
1. mucus in stool;
2. ointment-like consistency of the feces;
3. steatorrhea;
4. creatorrhea;
5. amylorrhea.

19. Iliocecal maldigestion is characterized by:
1. steatorrhea;
2. acid smell of the stool;
3. undigested cellulose;
4. creatorrhea;
5. amylorrhea.

20. Colitis maldigestion is characterized by:
1. creatorrhea;
2. amylorrhea;
3. mucus in stool;
4. "sheep's" stool;
5. leucocytes, erythrocytes, epithelial cells in the stool;
6. ointment-like consistency of the feces.

21. Gastrogenic maldigestion is characterized by:
1. creatorrhea;
2. amylorrhea;
3. mucus in stool;
4. undigested muscle fibers in the stool;
5. leucocytes, erythrocytes, epithelial cells in the stool.

22. Bile deficiency maldigestion is characterized by:
1. creatorrhea;
2. steatorrhea;
3. grey colour of the feces;
4. stercobilin negative test;
5. leucocytes, erythrocytes, epithelial cells in the stool.

Unit V. Liver and Biliary Tract Examination

CHAPTER 18. Subjective and Objective Examination of Patients with Diseases of the Liver and Biliary Tract

Goals: to enable students to learn -

1. subjective examination (inquiry) of patients with hepatobiliary pathology and interpretation of the obtained results;
2. technique of the general and local survey in patients with hepatobiliary pathology and its diagnostic value;
3. technique and diagnostic value of the percussion and palpation of the liver and spleen.

18.1. Subjective examination (inquiry) of patients with pathology of the liver and biliary tract

Complaints

Patients with disorders of the hepatobiliary system usually complain of the *abdominal pain, dyspepsia, skin itching, jaundice, enlargement of the abdomen, and fever*.

The pain settles in the right hypochondrium and sometimes in the epigastrium, and differs depending on the cause (Table 18-1). The pain is usually boring, or the patient feels pressure, heaviness, or distension in the right hypochondrium. The pain may radiate (by the right phrenic nerve) to the right shoulder, scapula, and in the interscapular space (in chronic cholecystitis, perihepatitis and pericholecystitis, i.e. when the process extends onto the peritoneum overlying the liver and the gallbladder, and also in rapid and considerable enlargement of the liver which causes distension of Glisson's capsule). The pain usually becomes more severe in deep breathing, with adhesions of the liver or the gallbladder to the neighboring organs. The pain is also intensified when the patient changes his posture, and sometimes during walking.

The biliary, or hepatic, colic is the pain attack in the right hypochondrium. The biliary colic develops suddenly and soon becomes quite severe and unbearable. The pain can spread from the right hypochondrium over the entire abdomen to radiate upwards, to the right, and posteriorly. The biliary colic may continue from several hours to a few days during which pain may subside and then intensify again. Attacks of pain occur mostly in *cholelithiasis* and in *dysfunction of the gallbladder and sphincter of Oddy* due to comparatively rapid distension of the gallbladder in congestion of bile (e.g. due to the obstruction of the common bile duct by a stone). They are provoked by fatty food or by jolting (as in riding). An attack of biliary colic can be attended by subfebrile fever, which

is followed by a slight transient jaundice of the sclera or pronounced jaundice in obstruction of the common bile duct by a stone.

Table 18-1. Basic complaints in hepatobiliary pathology

Complaints	Characteristics	Causes
Pain in the right upper quadrant of the abdomen (right hypo-chondrium and epigastrium)	dull, aching, pulling pain; often irradiation to the right shoulder, scapula, and interscapular space	hepatitis, perihepatitis, pericholecystitis, chronic cholecystitis, congested liver in the heart failure
	sharp, paroxysmal, cutting pain	biliary colic in the acute cholecystitis, cholelithi-asis, and biliary dysfunction
Jaundice (icterus) – yellow color of the skin and visible mucosa	*hepatic (parenchymatous) jaundice* - brown ("beer-like") color of the urine; - pale stool and itching may be	hepatitis, liver cirrhosis, cancer of the liver
	posthepatic (mechanic) jaundice - often after biliary colic; - - skin itching; - - brown color of urine, pale stool	cholelithiasis, cholangitis, cancer of the bile ducts and head of the pancreas
Enlargement of the abdomen	- - accumulation of fluid in abdominal cavity (ascites), meteorism, hepato- and splenomegaly	liver cirrhosis, tumors of the liver and spleen, congested liver
Skin itching	may be with jaundice or in absence of jaundice	hepatitis, liver cirrhosis, cancer of the liver; cholelithiasis, cholangitis, cancer of the bile ducts and the head of the pancreas
Dyspeptic complaints	decreased appetite, aversion to the fat food	hepatitis, liver cirrhosis
	gravity in the right hypochondrium, nausea, bitterness in the mouth after fat, spicy, fried food	chronic cholecystitis and cholangitis, biliary dysfunction
	vomiting	biliary colic in the acute cholecystitis, cholelithiasis
Astheno-neurotic complaints	weakness, depressed mood, insomnia, irritability, decreased working ability, cardialgia	chronic hepatitis, liver cirrhosis
Fever	with chills and profuse sweat	acute cholecystitis, cholangitis, liver abscess
	subfebrile fever	chronic hepatitis, liver cirrhosis, cancer of the liver

Pain developing in dysfunction of the bile ducts (*biliary dysfunction*) is characterized by the absence of the inflammation signs (leukocytosis, ESR, etc.).

Dyspeptic complaints include *decreased appetite*, often *bitter taste* in the mouth, *eructation, nausea, vomiting, distension of the abdomen and rumbling, constipations or diarrhea*. Causes of these symptoms are deranged secretion of bile (and hence impaired digestion of fats in the intestine) and disordered detoxification function of the liver in the diseases of the liver and bile ducts. These complaints are not characteristic of the hepatobiliary diseases and may raise in pathology of other parts of the digestive system (stomach, duodenum, and pancreas).

Fever occurs in the acute inflammation of the gallbladder and bile ducts, in abscess, cirrhosis and cancer of the liver, acute and chronic hepatitis.

Jaundice (icterus) *– a yellow color of the skin and the visible mucosa* due to the accumulation of the bile pigments in the blood and tissues. Jaundice may develop unnoticeably to the patient, and only the surrounding people may pay attention to the icteric coloration of the sclera and then the skin. In other cases, jaundice can develop suddenly or following an attack of the biliary colic (in obstruction of the common bile duct by a stone in cholelithiasis). Jaundice may be acute (in cholelithiasis) or chronic for months or even years, only slightly changing in intensity (in chronic hepatitis and cirrhosis of the liver).

Jaundice can develop with severe itching of the skin, skin hemorrhages and hemorrhages of the nose and the gastrointestinal tract.

There are ***prehepatic (hemolytic), hepatic (parenchymatous) and posthepatic (obstructive) types of jaundice.***

Prehepatic (hemolytic) occurs due to increased breakdown of red blood cells and the release of free bilirubin from them. This condition occurs with hemolytic anemia, poisoning with various toxic substances and poisons, hypothermia, injury, infection. The patient complains of jaundice with pale skin, dark urine and feces. Weakness, drowsiness, dizziness, shortness of breath during physical exertion occur due to anemia. Due to acute development of hemolysis, pains in the bones and muscles appear.

Hepatic (parenchymatous, hepatocellular) jaundice develops due to the damage of the hepatocytes resulting in impaired capture of *free (unconjugated, indirect) bilirubin* and its inadequate combination with glucuronic acid. The content of *free and bound (conjugated, direct) bilirubin* in the blood serum thus increases by 4-10 times. The bound bilirubin appears in the urine. Excretion of *stercobilinogen* (*stercobilin*) with feces also decreases because the amount of bilirubin excreted by the liver into the intestine decreases.

This type of jaundice presents in infections (virus hepatitis, leptospirosis), toxic affections of the liver (poisoning with mushrooms, phosphorus, arsenic and other chemical substances, medicinal preparations included), chronic hepatitis and liver cirrhosis, and in congenital pigmentary hepatosis (*Gilbert syndrome*).

The skin of patients with this jaundice is typically yellow with a reddish tint. Color of the urine becomes dark brown ("beer-like"); pale stool may be. Skin itching is less frequent than in obstructive jaundice because the synthesis of bile acids by the affected liver cells is upset. Symptoms of the pronounced hepatic insufficiency (hepatic failure) may develop in severe course of the disease.

Posthepatic (obstructive, mechanical, surgical) jaundice develops due to the partial or complete obstruction of the common bile duct, resulting in *disordered excretion of the bound (conjugated, direct) bilirubin* with bile into the intestine and reabsorption of bound bilirubin in the blood. The *bound bilirubin content in the blood is as high as 25.0-34.0 mmol/1, and more*.

This occurs mostly due to the compression of the duct from the outside, by a growing tumor (usually cancer of the head of the pancreas, cancer of the major duodenal papilla, etc.), or due to the obstruction by a stone (in cholelithiasis).

Skin and mucosa of patients with posthepatic jaundice are yellow. Later, as bilirubin is oxidized to *biliverdin*, the skin and mucosa turn green and dark-olive. Pronounced skin itching develops because of the accumulation of bile acids. Bound bilirubin in the urine gives it a brown color and bright-yellow foaming. Feces are colorless either periodically (in incomplete obstruction, usually by a stone), or for lengthy periods of the time (in compression of the bile duct by tumor). In complete obstruction of the bile ducts, feces become colorless (*acholic stool*); their color is clayish and grey-white; stercobilin is absent from feces.

Skin itching *attends hepatic and posthepatic jaundice*. It can develop without jaundice, as an early forerunner of the liver disease. *Itching is caused by the accumulation of the bile acids in the blood*, which are otherwise excreted together with bile, or by stimulation of sensitive nerve endings in the skin. Itching is usually persistent and increases during the night sleep (to cause insomnia). Severe itching causes scratching of the skin with its subsequent infection.

Enlargement of the abdomen (sometimes rapid) can be due to the accumulation of the *ascites fluid* in the abdominal cavity (due to the *portal vein hypertension*), in considerable *meteorism* (due to deranged digestion in the intestine in an upset bile excretory function), or in pronounced *hepato- or splenomegaly*.

General complaints. Many chronic diseases of the liver and biliary tracts are attended by the symptoms of the *asthenovegetative* syndrome: *weakness, non-motivated fatigue, depressed mood, insomnia, irritability, decreased work capacity.* Failure of the liver functions due to chronic hepatitis and liver cirrhosis may cause *skin hemorrhages and hemorrhages of the nose and the gastro-intestinal tract, and decreased libido and potency, dysmenorrhea and amenorrhea.*

Anamnesis

History of the present disease. It is necessary to find out if the patient had in his/her past history jaundice or acute diseases of the liver or the gallbladder (virus hepatitis, acute cholecystitis, cholangitis), attacks of the hepatic colic,

enlargement of the liver or the spleen, which might be an early symptom of the present disease (chronic hepatitis, liver cirrhosis, chronic cholangitis).

Past life history of the patient. It is necessary to find out risk factors of the present hepatobiliary diseases: excess of fat and fried food and alcohol, poisoning with chemicals (carbon tetrachloride, compounds of phosphorus, copper, lead, arsenic, etc.), mushrooms, some infectious diseases (virus hepatitis, AIDS, typhoid fever, malaria, syphilis, etc.), diseases of the gastrointestinal tract, and diabetes mellitus. Familial predisposition is important for development the of some liver diseases (*hemochromatosis, cystic fibrosis, congenital benign hyperbilirubinemia*, such as Gilbert's syndrome, etc.) and diseases of the gallbladder (cholelithiasis).

18.2. General survey in diseases of the liver and biliary tract

The *general condition* of patients can remain satisfactory for a long time in chronic diseases of the liver and biliary tract.

Mental state of patients is changed in case of *the hepatic encephalopathy* due to the expressed liver failure (decompensation of the liver cirrhosis, or severe acute or chronic hepatitis). Manifestations of the hepatic encephalopathy are vary widely: from subclinical forms to *lethargy, obtundation, stupo*r, and up to deep *hepatic coma*. It is a result of exposure to toxic products absorbed from intestine into the blood and get into the central nervous system by the anastomosis, bypassing the detoxification in the affected hepatic cells.

Asterixis (*flapping tremor, or liver flap*) is a tremor of the hand when the wrist is extended, sometimes said to resemble a bird flapping its wings (Fig. 18-1). This motor disorder is characterized by an inability to maintain a position, which is demonstrated by jerking movements of the outstretched hands when bent upward at the wrist. The tremor is caused by an abnormal function of the diencephalic motor centers in the brain, which regulate the muscles involved in a maintaining position. Asterixis is associated with hepatic encephalopathy.

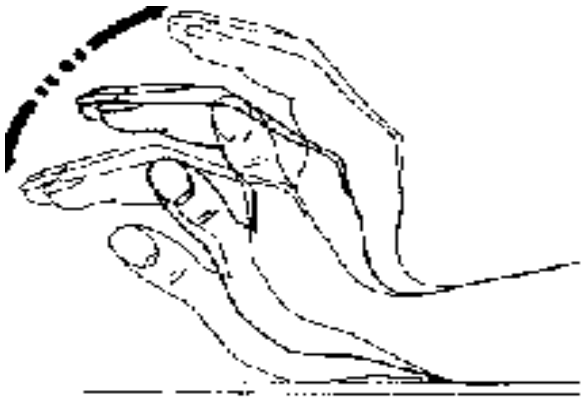


Fig. 18-1. Asterixis

The general appearance (*habitus*) of the patient usually does not change. However, a hypersthenic constitution and obesity are often characteristics of the

patients with cholelithiasis. Hypoproteinemia due to the reduction of protein-synthetic function of the liver results in the mild *hypoproteinemic edema*, usually combined with loss of weight, muscle and subcutaneous fat tissue atrophy. An expressed loss of body mass (to *cachexia*) occurs in cirrhosis and malignant tumors of the liver or the bile ducts.

Examination of the skin and visible mucous membranes. The most important is the identification of *jaundice* (*icterus*). To avoid a mistake in the assessment of the skin and mucosa color, the patient should be inspected in daylight or in the light of the white light lamp. The earliest manifestation of the jaundice is a yellowness of the sclera and mucous membrane (especially the hard palate and lower surface of a tongue); further colored are the palms, soles, and finally the entire skin.

Inspection of the sclera helps differentiate between *true (bilirubinogenic) and exogenic jaundice*. Prolonged use of rifabutin, ethacridine lactate (rivanol), carotene (provitamin A), excess carrots, tangerines and oranges, exposure to trinitrotoluene and picric acid can cause slight jaundice of the skin (*false jaundice*) but the sclera is not colored in such cases.

Hepatic and posthepatic jaundice is usually attended by itching and scratches of the skin. The scratches are often infected and purulent.

Hepatic jaundice can be attended by *petechia* (small hemorrhagic eruptions) and bruises into the skin (*ecchymosis*). Skin hemorrhages are associated with failed synthesis of liver coagulation factors in the blood (primarily prothrombin) and thrombocytopenia due to *hypersplenism* (increased hemolysis, including destruction of platelets in *splenomegaly*).

Paleness of skin accompanies anemia observed in liver cirrhosis.

Greyish-brown or brown pigmentation of the skin is characteristic of *hemochromatosis*, the disease associated with primary or secondary excessive absorption of iron in the intestine and accumulation of hemosiderin in various organs and tissues (in the first instance in the liver and the pancreas).

Xanthomatosis. Cholesterol metabolism disorders in patients with biliary cirrhosis of the liver results in the formation of yellow cholesterol plaques (*xanthomatosis*) which are often located on the eyelids (*xanthelasma*) and less frequently on the hands, elbows and soles (*xanthomas*). Xanthomatosis occurs also in other diseases attended by cholesterol metabolic defect (atherosclerosis, diabetes mellitus, essential hyperlipidemia, etc.) (Table 18-2).

Dupuytren's contracture is a painless deformity of the hand in which one or more fingers (in this case, the pinky) are bent toward the palm, and can not be fully straightened. It results from a thickening and scarring of the connective tissue under the skin in the palm of the hand and in the fingers. Dupuytren's contracture is typical in the chronic liver diseases (hepatitis, liver cirrhosis), associated with alcohol abuse; other risk factors are familial predisposition, smoking, thyroid problems, diabetes melitus, previous hand trauma, and epilepsy.

Table 18-2. Signs of the chronic liver disease in general survey

Signs	Characteristics	Causes
Hepatic jaundice	a reddish shade of the yellow skin	hepatitis, liver cirrhosis, cancer of the liver
Visible enlargement of the abdomen	- - accumulation of the fluid in abdominal cavity (ascites) – "frog-like abdomen"; - - hepato- and splenomegaly – bulging right and/or left hypochondrium	liver cirrhosis, tumors of the liver and spleen, congested liver in the heart failure
Visible skin scratches	due to skin itching with or in absence jaundice	in cholestatic liver diseases (primary biliary cholangitis, cholestatic hepatitis); hepatic and posthepatic jaundice
Signs of the hyperestro-genemia	"spider angiomas" (telangiectasia)	in chronic liver disease (hepatitis, liver cirrhosis)
	palmar erythema ("liver palms")	
	gynecomastia and testicular atrophy in males	
	"raspberry" tongue	
	hair loss in armpits and on the pubis	
Xanthomato-sis	yellow cholesterol subcutaneous plaques on the eyelids (*xanthelasma*) and the hands, elbows and soles *(xanthomas)*, accompanied itching	in cholestatic liver diseases (primary biliary cholangitis, cholestatic hepatitis)
Signs of the chronic alcohol abuse	Dupuytren's contracture	in chronic alcohol liver diseases, less common - in absence of the liver pathology
	parotid gland swelling	
Signs of the hepatic failure	*Fetor hepaticus* (*hepatic smell*) - characteristic sweet-smelling breath	hepatic precoma or coma
	asterixis (liver flap) - flapping tremor of the hand when the wrist is extended	in hepatic failure, portal encephalopathy
	skin hemorrhages (*petechia* and *ecchymosis)*	hypoprothrombinemia, thrombocytopenia

Inspection of the mouth can reveal *angular stomatitis* (*cheilosis*). It is an inflammation of the mucosa and skin in the mouth angles that is a characteristic of the vitamin B2 (riboflavin) and/or iron deficiency in the chronic liver diseases.

It is important to pay attention to the condition of the papilla and color of the tongue. Smooth with atrophied papillae red tongue (*raspberry tongue*) is typical in severe deficiency of the group B vitamins and *hyperestrogenemia* in cases of hepatic failure.

Hepatic smell (*Fetor hepaticus*) is a sweet aromatic odour of breath from the oral cavity due to the violation of the amino acid exchange and accumulation aromatic substances (thiols, dimethyl sulfide, methyl mercaptan, ammonia, ketones, and others) in the expired air. It is a sign of the portal hypertension and severe hepatic failure that is typical for patients in hepatic precoma and coma.

A *greenish-brown Kayser-Reischer ring* round the outer edge of the cornea is characteristic of the *Wilson disease* (congenital disease characterized by an increased copper deposition in the tissues particularly of the liver, brain, and corneas of the eyes).

Signs of hyperestrogenemia in chronic hepatic failure. An increased estrogen level in the blood is the result of the disordered utilization of steroid hormones in hepatocytes with the chronic liver failure. It is associated with an increased conversion of androgenic steroids into estrogens in peripheral tissues (fat tissue, muscles, and bone). A general inspection finds signs of *hyperestrogenemi*a – "*spider angiomas", palmar erythema, gynecomastia, raspberry (crimson) tongue, loss of the secondary sexual signs.*

"Spider angiomas" are telangiectasia (local expansion of capillaries and small blood vessels slightly rising above the surface of the skin). They are located on the neck, shoulders, face, hands, and chest. "Spider angiomas" are the result of hyperestrogenemia and the development of arteriovenous bypass due to the liver failure in chronic hepatitis and liver cirrhosis.

Palmar erythema, or liver palm, is a bright red symmetrical reddening in the thenar and hypothenar region. When pressed, the reddened site becomes pale but when the pressure is removed, the redness is quickly restored. On the palpation of the palms, the skin is a thin velvety like a child's.

A glassy crimson tongue (*raspberry tongue*) can be in patients with chronic diseases of the liver.

Gynecomastia (an increase in the size of the male breast tissue) and atrophy of the testicles occurs in the liver failure due to hyperestrogenemia as well. This combines with the loss of the hair growth on chin, chest, and abdomen.

Hair growth is decreased in armpits and on the pubis both in males and females. When the, hepatic condition improves, the hair growth is restored.

Drum (Hippocratic) fingers, sometimes with white nails (*leuokonychia*), occur in patients with chronic diseases of the liver. It depends on excess estrogens and serotonin in the blood, and chronic anemia in the liver diseases.

18.3. Inspection of the abdomen in diseases of the liver and biliary tract

When examining the abdomen, a physician would determine:

- the shape of the abdomen (flat, concave, "frog-like", increased in volume);
- symmetry, participation in breathing;
- abdominal circumference (in cm) estimated in dynamics;
- presence of the ascites;
- collateral venous network, the presence of the "caput medusae";
- hernia and protrusion.

Inspection of the abdomen is conducted in vertical and horizontal positions (See Chapter 14. Section 14.4. Survey of abdomen; Table 14-6. Differences of enlarged abdomen in ascites, meteorism, and obesity).

The abdomen enlarges due to the accumulation of free fluid (ascites). This occurs in liver cirrhosis concurrent with portal hypertension. *The abdomen may be enlarged due to pronounced hepato- and/or splenomegaly*.

Asymmetric enlargement of abdomen. The right hypochondrium and epigastrium are protruded in patients with pronounced hepatomegaly, and especially in cachectic patients with malignant tumors (in hydrops of the gallbladder due to cancer of the common bile duct, or cancer of the pancreas head which compresses the common bile duct). The left hypochondrium is protruded in considerable splenomegaly attending cirrhosis of the liver, and in diseases of the blood (leucosis, hemolytic anemia).

The inspection of the abdomen reveals another *important sign of the portal hypertension*, the presence of *dilated venous network on the anterior abdominal around the umbilicus (“caput medusae*”). It is formed by anastomoses of the portal vein and both vena cava systems. The *superior vena cava and portal veins* are anastomosed above the umbilicus, while the portal and inferior cava veins are anastomosed below the umbilicus. *“Caput medusae”* is a characteristic of the portal hypertension syndrome occurring in the liver cirrhosis, thrombosis and compression of the portal vein, and in the inferior vena cava occlusion (thrombosis, compression, etc.).

Percussion of the abdomen in a vertical and horizontal position can reveal a free fluid in the abdomen (ascites) by detecting a dull sound lower than fluid level (see Section 14.5. Percussion of the abdomen).

18.4. Percussion of the liver

18.4.1. General rules of the liver percussion

Percussion determines the borders, size and configuration of the liver. Superior and inferior borders of the liver are determined.

Two *superior borders of the liver (hepatic) dullness* are distinguished: *superior border of relative dullness*, which is the true upper border of the liver, and *superior border of absolute dullness*, which is directly adjacent to the chest and is not covered by the lungs.

Practically, *superior border of absolute dullness of the liver* is determined just because the superior border of the relative dullness varies depending on the size and shape of the chest, the height of the right dome of the diaphragm, and because the upper edge of the liver is deeply behind the lungs. Finally, the liver usually enlarges in the downward direction. *Hepatomegaly (enlarged liver)* should be detected by downshift of the liver inferior edge.

The liver (as the dense organ) produces dull percussion sound; right lung adjoining above – a resonant sound; stomach and intestine adjoining below – a tympanic sound. As the right pulmonary inferior edge locates into space between the anterior chest wall and the liver, filling costal-diaphragmatic sinus, a transfer to a hyporesonant sound corresponds to the superior border of the liver relative dullness (true superior edge of the liver). Appearance of the dull percussion sound corresponds to the liver absolute dullness, which is not covered with the edge of the lung (Fig. 18-2). *The border between hyporesonant and dull sound is designed as a superior border of the absolute hepatic dullness.* Superior border of the liver determined by percussion is always below the true anatomical border.

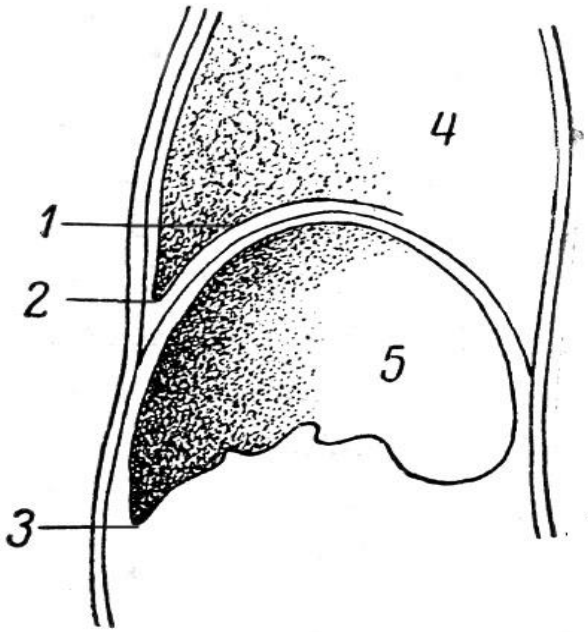


Fig. 18-2. The scheme of a sagittal section through the liver and the right lung:

1 - hyporesonant sound; 2, 3 - dull sound; 4 – right lung, 5 – liver.

Percussion of the liver is performed according to the general rules of topographic percussion:

- position of the pleximeter-finger should be parallel to the finding border;
- percussion should be from a resonant to a dull sound;
- the border is marked from the side of the resonant sound;

- light (quiet) or lightest (quietest) percussion should be used.

18.4.2. Percussion of the absolute liver dullness borders

Percussion of the superior border of the absolute liver dullness

Percussion is conducted on the right parasternal, midclavicular, and anterior axillary lines by intercostal spaces (Fig. 18-3, Table 18-3).

Position of the patient is horizontal.

The direction of percussion is from top to bottom, along the vertical lines, like in determining inferior borders of the right lung. The border is detected by contrast between the pulmonary resonant and liver dull sound.

The light (quiet) percussion should be used.

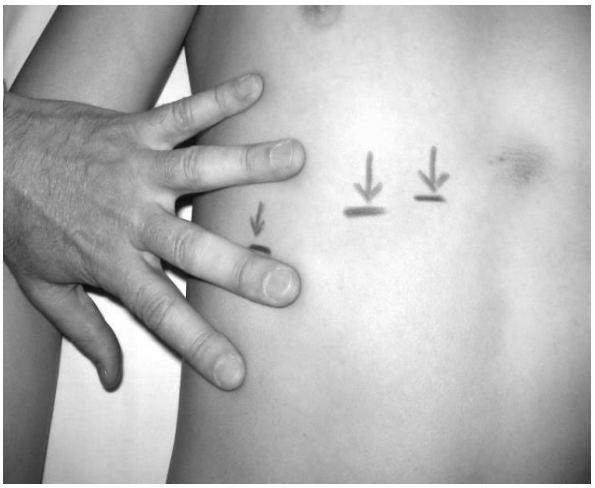


Fig. 18-3. Percussion of the superior border of the absolute liver dullness.

The finding border for each vertical line is marked by the upper edge of the pleximeter-finger.

The position of the border on the right parasternal line is specified by the percussion by two overlying ribs above the dullness. Having received a different percussion sound above them, a physician marks the border on the upper edge of the subjacent rib from them (routinely the VI-th).

Superior border of the relative dullness of the liver is placed on one rib above absolute dullness of the liver.

Table 18-3. Borders of the absolute liver dullness

Topographic lines	Superior border	Inferior border	Height
right anterior axillary line	VII intercostal space	superior edge of the X rib	10-12 cm
right midclavicular line	inferior edge of the VI-th rib (VI-th intercostal space)	inferior edge of the right costal arch	9-11 cm
right parasternal line	superior edge of the VI rib	2 cm below inferior edge of the right costal arch	8-10 cm
anterior median line		at the upper third of the distance between xiphoid process and umbilicus (3-6 cm below the xiphoid process)	
left parasternal line		at the inferior edge of the left costal arch	

Percussion of the inferior border of the absolute liver dullness is difficult because of the presence of the hollow organs surrounding the liver. The stomach and intestines give high tympanic sound that masks the liver dullness. Therefore, *the lightest (quietest) percussion should be used.*

The inferior border of the absolute liver dullness is defined on the right anterior axillary, midclavicular, parasternal lines, anterior median line and left parasternal lines.

Percussion should begin from the right part of the abdomen along the right anterior axillary line with the patient *in a horizontal position* (Fig. 18-4).

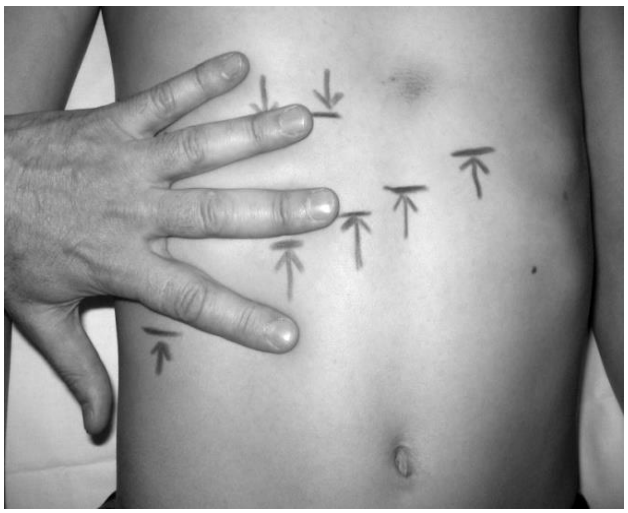


Fig. 18-4. Percussion of the inferior border of the absolute liver dullness.

The pleximeter-finger is placed parallel to the finding inferior border of the liver, some distance away from it (at the umbilical level or slightly below the umbilicus). As the pleximeter-finger is then moved upward, an abdominal tympanic sound is followed by the liver absolute dullness.

The border (point of the tympanic sound disappearance) is marked on the inferior edge of the pleximeter-finger.

The position of the inferior border of the liver is very depending on the shape of the chest and the patient's body-build type, but it has just an effect on the position at the anterior median line. The inferior border of the liver in hypersthenic chest is slightly above the mentioned level, while in an asthenic chest - below it, approximately at the midway between the base of the xiphoid process and umbilicus. If a patient in a vertical position, the inferior border of the liver descends 1-1.5 cm. If the liver enlarges, its inferior border is defined in centimeters from the costal arch and the xiphoid process.

18.4.3. Height of the absolute liver (hepatic) dullness

Percussion gives information about vertical dimensions of the liver dullness. The distance between superior and inferior borders of the liver absolute dullness represents the *height of the absolute liver dullness* (Fig. 18-5).

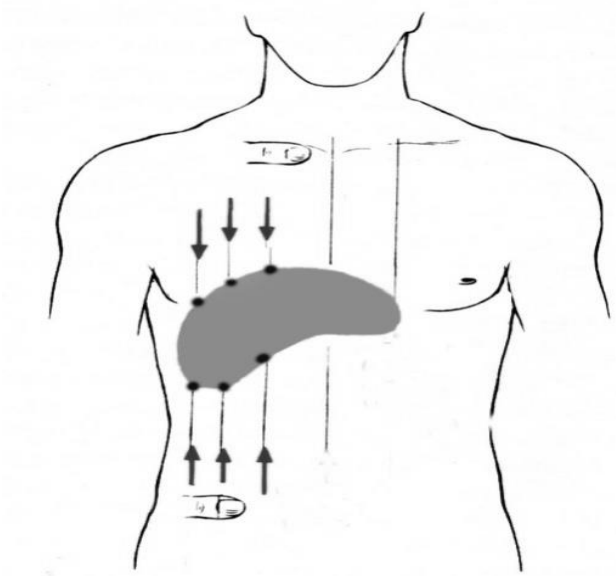


Fig. 18-5. Determination of the height of the liver absolute dullness.

The absolute liver dullness height is measured between the superior and inferior borders on three vertical lines:

- on the right anterior axillary line is normally 10-12 cm,
- on the right midclavicular line – 9-11 cm,
- on the right parasternal line – 8-10 cm.

Increase of the height of the absolute liver dullness is a result mainly of the enlargement of the right lobe of the liver. Determining the height of the absolute

dullness of the liver can distinguish an enlarged liver from its shift because lowering diaphragm due to the pulmonary emphysema or general *visceroptosis* (lowering abdominal organs).

18.4.4. Percussion of the liver according to M.G. Kurlov's method

The size determination of the liver according to M.G. Kurlov's method is widely used in clinical practice. According to this method, five points are marked, and three dimensions are taken (Fig. 18-6, Table 18-4).

The first and second points of Kurlov correspond to superior and inferior borders of the absolute liver dullness on the right midclavicular line, the ***I dimension of the liver according to M.G. Kurlov*** is measured between them (in norm of 9 cm).

The third point of Kurlov is marked at intersection of the anterior median line and the perpendicular line installed from the first point of Kurlov (the level of superior border of the liver absolute dullness on the right midclavicular line). This point conventionally corresponds to the superior border of the liver on the anterior median line.

The fourth point according to Kurlov is marked on the inferior border of the liver absolute dullness on the anterior median line. ***The II dimension of the liver according to M.G. Kurlov*** is measured between superior and inferior borders of the liver absolute dullness on the anterior median line (in norm 8 cm).

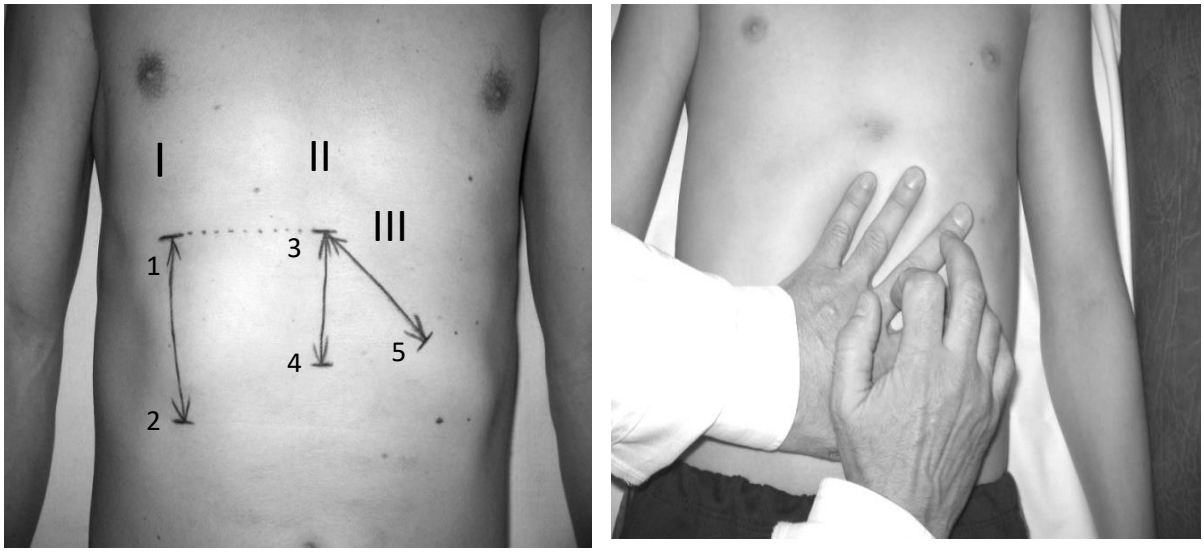


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Fig. 18-6. Determination of sizes of liver according to M.G. Kurlov:

(1) I (right midclavicular line), II (anterior median line) and III (oblique) dimensions of the liver; 1-5 – points of the liver percussion;

(2) percussion of the fifth point according to M.G. Kurlov by the left costal arch.

Table 18-4. Liver sizes in norm according to M.G. Kurlov.

Dimensions	Size (cm)
I Right midclavicular line	9±1
II Anterior median line	8±1
III Oblique (Left costal arch – anterior median line)	7±1

The fifth point according to M.G. Kurlov corresponds to the left border of the liver dullness. The pleximeter-finger is placed perpendicularly to the edge of the left costal arch, at the level of the 8-9-th ribs between the left anterior axillary and midclavicular lines, and quiet percussion is performed to the right, directly over the edge of the costal arch, to the point where a tympanic sound changes to dullness. The ***III dimension of the liver according to M.G. Kurlov*** is measured between the third and fifth point of Kurlov (superior border on anterior midline and left border of liver dullness on a costal arch - in norm 7 cm). An increase of the II and III dimensions testifies a pathological process of the left hepatic lobe, an increase of the I dimension – of right hepatic lobe.

18.4.5. Diagnostic value of the liver percussion

Outlining the liver by percussion is diagnostically important (Table 18-5). Dislocation of the superior border of the liver is mainly associated with extrahepatic changes (high or low diaphragm, subdiaphragmatic abscess, pneumothorax, or pleurisy with effusion). A superior border of the liver can elevate in echynococcosis or cancer of the liver.

Table 18-5. Diagnostic value of the liver percussion

Borders displacement	Superior border	Inferior border
Dislocation upward	- High position of the diaphragm (meteorism, ascites, pregnancy); - Cancer of the liver; - Echinococcus cyst of the liver	- Decrease of the liver (degeneration, terminal stage of the liver cirrhosis); - High position of the diaphragm (meteorism, ascites, pregnancy)
Dislocation downward	- Low position of the diaphragm (in asthenic body-build, visceroptosis); - Subdiaphragmatic abscess; - Right pneumothorax, hydrothorax	- Enlarged liver (in hepatitis, liver cirrhosis, liver cancer, congestive heart failure); - Hepatoptosis (a low position of the diaphragm, pulmonary emphysema)

Elevation of the inferior border indicates the decrease of the liver; it can also occur in meteorism and ascites which can displace the liver upwards.

The inferior border of the liver usually descends in hepatomegaly (due to hepatitis, cirrhosis, cancer, echynococcosis, congested liver associated with a right ventricular heart failure, etc.). It can be due to lowering the diaphragm in asthenics, pulmonary emphysema or visceroptosis.

The increase of the absolute dullness height is related to the enlargement of the right lobe of the liver. Percussion according to M.G. Kurlov's method provides information about the size of both liver lobes. The increase of the I dimension by M.G. Kurlov is a characteristic of the right lobe enlargement, and the increase of the II and III dimensions – enlargement of the left lobe of the liver.

18.5. Palpation of the liver

Superficial (light touch) palpation *is necessary before the deep palpation of the liver.* Superficial palpation can reveal a tenderness in the right hypochondrium and epigastrium when the diagnosis of the liver and biliary tract diseases is suspected. A severe local pain in the zone overlying the gallbladder is observed in acute cholecystitis and biliary colic. A slight or moderate tenderness is revealed at the projection of the gallbladder in the chronic cholecystitis and biliary dysfunction. Projection of the gallbladder onto the anterior abdominal wall is placed immediately below the right costal arch by the lateral edge of the right rectus abdominis muscle.

Purposes of the liver palpation *are detection of the inferior edge of the liver, its localization, shape, contours, consistence, character of the surface and tenderness.*

Technique of the liver palpation

Position of the patient. The patient should lay horizontally with a slightly raised head and stretched legs. The hands routinely settle down along the body or cross on the chest with the purpose of the restriction of the side mobility of the chest on an inspiration. It promotes the increase of the diaphragm motility in the upper-inferior direction that is important for a palpation of the lower edge of the liver.

Position of the physician-examiner should be seated by the right side, facing the patient.

Technique of the liver palpation. The patient is asked to make a deep breath. The liver descends to touch the palpating fingers and then slides to bypass them. The procedure would be repeated several times. The position of the liver margin varies depending on the conditions. ***It is therefore necessary first to determine the position of the inferior edge of the liver by percussion before installation palpating fingers.***

For palpation of the liver, it is necessary to perform four steps of deep sliding palpation according to V.P. Obraztsov (Fig. 18-7):

The first step is an installation of arms on a proper position. The right arm is placed at the region of the right hypochondrium between the right midclavicular and parasternal lines with slightly bent fingers which tips should be 3-5 cm lower than the percussion found inferior border of the liver. The left arm covers the inferior department of the right half of the chest so that the 1-t finger is placed on the anterior surface of the right costal arch while other fingers (2-5-th fingers) settled down behind. Thus, we aspire to confine the motility of the chest during an inspiration and to strengthen a motion of the diaphragm from top to bottom.

The second and the third steps (formation of the artificial pouch according to V.P. Obraztsov) are combined, and performed during the one expiration (Fig. 18-8). For this purpose, it is necessary to make a superficial motion to dislocate skin fold downwards and to plunge the tips of the fingers of the right arm in depth of the abdominal cavity during the one expiration when there is a maximal release of the anterior abdominal wall muscles, and the liver follows the diaphragm.

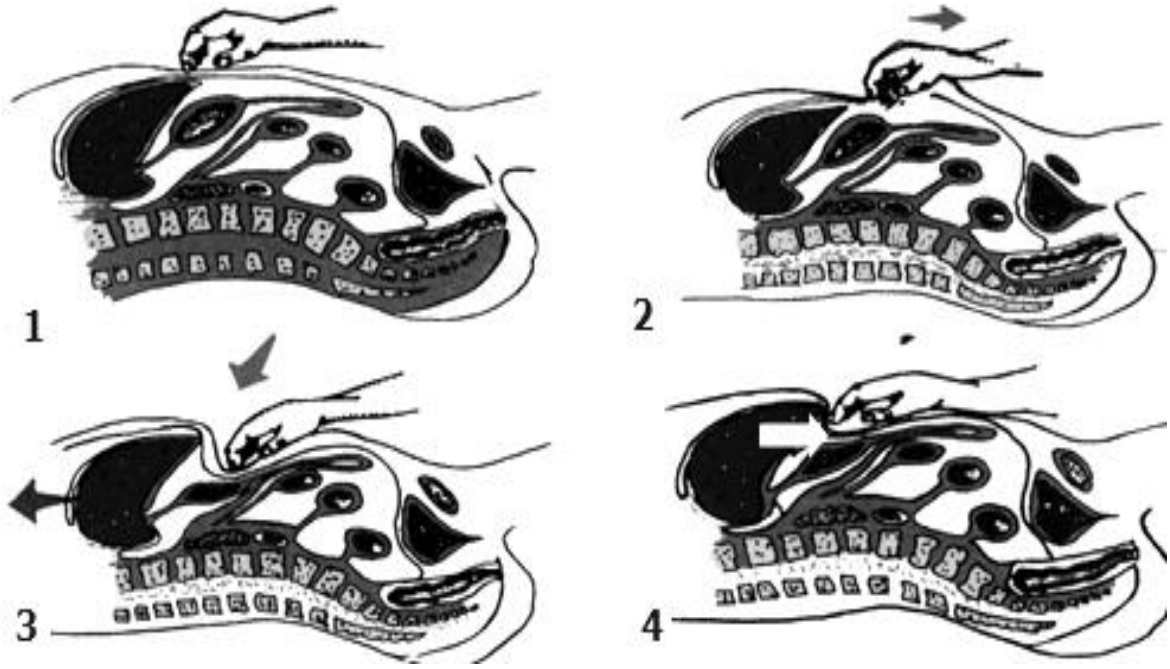

Fig. 18-7. Four steps of the liver palpation according to V.P. Obraztsov:

1 – installation of the palpating arm; 2 – formation of the skin fold downwards;

3 – dipping fingers of the right arm in the abdomen and the formation of the artificial pouch; 4 – a sliding palpation of the inferior edge of the liver (a patient is asked to take a deep inspiration).

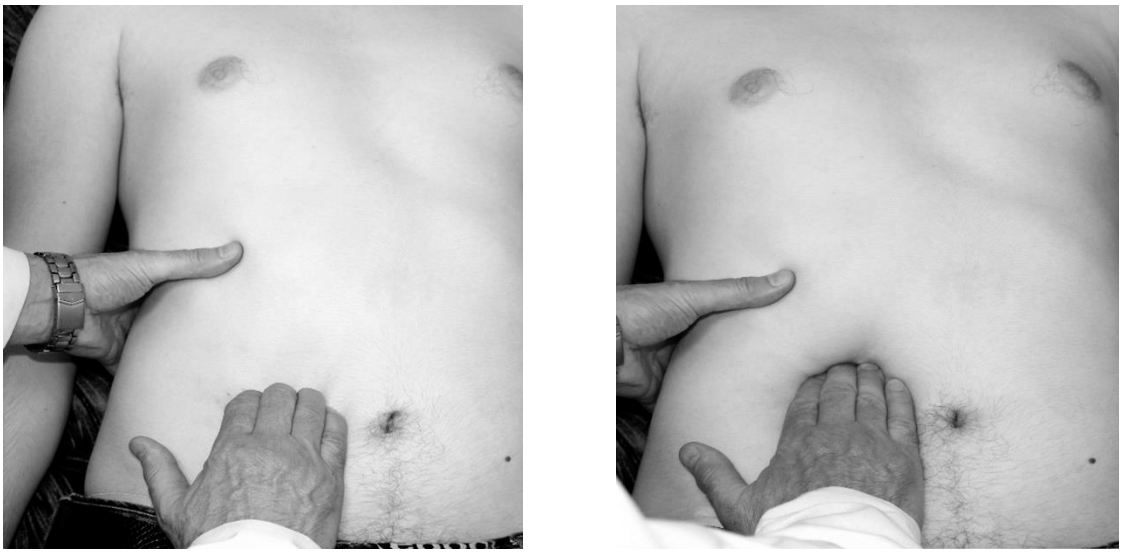

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Fig. 18-8. The palpation of the liver according to V.P. Obraztsov: (1) the formation of the skin fold downwards; (2) fingers sliding.

The fourth step is a palpation of the inferior edge of the liver. After dipping the palpating arm in the abdomen and the formation of the artificial pouch, the patient is asked to take a deep breath. The liver descends to touch the palpating fingers and then slides to bypass them.

If by time of the inspiration the perception of the liver edge is not possible, the palpation of the liver would be repeated. The tips of the right arm fingers must be transferred 1-2 cm upwards. If a repeated result is negative, the research is repeated again and again, positioning the tips of the fingers each time - higher and higher. An unsuccessful final palpation of the liver is considered in that case, when the right arm reaches the edge of the costal arch. In this case, the palpation of the liver is recommended to be repeated from the beginning. The tips of the right arm fingers must be transferred 2-3 cm lower than their initial position.

Inferior edge of the normal liver is usually palpated between the right parasternal and midclavicular lines. The liver is impalpable to the right of the midclavicular line because it is located behind the costal arch. It is easily to palpate the liver on the right parasternal line as here the inferior edge of the liver settles down in standard conditions 2 cm of a below costal arch. The liver is hardly palpable to the left of the line because of the abdominal muscles strain.

An enlarged or consolidated liver can be palpated on all lines. Special attention should be paid to the anterior-inferior edge of the liver which properties (its position, contours, shape, tenderness, consistency) are indicative of the condition of the liver. In many cases (if the liver is enlarged or lowered), the liver inferior edge can be palpated not only from the left hypochondrium to the right hypochondrium, but its anterior surface becomes palpable as well.

A decreased liver is usually not possible to the palpation.

In an expressed accumulation of the fluid in the abdominal cavity (ascites), the liver is not always palpable if the patient is lying. The patient should then be examined in a vertical position, or he/she may lie on his left side. If the volume of the fluid in the abdominal cavity is very large, it should be released by *laparocentesis (abdominal puncture).*

In expressed ascites, *the technique of the ballotment* can be used to palpate the liver. The right hand (two or four flexed fingers) should be placed on the right part of the abdomen, perpendicularly to the expected inferior edge of the liver. The abdominal wall is given a sharp push from the fingers, which move upward to meet a solid object, the liver, which first moves to the deeper parts of the abdominal cavity, and then returns back to hit the fingers (*sign* of the "*floating ice*").

Diagnostic value of the liver palpation

According to V.P. Obraztsov, a normal liver can be palpated in 88% of cases. Physical properties of the liver can be determined by palpating its inferior edge (it may be soft, firm, rough, acute, rounded, tender, etc.) (Table 18-6).

The edge of the normal liver is palpated at the height of a deep inspiration is 1-2 cm below the costal arch between the right midclavicular and parasternal lines. It is soft, acute or slightly rounded in shape, smooth and insensitive.

Table 18-6. Characteristics of the liver edge in norm and pathology

Liver edge	Condition of the liver
Acute, mild, painless	Normal liver edge
Thick, dense/elastic, sensitive	Hepatitis
Acute, dense, irregular, slightly painful	Liver cirrhosis, malignant tumor
Rounded, dense – elastic, painless	Metabolic abnormalities (fatty hepatosis, amyloidosis)

In hepatomegaly, a position of the liver inferior edge is estimated how much below the costal arch is. The palpation verifies the findings obtained by the percussion of the liver.

The palpation is painful in case of the liver tissue inflammation with the involvement of the liver capsule. The liver is also tender when it is distended (e.g., in blood congestion due to a heart failure) (Table 18-7).

The liver becomes firmer in hepatitis, hepatosis, and liver congestion due to a cardiac failure. The liver is especially firm in cirrhosis. Its edge becomes sharp, and the surface – smooth or covered with small tubercles. The liver is also firm in amyloidosis. The liver is firm with a rough edge and irregular tuberous surface (surface metastases) in the presence of the malignant tumor and multiple metastases of a cancer. Comparatively small tumors and echinococcus cysts can be sometimes palpated.

Table 18-7. Characteristics of the palpated liver in pathology

Characteristics of liver	Pathology of the liver
Enlargement of the liver	- hepatitis, cirrhosis, tumor; - congestive heart failure; - diseases of the blood system (leucosis, B_{12} –-deficiency anemia, lymphogranulomatosis); - some acute and chronic infectious diseases (typhoid fever, malaria, syphilis, tuberculosis, AIDS)
Intensive palpatory tenderness of the liver	- expressed rapid distension of the liver capsule (heart failure, diseases of the intrahepatic biliary ducts with disordered bile outflow); - perihepatitis
Evident consolidation of the liver	- chronic hepatitis; - liver cirrhosis; - liver cancer
Irregular surface and edge of the liver	- liver cancer; - hepatic hydatid (echinococcus cyst); - syphilis of the liver; - macronodular cirrhosis of the liver

The liver becomes firmer in hepatitis, hepatosis, and liver congestion due to a cardiac failure. The liver is especially firm in cirrhosis. Its edge becomes sharp, and the surface – smooth or covered with small tubercles. The liver is also firm in amyloidosis. The liver is firm with a rough edge and irregular tuberous surface (surface metastases) in the presence of the malignant tumor and multiple metastases of a cancer. Comparatively small tumors and echinococcus cysts can be sometimes palpated.

18.6. Palpation and percussion in the gallbladder pathology

Surface palpation can reveal pain and local tension of the abdominal wall in the right hypochondrium with acute cholecystitis, exacerbation of the chronic cholecystitis, and cholelithiasis.

Characteristic signs suggest acute cholecystitis and exacerbation of the chronic cholecystitis:

- *Murphy sign* – a sharp pain in the right hypochondrium when the examiner's hands press the gall bladder at the height of inspiration. The examiner can stay behind the patient;
- *Ortner's sign* – a pain during tapping over the right costal arch by the edge of the hand;
- *Lepene sign* – a pain during light tapping of the right hypochondrium by the edge of the hand;

- *phrenic sign, or de Mussy-Georgievski sign* – tender to pressure in the region between the anterior heads of the right sternocleidomastoid muscle.
- *Zakharin-Head zones* are certain areas of the skin that develop tenderness in the course of the visceral disease. Tenderness on palpation in these zones is detected in patients with gall bladder and biliary ducts diseases (Fig. 18-9).

These signs are usually tested by comparing the patient's discomfort on both sides.

The gall bladder is not palpable in healthy individuals because of its soft consistency and relatively small size. In the presence of the cholecystitis and cholelithiasis, the palpation is difficult because of the sharp pain and the muscles strain of the anterior abdominal wall.

The gall bladder may be palpable, if it is markedly enlarged (hydrops, empyema, stones in the bladder, cancer, etc.). In these cases, it is palpated as a sacciform formation of the dense or elastic consistency (depending on the character of the pathology) in the area between the inferior edge of the liver and the outer edge of the right rectus abdominis muscle.

The gall bladder is a firm and tuberous in the presence of the tumors in its wall, in overfilling with stones, and in inflammation of the wall. An enlarged gall bladder is mobile during respiration (it performs lateral pendulum-like movements). The gall bladder loses its mobility in pericholecystitis because of peritoneal adhesions.

Courvoisier-Terrier sign – palpation of the significantly increased elastic painless gallbladder in combination with posthepatic jaundice due to the common bile duct (choledochus) obstruction by a tumor of the pancreas head or in the area of the major duodenal papilla.

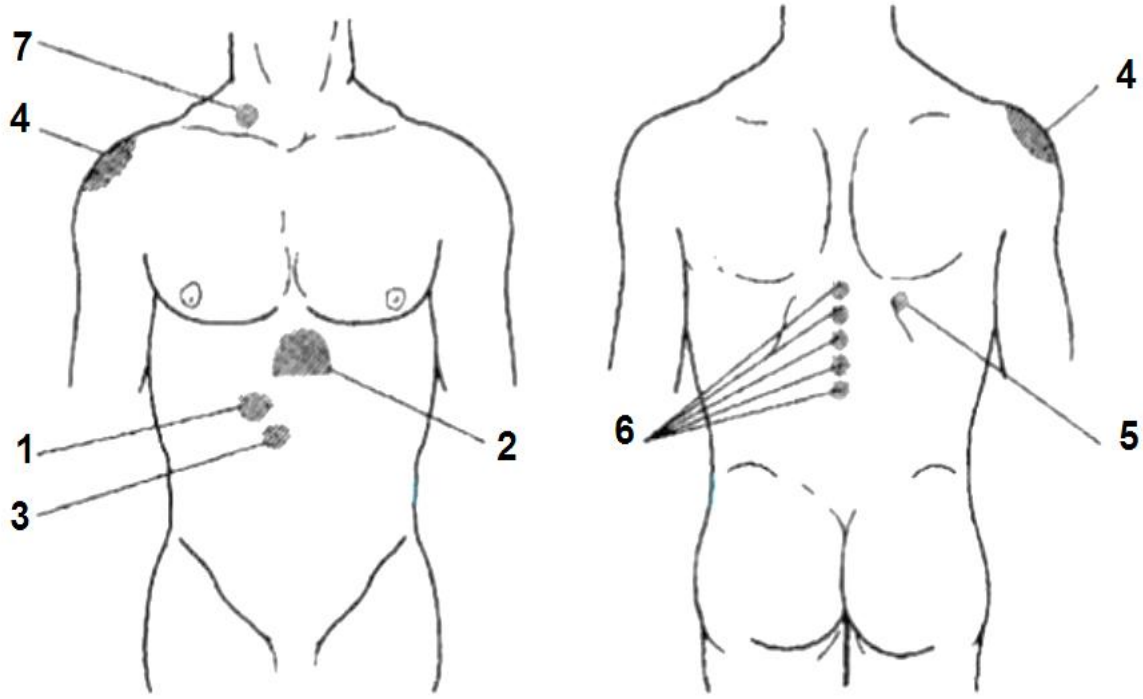
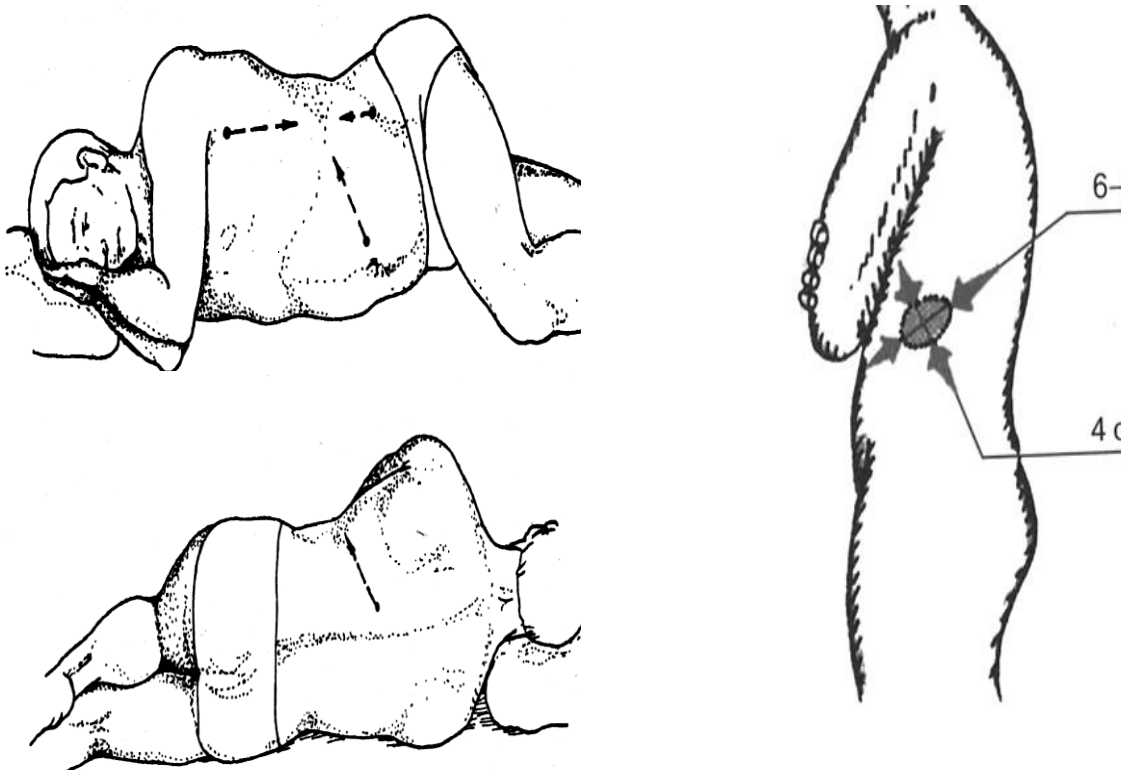


Fig. 18-9. Painful palpatory areas and points in pathology of the gallbladder according to Zakharin-Head zones (by *V.K. Vasilenko, A.L. Grebenev*, *1983*): 1) the region of the gall bladder; 2) epigastrium; 3) pancreato-biliary-cystic point; 4) shoulder zone; 5) point of the scapular angle; 6) paravertebral points to the right of the VIII to XI thoracic vertebra; (7) phrenic nerve site.

18.7. Percussion of the spleen

Spleen is located deeply in the lateral part of the left hypochondrium under the left dome of the diaphragm, adjoining chest wall between the IX and XI ribs. Longitudinal axis of the spleen passes in oblique, anterior-posterior direction, collateral to the X rib. Percussion of the spleen is inconvenient in view of the close surrounding with gas-containing organs (stomach and intestines) which give a loud resonant (the left lung) and tympanic sound (stomach and intestines). That is why it is impossible to determine accurately spleen borders (*absolute dullness of the spleen*) by percussion. The actual anatomical size of the spleen is approximately 1.5-2 times the size determined by percussion.

During percussion, ***the patient lies usually on his/her right side with a little bit bent left leg and left arm stretched forward***, more rarely the patient stands upright. ***The quiet (light) percussion should be used with transition from a resonant (pulmonary) sound to a hyporesonant sound***. Percussion of superior and inferior borders of the spleen is performed first, anterior and posterior borders of the spleen are examined second (Fig. 18-10).



(1) (2)

Fig. 18-10. Technique of the spleen percussion:
(1) position of the patient and directions of the spleen percussion;
(2) measurement of the spleen dullness.

For delimitation of the ***superior border of the spleen***, the finger-pleximeter is placed parallel to the ribs at the III or IV intercostal space (within the left axillary space) on the left medium axillary line. Percussion is conducted from top downward before appearance of the hyporesonant sound. The border is marked on the edge of the finger-pleximeter from the side of the resonant (pulmonary) sound.

Delimitation of the ***inferior border of the spleen*** is also performed on the left medium axillary line. The finger-pleximeter is placed below the inferior edge of the left costal arch. Percussion is conducted upwards the spleen dullness, marking the border from the side of the tympanic sound. For delimitation of the ***anterior border of the spleen,*** it is necessary to continue mentally its superior and inferior borders in the line to umbilicus. In the interspace between them, the finger-pleximeter is placed parallel to the required border. Starting from the umbilicus, a quiet percussion is proceeded of the abdominal wall on the X intercostal space. The required border of the spleen is marked on the side of the tympanic sound (Fig. 18-11).

For delimitation of the ***posterior border of the spleen,*** it is necessary to find the X rib, corresponding to the spleen longitudinal axis, and to place the finger-pleximeter parallel to the required border (i.e., upright) in the space between the

left posterior axillary and scapular lines. Percussion is performed immediately along the X rib before appearance of the hyporesonant sound. The posterior border of the spleen is marked from the side of the resonant (pulmonary) sound.

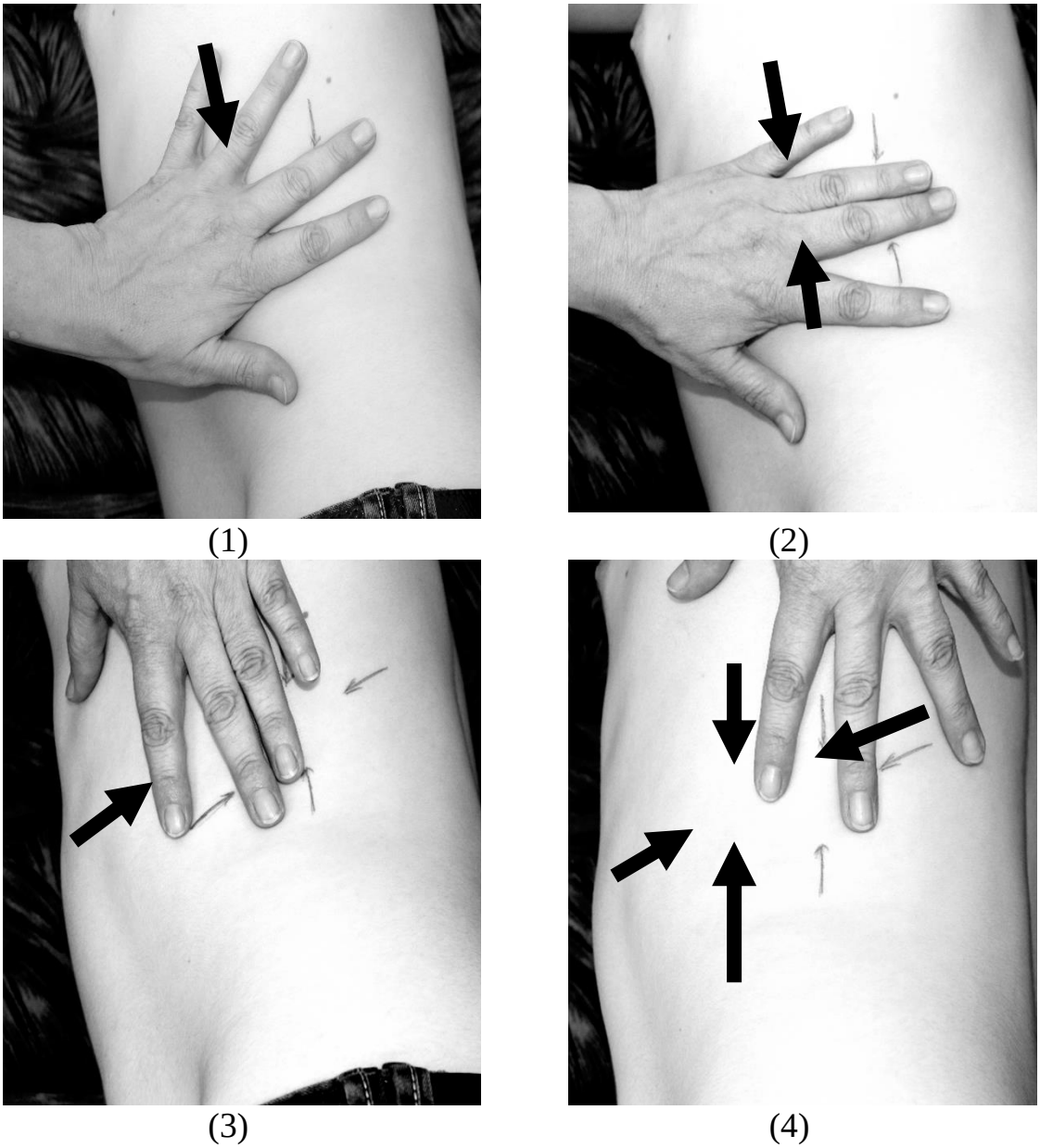


Fig. 18-11. Percussion of the spleen dullness borders:
(1) superior border; (2) inferior border;
(3) anterior border; (4) posterior border.

Normal position of the spleen dullness borders:

- a superior border corresponds to the lower edge of the IX rib;
- an inferior border – to the lower edge of the XI ribs;
- anterior border – 1-2 cm to the left of the anterior axillary line at the X intercostal space;

- posterior border – about the posterior axillary line at the X intercostal space.

Measurement of the lines bridging superior and inferior, anterior and posterior borders of splenic dullness gives conception about ***the size of the spleen dullness in the norm:***

- width of the spleen dullness – 4-6 cm,
- length of the spleen dullness – 6-8 cm.

Percussion distinguishes the enlargement (***splenomegaly***) and descent (***splenoptosis)*** of the spleen, and adds to palpation in recognition of the various changes of this organ.

18.8. Palpation of the spleen

*The size, shape, character of the surface, sensitivity, consistence, mobility, and configuration of the anterior edge of the spleen should be determined by palpation***.**

In norm, the spleen is not palpated as it is placed deeply in the left hypochondrium. Its inferior pole does not reach the lower edge of the left costal arch on 3-4 cm. That is why any case of a successful palpation of the spleen testifies its enlargement (*splenomegaly*) or s*plenoptosis* (lowering spleen).

Palpation of the spleen is basically the same as the liver palpation. The essence of it consists in the reception of tactile perception of the edge of the spleen at its shift together with the diaphragm downwards during a deep inspiration.

The spleen should be palpated with a patient in a recumbent position or on his/her right side. In the former case, the patient should lie on a low pillow. The arms and legs ought to be straight.

If the patient lies on his/her right side, his/her head should be slightly down, the left elbow bent and resting freely on the chest. The right leg should be stretched and the left knee bent and drawn up to the chest. The abdominal wall is relaxed to a maximum. In this position, the spleen is shifting anteriorly to facilitate its palpation.

The examiner-physician sits on the right side of the patient and faces him/her.

The first step is an installation of the arms at the proper position. The left arm of the physician is placed on the left part of the patient's chest, between VII and X ribs on axillary lines, and it is slightly pressed on the chest to limit its respiratory movements. A physician's right hand is placed on the antero-lateral surface of the patient's abdominal wall so that the tips of the 2-5-th fingers are positioned opposite X rib 3-5 cm below the left costal arch, and the back of the arm is in range of the umbilicus (Fig. 18-12).

The position of the palpating fingers depends on the localization of the anterior border of the spleen preliminarily found by means of percussion. If it is below the level of the costal arch, the palpating fingers would be shifted in a

direction of the umbilicus, 3-5 cm downwards from the anterior border of the spleen.

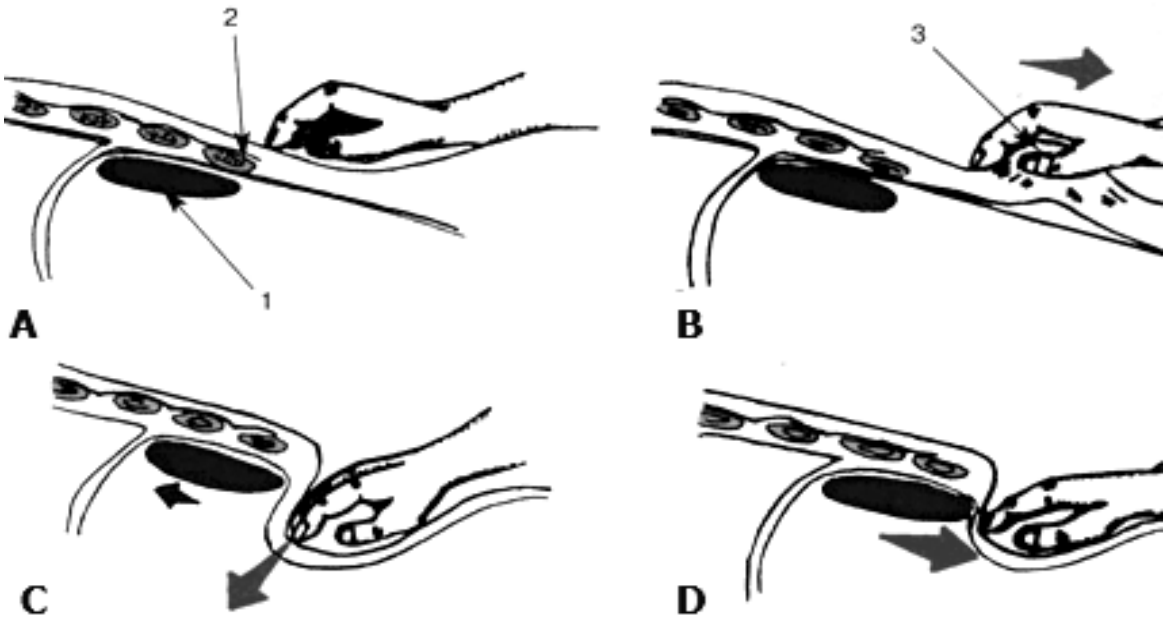


Fig. 18-12. Four steps of the spleen palpation:

(A) – installation of the palpating arm; (B) – formation of the skin fold to umbilicus; (C) – dipping the fingers of the right arm in the abdomen and formation of the artificial pouch; (D) – sliding palpation of the inferior edge of the spleen

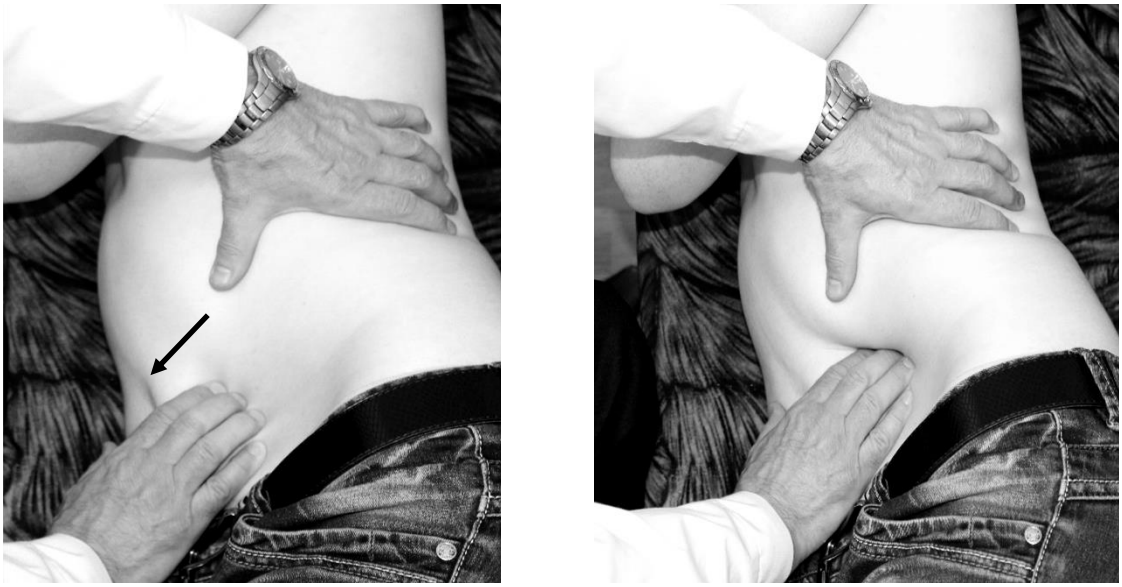
(a patient is asked to take a deep inspiration); 1 – spleen, 2 – inferior edge of the left costal edge, 3 – right arm.

The second and the third steps (formation of an artificial pouch according to V.P. Obraztsov and dipping fingers) are combined, and performed during one expiration. For this purpose, it is necessary to make a superficial motion to dislocate the skin fold downwards to umbilicus and to plunge the tips of the fingers of the right arm in depth of the abdominal cavity when a maximal release of the anterior abdominal wall and the spleen departs up after diaphragm.

The fourth step is a palpation of the spleen. After dipping the palpating arm in the depth of the abdomen and formation of an artificial pouch according to V.P. Obraztsov, the patient is asked to make a deep inspiration. If the spleen is palpable (and provided palpation is performed correctly), it is displaced during the inspiration by the descending diaphragm to come in contact with palpating fingers of the right arm and to slip over them (Fig. 18-13). This manipulation would be repeated several times in order to examine the entire palpable edge of the spleen.

If in the time of inspiration the perception of the edge of the spleen is not possibly received, the palpation of the spleen is retried. The fingers of the right arm must be transferred 1-2 cm upwards in the direction of the edge of the left costal arch. Palpation of the spleen is performed until the fingers of the right arm feel the spleen or the edge of the left costal arch. In the latter case, it is considered

that the palpation of the spleen is not possible and, hence, the spleen is not enlarged. If the spleen is determined by the palpation at the inferior edge of the left costal arch, there is nearly 1.5 (and more) times increase of the spleen.



(1) (2)

Fig. 18-13. Palpation of the spleen:
(1) formation of the skin fold; (2) dipping the fingers of the right arm in abdomen and formation of the artificial pouch according to V.P. Obraztsov

The characteristic peculiarity of the spleen is one or several notches (*incisures*) on the anterior edge of the spleen that can be palpated in case of its considerable enlargement. The notches are used to identify the spleen (to differentiate it from other organs, e.g., from the left kidney, tumors originated from the left kidney, splenic curvature of the transverse colon, and caudal part of the pancreas).

Normal spleen is impalpable. Considerable enlargement of the spleen is called splenomegaly. The spleen is only palpable in in splenomegaly and in rare cases of splenoptosis. The anterior surface of the enlarged spleen emerges from under the costal arch, and it becomes palpable (Table 18-8).

The spleen is enlarged in some acute and chronic infectious diseases (typhus, viral hepatitis, sepsis, malaria, etc.), in liver cirrhosis, thrombosis or compression of the splenic vein, and also in many diseases of the hemopoietic system (hemolytic anemia, thrombocytopenic purpura, acute and chronic leucosis). *The greatest enlargement of the spleen is observed in a terminal stage of the chronic myeloleucosis*: it often occupies the entire left part of the abdomen, while its lower pole is found in the small pelvis.

The spleen is not firm in acute infectious diseases; it is especially soft (the consistency of dough) in sepsis. *In chronic infectious diseases, liver cirrhosis, and leucosis the spleen is firm*. *Especially firm spleen presents in amyloidosis*.

Table 18-8. Diagnostic value of the spleen palpation

Spleen characteristics	Pathologic conditions
Impalpable spleen	norm
Palpable spleen	enlargement of the spleen more than one and a half
Considerable enlargement of the spleen (splenomegaly)	diseases of the blood system (leucosis, lymphogranulomatosis), liver cirrhosis, acute and chronic infectious diseases (typhus, viral hepatitis, sepsis, malaria, etc.), splenic vein thrombosis
Palpatory tenderness of the spleen	infarction, perisplenitis, thrombosis of the splenic vein
Soft enlarged spleen	sepsis, in acute infectious diseases
Irregular spleen surface	perisplenitis, past splenic infarctions, cysts, tumors

In most diseases, the spleen is insensitive to palpation. It becomes tender in infarction, perisplenitis, and in distension of the splenic capsule, due to the rapid enlargement, e.g., in venous blood congestion due to thrombosis of the splenic vein. The spleen surface is usually smooth; the edges and the surface are irregular in perisplenitis and old infarctions (depressions in the surface). In echinococcosis, cysts and very rare tumors of the spleen its surface is tuberous.

The spleen is normally quite mobile, but the mobility becomes limited in peri-splenitis. A markedly enlarged spleen remains motionless during respiration, but the palpating fingers can displace it.

18.9. The key points of the theme "Subjective and Objective Examination of Patients with Diseases of the Liver and Biliary Tract"

Patients with hepatobiliary diseases usually complain of the *pain* in *the right hypochondrium (sometimes in the epigastrium), dyspepsia, fat food intolerance, skin itching, jaundice, enlargement of the abdomen, fever*. Symptoms of the ***astheno-vegetative syndrome*** (weakness, non-motivated fatigue depressed mood, insomnia, irritability) are typical in chronic liver pathology.

General inspection finds *signs of the hepatic failure*: *hepatic jaundice, fetor hepaticus* (characteristic sweet-smelling breath), *hypoproteinemic edema, skin hemorrhages, and manifestations of hepatic encephalopathy – asterixis (flapping tremor), and mental state disorders from lethargy, obtundation, stupor, and up to deep hepatic coma*. The ***signs of the chronic liver failure*** (due to disordered utilization of steroid hormones in hepatocytes) are *"spider" angiomas*

palmar erythema, gynecomastia, "raspberry" tongue, loss of secondary sexual signs.

Hepatic jaundice develops due to the damage of the hepatocytes in acute and chronic hepatitis of various etiology, liver cirrhosis, toxic affections of the liver. There are yellow-reddish skin and dark brown ("beer-like") urine. Skin itching and pale stool may be.

Posthepatic jaundice develops due to the obstruction of the common bile duct by stones or growing tumors. There are yellow (later green and dark-olive) skin and mucosa, dark brown ("beer-like") urine, skin itching and pale stool. Posthepatic (mechanic) jaundice develops often after *biliary colic*.

Enlargement of the abdomen in liver diseases is a result of the *ascites* ("frog-like abdomen") and *hepato- and splenomegaly* with bulging right and/or left hypochondrium. The dilated venous network on the anterior abdominal around the umbilicus *("caput medusae*") is a sign of the portal hypertension.

Percussion determines borders and size of the liver. *Increase of the absolute dullness height relates to enlargement of the right lobe of the liver. Percussion according to M.G. Kurlov's method provides information about the size of the both liver lobes.* Inferior border of the liver descends in *hepatomegaly* (due to hepatitis, cirrhosis, cancer, congested liver in the heart failure, etc.). It can be due to lowering the diaphragm in asthenics, pulmonary emphysema or visceroptosis.

The inferior edge of the normal liver is palpated 1-2 cm below the costal arch between the right midclavicular and parasternal lines. *It is soft, acute or slightly rounded, smooth and insensitive.* The liver becomes firmer in hepatitis, congested liver, and in the liver cirrhosis and cancer (with irregular surface).

Percussion distinguishes the enlargement ***(splenomegaly)*** and descent **(*splenoptosis*)** *of the spleen. Normal spleen is impalpable*. It is palpated in splenomegaly (acute and chronic infections, liver cirrhosis, thrombosis of the splenic vein, diseases of the hemopoietic system) and in *splenoptosis*.

The ***gall bladder may be palpable, if it is markedly enlarged*** (hydrops, empyema, stones in the bladder, cancer, etc.). Palpation and percussion detects characteristic ***signs of the gall bladder inflammation*** (acute cholecystitis and exacerbation of the chronic cholecystitis) such as *signs of Murphy, Ortner, Lepene, de Mussy* (*phrenic) sign*, and tenderness in *Zakharin-Head zones.*

18.10. Assessment tests on the theme "Subjective and Objective Examination of Patients with Diseases of the Liver and Biliary Tract"

1. Typical localization of the pain in the hepatobiliary diseases:

1. right hypochondrium;
2. left hypochondrium;
3. epigastrium;
4. mesogastrium;
5. right ileum.

2. Hepatic (or biliary) colic is characterized by:

1. pain is the first localized in the right hypochondrium;
2. attacks of the pain develop suddenly;
3. pain may continue from several hours to a few days;
4. pain is provoked by fatty food;
5. pain is provoked by acid and salty food.

3. Hepatic (parenchymatous, hepatocellular) jaundice characteristics:

1. colour of the skin is typically lemon-yellow;
2. colour of the skin is typically yellow with a reddish tint;
3. skin itching absents;
4. skin itching may be;
5. colour of the stool and urine is not changed.

4. Posthepatic (obstructive, mechanical) jaundice characteristics:

1. colour of the skin is typically yellow with a green or dark-olive tint;
2. colour of the skin is typically lemon-yellow;
3. skin itching presents;
4. skin itching absents;
5. colour of the stool is dark.

5. Appearance of a bitter taste in mouth is typical to pathology of:

1. gallbladder and duodenum;
2. transverse colon;
3. large bowels;
4. esophagus;
5. small intestines.

6. What is typical to ascites?

1. enlargement of the abdomen;
2. "frog" shape of the abdomen in a horizontal position of the patient;
3. the “sign of the fluctuation” is determined;
4. venous network on anterior abdominal wall is well visible;
5. protrusion of the umbilicus.

7. Specify the "liver" signs detected at the general survey of the patients:

1. pale skin;
2. “spiders” angiomas;
3. redness of palms in the thenar and hypothenar region (palmar erythema, liver palms);
4. gynecomastia in males;

5. greenish-brown ring around the periphery of the cornea.

8. The cause of the venous network on the anterior abdominal wall is:
1. right ventricle failure;
2. portal hypertension;
3. anterior abdominal phlebitis;
4. ascites;
5. arterial hypertension.

9. Dimensions of the liver accordingly to M.G. Kurlov are:
1. 9-8-7 cm;
2. 12-11-10 cm;
3. 11-10-9 cm;
4. 11-9-7 cm;
5. 10-9-8 cm.

10. Height of the absolute liver dullness on the right anterior axillary line:
1. 7-9 cm;
2. 8-10 cm;
3. 9-11 cm;
4. 10-12 cm;
5. 12-14 cm.

11. Height of the absolute liver dullness on the right midclavicular line:
1. 9-11 cm;
2. 10-13 cm;
3. 8-10 cm;
4. 7-9 cm;
5. 11-13 cm.

12. Height of the absolute liver dullness on the right parasternal line:
1. 9-11 cm;
2. 10-13 cm;
3. 8-10 cm;
4. 7-9 cm;
5. 11-13 cm.

13. Palpation of the liver is performed:
1. after the percussion of the inferior border of the liver absolute dullness;
2. between the right parasternal and midclavicular lines;
3. between the right parasternal line and anterior median lines;

4. after installation of the left arm on the right costal arch;
5. after installation of the left arm on the right lumbar area.

14. Procedure of the deep liver palpation includes:

1. installation of the palpating arm on 3-5 cm below the liver inferior edge;
2. formation of the skin fold opposite of inferior edge of the liver;
3. dipping fingers of the palpating arm in abdomen;
4. sliding tips of palpating fingers up to inferior edge of the liver;
5. II and III steps of the liver palpation are during the same expiration.

15. Palpated characteristics of the liver inferior edge in norm are:

1. sensitive at palpation;
2. acute or slightly rounded shape;
3. elastic or dense;
4. smooth and mild;
5. 2-3 cm below the inferior edge of the costal arch.

16. Hepatomegaly causes are:

1. hepatitis;
2. tumour of the liver;
3. liver cirrhosis;
4. cardiac insufficiency;
5. chronic myeloleucosis.

17. With the percussion of the spleen superior border, the sound varies:

1. from resonant (pulmonary) to dull sound;
2. from dull to resonant (pulmonary) sound;
3. from tympanic to dull sound;
4. from hyporesonant to dull sound;
5. from resonant (pulmonary) to hyporesonant sound.

18. With the percussion of the spleen inferior border, the sound varies:

1. from a resonant (pulmonary) to a hyporesonant sound;
2. from a dull to a resonant (pulmonary) sound;
3. from a resonant (pulmonary) to a dull sound;
4. from a hyporesonant to a dull sound;
5. from a tympanic to a dull sound.

19. Percussion dimensions of the normal spleen are:

1. width - 2-4 cm, length - 5-7 cm;

2. width - 3-5 cm, length - 4-6 cm;
3. width - 4-6 cm, length - 6-8 cm;
4. width - 5-8 cm, length - 8-10 cm;
5. width - 6-9 cm, length - 9-11 cm.

20. Isolated splenomegaly (enlargement of the spleen) causes are:
1. cardiac insufficiency;
2. chronic myeloleucosis;
3. cyst of the spleen;
4. thrombosis of the splenic vein;
5. tumour of the spleen.

21. Characteristic signs of the gallbladder inflammation:
1. Murphy sign;
2. Ortner's sign;
3. pain in the right hypochondrium;
4. pain in the right ileum;
5. Courvoisier-Terrier sign.

22. Gall bladder is palpable:
1. in healthy people;
2. if the increased size;
3. in acute cholecystitis;
4. in acute hepatitis;
5. in hepatomegaly.

23. Painful palpatory areas and points in pathology of the gallbladder according to Zakharin-Head zones:
1. epigastrium;
2. the right shoulder zone;
3. point of the right scapular angle;
4. paravertebral points to the right of the VIII to XI thoracic vertebra;
5. the right phrenic nerve site.

CHAPTER 19. Laboratory and Instrumental Examination of the Liver and Biliary Tract

Goals: to enable students to learn -

1. biochemical liver function tests (pigmentary, protein, lipid liver enzymes, and microelements metabolism) and interpretation of the obtained results;

2. diagnostic value of serologic tests in hepatobiliary pathology*;*

3. diagnostic value of the instrumental methods for evaluation of structural and functional changes of the liver;

4. diagnostic value of the instrumental methods of the portal hypertension evaluation;

5. laboratory-instrumental methods for evaluation of the gallbladder and bile ducts (study of the bile, ultrasonography, endoscopic retrograde cholangiopancreatography, cholescintigraphy) and their diagnostic value.

19.1. Functional study of the liver (biochemical blood tests)

19.1.1. Pigmentary metabolism

Concentration of the bilirubin and its reduction products in the blood, feces, and urine demonstrates the pigment function of the liver. Deranged pigment metabolism indicates a disordered functional condition of the liver and helps to differentiate between various types of the jaundice.

Bilirubin is the final product of the *hem* utilization during natural *hemolysis* (destruction) of the aged red blood cells. Bilirubin is produced in the reticuloendothelial cells of the bone marrow, lymph nodes, and mainly in the spleen and the *stellar cells* of the liver.

The liver participates in bilirubin metabolism with the following functions:

- formation of the *indirect (unbound, unconjugated) bilirubin* in stellar reticuloendothelial cells;
- capture of the *indirect bilirubin* from the blood;
- bilirubin conjugation with glucuronic acid;
- secretion of the *bilirubin glucuronide (bound, or direct, conjugated bilirubin)* into bile.

Hyperbilirubinemia results from an increased bilirubin production, a decreased liver uptake or conjugation of the unbound bilirubin, or a decreased biliary excretion. An increased bilirubin production (e.g., in hemolysis), or decreased liver uptake, or conjugation (e.g., *Gilbert's disease*) causes *unconjugated (indirect, unbound) bilirubin* in the blood serum to increase. A decreased bile formation and excretion (*cholestasis*) elevates *conjugated (direct, bound) bilirubin* in the blood serum, and the latter appears in the urine.

Total bilirubin is normally under 20.5 μmol/l (Table 19-1). *Unconjugated hyperbilirubinemia* presents when the unconjugated fraction is above 15% of the total bilirubin.

Table 19-1. Biochemical blood serum tests in a functional study of the liver

Tests	Normal values[1] (SI units)
Bilirubin: total indirect direct	8.5 – 20.5 μmol/l <16.5 μmol/l 0.4 – 5.1 μmol/l
Total protein	65 – 85 g/l
Protein fractions: albumins globulins α_1- globulins α_2- globulins β- globulins γ-globulins	56-66% 34-44% 2,5-5% 5-9% 8-12% 12,8-19%
Total cholesterol	3.2 – 5.2 mmol/l
Triglycerides	0.41 –1.80 mmol/l
Serum iron : male female	13.0 – 27.0 μmol/l 11.0 – 25.0 μmol/l
Serum Fe-binding capacity	45-81 μmol/l
Serum ferritin	30-300 μg/l
Transferrin saturation	20–50%
Free serum copper	1.6-2.4 μmol/L or 10-15μg/dL
Total copper	10-22 μmol/L or 63.7-140.12 μg/dL
Serum ceruloplasmin	2.83-5.50 μmol/L or 18-35 μg/dL
Aspartate aminotransferase (AsAT, AST) : male female	 ≤37 U/l ≤31 U/l
Alanine aminotransferase (AlAT, ALT): male female	 ≤41IU/l <31 U/l
Creatine phosphokinase (CPK)	24-170 U/l
Lactate dehydrogenase (LDH, ЛДГ) $LDH_{4,5}$ - fractions	0,8- 4,0 mmol/l or ≤ 460 U/l 8-18%
γ- Glutamyl transpeptidase (γ-GGT, GTP): male female	 ≤35 U/l (МЕ/л) ≤50 U/l (МЕ/л)
Alkaline phosphatase (AP, ALP)	≤120 U/l (МЕ/л)

Note: 1 - Reference range can differ depending on the used test-systems; SI units – Standard International Units.

*Unconjugated hyperbilirubinemia is typical in prehepatic (hemolytic) jaundic*e, and in decreased bilirubin capture and/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 presents in hepatic jaundice*.

Urine bilirubin is absent in norm. *Bilirubinuria* (a positive test for the urine bilirubin) confirms any elevated levels of the conjugated hyperbilirubinemia.

Urobilinogen (urobilin) normally presents in trace amounts in the urine. This intestinal metabolite of bilirubin elevates due to hemolysis or from mildly impaired liver capture and excretion of the bilirubin (i.e., when the enterohepatic circulation of this pigment exceeds the liver's capacity to clear and excrete it). *Urobilinuria* is an early and a very sensitive sign of the liver dysfunction. Failure of the bilirubin excretion into the small intestine reduces urobilinogen formation so that the urine may test falsely low or absent.

The greater portion of the bilirubin is reduced in the intestine to *stercobilinogen.* It is converted into stercobilin to give feces its normal colour (upon exposure to air and light).

In prehepatic (hemolytic) jaundice, an increased production of stercobilin intensifies its excretion (under the name of urobilin) with urine (*urobilinuria*). *In posthepatic (obstructive) jaundice*, when bile is not excreted to the intestine, stercobilin is absent in feces and the urine is free from urobilin.

19.1.2. Protein metabolism

Amino acids, polypeptides of the food, and products of the tissue proteins breakdown 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 the 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 protein-synthesizing dysfunction of the liver 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 a characteristic of the most liver pathologies.*

Normal total serum protein content is 65-85 g/L. *Hypoproteinemia* (total plasma protein less than 65 g/L) is typical in a severe hepatocellular failure.

Serum albumin is produced in the liver by hepatocytes. Serum albumin is the main determinant of the plasma oncotic pressure, it transports numerous

substances (e.g., unconjugated bilirubin). Normal serum albumin fraction is 55-70% of the total serum protein. Its biologic half-life is about 20 days; thus, serum albumin levels are not diagnostic in acute hepatocellular failure.

Hypoalbuminemia (a decreased blood serum albumin) develops in the chronic liver disease with hepatocellular failure (liver cirrhosis, chronic hepatitis). Alcoholism, chronic inflammation of various internal organs, and malnutrition depress albumin synthesis. Hypoalbuminemia can result due to the albumin loss by the kidney (*albuminuria* in nephrotic syndrome), the 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).

Hyperglobulinemia (increased blood serum globulins) is a characteristic of the liver inflammation. The content of *α2-globulins* in the blood serum increases in patients with acute hepatitis, while in chronic hepatitis the *γ-globulin* content increases probably due to the accumulation of antibodies. *Hyperproteinemia* (increased total serum protein) often presents as well in hepatitis.

Hypoproteinemia (decreased total serum protein from the low serum albumin) is characteristic in patients with the liver cirrhosis; the content of γ-globulins, however, increases markedly.

Prothrombin (factor II of the blood coagulation) is produced in the liver with participation of the vitamin K. *Normal serum prothrombin index is 80-105%. Hypoprothrombinemia* develops due to hepatocellular failure (upset synthesis of the prothrombin by the hepatocytes) or vitamin K deficiency (the fat-soluble vitamin K is delivered to the liver from the intestine). Hypoprothrombinemia can be in posthepatic jaundice as a result of the deranged absorption of the vitamin K due to the obstructed delivery of the bile acids to the intestine.

Fibrinogen (factor I of the blood coagulation) is synthesized in hepatocytes. *Hypofibrinogenemia* is a sign of a serious liver pathology. The normal serum fibrinogen content is 2-4 g/1. *Hypoprothrombinemia and hypofibrinogenemia* are typical in the liver failure and manifested by hemorrhagic syndrome.

Alpha-fetoprotein (AFP) is a glycoprotein normally synthesized by the liver in an embryonal stage. It is elevated in neonates and the pregnant women. AFP reaches adult values (< 10 to 20 ng/mL) by the age of 1 year. An increase in AFP should suspect of the primary hepatocellular carcinoma. Mild elevation of the AFP also occur in the acute and chronic hepatitis, liver cirrhosis and sometimes in the acute (fulminant) liver failure. High AFP levels can occur in a few other malignancy of the liver (liver metastases of gastrointestinal tract cancers, cholangiocarcinoma).

Amino acids, urea, residual nitrogen and ammonia are the products of the protein decomposition. 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 the blood is a simultaneous liver and renal (hepatorenal) failure. Increased residual nitrogen occurring in the renal failure alone differs from that in the hepatorenal failure by the main component of the residual nitrogen. This are urea in the renal failure and amino acids in the hepatorenal failure.

The *blood ammonia* content increases when the liver is unable to detoxicate ammonia delivered from the intestine (by synthesizing urea). Accumulation of the ammonia in the blood produces a toxic effect on the central nervous system. *Hyperammoniaemia* is a forerunner of the coming hepatic coma.

19.1.3. Lipid metabolism

The liver performs synthesis and splitting of the fats, phospholipids, and cholesterol. Blood lipids change their concentration in the liver pathology.

Normal *total serum cholesterol* content is 3.2-5.2 mmol/1. Cholesterol concentration decreases in patients with hepatocellular failure (in severe acute and chronic hepatitis, and liver cirrhosis). *Serum cholesterol, triglycerides, and low-density lipoproteins increase* in posthepatic jaundice, and in the liver cholestasis (cholestatic hepatitis, biliary cirrhosis).

19.1.4. Liver enzymes

Biochemical signs of the liver damage are often the changes in the activity of a number of enzymes produced mainly by hepatocytes.

Serum enzyme tests can be grouped into three categories:

- enzymes which elevation in the blood reflects damage to hepatocytes;
- enzymes which elevation in the blood reflects cholestasis (It is a condition when the flow of the bile from liver is reduced or blocked);
- enzyme tests that do not fit precisely into either pattern.

Enzymes that reflect damage to hepatocytes (cytolisis). The aminotransferases (transaminases) are sensitive indicators of the liver cell injury in acute hepatocellular diseases such as hepatitis. They include the ***aspartate aminotransferase (AsAT, or AST)*** and the ***alanine aminotransferase (AlAT, or ALT).***

AST is found in the liver, myocardium and skeletal muscle, kidneys, brain, pancreas, lungs, leukocytes, and erythrocytes in decreasing order of concentration. ALT is found primarily in the liver. The aminotransferases concentration in blood serum is low in norm.

Normal blood serum concentrations of ALT are ≤41 U/L in males and ≤31 U/L in females, and AST – ≤37 U/L in males and ≤31 U/L in females.

These enzymes are released into the blood serum in greater amounts when there is a damage to the liver cell membranes resulting in increased permeability. The pattern of the aminotransferase elevation can be diagnostic.

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 the alcoholic liver disease and chronic autoimmune hepatitis.

Affection of hepatocytes also may be reflected by elevation of such blood serum enzymes such as *lactic dehydrogenase – fifth fraction (LDG_5), aldolase (fructose 1,6-phosphate aldolase)*, and sometimes *γ-glutamyl transpeptidase (GGT)*.

Enzymes that reflect cholestasis. The activities of the ***alkaline phosphatase (AP, ALP) and gamma glutamyl transpeptidase (GGT)*** are usually elevated in cholestasis. *Alkaline phosphatase* presents in the bile canalicular membrane of the hepatocytes, while *GGT* is located in the endoplasmic reticulum and in the bile duct epithelial cells.

Reflecting its more diffuse localization in the liver, *GGT elevation in serum is less specific for cholestasis than elevations of the AP*. The increase in the activity of these enzymes is most evident in posthepatic (obstructive) jaundice due to malignant tumour, and in intrahepatic cholestasis and biliary cirrhosis. In patients with affected liver parenchyma, the activity of the GGT and AP increases moderately. GGT can also increase in patients with alcohol diseases of the liver. AP increases also in extrahepatic malignant tumours (bronchogenic carcinoma, hypernephroma, Hodgkin's lymphoma).

19.1.5. Blood serum microelements

Certain blood *microelements* (*iron and copper***)** are important diagnostically in the liver pathology.

Iron is deposited in the liver as *ferritin*, an iron-protein complex that is a reserve of the iron used for the synthesis of the hemoglobin in the bone marrow. Another iron compound is *hemosiderin*, the product of the hemoglobin decomposition, which is accumulated in the liver in increased hemolysis and in some liver diseases. *Transferrin* (the transport protein) which carries iron from the liver to the bone marrow is synthesized in the liver.

Serum iron increases with damage to hepatocytes (cytolisis) in acute and chronic hepatitis, and in liver cirrhosis. *Elevated serum ferritin, iron, and transferrin saturation levels* are diagnostic in *hemochromatosis* (a genetic disorder characterized by excessive iron accumulation that results in the tissue damage of the liver, myocardium, pancreas, and suprarenal glands).

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 intrahepatic cholestasis (primary biliary cholangitis, cholestatic hepatitis), and in posthepatic jaundice.

Reduced serum ceruloplasmin and elevated urinary copper are diagnostic in the Wilson's disease (a genetic disorder characterized by excessive iron copper accumulation in the liver, central nervous system and other organs).

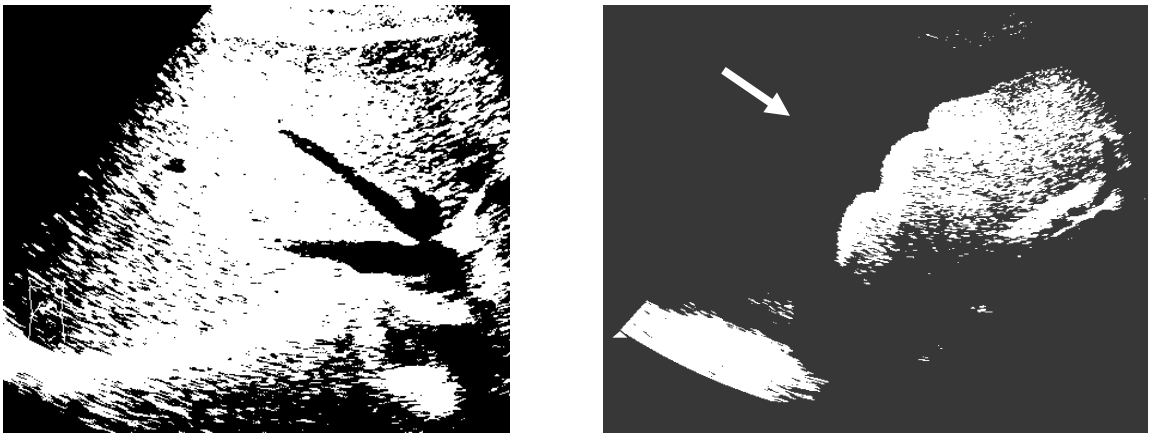
19.2. Serologic tests

Following serologic tests (measurement of immunoglobulins, antibodies, and autoantibodies) are diagnostic in the liver diseases:

- *IgM antibody to hepatitis A virus (anti-HAV)* for acute hepatitis A;
- *hepatitis B surface antigen (HBsAg)* for acute and/or chronic hepatitis B;
- *antibody to hepatitis C virus (anti-HCV) and HCV-RNA* for acute and/or chronic hepatitis C;
- *antimitochondrial antibody* for primary biliary cholangitis;
- *smooth muscle antibodies* against actin, *antinuclear antibodies (ANA),* and *antibodies to liver-kidney microsome type 1 (anti-LKM1)* in the autoimmune hepatitis.
-

19.3. Instrumental methods for evaluation of the liver structural and functional changes

Ultrasonography (US, echography) can be used to assess sizes of the liver, diffuse and local parenchymal changes of the liver, to detect cysts (almost in 90 % of cases), abscesses and tumours of the liver (almost in 80 % of cases). US helps to perform sighting biopsy of the liver and to differentiate between cirrhosis, hepatitis, and fatty liver (Fig. 19-1).



(1) (2)

Fig. 19-1. Liver ultrasound examination:
(1) liver in norm; (2) cirrhotic liver on the background of the ascites.

This method reveals liver affections at a comparatively early stage of the process. The US is used to study the *v. portae hepatis*, e.g. to detect dilated portal veins in the portal hypertension. Examination of the spleen establishes its position, reveals possible enlargement (which may be an indirect sign of the liver cirrhosis), and determines the structure of this organ.

Ultrasound elastography can measure the liver stiffness as an index of the hepatic fibrosis. In this procedure, the transducer emits a vibration that induces an

elastic shear wave. The rate at which the wave is propagated through the liver is measured; liver stiffness speeds this propagation. Elastography is often used in combination with blood tests to assess hepatic fibrosis, particularly in patients with chronic hepatitis. It is important for early diagnosis of the liver cirrhosis.

X-ray study. The plain X-ray of the abdomen can identify calcifications in the liver or gall bladder, opaque gall stones, and air in the biliary tract. Hepatic or splenic enlargement and ascites can be found.

Computed tomography (CT) helps to differentiate variations in density of the hepatic lesions, and with addition of an intravenous contrast make clearly visible abnormalities of the vascular system of the liver. CT is especially sensitive for visualizing malignant tumours and their metastases in the liver and masses in the pancreas. CT can detect fatty liver and the increased hepatic density associated with iron overload.

Magnetic resonance imaging (MRI, MRT) is a technology that may prove advantageous for identification of the liver tumors, biliary ducts and hepatic blood flow. Blood vessels are easily identified without contrast agents. MRI is comparable to CT in diagnostic value for detecting mass lesions.

Liver radioisotope hepatography is performed with *rose bengal labelled with* ^{131}I. The liver function is then examined by radiometric transmitters that are fixed over the heart region (to determine stain withdrawal from the blood), over the liver right lobe (to determine stain accumulation and withdrawal), and the central part of the abdomen (to control stain discharge via the biliary system ducts to the intestine). Radiohepatography can thus assess a 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 the rose bengal decreases. The secretory function of the liver is predominantly affected in inflammation and in obstruction of the bile ducts.

Radionuclide scanning is based on hepatic extraction of the injected radiopharmaceutical preparation (radioactive technetium; 99mTc) from the blood. Radioactivity in norm is uniformly distributed in the liver and spleen. In a space-occupying mass (e.g., cyst, abscess, metastasis, hepatic tumor), the replaced liver cells produce a cold spot. A generalized liver disease (e.g., cirrhosis, hepatitis) causes a heterogenous decrease in the liver uptake and the increased uptake by the spleen and bone marrow.

Liver puncture biopsy (percutaneous, laparoscopy) and transjugular liver biopsy are the "gold standards" in the evaluation of the liver tissue, particularly in patients with chronic liver diseases (e.g. chronic viral and autoimmune hepatitis, hemochromatosis, Wilson disease), liver cirrhosis and in a suspected liver malignancy. In selected cases, the liver biopsy is necessary for diagnosis but is more often useful in assessing the grade and stage of the liver damage, in predicting prognosis, and in monitoring response to the treatment.

19.4. Instrumental methods for the portal hypertension evaluation

Portal hypertension is an elevated pressure in the portal vein. It is most often due to liver cirrhosis.

Transjugular catheterization of the hepatic vein with measurement of the *hepatic portal venous pressure gradient (HVPG)* is considered the "gold standard" to determine the portal hypertension. Normal portal vein pressure is 5 to 10 mm Hg (7 to 14 cm H_2O), which exceeds inferior vena cava pressure by 4 to 5 mm Hg (*portal venous gradient*). Higher values supports a portal hypertension. Proof of the portal hypertension requires measurement of *the HVPG*, which approximates a portal pressure, by a transjugular catheter. However, this procedure is invasive and usually not performed.

Imaging studies such as ultrasonography, CT or MRI often reveal dilated intra-abdominal portacaval venous collaterals that present in portal hypertension. They can also demonstrate portal flow and helps in diagnosing portal vein thrombosis and splenic vein thrombosis.

Doppler ultrasonography is a noninvasive method used to assess direction of the blood flow and patency of the blood vessels, particularly the portal vein. Its diagnostic value includes detecting portal hypertension (e.g., indicated by significant collateral flow and the direction of the flow, increased diameter of the portal vein more than13 to 15 mm), and assessing the patency of the liver venous shunts (e.g., surgical portacaval, percutaneous transhepatic).

Upper GI endoscopy (or, esophagogastroduodenoscopy) is a standard for the assessment of the varices at any suspected case of the liver cirrhosis. *Esophagogastric varices (varicose dilated veins) and portal hypertensive gastropathy* are diagnosed by endoscopy. The presence of variceal red color signs ("cherry" red spots, "red wale" - longitudinal red streaks on varices), blue varices and the "white nipple sign" (platelet fibrin plug overlying a varix, resembling a white nipple) indicates an increased risk of the esophagogastric variceal bleeding.

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 can be used to expose ultra- and extrahepatic causes of the portal hypertension, the development of the collateral circulation, the character of the extension and the degree of the liver pathology (cirrhosis, primary and metastatic tumours, cysts).

19.5. Laboratory and instrumental methods for the evaluation of the gallbladder and bile ducts

19.5.1. Study of the bile

Until recent times, it was very common to study the biliary tract using multifactional duodenal intubation - a research method by introducing a probe into duodenum in order to receive its contents in different phases of the bile excretion. Duodenal contents were studied for determining the bile composition and bile culture.

However, the contents of the duodenum are a mixture of the bile, pancreas and duodenum secretions with a certain amount of the gastric juice. Therefore, duodenal intubation is now recognized as an inaccurate way to study bile characteristics and the functional state of the biliary system, and has been replaced by a modern ultrasound and endoscopic techniques.

In current times the bile samples from the common bile duct (*choledochu*s) can be collected with the use of the endoscopic cannulation of the *Vater's papilla* during a fibrogastroduodenoscopy and an *endoscopic retrograde cholangiopancreatography* (ERCP). Microscopic and microbiological examination of the fresh bile directly obtained from the choledochus yields may help in diagnosis of many gallbladder and biliary ducts lesions in early stages, thereby reducing the morbidity and mortality.

Microscopy of the bile samples may find *crystals of the cholesterol* (rectangular or rhomboid plates with notched corners) and *calcium bilirubinate* (brown rhomboid plates and needle-shaped clumps). *Biliary crystals* may be found in small quantities in healthy subjects, but in the large numbers (>4-5 in the microscope field ×200) they suggest *biliary microlithiasis, which may be associated with a biliary colic, a cholelithiasis and a recurrent pancreatitis*. The biliary microlithiasis progresses to the cholelithiasis.

Epithelial cells with dysplasia in microscopy of bile samples are important for early diagnosis of the malignant tumors. Special techniques like the immunocytochemical staining may increase the sensitivity for the detection of a malignancy.

Microscopy reveals *parasites in the bile*. *Lamblia intestinalis (or Giardia intestinalis)* occur frequently in cases of the diarrhea, abdominal pain, and biliary dysfunction. Research of the bile samples and the duodenal contents is recommended in suspicion of helminthiases of the liver and gallbladder (*Ascaris lumbricoides, Clonorchis sinensis, Opisthorchis viverrini, Opisthorchis felineus, Dicrocoelium dendriticum, Fasciola hepatica, and Fasciola gigantica*). The diagnosis of the helminthiasis is confirmed by the detection of the eggs by a microscopy of the bile, duodenal contents, or stool samples.

Microbiologic study of the bile culture and antibiotic sensitivity test are required to detect disease-causing microorganisms and choose etiological antibiotic therapy in cholecystitis and cholangitis. The most common pathogens are *E. coli, Klebsiella, Pseudomonas, S. aureus, Salmonella and Bacteroids fragalis.*

19.5.2. Instrumental methods for evaluation of the gallbladder and bile ducts

X-ray study. The *plain X-ray of the abdomen* can identify calcifications in the liver or gall bladder, opaque gall stones, and air in the biliary tract.

Endoscopic retrograde cholangiopancreatography (ERCP) combines endoscopy for identifying and cannulating the *Vater's papilla (major duodenal*

papilla) and radiology study after injection of a contrast agent into the biliary and pancreatic ducts. ERCP is especially valuable in assessing the biliary tract in case of persistent jaundice.

Computed tomography *(CT)* and m***agnetic resonance imaging (MRI, MRT)*** may identify structural abnormalities of the biliary ducts and gall bladder.

Ultrasonography (US, echography) *is especially useful to diagnose diseases of the gall bladder* (Fig. 19-3). *The 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 (choledochus) and sometimes to establish the cause of its obstruction (stones, tumor).

Echography is used to diagnose obstruction of the gall bladder by a stone, hydrops or empyema of the gall bladder, which arise in such obstructions, and also a cancer of the gall bladder, which often occurs.

(1) (2)

Fig. 19-3. Gall bladder ultrasound:
(1) gall bladder in norm; (2) cholelithiasis (gallstones).

Ultrasonography signs of gallstones are high echogenic foci within gallbladder lumen, posterior acoustic shadow, gravity-dependent movement of gallstones with a change of the patient position (the *rolling stone sign*).

Ultrasonography signs of the cholecystitis are a thickening the gallbladder wall (> 3 mm), pericholecystic fluid, an impacted stone in the gall bladder neck, tenderness when the gallbladder is palpated with the ultrasound probe (*ultrasonographic Murphy sign*).

Ultrasonography with cholekinetic test can evaluate gall bladder emptying

- *normal gall bladder emptying* is more than 40% to 70% of the fasting gallbladder volume in 30 minutes up to 1 hour after “cholekinetic breakfast” (per os 25-50 ml of the warm 25-33% solution of the magnesium sulphate, or vegetable oil, or 10% sodium chloride solution, or 40 % glucose solution or 40% sorbitol

solution), and also hormones (*cholecystokinin, pituitrin*) which are given subcutaneously);

- *gall bladder hypokinetic dysfunction* – emptying volume <40% of the fasting gallbladder volume after cholekynetic breakfast;

- *gall bladder hyperkinetic dysfunction* - emptying volume >70% of the fasting gallbladder volume after cholekinetic breakfast.

Liver radioisotope hepatography *with rose bengal labelled with* ^{131}I can assess patency of the bile ducts. The secretory function of the liver is affected in in the bile ducts obstruction (gallstones, tumours, etc.).

Cholescintigraphy *with 99mTc-iminodiacetic acid derivatives* is used for scanning the hepatobiliary excretory system. The liver clears these radiopharmaceuticals from plasma into bile much like bilirubin. A normal scan shows rapid uniform liver uptake, prompt excretion into the bile ducts, and a visible gall bladder and duodenum by 1 h. In acute cholecystitis (with cystic duct obstruction), the gallbladder is not visible by 1 hour. After cholecystectomy, this biliary scan can assess a quantitative biliary drainage and define the sphincter of Oddi dysfunction.

Cholescintigraphy with infusion of the cholecystokinin is the "gold standard" of the gall bladder motility study. An abnormal gall bladder emptying volume is defined as <38% of the fasting gallbladder volume over 60 minutes after infusion of 0.02 mg/kg of Sincalide (a synthetic C-terminal octapeptide identical to the sequences of the endogenous cholecystokinin hormone, CCK-8).

19.6. The key points of the theme "Laboratory and Instrumental Examination of the Liver and Biliary Tract"

Biochemical blood tests allow assess the functional state of the liver: pigmentary metabolism *(total, conjugated and unconjugated bilirubin);* protein metabolism (*total protein, albumin, globulins fractions, prothrombin, fibrinogen*); fat metabolism (*total cholesterol, triglycerides, high and low-density lipoproteins*); liver enzymes (*cytolysis markers – ALT, AST; cholestasis markers – AP, GGT*).

Immunology serologic tests are diagnostic in the liver diseases: *hepatitis B surface antigen (HBsAg)* for acute and/or chronic hepatitis B; *antibody to hepatitis C virus (anti-HCV) and HCV-RNA* for acute and/or chronic hepatitis C; *antimitochondrial antibody* for primary biliary cholangitis; *smooth muscle antibodies against actin, antinuclear antibodies (ANA), and antibodies to liver-kidney microsome type 1 (anti-LKM1)* in the autoimmune hepatitis.

Liver puncture biopsy (percutaneous, laparoscopy) and transjugular liver biopsy are the standard tests in the evaluation of the liver tissue with chronic liver diseases (e.g. chronic viral and autoimmune hepatitis, hemochromatosis, Wilson disease) and in a suspected liver malignancy.

Ultrasonography (US, echography), computed tomography (CT) and magnetic resonance imaging (MRI, MRT) are used to assess the condition of the liver tissue, to detect focal lesions (cysts, abscesses and tumours) of the liver.

Portal hypertension *is an elevated pressure in the portal vein. It is most often due to liver cirrhosis. Transjugular catheterization of the hepatic vein* with measurement of the hepatic portal venous pressure gradient (HVPG) is considered the "gold standard" to determine the portal hypertension. *Imaging studies such as ultrasonography, CT or MRI* often reveal dilated intra-abdominal portacaval venous collaterals that present in portal hypertension. *Upper GI endoscopy (or, esophagogastroduodenoscopy)* is a standard for assessment of the esophageal varicose veins dilatation at any suspected case of the liver cirrhosis.

Gallbladder and bile ducts functional state are evaluated by:

Ultrasonography (US, echography), computed tomography (CT) and magnetic resonance imaging (MRI, MRT) can be used for diagnosis diseases of the gall bladder (cholelithiasis, cholecystitis), posthepatic jaundice and to establish ductus choledochus obstruction. Ultrasonography with cholekinetic test can evaluate gall bladder emptying.

Cholescintigraphy with infusion of the cholecystokinin is the "gold standard" of the gall bladder motility study. An abnormal gall bladder emptying volume is defined as <38% of the fasting gallbladder volume over 60 minutes after infusion of the CCK-8.

19.7. Assessment tests on the theme "Laboratory and Instrumental Examination of the Liver and Biliary Tract"

1. Diagnostic serologic tests in viral hepatitis:

1. anti-HAV;
2. echinococcus antigen;
3. HBsAg;
4. anti-citrullinated protein antibody;
5. anti-HCV.

2. Diagnostic serologic tests in autoimmune hepatitis:

1. antinuclear antibodies (ANA);
2. antibodies to liver-kidney microsome type 1 (anti-LKM1);
3. HBsAg;
4. anti-HAV;
5. anti-HCV.

3. Standard tests in the evaluation of the histopathological changes in hepatitis and liver cirrhosis:

1. abdominal X-ray;
2. ultrasonography;
3. ultrasound elastography;

4. liver puncture biopsy;
5. radioisotope hepatography.

4. Imaging techniques for macroscopical pathological changes of the liver and the biliary system:

1. gastroduodenoscopy;
2. ultrasonography;
3. magnetic resonance imaging;
4. liver puncture biopsy;
5. computed tomography (CT).

5. Excretory function of the liver can be examined by:

1. radioisotope hepatography;
2. magnetic resonance imaging (MRI);
3. ultrasonography;
4. duodenal intubation;
5. computed tomography (CT).

6. Portal hypertension means:

1. elevated pressure in the portal vein;
2. symptomatic arterial hypertension due to liver fibrosis;
3. elevated pressure in hepatic veins;
4. elevated pressure in hepatic arteries;
5. elevated pressure in hepatic bile ducts.

7. Instrumental methods for the portal hypertension evaluation:

1. Transjugular catheterization of the hepatic vein;
2. Doppler ultrasonography;
3. radioisotope hepatography;
4. magnetic resonance imaging (MRI);
5. ultrasound elastography.

8. Normal portal vein pressure is:

1. systolic pressure –120 mm Hg, diastolic pressure – 80 mm Hg;
2. 5–10 mm Hg (7 –14 cm H2O);
3. 60–80 cm H_2O;
4. 25–30 mm Hg;
5. 15-25 cm H_2O.

9. Esophagogastric varices (varicose dilated veins) are diagnostic in:

1. gastroesophageal reflux disease (GERD);
2. hepatic failure;
3. heart failure;

4. syndrome of the portal hypertension;
5. chronic gastritis.

10. Which data of the bile microscopy indicates a predisposition to formation of the gallstones (cholelithiasis)?

1. crystals of the cholesterol;
2. crystals of the calcium bilirubinate;
3. epithelial cells with dysplasia;
4. Lamblia intestinalis (or Giardia intestinalis);
5. helminth eggs.

11. Ultrasonography signs of gallstones are:

1. low homogeneous echoes within gallbladder lumen;
2. posterior acoustic shadow;
3. gravity-dependent movement of gallstones with a change of the patient position (the rolling stone sign);
4. high echogenic foci within gallbladder lumen;
5. no posterior acoustic shadows.

12. It is typically in hepatic jaundice:

1. free and bound bilirubin in the blood are increased;
2. detection of the bilirubin in the urine;
3. detection of the urobilin in the urine;
4. decreased contents of the stercobilin in feces;
5. increased contents of the stercobilin in a feces.

13. It is typically in poshepatic jaundice:

1. free and bound serum bilirubin are increased;
2. total and serum bound bilirubin are increased;
3. presence of the urobilin in urine;
4. presence of the bilirubin in urine;
5. absence of the stercobilin in feces;
6. increased contents of the stercobilin in a feces.

14. Urobilinuria is typical in:

1. posthepatic (obstructive) jaundice;
2. hepatic (parenchymatous) jaundice;
3. prehepatic (hemolytic) jaundice;
4. uremia;
5. polyuria.

15. Bilirubinuria is typical in:

1. posthepatic (obstructive) jaundice;

2. hepatic (parenchymatous) jaundice;
3. prehepatic (hemolytic) jaundice;
4. uremia;
5. olygouria.

16. Liver failure is characterized by dysproteinemia that includes:
1. hypoproteinemia;
2. hypoalbuminemia;
3. hypoprothrombinemia;
4. hypofibrinogenemia;
5. hyperglobulinemia.

17. Laboratory tests that reflect damage to hepatocytes (cytolysis):
1. alanine aminotransferase;
2. aspartate aminotransferase;
3. lactate dehydrogenase;
4. alkaline phosphatase;
5. γ- glutamyl transpeptidase.

18. Laboratory tests that reflect cholestasis:
1. alanine aminotransferase;
2. serum cholesterol;
3. bound bilirubin;
4. γ- glutamyl transpeptidase;
5. alkaline phosphatase.

19. Laboratory biochemical tests for diagnosis of the liver failure:
1. alanine aminotransferase;
2. total protein;
3. serum albumin;
4. serum cholesterol;
5. serum prothrombin.

20. Dysfunction of the gall bladder is characterized by:
1. thickening the gallbladder wall (> 3 mm);
2. multiseptate gallbladder;
3. gall bladder emptying is more than 60 % of fasting volume by cholescintigraphy with infusion of the cholecyctokinin;
4. gall bladder emptying is less than 38% of fasting volume by cholescintigraphy with infusion of the cholecyctokinin;
5. gall bladder emptying is less than 40% of fasting volume by ultrasound with oral cholekinetic tests.

21. Ultrasonography signs of the cholecystitis are:
1. thickening the gallbladder wall (> 3 mm);
2. multiseptate gallbladder;
3. ultrasonographic Murphy sign;
4. moving gallstones within gallbladder lumen;
5. pericholecystic fluid.

CHAPTER 20. Clinical and laboratory Syndromes of the Liver and Biliary System Diseases

Goals: to enable students to learn –

1. clinical syndromes of the hepatobiliary disorders - jaundice, hepatic failure, portal hypertension, hepatic (portal-systemic) encephalopathy, hepatolienal syndrome, hypersplenism; asthenic syndrome, hyperestrogenemia syndrome, biliary pain;

2. laboratory biochemical syndromes of the hepatoboliary pathology (cytolysis, cholestasis, hepatocellular failure, mesenchymal inflammation).

20.1. Syndrome of the jaundice

Definition: Jaundice is a yellowish (icteric) colouration of the skin and mucosa by the increased content of the bilirubin in the tissues and the blood.

Causes of the jaundice include many diseases of the liver, bile ducts, blood, and also other organs and systems diseases, to which bilirubin metabolic disorders are secondary. Accurate diagnosis of various types of the jaundice is possible with special laboratory studies.

Classification of the jaundice:

I. According to causes-

- *prehepatic (hemolytic) jaundice* – due to excessive decomposition of erythrocytes (hemolysis) and increased secretion of bilirubin;
- *hepatic (parenchymatous, hepatocellular) jaundice* - due to impaired capture of unbound bilirubin by the liver cells and its inadequate combination with glucuronic acid (in the liver diseases);
- *posthepatic (obstructive, mechanic) jaundice* – due to the obstacles to the excretion of the bilirubin with bile into the intestine and reabsorption of the bound bilirubin in the blood *(in cholelithiasis, or in external compression of the choledochus by the pancreas tumour or cysts, cancer of the major duodenal papilla).*

II. According to the character of the hyperbilirubinemia

(1) *unconjugated hyperbilirubinemia* is due to –

- hemolysis, resorption of the large hematoma,
- decreased hepatic bilirubin uptake in the right ventrical heart failure, less common in hepatotoxic drugs, fasting, portosystemic shunts;
- decreased hepatic conjugation in Gilbert syndrome, hyperthyroidism, ethinyl estradiol (oral contraceptive) intake.

(2) *conjugated hyperbilirubinemia* is due to –

- hepatocellular dysfunction in hepatitis, liver cirrhosis, hemachromtosis, Wilson diseases, cholangitis;

- intrahepatic cholestasis in – an alcohol-related liver disease, drugs, toxins, viral hepatitis, primary biliary cholangitis, steatohepatitis;
- extrahepatic cholestasis in the bile duct stone, pancreatic cancer, cholangitis;
- hereditary disorders (Dubin-Johnson syndrome and Rotor syndrome).

Clinical picture:

Jaundice (icterus) can develop very quickly, within 1-2 days, to become very intensive when patients or their relatives see a yellow colour of the skin and icteric (yellow) sclera. A yellow colour of the skin and mucosa becomes visible when the serum bilirubin in the blood is above 35-40 mcmol/l. At other times, jaundice can develop gradually and be not pronounced (subicteric). Hepatic and posthepatic 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 in the hepatic and posthepatic jaundice, or on the contrary, dark-brown – in prehepatic jaundice. Accurate diagnosis of various types of the jaundice is possible with special laboratory studies.

Clinical-laboratory types of the jaundice

Prehepatic (hemolytic) jaundice develops as a result of the excessive destruction of erythrocytes (hemolysis) in the cells of the reticuloendothelial system (spleen, liver, bone marrow). The amount of the unconjugated (unbound) bilirubin formed from hemoglobin is so great that it exceeds the excretory liver capacity and results in its accumulation in the blood and the development of the jaundice. *Prehepatic (hemolytic) jaundice is the main sign of the hemolytic anemia.* It can also be a sign of other diseases, such as vitamin B_{12}-(folic)-deficiency anemia, malaria, infective endocarditis, etc.

The skin of the patient with hemolytic jaundice is a lemon-yellow. The skin itching is absent. Splenomegaly is often found in prehepatic jaundice. The amount of the unbound bilirubin in the blood is moderately increased. The urine is intensely dark-brown due to the markedly increased (5-10 times) urobilinogen. Feces are intense dark due to the considerable amount of the stercobilinogen (Table 20-1).

Hepatic (parenchymatous, hepatocellular) jaundice develops due to the damage of the parenchyma cells (hepatocytes). The serum content of the unconjugated (unbound) and conjugated (bound) bilirubin increases 4-10 times in the blood serum. The conjugated bilirubin appears in the urine (bilirubinuria). Excretion of the stercobilinogen with feces also decreases because the amount of the bilirubin excreted by the liver into the intestine decreases, but feces are rarely completely decoloured.

Common diseases in the hepatic jaundice are hepatitis, liver 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 and alcohol included).

The skin of patients with this type of jaundice is typically yellow with a reddish tint. Skin itching is less frequent than in posthepatic (obstructive) jaundice due to the upset of the bile acids synthesis by the affected liver. Symptoms of pronounced hepatic failure can develop in the severe liver disease. Hepatomegaly or hepatosplenomegaly often present in hepatic failure.

Table 20-1. Clinical-laboratory types of the jaundice

Type of the jaundice	Prehepatic (hemolytic) jaundice	Hepatic (parenchymatous) jaundice	Posthepatic (obstructive, mechanic) jaundice
Causes	hemolytic anaemia, malaria, infective endocarditis, B_{12}-(folic)-deficiency anemia	hepatitis, liver cirrhosis, cancer of the liver	cholelithiasis, cancer of the pancreas head or major duodenal papilla
Skin and visible mucosa	lemon-yellow, no itching	yellow with a reddish shade, itching can be	yellow, green and dark-olive
Abdominal examina-tion	splenomegaly (often)	hepatomegaly or hepato-splenomegaly	biliary colic episode is previous jaundice; Courvoisier-Terrier sign occur
Hyperbili-rubinemia	increase of the free (unconjugated) bilirubin	increase of the free (unconjugated) and (bound, or direct) conjugated bilirubin	increase of the conjugated bilirubin
Urine	intense coloring dark-brown, urobilinuria (increase of the urobilinogen)	intense coloring brown, bilirubinuria and urobilinuria	brown color, bilirubinuria (increase of the bound bilirubin)
Stool	intense dark, increase of the stercobilinogen	some decoloured, decrease of the stercobilinogen	colourless (acholic), stercobilinogen is absent

Posthepatic (obstructive, mechanical) jaundice develops due to a partial or a complete obstruction of the common bile duct (choledochus). This occurs mostly due to the 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 the obstruction by a gallstone.

The posthepatic (mechanic) jaundice often develops after biliary colic. 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. Abdominal palpation in the right hypochondrium can detect the significantly enlarged elastic painless gallbladder (*Courvoisier-Terrier sign*) in posthepatic jaundice due to the common bile duct (choledochus) obstruction by tumors of the pancreas head or the major duodenal papilla.

The conjugated bilirubin in the blood may be elevated up to 10-15 times and more. In protracted jaundice associated with the liver dysfunction, free (unconjugated) bilirubin content increases as well. The conjugated bilirubin in the urine (bilirubinuria) gives a brown color and a bright-yellow foam of the urine. In the complete obstruction of the bile ducts, feces become colourless (*acholic*). A stool color is grey-white and clayish because a stercobilinogen is absent in feces.

There is ***cholemia*** (an ample quantity of the conjugated bilirubin and bile acids in blood serum) in this type of the jaundice. *Cholemia results in a toxicosis with characteristic clinical manifestations, such as:*

- pronounced skin itching (*pruritus*), which intensifies by night;
- bradycardia (bile acids increase the vagus nerve tone);
- rapid fatigue, general weakness, adynamia, irritability, headache, and insomnia (due to the central nervous system affection);
- hepatic failure gradually develops if it is impossible to remove the cause of the impatency of the common bile duct (stones or a tumour).

Warning ("alarm") symptoms and signs in jaundice:

- pronounced pain in the right upper quadrant of the abdomen and fever – at suspicion on the acute biliary tract obstruction;
- painless jaundice, weight loss, a palpable abdominal mass in the aged patient – at suspicion on the biliary obstruction due to cancer;
- altered mental status, gastrointestinal bleeding, skin hemorrhages (*ecchymoses, petechiae, or purpura*) – at suspicion of the hepatic failure;
- acute jaundice in a young patient – at suspicion of the acute viral hepatitis.

Laboratory tests *are necessary to confirm a syndrome of the jaundice*:

- total and conjugated serum bilirubin;
- bile pigments of the urine (bilirubin, urobilinogen);
- stercobilinogen of feces.

Subsequent laboratory studies are:

- coagulation tests (platelet count, prothrombin time, fibrinogen, partial thromboplastin time) and liver biochemical tests (bilirubin, albumin, AST, ALT, ALP, GTP) for suspected hypocoagulation state and liver pathology;
- complete blood count - for suspected hemolysis for suspected acute cholecystitis and cholangitis, and a hemolysis can be confirmed by a peripheral blood smear.

Laboratory-instrumental imaging tests are abdominal ultrasonography. CT and MRI. Abdominal ultrasonography is indicated first to detect extrahepatic obstruction of the bile ducts (gallstones, common bile duct dilation, etc.). CT and MRI are more accurate for pancreatic lesions.

Endoscopic retrograde cholangiopancreatography (ERCP) is used in diagnosis and treatment of some obstructive lesions (choledochus stone removal, stenting of the choledochus and the major duodenal papilla strictures).

The *liver biopsy* can help in diagnosis of the intrahepatic cholestasis, chronic hepatitis, hemochromatosis, Wilson disease). The liver biopsy is also indicated in unexplained liver biochemical tests.

20.2. Syndrome of the hepatic failure

Definition*: *Hepatic failure *(liver failure, hepatic insufficiency*) is a clinical syndrome of disorders in important functions of the liver due to the marked dystrophy and destruction of hepatocytes.

Causes of a hepatic failure are acute and chronic hepatitis, liver cirrhosis, tumours of the liver, poisoning with hepatotropic chemical substances (phosphorus compounds, arsenic, large doses of the alcohol) or vegetable poisons (inedible mushrooms), adverse drug effects (acetaminophen, amoxicillin/clavulanate, halothane, iron compounds, isoniazid, nonsteroidal anti-inflammatory drugs [NSAIDs]), some compounds in herbal products and nutritional supplements.

Hepatic failure develops due to various complicated metabolic disorders in the liver, upset bile secretory and excretory function, and an impaired detoxicating function of the liver.

Hepatic failure is worsened by a portal hypertension. Portocaval shunting venous blood results in poisoning by nitrogenous substances of the intestinal (bacterial) protein decomposition and especially ammonia that pass into the greater circulation and lead to the hepatic encephalopathy up to coma. Hepatic coma may be provoked by intake of the alcohol, barbiturates and other hypnotic medications, some narcotic analgesics (morphine, fentanyl, etc.), psychotropic medications (neuroleptics, tranquilizers, sedatives), protein-rich diet, profuse hemorrhage from the digestive tract, by large doses of diuretics, abdominal withdrawal of large amounts of the ascites fluid, severe diarrhea, and the attending infectious diseases.

Classification of the hepatic failure*:*

1. *According to the course* – acute (up to 2 months), subacute (2-6 months) and chronic (> 6 months) hepatic failure.

2. *Stages of the hepatic failure* – (1) an early compensated stage; (2) pronounced decompensated; (3) a terminal dystrophic stage that ends in the hepatic coma and death.

Clinical picture*: The clinical symptoms are absent during the early stage of the hepatic failure*.

During the *second stage*, clinical manifestations of the hepatic failure develop. A patient complains of a non-motivated fatigue, poor appetite, increased weakness, frequent dyspepsia, poor tolerance of fat food, meteorism, rumbling and a pain in the abdomen, changed stools.

Loss of weight, hypoproteinemic edema and ascites develop due to deranged albumin synthesis in the liver (Fig. 20-1). *Hemorrhagic diathesis* (skin hemorrhages, nasal bleeding, hemorrhage in the intestinal tract) may be because of the upset synthesis of some blood coagulating factors (fibrinogen, prothrombin, proconvertin) and thrombocytopenia (due to hypersplenism that attends many chronic diseases of the liver). *Hepatic jaundice* with accumulation of the free (indirect) and bound (direct) bilirubin in the blood are frequent in hepatic failure. *Inadequate inactivation of estrogens* in chronic hepatic failure provokes *endocrine disorders (gynecomastia in men, menstrual disorders in women)* and *skin signs (palmar erythema and spiders angiomas).*

The third terminal stage of the hepatic failure is characterized by 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 (*hepatic encephalopathy*) which are precursors of the hepatic coma: decreased mental ability, slow thinking, slight euphoria, sometimes depression, and apathy. The patient becomes easily irritable, with quickly changed moods, and deranged sleep. Specific tremor (*asterixis*) of the upper and lower limbs is characteristic (*see Fig. 18-1. Asterixis*). The precoma period may last from a few hours to several days and even weeks.

Respiratory and urinary tract infections and sepsis can develop because of the immune deficiency.

A *clinical picture of the hepatic coma* is characterized first by excitation and then by general inhibition (stupor) and progressive derangement of consciousness to its complete loss (coma). The reflexes are decreased, but hyperreflexia and pathological reflexes (sucking and grasping) develop. Motor anxiety, clonic convulsions due to hypokalemia, muscular twitching, and tremor (arrhythmical and rhythmical twitching) of fingers and toes are characteristic. *Kussmaul respiration* (*less often Cheyne-Stokes respiration*) develops. Urine and stools incontinence presents. The patient's breath air (and also urine and sweat) smells "sweety" (*fetor hepaticus*). Inspection of the patient often reveals bleeding

gums, nasal and skin hemorrhage. Hepatic jaundice is intensified. The liver may remain enlarged or its size may decrease.

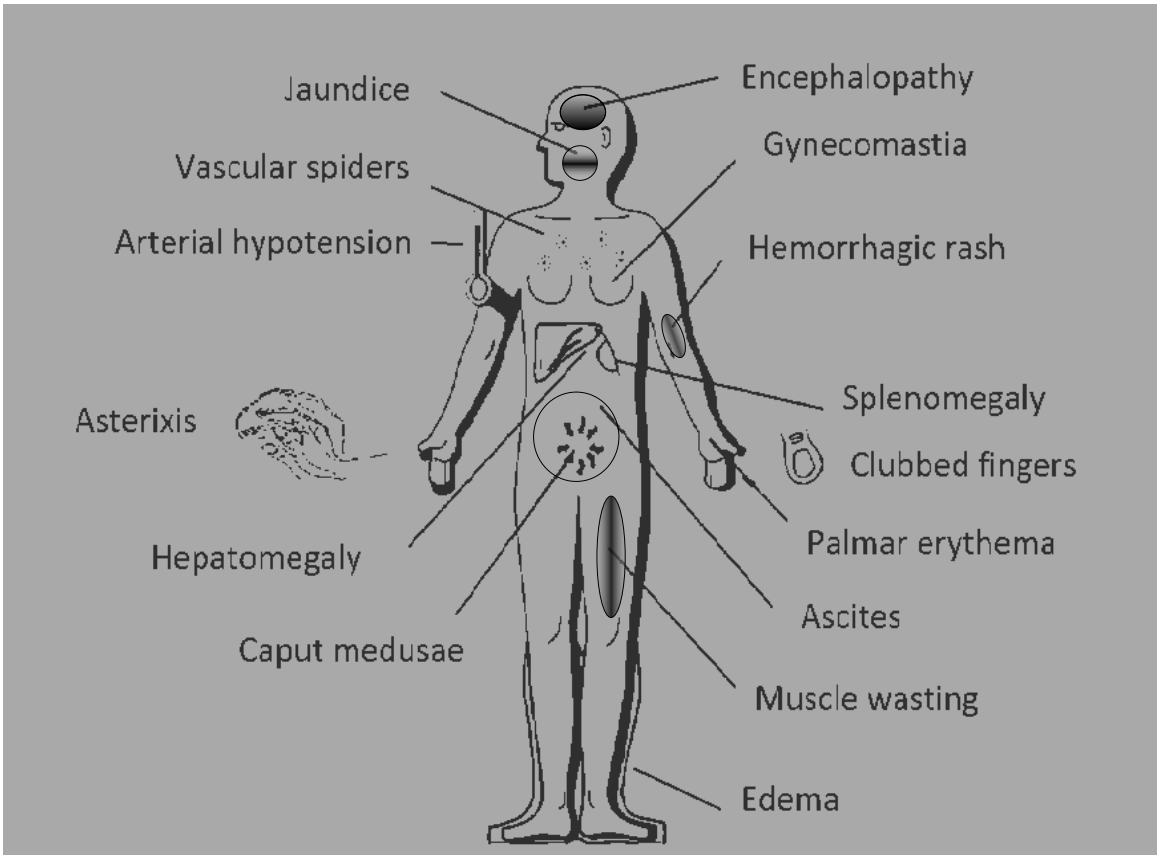


Fig. 20-1. Clinical manifestations in patients with chronic liver diseases.

Laboratory tests show anemia, thrombocytopenia, increased ESR. Hyperbilirubinemia and elevated serum level of aminotransferases (ALT, AST) are common. The characteristic is the decreased content of substances produced by hepatocytes: hypoalbuminemia, hypocholesterolemia, hypofibrinogenemia, hypoprothrombinemia. *Hypoglycemia* may be due to the depletion of the hepatic glycogen and an impaired gluconeogenesis.

The blood content of the urea decreases in the acute hepatic failure. The increase content of the residual nitrogen, ammonia, urea and creatinine in the blood serum indicates a secondary renal failure (*hepatorenal syndrome*).

Electrolyte and acid-base disorders such as hypokalemia, hyponatriemia, hypophosphatemia, hypomagnesemia and metabolic acidosis may develop. There are a respiratory and metabolic alkalosis at early stages of the acute hepatic failure.

Diagnosis of the hepatic failure is commonly confirmed by characteristic clinical manifestations of the liver encephalopathy and decreased content of substances produced by hepatocytes (hypoalbuminemia, hypocholesterolemia,

hypofibrinogenemia, hypoprothrombinemia) in patients with hyperbilirubinemia and elevated aminotransferase levels.

Prognosis of the hepatic failure can be serious when the patient has severe degree of the encephalopathy (precoma, coma), age > 40 years of old, hypoprothrombinemia and hypocoagulation.

20.3. Syndrome of the hyperestrogenemia (hypestrogenism)

Definition: Hyperestrogenemia is a clinical syndrome characterized by an excessive estrogenic activity in the body.

Causes and classification.

Hyperestrogenemia may be primary and secondary according to an origin.

Primary hyperestrogenemia develops due to an increased synthesis of estrogens by the corresponding glands (in female patients – by ovaries, adipose tissue and adrenal glands; in male patients – by testes, adrenal glands and adipose tissue).

Immediate causes of the primary hyperestrogenenemia causes are ovarian tumors, tumors of the pituitary gland and hypothalamus, stimulating an excessive production of estrogenes; pituitary and adrenal gland tumors, and chorionepithelioma (a uterine malignancy).

Secondary hyperestrogenemia is not due to a direct increase of the estrogen production by the endocrine glands. Exciting causes of the secondary hyperestrogenenemia include:

- uncontrolled use of the oral contraceptives or hormone replacement therapy in female patients;
- increased conversion of the androgenic steroids into estrogens (in skin, adipose tissue, muscle, and bones) in patients with obesity and/or chronic hepatic failure (due to chronic hepatitis and/ liver cirrhosis);
- aromatase excess syndrome – a genetic condition due to an increased aromatase enzyme activity and subsequent conversion of androgens to estrogen.

Clinical manifestations

Characteristic complaints are impotence and loss of libido – in males; and menstrual irregularities, amenorrhea, abnormal vaginal bleeding – in females.

General inspection detects “spider angiomas”, palmar erythema, gynecomastia, raspberry (crimson) tongue, loss of secondary sexual signs (loss of axillary and pubic hair), atrophy of testicles. *Drum (Hippocratic) fingers*, sometimes with white nails (*leuokonychia*) can be also caused by excess estrogens and chronic anemia in the liver diseases.

Laboratory tests detect elevated levels of the estrogen hormones, lowered levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), and lowered levels of testosterone (only in males).

Diagnosis of the secondary hyperestrogenemia in liver diseases is based on the typical clinical manifestations (“spider angiomas”, palmar erythema,

gynecomastia, raspberry tongue, loss of secondary sexual signs) combined with clinical and laboratory signs of the chronic liver pathology.

In addition to that, an identification of one or more clinical manifestations of the hyperestrogenemia indicates a diagnostic search for chronic liver disease (liver function tests, liver ultrasound).

Prognosis. *The syndrome of the hyperestrogenemia is considered as a marker of the developing hepatic failure in patients with the liver disease*. Some manifestations of the hyperestrogenemia (e.g., skin signs, hair loss) may be reversible with an effective treatment of the underlying liver disease. An untreated long-term gynecomastia is a risk factor for the breast cancer and needs to be consulted by an oncologist.

20.4. Portal hypertension

***Definition*:** Portal hypertension is a syndrome of the elevated pressure in the portal venous system.

Causes: Portal hypertension results from an increased portal flow or, in most cases, an increased resistance to flow. Portal hypertension is caused most commonly by the liver cirrhosis (in developed countries), schistosomiasis (in endemic areas), or hepatic vascular abnormalities.

Classification of the portal hypertension according to etiology:

I. ***prehepatic portal hypertension*** – due to

- obstruction of the portal vein and its prehepatic branches, such as portal or splenic vein thrombosis;

- increased portal flow in arteriovenous fistula, massive splenomegaly with primary hematologic disease (leucosis, lymphoma, etc.);

II. ***hepatic portal hypertension*** – due to the affection of the intrahepatic portal vein branches in liver cirrhosis, hepatitis, congenital hepatic fibrosis, schistosomiasis (blood flukes invasion that can result in the liver fibrosis and cirrhosis), etc.;

III. ***posthepatic portal hypertension*** – due to the affection of the hepatic veins or inferior vena cava, such as hepatic vein thrombosis (Budd-Chiari syndrome), obstruction of the inferior vena cava, cardiac causes (e.g., constrictive pericarditis, restrictive cardiomyopathy).

Clinical picture of the portal hypertension includes the symptoms due to portocaval anastomoses dilatation, ascites, and the enlargement of the spleen (*splenomegaly*). Portal hypertension can be for a long time asymptomatic until serious complications of the diseases develop.

The most important is an *acute variceal bleeding* - usually from the distal esophagus and fundus of the stomach, more rarely – rectal hemorrhage. “Caput medusae” is a symptom of the varicose veins radiated from the umbilicus.

Ascites is an accumulation of the free fluid in the abdominal cavity. Massive ascites may cause a nonspecific abdominal discomfort and dyspnea, but lesser amounts are usually asymptomatic. Ascites is diagnosed by a shifting dullness on

the abdominal percussion. Abdominal ultrasound or CT can detect a much smaller volume of the ascitic fluid. In advanced ascites, there is a prominent inferior part of the abdomen and protruding umbilicus in a vertical position, *"frog belly"* and flat umbilicus in a horizontal position, and a detected fluid wave (the *fluctuation sign*).

Usually, portal hypertension is suggested if a patient with a chronic liver disease has *hepatosplenomegaly and portal-systemic encephalopathy* (*see below*).

Diagnostic methods to detect portal hypertension:

- *transjugular catheterization* of the hepatic vein with measurement of the *hepatic portal venous pressure gradient (HVPG)* is the proof of the portal hypertension. However, this procedure is usually not done because of the invasive intervention;
- ultrasonography can reveal dilated intra-abdominal collaterals, and Doppler ultrasound can determine portal vein patency and flow;
- CT or MRI often reveal dilated intra-abdominal portacaval venous collaterals that present in portal hypertension;
- GI endoscopy detects esophagogastric varices and can also identify a high bleeding risk;
- splenoportography is a contrast technique to reveal the obstruction of the portal vein.

Diagnosis of the portal hypertension is suggested if a patient with a chronic liver disease has ascites, splenomegaly and/or symptoms of the portosystemic encephalopathy. The diagnosis should be confirmed by the data of the instrumental methods such as abdominal ultrasound, GI endoscopy, and in some cases – CT or MRI, and transjugular catheterization of the hepatic vein with measurement of the hepatic portal venous pressure gradient (HVPG).

Prognosis depends on severity of complications, such as portal-systemic encephalopathy, renal failure, ascites, spontaneous bacterial peritonitis, vascular collapse, cardiomyopathy. The most frequent lethal complication is a gastroesophageal variceal bleeding.

20.5. Hepatic (portal-systemic) encephalopathy

Definition: *Hepatic (portal-systemic) encephalopathy* is a neuropsychiatric syndrome caused by liver diseases and usually associated with liver dysfunction and portal-systemic shunting of the venous blood.

Causes. Hepatic (portal-systemic) encephalopathy may occur in severe acute hepatitis caused by viruses, drugs, or toxins, but it more commonly occurs in cirrhosis or other chronic liver disorders when extensive portal-systemic collaterals developed due to portal hypertension. Surgery created portacaval shunt or *transjugular intrahepatic portosystemic shunting (TIPS)* can be further complicated by portosystemic encephalopathy.

Predisposing factors are gastrointestinal bleeding; infection; electrolyte imbalance, especially hypokalemia; alcohol), iatrogenic causes (tranquilizers, sedatives, analgesics, diuretics), and a high protein diet.

Pathogenesis. The liver metabolizes and detoxifies digestive products brought from the intestine by the portal vein. In liver diseases, 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 in disorders of the cerebral neurotransmission. Biogenic amines, short chain fatty acids, and some other enteric products may also act with ammonia.

Clinical picture.

Early manifestations of the hepatic encephalopathy are not specific, and include changes in a sleep pattern (daytime sleepiness, night insomnia, hypersomnia), an inappropriate behavior, altered mood, error of judgement.

The advanced encephalopathy commonly shows an *impaired mental state (drowsiness, confusion, stupor, and hepatic coma* can develop). Sluggish movements and speech may occur.

There is a characteristic *flapping tremor (asterixis)* that can be detected when a patient holds his/her arms outstretched with wrists dorsiflexed (*see Chapter 18. Fig. 18-1*.). Asterixis disappears as coma progresses. Hyperactive deep tendon reflexes can occur.

Patients with hepatic encephalopathy usually have the accompanying physical signs of the advanced hepatic dysfunction and portal hypertension (see Fig. 20-1): jaundice, hepatosplenomegaly, ascites, edema, palmar erythema, “spider angiomas”, skin hemorrhages (petechia and ecchymosis), and *fetor hepaticus* (a typical musty sweet odor of the breath).

There are four stages of the hepatic (portal-systemic) encephalopathy (Table 20-2).

Laboratory and instrumental examination.

Hyperammoniaemia is the most characteristic laboratory sign in advanced stages of the portosystemic encephalopathy.

Laboratory biochemical blood tests usually find signs of the hepatocellular failure (hypoalbuminemia, hypocholesterolemia, hypoprothrombinemia, hypofibrinogenemia) and hyperbilirubinemia. Electrolyte disturbances (hyponatremia and hypokalemia) occur as a result of the portal hypertension and use of diuretics.

EEG (electroencephalography) shows a characteristic diffuse slow-wave activity, and can be useful in diagnosis of the early encephalopathy.

Psychometric tests (number connection test, paper-pencil tests, measurement of reaction times to auditory and visual stimuli) can reveal early neuropsychiatric abnormalities in the hepatic encephalopathy.

Table 20-2. Stages of the hepatic (portal-systemic) encephalopathy

Stage	Mental Status	Neuromuscular disorders	EEG*
I	Euphoria or depression, mild confusion, slurred speech, disordered sleep	Monotone voice Asterixis Poor handwriting	Triphasic waves
II	Drowsiness Disorientation Poor short-term memory Disinhibited behavior	Dysarthria Asterixis Automatisms (yawning, blinking, sucking)	Triphasic waves
III	Marked confusion, amnesia, incoherent speech, sleeping but arousable	Asterixis Nystagmus Muscular rigidity Hyperreflexia or Hyporeflexia	Triphasic waves
IV	Coma; initially responsive to noxious stimuli, later unresponsive	Dilated pupils Oculocephalic or oculovestibular reflexes Decerebrate posturing	Delta activity

Note: * EEG – electroencephalography.

Diagnosis is based on clinical a picture. There is no direct correlation with liver function tests. Laboratory and instrumental examination (ammonia level, electroencephalogram) with psychometric tests can help in diagnosis.

Prognosis is serious in case of the stages III-IV of the portosystemic encephalopathy (precoma and coma) associated with a severe liver failure.

20.6. Hepatolienal syndrome

Definition. *The hepatolienal (splenohepatomegaly, or hepatosplenomegaly) syndrome* is characterized by a concomitant enlargement of the liver (hepatomegaly) and spleen (splenomegaly) with a primary lesion of one of these organs.

Causes. The most common causes of the hepatolienal syndrome (up to 90% of cases) are acute and chronic diffuse liver diseases, less often chronic infections and parasitic diseases, metabolic diseases, blood diseases (Table 20-3).

Clinical manifestations of the hepatolienal syndrome in liver diseases

Splenomegaly develops later than hepatomegaly in patients with liver cirrhosis and chronic hepatitis. The degree of the splenomegaly usually depends

on the severity of the portal hypertension. A palpatory tenderness of the spleen presents in a case of the perisplenitis.

Table 20-3. Causes of the hepatolienal syndrome

Group of diseases	Causes
Liver cirrhosis and hepatitis	viral infection, autoimmune disorders, primary sclerosing cholangitis, metabolic disorder of copper, iron, alcoholic, primary biliary cirrhosis
Congestive hepato-pathy due to cardiovascular failure	cardiomyopathy, tricuspid regurgitation, right ventricle failure, cor pulmonale, constrictive pericarditis, etc.
Infections and parasitic diseases	acute infections – infectious mononucleosis, psittacosis, subacute bacterial endocarditis, sepsis
	chronic infections – brucellosis, candidiasis, histoplasmosis, malaria, miliary tuberculosis, visceral leishmaniasis, syphilis, schistosomiasis
Connective tissue systemic diseases and granulamatosis	systemic lupus erythematosus, sarcoidosis, histiocytosis, beryllium disease, histoplasmosis
Blood system diseases	- hemolytic anemias; - myeloproliferative diseases – polycythemia vera (erythremia), myelofibrosis, chronic myeloid leucosis; - lymphoproliferative diseases – chronic lymphocytic leucosis, lymphomas, lympho-granulomatosis, Waldenstrom's disease (macroglobulinemia)
Vascular disorders	external compression or thrombosis of the portal, splenic, and hepatic veins (the last – Budd-Chiari syndrome), malformations of the portal vein
Storage diseases	amyloidosis, Gaucher disease, Niemann-Pick disease, etc.

Hepatosplenomegaly (in dependence with the cause) has distinguishing characteristic signs:

- in the liver diseases, the consistency of both organs (liver and spleen) is dense, especially in the liver cirrhosis and cancer;
- in portal hypertension, the spleen enlarges significantly and often may be accompanied by a syndrome of the hypersplenism (a pancytopenia);
- in congestive hepatopathy due to a cardiovascular failure, the spleen enlarges slightly, and hypersplenism is absent;

- in infectious diseases (e.g., sepsis, infective endocarditis), both organs (liver and spleen) enlargement can be expressed equally.

Diagnosis of the hepatolienal syndrome is based on a physical examination and ultrasonography data (splenohepatomegaly, signs of the portal hypertension and hepatic failure), and supported by the data of the clinical blood analysis (anemia, thrombocytopenia, and sometimes leucopenia), biochemical liver functional tests, blood serum tests for virus hepatitis.

20.7. Syndrome of the hypersplenism

Definition: Hypersplenism is a clinical laboratory syndrome of the cytopenia (anemia, leucopenia, thrombocytopenia) and hemorrhagic complications due to considerable enlargement of the spleen (splenomegaly).

Causes of the hypersplenism can be splenomegaly of every etiology such as diseases of the liver (cirrhosis, acute and chronic hepatitis), infections (tuberculosis, infective endocarditis, malaria, syphilis, etc.) and systemic inflammatory diseases (lupus erythematosus, sarcoidosis), amyloidosis, diseases of the blood system (leucosis, lymphomas, hemolytic anemias), portal or splenic veins thrombosis, etc. Hypersplenism develops most frequently in the liver cirrhosis.

Pathogenesis. Splenomegaly in hepatobiliary diseases is a result of the increased splenic vein pressure and hypertrophy of the reticulohistiocytic tissue. A considerable enlargement of the spleen is usually attended by its hyperfunction *(hypersplenism)*, including an intensified destruction of the blood cells in the spleen, an inhibition of the hemopoiesis in the bone marrow, and antierythrocytic, antileucocytic, and antithrombocytic autoantibodies production in the spleen.

Clinical picture. The leading sign is splenomegaly that can be found with percussion and palpation. Intensity of other clinical manifestations (anemia, hemorrhagic symptoms and signs due to thrombocytopenia) of the hypersplenism depends on the size of the spleen.

Patients complain of weakness and easy fatigability (due to anemia), gingival hemorrhage, repeating nasal and other localization bleeding (due to thrombocytopenia).

General inspection detects paleness (due to anemia) and hemorrhagic spots on the skin and visible mucosa (conjunctivae, gums). Jaundice is commonly in liver diseases.

Severe leucopenia causes infectious complications (pneumonia, stomatitis, tonsillitis, pus infections, etc.).

Laboratory and instrumental examination

Ultrasonography can accurately measure the size of the spleen and detect a slight splenomegaly. *The size of the spleen is enlarged if its length is less than 13 cm and/or its width is less than 5 cm on an ultrasound examination.*

Clinical blood analysis in clinically apparent hypersplenism finds a platelet count $<50\text{-}100\times10^9$/l, leucocyte count $<2.5\times10^9$/l, and erythrocyte count <3.0-

3.5×10^{12}/l. Erythrocyte morphology is generally normal except in the case of *microspherocytosis and ovalocytosis*. Reticulocytosis usually presents.

Mild changes of the clinical blood analysis with a normal leucocyte formula are commonly asymptomatic.

Diagnosis of the hypersplenism is based on a physical examination and ultrasonography data (splenomegaly), and data of the common blood (anemia, thrombocytopenia, and sometimes leucopenia).

20.8. Asthenic syndrome in the liver pathology

Definition: Asthenic syndrome is a psychopathological condition characterized by a persistent and distressing complaint of the increased fatigue after a mental effort, or persistent and distressing complaints of the weakness and exhaustion after a minimal effort.

Causes. The etiology is a multifactorial, including genetic predisposition, infections (tuberculosis, viral hepatitis, Epstein–Barr virus infection, chronic herpes infection, etc.), exogenous (e.g., alcohol, smoking) and endogenous (hepatic failure, renal failure) intoxications, cardiovascular diseases (arterial hypertension, atherosclerosis, heart failure), endocrine pathology (e.g., thyrotoxicosis, decompensated diabetes mellitus) and other physical and/or emotional factors (excessive physical exertion, extreme situations, neuropsychic prolonged stress, physical inactivity and unstable weather conditions).

Clinical picture of the asthenic syndrome includes three stages of the symptoms development:

Stage I - irritability and excitability, possible aggressiveness, imbalance with frequent mood swings;

Stage II - increased fatigue and decreased performance capability, insomnia and headaches, unstable blood pressure and tachycardia, lack of the air;

Stage III - apathy and lethargy, decreased interpersonal contacts, manifestations of the panic, depression and various phobias.

The physical examination may be normal in some patients without objective signs of the hepatobiliary pathology. However, some patients have such non-specific symptoms as a loss of the appetite, loss of weight and muscle wasting, low-grade fever, nausea, meteorism, discomfort in the right upper quadrant of the abdomen, and unstable stool.

Asthenic syndrome in the liver diseases is usually combined with mild hepatic failure and hepatic encephalopathy. The typical accompanying objective signs include an icterus and hepatomegaly of the varying degrees, signs of the hyperestrogenemia syndrome (“spider angiomas”, palmar erythema, gynecomastia, raspberry tongue, etc.). Skin itching and xanthomas of the skin (most commonly – xanthoma palpebrarum) and mucosa present in the chronic intrahepatic cholestasis.

Laboratory-instrumental tests *can expose the hidden liver disease.* Biochemical blood analysis shows a decreased blood content of substances

produced by hepatocytes (hypoalbuminemia, hypocholesterolemia, hypofibrinogenemia, hypoprothrombinemia), hyperbilirubinemia and elevated aminotransferase levels, and positive serologic tests for virus hepatitis. Common blood analysis can find an anemia and thrombocytopenia. Abdominal ultrasonography can detect mild hepatomegaly and splenomegaly, some signs of the portal hypertension and assess the condition of the liver tissue. Esophagogastric varices (*varicose dilated veins*) are diagnosed by endoscopy.

Prognosis. Asthenic syndrome is commonly an early precursory manifestation of the hepatic failure and hepatic encephalopathy. Asthenic syndrome can be reversible with an effective treatment of the underlying liver disease.

20.9. Biliary pain

Definition: Biliary pain is an intense pain following the ingestion of the fatty food, it is located in the right upper quadrant of the abdomen or epigastrium.

Causes of the biliary pain are not only diseases of the biliary system (cholecystitis, gallstones, gallbladder and sphincter of Oddi dysfunction, biliary parasites), liver diseases (hepatitis, liver cirrhosis), but also of other parts of the digestive system (pancreatitis, peptic ulcers of the stomach and duodenum, duodenitis).

Predisposing factors are intake of the fat, fried, smoked and spicy food, alcohol, rare meals, and physical inactivity (hypodynamia).

Clinical picture includes *episodes of the steady pain (longer than 30 minutes) in the epigastrium and right upper quadrant of abdomen* (according to Rome IV criteria for biliary pain) (2016). *The pain commonly irradiates to the right and up - into the right scapula, the right subscapular region, the right shoulder, the right clavicle and /or the right subclavian region, the right half of the neck, right half of the lower jaw, sometimes the right frontal region, and the right eye* (see Chapter 18. Section 18.6. “Palpation and percussion in the gallbladder pathology”, Fig. 18-9).

Biliary pain may be acute (e.g. *bilary colic* due to acute obstruction of the common bile duct by gallstone in cholelithiasis, and in acute cholecystitis and cholangitis) *and chronic recurrent* (due to gallbladder and sphincter of Oddi dysfunction, chronic calculous cholecystitis).

The pain is not relieved by bowel movements (defection and gas passage), by a change of the body position, by intake of antacids. Recurrent pains occur at different intervals (not daily). The pain can awake a patient at night sleep. The pain is moderate to severe enough to interrupt the patient’s daily activities or call an ambulance (Table 20-4).

*The pain is usually associated with the “**biliary dyspepsia**” that include fatty food intolerance, an abdominal discomfort, a sensation of the fullness, nausea, and vomiting.*

Laboratory and instrumental examinations are necessary to diagnosis of the underlying biliary disease:

- tests of the liver biochemistries and pancreatic enzymes (for liver and pancreas diseases);
- ultrasonography of the liver, gall bladder and biliary tract, pancreas (to detect gallstones and structural abnormalities of these organs);

Table 20-4. Biliary pain characteristics

Characteristics	Clinical symptoms
Main causes	– biliary system diseases (e.g., cholecystitis, cholangitis, gallstones, gallbladder and sphincter of Oddi dysfunction, biliary parasites), – liver diseases (e.g., acute and chronic hepatitis) – pancreatitis
Pathological mechanisms	- obstruction of the common bile duct or the cystic duct by a gallstone; - dysfunction of the gallbladder and sphincter of Oddi
Localization	epigastrium and/or right upper quadrant
Time mode	– episodes last 30 minutes or longer; – recurrent pains occur at different intervals (not daily); – the pain can awaken the patient from sleep in the middle of the night
Perception level of the pain	– the pain builds up to a steady level; – the pain is moderate to severe enough to interrupt the patient's daily activities or lead to an emergency department visit
Irradiation	– to the back and/or right infrascapular region
Pain promoter	– fatty food
The pain is not relieved by	– bowel movements (stools, gas passages); – postural (body positioning) change; – antacids intake
Pain can be associated with	– nausea and vomiting
Biochemical blood analysis	– elevated ALT, AST – in liver diseases, – elevated lipase, alpha-amylase – in pancreatitis; – elevated bound bilirubin, alkaline phosphatase (ALP, AP) – in obstruction of the common bile duct

- duodenal intubation and microscopy of the bile (for laboratory signs of biliary microlithiasis, biliary dysfunction, inflammation and biliary parasite pathology, such as giardiasis, lambliasis, opisthorchosis., etc.);

- gastroduodenal endoscopy;
- CCK-cholescintigraphy or ultrasonography assessment of the gall bladder emptying;
- ERCP with biliary manometry detects sphincter of Oddi dysfunction.

20.10. Biochemical syndromes of the liver pathology

20.10.1. Hepatocellular insufficiency

Definition: Hepatocellular insufficiency is a set of the abnormal liver function tests due to hepatocyte cell damage that results in a decreased synthetic capacity, disordered pigmentary metabolism and detoxication function of the liver.

Causes of the hepatocellular insufficiency are acute and chronic hepatitis, liver cirrhosis, tumours of the liver, poisoning with hepatotropic drugs, mushrooms, some herbal compounds and nutritional supplements.

Liver functional tests in hepatocellular insufficiency show (Table 20-5):

- *decreased blood serum concentration of substances synthesized by hepatocytes* – hypoproteinemia, hypoalbuminemia, hypocholesterolemia, hypotriglyceridemia; hypoprothrombinemia, hypofibrinogenemia, and low serum cholinesterase (pseudocholinesterase); and in severe acute cases – hypoglycemia, low serum urea and hyperammoniemia.
- *hyperbilirubinemia may be due to hepatic jaundice* with an increased unconjugated (unbound) and conjugated (bound) bilirubin (because of decreased liver uptake or conjugation of the unbound bilirubin).
- There are bilirubinuria and urobilinuria, and decoloured stool may be (decrease of the stercobilinogen).

Table 20-5. Laboratory syndrome of the hepatocellular insufficiency

Underlying diseases	Laboratory indicators
• acute and chronic hepatitis, • liver cirrhosis, • tumours of the liver, • poisoning by hepatotropic drugs, mushrooms, etc.	• decrease in serum total protein, albumin, cholesterol, triglycerides, prothrombin, fibrinogen, pseudocholinesterase, glucose, urea, cobalamin, folates, iron; • increase in serum unconjugated bilirubin, ammonia

Clinical manifestations of the hepatocellular insufficiency are clinical syndromes of the *hepatic failure, hepatic jaundice, hepatic encephalopathy, hypocoagulation disorders, and anemia* (Table 20-6).

Table 20-6. Clinical importance of the hepatocellular insufficiency

Abnormal liver function tests	Disorders of the liver function	Clinical manifestations
Hypoproteinemia	decreased protein synthetic capacity of hepatocytes	weight loss, muscle atrophy, immunodeficiency and secondary infections
Hypoalbuminemia		mild edemas of lower extremities, ascites, hydrothorax
Hypoprothrombinemia, hypoproconvertinemia, hypofibrinogenemia	decreased production of blood coagulation factors	hemorrhagic syndrome with spontaneous hematomas and prolonged bleeding with injury, tooth extraction, or surgery, easy bruising, nasal and oral mucosal bleeding, melena, hematochezia, hematuria, intracranial hemorrhage
Hypolipidemia (hypocholesterolemia, hypotrigliceredemia)	decreased lipid synthetic function	weight loss, subcutaneous fat atrophy, vitamin E deficiency with neurology function deficiency (sensory neuropathy, paresthesias, ataxia, and spasticity) and visual changes, possibly hemolysis
Hypoglycemia	liver glycogen depletion	weight loss, general weakness dizziness, headache, hunger, nausea, profuse sweating, tremor, drowsiness
Reduction serum urea (in acute hepatic failure) and hyperammoniemia	decreased urea synthesis	hepatic encephalopathy
Decreased serum cobalamins (vitamin B_{12}), folates, and iron	absence of the liver stores	multiple-factor anemia, and neurology disorders

20.10.2. Cholestasis

Definition. Cholestasis is a decrease in bile flow due to impaired secretion by hepatocytes or to obstruction of bile flow through intra-or extrahepatic bile ducts that result in an increased blood concentration of substances normally excreted in bile by hepatocytes.

Causes

Obstructive cholestasis - cholelithiasis, cholangitis (primary sclerosing and infectious), congenital bile duct anomalies (choledochal cysts, biliary ducts atresia), biliary tract tumours.

Hepatocellular cholestasis – acute and chronic hepatitis, liver cirrhosis, drug-induced cholestasis, intrahepatic cholestasis of pregnancy, total parenteral nutrition-associated cholestasis, liver carcinoma and cancer metastases.

Liver function tests in cholestasis show increased serum concentration of substances normally excreted in bile by hepatocytes (Table 20-7)*:*

- hyperbilirubinemia (with mainly increased serum bound bilirubin),
- hypercholesterolemia (mainly in obstructive cholestasis),
- bile acids (*hypercholemia, cholemia*),
- alkaline phosphatase (ALP), γ-glutamyl transpeptidase (GGT), serum 5'-nucleotidase, and
- serum copper.

There is bilirubinuria and decoloured acholic stool (due to the decrease of the stercobilinogen).

Table 20-7. Laboratory syndrome of the cholestasis

Underlying diseases	Laboratory indicators
• cholelithiasis, • cholangitis • choledochal cysts, • biliary tract and liver cancer, • acute and chronic hepatitis, • liver cirrhosis, • drug-induced cholestasis	• increase in serum - conjugated bilirubin, - bile acids, - cholesterol, - alkaline phosphatase (ALP), - γ-glutamyl transpeptidase (GGT), - serum 5'-nucleotidase, - serum copper; • decrease in stool stercobilinogen

Clinical manifestations of the cholestasis *are pruritus (itching), posthepatic or hepatic jaundice, xantomas and xanthelasmas* due to retention of the bilirubin and other components of the bile and their regurgitation into blood serum (Table 20-8).

Pruritus (itching) is usually a few weeks (months) prior hepatic jaundice in cases of the hepatocellular cholestasis. *Steatorrhea, fat-soluble vitamin deficiency and malnutrition may develop due to acholia (insufficient bile secretion into intestine).*

Imaging instrumental examinations *(e.g., ultrasonography of the liver and bile ducts, abdominal CT, endoscopic retrograde cholangiography)* are necessary to diagnosis the underlying biliary disease (cholelithiasis, cholangitis, choledochal cysts, etc.) in case of the obstructive cholestasis.

Table 20-8. Clinical importance of the cholestasis

Abnormal tests	Clinical manifestations
Conjugated hyperbilirubinemia	posthepatic or hepatic jaundice
Hypercholemia (cholemia), increased levels of AP and GGT	pruritus (itching) and scratching
Hypercholesterolemia	xantomas and xanthelasmas
Acholia (insufficient bile secretion into intestine)	steatorrhea, malabsorbtion, weight loss
Fat-soluble vitamins deficiency due to steatorrhea	- vitamin E deficiency (peripheral neuropathy and possibly hemolysis), - vitamin D deficiency (osteoporosis, osteal pains, pathologic fractures of bones), - vitamin K deficiency (hypocoagulation due to hypoprothrombinemia), - vitamin A deficiency (skin rashes and ocular effects – xerophthalmia, night blindness)

20.10.3. Cytolysis

Definition. Cytolysis (violation of the hepatocytes integrity) is a clinical laboratory syndrome characterized by *hypertransaminasemia* (or an increase of the AST and ALT serum levels) as a nonspecific response of liver cells to the action of damaging factors with destruction of the hepatocyte membrane and intracellular organelles.

Causes. The main causes of the cytolysis are acute and chronic hepatitis (viral, toxic, drug-induced, auto-immune), acute biliary obstruction, liver cirrhosis, alcoholic liver diseases, non-alcoholic fatty liver diseases, hemochromatosis, Wilson's disease, liver cancer, vascular liver diseases, a_1-antitrypsin deficiency. Extrahepatic hypertransaminasemia causes frequently are myopathies, myositis, acute myocardial infarction, myocarditis, thyroid dysfunctions, celiac disease (gluten-sensitive enteropathy), adrenal gland insufficiency.

Clinical manifestations *in patients with the cytolysis are usually hepatomegaly and hepatic jaundice of a various intensity, and asthenic syndrome*. The high grade cytolysis may result in severe hepatic failure and encephalopathy.

Mild cytolysis may only manifest itself as asthenic syndrome and dyspeptic symptoms.

Laboratory tests of the cytolysis **are** increased blood levels of cytoplasmatic enzymes of the hepatocyte (see Table 20-9):

- aspartate aminotransferases (AsAT, AST);
- alanine aminotransferase (AlAT, ALT);
- lactic dehydrogenase (LDG) and 5th- fraction (LDG_5);
- γ-glutamyl transpeptidase (GGT, GTP); and
- serum ferritin and iron.

The *grade of the cytolysis* is assessed by the level of the AST and ALT increase: *mild cytolysis – less than 3 times, moderate cytolysis – 3-10 times, high grade cytolysis – above 10 times*. The high grade of cytolysis is a characteristic of the acute hepatitis (especially in viral etiology), and chronic hepatitis is commonly accompanied by a mild or moderate cytolysis.

Table 20-9. Laboratory syndrome of the cytolysis

Underlying diseases	Laboratory indicators	Accompanying clinical manifestations
• acute and chronic hepatitis, • liver cirrhosis, • alcoholic liver diseases, non-alcoholic fatty liver disease, • acute biliary obstruction, • liver cancer, • vascular liver diseases	• increase in serum - aspartate aminotransferase (AST), - alanine aminotransferase (ALT), - lactic dehydrogenase (LDG) and 5th- fraction (LDG_5), - γ-glutamyl transpeptidase (GGT), - serum ferritin and iron	• hepatomegaly, • hepatic jaundice, • asthenic syndrome, • dyspepsia

De Ritis ratio (ratio of the AsAT / ALAT) reflects the severity of the liver damage (normally 1.3-1.4). In most acute hepatocellular disorders, the ALT is higher than or equal to the AST, and De Ritis ratio is not more than 1.0. An increase in the De Ritis ratio of more than 1.4 (mainly due to AST) is observed in damage with destruction of most the liver cells (autoimmune hepatitis, liver cirrhosis, cancer of the liver). AST/ALT ratio more than 2:1 - 3:1 is highly suggestive for the alcoholic liver disease and chronic autoimmune hepatitis.

Subsequent laboratory instrumental studies commonly include serologic tests for viral and autoimmune hepatitis (see Chapter 19. Section 19.2. Serologic tests), serum ferritin, iron, and transferrin saturation levels (for hemochromatosis), serum ceruloplasmin and urinary copper (for Wilson's

disease) [see Chapter 19. Section 19.1. Functional study of the liver (biochemical blood tests)], an abdominal ultrasonography and liver biopsy.

Diagnostic importance of the cytolysis syndrome consists in a general indication of an inflammation (hepatitis) or other liver damages (e.g. toxic, vascular) with violation of the hepatocytes membranes integrity.

20.10.4. Mesenchymal inflammation

Definition: Mesenchymal inflammation is an inflammatory laboratory syndrome due to the development immune inflammation in the liver (sensitization of the immunocompetent cells, and infiltration of the portal tract and intralobular stroma) that results in an increased content of various globulin fractions produced by reticulohistiocytary cells of the liver.

Causes. The underlying causes are acute viral and chronic active (e.g. viral, autoimmune) hepatitis, chronic alcoholic liver disease, liver cirrhosis.

Laboratory tests of the mesenchymal inflammation (see Table 20-10) are increase in –

- serum globulins (alpha-, beta-, gamma globulins),
- immunoglobulin (Ig) of various classes,
- circulating immune complexes,
- nonspecific antibodies (antimitochondrial; anti-smooth muscle, anti-DNA, antinuclear, and liver antimicrosomal),
- indicators of protein-sediment tests (e.g. thymol turbidity test);
- breakdown products of the connective tissue – C-reactive protein (CRP), seromucoid;
- ESR,
- detection of the blood LE-cells (Lupus Erythematosus cell),
- changes in the number and functional activity of T- and B-lymphocytes.

Table 20-10. Laboratory syndrome of the mesenchymal inflammation

Underlying diseases	Laboratory indicators	Accompanying clinical manifestations
• acute viral and chronic active hepatitis, • chronic alcohol liver disease, • liver cirrhosis	• increase in serum - globulins (alpha-, beta-, gamma globulins), - immunoglobulins (Ig), - circulating immune complexes, - thymol turbidity test, - C-reactive protein (CRP), - seromucoid; • increase in ESR	• fever • splenomegaly • lymphadenopathy • polyarthralgia, • skin rashes, • vasculitis

Clinical manifestations of the mesenchymal inflammation can be *fever, splenomegaly, lymphadenopathy, polyarthralgia, skin rashes, vasculitis (with a skin, lung, and kidney lesions).*

20.11. The key points on the theme "Clinical and laboratory Syndromes of the Liver and Biliary System Diseases"

Jaundice *is an yellowish (icteric) colouration of the skin and mucosa due to an increased content of the bilirubin in the tissues and the blood.*

Hepatic (parenchymatous, hepatocellular) jaundice *is specifically attributed to liver diseases* (e.g., acute and chronic hepatitis, liver cirrhosis, liver cancer; alcohol, toxic and metabolic liver pathology). *The characteristic laboratory tests are elevated serum unbound and bound bilirubin, bilirubinuria and urobilinuria*. Acholic stool can be due to a stercobilinogen deficiency.

Posthepatic (obstructive, mechanic) jaundice *is specifically attributed to bile ducts obstruction* (e.g., in cholelithiasis, cancer of the major duodenal papilla). *The characteristic laboratory tests are elevated serum bound bilirubin, and bilirubinuria. Acholic stool can be due to a stercobilinogen deficiency.*

Hepatic failure (liver failure, hepatic insufficiency) *is a clinical syndrome due to the marked dystrophy and destruction of hepatocytes* (e.g. in acute and chronic hepatitis, liver cirrhosis, hepatotropic poisoning) that result in decrease of the synthetic and detoxication functions. *Characteristic manifestations are loss of weight, hypoproteinemic edema, ascites, hepatic jaundice, skin and mucosal hemorrhages, asterixis, and encephalopathy.*

Hyperestrogenemia develops in chronic hepatic failure due to an increased conversion of the androgenic steroids into estrogens (in skin, adipose tissue, muscle, and bones). It manifests with *endocrine disorders (gynecomastia in men, menstrual disorders in women) and skin signs (palmar erythema and spiders angiomas).*

Portal hypertension *is a syndrome of the elevated pressure in the portal venous system.* Portal hypertension develops most commonly in the liver cirrhosis due to an increased resistance to portal flow. *It manifests by ascites, splenomegaly, portocaval anastomoses dilatation (e.g. "caput medusae', esophagogastric varices).* The complications are gastroesophageal variceal bleeding, portal-systemic encephalopathy, renal failure, spontaneous bacterial peritonitis, vascular collapse, cardiomyopathy.

Hepatic (portal-systemic) encephalopathy *is a neuropsychiatric syndrome caused by liver diseases and associated with hepatic failure and portal-systemic shunting of the venous blood.*

Hepatolienal (hepatosplenomegaly) syndrome *is a concomitant enlargement of the liver (hepatomegaly) and spleen (splenomegaly) with a primary lesion of one of these organs.* The most common causes are acute and chronic hepatitis, liver cirrhosis, less often chronic infections and parasitic diseases, blood diseases.

Hypersplenism *is a clinical laboratory syndrome of the cytopenia (anemia, leucopenia, thrombocytopenia and hemorrhagic complications) due to considerable enlargement of the spleen (splenomegaly).*

Asthenic syndrome in the liver diseases is usually combined with a mild hepatic failure and hepatic encephalopathy.

Biliary-type pain *is an intense pain following the ingestion of the fatty food, and it is located in the right upper quadrant of the abdomen or epigastrium*. Causes of the biliary-type pain are mainly diseases of the biliary system (cholecystitis, gallstones, gallbladder and sphincter of Oddi dysfunction, biliary parasites), but also liver diseases, and pancreatitis.

Biochemical syndromes of the liver pathology:

Hepatocellular insufficiency is a set of the abnormal liver function tests due to hepatocyte cell damage that results in a decreased synthetic capacity (*hypoproteinemia, hypoalbuminemia, hypocholesterolemia, hypoprothrombinemia, hypofibrinogenemia*), disordered pigmentary metabolism (*hyperbilirubinemia with an increased unconjugated and conjugated bilirubin*) and detoxication function of the liver (*hyperammoniemia*).

Cholestasis is a decrease in a bile flow due to the impaired secretion by hepatocytes or to obstruction of a bile flow through intra-or extrahepatic bile ducts that result in an increased blood concentration of substances normally excreted in bile by hepatocytes [(*conjugated bilirubin, bile acids, cholesterol, alkaline phosphatase (ALP), γ-glutamyl transpeptidase (GGT)]*.

Cytolysis is characterized by *hyperenzemia (hypertransaminasemia, or an increase of the AST and ALT serum levels)* as a nonspecific response of the liver cells to the action of damaging factors with destruction of the hepatocyte membrane and intracellular organelles (e.g., in acute and chronic hepatitis, acute biliary obstruction, liver cirrhosis).

Mesenchymal inflammation is an immune inflammation in the liver with infiltration of the portal tract and intralobular stroma that results in an increased content of various globulin fractions [e.g., *serum globulins (alpha-, beta-, gamma globulins), immunoglobulin (Ig) of various classes, circulating immune complexes, CRP*).

20.12. Assessment tests on the theme "Clinical and laboratory Syndromes of the Liver and Biliary System Diseases"

1. What is typical in posthepatic jaundice?

1. free and bound bilirubin in the blood are elevated;
2. bilirubinuria;
3. urobilinuria;
4. elevated free bilirubin in the blood;
5. elevated bound bilirubin in the blood.

2. Clinical signs of the posthepatic jaundice are:

1. yellow-green colour of the skin;
2. skin itching;
3. dark-brown urine (colour of "beer");
4. acholic stool (decolouration of feces);
5. yellow-green stool;
6. acholic urine (decoloration of the urine).

3. **Clinical signs of the hepatic jaundice are:**

1. yellow-reddish colour of the skin;
2. skin itching absent;
3. dark-brown urine (colour of "beer");
4. hepatosplenomegaly;
5. dark-brown stool;
6. acholic urine (decolouration of the urine).

4. Clinical manifestations of the hepatic failure are:

1. "caput medusae";
2. hypoproteinemic edema;
3. jaundice;
4. hepatosplenomegaly;
5. asterixis.

5. Which laboratory tests are characteristics of the hepatocellular failure?

1. elevated serum levels of aminotransferases (ALT, AST);
2. elevated serum levels of the urea and creatinine;
3. hypoalbuminemia;
4. hypocholesterolemia;
5. hypofibrinogenemia;
6. hypobilirubinemia.

6. What is typical of the syndrome of portal hypertension?

1. enlargement of the abdomen;
2. "frog" shape of the abdomen in a horizontal position of a patient;
3. ascites;
4. venous network on anterior abdominal wall is well visible;
5. protrusion of the umbilicus.

7. Specify the signs of the hepatic failure detected at the general survey of patients:

1. pale skin;
2. “spiders angiomas”;

3. redness of palms in the thenar and hypothenar region (palmar erythema, liver palms);
4. gynecomastia in males;
5. greenish-brown ring around the periphery of the cornea.

8. A patient has a visible venous network on the anterior abdominal wall around umbilicus ("caput medusae"). What is the cause?
1. right ventricle failure;
2. portal hypertension;
3. anterior abdominal phlebitis
4. hepatic failure;
5. arterial hypertension.

9. Hepatosplenomegaly can be caused by:
1. thrombosis of the splenic vein;
2. tumor of the spleen;
3. liver cirrhosis;
4. right ventricle failure;
5. chronic myeloid leucosis.

10. It is typically of the syndrome of portal hypertension:
1. ascites;
2. arterial hypertension;
3. varicose dilation of esophageal veins;
4. splenomegaly;
5. varicose phlebectasia of the anterior abdominal wall ("caput medusae").

11. Clinical signs of the cholestasis syndrome are:
1. yellow-green colour of the skin;
2. skin itching;
3. dark urine (colour of "beer");
4. decolorization of feces;
5. yellow-green stool.

12. What is typical in hepatic jaundice?
1. free and bound bilirubin in the blood are increased;
2. detection of the bilirubin in the urine;
3. detection of the urobilin in the urine;
4. decreased contents of the stercobilinogen in feces;
5. increased contents of the stercobilinogen in feces.

13. Characteristics of the hyperestrogenemia in liver diseases:
1. "spider angiomas";

2. “caput medusae”;
3. ascites;
4. gynecomastia;
5. asterixis.

14. What syndrome distinguishes between chronic hepatitis and cirrhosis of the liver?

1. expressed portal hypertension;
2. dyspeptic syndrome;
3. asthenic-vegetative syndrome;
4. abdominal pain syndrome;
5. hepatic jaundice.

15. Diagnostic methods to detect portal hypertension:

1. taking arterial blood pressure;
2. ultrasonography (to reveal dilated portal vein abdominal collaterals;
3. endoscopy (to detect esophagogastric varices);
4. transjugular catheterization of the hepatic vein with measurement of the hepatic portal venous pressure gradient (HVPG);
5. measurement central venous pressure.

16. Clinical manifestations of the hepatic encephalopathy:

1. Ortner's symptom;
2. dysarthria;
3. flapping tremor (asterixis);
4. exophthalmos;
5. poor handwriting;
6. Graefe's sign.

17. Laboratory characteristics of the hypersplenism:

1. anemia;
2. leucopenia;
3. thrombocytopenia;
4. retyculocytopenia;
5. sarcopenia;
6. myeloplegia.

18. Clinical manifestations of the hypersplenism:

1. splenomegaly;
2. repeating nasal and gingival hemorrhage;
3. hepatomegaly;
4. generalized lymphadenopathy;
5. hepatic jaundice;

6. perisplenitis.

19. Laboratory tests for diagnosis of the cytolysis syndrome:
1. alanine aminotransferase (ALT);
2. aspartate aminotransferase (AST);
3. lactate dehydrogenase (LDH);
4. γ- glutamyl transpeptidase (GGT);
5. alkaline phosphatase (ALP).

20. **Laboratory tests for diagnosis of cholestasis syndrome:**
1. alanine aminotransferase (ALT);
2. cholesterol;
3. conjugated bilirubin;
4. aspartate aminotransferase (AST);
5. alkaline phosphatase (ALP).

21. Asthenic syndrome in the liver pathology is typical in:
1. hepatomegaly;
2. splenomegaly;
3. mild hepatic failure;
4. mild hepatic encephalopathy;
5. posthepatic jaundice.

22. Biliary-type pain characteristics:
1. steady pain (longer than 30 minutes);
2. in the epigastrium and right upper quadrant of the abdomen;
3. usually 10-15 minutes;
4. in the right hypogastrium alone;
5. antacids relive the pain.

23. Laboratory tests of the mesenchymal inflammation:
1. elevated serum levels of aminotransferases (ALT, AST);
2. elevated serum levels of the urea and creatinine;
3. hypoalbuminemia;
4. hyperglobulinemia;
5. elevated serum level of the C-reactive protein.

Unit VI. Urinary System Examination

CHAPTER 21. Subjective and Objective Examination of Patients with Diseases of the Urinary System

Goals: to enable students to learn -

1. subjective examination (inquiry) of patients with kidneys and urinary tract pathology, and interpretation of the obtained results;
2. technique of the general inspection in patients with urinary system pathology, and its diagnostic value;
3. technique and diagnostic value of the percussion and palpation of the kidneys and the urinary tract, and auscultation of renal arteries.

21.1. Subjective examination of patients with the urinary system diseases

Complaints

Patients with disorders of the urinary system usually complain of **specific (kidneys and urinary tract) symptoms and systemic symptoms.**

21.1.1. Specific complaints of the urinary system diseases

The ***specific complaints*** *are pains in the lumbar region and other parts of the abdomen (right and left flanks, suprapubic region), an impaired urinary excretion (amount of urine) and an urination (frequency changes, dysuria), a discoloration of the urine, and edema.*

The general principle is a detailing each complaint: in the case of a pain, it is necessary to specify the exact localization, character, frequency, duration of the pain, and conditions of the pain onset, the connection with urination, the pain radiation, combinations with dysuric manifestations and a fever.

21.1.1.1. Urinary system pain

Kidney pain is usually felt in the flank or lumbar region between the XII rib and the iliac crest, the costovertebral angle formed by the XII rib and the lumbar spine, with the occasional radiation to the epigastrium. The renal tissue does not contain pain receptors. The kidney pain is due to distension of the renal capsule or the renal pelvis (Table 21-1).

The kidney pain is typical in acute glomerulonephritis, pyelonephritis, acute ureteral obstruction, tumors, and in a "congestive kidney" due to cardiovascular failure decompensation.

Renal colic is a periodical severe unilateral pain over the lumbar area, in flanks and hypochondria, with radiation into the iliac area, and often into the upper thigh, urethra and external genital organs (testicle or labium) (Fig. 21.1). The most common causes of the renal colic are an obstruction of the ureter by a urinary stone or its bending (“movable kidney”), an inflammation or acute distention of the renal pelvis in nephrolithiasis and acute pyelonephritis. The pain can be

provoked by taking much liquid and jolting motion in nephrolithiasis, and abrupt motions of the body in “movable kidney”.

Table 21-1. Urinary system pain

Pathophysiologic types	Characteristics of the pain	Localization of the pain	Underlying disease
Spasm of the urinary tract	acute attacks of the intensive pain	• lumbar area and along the ureter (flank and ileum region); • pain radiation to the groin and genital organs	urolithiasis
Inflammatory mucosal edema and / or distension of the renal pelvis	increasing and decreasing intensive pain	• lumbar area	acute and chronic pyelonephritis
Distension of the renal capsule	• dull, aching mild pain • constant long-standing pain	• lumbar area	acute glome-rulonephritis, amyloidosis of the kidney, etc.

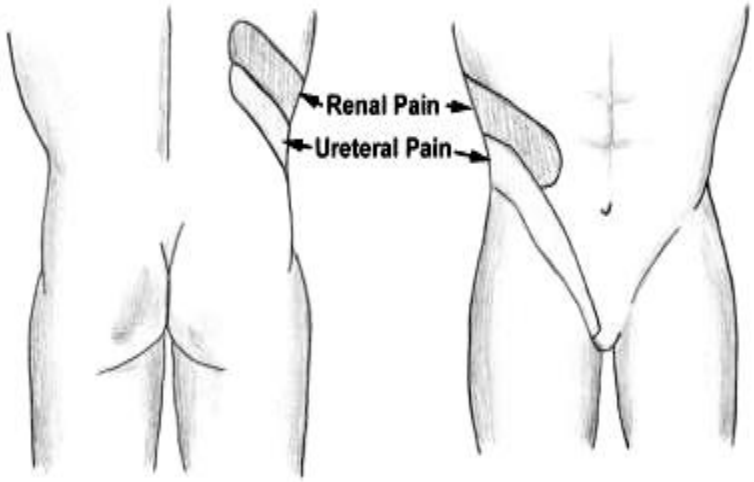


Fig. 21.1. Localization of the pain in renal colic.

The pain is intermittent, but a complete pain relief is not observed between waves of the renal colic. Patients’ toss and turn in bed by contrast with patients with other etiology of the severe pains (when movements may intensify the pain). The pain may lessen with the change of the patient position due to the

improvement of the urine outflow. A hot application, a hot bath, spasmolytic and analgesic medications can relieve the renal colic.

Urinary bladder pain is usually caused by bacterial cystitis. It is felt in suprapubic region during urination.

Patients with urethritis feel a burning pain in the urethra during or after urination.

Stranguria (Strangury) *is a condition of a frequent, slow and painful urination of small volumes.* It is accompanied by a sense of straining and usually with the residual feeling of the incomplete emptying (*urinary, or vesical tenesmus*). Stranguria is caused by muscular spasms of the urethra and urinary bladder in urolithiasis, (especially when a stone is impacted at the vesicourethral junction), cystitis, and the urinary bladder cancer.

Prostate gland pain *may be felt as a fullness or discomfort in the perineal or rectal area.*

21.1.1.2. Dysuric symptom complex

Dysuria (dysuric symptom complex) ***includes difficulty and pain when urinating, changes in the urine stream and deranged excretion of the urine (changes in the daily volume of the excreted urine and in the daily rhythm of the urination).***

Dysuria can be an independent phenomenon and a concomitant pain syndrome. Dysuria with *difficult and painful urination is observed in cystitis, urethritis, urolithiasis, prostate adenoma.*

Changes in the urine stream (strong or weak, thin, intermittent) are signs of the lower urinary tract pathology (e.g., prostate adenoma, urethritis, urethrostenosis). It can be combined with urinary incontinence.

Changes in the daily volume of the excreted urine

Diuresis *is an urinary excretion during a certain period of the time.*

The daily diuresis is a volume of the 24-hours urination from the first early morning urination including urination in the evening and at night time, but except for the first urination volume in the next morning.

Positive diuresis is a situation when the excreted urine volume exceeds the volume of the liquid intake. It occurs in resolution of the edema, after administration of diuretics, and in some other cases.

Negative diuresis is a situation when the liquid intake volume exceeds the excreted urine volume. It occurs in an increased liquid retention in the body (e.g. in an increased edema, hydrothorax, ascites) or its excess excretion through the skin (excessive sweating, or *hyperhidrosis*), by the lungs (e.g. in dry and hot weather, tachypnoe).

Polyuria *is an increased volume of the daily diuresis (over 2 1itres urine a day). Physiological polyuria* (in normal patients) can be due to the use of large amounts of the liquid, sugar, and in the temperature reduction of the environment (Table 21-2).

Table 21-2. Urinary excretion disorders

Urinary excretion disorder	Characteristics	Causes
Polyuria	an increased volume of the daily diuresis (over 2.0 1itres urine a day)	• massive water input; • introducing osmotically active agents (mannitol; 40% glucose solution; albumin); • diuretics; • renal failure; • pyelonephritis; • diabetes mellitus; • diabetes insipidus
Oliguria	a decreased daily diuresis (less than 500 ml per day)	• *prerenal cause* – limited fluid intake; profuse sweating; profuse diarrhea; uncontrollable vomiting; heart failure; • *renal causes* – various kidney diseases, renal failure; • *postrenal causes* – urinary tract obstruction
Anuria	an absence of the diuresis or less than 50 ml per day of the excreted urine	• violation of glomerular filtration (shock, acute blood loss, uremia); • violation of the urine passage along the urethra (paresis of the urinary bladder; the prostate gland enlargement; urethra strictures)
Ischuria	a stoppage or reduction in the urine flow due to the urine retention in the urine bladder	• obstruction of the urethra by enlarged prostate gland, bladder stones or urethra strictures, compression or other affection of the spinal cord
Pollakiuria	a frequent repeated (more than 7 times a day) urination	• during an edema reduction; • taking diuretics; • cystitis, urethritis
Stranguria	a frequent, slow and painful urination of small volumes	• muscular spasms of the urethra and urinary bladder in urolithiasis, and cystitis; • urinary bladder cancer

There are *renal and extrarenal polyuria* (according to causes*)*. Polyuria is observed during the (cardiac or renal) edema resolution, with resorption of pleural

exudate, ascites, the use of diuretics, after an episode of the angina pectoris, hypertensive crisis and paroxysmal tachycardia (*urina spastica*).

Diabetes mellitus is characterized by a persistent polyuria up to 8-10 liters per day with an increased specific gravity of the urine (*hypersthenuri*a).

In diabetes insipidus (due to antidiuretic hormone deficiency or decreased sensitivity of renal tubules to this hormone), polyuria is over 10 liters per day, but with a low specific gravity (*hyposthenuria*).

Persistent polyuria with hyposthenuria is observed due to decreased reabsorption in renal tubules in chronic kidney disease (e.g., chronic glomerulonephritis, pyelonephritis, renal amyloidosis, polycystic kidney disease, and glomerulosclerosis) and in the high output stage of the acute renal failure, acute kidney injury with affected renal medulla of various nature, in mineral metabolism disorders (hypokalemia, and hypo- and hypercalcemia).

Oliguria *is a decreased daily diuresis (less than 500 ml per day). Prerenal oliguria is not associated with urinary system pathology. Prerenal oliguria* is due to limited intake of liquids, during staying in a hot and dry room, in cases of the profuse sweating, uncontrollable vomiting, profuse diarrhea, accumulation of the fluid in the body (decompensated heart failure), a large blood loss, shock.

Renal oliguria is the result of the kidneys diseases, such as acute nephritis, acute kidneys injury in poisoning with corrosive sublimate (mercuric chloride), nephrotoxic medications, and in transfusion of the incompatible blood.

Postrenal oliguria is the result of the urinary tract obstruction (in prostatic hypertrophy, urinary calculi) and urinary bladder or sphincter dysfunction.

Anuria is a complete absence of the diuresis or a volume reduction of the excreted urine (less than 50 ml per day - by the urinary catheter).

True renal anuria (secretory anuria) is a characteristic of the severe acute glomerulonephritis, chronic glomerulonephritis, and some general diseases such as a severe heart failure, shock, collapse or a profuse blood loss.

Excretory (obstructive) anuria develops due to the obstruction of the urinary tract (urinary calculi, tumor). Excretory anuria is often attended by a renal colic.

Anuria can be short-term (about a day) and long-term. Long-term anuria more than 3-5 days threatens with development of the acute renal failure (uremia) due to nitrogen substance accumulations in the blood.

Anuria should be differentiated from *ischuria*.

Ischuria is a stoppage or reduction in the flow of the urine either from blockage of a passage when the urine is retained in the bladder, and the patient is unable to evacuate it. Causes of ischuria include the obstruction of the urethra by enlarged prostate gland, bladder stones or urethral scar, compression or other affection of the spinal cord.

Changes in the daily rhythm of the urination

A healthy person urinates from 3 to 5-7 times during the day time. The amount of excreted urine during one micturition is from 200 to 300 ml (usually

1000-1500 ml a day). Urinating at night does not arise a healthy person more than once.

An urinary frequency varies under certain conditions. It decreases in limited intake of the liquid, in excess of the sodium chloride intake, an excessive sweating, fever, and the like. The frequency increases in excessive intake of liquid, when getting cold, and in stress situations.

Pollakiuria *is a frequent repeated (more than 7 times a day) urination.* In pollakiuria, the patient feels the desire to urinate during both day and night. Pollakiuria is observed in inflammatory diseases of the urinary bladder (cystitis) and urethra (urethritis). Pollakiuria is combined with other dysuric manifestations. Frequent urination with a scanty excretion of the urine is a characteristic of the cystitis. Pollakiuria can accompany polyuria.

Isuria *is a condition when the patient urinates at nearly equal intervals with equal volumes of the urine.* Isuria develops in the chronic renal insufficiency when the kidneys lose the control of the volume and concentration of the excreted urine in accordance with daily activities of the patient (e.g., amount of the water and food intake, physical exertions, a body temperature, environmental conditions and other factors important for a water balance.

Nocturia *is the condition when the patient waking up to pass urine during the main sleep period* [according to the definition of the International Continence Society (ICS, 2018)]. The first nocturia episode must be preceded by sleep. Subsequent nocturia episodes must be followed by the intention of getting back to sleep.

Nycturia *is an excessive urination at night; especially common in older men. The nycturia characteristic is a urinary excretion of more than 1/3 of the daily volume of the urine at night.*

Renal nycturia combines with polyuria and indicates a renal failure in kidney diseases (e.g., chronic glomerulonephritis, pyelonephritis, nephrosclerosis). Nycturia combined with oliguria during the day is a characteristic of the heart failure (*cardiac nycturia).*

The patient would complain of the change in the colour of the urine, its cloudiness, and traces of the blood.

Changes in the color of the urine may depend on the excretion of some medicinal substances by the kidneys (rifampicin – red urine, nitrofurans – black-yellow or brown urine), from an admixture of the bile pigments (urobulinuria and bilirubinuria – beer-colored, or green-brown beer-colored urine), vegetable pigments (green vegetables – greenish color, beetroot – red), blood (hematuria) or pus (pyuria) in the urine. For the diagnosis of the kidneys and urinary tract diseases, the blood (hematuria) and pus (pyuria) in the urine are most important.

Hematuria *is an admixture of the blood in the urine. Macrohematuria* is a visible red staining of the urine with blood. Blood admixture of 1 ml in 1 liter of the urine is sufficient to detect this impurity with the unaided eye. *Microhematuria*

is an admixture of the blood to the urine that is determined only by a laboratory microscopy.

Hematuria is observed in acute and chronic glomerulonephritis (*a urine color of the "meat waste water"*), nephrolithiasis, tumors of the kidneys and a urinary tract, cystitis, hemorrhagic syndrome of various etiologies (the urine is red).

Hematuria should be distinguished from ***hemoglobinuria***, i.e., release of the free hemoglobin due to hemolysis (an increased destruction of erythrocytes). The urine gains on the brownish-red color. Hemoglobinuria can be a result of the transfusion of the incompatible blood, in hemolytic anemia, toxic hemolysis in cases of the poisoning, bites of poisonous animals, and infections (e.g., malaria, infectious mononucleosis, anaerobic sepsis); and after many kilometers foot marches (*marching hemoglobinuria*).

Pyuria is an admixture of the pus in the urine. Pyuria is detected by an examination with the unaided eye and a microscope. The urine becomes cloudy and, depending on the amount of the pus admixture, a grayish-cream shade. Pyuria can be in pyelonephritis, purulent urethritis, renal tuberculosis, cystitis.

21.1.1.4. Complaints of the renal edema

A complaint about edema is subjective-objective in nature. It is important to specify about the site and time of the edema onset, the sequence of the edema spreading, and the rate of the edema intensification.

Edema is a typical in the acute and chronic glomerulonephritis, glomerulosclerosis, nephrotic syndrome, amyloidosis (lardaceous), and a renal failure with the urine excretory dysfunction (anuria and oliguria).

Characteristics of the renal edema:

- *it develops very quickly, sometimes, even suddenly in the morning;*
- *at first, it appears on the sites of the most loose subcutaneous tissue (face, especially on eyelids, around eyes);*
- *hands and feet become swollen at the same time (it can be seen by sudden tightness of rings, shoes);*
- *it is mild pitting edema;*
- *a pale and dry skin at the sites of the edema.*

Edema can only occupy the subcutaneous tissue (*superficial edema*) or spreads to the internal organs and the body cavities (*deep edema*). Deep renal edema is sometimes hidden. It has been set that before the appearance of the manifested edema, from 3 to 5 liters of the fluid can be retained in the patient's body. This can be found when weighing the patient.

Nephrotic syndrome characteristics are a generalized edema (renal anasarca) with the development of the hydrothorax, hydropericardium, ascites.

Cerebral edema can manifest itself as a headache, loss of the vision, and epileptiform fit (convulsions).

21.1.2. Systemic complaints of the urinary system diseases

Headache, dizziness, noise in the head, weakness, indisposition, impaired memory and work capacity and deranged sleep occur in renal diseases complicated by *renal arterial hypertension* and/or uremic intoxication (e.g., in acute and chronic glomerulonephritis, glomerulosclerosis, acute and chronic renal failure). *An impaired vision* can be a result of the significant and persistent increase of the arterial pressure.

Renal arterial hypertension is often accompanied by ***dyspnea, heart palpitations, heart pain or unpleasant sensations in the heart area***. Dyspnea in acute glomerulonephritis can be associated with an acute left ventricular failure (pulmonary edema).

Patients with decompensated renal failure (uremia) can also complain of the ***skin itching and bad breath smell (uriniferous breath, or uriniferous mouth).*** *Itching of the skin* is caused by the release of nitrogenous toxins by sweat glands. *Uriniferous breath is* a result of the excretion of the nitrogenous substances (e.g., ammonia, urea, ammonium salts) by salivary glands and mucosal glands of airways.

Dyspeptic disorders include a loss of appetite, dryness and unpleasant taste in the mouth, nausea, vomiting, diarrhea, and an epigastric discomfort. These dyspeptic disorders are due to a renal failure that is associated with a retention of nitrogenous toxins and their excretion by the salivary and gastrointestinal tract glands (stomach, duodenum, small intestine). *Nitrogenous toxins (e.g., urea, ammonium salts*) can cause inflammatory and erosive-ulcerative affection of the entire gastrointestinal mucosa *("uremic" gastritis, duodenitis, enterocolitis).*

Weight loss can be in patients with renal failure due to *glomerular protein loss* (proteinuria), *gastrointestinal protein loss* in case of the small intestine damage (malabsorption), and dehydration of patients in case of polyuria.

Bleeding and hemorrhages of various localizations are typical in a chronic renal failure due to insufficient absorption of vitamins C and K and thrombocytopenia because of disordered hematopoiesis.

Bone pain (ostealgia, or osteodynia, or bone ache), muscle pain (muscle ache, myalgia) and cramps arise in patients with a chronic renal failure due to the vitamin D deficiency and hypocalcemia. There is a decrease in the bone mineralization (*osteoporosis*) and the softening of bones (*ostemalacia*), the bone cysts formation, and a risk of the pathological bone fractures in a progressive chronic kidney disease.

Painful joints (arthralgia) and joint swelling can occur in case of the so-called *uremic gout* (*gouty arthritis*). It is a result of the nitrogenous toxins (uric acid, urea and others) accumulation in joints with uremic intoxication.

Fever is the common symptom of infectious inflammatory diseases of the kidneys (acute and chronic pyelonephritis), the urinary ducts (cystitis, urethritis) and perirenal cellular tissue (paranephritis).

21.1.3. Medical history in diseases of the urinary system

When taking a ***history of a present disease (anamnesis morbi),*** it is important to fix the time of the onset of the urinary system symptoms, their relationship with previous infections (acute respiratory infections, tonsillitis, otitis, etc.), chilling of the patient; to specify a latent stage of the disease. These findings are essential to the diagnosis of the acute glomerulonephritis and pyelonephritis.

Questions about the *course of the disease* course have a diagnostic significance: chronicity with periodical exacerbations is typical in chronic pyelonephritis, chronic glomerulonephritis; chronic progressive course of the diseases – in amyloidosis of the kidneys, atherosclerotic glomerulosclerosis, chronic diffuse glomerulonephritis. A latent course of some kidney diseases is possible (e.g., chronic pyelonephritis and glomerulonephritis, polycystic kidney disease) without clinical manifestations for many years in succession.

It is necessary to establish the cause of exacerbations, their frequency, clinical signs, the character of therapy given and its efficacy, the causes inducing the patient to seek medical help.

A physician should ask clarifying questions: if the patient has *hazardous substance exposure* (e.g. corrosive sublimate, bismuth, phosphorus, sulfur, silver), introducing *nephrotoxic medications* (e.g. antibiotics of the aminoglycosides and tetracycline groups, analgesics, iodine-containing contrast agents) or other *provocative factors* (chilling, vaccination, transfusion of the incompatible blood, allergic reactions, infections) before the onset of the acute kidney injury or exacerbation of the chronic kidney disease.

When examining a female patient, it is important to ask her about the duration of the gestation, because a pregnancy can cause the so-called *pregnancy nephropathy (late gestosis*) and an exacerbation of the chronic kidney disease.

From the ***past life history (anamnesis vitae)*** of the patient, a physician pays attention to the risk factors of the urinary system diseases: adverse living and working conditions (stay in a damp room, hazardous substance exposure), intake of the nephrotoxic medications, bad habits. It is important to pay attention to the course of pregnancy and childbirth.

It is necessary to specify if the patient had previous urinary system diseases, kidney and urinary tract surgery operation, other system diseases which can affect the kidneys, such as connective tissue systemic diseases (e.g., systemic lupus erythematosus, systemic sclerosis**),** cardiovascular system pathology **(**essential arteria hypertension, a chronic heart failure)**,** diabetes mellitus, certain diseases of the blood (multiple myeloma, sickle cell anemia)**,** etc. Chronic purulent diseases (osteomyelitis, bronchiectasis) and rheumatoid arthritis can cause the amyloidosis of the kidneys (lardaceous kidney)**.** Previous genitalia infections can cause acute pyelonephritis and cystitis. A previous tuberculosis of the lungs or other organs can help to diagnosis the present kidney and urogenital tuberculosis.

The patient's hereditary history should be given in details because some kidneys diseases (e.g., polycystic kidney disease, nephrolithiasis, amyloidosis) can be inherited.

21.2. Objective examination of patients in diseases of the urinary system

21.2.1. General survey (inspection)

General survey gives the information about the patient's general condition.

A severe condition of the patient and impairment of the consciousness (stupor, sopor, and uremic coma) can be due to an acute kidney injury and decompensated chronic kidney diseases with severe renal dysfunction and nitrogen-containing substances intoxication. *Generalized convulsions* with a mental state confusion is observed in *renal eclampsia* (a condition characterized by a high renal arterial hypertension and brain edema) which can complicate acute glomerulonephritis and *pregnancy nephropathy (late gestosis)*.

The patient's position is commonly active. The *passive position* presents in uremic coma (due to severe renal failure). The *forced position* is a characteristic of the *paranephritis* (a purulent inflammation of the connective tissue surrounding the kidney): the patient (in the lateral recumbent position) pulls up the leg bent at the knee brining to the abdomen on the affected side.

In a renal colic, the patient is restless, tosses and turns in the bed; being unable to be well positioned to reduce the pain.

Examination of patients with diseases of the kidneys and urinary tract can reveal edema, pallor of the skin, hemorrhages, traces of scratching, ashy plaque on the skin.

The pale edematous skin is typical in acute and chronic glomerulonephritis due to the vascular spasm and anemia. The waxy pale skin is typical in amyloidosis and in a nephrotic syndrome.

There are *ashy-gray plaques* (*uremic frost*, or crystals of the urea and other nitrogenous substances released with sweat), traces of scratches, and hemorrhages on the skin surface in patients with a decompensated chronic renal failure.

Renal edema is a characteristic of the acute glomerulonephritis, other acute kidney injuries and chronic kidney diseases. Renal edema can develop and resolve quickly. Firstly, it appears in the morning time on the face, especially on eyelids, around eyes where the loosest subcutaneous tissue is. The pale face with edematous eyelids and narrowed eye-slits is known as *facies nephritica* (Fig. 21.2). The mild pitting edema with a pale and dry skin appears at the same time on the hands and feet.

In patients with nephrotic syndrome, it is a characteristic generalized edema of the patient's body (*anasarca*) including an enlarged liver and fluid accumulation in serous cavities (*ascites, hydrothorax, hydropericardium*).

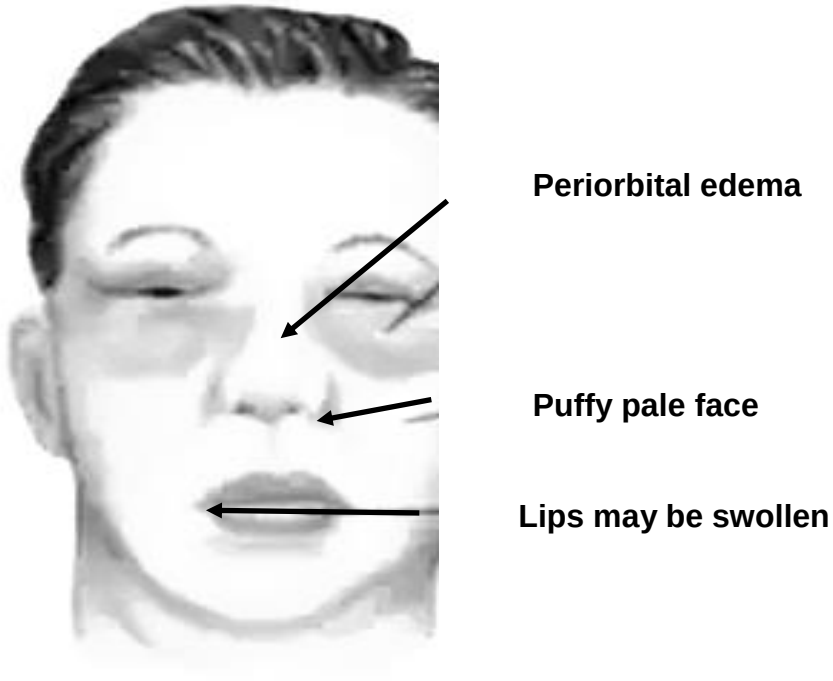


Fig. 21.2. Facies nephritica.

Renal edema should be distinguished from an edema in a congestive heart failure (Table 21-3).

Table 21-3. Differences between renal and cardiac edema

Differences	Renal edema	Cardiac edema
Early localization	on the face, in the morning	on the feet, in the evening
Late localization	swelling of all subcutaneous tissue on the body	gradual upward increase in edematous syndrome
Skin color	pale	cyanotic

An oral cavity survey detects a dry coated tongue and an unpleasant ammonia smell from the mouth and the patient's skin (*factor uremicus*) in a decompensated chronic renal failure (uremia).

The survey does not generally find visible changes of the abdomen and lumbar region. In paranephritis, it is possible to find a swelling and hyperemia of the skin on the affected side of the lumbar region. Bulging up of the hypogastric area over the pubic bone can be due to overfilling of the urinary bladder (e.g.,

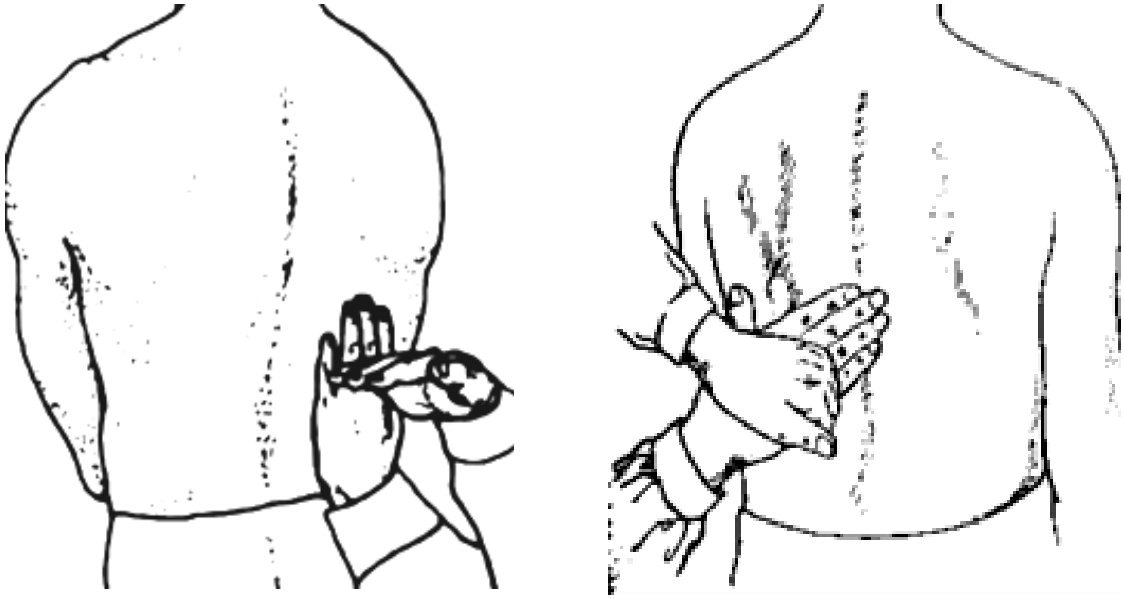
after general anesthesia, urinary tract obstruction by the prostate tumor, bladder paralysis in a spinal cord affection).

21.2.2. Percussion of the kidneys

The standard technique of the percussion is not applied for the kidneys due to their deep topographic location. However, the *costovertebral angle tenderness method (CVA tenderness, or CVAT), or Murphy's percussion test, or tapping the kidney (lumbar) area [a literal translation from the Russian – pokolachivanie oblasti pochek (poyasnichnoi oblasti)]* offer the opportunity to obtain an important diagnostic information in diseases of the kidneys.

The costovertebral angle tenderness (tapping the kidney area) is commonly examined in the vertical position of the patient (the patient can be either in horizontal prone or sitting position). The physician applies palmar surface of left hand to the right or the left parts of the patient's lumbar region over the costovertebral angle (CVA). The right physician's hand, clenched into the fist or the palm edge, taps with a moderate force on the back of the left hand, thereby causing a *concussion* of the underlying tissues (Fig. 21.3).

If the patient feels pain, the *costovertebral angle tenderness (CVAT) is positive* (Table 21-4). *CVAT is positive in nephrolithiasis, paranephritis, pyelonephritis,* and in the lumbar myositis and radiculitis. This decreases the diagnostic value of the CVAT. *Unilateral positive CVAT is more specific to the kidney diseases than a bilateral pain. The specificity of positive CVAT in* the *kidney diseases is confirmed by Pasternatsky's symptom*.



(1) (2)

Fig. 21.3. Costovertebral angle tenderness method (tapping lumbar area) by (1) the palm edge or (2) the fist.

Pasternatsky's symptom *is a combination of the pain when tapping in the lumbar region (positive CVAT) with the onset of the hematuria or increase in the number of red blood cells in the urine*. After examination of the CVAT, the patient should pass a urinalysis. With a positive Pasternatsky symptom, the patient feels pain during the tapping the lumbar region in a costovertebral angle, with red blood cells being present in the urinalysis.

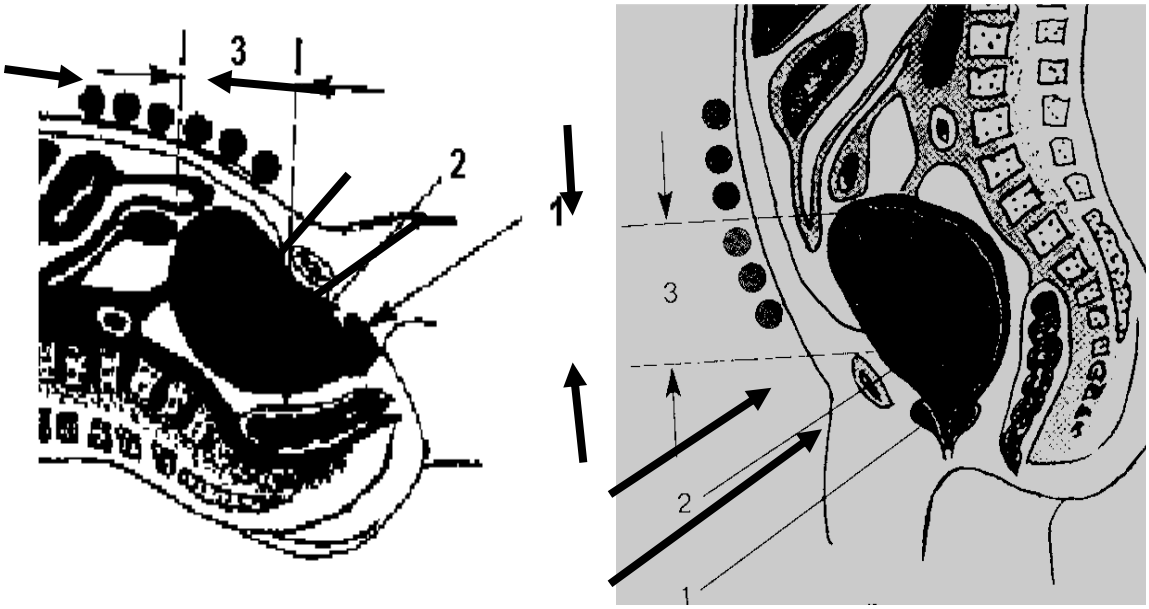
Table 21-4. Diagnostic value of the kidney area percussion

Diagnostic technique	Pathological mechanism of the pain	Underlying disease
Positive costovertebral angle tenderness (CVAT) and positive Pasternatsky's symptom	concussion of the stretched and tense kidney capsule	glomerulonephritis, polycystic kidney disease; renal tumor, tuberculosis, amyloidosis of the kidney
	concussion of the inflamed or distended renal pelvis	pyelonephritis
	concussion of calculi	nephrolithiasis
	suppuration of the perirenal tissue	paranephritis

21.2.3. Percussion of the urinary bladder

The urinary bladder percussion is performed in a vertical and a horizontal position of the patient. The finger-pleximeter is placed horizontally, parallel to the pubis at the level of the umbilicus or just below it. A quiet (soft) percussion is conducted from top to bottom along the *linea mediana anterior* towards the pubis (Fig. 21.4). If the bladder is stretched with the urine, a dull percussion sound above the pubis appears. If it is empty, a tympanic sound is determined up to the pubic symphysis in vertical and horizontal positions of the patient.

The upper limit of the urinary bladder dullness above the middle of the line between umbilicus and pubis is characteristic of the bladder emptying disorders (e.g., the bladder paresis after general anesthesia, in the urinary tract obstruction by the prostate tumor, bladder paralysis in a spinal cord affection, the bladder hypotony in some senile patients).



(A) **(B)**

Fig. 21.4. Percussion of the urinary bladder:
(A) – horizontal position, (B) – vertical position, 1 – enlarged prostate gland,
2 – urinary bladder, 3 – dull sound urea.

21.2.4. Palpation of the ureteric points

Ureteric points are the tender points associated with the damage to the kidneys and the urinary tract. Their presence has a certain diagnostic value and can be determined in some cases by the palpation of the anterior surface of the abdomen and lumbar region.

There are three pairs of the ureteric points at the anterior surface of the abdomen (Fig. 21.5):

• *subcostal points* – at the anterior end of the X rib;

• *superior ureteric points* – on the outer edge of the *rectus abdominis muscle* on the umbilicus level;

• *medium ureteric points* - on the the *linea biiliaca (intercristal line, or linea cristarum)* at the one third of the distance from the *linea mediana anterior* to the *spina iliaca anterior superior*.

Posterior pair of the ureteric points:

• *costovertebral points*- in the costovertebral corner formed by the inferior edge of the XII rib and the vertebral column.

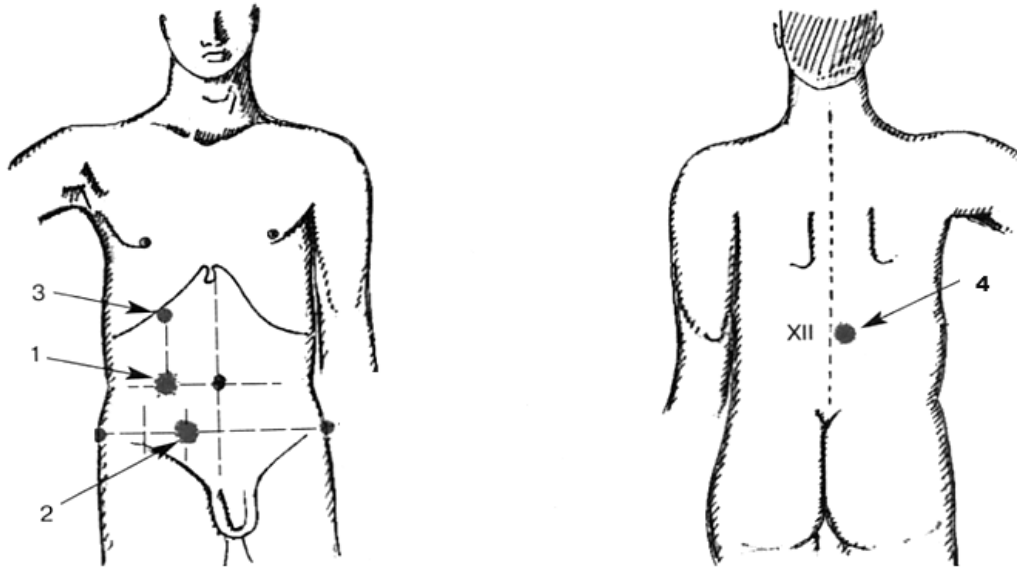


Fig. 21.5. Ureteric points:

1 – superior ureteric point, 2 – medium ureteric point, 3 – subcostal point, 4 - costovertebral point.

The pressure at these points (in norm it is usually painless) becomes sharply sensitive in urolithiasis, pyelonephritis, paranephritis, tumors and tuberculous of the kidneys and the urinary tract. An unilateral pain at palpation of the ureter points is more specific for urinary system diseases, than a symmetrical pain.

21.2.5. Palpation of the kidneys

The kidneys are located in the retroperitoneal space. However, their palpation is performed simultaneously with the study of the abdominal organs. All the basic principles of the deep sliding methodical palpation according to V.P. Obraztsov are observed. *The kidneys become palpable in their considerable enlargement (due to a cyst or a tumor) or in their position lowering (nephroptosis).*

Patient position

Palpation of the kidneys should be performed in the vertical and horizontal positions of the patient.

Passive movements of the kidneys present in norm about 2-3 cm in the proximal and distal directions when the patients changes his/her position from horizontal to vertical (or from a vertical to a horizontal position), and during the respiratory movements of the diaphragm. When interpreting the results of the kidneys palpation it is necessary to take into account these passive movements of the kidneys.

Palpation of the kidneys in the vertical (standing) position of the patient is convenient for diagnosis of the *nephroptosis*, especially in case of the kidney slight displacement. In a horizontal position, the kidney can return to its bed, and

even deep breathing movements of the diaphragm are not able to force it to move down so that it becomes palpable.

During the *kidneys palpation in a vertical position (Fig. 21.6),* the patient stands facing a physician who is sitting on a chair. For a better palpation of the kidneys in the vertical position of the patient, he/she can slightly tilt his/her body forward.

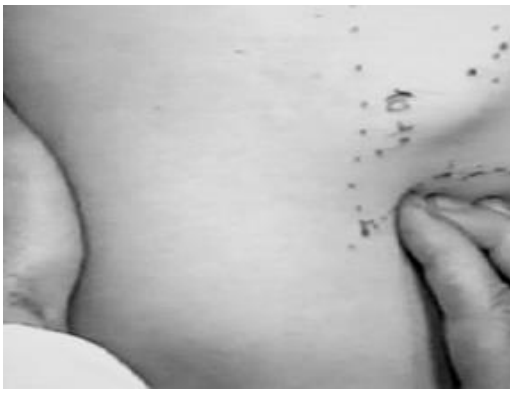
During the kidneys palpation in a horizontal position), a physician takes his/her place by the right side of the patient's bed, facing the patient. The patient should be with the stretched legs and the head placed on a low pillow. The anterior abdominal wall is relaxed, and the arms are freely placed on the chest.

Palpation technique

Step I *of the palpation is placing the hands. The palpation of the kidneys is done bimanually (with two hands) in a horizontal position of the patient, as well as in a vertical position.*

The left arm is placed under the patient's right lumbar region, slightly below the 12-th rib so that the finger tips are placed near the vertebral column. During the palpation of the left kidney, the physician's left arm should be moved to the other side of the vertebral column on the left part of the lumbar region.

The physician puts the right arm to the corresponding flank. The tips of the bent fingers are 3-5 cm below the edge of the costal arch with a slight turn of the heel of the hand outward. The fingers of the palpating arm are set perpendicular to the costal arch and outside of the *rectus abdominis muscle*. *It is corresponded to an anatomical location* of the kidneys that their inferior pole is further from the spine than the superior one.



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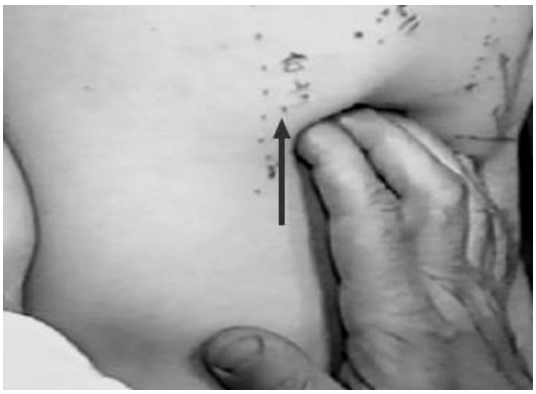

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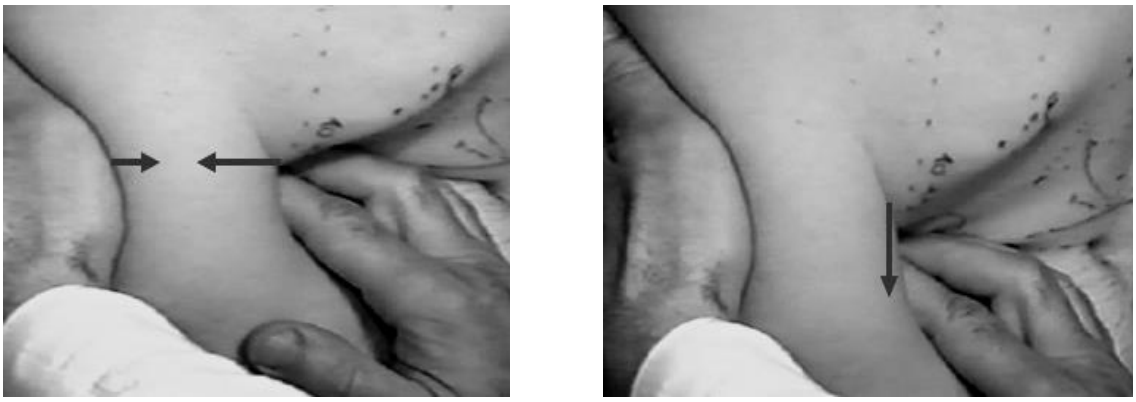


(3) (4)

Fig. 21.6. Palpation of the kidneys in a vertical position of the patient:
(1) the position of the palpating arms; (2) the formation of the skin fold by the movement of the palpating arm upward; (3) dipping tips of the right arm fingers while the left arm presses the lumbar region to meet the fingers of the right arm; (4) palpation of the kidney at the deep inspiration.

Step II *is the formation of the skin fold by a surface upward movement of the palpating arm.*

Step III *is dipping the right hand into the abdomen on an expiration, when the abdominal muscles are relaxed maximally*. It usually takes 2-3 breaths to reach the posterior abdominal wall with the fingertips.

At the same time, the left hand actively helps the right, displacing the lumbar region anteriorly and bringing the kidney closer to the fingers of the palpating hand. The physician strives to bring both hands together as much as possible (Fig. 21.7).

Step IV *is a sliding palpation of the kidney.* When both hands come closer, the patient is asked to take a deep inspiration, during which the kidney goes down and reaches the fingers of the right arm.

After that, the tips of the fingers slide from top downward over the anterior surface of the kidney to its inferior pole, making it possible to assess the physical characteristics of the palpated kidney. Sometimes the palpation of the kidney is possible only by the use of a special method - *ballottement*: rhythmic jerky movements of the fingers of the left arm towards the right arm are added to the above-described technique of the standard bimanual palpation.

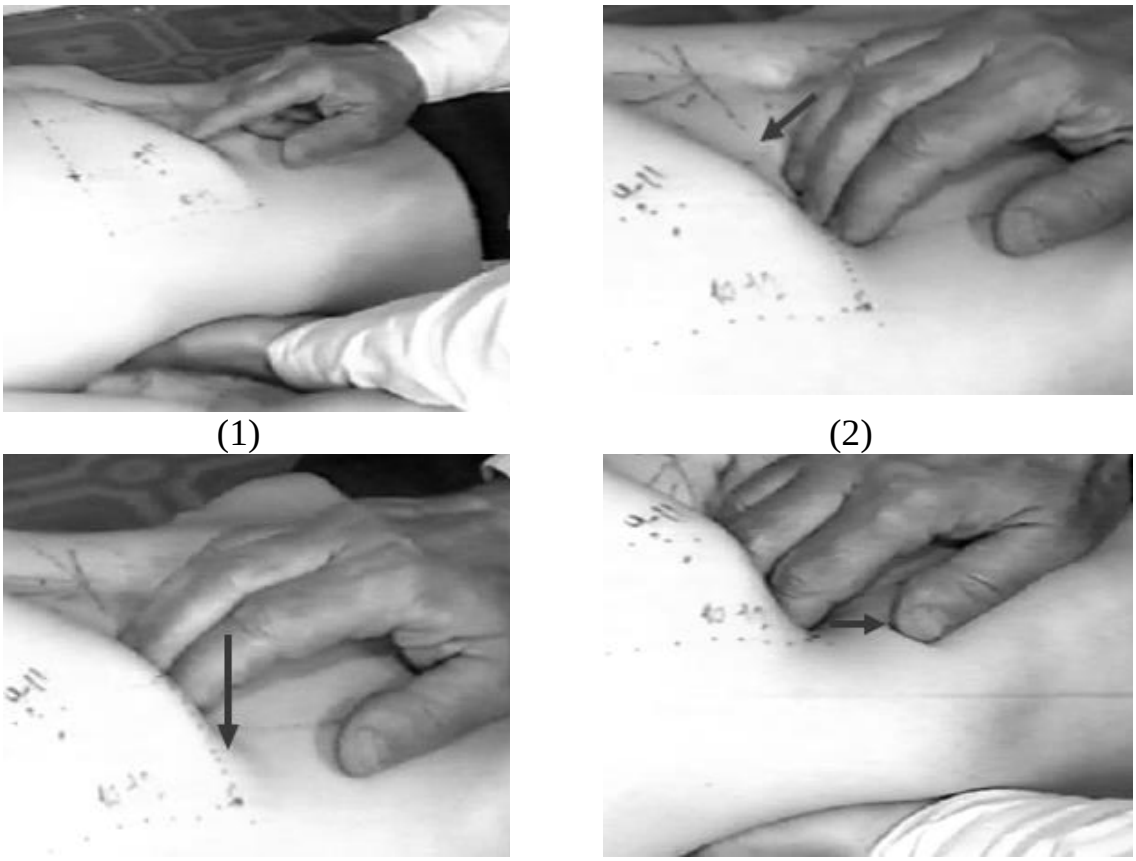


Fig. 21.7. Palpation of the kidneys in a horizontal position of the patient:
(1) the position of the palpating arms; (2) the formation of the skin fold by the movement of the palpating arm upward; (3) the dipping tips of the right arm fingers while the left arm presses the lumbar region to meet the fingers of the right arm; (4) the palpation of the kidney at a deep inspiration.

In large degrees of the nephroptosis, both poles and the entire anterior surface of the kidney can be palpated. The physician can assess the shape, size, surface (smooth or tuberous), tenderness, mobility, and consistency of the kidneys.

Diagnostic value of the kidneys palpation

The kidneys are not palpable in norm with the exception of the inferior pole of the right kidney at the vertical position in some asthenic healthy persons.

Palpation of the kidneys becomes possible in *nephroptosis and* an *increase in the kidney's size greater than 1.5-2 times* (Table 21-5). It is not possible to palpate the kidneys in most cases of the marked meteorism, ascites, and obesity.

The kidney is a bean-shaped organ with a smooth surface, slipping upwards under the palpating fingers and returning to normal position, dense-elastic consistency, and painless.

Palpation can diagnose nephroptosis.

Nephroptosis *is a condition when the patient's kidney drops down into the pelvis more than two vertebral bodies or >5 cm when he/she stands up.*

Nephroptosis is more often observed in thin and multipara women of the asthenic body-build type with a soft sluggish abdominal wall.

Nephroptosis primarily develops on the right side, because of the higher location and firm fixation of the left kidney. Nephroptosis can be isolated or in combination with a the lowering of other abdominal organs (*visceroptosis*).

Table 21-5. Diagnostic value of the kidney palpation

Characteristics of the kidney	Causes
bean-shaped movable painless organ with a smooth surface and dense-elastic consistency	nephroptosis
movable organ with asmooth surface, dense-elastic consistency, and a pain on palpation	nephroptosis combined with pyelonephritis and /or urolithiasis
a painless enlarged organ with a soft-elastic surface, fluctuating consistency,	chronic hydronephrosis
a tender enlarged organ with a soft-elastic surface, fluctuating consistency	acute hydronephrosis, pyonephrosis
a tuberous surface and increased density of both palpated kidneys (bilateral process)	polycystic disease of kidneys
one of the kidneys (unilateral process) with a tuberous surface and a very dense consistency; a pain and a restricted mobility on the kidney palpation can be	hypernephroma or other tumours of the kidney
the enlarged immobile kidney with expressed tenderness on palpation, and bulging the lumbar region	paranephritis
the kidneys are not palpable	in norm; mild degree of the kidney enlargement

There are ***three degrees of nephroptosis***:

Degree I – a palpated kidney (*ren palpabilis*), its inferior pole can be palpated only. The mobility of kidneys is small;

Degree II – a *movable kidney* (*ren mobilis*), the entire kidney can be palpated; it is easily displaced, not translocated for a *white line (linea alba)* of the abdomen.

Degree III - a *wandering (vage) kidney* (*ren migrans*), the kidney freely moves about in all directions to pass beyond the vertebral column in the side of the other kidney, and to sink downwards at a considerable distance.

After the palpation of the lowered kidney, a proteinuria (*Zhebrovsky's sign*) and /or hematuria sometimes appears in the urinalysis. The palpation proteinuria and ballottement can be a hallmark of the kidney in doubtful cases of the palpating of the oval dense body in the abdominal cavity.

Palpation of the enlarged kidney

The most often causes of the kidney enlargement are hypernephroma (renal cell carcinoma), a large solitary kidney cyst, polycystic disease of kidneys and hydropyonephrosis (an accumulation of the purulent urine in the pelvis due to bacterial infection following an obstruction of the ureter). There are changes of the shape, the surface and consistency of the kidney in all these cases.

A soft elastic, fluctuating consistency of the palpated kidney is characteristic of the hydronephrosis and pyonephrosis. A tuberous surface and a very dense consistency of the large palpated kidney indicates a tumor. A polycystic disease of ballottement kidneys is also accompanied by a tuberous surface and increased density of ballottement palpated kidneys, however by contrast with tumor, this process is bilateral.

21.2.6. Palpation of the urinary bladder

Palpation of the urinary bladder is conducted from top to bottom along the anterior median line according to all rules of the deep sliding methodical palpation.

The palpation is performed in a horizontal position of the patient.

*Step I***:** The right hand is placed flat on the anterior abdominal wall perpendicular to the anterior median line on 2-3 cm upward the upper limit of the urinary bladder dullness.

Step II: formation of the skin fold (in direction from examining organ) upward.

Step III: dipping the right fingers into the abdomen during three deep expirations when the abdominal wall is relaxed.

IV step: sliding movement of the fingertips downward to the bladder.

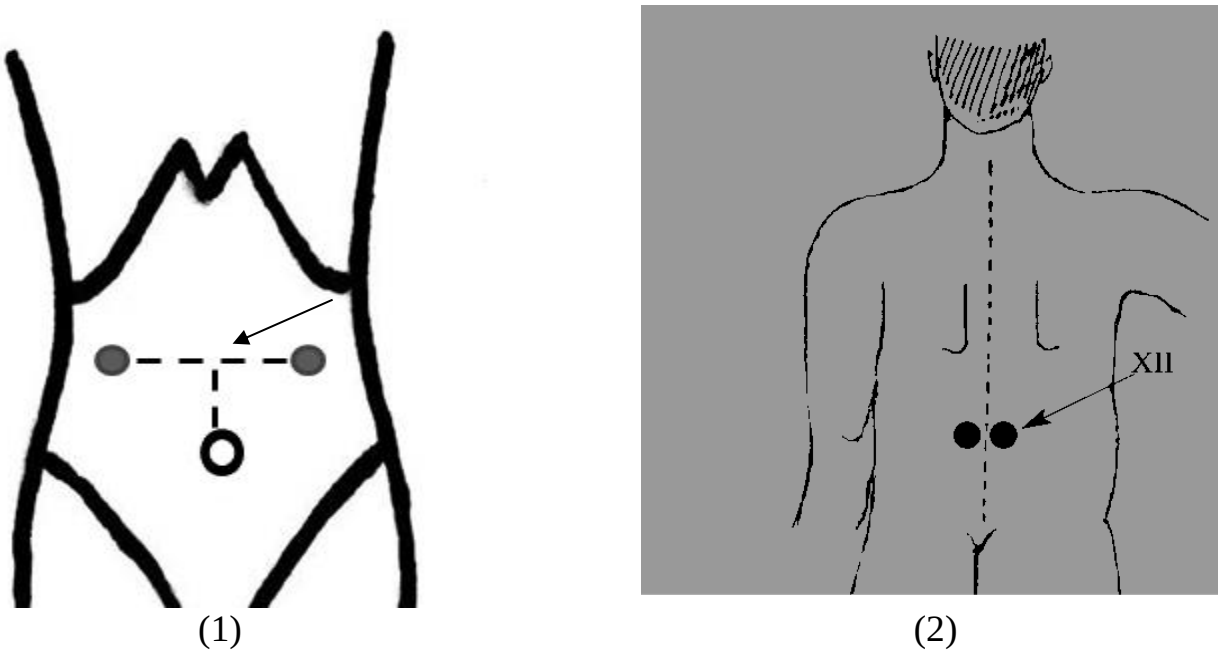
Urinary bladder is not palpable in norm.

In prolonged urinary retention (ischuria), the urinary bladder can be palpable like a rounded elastic body in the suprapubic region of the abdomen. The superior border of the overfilled bladder is markedly can reach the umbilicus. The urinary bladder tumors and stones (only in cases of their very large sizes and a soft abdominal wall) are sometimes possible to palpate as a formation in depths of the hypogastrium behind the pubic symphysis.

21.2.7. Auscultation of renal arteries

Auscultation in diagnostics of a kidneys disease is used for the recognition of pathology of the renal arteries. Systolodiastolic murmurs of the renal artery stenosis can be auscultated at the costovertebral points (costovertebral angles)

and on the anterior abdominal wall in points placed 5 cm above umbilicus and near 4-5 cm on each side of the linea mediana anterior (Fig. 21.8).



(1) (2)

Fig. 21.8. Points of renal arteries auscultation on (1) anterior surface and (2) posterior surface.

Murmurs with both systolic and diastolic components suggest the turbulent blood flow of the partial arterial stenosis. *A systolodiastolic murmur in one of these points strongly suggests renal artery stenosis as the cause of the arterial hypertension.*

21.3. The key points of the theme "Subjective and Objective Examination of Patients with Diseases of the Urinary System"

Specific complaints of the urinary system diseases are pains in the lumbar region and other parts of the abdomen (right and left flanks, suprapubic region), an impaired urinary excretion (amount of urine) and an urination (frequency changes, dysuria), a discoloration of the urine, and edema.

Systemic complaints of the urinary system diseases are due to a renal arterial hypertension and/or uremic intoxication: headache, dizziness, noise in the head, headache, dyspnea, heart palpitations, heart pain, weakness, indisposition, impaired memory and work capacity, deranged sleep, and an impaired vision. Patients with ***decompensated renal failure (uremia)*** can also complain of the skin itching, uriniferous breath (bad breath smell), dyspeptic disorders (loss of appetite, dryness and unpleasant taste in the mouth, nausea, vomiting, and diarrhea, and an epigastric discomfort), weight loss, hemorrhages of various localizations, bone and muscle pains, cramps, painful joints. Fever is typical in

infectious inflammatory diseases of the kidneys and urinary ducts (e.g. pyelonephritis, paranephritis, cystitis).

General inspection of the patients with diseases of the kidneys and urinary tract can reveal edema, pallor of the skin, hemorrhages, traces of scratching, ashy plaque on the skin.

Costovertebral angle tenderness (CVAT) and Pasternatsky's symptom are positive in nephrolithiasis, paranephritis, and pyelonephritis.

The upper limit of the urinary bladder dullness above the middle of the line between umbilicus and pubis is characteristic of the bladder emptying disorders (e.g., the bladder paresis after general anesthesia, in the urinary tract obstruction by the prostate tumor).

Ureteric points (subcostal, superior and medium ureteric, and costovertebral) are the tender on the palpation points associated with the damage to the kidneys and urinary tract (e.g., urolithiasis, pyelonephritis, paranephritis, tumors of the kidneys).

Kidneys are palpated by general rules of the deep sliding methodical palpation in vertical and horizontal positions. The kidneys are not palpable in norm with the exception of the inferior pole of the right kidney at the vertical position in some asthenic patients.

The kidneys are palpable in their considerable enlargement (due to a cyst or a tumor) or in their position lowering (nephroptosis).

The urinary bladder is not palpable in norm. *In prolonged urinary retention (ischuria), the urinary bladder can be palpabl*e like a rounded elastic body in the suprapubic region of the abdomen

The ***systolodiastolic murmur on the renal arteries*** strongly suggests renal artery stenosis as the cause of the arterial hypertension.

21.4. Assessment tests on the theme "Subjective and Objective Examination of Patients with Diseases of the Urinary System"

1. Specify the typical symptoms in the diseases of the kidney and urinary tract:

1. lumbar pain;
2. dysuria;
3. early edema on the face;
4. epigastric pain;
5. diarrhea.

2. Specify typical localization of the pain associated with the diseases of the kidneys, ureters, and urinary bladder:

1. lumbar region;
2. flanks;
3. suprapubic area;

4. epigastric area;
5. mesogastrium.

3. Renal colic is:

1. acute cramping pain in the lumbar region, radiating into iliac area, urethra and external genital organs;
2. pain in the epigastric region;
3. pain in the right upper quadrant of abdomen, radiating to the right clavicle;
4. long aching pain in the left upper quadrant of abdomen;
5. long aching pain in the in the lumbar region.

4. Early edemas in the diseases of the kidney and urinary tract arise:

1. on eyelids;
2. on face;
3. on legs;
4. on feet;
5. on hands.

5. Renal edema characteristics are:

1. early localization on the face in morning;
2. early localization on the feet in the evening;
3. late swelling of all subcutaneous tissue on the body;
4. gradual upward increase in edematous syndrome;
5. pale skin color;
6. cyanotic skin color.

6. Which diseases can cause an ischuria?

1. an obstruction of the urethra;
2. diseases of the urinary bladder;
3. chronic and acute renal failure;
4. glomerulonephritis;
5. nephrosclerosis.

7. In patients with edemas, it is necessary to observe:

1. weight of the patient and food intake;
2. fluid intake only;
3. stool volume;
4. pulse and blood pressure;
5. diuresis and water balance.

8. Positive diuresis is a condition in which:

1. diuresis is less than the fluids intake;

2. diuresis is more than fluids intake;
3. diuresis equals fluids intake;
4. the patient does not urinate during the day;
5. diuresis is more than 2.0 liters a day.

9. Negative diuresis is a condition in which:
1. diuresis is more than fluids intake;
2. diuresis equals fluids intake;
3. diuresis is less than the fluids intake;
4. the patient is not urinating during the day;
5. diuresis is less than 1.0 liters a day.

10. Normal 24-hours diuresis equals:
1. < 0.5 liters;
2. < 150 ml via catheter;
3. 0.5-1.0 liters;
4. 1 – 1.5 liters;
5. > 2 liters.

11. 24-hours diuresis in oliguria equals:
1. < 250 ml via catheter;
2. < 0.5 liters;
3. 1 – 1.5 liters;
4. > 2 liters;
5. 0.5-1.0 liters.

12. 24-hours diuresis in anuria equals:
1. < 50 ml via catheter;
2. 1 – 1.5 liters;
3. < 2 liters;
4. < 0.5 liters;
5. < 1.0 liters.

13. 24-hours diuresis in polyuria equals:
1. < 50 ml via catheter;
2. < 0,5 liters;
3. > 1.0 liters;
4. 1 – 1,5 liters;
5. > 2 liters.

14. Pollakiuria is:
1. difficult urination;
2. frequent urination (> 4-7 times a day and > 1 times in the night);
3. frequent urination at night (3-4 times and more);

4. daily diuresis > 2 liters;
5. daily diuresis < 0.5 liters.

15. What is true about an ischuria?

1. a stoppage in the urine flow due to the urine retention in the urine bladder;
2. a reduction in the urine flow due to the urine retention in the urine bladder;
3. a frequent, slow and painful urination of small volumes;
4. a condition when the patient has to wake at night one or more times to urinate;
5. an admixture of the blood in the urine.

16. What is true about a stranguria?

1. a frequent, slow and painful urination of small volumes;
2. a reduction in the urine flow due to the urine retention in the urine bladder;
3. it is combined with feeling of straining and the incomplete emptying;
4. a fullness or discomfort in the perineal or rectal area;
5. an absence of the diuresis or less than 50 ml per day of the excreted urine.

17. Positive Pasternatsky's symptom means:

1. pain in flanks at percussion;
2. pain in lumbar area at palpation;
3. pain in flanks at palpation;
4. pain in costovertebral angle at percussion combined with onset of the hematuria;
5. pain in costovertebral angle at percussion.

18. Palpation of the kidneys is performed at:

1. a vertical position of the patient;
2. a sitting position of the patient;
3. a horizontal position of the patient;
4. a lateral recumbent position;
5. a position on abdomen in lumbar area.

19. Normal characteristics of palpated kidneys:

1. a smooth mild organ of the cylindrical shape;
2. a smooth dense organ of the ellipsoid shape;
3. the kidneys are not palpable;
4. an inferior poles of kidneys are palpable as a smooth, elastic and rounded shape;

5. inferior pole of the right kidney may be palpable in some healthy asthenic persons as smooth, elastic and rounded shape.

20. Ureteric points are:
1. superior ureteric point;
2. medium ureteric point;
3. inferior ureteric point;
4. costavertebral point;
5. subcostal point.

21. Points of renal arteries auscultation are:
1. superior ureteric points;
2. points on the level 5cm above umbilicus and 4-5cm aside;
3. inferior ureteric points;
4. costavertebral points;
5. subcostal points.

22. What is true for the costovertebral angle tenderness (CVAT)?
1. positive in nephrolithiasis;
2. positive in paranephritis;
3. positive in pyelonephritis;
4. bilateral positive CVAT is more specific to kidney diseases;
5. unilateral positive CVAT is more specific to kidney diseases.

23. The upper limit of the bladder dullness is a characteristic of the bladder urine retention if:
1. above the middle of the line between umbilicus and pubis;
2. 2-3 cm above pubis;
3. above the middle of the line between umbilicus and xiphoid process;
4. above umbilicus;
5. 3-5 cm below xiphoid process.

24. The kidneys are palpable in cases of:
1. nephroptosis;
2. increase in the kidney's size greater than 1.5-2 times;
3. healthy persons;
4. in some healthy asthenics (for the inferior pole of the right kidney);
5. in all cases of the kidney diseases.

CHAPTER 22. Laboratory and Instrumental Examination of the Urinary System

Goals: to enable students to learn –

1. laboratory assessment of the urine in diseases of the kidneys and the urinary tract (e.g., common urine analysis, Nechiporenko test, Zimnitskiy's test) and its diagnostic value;
2. diagnostic value of the blood serum tests in the kidneys and the urinary tract diseases;
3. assessment of the glomerular filtration and renal water reabsorption [assay of Rehberg, Cockcroft-Gault (CG) formula, etc.] and their diagnostic value;
4. instrumental examinations in the kidneys and the urinary tract diseases (e.g., X-ray, CT, MRI, ultrasonography, radioisotope study) and their diagnostic value.

22.1. Laboratory assessment of the urine

22.1.1. Common urine analysis (clinical urinalysis, clinical urine examination)

A clinical urine examination should be performed by every patient regardless the nature of their disease. For the common urine analysis, about 100 ml of the urine from the first morning portion is collected in a clean, dry glass or plastic lidded dishes after the obligatory intimate washing of the patient's external genitourinary organs.

Common urine analysis includes the study of the physical, chemical properties of the urine, and microscopy of the organized and unorganized urine sediment).

22.1.1.1. Physical properties of the urine

The study of the physical properties of the urine includes the assessment of the volume, color, smell, transparency, and specific gravity of the urine.

The* urine volume *excreted per day (daily urine output, or daily diuresis) in adult healthy people ranges from 1 to 2 liters, averaging about 75% of the water input (Table 21-1). Daily diuresis depends on a number of renal and extrarenal factors.

Polyuria *is an increase in daily diuresis over 2,000 ml.* Diuresis physiologically increases with the intake of a large amount of the liquid, with food that increase the urine excretion (e.g., watermelon, melon).

Pathological polyuria is a characteristic of the chronic renal failure (chronic kidney disease), an acute kidney injury (polyuric stage), an edema reduction, diuretics intake, in decompensated diabetes mellitus, and diabetes insipidus. In the two last cases, polyuria is more pronounced (3-5 liters per day or more).

Oliguria is a decrease in daily diuresis less than 500 ml. The oliguria is an indicator of the functional deterioration of the kidneys and the urinary tract. Oliguria is observed in acute glomerulonephritis, nephrotic syndrome, acute kidney injury (oliguric stage), a chronic kidney disease (a terminal stage), and in an acute and chronic heart failure. Oliguria can also be due to a large fluid loss by the extrarenal route (severe sweating in hyperthermia, with burns, profuse diarrhea, vomiting, and blood loss).

Table 22-1. Common physical properties of the urine

Urine properties	Characteristics	Leading causes
Daily (24 hour) urine (daily diuresis)	1000-2000 ml	in norm
	polyuria (>2000 ml)	renal failure (polyuric stage), edema reduction, diuretics intake, diabetes mellitus and diabetes insipidus
	oliguria (<500 ml)	acute glomerulonephritis, nephrotic syndrome, renal failure (oliguric stage), in a decompensated heart failure
	anuria (<50 ml)	an acute renal failure, an obstruction of the urinary tract
Urine transparency	clear	in norm
	urine turbidity	a large amount of salts (in urolithiasis), cellular elements, casts (in nephritis), bacteria, and mucus (in urinary infections)
Color	straw yellow	in norm
	pale yellow	diluted urine
	darken yellow	concentrated urine
	dark-brown	jaundice, high protein breakdown (fever, hyperthyroidism)
	rich yellow	nitrofurans, B-group vitamins
	orange red	rifampicin
	pink	beetroot, phenyndion
Specific gravity	1.005-1.025	in norm (diurnal fluctuations)
	hypersthenuria (>1.030)	massive glucosuria and proteinuria, acute renal failure (oliguric stage)
	hyposthenuria (<1.010)	a diminished concentration function of the kidneys in chronic kidney disease, interstitial nephritis, and polyuric stage of the acute kidney injury), edema decongestion

Anuria *is a complete cessation of the urine flow of the diuresis or a volume reduction of the excreted urine (less than 50 ml per day - by the urinary catheter)*.

A **color** of the urine varies in norm from light yellow (or straw yellow) to deep yellow. The normal color is due to the *urochromes (urine pigments)* content in the urine.

The *intensity of the color depends on concentration of the urine and on the presence of various admixtures in it*. The darken yellow urine is usually concentrated; it has a high specific gravity, and is excreted in small volume. Pale urine is less concentrated; often it has a low specific gravity, and is observed in polyuria.

The color of the urine may change after taking certain medications, food, herbal infusion: e.g., *red (pink) color* appears after taking rifampicin, eating beetroot; *greenish yellow (brown)* – after ingestion of the rhubarb, Alexandrine senna.

In diseases, the color is variable:

- *greenish-yellow* - Pseudomonas infection, elevated urinary copper (Wilson's disease)*;*
- *brown ("beer color")* – in the presence of bile pigments in the urine;
- *red, brown* – due to admixture of the blood ("the color of meat slops"); myoglobin and hemoglobin;
- *purpuric* – in *porphyria (a group of hereditary disorders of the heme metabolism) due to uroporphyrin excretion;*
- *black – alkaptonuria (an inherited condition when the urine color turns black after exposition to air);*
- *milky – due to admixture of the pus (pyuria), chyle (lymph); phosphates.*

The **urine transparency** is assessed by reading printed text through a layer of the urine poured into a test tube. The urine is transparent (clear) if the printed text is easy to read through the urine layer. The urine is clear in norm.

The urine turbidity is due to the urine content of the large amount of salts, cellular elements, casts, bacteria, fats, and mucus.

The **smell of the urine** depends on the presence of the volatile substances in it. The freshly voided urine has a *specific weak aromatic (urinary) odor*. The long-time standing urine acquires an ammonia odor because of the alkaline fermentation.

In the freshly voided urine, an *ammoniac odor* appears in cystitis, pyelitis (an inflammation of the pelvis or outlet of kidneys), and pyelonephritis. In diabetic ketoacidosis, the urine has a *sugary-sweetish odor*. It is reminiscent of the smell of overripe apples, which is associated with ketone bodies content in the urine.

The ***specific gravity of the urine*** depends on the dissolved substances in the concentration (e.g. urea, uric acid, creatinine, various salts, protein, and glucose) and their molecular weight. The specific gravity of the urine is a characteristic of the concentrating and diluting functions of the kidneys.

The specific gravity of the urine is 1.005-1.028 in the range of norm. In a healthy person, the specific gravity of the urine varies significantly during the day

due to the periodic intake of the food, water and loss of fluid with sweat and exhaled air.

Hyposthenuria is a decrease in the specific gravity of the urine below 1.010 (in all samples during the day). It is a characteristic of the diminished concentration function of the kidneys (in a chronic kidney disease, interstitial nephritis, and polyuric stage of the acute kidney injury). Hyposthenuria can also be in polyuria, due to edema decongestion, after drinking plenty of fluids.

Hypersthenuria is an increased specific gravity of the urine more than 1.025 (in all samples during the day). It is combined with oliguria in patients with acute glomerulonephritis, circulatory failure, an acute kidney injury, and a nephrotic syndrome. Hypersthenuria may be associated with an edema progression, the fluid accumulation in the pleural and/or abdominal cavity, and decompensated diabetes mellitus (combining with polyuria). In cases of the massive glucosuria and proteinuria, the specific gravity of the urine can reach 1.040 – 1.050.

Isosthenuria is a monotonous specific gravity of the urine (<0.005) due to the reduction of the renal concentration function. ***Isohyposthenuria*** is a combination of the isosthenuria and the hyposthenuria.

22.1.1.2. Chemical properties of the urine

Chemical research of the urine includes examination the urine reaction and the content of the protein, glucose, ketone bodies and bile pigments.

Reaction of the urine.

The kidneys are involved in maintaining the acid-base balance in the body. *Urinary pH varies from 4.5 to 8.0 in norm (Table 22-2). The reaction of the urine is a slightly acidic (pH 5.5-6.5) in a healthy person on a mixed balanced diet.* It is determined by the litmus test.

*The reaction of the urine can vary depending on the food natur*e. The excess of the animal protein in the diet can result in an extremely acid reaction of the urine, a vegetable diet - in an alkaline reaction.

In pathology, an *extremely acid reaction of the urine* is observed in a febrile state, decompensated diabetes mellitus, during starvation, and in a renal failure.

An *alkaline reaction of the urine* is noted in *renal tubular acidosis* (a failure of the kidneys to appropriately acidify the urine), cystitis, pyelitis, significant hematuria, after vomiting, diarrhea, taking certain medications (e.g., in high doses of the baking soda, antacids), with the use of alkaline mineral water. The urine reaction is alkaline in the urinary tract infection due to bacterial-ammoniac fermentation.

Table 22-2. Common chemical properties of the urine

Urine properties	Characteristics	Leading causes
Reaction	acid	in norm
	alkaline	vegetarian diet
	extremely alkaline	renal tubular acidosis, urinary infection
Proteinuria	absent	in norm
	mild daily protein loss (<0.5 g/day)	urinary tract inflammation, renal carcinoma, hypertensive nephrosclerosis, orthostatic proteinuria
	moderate daily protein loss (0.5 – 3.0 g/day)	acute and chronic glomerulo- and pyelonephritis, obstructive nephropathy, diabetic nephropathy, urinary infection
	severe daily protein loss (> 3.5 g/day)	nephrotic syndrome
Glucosuria	absent	in norm
	extrarenal glucosuria	in hyperglycemia > 8.9-10.0 mmol/1 (diabetes mellitus, emotional stress glucosuria, corticosteroids intake)
	renal glucosuria	renal diabetes, chronic kidney diseases (in normal blood glucose)
Ketonuria (acetonuria)	absent	in norm
	present	in ketoacidosis (e.g. diabetes mellitus, starvation, gastrointestinal disorders with vomiting and diarrhea, vomiting of pregnancy)
Bile pigments	urobilin traces	in norm
	urobilinuria	hepatic and prehepatic jaundice
	bilirubinuria	hepatic and posthepatic jaundice

Urinary protein.

The urine in norm contains a very small amount of the protein (50 mg per day), which is not determined by the qualitative tests used in practical medicine. On this basis, *it is widely accepted that that the urine of a healthy person is free of the protein.*

Proteinuria is the presence of urinary proteins in concentrations detectable by qualitative methods.

Extrarenal proteinuria is observed in inflammatory diseases of the urinary tract (e.g., pyelitis, cystitis, and urethritis). In these situations, an exudate (an inflammatory fluid) enters the urine. The concentration of the urinary protein in these diseases is not high (usually <1 g/1).

Renal proteinuria can be of the functional or organic origin.

Functional renal proteinuria is observed when the kidneys are severely irritated by physical, chemical, thermal and other factors, which slow the blood flow in the renal glomeruli and increase permeability of glomerular membrane*:*

- during physical work, prolonged walking ***(march proteinuria)***,
- prolonged stay in an upright position ***(orthostatic proteinuria)***,
- strong cooling, emotional overstrain.

Organic renal proteinuria is the result of the damage to the renal parenchyma and an increase in the permeability of the capillaries of the renal glomeruli (e.g. in acute and chronic glomerulonephritis, glomerulopathy in infectious-toxic, immune and circulatory pathology of the kidneys).

There are ***selective renal proteinuria (low-molecular proteins loss) and non-selective renal proteinuria (both low-molecular and high-molecular proteins loss).*** The non-selective renal proteinuria is a serious prognostic sign of the progressive structural disorganization of the glomerular membranes.

The level of the protein in the urine in the renal proteinuria can be significant. Measurements of the daily (24-hour) protein excretion are useful for diagnosis, especially in cases of the persistent proteinuria. A severe proteinuria (more than 3.5 g per day) is a characteristic of the nephrotic syndrome. *Normally, an average proteinuria of the adult person is 50 mg/day. When the true renal proteinuria, a urinary protein loss is more than 300 mg/ day.*

Microalbuminuria *is the urinary albumin loss in 30 mg/day and more.* Microalbuminuria is an early marker of the kidney lesions in diabetes mellitus and essential arterial hypertension. Specific antibodies to albumin are used to identify microalbuminuria in the urine dipstick analysis.

Urine glucose.

The urine in norm contains a glucose level less than 0.02%, which is not detected by ordinary high-quality tests.

Glucosuria *is the urinary glucose excretion in concentrations detectable by qualitative methods.*

Physiological glucosuria is observed in the presence of the normal renal function with the use of the high-carbohydrate diet ***(alimentary glucosuria)***, after emotional and other stresses ***(emotional /stress glucosuria)***, after taking certain medications (caffeine, corticosteroids).

Physiological glucosuria is due to an increased concentration of the glucose in the blood (hyperglycemia) more than 8.9-10.0 mmol/1.

Pathological glucosuria can be of the pancreatic origin (most frequently in diabetes mellitus), thyrogenic origin (in hyperthyroidism), pituitary origin (in the Itsenko-Cushing's disease), and in cases of the poisoning with morphine, chloroform, phosphorus.

For a reliable assessment of the glucosuria (especially in diabetes mellitus), it is necessary to determine a daily urinary glucose excretion. *The daily glucosuria*

(amount of the glucose excreted with urine per 24 hours) determines the tactics of the treatment.

***Renal glucosuria** is a condition of the rare occurrence due to disorders of the tubular resorption glucose in the presence of the normal blood glucose concentrations.*

Primary renal glucosuria occurs in the inherited *renal diabetes*. *Secondary renal glucosuria* can be in chronic kidney diseases.

Urine ketones

Urine ketones (ketone, or acetone, bodies; KET) include acetone, acetoacetic and β-oxybutyric acid). *Ketonuria (acetonuria)* is a presence of the ketone bodies in the urine. Ketonuria is commonly detected by the *Lange test*.

Ketones are end-products of the fatty acid metabolism. *Ketonuria is a sign of the ketoacidosis*, in which the body produces excess ketones because of using fatty acids as an alternative source of the energy. Ketoacidosis develops due to carbohydrate deficiency (in starvation, long standing gastrointestinal disorders with vomiting and diarrhea, vomiting of pregnancy, alcohol intoxication, etc.) and insulin deficiency in decompensated type 1 diabetes mellitus. The *diabetic ketoacidosis* is a life-threatening complication of the type 1 diabetes mellitus and a precursor of the *diabetic ketoacidotic hyperglycaemic coma*.

Bile pigments in the urine

The *urine bilirubi*n is absent in norm. ***Bilirubinuria*** (a positive test for the urine bilirubin) confirms any elevated levels of the conjugated hyperbilirubinemia. Bilirubinuria is a characteristic of the posthepatic (mechanic, obstructive) jaundice (e.g., in cholelithiasis, obstruction of the common bile duct with a tumor or enlarged lymph nodes) and hepatic (parenchymal) jaundice (e.g., in acute and chronic hepatitis, liver cirrhosis). Bilirubinuria is not detected in the prehepatic (hemolytic) jaundice.

Urobilin (urobilinogen) and stercobilin (stercobilinogen) normally present in small amounts (as a trace component) in the urine. *Urobilinoids (urobilin and stercobilin in total)* are not tested separately. These intestinal metabolites of the bilirubin elevate due to hemolysis or from the impaired liver capture and excretion of the bilirubin. ***Urobilinuria** is an excretion of a large amount of urobilinoids in the urine. Urobilinuria* is a characteristic of the hepatic jaundice (e.g., in hepatitis, liver cirrhosis) and prehepatic jaundice (hemolytic anemia).

Urinary nitrites

Nitrituria *is a positive test for nitrites in the urine*. Normal urine contains nitrates, which can be turned in nitrites if gram negative bacteria (e.g., Escherichia coli, Proteus spp.) enter the urinary tract.

Nitrituria is a highly specific test for urinary tract infection, because of the urease-splitting organisms (e.g., Proteus spp., Escherichia coli). Nitrituria absents in case of the urinary infections with bacteria unable to turn nitrates to nitrites (e.g., enterococci, staphylococci, Acinetobacter spp.).

Hemoglobin in the urine

Normally, hemoglobin is absent in the urine. ***Hemoglobinuria*** *is a result of the intravascular hemolysis of erythrocytes with the release of the hemoglobin*. Intravascular hemolysis occurs in some cases of the hemolytic anemia, the transfusion of the incompatible blood, bites of poisonous animals, infections (e.g., malaria, anaerobic sepsis), glucose-6-phosphate dehydrogenase deficiency, a drug side effect (dapsone), and after many kilometers foot marches (marching hemoglobinuria).

Hemoglobinuria is characterized by red or dark brown urine, dysuria, and often lumbar pain. Erythrocytes are not present in the urine sediment in hemoglobinuria. Hemoglobinuria can be complicated by an acute renal failure.

Urine myoglobin

Myoglobinuria *is the presence of the myoglobin* (a heme protein of the muscle tissue) in the urine. Myoglobinuria is a result of the myopathy caused by trauma, necrosis, ischemia, or toxicosis.

Myoglobinuria manifests with red-brown transparent urine. Myoglobin is characterized by a positive blood test on the urine test strip. The red color of the urine remains after centrifugation. Myoglobinuria can be complicated by an acute kidney injury.

22.1.1.3. Microscopy of the urine sediment

Microscopy of the urine sediment should be performed no later than 2 hours after the urine collection, at a low specific gravity (less than 1.010) - immediately after the urine collection.

The elements of the urine sediment, visible by a microscope, are divided into organized (cellular elements, casts) and unorganized (salts, mucus) urine sediment.

Organized urine sediment

Organized urine sediment includes *epithelial cells, leucocytes, erythrocytes, and casts* (Table 22-3).

Squamous epithelial cells (pavement cells) enter the urine from the genital tract and partly from the urethra. *Normally, there are single (up to 5) squamous epithelial cells in the field of a vision of the microscope* (*per high-power field, hpf*).

A large number of them is a sign of the improperly collected urine without a previous perineal toilet. The *large number of squamous epithelial cells in the urine together with dysuria is a characteristic of the cystitis and urethritis* due to intense desquamation of the mucous membrane.

Table 22-3. Microscopic study of the urine sediment

Components	Characteristics	Leading causes
Organized urine sediment		
Squamous epithelial cells	up to 5 hpf *	in norm
	>5 hpf	cystitis, urethritis (together with dysuria)
		improperly collected urine
Renal (cubical) epithelial cells	absent	in norm
	present	the damage to the renal parenchyma (glomerulonephritis, tubular necrosis)
White blood cells (WBC, leucocytes)	up to 5 hpf	in norm
	leucocyturia (6-50 hpf)	infections and inflammations of the kidneys and urinary tract (pyelonephritis, cystitis, urethritis, kidney tuberculosis, and prostatitis)
	pyuria (>50 hpf)	
Red blood cells (RBC, erythrocytes)	absent (or 0-2 hpf)	in norm
	hematuria (>3 hpf)	diseases of the renal parenchyma and urinary tract, pathology of the blood coagulation system and anticoagulant treatment
	glomerular hematuria (altered RBC)	glomerulonephritis, renal tuberculosis, kidney infarction, hypernephroma
	non-glomerular hematuria (unaltered RBC)	urolithiasis, urinary tract inflammation (cystitis, urethritis) and tumors
Casts	absent	in norm
	hyaline casts	kidney diseases (glomerulonephritis, pyelonephritis, etc.) and in healthy persons after physical stress (0-2 hpf)
	waxy and granular casts	in advanced chronic kidney disease (e.g., nephrotic syndrome, renal amyloidosis)
	fatty casts and lipiduria	nephrotic syndrome
Unorganized urine sediment		
Crystals of salts	absent or a few (0-2 hpf)	in norm
	uric acid, urates	urolithiasis, gout
	oxalates, calcium carbonate, phosphates	urolithiasis
Mucus	absent or a few	in norm
	excess mucus	urinary tract infections, urolithiasis, and urinary bladder cancer

*Note: * hpf – in the field of vision of the microscope (per high-power field).*

A large number of the *transitional epithelium* in the urine can indicate an inflammation in the kidney pelvis (pyelitis) or the urinary bladder (cystitis).

The renal (cubical) epithelial cells in the urine are a sign of the damage to the renal parenchyma in glomerulonephritis, tubular necrosis, and in fever, toxicosis, and infectious diseases.

White blood cells (WBC, leucocytes)

Normally, *single leucocytes can be detected in the preparation of the urinary sediment (up to 5 hpf in children, women).*

Leucocyturia is a detection up to 50 leucocytes hpf.

Pyuria (pus in the urine) is a detection more than 50 leucocytes hpf.

There is leucocyturia (pyuria) in inflammatory and infectious diseases of the kidneys and the urinary tract (pyelonephritis, cystitis, urethritis, kidney tuberculosis, and prostatitis).

Neutrophils prevail (90-100% of the total number of WBC in the urine sediment) in urinary infections. The lymphocytes percentage more than 20% is characteristic of the immune inflammation of the kidneys (e.g., acute glomerulonephritis, exacerbation of the chronic glomerulonephritis or interstitial nephritis, renal acute graft versus host disease).

The appearance of a large number of eosinophils in the urine sediment occurs in the drug-induced nephritis, rapidly progressive glomerulonephritis, and sometimes with Ig A-nephropathy. The predominance of macrophages is typical in the renal amyloidosis, exacerbation of the chronic glomerulonephritis, and Ig A-nephropathy.

Red blood cells (RBC, erythrocytes)

Normally, erythrocytes are not detected in the urinary sediment in most people. In the normal condition sometimes, single erythrocytes can be detected (up to 2 hpf) more often in females. Such cases require a mandatory repeated control of the clinical urinalysis.

Hematuria *is the presence of the red blood cells in the urine*.

Macrohematuria *is a detection of the blood on examination of urine by the unaided eye.*

Microhematuria *is a hematuria when erythrocytes in the urine that can be detected only by a microscopy.*

The *urine erythrocytes can be altered and unaltered*. *The unaltered erythrocytes* contain hemoglobin and look like greenish-yellow discs. *The altered (abnormal, "leached") erythrocytes* are free from hemoglobin, and they look like colourless one- or two-contour rings. The altered erythrocytes have a renal origin, they are damaged when passing through the basic membrane of glomerular capillaries.

Hematuria with a predominance of the altered erythrocytes is characteristic of the ***glomerular hematuria*** in the kidney diseases (e.g., acute and chronic

glomerulonephritis, renal tuberculosis, kidney infarction, hypernephroma). The *glomerular hematuria commonly combines with moderate or massive proteinuria.*

Hematuria with a predominance of unaltered erythrocytes is characteristic of the ***non-glomerular hematuria*** in urolithiasis, the urinary tract inflammation (cystitis, urethritis) and tumors. The non-glomerular hematuria usually combines with insignificant proteinuria.

The ***three-glass test*** *can be applied to find a* source *of the hematuria and/or leucocyturia*. The patient should collect the urine into three vessels. The 1-t portion of an early morning urine sample is collected in the first vessel, the main 2-d part of the urine volume – in the second vessel, and only the residual 3-d urine – in the third vessel. If the blood cells (RBC, WBC) come from the urinary tract (urethra), the highest amount of blood cells present in the I-t portion of the urine. If lesions affect the urinary bladder, the highest number of the blood cells present the last III-d portion. The uniform distribution of the RBC and WBC in all three portions of the urine suggests a kidney disease.

Urinary casts

Urinary casts (renal casts, urinary cylinders) *can be protein (hyaline, waxy) and cellular. The place of their formation is the renal tubules*.

Casts have a cylindrical configurtion and variable size. The casts composition includes glycoprotein (*Tamm-Horsfall protein*) secreted from the thick ascending loop of Henle, protein, and cellular elements of the urine.

Cylindruria *is an urinary excretion of casts. Cylindruria indicates the renal pathology.* Cylindruria is observed in a number of kidney diseases. Cylindruria is combined with the urinary excretion of protein, epithelium, erythrocytes and leucocytes (e.g., in glomerulonephritis, pyelonephritis, nephrotic syndrome). *Cylindruria confirms the renal causes of the proteinuria, hematuria and leucocyturia.*

Hyaline casts are composed of the glycoprotein matrix consisting mainly of Tamm-Horsfall protein secreted by the renal tubules. *Hyaline casts can be found in combination with a moderate proteinuria (e.g., in glomerulonephritis, pyelonephritis, in febrile patients).* Single hyaline casts can be detected in urine of healthy people (e.g., after physical stresses) or in patients with a low urine flow (e.g., due to dehydration, after diuretic therapy).

Waxy casts are composed of the glycoprotein matrix with degraded protein. They are formed in atrophic renal tubules. *Waxy casts combine with a severe proteinuria, and present in an advanced chronic kidney disease (e.g., a nephrotic syndrome, renal amyloidosis).*

Cellular casts (epithelial, leukocyte, erythrocytic) are composed of a protein base which is covered by a large number of the adhered cells. The ***granular casts*** are formed during the destruction of the adhered cells. *Granular and waxy casts are detected in severe lesions of the renal parenchyma.*

Fatty casts *in large numbers strongly suggest a nephrotic syndrome*.

The urine can also contain combined casts and cylindrical formations of the clumped cells, bacteria, parasites (*Schistosoma haematobium* eggs, *Trichomonas vaginalis*), and amorphous salts (*pseudocasts*), which are not diagnostically important.

Unorganized urine sediment

Unorganized urine sediment *consists of various salts, organic compounds and medicinal substances that have settled in the urine in the form of crystals or amorphous bodies.* However, the unorganized sediment substantially consists of salts.

Crystalluria *is the presence of crystals in the urine*. The nature of the ***urinary salts*** mainly depends on the colloidal state and the reaction of the urine. Crystals of the uric acid, urates, oxalates are detected in the acid urine. Crystals of the ammonium urate, calcium carbonate, triple phosphates, amorphous phosphates, and neutral calcium phosphate are detected in the alkaline urine. Crystals of the oxalates may also occur in alkaline urine.

Crystals of the uric acid and urates are found in urolithiasis, gout, massive degradation of tumor cells, as well as in febrile conditions. Crystals of the oxalates, calcium carbonate, phosphates salts can also present in urolithiasis. ***The detection of salts in the sediment in a single study can not be regarded as a pathological phenomenon***.

The presence of tyrosine and leucine in the urine is characteristic of the severe dystrophy of the liver, leucosis and phosphorus poisoning.

Lipiduria *is the presence of lipids and cholesterol in the urine*. In a polarizing microscope, cholesterol gives a dual reflection and appears as a Maltese crosses. Lipids appear microscopically as oval bodies. Lipids and cholesterol can also be in composition of casts. *Lipiduria is characteristic of the nephrotic syndrome.*

Mucus *is a gel that is produced by the cells of the urinary tract to protect against the aggressive effects of the urine and its components, especially salts.* It is normal to detect small amounts of the mucus in the urine.

The most common causes of the excess mucus in the urine are urinary tract infections, urolithiasis, and urinary bladder cancer.

Positive (active) urinary sediment *is a microscopic finding of formed elements (RBC, WBC, casts) greater than in norm (see Table 22-3), a large number (3-5 hpf) of the salts crystals and microorganisms (bacteria, fungi, parasites).* Positive (active) urinary sediment confirms an abnormality of the kidneys and the urinary tract.

22.1.2. Bacterioscopic and bacteriological study of the urine

The renal urine is normally sterile, but the urine can be a good growth medium for bacteria, which enter the urinary tract and urinary bladder from the urogenital region and are not eliminated.

If bacterioscopy of the truly fresh urine finds the presence of even 1 bacterium per oil immersion field of the unspun gram-stained urine, it correlates with a colony count of the greater than 100,000 colony-forming units per ml ($\geq 10^5$ cfu/ml).

Urine cultures are used to establish the infectious nature of a disease of the urinary system. The urine is studied bacteriologically to determine qualitative and quantitative composition of its microbial flora.

The urine is a sterile body fluid that is easily contaminated by the microflora of the perineum, urethra and vagina. Microbes that colonize the urogenital tract can cause an infection in the urinary tract. For this reason, the correct sampling, transportation and storage are very important in a microbiological examination of the urine. Only the midstream morning urine is used. In some cases, the urine collection is allowed with the use of a catheter or a puncture from the urinary bladder.

The *normal urogenital microflora* includes *Streptococcus spp. of the viridans variety, Neisseria spp., Corynebacterium spp., Lactobacillus spp., Staphylococcus spp.*

The *most common pathogens of the urinary infections are Escherichia coli, Klebsiella spp., Proteus spp., Enterococcus spp., Staphylococcus saprophyticus, and Pseudomonas spp..*

Bacteriuria is characterized by the bacterial count $\geq 10^5$ cfu/ml. *Bacteriuria* is typical in the urinary tract and the kidneys infections (pyelonephritis, cystitis, urethritis, prostatitis). In the presence of the *bacteriuria*, it is very important to determine its degree and a microorganism sensitivity to various antibiotics.

Bacterial count 10^3 - 10^5 cfu/ml can also be clinically important if:

- the patient has symptoms suggestive of the urinary infection (dysuria, the lumbar or lower abdominal pains, pollakiuria, etc.);
- there is pyuria in the urine;
- the patient has previously received antibacterial treatment;
- there is a suspicion of pyelonephritis or prostatitis;
- immunocompromised patients and pregnant women.

The bacterial count < 10^3 cfu/ml is not considered as clinically significant microbial growth.

22.1.3. Quantitative methods of the urine sediment assessment

Nechiporenko test

Nechiporenko test is the quantitative method of the microscopic examination of the urine sediment. The midstream morning urine is collected. It is based on determining the number of the formed elements of the organized urine sediment with the use of the Gorjaev's count chamber in 1 ml of the urine.

The normal urine contains in 1 ml not more than 4,000 leucocytes (or <4.0×10^6 / l), not more than 1000 erythrocytes (<1.0×10^6 / l), and not more than 20 hyaline cylinders (2.0×10^4 / l) (Table 22-4).

There is a predominant increase in the number of leucocytes in acute and exacerbation of the chronic pyelonephritis. A predominant expansion in the number of erythrocytes is typical in acute and chronic glomerulonephritis.

Table 22-4. Nechiporenko test

Index	Normal value
Leucocytes	≤ 4000 /ml (≤ 4.0×10^6 /l)
Erythrocytes	≤ 1000 /ml (≤ 1.0×10^6 /l)
Casts (cylinders)	≤ 20 /ml (≤ 2.0×10^4/l)

The simultaneous expansion in the number of casts confirms a renal origin of the hematuria and/ or leucocytouria.

22.2. Renal function tests

22.2.1. Zimnitskiy test

The essence of the Zimnitskiy test is to determine the renal concentrating ability of the kidneys according to the amount and specific gravity of the urine. The urine is collected during the day in 8 containers every three hours (24 hours) in compliance with the usual water-intake and food regime of the patient.

The each portion volume and specific gravity are estimated. The daily (24-hours) urine output (daily diuresis) is divided into daytime (the sum of the first four portions according to Zimnitskiy) and nighttime (the sum of the last four portions according to Zimnitskiy). The volumes of the daytime and nighttime diuresis are compared.

To assess the diurnal (24 hours) fluctuations in the urine specific gravity, two portions with the maximum and minimum specific gravity are determined, and the difference between these values is estimated.

In norm, the ratio of the daytime diuresis to nighttime diuresis is ≥ 3:1; volumes of the urine portions can vary from 50 to 250 ml; and their specific gravity varies from 1.005 to 1.028; the daily fluctuations of the urine specific gravity is > 0.008 in norm (Table 22-5).

Nycturia (nocturia) *is an increase in the volume of nighttime diuresis more than 1/3 of the daytime diuresis. Renal nycturia* is observed in chronic renal failure (chronic kidney disease) and polyuric stage of the acute kidney injury (acute renal failure). *Cardiac nycturia* is a characteristic of the heart failure.

Table 22-5. Zimnitskiy's test

Index	Normal value
Daily (24 hours) diuresis	1000-2000 ml (65 - 75% of the water input)
Daytime diuresis	3/4 of the daily (24-hours) diuresis
Specific gravity (within the range)	1.005 – 1.028
Diurnal (24 hours) fluctuations in the urine specific gravity	$\geq$ 0.008

The concentrating ability of the kidneys is not impaired if the difference between the maximum and minimum specific gravity is at least 0.008. The relative density of the urine within the range 1.010 – 1.025 indicates a good renal concentrating ability.

Hypersthenuria is indicated if the urine specific gravity in all portions is more than 1025 due to the appearance in the urine of the highly osmotic substances (protein, glucose).

Hyposthenuria is indicated if the specific gravity of the urine below the relative density of blood serum (below 1.010).

Isothenuria is the monotony of the specific gravity of the urine during the day (the daily fluctuations do not come up 0.008).

Hyposthenuria and isosthenuria (*isohyposthenuri*a) indicate a decrease in the concentrating ability of the kidneys (renal failure) with the development of the *primary shrunken kidney* (nephroangiosclerosis due to essential arterial hypertension*), and secondary shrunken kidney due to renal arterial stenosis, obstructive uropathy, and chronic renal disease (e.g., chronic glomerulonephritis, chronic pyelonephritis, diabetic nephropathy).*

Nycturia prevails in the renal insufficiency and indicates a longer work of the kidneys because of their impaired functional capacity. The renal nycturia is combined with polyuria and hyposthenuria, it is a specific sign of the renal dysfunction. The cardiac nycturia combines with oligiuria.

22.2.2. Assessment of the glomerular filtration

Glomerular filtration rate (GFR) *is the volume of the blood plasma, which is filtered through the glomeruli per minute.*

GFR is the important overall index of the kidney function; it is expressed in ml/min.

Creatinine is produced by a muscle metabolism and is freely filtered by the glomeruli. The *renal clearance* means the volume of the blood or plasma could be freed of the specified substance per minute by excretion of the substance into the urine through the kidneys. The renal clearance of the creatinine is practically equal to the glomerular filtration.

Rehberg test *is a study of the glomerular filtration (GFR) by endogenic creatinine.* Rehberg test makes it possible to assess GFR and the tubular water reabsorption function of the kidneys based on the determination of the minute urine output and the concentration of the plasma creatinine and urine creatinine.

In the morning, the patient should urinate, right after that he/she drinks 400 ml of the water. In 30 minutes, the blood sample is taken from a vein to determine the plasma level of the creatinine. In 30 minutes after blood sampling, all the urine is collected to determine the concentration of the creatinine and the minute urine output. Next, the GFR and the reabsorption percentage are calculated by the formulae.

Normally in the Rehberg test, GRF (glomerular filtration rate) is from 75 to 125 ml / min, and the tubular reabsorption is from 97 to 99%.

In a chronic kidney disease (chronic renal failure), GFR and tubular reabsorption are reduced, with a more pronounced decrease in GFR in chronic glomerulonephritis, and tubular reabsorption – in pyelonephritis.

The chronic renal failure arises if the mass of the active nephrons is 20 per cent (and lower) of the normal weight. The measure of the active nephrons is the GFR. GFR can decrease gradually as low values as 5-2-1 ml/min in the chronic renal failure. The tubular reabsorption decreases in a lesser extent, in case of the severe renal insufficiency – to 80-60 %.

Estimation of creatinine clearance rate (eC_{Cr}) using Cockcroft-Gault formula

The ***Cockcroft-Gault (CG) formula*** *is a commonly used surrogate marker for estimate of creatinine clearance, which estimates GFR (eCCr) in ml/min.* The CG formula employs serum creatinine measurements and a patient's weight to predict the creatinine clearance. When serum creatinine is measured in μmol/L:

$$eC_{Cr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times Constant}{\text{Serum Creatinine (in } \mu\text{mol/L)}},$$

where *Constant* is 1.23 for males and 1.04 for females.

The Cockcroft and Gault equation shows how the estimation of CCr in dependence to a patient’s age. The age term is (140 - age). This means that a 20-year-old person (140-20 = 120) will have twice the creatinine clearance as an 80-year-old (140-80 = 60) for the same level of the serum creatinine. The C-G equation assumes that a woman will have a 15% lower creatinine clearance than a man at the same level of serum creatinine.

The normal values are for males - 97-137 ml/min; for females – 88-128 ml/min.

Estimation of the GFR (glomerular filtration rate) by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI equation)

CKD-EPI equation makes it possible to assess GFR by the plasma creatinine level to define different stages of the chronic kidney disease.

CKD-EPI equation applies a correction factor using body surface area (BSA), because normal GFR increases with increasing body size. This correction factor is necessary to compare the patient's GFR to normal values. The correction factor is 1.73/patient BSA due to the mean normal BSA is 1.73 $m^{2.}$. GFR results (by CKD-EPI) are expressed as mL/min/1.73 m^2.

CKD-EPI GFR = 141 × (serum creatinine) -1.209× 0.993 age

The result is multiplied by 1.018 if the patient is female and by 1.159 if the patient is African American. For female African Americans, the result is multiplied by 1.018 × 1.159 (1.1799). *The normal CKD-EPI GFR in young healthy adults is about 120 to 130 mL/min/1.73 m^2 and declines with age to about 75 mL/min/1.73 m^2 at the age 70 years. Chronic kidney disease is defined by a GFR < 60 mL/min/1.73 m^2 above 3 months.*

The 2021 CKD-EPI equation is now the recommended standard to assess GFR by the plasma creatinine level to define different stages of the chronic kidney disease. With the 2021 equation, for the same creatinine value, the 2021 equation will estimate a lower GFR for Black patients and a higher GFR for non-Black patients. *The CFR can be calculated using an online medical calculator (https://www.mdcalc.com/calc/3939/ckd-epi-equations-glomerular-filtration-rate-gfr).*

The Modification of Diet in Renal Disease (MDRD-GFR) study formula (current 4-factor formula) can also be used, it requires a calculator or computer *(https://www.mdcalc.com/calc/76/mdrd-gfr-equation).*

GFR is more accurately estimated by CKD-EPI equation based on creatinine than by CG formula. Calculation of the GFR by the CG formula cannot be used in patients with low muscle mass, on a low-protein or vegetarian diet, during pregnancy and obesity.

22.3. Diagnostic value of the blood examination in kidneys and urinary tract diseases

Biochemical blood tests

Serum creatinine is a key biochemical index of the renal function because a creatinine production and excretion are virtually free of fluctuations in the absence of the muscle disease. The creatinine concentration depends on creatinine generation (due to the muscle creatine catabolism) as well as renal creatinine excretion. Serum concentration of the creatinine varies in an inverse proportion to GFR. Serum creatinine is higher in males (due to a higher body mass and muscle mass) compared to females, and healthy older persons and undernourished people have lower levels of the creatinine.

Serum creatinine levels above 0.115 mmol/l in males and above 0.097 mlmol/l in females are usually abnormal, and can indicate the renal insufficiency (Table 22-6).

Table 22-6. Rest (nonprotein) nitrogen and its some components in blood serum

Tests	SI units
Creatinine: male female	0.062- 0.115 mmol/l 0.053 – 0.097 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
Residual nitrogen	20 — 40 mg%
Blood urea nitrogen (BUN)	3-20 mg/dL
Glomerular filtration (Rehberg test	75-125 ml/min
Tubular reabsorption	97-99%

Serum creatinine may also be increased due to the intake of the meat food in greater amount, and use of some medications, most notably angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), nephrotoxic antibiotics (e.g., aminoglycosides, cephalosporins, amphotericin B, bacitracin, and vancomycin), etc.

It is possible approximately to assess the renal failure by increased blood levels of the ***nitrogen substances*** *– creatinine, urea, uric acid, indican, residual nitrogen, blood urea nitrogen (BUN)*. However, nitrogen substances concentrations in the blood are substantially not change in a minor decrease of the GFR. In general, the GFR estimation is more precise in the assessment of the renal failure compared with nitrogen substances.

Electrolytes of the blood plasma can significantly change in acute and chronic pathology of the kidney and urinary system (Table 22-7). *Hyperphosphatemia and hypocalcemia* are typical in an advanced chronic kidney disease, and result in osteoporosis and ostemalacia. The elevated serum *alkaline phosphatase (ALP)* can be found in osteoporosis due to ALP bone fraction release into the blood.

Hyperkalemia (hyperpotassemia) is an elevated level of the potassium K+ in the blood serum; it is characteristic of the renal tubular acidosis, acute kidney injury (anuric and oliguric stages) and a terminal stage of the chronic kidney disease. Hyperkalemia is significantly associated with a high risk of the cardiac arrhythmia and cardiac arrest.

Hypermagnesemia (an elevated level of the potassium Mg++ in the blood serum) can develop in the renal failure due to a diminished glomerular filtration.

In the terminal stage of the chronic kidney disease, sodium loss (*hyponatremia*) and chlorides (*hypochloremia*) can be due to a vomiting and diarrhea, and *hypochloremic alkalosis* develops. *Hyperchloremia and metabolic acidosis* are typical in the renal tubular acidosis.

Table 22-7. Blood serum ionogram

Tests	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

Decrease of the serum total protein (*hypoproteinemia*) due to albumin (*hypoalbuminemia)* and increased total cholesterol (*hypercholesteremia*) are biochemical characteristics of the nephrotic syndrome.

Common blood analysis. *Normochromic anemia (due to a lack of the erythropoietin) is a typical complication of the chronic renal failure*. The renal cell carcinoma and polycystic kidney disease can cause an erythrocytosis. *Neutrophilia (neutrophilic leucocytosis)* can be in severe urinary infections.

22.4. Instrumental methods of the kidney examination

Plain abdominal radiography can demonstrate the size and location of the kidneys, and identify the shadows of the urinary calculi. The plain radiography of the kidneys is usually at the first stage of the examination in the urinary system disease, and mostly is not very informative.

Intravenous urography (IVU; excretory urography) is used to visualize the kidneys and the urinary tract. Following intravenous administration of the iodine-containing contrast agent, a series of the urograms are taken.

Excretory urography provides:

(1) a contrast study of the kidneys shadow, pyelocaliceal system and urinary tract:

- bulging contour of the kidney - in cicatricial changes, tumor mass, polycystic kidney disease;
- changes in the pyelocaliceal system – in chronic pyelonephritis, papillary necrosis, obstructive nephropathy, renal tuberculosis;

(2) assessment of the cumulative-excretory kidney function.

The best urograms are obtained in patients with a normal GFR. There is a high risk of the acute renal failure after introducing the iodine-containing contrast agent in patients with even a slight decrease in the GFR, especially in a chronic kidney disease, diabetes mellitus, and multiple myeloma.

Renal angiography is a contrast radiography imaging used to diagnose disorders of the kidneys blood supply.

Renal angiography (arteriography, venography) provides:

- exclusion of the renal artery stenosis;
- conducting balloon angioplasty, stenting in case of the renal artery stenosis;
- diagnosis of the renal vein thrombosis.

CT (computed tomography) allows to diagnose the kidney and urinary tract neoplasms (tumors, cysts), and retroperitoneal masses, but the diagnostic value of the method significantly increases with the contrast agent administration.

MRI (magnetic resonance imaging) produce the layer-by-layer images of the investigated organ in three dimensions. The advantage of the method is the absence of a radiation exposure and possibility of the use in case of the renal insufficiency. In addition to diagnosis of the renal and urinary tract neoplasms, MRI defines vascular and perirenal structures, and can detect the thrombosis, aneurysms, arteriovenous fistula, and a neoplastic extension. MRI with the contrast administration provides information about GFR and tubular function.

Ultrasonography (US) is a widely applied for the kidney diagnostic imaging (Fig. 22.1), since the US does not have contraindications and a harmful effect on health. The US can be used in patients with renal insufficiency, when an X-ray examination with the contrast agent administrations is contraindicated.

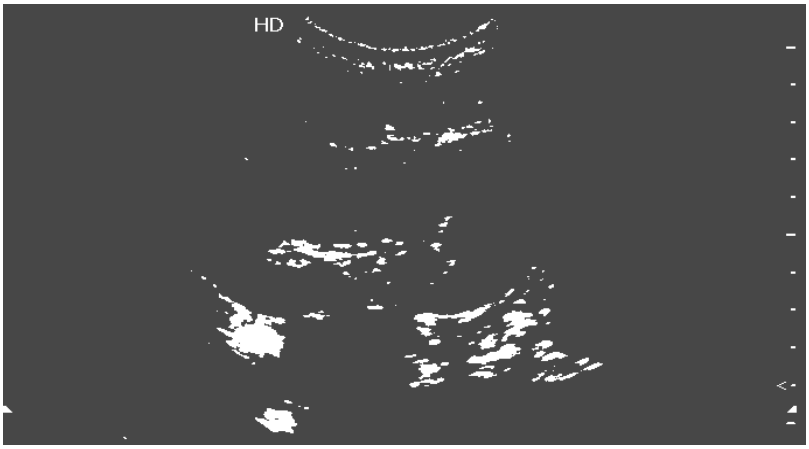


Fig. 22.1. Ultrasonogram of the normal kidney. The kidney has a bean-shaped form, clear and smooth contours.

The US provides a visualization of the kidney contours, the renal cortical-medullary area, the pyelocaliceal system, urinary stones (calculi), tumors, cysts, abscesses, and of the urinary bladder (Fig. 22.2-22.3). The *Doppler US* provides

the study of the renal blood flow; it is a screening procedure for detecting renal vascular stenosis or thrombosis.

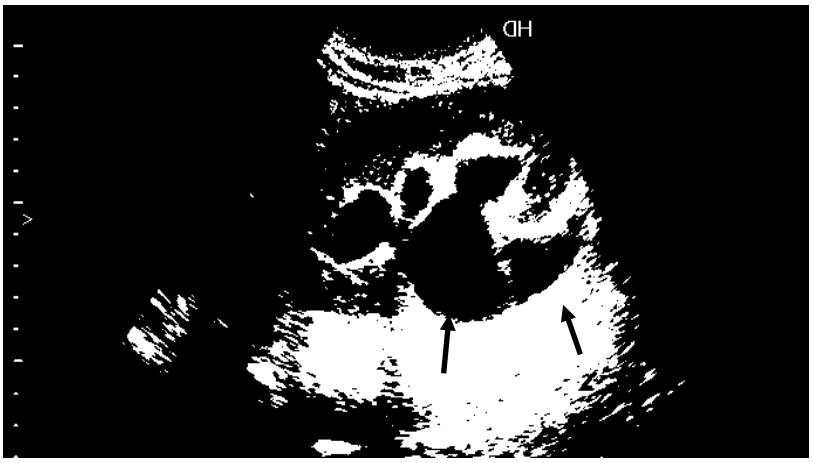


Fig. 22.2. Ultrasonogram of the kidney in hydronephrosis. The pyelocaliceal system expanded, filled with acoustically transparent urine.

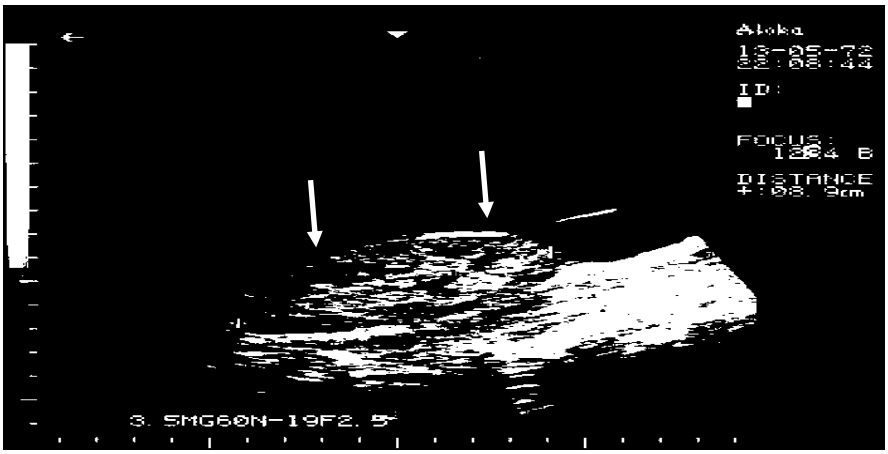


Fig. 22.3. Ultrasonogram of the kidney in chronic glomerulonephritis and chronic renal failure. The kidney is reduced in size, echogenicity of the parenchyma increased. The free fluid in the abdominal cavity is determined.

Radioisotope renography (hippuran labelled ^{131}I) is used to study the cumulative-excretory function of the kidneys (by the rate of the blood clearance of the labelled preparation), and to an urodynamics study of the upper urinary tract (by an accumulation of the radioisotope in the urinary bladder). Radioisotope renography is a non-invasive procedure with a low radiation exposure. That is why it can be performed in patients with a reduced function of the kidneys.

Radionuclide (radioisotope) scanning (with ^{99m}Tc) uses accumulation of the labelled radioactive preparation to produce images of the kidneys.

Radionuclide scanning provides:

- assessment of the cumulative and excretory functions of the kidneys (he intensity of the radioactive preparation accumulation);
- assessment of the shape, size, location of the kidneys by the renal scanogram;
- indication of the focal defects of the radioactive preparation accumulation (in tumours, cysts, tuberculous affections, and other destructive processes of the kidneys).

The advantage of the radionuclide scanning is the absence of the radioactive nephrotoxicity, and the possibility of performing this procedure in patients with a renal failure.

Renal puncture biopsy is performed to a diagnosis specification, to select a choice of the treatment option, and to specify a prognosis for a disease.

Most often a percutaneous puncture biopsy of the kidney is performed, less often – a half-open biopsy. The indications for renal biopsy are acute and a chronic renal failure of the undefined origin, a nephrotic syndrome, and renal hematuria of an undefined origin. The absolute contraindications are the blood coagulation failure, alteration of consciousness (coma, psychosis), the only functioning kidney, and a shrunken kidney.

22.5. The key points of the theme "Laboratory and Instrumental Examination of the Urinary System"

In healthy adult people, the daily diuresis ranges from 1 to 2 liters, and the urine specific gravity – 1.005-1.028.

Polyuria (the daily diuresis over 2000 ml) *and hyposthenuria* (the specific gravity below 1.010 in all daily samples) are characteristics of the chronic renal failure (a chronic kidney disease) and an acute kidney injury (polyuric stage).

Oliguria (the daily diuresis less than 500 ml) and ***anuria*** are indicators of serious functional disorders of the kidneys and the urinary tract, and typically observed in an acute kidney injury (oliguric stage), a chronic kidney disease (a terminal stage), and in a decompensated heart failure. ***Hypersthenuria*** (the specific gravity more than 1.025 in all samples) is combined with oliguria in acute glomerulonephritis, an acute kidney injury, and nephrotic syndrome.

Nycturia (nighttime diuresis more than 1/3 of the daytime diuresis) is and characteristic of a chronic renal failure and a heart failure.

Renal proteinuria is the result of the damage to the renal glomeruli (e.g., in acute and chronic glomerulonephritis, glomerulopathy in infectious-toxic, immune and circulatory pathology of the kidneys).

Extrarenal proteinuria is observed in inflammatory diseases of the urinary tract (e.g., pyelitis, cystitis, urethritis).

Positive (active) urinary sediment is a microscopic finding of the formed elements (hematuria, leucocytouria, cylindruria) greater than in norm (see Table 22-3), a large number (3-5 hpf) of the salts crystals and microorganisms (bacteria,

fungi, parasites)**.** ***Positive (active) urinary sediment confirms an abnormality of the kidneys and urinary tract.***

Bacteriuria (the bacterial count > 10^5 cfu/ml) is typical in the urinary tract and the kidneys infections (pyelonephritis, cystitis, urethritis, prostatitis).

Normally in the Rehberg test, GRF (glomerular filtration) is from 75 to 125 ml / min, and the tubular reabsorption is from 97 to 99%. A more pronounced decrease in GFR is observed in chronic glomerulonephritis, and tubular reabsorption – in pyelonephritis. GFR is reduced in a renal failure. ***According to CKD-EPI equation*** *GFR* makes it possible to define different stages of the chronic kidney disease.

Serum creatinine levels above 0.115 mmol/l in males and above 0.097 mlmol/l in females indicate the renal failure.

Hyperphosphatemia and hypocalcemia are typical of an advanced chronic kidney disease, and result in osteoporosis. ***Hyperkalemia*** is characteristic of the renal tubular acidosis, a severe acute and chronic renal failure.

Hypoproteinemia due to hypoalbuminemia is a biochemical characteristic of patients with a heavy proteinuria renal proteinuria (e.g., nephrotic syndrome).

Instrumental methods *(ultrasonography, roentgenologic, CT, MRI, radioisotope, renal biopsy)* allow you to evaluate anatomical, morphological characteristics and a functional state of the kidneys and the urinary tract.

22.6. Assessment tests on the theme "Laboratory and Instrumental Examination of the Urinary System"

1. What is the volume of the daily diuresis in polyuria?

1. 500-700 ml;
2. 800-1000 ml;
3. 1000-2000 ml;
4. > 2000 ml;
5. > 3500 ml.

2. What is the volume of the daily diuresis in oliguria?

1. <100 ml;
2. <200 ml;
3. <500 ml;
4. <750 ml;
5. <1000 ml.

3. What are the causes of the polyuria?

1. intake of a large amount of the liquid;
2. chronic renal failure;
3. decompensated diabetes mellitus;
4. heart failure;

5. nephrotic syndrome.

4. What are the causes of the oliguria?
1. acute glomerulonephritis;
2. chronic glomerulonephritis;
3. diabetes insipidans;
4. heart failure;
5. nephrotic syndrome.

5. What are the causes of the anuria?
1. acute glomerulonephritis;
2. chronic glomerulonephritis;
3. obstruction of the urinary tract;
4. acute renal failure;
5. cystitis.

6. Normal specific gravity of the urine is:
1. 1.012-1.025;
2. 1.005-1.010;
3. 1.030-1.040;
4. 0.05-0.125;
5. 1000-1005.

7. The maximal quantity of the protein in the urine can be in:
1. nephrotic syndrome;
2. acute glomerulonephritis;
3. chronic pyelonephritis;
4. pyelitis;
5. urolithiasis.

8. Normal diurnal (24 hours) fluctuations in the urine specific gravity in analysis of the urine according to Zimnitskiy should be:
1. < 0.005;
2. > 0.008;
3. 0.015-0.020;
4. 0.010-0.015;
5. >0.025-.

9. What is true for hypersthenuria?
1. specific gravity of the urine > 1.020 (in all samples during the day);
2. specific gravity of the urine > 1.025 (in all samples during the day);
3. in decompensated diabetes mellitus;
4. in chronic renal failure;

5. in acute glomerulonephritis;
6. in chronic pyelonephritis.

10. What is true for hyposthenuria?
1. specific gravity of the urine < 1.010 (in all samples during the day);
2. specific gravity of the urine < 1.015 (in all samples during the day);
3. in decompensated diabetes mellitus;
4. in chronic pyelonephritis;
5. in chronic renal failure.

11. Normal proportion of the daytime and nighttime diuresis is:
1. 1:2;
2. 2:1;
3. 3:1;
4. 1:4;
5. 1:3.

12. Analysis of the urine according to Zimnitskiy takes into account:
1. daily urine output;
2. ratio of the of the daytime and nighttime diuresis;
3. diurnal fluctuation of the urine specific gravity;
4. diurnal proteinuria;
5. diurnal glucosuria.

13. Presence of bilirubin in the urine is typical in:
1. prehepatic (obstructive) jaundice;
2. hepatic (parenchymatous) jaundice;
3. posthepatic (hemolytic) jaundice;
4. acute renal failure;
5. chronic glomerulonephritis.

14. Hematuria is a characteristic sign in:
1. urinary infection;
2. urolithiasis;
3. cancer of the kidney;
4. glomerulonephritis;
5. pyelonephritis.

15. Normal analysis of the urine according to Nechiporenko:
1. leucocytes $\leq$ 4000 / ml;
2. leucocytes < 6000 / ml;
3. erythrocytes $\leq$ 1000 / ml;
4. erythrocytes $\leq$ 3000 / ml;

5. cylinders < 20 / ml;
6. cylinders ≤ 250 / ml.

16. Organized sediment of the urine includes:
1. epithelial cells;
2. casts;
3. erythrocytes;
4. leucocytes;
5. crystals of salts;
6. Mucus.

17. Non-organized sediment of the urine includes:
1. epithelial cells;
2. casts;
3. urates crystals;
4. uric acid crystals;
5. phosphates crystals;
6. mucus.

18. Biochemical markers of the renal failure (uremia)?
1. hypercreatininemia;
2. hyperproteinemia;
3. hyperbilirubinemia;
4. increased blood serum urea;
5. increased residual nitrogen in blood.

19. Bacteriuria is characterized by:
1. findings of any bacteria in microscopy of the urine sediment;
2. bacterial count < 10^3 cfu/ml (colony-forming units per ml);
3. bacterial count 10^3 - 10^5 cfu/ml (colony-forming units per ml);
4. bacterial count > 10^5 cfu/ml (colony-forming units per ml);
5. findings bacteria in the renal biopsy specimen.

20. Normal values of the Rehberg test are:
1. GRF (glomerular filtration rate) is 45-65 ml / min;
2. GRF (glomerular filtration rate) is 75–125 ml / min;
3. GRF (glomerular filtration rate) is 97-99%;
4. tubular reabsorption is 90-95%;
5. tubular reabsorption is 97-99%.

21. Which laboratory tests are important for diagnosis of the renal failure?

1. GRF (glomerular filtration rate) bellow 60 ml / min;
2. GRF (glomerular filtration rate) more than 115 ml / min;
3. serum creatinine above 0.115 mmol/l;
4. serum creatinine below 0.115 mmol;
5. serum bilirubin above 20.5 mcmol/l;
6. serum bilirubin below 8.5 mcmol/.

22. Blood electrolytes changes are typical in a chronic renal failure:
1. hypercalcemia;
2. hyperkalemia;
3. hyperphosphatemia;
4. hypocalcemia;
5. hypomagnesemia;
6. hypokalemia.

CHAPTER 23. Basic Clinical-Laboratory Syndromes of the Kidneys and Urinary Tract Diseases

Goals: to enable students to learn –

1. Clinical symptoms and laboratory and instrumental signs of the basic clinical syndromes in diseases of the kidneys and the urinary tract:

2. A urinary syndrome, nephritic syndrome, nephrotic syndrome, syndromes of the urinary tract infection, a tubular damage, a renal arterial hypertension, an acute kidney injury (acute renal failure), a chronic kidney disease (chronic renal insufficiency).

23.1. Urinary syndrome

A urinary syndrome *is a complex of pathological changes in the physical and chemical properties of the urine including microscopic characteristics of the urine sediment (e.g., proteinuria, hematuria, leucocyturia, cylindruria).* A urinary syndrome is the most common nephrological syndrome.

Causes of the urinary syndrome are infectious and other inflammatory processes in kidneys and urinary tract, nephrolithiasis, diabetic nephropathy, neoplasms, hereditary diseases (polycystic disease, hereditary nephropathy), nephrosclerosis, lardaceous kidney (renal amyloidosis), traumas, neurology and genitalia disorders, systemic autoimmune diseases, cardiovascular disorders, intoxication, and allergy.

Clinical picture. *A urinary syndrome is usually a nonmanifest (latent) medical condition.* It can be detected incidentally in urine tests during a standard medical examination without any renal and urinary symptoms.

A urinary syndrome may be accompanied by clinical manifestations of the kidney and urinary tract diseases: e.g., lumbar pain, dysuria, disorders in the daily volume of the excreted urine, rhythm and character of the urination, such as pollakiuria, polyuria (>2000 ml/day), oliguria (<500 ml/day, or 24ml/hour), anuria (< 50 ml/day), nycturia, changes in the color of the urine, edema, arterial hypertension.

Laboratory and instrumental data (See Chapter 22. Laboratory and Instrumental Examination of the Urinary System. Sections 22.1-22.2)

- *Common urine analysis:* proteinuria, glycosuria, hematuria, leucocyturia, pyuria, cylindruria.
- *Nechiporenko test*: hematuria, leucocyturia, cylindruria.
- *Zimnitskiy test:* polyuria or oliguria (anuria), nycturia, hypersthenuria or hyposthenuria, isosthenuria.

Characteristic features of the most common variants of urinary syndrome are presented in the Table 23-1.

Subsequent laboratory and instrumental tests:

- general blood analysis with differential leucocyte count – leukocytosis and increase of the ESR (for suspected infectious and inflammatory processes in the kidneys and the urinary tract);
- biochemical blood analysis – increase of the CRP (for suspected inflammatory processes), serum creatinine, urea and potassium concentration (for suspected renal failure);
- bacteriological examination of the urine (for suspected urinary infections);
- assessment of the GFR (for a suspected renal failure);
- ultrasonography and CT of the kidneys and urinary tract;
- excretory urography and cystoscopy are indicated in case of a suspected obstructive uropathy.

Table 23-1. Most common variants of the urinary syndrome

Causes	Characteristics of the urinary syndrome
Acute glomerulonephritis	proteinuria, hematuria (with altered erythrocytes, cylindruria, renal (cubical) epithelial cells, oliguria (may be), hypersthenuria (may be)
Chronic glomerulonephritis	proteinuria, hematuria (with unaltered erythrocytes), cylindruria, renal (cubical) epithelial cells, polyuria (may be), hyposthenuria (may be)
Pyelonephritis	proteinuria, leucocyturia, cylindruria, bacteriuria, hyposthenuria (in chronic pyelonephritis)
Lower urinary tract infection	proteinuria, leucocyturia, bacteriuria, mucus, squamous epithelial cells, pyuria (may be)
Diabetic nephropathy	glucosuria, proteinuria, hematuria, cylindruria, polyuria (may be), hypersthenuria (may be), ketonuria (may be)
Lardaceous kidney (amyloidosis)	proteinuria, cylindruria, oliguria, hypersthenuria
Urolithiasis	hematuria (with unaltered erythrocytes), crystalluria, oliguria (may be), mucus (may be)
Gouty nephropathy	persistent acid urine reaction, proteinuria (microalbuminuria), hematuria, crystalluria (urates)

Warning symptoms and signs of the urinary syndrome are a rapid deterioration in the patient's condition, an onset and a quick growth of the edema, a sharp increase in the arterial blood pressure, macrohematuria, hemorrhagic eruptions, negative changes in laboratory tests (an increase in proteinuria,

hematuria, increase of ESR, a rapid decrease in GFR and an increase in the level of the serum creatinine.

23.2. Nephritic syndrome

Nephritic syndrome *is a clinical and laboratory syndrome that presents a group of symptoms and signs (e.g., hematuria, proteinuria, decreased serum creatinine, elevated blood pressure, oliguria, and edema) due to an inflammation of the glomeruli in the kidney (glomerulonephritis).*

Classification of the nephritic syndrome:

I. According to the causes of the nephritic syndrome:

1. Glomerulonephritis associated with the infection

1.1. Postinfectious (post-streptococcal) glomerulonephritis – due to g*roup the A beta-streptococcal infection* (with the onset in 1-6 weeks after tonsillitis, rhinopharyngitis, a scarlet fever, or other streptococcal infections);

1.2. other glomerulonephritis associated with infection:

1.2.1. bacterial infections – *Mycoplasma* (pneumonia, genito-urinary infections), *Neisseria meningitidis*, *Salmonella typhi* (acute intestinal infection), *Staphylococcal infections* (especially in bacterial endocarditis, sepsis); *Streptococcus pneumoniae*; visceral abscesses (e.g., *Escherichia coli, Pseudomonas, Klebsiella, Proteus);*

1.2.2. viral infection: *hepatitis B and C, infectious mononucleosis, chickenpox*, Herpes zoster, *Coxsackievirus infection*;

1.2.3. parasitic infections: *malaria, toxoplasmosis*.

2. Primary chronic glomerulonephritis;

3. Systemic connective tissue and immune diseases: systemic lupus erythematosus; systemic vasculitis; Goodpasture syndrome; IgA nephropathy; acute serum (vaccine) glomerulonephritis.

4. Hereditary disorders – Alport's syndrome, etc.

5. Idiopathic glomerulonephritis.

II. According to the course of the disease:

1. Acute nephritic syndrome (serum creatinine rises over weeks);

2. Chronic nephritic syndrome (renal insufficiency may progress over years).

Clinical picture

Complaints of patients in a nephritic syndrome are a dull aching pain in the lumbar region, a decrease in the urine output (oliguria), a change in the urine color (the “meat waste water” due to macrohematuria), the edema, headache, visual impairment, pain in the heart, palpitations, shortness of breath.

General inspection finds a pale puffy face and eyelids (“facies nephritica” is the most noticeable in the morning), and edema. Edema most often develops against a background of the pronounced and persistent oliguria.

Cardiovascular examination can detect an increased blood pressure (renal hypertension) and signs of the left ventricular overload due to arterial

hypertension (the left shift of the apical impulse and the left border of the relative heart dullness). The heart auscultation shows the accented II sound above aorta, sometimes with a metallic shade, and bradycardia.

The mild bilateral positive CVAT (costovertebral angle tenderness) and a positive Pasternatsky's symptom may be due to distension of the renal capsule.

An acute nephritic syndrome has an abrupt onset of the disease. A chronic nephritic syndrome usually manifests only with mild symptoms with insidious onset. It may be not detected for years. Arterial hypertension and renal edema are typical. A chronic nephritic syndrome may progress gradually to a chronic renal failure.

Laboratory and instrumental data

General urine analysis: proteinuria, hematuria (with altered erythrocytes, cylindruria, renal epithelial cells, oliguria and hypersthenuria (the more typical in acute nephritic syndrome), polyuria and hyposthenuria (the more typical in chronic nephritic syndrome).

Nechiporenko test: hematuria, cylindruria.

Zimnitskiy test: oliguria and hypersthenuria are typical in the initial stage of the acute nephritic syndrome (a growth of the edema); polyuria and hyposthenuria are typical in the chronic nephritic syndrome and during the resolution stage of the acute nephritic.

Biochemical blood tests: hypergammaglobulinemia –in an acute phase of the inflammation; increased blood levels of the nitrogen substances – creatinine, urea, uric acid, indican, blood urea nitrogen (BUN) –in a renal failure.

Rehberg test: GFR and tubular reabsorption are reduced.

Antistreptolysin-O (antibody against streptolysin-O, an immunogenic streptococcal hemolytic exotoxin) titer is positive in the acute poststreptococcal glomerulonephritis.

Ultrasonography: in an acute nephritic syndrome – an increase in the kidneys size and the thickness of the renal cortex; in a chronic nephritic syndrome – a decrease in the size of the kidneys and the thickness of the renal cortex.

ECG – signs of the left ventricle hypertrophy.

Ophthalmic fundus examination – narrowing of arterioles, often papilledema, and punctate hemorrhages.

Criteria of the diagnosis

Diagnosis of the nephritic syndrome is based on anamnesis, arterial hypertension, urinary tests (hematuria, proteinuria, cylindruria, oliguria), biochemical blood tests (increase in serum creatinine, urea, potassium), decrease in a glomerular filtration rate (GFR), and renal biopsy (in an indeterminate diagnosis of the disease).

Complications can be renal eclampsia (a significant increase of the blood pressure, vision disorders, vomiting, convulsions, and coma), an acute left ventricle failure (cardiac asthma, pulmonary edema), an acute and a chronic renal failure.

23.3. Nephrotic syndrome

Nephrotic syndrome *is a clinical and laboratory syndrome characterized by a massive persistent proteinuria (> 3.5 g/day), hypoproteinemia and hypoalbuminemia (<25 g/l), generalized edema, hyperlipidemia and lipiduria.*

The nephrotic syndrome is a result of the renal glomeruli damage with an increase of its permeability to blood plasma proteins and a decrease of the tubular reabsorption of proteins. An excessive proteinuria leads to hypoalbuminemia and a water retention in the body (edema) and high levels of fats in the blood (hypercholesterolemia and hypertriglyceridemia).

Causes of the nephrotic syndrome:

- Acute and (more often) chronic glomerulonephritis;
- Infectious diseases (infective endocarditis, purulent lung diseases, viral hepatitis B and C, HIV infections, COVID-19 infection, etc.);
- Drug-related glomeruli damage [medicinal preparation of gold, mercury, lithium, D-penicillamine, antibiotics, interferon alfa, NSAIDs (nonsteroidal anti-inflammatory drugs), etc.];
- The systemic connective tissue and an immune disease (e.g., systemic lupus erythematosus, vasculitis, rheumatoid arthritis, IgA nephropathy);
- Metabolic diseases (amyloidosis, diabetes mellitus);
- Neoplastic diseases (malignant tumors – cancer of bronchi, breasts, colon, stomach, kidney, etc.; multiple myeloma, lymphomas), leucosis;
- Hereditary diseases (e.g., Alport's syndrome, periodic disease);
- Allergy (e.g., insect stings, snake venom).

The most common primary cause in adult patients is a chronic glomerulonephritis, diabetic nephropathy, paraneoplastic process in malignancy, HIV-associated nephropathy, and amyloidosis.

Clinical picture

Complaints are pronounced persistent edema, weakness, malaise, muscle wasting, and frothy urine (due to the high concentration of the protein). The patient with anasarca can complain of a dyspnea (in hydrothorax or laryngeal edema), substernal chest pains (in hydropericardium), arthralgias (in hydrarthrosis), an abdominal distention (in ascites), and abdominal pains (in edema of the mesentery).

Anamnesis: The onset of the nephrotic syndrome can be abrupt or gradual. A detailed medical history can manifest the obvious reason of the nephrotic syndrome (e.g., diabetes mellitus with a history of the progressive proteinuria).

Objective examination detects characteristics of a generalized mild pale edema of the patient’s body (*anasarca*) including an enlarged liver

(hepatomegaly) and fluid accumulation in serous cavities (ascites, hydrothorax, hydropericardium).

Edema is especially pronounced on the face in the morning. There is an edema on other parts of the body (legs, hands, skin of the abdomen). The subungual edema is manifested with collateral white lines in fingernail beds.

Most often, the edema is mobile (e.g., detected in the eyelids in the morning and in the ankles after ambulation).

The blood pressure commonly remains within a normal range, or even arterial hypotension can be due to a hypovolemia (a decreased volume of the circulation blood). Arterial hypertension can be in some adult patients.

Laboratory and instrumental data

Urine tests: oliguria, hypersthenuria (specific gravity is 1,030-1,040)), severe proteinuria (more than 3.5 g per day, or 50 mg per kg body mass/day), cylindruria (fatty, hyaline, waxy), lipiduria (lipids and cholesterol in the unorganized urine sediment).

Biochemical blood tests: hypoproteinemia, hypoalbuminemia (<25 g/l), hyperlipidemia (hypercholesterolemia > 6.5 mmol/l and hypertriglyceridemia).

Blood levels of the nitrogen substances (creatinine, urea, uric acid, indican, BUN) and GFR are not changed for a long time.

Coagulation profile is characterized by hyperfibrinogenemia and elevated serum plasma factor VIII (antihemophilic globulin A).

General blood analysis: an anemia and high platelet count (thrombocytosis) are common.

Ultrasonography and other imaging studies (radiography, CT, MRI) can detect fluid in serous cavities (ascites, hydrothorax, hydropericardium).

Renal biopsy is indicated to find the cause of the nephrotic syndrome (in an indeterminate diagnosis of the disease).

Diagnosis of the nephrotic syndrome is based on the generalized persistent edema, pronounced proteinuria (>3.5 g/ day), hypoproteinemia (mainly due to hypoalbuminemia < 25 g/l), hyperlipidemia (hypercholesterolemia >6.5 mmol/l). Severe proteinuria is essential to the diagnosis. Renal biopsy supplies valuable information concerning the nature of the nephrotic syndrome in chronic renal diseases.

Complications of the nephrotic syndrome can be

- infections [e.g., spontaneous bacterial peritonitis, erysipelas (acute streptococcal cellulitis) and opportunistic bacterial, viral, fungal infections may occur] due to a urinary loss of immunoglobulins;
- hypovolemic nephrotic shock (due to a significant hypoalbuminemia);
- acute and chronic renal failure;
- cerebral edema, and macular (the eye's retina) edema;

- vascular complications due to a dyslipidemia and hypercoagulable disorders (ischemic heart disease, myocardial infarction, cerebral stroke, phlebothrombosis, pulmonary embolism);
- malnutrition in a prolonged nephrotic syndrome.

23.4. Renal arterial hypertension

Definition. ***Renal arterial hypertension*** *is a symptomatic arterial hypertension due to a pathology of the renal parenchyma (a* ***renoparenchymal hypertension****) and/or renal blood vessels (a* ***renovascular hypertension****) leading to impaired renal mechanisms of the arterial blood pressure regulation.*

Causes. The most important causes are acute and chronic glomerulonephritis, pyelonephritis, interstitial nephritis; polycystic kidney disease; systemic connective tissue diseases (systemic lupus erythematosus, systemic sclerosis, vasculitis, etc.), ischemic nephropathy, diabetic nephropathy; and the renal artery stenosis (due to fibromuscular dysplasia, atherosclerosis, aneurysm, thrombosis, etc.).

About 4-5% of the patients with arterial hypertension have an underlying disease of the kidneys and renovascular problems.

Clinical features of the renal arterial hypertension are

- high persistent levels of the BP (particularly high diastolic BP and low the pulse BP);
- the hypertensive crisis is observed on rare occasions;
- urinary and kidneys disorders in the past history often precede the high BP;
- a pronounced urinary syndrome (often it precedes to the high BP);
- serious changes in the functional test of the kidneys;
- renal hypertension often tends to an especially rapid and malignant course (*malignant hypertension*) accompanied by a progressive damage of the target-organs as the left ventricle, cerebral circulation, the eye's retina;
- evident hypertrophy and dilatation of the left ventricle, complicated often by an acute left ventricular failure with attacks of the cardiac asthma and pulmonary edema;
- angina pectoris and myocardial infarction often present;
- changes in the fundus of the eye (renal retinopathy) and deranged vision;
- encephalopathy due to disorders in cerebral circulation (a headache, nausea, visual disturbances, confusion and seizures, and paralysis may occur).

Diagnostic criteria: *the history of the kidney disease and changes in the urine analysis and renal functional tests precede the increase in BP*.

Substantiation of the renal hypertension includes typical clinical features and laboratory and instrumental findings that confirm the pathology of the kidneys and the renovascular problems.

Screening tests required for diagnosis of the renal hypertension are common urinalysis, Nechiporenko test, Zimnitskiy test, blood serum urea and creatinine, test of Rehberg, GFR, ultrasonography of the kidneys and the urinary tract.

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 hypertension may be an acute left ventricular failure (cardiac asthma, pulmonary edema), angina pectoris, myocardial infarction, renal retinopathy with a deranged vision, a cerebral stroke, nephrosclerosis, a renal failure progression.

23.5. Syndrome of the tubular damage

Tubular damage *is a clinical and laboratory syndrome characterized by a partial or generalized damage to the renal tubular apparatus that result in the inability to generate appropriately concentrated urine in response to a physiologic stimulus under the normal or subnormal glomerular filtration rate.*

Causes of the tubular damage are hereditary nephropathy (e.g., Fanconi syndrome), renal tubular acidosis, acute and chronic interstitial nephritis, pyelonephritis, autoimmune diseases (e.g., Sjögren syndrome, rheumatoid arthritis), and malignant tumors.

Clinical-laboratory features **of the tubular damage:**

- polyuria, hyposthenuria, nycturia;
- proteinuria < 2g/day (due to violation of the tubular reabsorption of the low molecular weight proteins);
- renal glucosuria may be;
- cylindruria (hyaline, waxy and granular casts);
- serum urea, creatinine and GFR (glomerular filtration rate) remain within the normal range for a long time;
- electrolyte imbalance (decreased plasma bicarbonate, hypocalcemia, hypokalemia, the less often hyperkalemia) with possible symptoms including muscle weakness, hyporeflexia, cardiac arrhythmias, and paralysis;
- hyperchloremic acidosis, and urine pH < 5.5 if depleted plasma bicarbonate;
- renal osteodystrophy (bone pains, osteomalacia or osteopenia) due to hypercalciuria, hyperphosphaturia, and secondary hyperparathyroidism.

Diagnostic criteria of the tubular damage are polyuria, nycturia, hyposthenuria. An electrolyte imbalance (decreased plasma bicarbonate, hypocalcemia, hypokalemia, the less often hyperkalemia) and acidosis confirm the diagnosis.

Screening tests required for diagnosis of the tubular damage are common urinalysis, Nechiporenko test, Zimnitskiy test, blood serum urea and creatinine, blood electrolytes (potassium, calcium, bicarbonate, etc.), test of Rehberg, GFR, ultrasonography of the kidneys and the urinary tract.

The combination of tubular damage syndrome with others worsens prognosis and accelerates the development of the renal failure.

23.6. Syndrome of the urinary tract infection

Urinary tract infection *is a clinical and laboratory syndrome due to an inflammatory process in the urinary system caused by an infectious agent.*

Urinary tract infection (UTI) includes a group of diseases which require the antibiotic therapy*:*

There are *upper urinary tract infections (acute and chronic pyelonephritis)* and *a lower urinary tract (acute and chronic cystitis, urethritis, prostatitis)*, as well as *asymptomatic bacteriuria*.

Etiologic classification of the urinary infections

1. *Uncomplicated UTI* (anatomically and functionally normal urinary tract): *Escherichia coli; Staphylococcus saprophyticus.*

2. *Complicated UTI* [presence of the urinary stones, urinary tract obstruction, vesicoureteral reflux, concomitant diseases – diabetes mellitus, gout, etc., all UTI (urinary tract infection) in adult males (prostatitis, epididymitis, orchitis, pyelonephritis, cystitis, urethritis, and urinary catheters)]:

- Bacteria – *Proteus spp., Klebsiella spp., Enterococcus spp., Pseudomonas spp., Staphylococcus epidermidis;*
- yeast fungi;
- mixed microflora.

The prevalence of UTIs varies with the gender and the age of the patients: during the first year of the life, boys are mostly ill; in the subsequent years, UTIs are more often detected in girls and females of the childbearing age, and in the elderly patients UTIs are not influenced by the gender.

Clinical and laboratory features of the urinary tract infection:

- dysuria;
- fever;
- pain in the lumbar region;
- urine tests – leucocyturia and bacteriuria;
- blood tests – leucocytosis, increased ESR, and CRP (in pyelonephritis).

The *upper urinary tract infections* are characterized by fever, chills; and, sometimes, lumbar pains, costovertebral angle tenderness (CVAT) and positive Pasternatskiy symptom may be. *The lower urinary tract infections* usually manifested by a painful frequent urination without the change of the patient's general condition. In both cases, there are leucocyturia, bacteriuria, and sometimes proteinuria and hematuria. *The characteristic laboratory sign of the upper urinary tract infections (pyelonephritis) is cylindruria, and hyposthenuria can be in chronic pyelonephritis.*

Asymptomatic bacteriuria means to get the diagnostically significant number of bacteria into the culture (> 10^5 cfu/ml) from correctly collected urine analysis obtained from patients without the symptoms or signs of UTI.

Diagnosis of the UTI is confirmed by (1) common urinalysis (leucocyturia, bacteriuria, and cylindruria in case of the pyelonephritis), and (2) sometimes urine culture (> 10^5 cfu/ml) is necessary.

Subsequent laboratory-instrumental tests:

- Urine tests: common urinalysis, Nechiporenko test, Zimnitskiy test; bacteriological study.
- General blood analysis – leukocyte count, leukocyte formula, ESR;
- Biochemical blood tests – CRP (for evaluation of the systemic inflammatory response); serum creatinine, urea, electrolytes (potassium) at suspicion on the renal failure;
- Ultrasonography and CT of the kidneys and the urinary tract
- If severe pain, fever, macrohematuria, pyuria and leucocytosis present, the patient should be consulted by a surgeon-urologist. Excretory urography and cystoscopy are indicated by a urologist in case of the (for suspected obstructive uropathy).

Complications of the UTI may be ascending infections of the genitalia, ascending pyelonephritis, the kidney abscess, perinephric abscess, and sepsis.

23.7. Syndromes of the renal failure

A renal failure ***is a syndrome due to impairment of all kidney functions (renal blood flow, glomerular filtration, tubular secretion, tubular reabsorption), leading to a disorder of the nitrogen, water, electrolyte, and other types of metabolism.***

Nitrogenous substances (creatinine, urea, uric acid, etc.) accumulation in the blood and body tissues due to an inability of the kidneys to perform an excretory function is the most characteristic clinical and laboratory feature of the real failure.

A distinction is made between *an acute and chronic renal failure*.

In recent time, the term *"acute kidney injury" (AKI)* has replaced "*acute renal failure" (ARF)*, and the term *"chronic kidney disease"* (CKD) – "chronic renal failure" (CRF), because AKI and CKD include the entire clinical spectrum

from a mild increase in serum creatinine to a life-threatening increase of the nitrogen in the blood (uremia).

23.7.1. Acute kidney injury

Acute kidney injury (AKI, or acute renal failure, ARF, or acute uremia) *is a rapid decrease in a renal function over days to weeks, causing an accumulation of nitrogenous products in the blood (azotemia) with or without reduction in the amount of the urine output [KDIGO (Kidney Disease: Improving Global Outcomes), 2012]*.

Causes of the AKI

There are three basic etiopathogenetic variants of AKI:

Prerenal (hemodynamic) AKI arises due to an inadequate renal perfusion with an extracellular volume depletion, bleeding, hypoalbuminemia, a decrease in a cardiac output (e.g., in traumatic, anaphylactic, cardiogenic shock, a prolonged crushing syndrome, extensive burns and frostbites).

Renal (parenchymal) AKI arises due to an intrinsic kidney disease or a damage (to renal glomeruli, tubules, interstitium, and blood vessels) with acute glomerulonephritis, acute pyelonephritis, acute tubular necrosis, interstitial nephritis, nephrotoxicity (e.g., NSAIDs, iodinated contrast media, venomous snake and insect bites).

Postrenal (obstructive) AKI is due to an acute extrarenal urinary tract obstruction (e.g., calculi, tumors, urethral strictures, an enlarged prostate gland).

Classification of the AKI

1. According to the cause:
    - prerenal (in shock and the systemic circulatory disorders);
    - renal (in acute pathology of the kidneys or the renal vessels);
    - postrenal (in urinary obstruction);
2. According to the period:
    - an initial period (from several hours - to 6-7 day);
    - an oligoanuric period (2-3 weeks);
    - a polyuric period (5-10 days);
    - a recovery period (from 3 to 12 months).
3. AKI stages (I-III) for severity (according to KDIGO, 2012) (Table 23-2).

Clinical and laboratory manifestations of the AKI

Complaints depend on the period of the AKI: a decrease in the amount of the urine or its complete absence (oligoanuria) – in the oligoanuric period; a large amount of the pale yellow urine (polyuria), then the amount of the urine becomes normal.

The physical and laboratory data depend on the cause (prerenal, renal, postrenal) and period of the AKI.

I. Initial period (from a few hours - to 6-7 days) is characterized by the symptoms of the underlying disease, which caused AKI (a traumatic or a transfusion shock, a severe infectious disease, sepsis, poisoning, etc.).

II. Oligoanuric period (2-3 weeks) characteristics:

- a rapid onset of the oliguria (or anuria) and edema, body weight gain (due to hyperhydration and edema), nausea, vomiting;
- pulmonary and cerebral edema with coma can worsen the patient's condition;
- an elevated blood concentration of the serum creatinine (hypercreatininemia) >0.115 mmol/l, urea > 8.3 mmol/l, potassium (hyperkalemia) >6.3 mmol/l, and metabolic acidosis;
- urine tests detects oliguria, hypersthenuria, proteinuria, hematuria, cylindruria. The urine sediment may be normal in a prerenal acute renal failure.

3. Polyuric period (5-10 days) characteristics:

- polyuria, hyposthenuria;
- dehydration;
- a decreased concentration of the serum potassium (hypokalemia) < 3.4 mmol/l, sodium (hyponatremia) < 130 mmol/l, but elevated serum creatinine and urea do not normalize for a longer time.

IV. Recovery period (6-12 months) starts with the normalization of the diuresis, properties of the urine and elevated serum levels of the creatinine and urea.

Table 23-2. Stages (1-3) of the acute kidney injury (according to KDIGO, 2012)

Stage	Rise in serum creatinine	Decline in the amount of the urine output	* Renal replacement therapy
1	≥ 0.3 mg/dl (0.265 mmol/l) or 1.5–1.9 times baseline	< 0.5 ml/kg/hour for 6–12 hours	Not indicated
2	2–2.9 times baseline	< 0.5 ml/kg/hour for ≥ 12 hours	Not indicated
3	≥ 4.0 mg/dl (3.536 mmol/l) or ≥ 3 times baseline	< 0.3 ml/kg/hour for ≥ 24 hours or anuria for ≥ 12 hours	Indicated

Note: A renal replacement therapy includes hemodialysis ("artificial kidney") or hemofiltarion.

AKI can be an asymptomatic or atypical (without a significant decrease of the urine output) in many cases of the 1-t stage AKI. It can be detected incidentally in biochemical blood tests (by a *moderate elevation of the serum creatinine and urea*), in urine tests (*proteinuria, microhematuria, and cylindruria*) during a standard medical examination without any renal and urinary symptoms.

Diagnosis of the AKI

An acute kidney injury (AKI) is suspected when the daily diuresis falls (oliguria) or serum levels of the urea and creatinine rise. Diagnosis of the AKI is based on a progressive daily rise in serum creatinine accompanied by oliguria or anuria.

Criteria of the AKI is defined as any of the following (according to KDIGO, 2012):

- *oliguria or anuria;*
- *urine volume < 0.5 ml/kg/hour for 6 hours;*
- *increase in the serum creatinine value of ≥ 0,265 mmol/l in 48 hours.*

Subsequent laboratory-instrumental tests:

1. Urine tests:

- *common urinalysis* - proteinuria, urine sediment – hematuria (e.g., in glomerulonephritis), leucocyturia (e.g., in pyelonephritis), cylindruria;
- *Nechiporenko test* depends on the underlying kidney disease (hematuria – in glomerulonephritis, leucocyturia – in pyelonephritis); or a normal in prerenal acute renal failure;
- *Zimnitskiy test* depends on the period of the AKI (oliguria, hypersthenuria – in the oliguric period; polyuria, hypoisosthenuria, nycturia – in the polyuric period);

2. Biochemical blood tests – hypercreatininemia, increase in the serum urea, hyperkalemia, hyponatremia, and metabolic acidosis; and hyperphosphatemia and hypocalcemia may be.

3. Rehberg test - glomerular filtration (GFR) less than 75 ml / min, tubular reabsorption less than 97%.

4. Imaging study – Ultrasonography and CT of the kidneys and urinary tract) detect a calculi and urinary tract obstruction.

5. Cystoscopy and urinary bladder catheterization should be performed by a urologist to make sure that there is no urine in the bladder in a case of the severe progressive AKI.

Complicationы and prognosis. AKI of the 3-d stage and its immediate complications (e.g., metabolic acidosis, hyperkalemia, azotemia, hypervolemia, pulmonary and cerebral edema) are treatable, but the survival rate remains about 50-60% despite renal replacement therapy (hemodialysis or hemofiltarion). Unfavorable prognosis for a further improvement may be due to the commonly associated sepsis, pulmonary and cardiac failure, severe wounds, burns, surgical complications, and consumption coagulopathy.

23.7.2. Chronic kidney disease

A chronic kidney disease (CKD, or a chronic renal failure, CRF; or chronic uremia) *is defined as abnormalities of the kidney structure and/or function, present for > 3 months, with implications for health [KDIGO (Kidney Disease: Improving Global Outcomes), 2017]*.

The characteristic laboratory features of the CKD are elevated serum creatinine and/or glomerular filtration rate (GFR) < 60 ml/min/1.73 m^2 for more than 3 months.

Causes of the CKD are:

- chronic renal inflammatory diseases (chronic glomerulonephritis, pyelonephritis, tubulointerstitial nephritis);
- hereditary nephropathies (e.g., polycystic kidney disease);
- diabetic nephrosclerosis (nephropathy);
- hypertensive nephrosclerosis (primary shrunken kidney);
- metabolic syndrome (in which arterial hypertension and type 2 of the diabetes mellitus are present);
- renal amyloidosis;
- affections of the renal blood vessels (e.g., renal artery stenosis due to atherosclerosis or fibromuscular dysplasia), systemic connective tissue diseases (e.g., systemic lupus erythematosus, systemic sclerosis);
- obstructive uropathy (e.g., in benign prostatic hyperplasia, ureteral obstruction by calculi or tumours).

Pathogenesis. *CKD* develops due to a progressive affection of the kidney parenchyma. The early symptoms of the CKD appear when the renal functioning parenchyma is reduced to at least 25% of the normal size.

Mechanisms of the CKD progression include: (1) an activity of the underlying disease, (2) hyperfiltration and intra-glomerular hypertension; (3) systemic arterial hypertension; (4) metabolic factors (e.g., hyperlipidemia, hyperglycemia, hyperuricemia, hyperphosphatemia, hypercalcemia).

Aggravating factors of the CKD progression may be intercurrent infections, urinary tract obstruction, UTI (urinary tract), pregnancy, allergic reactions, drug nephrotoxicity, hyponatremia, hypokalemia, hypovolemia, dehydration, and blood loss.

Predisposing factors are the elderly and senile age, and the familial history of the CKD.

The functional characteristics of the CKD are the decreased glomerular filtration, azotemia, diminished ability to concentrate the urine, and a decrease in ability to excrete excess phosphate, acid, and potassium.

Classification of the CKD

I. *According to GFR (glomerular filtration rate) and albuminuria category* (Table 23-3).

Table 23-3. Grades (stages) of the chronic kidney disease (according to KDIGO, 2017)

Grade (Stage)	Characteristics	GFR (ml/min/1.73 m^2)
1	Normal or high GFR	$\geq$ 90
2	Mildly decreased GFR	60-89
3a	Mildly to moderately decreased GFR	45-59
3b	Moderately to severely decreased GFR	30-44
4	Severely decreased GFR (preparing for the renal replacement therapy)	15-29
5	Kidney failure, or the end-stage renal disease (ESRD), when a patient needs the renal replacement therapy	$\leq$ 15
		Albuminuria (mg/day)
1	Normal to mildly increased	<30
2	Moderately increased	30-299
3	Severely increased	$\geq$ 300

II. According to a severity of the clinical manifestations:

(1) latency stage;

(2) intermittent stage;

(3) progressive (pronounced) stage;

(4) terminal stage (uremia).

A clinical picture of the CKD depends on the grade (stage). Changes in serum creatinine and urea concentrations and clinical symptoms can be minimal or transient (reversible) for a long time (e g., several years) in the grade 1-3 of the CKD. However, when the GFR falls below 6-10 ml/min (grade 5), the serum creatinine and urea levels are increased rapidly and associated with systemic clinical manifestations.

Complaints. The *first symptoms can be polyuria and nycturia* (due to an inability to concentrate the urine), weakness, fatigue, an impaired memory and work capacity, and deranged sleep.

In the advanced CKD, patients complain of the *skin itching and bad breath smell (uriniferous breath, or uriniferous mouth)* due to a release of the nitrogenous substances (e.g., ammonia, urea, ammonium salts) by sweat glands in the former case, and by salivary glands and mucosal glands of airways – in the latter case.

Complaints of the dyspnea and edema can be due to the renal retention of sodium and water, renal arterial hypertension, and the left ventricular failure.

Dyspeptic disorders (loss of an appetite, dryness and unpleasant taste in the mouth, nausea, vomiting, diarrhea, and an epigastric pain or discomfort) are due to an excretion of the nitrogenous substances by the salivary and gastrointestinal tract glands (stomach, duodenum, small intestine) that results in the inflammatory

and erosive-ulcerative affection of the entire gastrointestinal mucosa *("uremic" gastritis, duodenitis, enterocolitis).*

The patient can also can complain of the weight loss (due to proteinuria and malabsorption in uremic enterocolitis), *bleeding and hemorrhages of various localizations* (due to vitamins C- and K-deficiency and thrombocytopenia*), bone pains, muscle pains and cramps* (due to the vitamin D deficiency and hypocalcemia). *Painful joints (arthralgia)* and joint swelling can be in case of the *uremic gout (*due to nitrogenous toxins accumulation in joints).

General inspection

A grave condition of the patient and impairment of the consciousness (obtundation, stupor, and uremic coma) can be due to decompensated CKD with a severe renal dysfunction (grade 5) and azotemia.

An examination of patients with decompensated CKD can reveal edema, a pale or waxy (sometimes yellow-brown) dry skin, hemorrhages, traces of scratching, *ashy plaque* (*uremic frost*, or crystals of the urea and other nitrogenous substances released with sweat) on the skin.

Undernutrition results in the generalized atrophy of the sceletal muscles and subcutaneous fat. An examination of the muscles can find both a palpatory tenderness and tonic seizures (convulsions). There are a swelling, redness and tenderness of joints in attacks of the *uremic gout* (typically in the big toe, and in any of the body's joints). Bones pains at palpation, deformation and spontaneous fractures of bones may be due *to renal fibrous osteodystrophy and osteomalacia.*

Oral cavity survey detects a dry coated tongue and an unpleasant ammonia smell from the mouth and patient's skin (*factor uremicus*) in decompensated CKD (uremia). Ulcerative stomatitis and gingivitis can develop.

Examination of the patient in the advanced CKD detects systemic change of the internal organs.

Respiratory system manifestations due to the irritation of the respiratory tract mucosa and pleural membranes by nitrogenous substances:

- *Uremic laryngitis*. There is a discomfort in the neck or a foreign object sensation, barking cough, pain when swallowing, loss of voice or hoarseness;

- *Uremic tracheitis*. There is a paroxysmal dry cough or with thick mucous or mucopurulent sputum, a pain behind the sternum during and after coughing. During the lung auscultation in the initial stage of the tracheobronchitis - rhonchi (dry buzzing rales); later crackles (non-consonating wet large- and medium-bubbling) are heard over both lungs.

- *Uremic bronchitis*. There is cough with purulent or mucopurulent sputum, during the lung auscultation - harsh vesicular breathing, rhonchi and wheezes (dry rales);

- *Uremic pneumonitis*. There is a dry cough and dyspnea, a dull or hyporesonant percussion sound, harsh or weakened vesicular breathing, sometimes a small amount of rhonchi or fine crackles at the lung examination.

The X-ray findings can be an increased pulmonary vascularity (a pulmonary pattern) and small focal shadows of the lungs;

- *Uremic pleurisy*. *Dry (fibrinous) pleurisy* is manifested by an intense pain in the chest aggravated by breathing and dry coughing, a weakened vesicular breathing and pleural rub on the affected side (because of the limitation of respiratory excursion of the lung due to severe pain). *Exudative pleurisy* is characterized by severe shortness of breath, diffuse or central cyanosis, enlargement of the affected side of the chest, with the dull sound and a sharp weakening of the vesicular breathing up to its complete disappearance, and homogenous X-ray shadow on the affected side.

Patients with CKD are also highly predisposed to *acute bacterial pneumonia*, which usually presents a typical clinical picture. *Nephrogenic pulmonary edema* due to overhydration is observed in 20-60% of patients in the advanced CKD.

Cardiovascular system manifestations in CKD:

- *Arterial hypertension* is detected in the majority of patients (nearly to 100%) (see section 23.4. Renal arterial hypertension);

- *Myocardial dystrophy ("uremic cardiopathy").* It is manifested with a constant pain in the heart area, dyspnea, heart palpitations, interruptions in the heart, widening the left border of the relative cardiac dullness, muffled heart sounds, and in severe cases – a gallop rhythm. The left ventricular failure (cardiac asthma, pulmonary edema) can complicate the severe cases. ECG commonly shows a decrease in the T wave amplitude, and the ST interval downshift from the isoelectric line;

- *Uremic pericarditis* is due to the irritation of the pericardium membranes by by nitrogenous substances which are accumulated in pericardium the cavity. Uremic pericarditis is especially characteristic in the advanced CKD.

Dry (fibrinous) pericarditis is manifested by a constant pain in the heart region. The pain is intensified by cough and deep breath, and it is facilitated in a position leaning forward. Dry pericarditis can be diagnosed by auscultation of the heart by the specific *pericardial rub (murmur)* heard in the area of absolute dullness of the heart. ECG may demonstrate a concordant concave elevation of the ST segment

Exudative (wet) pericarditis is manifested by dyspnea, arterial hypotension, and jugular veins swelling, heaviness in the right hypochondrium due to hepatomegaly, ascites, edema in the *pericardial tamponade*. The forced sitting position with forward inclination can be observed. Percussion detects a triangle heart configuration in the exudative pericarditis. Pericardial rub disappears with an accumulation of the exudate in the wet pericarditis. ECG shows a decrease in the amplitude of the ECG waves with exudative pericarditis.

Gastrointestinal manifestations are characteristic of the advanced CKD due to the irritation of the digestive tract mucosa by nitrogenous substances:

- *Uremic gastritis*. There are nausea and vomiting (not always associated with food intake), heaviness and pain in the epigastric region after eating, a tenderness to a superficial palpation and muscle resistance of the anterior abdominal wall in the epigastric region;

- *Uremic enterocolitis*. There are colicky abdominal pains, meteorism, diarrhea, and malabsorption syndrome.

- *Gastrointestinal ulceration and bleeding* can complicate uremic gastritis and enterocolitis. Gastrointestinal bleeding can be manifested by vomiting blood (*hematemesis*) or black tarry stools (*melena*); a vomitus looks like clotted blood or coffee grounds.

Neurological disorders. *Uremic encephalopathy* characteristics are memory problems, impaired concentration, weakness, headache, somnolence, apathy, hypersomnia or insomnia, and deranged vision. At the terminal stage of the CKD, convulsions, stupor and uremic coma are possible. Uremic coma can develop gradually or suddenly. Periods of the stupor alternate with periods of excitation. Deep noisy Kussmaul's respiration and periodical Cheyne-Stokes respiration (less frequently) can be observed in the uremic coma.

Uremic polyneuropathy can present a restless legs syndrome, paresthesia, a burning sensation in the lower extremities, muscle cramps, paresis, and paralysis (at later stages).

Laboratory and instrumental data

Common urine analysis depends on the underlying kidney disease (glomerulonephritis, pyelonephritis).

Nechiporenko urine test depends on the underlying kidney disease (glomerulonephritis, pyelonephritis).

Zimnitskiy urine test: polyuria or oliguria (anuria), nycturia, hyposthenuria, isoshtenuria.

Rehberg test: glomerular filtration rate (GFR) is less than 75 ml/min, tubular reabsorption – less than 97%.

24-hour urine collection – daily proteinuria is more than 300 mg/ day, daily albiminuria in the range of 30 mg/day and more.

Clinical blood analysis: normochromic anemia (due to deficient erythropoietin production in renal glomeruli), thrombocytopenia, leucopenia, sometimes lymphocytopenia.

Biochemical blood test: serum urea is more than 8.3 mmol/l, serum creatinine in women is more than 0.97 mmol/l, in men - more than 0.115 mmol/l. Hypocalcemia, hyperphosphatemia may be due to secondary hyperparathyroidism. Hyperkalemia is observed in the advanced (IV-V stages) of CKD, especially in the V (terminal) stage. *Hyperkalemia* can lead to bradycardia, atrioventricular block and even cardiac arrest.

Hyperkalemia causes characteristic ECG changes: sinus bradycardia, atrioventricular block, and high narrow T waves (but a decreased amplitude of the T wave can be in severe hyperkalemia).

Ultrasonography finds a small shrunken kidney (less than 10 cm in length) with a thin hyperechogenic cortex in the majority of the CKD cases. A normal size of the kidneys is observed in CKD due to amyloidosis, diabetic nephropathy, and mainly in the acute kidney injury. There are enlarged kidneys with multiple cysts in the CKD due to a polycystic kidney disease.

Contrast-enhanced imaging studies (e.g., renal angiography, CT) are infrequently used studies because of the high risk of the renal failure progression.

Renal biopsy can find the cause of the CKD with a normal size of the kidneys. Renal biopsy is not used when ultrasonography detects small shrunken kidneys because of a high risk of complications.

Diagnosis of the CKD *is based on abnormalities of the kidney structure and/or function, present for 3 and more months, with implications for health* [KDIGO (Kidney Disease: Improving Global Outcomes), 2017]:

- a decreased kidney function that is defined as glomerular filtration rate (GFR) less than 60 ml/min / 1.73 m^2 and/or elevated serum creatinine (more than 0.97 mmol/l in females and more than 0.115 mmol/l in males);
- presence of the kidney damage that is defined as daily albiminuria 30 mg/day and more;
- renal biopsy, when the kidneys are not small and fibrotic.

Prognosis depends on the nature of the underlying disorder and superimposed complications. Acute reductions in a renal function may be reversible with therapy. Controlling hyperglycemia in diabetic nephropathy and hypertension substantially reduces deterioration of the CKD. Protein restriction has probably a modest benefit.

Factors aggravating or producing chronic renal failure (e.g., Na and water depletion, nephrotoxins, heart failure, infection, hypercalcemia, urinary obstruction) must be treated specifically. If the CKD results from a progressive and untreatable disorder, therapy is palliative until hemodialysis or the kidney transplantation is required.

23.8. The key points of the theme “Basic Clinical and Laboratory Syndromes of the Kidneys and Urinary Tract Diseases”

The key features of the basic syndromes in diseases of the kidneys and the urinary tract are placed in Table 23-4.

Table 23-4. Basic syndromes of the kidneys and urinary tract pathology

Syndrome	Main causes	Clinical laboratory diagnostics
Urinary syndrome	• acute and chronic glomerulonephritis, pyelo-nephritis, interstitial nephritis; • nephrolithiasis, • diabetic nephropathy, • polycystic kidney disease, • tumours of urinary system, • renal tuberculosis	• proteinuria < 3.5 g / day; • hematuria; • leucocyturia; • cylindruria; • urine volume and specific gravity changes (polyuria, oliguria; hyper-, hypo-, and isosthenuria)
Nephritic syndrome	• acute and chronic glomerulonephritis; • systemic connective tissue and immune diseases: (systemic lupus erythematosus; systemic vasculitis, etc.)	• anamnesis, • arterial hypertension, • urinary tests (hematuria, proteinuria, cylindruria, oliguria), • biochemical blood tests (increase in serum creatinine, urea, and potassium), • decrease of the GFR)
Nephrotic syndrome	• chronic glomerulonephritis, • diabetic nephropathy, • paraneoplastic process in malignancy, • HIV-associated nephropathy, • amyloidosis	• anasarca, edema, • pronounced proteinuria (>3.5 g/ day), • hypoproteinemia, • hypoalbuminemia< 25 g/l, • hypercholesterolemia>6.5 mmol/l)
Renal arterial hyperten-sion	• acute and chronic glomerulo-nephritis, pyelonephritis; • polycystic kidney disease; • ischemic nephropathy, • diabetic nephropathy; • renal artery stenosis	the history of the kidney disease and changes in the urine analysis, and renal functional tests precede increase in BP
Syndrome of the tubular damage	• hereditary nephropathy, • renal tubular acidosis, • acute and chronic interstitial nephritis, • pyelonephritis, • autoimmune diseases, • malignant tumors	• urine tests – polyuria, nycturia, hyposthenuria, cylindruria, proteinuria <2.0 g/l, • electrolyte imbalance (decrease in plasma bicarbonate, hypocalcemia, hypokalemia, hyperchloremic acidosis)

Table 23-4 (continuation)

Syndrome	Main causes	Clinical laboratory diagnostics
Syndrome of the urinary tract infection	• upper urinary tract infections (acute and chronic pyelonephritis); • lower urinary tract (acute and chronic cystitis, urethritis, prostatitis), • asymptomatic bacteriuria	• dysuria; • fever; • pain in the lumbar region; • urine tests – leucocyturia and bacteriuria; • blood tests – leucocytosis, increased ESR and CRP
Acute kidney injury	• inadequate renal perfusion (bleeding, acute heart failure, shock, hypoalbuminemia, etc.); • intrinsic kidney damage (acute glomerulonephritis, pyelonephritis, interstitial nephritis, nephrotoxicity (NSAIDs, iodinated contrast media, etc.); • urinary tract obstruction (calculi, tumors, urethral strictures, etc.)	• hypercreatininemia ≥ 0,265 mmol/l in 48 hours; • oliguria or anuria; • urine volume < 0.5 ml/kg/hour for 6 hours
Chronic kidney disease	• acute and chronic glomerulonephritis, pyelonephritis; • polycystic kidney disease; • ischemic nephropathy, • diabetic nephropathy; • renal artery stenosis	• poliuria и nycturia; • arterial hypertension; • the kidney structure and/or function disorders ≥ 3 months, • glomerular filtration rate (GFR) < 60 ml/min / 1.73 m^2 , • hypercreatininemia – > 0.97 mmol/l in females and > 0.115 mmol/l in males; • albuminuria >30 mg/day

23.9. Assessment tests on the theme "Basic Clinical and Laboratory Syndromes of the Kidneys and Urinary Tract Diseases"

1. A urinary syndrome includes the combination of the following signs:

1. proteinuria;
2. cylindruria;
3. hematuria;
4. arterial hypertension;
5. edema.

2. What is typical in nephrotic syndrome?

1. hyperproteinemia;

2. high proteinuria (more than 3.5 g daily);
3. dysproteinemia (hypoalbuminemia);
4. hypercholesterinemia;
5. edemas.

3. What is typical of the patient's skin in a nephritic syndrome?
1. jaundice;
2. pale skin;
3. puffy face in the morning;
4. swollen legs in the evening;
5. cyanosis.

4. A urinary syndrome in acute glomerulonephritis includes:
1. hematuria;
2. proteinuria;
3. cylindruria;
4. oliguria;
5. leucocyturia.

5. It is typically in a nephritic syndrome:
1. arterial hypertension;
2. hematuria;
3. bacteriuria;
4. bilirubinuria;
5. proteinuria.

6. A urinary syndrome in diabetic nephropathy includes a combination of the following signs:
1. edemas, leucocytouria, and polyuria;
2. acetonuria, vomiting, bacteriuria;
3. proteinuria, cylindruria, and hematuria;
4. glucosuria, polyuria, hypersthenuria;
5. arterial hypertension, polyuria, and bacteriuria.

7. Nephrotic syndrome includes a combination of the following signs:
1. anasarca, high proteinuria, hypoalbuminemia, and hypercholesterolemia;
2. proteinuria, cylindruria, and hematuria;
3. arterial hypertension, polyuria, and bacteriuria;
4. edemas, leucocytouria, and glucosuria;
5. bilirubinuria, hyperproteinemia, and hypocholesterolemia.

8. What is typical of the renal arterial hypertension?

1. arterial hypertension precedes the kidney disease and changes in the urine tests;
2. urinary and kidneys disorders in past history precede the high BP;
3. pronounced urinary syndrome;
4. particularly high systolic BP and low the diastolic BP,
5. ascites and “caput medusae” on the anterior abdominal wall.

9. What is typical in the syndrome of the acute kidney injury?

1. hypercreatininemia and anuria;
2. hyperbilirubinemia and jaundice
3. hyperproteinemia;
4. hyperchromic anemia;
5. hyposthenuria and polyuria.

10. What is typical in the chronic kidney disease?

1. hypercreatininemia and hyposthenuria
2. decreased glomerular filtration rate (GFR);
3. hyperproteinemia and hypersthenuria;
4. increased glomerular filtration rate (GFR);
5. hyperchromic anemia;
6. hyperbilirubinemia and jaundice.

11. The characteristic urine tests in the urinary tract infection:

1. hematuria;
2. oliguria;
3. cylindruria;
4. leucocytouria;
5. bacteriuria.

12. Diagnostic criteria of the urinary tract infection:

1. leucocyturia,
2. bacteriuria,
3. hematuria;
4. urine culture > 10^5 cfu/ml;
5. polyuria;
6. urine culture > 10^3 cfu/ml.

13. Clinical and laboratory features of the tubular damage:

1. proteinuria > 3.5 g/l;
2. polyuria;
3. hyposthenuria;

4. cylindruria;
5. hematuria;
6. osteodystrophy.

14. Clinical periods of the acute kidney injury:
1. prerenal period;
2. initial period;
3. renal period;
4. oligoanuric period;
5. polyuric period;
6. recovery;
7. postrenal.

15. Diagnostic criteria of the acute kidney injury:
1.oliguria;
2. hypocreatininemia;
3. hypercreatininemia;
4. anuria;
5. proteinuria;
6. hematuria.

16. Diagnostic criteria of the chronic kidney disease:
1. kidney structure and/or function disorders > 3 months;
2. kidney structure and/or function disorders > 9 months;
3. decreased glomerular filtration rate (GFR) < 60 ml/min / 1.73 m^2;
4. increased glomerular filtration rate (GFR) > 120 ml/min / 1.73 m^2;
5. hypercreatininemia;
6. hypocreatininemia.

17. A general inspection of the patient in decompensated CKD can reveal:
1. jaundice;
2. edema;
3. pale dry skin;
4. “uremic frost” on the skin;
5. “caput medusae”.

18. Cardiovascular system manifestations in the advanced CKD:
1. atrial fibrillation;
2. arterial hypertension;
3. “uremic pericarditis”;
4. hydropericrdium;

5. “uremic myocarditis”;
6. "uremic cardiopathy".

19. Gastrointestinal manifestations in the advanced CKD:
1. heartburn;
2. constipation;
3. vomiting;
4. diarrhea;
5. gastrointestinal bleeding.

20. Mineral metabolism tests are typical of the advanced CKD:
1. hypocalcemia;
2. hypercalcemia;
3. hyperkalemia;
4. hypokaliemia;
5. hyperphosphatemia.

21. The main causes of the chronic kidney disease:
1. chronic glomerulonephritis;
2. chronic obstructive pulmonary disease;
3. diabetic nephrosclerosis (nephropathy);
4. hypertensive nephrosclerosis;
5. nephroptosis;
6. metabolic syndrome.

22. Complications of the renal hypertension may be as follows:
1. acute left ventricular failure;
2. myocardial infarction;
3. bronchial asthma;
4. renal retinopathy with a deranged vision,
5. cerebral stroke,
6. malnutrition.

Unit VII. Blood System Examination

CHAPTER 24. Clinical Examination of Patients with Blood Diseases

Goals: to enable students to learn -

1. subjective examination (inquiry) of patients with blood diseases, and interpretation of the obtained results;
2. technique of the objective examination in blood diseases, and its diagnostic value;
3. technique of the lymph nodes examination and the excessive bleeding detection, and their diagnostic value.

24.1. Subjective examination (inquiry) of patients in blood diseases

Complaints. There are ***specific symptoms of the hematopoietic system*** in patients with the blood pathology and ***unspecific*** **(*general*)** complaints (e.g., general weakness, malaise, fatigue, dizziness, headaches, drowsiness, dyspnea) (Table 24-1).

Table 24-1. Subjective examination in diseases of the blood

Specific complaints	Unspecific complaints	Anamnesis
- bleeding from the nose, gums, intestines, uterus; - perverted appetite, - burning the tongue, - sore throat and pains in oral cavity - skin itching, - pain in bones (ossalgia), - fever, - lymph nodes enlargement, - heaviness and discomfort in abdomen (hepato- and splenomegaly)	- weakness, - fatigue, - dizziness, - dyspnea, - heart palpitations - loss of appetite, - loss of weight	- bleedings from the nose, gums, intestines, etc., - peptic ulcer disease; - malignant tumors, - past surgery operations, - drug history (cytostatic agents, non-steroidal anti-inflammatory drugs, anticoagulants), - ionizing radiation, - toxic substances, - nutritional profile (strict vegan), - obstetrics history, - familial predisposition (hemophilia, hemolytic anemia)

Specific complaints of the blood diseases are hemorrhagic disorders *due to thrombocytopenia, vascular wall disorders or deficiency of the blood coagulation factors. There are spontaneous bleeding from mucous membranes (any part of the oral cavity, nose); spontaneous or at little external causes (e.g., a push, mild contusion, pinch, injection) skin hemorrhages, and internal bleeding of various localization (e.g., gastrointestinal tract, urogenital region).*

Past life history. *A detailed medical history can find causes and risk factors of the blood system problems.*

It is necessary to pay attention to harmful working conditions (e.g., ionizing radiation, toxic substances), social and living conditions, nutritional profile (a strict vegan diet predisposes to the vitamin B_{12}- deficiency anemia; alcohol abuse – to the folate-deficiency anemia), previous diseases (helminthic invasions, chronic and acute infections, bleeding, surgical operations of the gastrointestinal tract).

Chronic drug administration can inhibit hemopoiesis (e.g., cytostatic agents, and immunosuppressants), or it is liable to cause bleeding complications (e.g., non-steroidal anti-inflammatory drugs, anticoagulants).

Closely spaced pregnancies and prolonged lactation bear the risks of the iron-deficiency anemia in females. Malignant tumors and chronic inflammatory and immunity-related diseases can suppress the blood cells production. Chronic liver diseases may be complicated by hemorrhagic syndrome due to deficiency of the hepatic coagulation factors (prothrombin, fibrinogen) and/or thrombocytopenia in cases of the hypersplenism.

Hereditary predisposition and transmission is a characteristic of the hemophilia and many cases of the hemolytic anemia.

Unspecific (general) complaints can prevail in diseases of the blood.

Common complaints due to *cardiovascular disorders* are heart palpitations, fainting, cold hands and feet, which is usually associated with anemia. At the same time, complaints of dyspnea, especially during physical load, which can be indicative of the myocardiodystrophy and respiratory failure due to impaired pulmonary gas exchange in anemia.

Gastrointestinal complaints may be the loss of an appetite, loss of weight, diarrhea and constipation.

Perverted appetite (pica perverta, or pica chlorotica) occurs *in the iron-deficiency anemia*. It is characterized by the desire to eat inedible materials such as charcoal, chalk, soil, petrol, etc.

Burning sensation at the tip and along the edges of the tongue is characteristic of the Hunter's glossitis in *vitamin B_{12} -deficiency anemia*.

Skin itching may be the first symptom of the hematopoietic system tumors, such as *Hodgkin disease* (*lymphogranulomatosis), polycythaemia vera (Vaquez-Osler disease)* and chronic lymphocytic leukemia (leucosis).

Subfebrile fever may be in case of anemia due to compensatory intensification of the basal metabolism, and in hemolytic anemia – due to a pyrogenic effect of the erythrocyte cellular debris.

Moderate or high fever occurs in acute and chronic leukemia, Hodgkin disease and agranulocytosis due to the secondary infections and the release of the leucocyte pyrogenic purines in the blood.

Pains in the bones (ossalgia) and joints (arthralgia) are typical of leukemia due to the intense bone marrow hyperplasia. A toothache (*dentalgia*) can be a variation of the ossalgia. *Arthralgia and hemarthrosis are found in hemophilia.* A *sore throat and pains in oral cavity* occur in acute leukemia and agranulocytosis because of *ulcerative-necrotic tonsillitis and stomatitis*.

An aching pain, feelings of the heaviness and swelling of the neck disturb patients due to the cervical lymph nodes enlargement in chronic leukemia and lymphogranulomatosis. *Similar sensations in the chest* occur in the mediastinal lymph nodes hyperplasia, *and in the abdominal cavity* – in the mesenteric or retroperitoneal lymph nodes enlargement.

An abdominal dull pain, feelings of the heaviness and discomfort can be in chronic myeloid or lymphatic leukemia, and hemolytic anemia due to a considerable hepatomegaly at the right hypochondrium, and due to a considerable splenomegaly – at the left hypochondrium. A *sharp pain in the right hypochondrium* may be associated with the formation of pigmented gallstones in hemolytic anemia, *in the left hypochondrium* – in cases of the splenic infarction with perisplenitis or spontaneous splenic rupture in patients with acute and chronic leukemia.

24.2. Objective examination of patients in blood diseases

A grave general state of the patient and loss of consciousness or a deranged mental state (obtundation, stupor) can be in severe diseases of the blood system (e.g., progressive anemia, leukemia).

A general inspection can find ***the characteristic changes in the color of the skin and visible mucous membranes*** (oral mucosa, conjunctiva of the sclera and inferior eyelids) in the blood system pathology.

The *skin pallor* is typical of anemia, however it may be masked by the skin pigmentation (e.g., due to the exposure to the sun, jaundice). Pale skin is not a specific sign of the anemia. The skin pallor may also be due to the arterial hypotension, cardiovascular failure (shock, collapse), deep vascularization of the skin, spasm of the skin blood vessels (in glomerulonephritis). *Paleness of the conjunctiva and oral mucosa is a more informative sign of the anemia.*

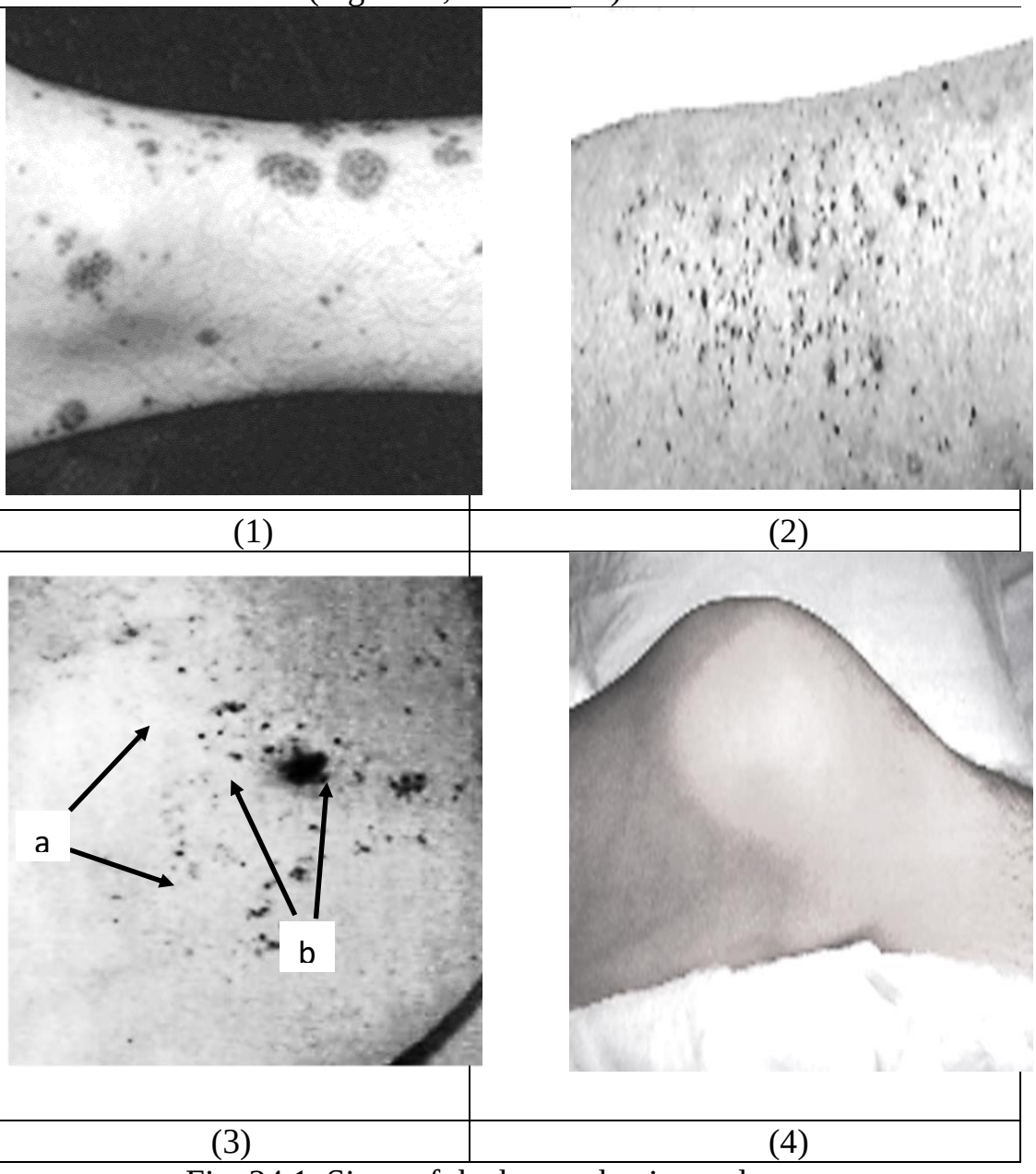
A *pronounced pallor of the skin and visible mucous membranes* is a characteristic of the severe posthemorrhagic anemia. The skin is usually cool in palpation.

The *skin pallor acquires a greenish tint* in young girls with iron-deficiency anemia (*juvenile chlorosis, or green sickness*). The *waxy pallor of the skin and subicteric (yellowish tint) sclera* can be observed in case with vitamin B_{12}- and

folate-deficiency anemia. The *skin pallor with a golden yellow tint* is due to the unconjugated hyperbilirubinemia (*prehepatic jaundice*) in hemolytic anemia.

The *intense red and warm skin of the face, palms and feet, and pronounced vascular congestion of the sclera blood vessels* are characteristics of the polycythemia. The *grey skin* may be in case of the chronic leukemia.

Excessive bleeding and spontaneous hemorrhagic rashes on the skin and mucous membrane of various shapes and size are the signs of a hemorrhagic syndrome due to various disorders of the coagulation system, pathology of the platelets or the vascular wall (Fig. 24.1, Table 24-2).



(1) (2)

(3) (4)

Fig. 24.1. Signs of the hemorrhagic syndrome:
(1) purpuric palpable rash in vasculitis, (2) petechiae in thrombocytopenia,
(3) purpura (a) and ecchymoses (b) in the patient with disseminated intravascular coagulation, (4) hemarthrosis of the knee joint in hemophilia.

Table 24-2. Clinical manifestations of the skin and joint bleeding

Types of the skin/joint bleeding	Characteristics	Main causes
Petechiae	- red-purple punctate rash, - flat (non-palpable), - diameter < 0.5 cm, - not disappearing when pressed	- thrombocytopenia
Ecchymoses (bruises)	- red-purple subcutaneous, - not disappearing when pressed, - large (different sizes) >0.5 cm	- clotting problems (e.g., coagulation factor deficiencies from liver disease or von Willebrand's disease)
Hematomas	- massive painful hemor-rhages in muscles, large joints (hemarthrosis), and serous membranes, - delayed bleeding (in few hours/days after trauma) may be	- hemophilias (factor VIII, IX, or XI deficiency), - vitamin K deficiency, - liver failure with coagulation factor deficiencies
Telangiectasias	- vasodilatation of the small blood vessels of lips, mu-cosa (nasal, gingival, etc.); - disappear when pressed, - potential hemoptysis, hematemesis, melena, hematuria	- Rendu-Osler-Weber disease
Purpura	- red-purple, multiple, - elevated (palpable), - intracutaneous, - non-fading when pressed, - < 0.5 cm in diameter	- hemorrhagic vasculitis (due to endovascular damage of immune complexes to endothelium, allergy)
Mixed type	- petechiae/ecchymoses and hematomas with a predominance of the first	- disseminated intra-vascular coagulation, - indirect anticoagulant overdose

Definition of the bleeding type has a certain diagnostic value: petechiae are characteristic of the thrombocytopenia, hematomas – coagulation factor deficiencies (e.g., hemophilia), purpura – hemorrhagic vasculitis, ecchymoses – clotting problems (e.g., von Willebrand's disease), a mixed type – disseminated

intravascular coagulation. Telangiectasias present in Rendu-Osler-Weber disease (hereditary hemorrhagic arteriovenous malformations in the skin, mucous membranes, and internal organs).

The *skin hemorrhagic rashes (excepting telangiectasias) do not disappear on pressing* by contrast with the skin erythema due to inflammatory, infectious, circulatory factors or various (chemical, mechanical, physical) irritants. Hemorrhagic rashes are firstly red, then subsequently the color changes to blue, green, and yellow due to hemoglobin convertion into biliverdin, bilirubin or its other colored products of oxidation.

Atrophic changes of the skin, visible mucous membranes, hair and nails can be observed *in the iron-deficiency anemia*. The skin is dry and flaking. Visible mucous membranes may also be dry. There are split ends of hair and hair loss up to the limited or widespread *alopecia (baldness)* in the pronounced iron deficiency. Nails may be thin, flatten and fractured. *Koilonychia (spooning of the nails) is a characteristic sign of the iron deficiency.*

Tapping the flat bones (especially the sternum) or epiphysis of the long bones often may be tender due to a marked bone marrow hyperplasia in the acute leukemia.

Inspection of the oral cavity can reveal hemorrhagic changes in the gingiva, the inner surface of the cheeks, the soft and hard palate, and the posterior pharyngeal wall.

Glossitis (inflammation of the tongue) is characteristic of the iron deficiency and vitamin B_{12}- folate deficiency anemias. *Atrophic glossitis and cheilitis* (or *cheilosis*, an inflammation of the red border, mucous membrane and the skin of the lips, with fissures in the angles of the mouth) is typical of the iron-deficiency anemia and vitamin B_2 (riboflavin) insufficient absorption.

Hunter's glossitis is the specific characteristic of B_{12}- deficiency anemia. The patient complains of the burning tongue. The inspection shows a raspberry bald tongue due to mucosa atrophy and papillary smoothing.

An inflammatory process of the *tongue resembling a "geographic map"* with swollen papillae, fissures and aphthae, with thick white, grey or brown coat may be in patients with leukemia. *Necrotizing ulcerative gingivitis and tonsillitis* with ulcers covered with a dirty gray coating can be detected in leukemia.

Examination of the abdomen.

The abdomen can be distended in left hypochondrium due to a considerable splenomegaly in *diseases of the blood system (e.g., acute and chronic leukemias, lymphogranulomatosis, lymphomas, hemolytic anemia).* Splenomegaly should be by percussion and palpation (see Chapter 18. Sections 18.7. Percussion of the spleen and 18.8. Palpation of the spleen).

The most considerable splenomegaly is observed in chronic myeloid leukemia. The spleen can occupy the entire left half of the abdominal cavity. Perisplenitis can complicate the considerable splenomegaly. There are tenderness,

irregular edges and unsmooth surface of the spleen in palpation, and peritoneal rub murmur at the left hypochodrium in perisplenitis.

Splenomegaly may be combined with hepatomegly (*hepatosplenomegaly*) in leukemias and hemolytic anemia (see Chapter 20. Section 20.6. Hepatolienal syndrome).

24.3. Examination of the lymph nodes

Normal lymph nodes are not visually detected in healthy adults. General inspection can find a lymph nodes enlargement by soft-tissue swelling on the neck, in the submandibular, supraclavicular, axillary and inguinal regions. A lymph nodes enlargement of other localization is less frequently revealed during general inspection of patients with certain forms of the leukemia and lymphomas.

Palpation of the lymph nodes

Palpation of the lymph nodes offer the opportunity to assess the node size, tenderness, consistency, mobility, and fixation to the adjacent tissue.

Technique of the lymph nodes palpation

Palpation of the subcutaneous lymph nodes starts with the occipital region.

A patient should stand or sit in a chair with the head slightly tilted forward. A doctor is opposite the patient. The palpation of the lymph nodes is performed by II-d – V-th fingers of both hands.

Occipital lymph nodes. The physician's hands are placed with the fingertips of the right and left hands parallel with the lateral edges of the *musculus occipitalis* (i.e. vertically). The fingers of the left and right hands at the same time feel the space above and below the edge of the occipital bone (Fig. 24.2). The fingers move slowly in a horizontal direction. Normally, these nodes are not palpable.

Auricular lymph nodes. *Preauricular (anterior auricular) lymph nodes* are palpated with the index and middle fingers, setting them vertically in front of the ear. *Retroauricular (posterior auricular) lymph nodes* palpation is performed by fingers groping behind the ear from the base of the ears and over the entire surface of the *processus mastoideus*. Normally, these lymph nodes are not palpable.

Submandibular lymph nodes. The submandibular lymph nodes are palpated by placing the palmar surfaces of the distal phalanges of the II-d – V-th fingers of the both hands under the left and right parts of the low jaw parallel with its edge. The fingers roll in the direction perpendicular to the inferior edge of the low jaw (Fig. 24. 3).

Submental lymph nodes *are located along the midline under the edge of the low jaw and palpable similarly to submandibular lymph nodes.*

Cervical lymph nodes.

The cervical lymph nodes are palpable at the anterior and posterior edges of the sternocleidomastoid muscles.

Supra- and infraclavicular lymph nodes. *Supraclavicular lymph nodes* are palpable above the clavicle. *Infraclavicular (subclavicular) lymph nodes* are palpable in the same way below the anterior edge of the clavicle (Fig 24.4-5).

Axillary lymph nodes. Palpation of the axillary lymph nodes begins with the initial abduction of both hands by the patient from the body at 90 degrees, which allows the examiner to bring palms into the patient's armpits as far as possible (Fig. 24.6). The palpation is conducted by the finger-cushions when they are moved in the superior-inferior and anterior-posterior directions, as well as by rotational movements.

The *central axillary lymph nodes* cite in the middle of the *axillary fossa.* The *lateral axillary lymph nodes* are palpated near the upper part of the humerus with the raised hands.

Then the patient lowers his/her hands a little (to about 45 degrees), which helps to relax the muscles surrounding the armpit, and makes it easier to palpate the regional lymph nodes. The *subscapular lymph nodes* are palpated under the anterior edge of the *musculus latissimus dorsi,* the *mammary (pectoral) lymph nodes* – below the lateral edge of *the musculus pectoralis major.*

Cubital lymph nodes. The cubital lymph nodes cite in the cubital fossa. The patient's elbow should be bent at the right angle, the muscles are relaxed. The examiner with one hand holds the hand of the patient, and palpates by sliding motions of other hand in the direction transverse to the medial angle of the cubital fossa.

Inguinal lymph nodes are palpated in the direction transverse to the *Poupart's (inguinal) ligament*.

Popliteal lymph nodes are palpable at the flexed knee in the popliteal fossa.

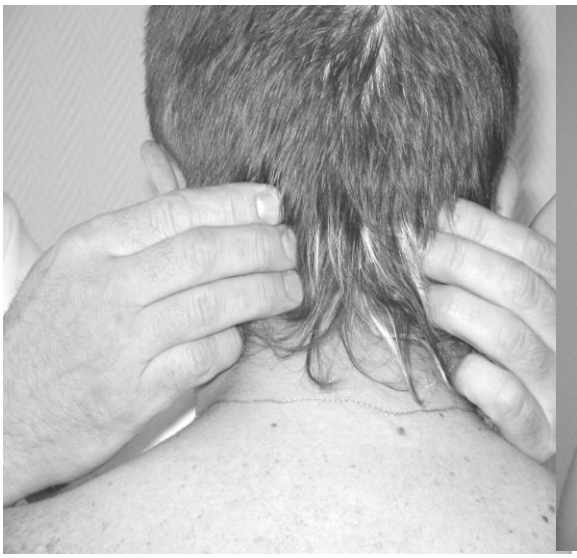


Fig. 24.2. Palpation of the occipital lymph nodes

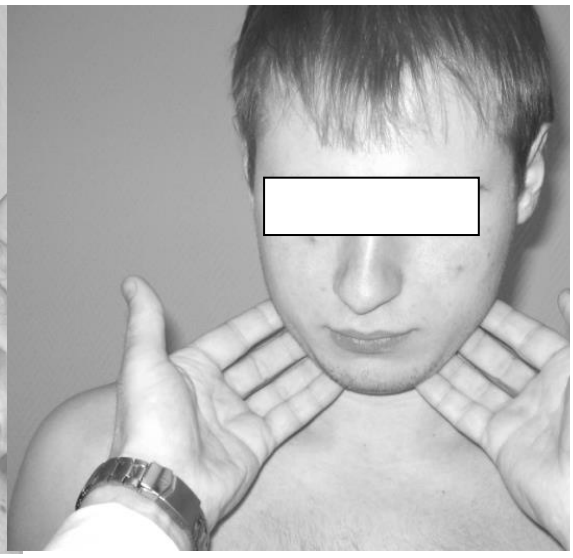


Fig. 24.3. Palpation of the submandibular lymph nodes

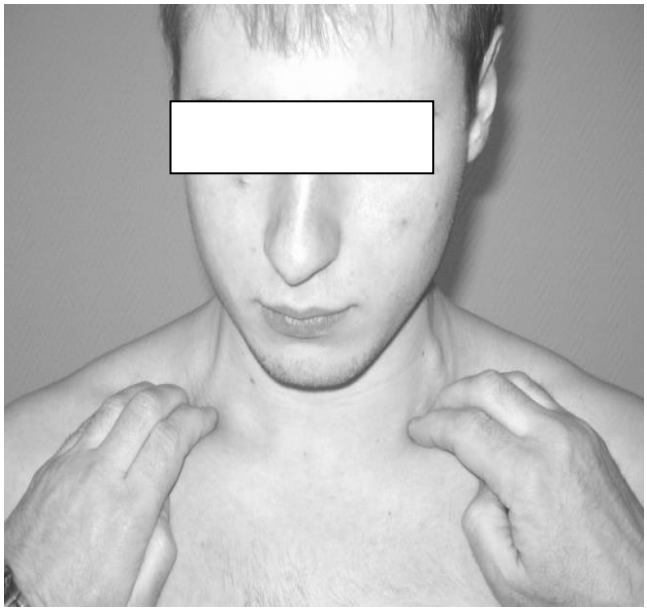


Fig. 24.4. Palpation of the supraclavicular lymph nodes

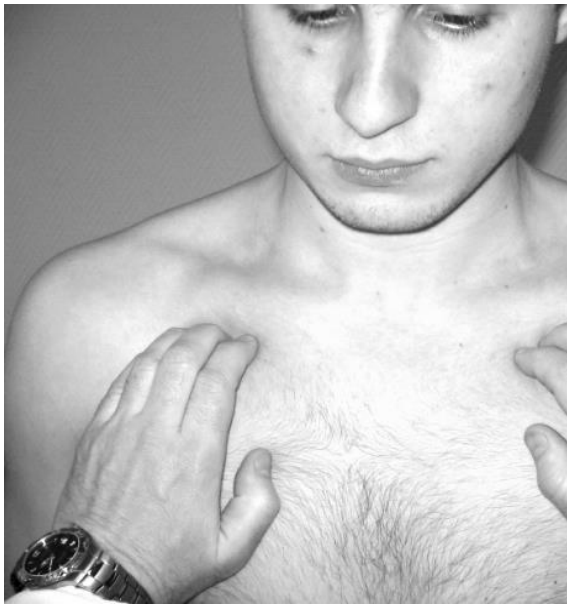
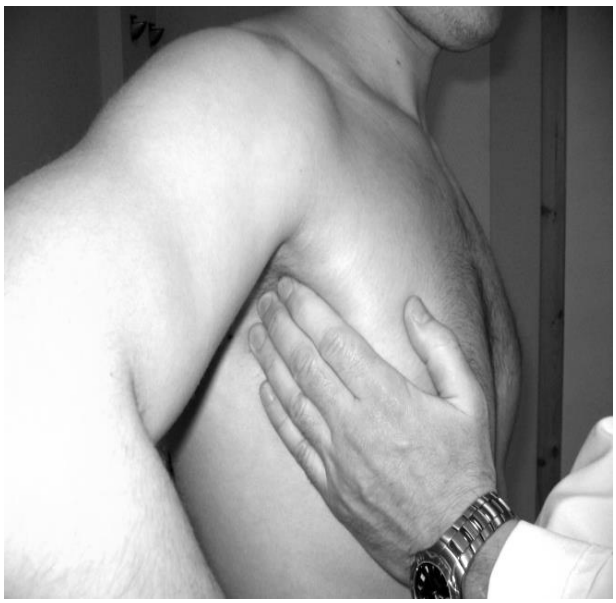


Fig. 24.5. Palpation of the infraclavicular lymph nodes



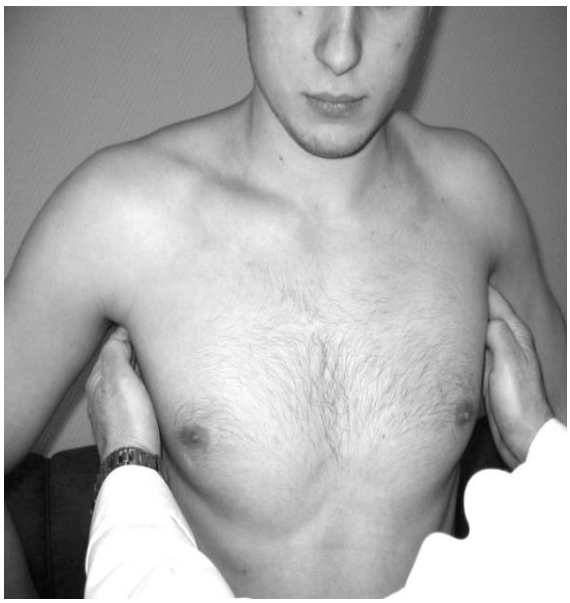


Fig. 24.6. Palpation of the axillary lymph nodes (side view and front view)

Diagnostic value of the lymph nodes examination

Lymph nodes are not palpable in healthy adults. *Excepted from the rule is a single lymph node of the axillary, cervical, submandibular, inguinal groups, which are not larger than 1 cm, soft or elastic, painless, removable during palpation, and not fixed to adjacent tissue.*

Lymphadenopathy *is a palpable enlargement (more than 1 cm) of lymph nodes.* There are *localized lymphadenopathy* (in only 1 body area) *and*

generalized lymphadenopathy (in 2 and more body areas). Lymphadenopathy is a pathology of the peripheral immune system due to a variety of infections, malignancy, autoimmune and metabolic disorders (Table 24-3).

Lymphadenitis is a lymphadenopathy due to inflammation with characteristic clinical manifestations (e.g., a pain on palpation, fever, local redness and puffiness of the overlying skin).

Causes of the lymphadenitis are infectious diseases (bacterial, viral, fungal, protozoal), local soft-tissue infections, and infected wounds. Lymphadenitis can be focal and multifocal.

Focal submandibular lymphadenitis complicates infections of the oral cavity and upper airways (e.g., dental caries, tonsillitis). Cervical lymphadenitis may be due to infections of the oral cavity, upper airways (e.g.; stomatitis, rhinosinusitis, pharyngitis, etc.). Inguinal lymphadenitis develops in inflammatory and infectious processes in the lower extremities and urogenital organs.

Multifocal lymphadenitis may occur in generalized infections (e.g., sepsis, tuberculosis, syphilis, brucellosis, cytomegalovirus infection, toxoplasmosis, HIV infection). Tuberculosis lymphadenitis can suppurate and form fistula.

Table 24-3. Clinical manifestations of the lymphadenopathy

Variant of the lymphadenopathy	Characteristics	Main causes
Lymphadenitis (focal and multifocal)	- pain on palpation of the lymph node(s), - local redness and puffiness of the overlying skin, - lympn nodes can suppurate and form fistula (in purulent infections, sepsis, tuberculosis), - fever, skin rash, arthralgia may be	- infectious diseases (bacterial, viral, fungal, protozoal), - local soft-tissue infections, - infected wounds, - connective tissue systemic diseases
Localized (noninfectious) lymphadenopathy	- lymph nodes are painless, dense, rough on palpation, painless, dense or often rubbery, matted together lymph nodes	- metastasis of the malignant tumor, - initial presentation of the lymphocytic leukemia, lymphoma
Generalized (noninfectious) lymphadenopathy	- lymph nodes are painless, rubbery, or often dense, matted together	- hemoblastosis (lymphocytic leuke-mia, lymphoma)

Localized noninfectious lymphadenopathy is most commonly due to the metastasis of the malignant tumor, and in hematologic malignancy (e.g., during initial presentation of the lymphocytic leukemia, lymphoma). *Characteristics of the lymph node metastasis are painless, dense, rough on palpation, and fixed to* the *adjacent tissues.*

Lymphadenopathy of the supraclavicular lymph nodes is a sign of the tumor metastasis from the chest organs, gastrointestinal tract, and lymphoma. *Virchow's node* is an enlarged supraclavicular node on the left with metastasis of the stomach cancer, as well as the pancreas or breast tumors. *Unilateral axillary lymphadenopathy* is a sign of the breast cancer metastasis. *Inguinal lymphadenopathy* occurs in tumor metastases of the pelvic organs (e.g., urogenital system, rectum).

Generalized lymphadenopathy is the most pronounced in hemoblastosis (e.g., acute lymphatic leukemia, chronic lymphocytic leukemia, lymphogranulomatosis). There are painless, dense or often rubbery, matted together lymph nodes. The early-stage disease affects only one group of the lymphatic nodes. The dense lymph nodes can fuse and form a large conglomeration in advanced stages of the lymphogranulomatosis (Hodgkin's disease) and lymphosarcoma.

Warning signs of the lymphadenopathy are a node with a size of more than 2 cm, dense, rough on palpation, fixed to the adjacent tissues; supraclavicular node, combined with fever, weight loss, anemia, a hemorrhagic syndrome, splenomegaly, suspected tuberculosis, HIV-infection, and malignant diseases.

Diagnostic biopsy of the lymph nodes is indicated in presence of the warning signs and complicated cases of the lymphadenopathy.

Lymphomas and leukemids may be detected at the exposed parts of the body (on the face and/or limbs).

Leukemids are changes in the skin due to its infiltration with blast (leukemic) cells in acute leukemia. Leukemids are characterized by multiple and widespread skin induration of the pink or light brown color, elevated above the skin surface, and variably sized from a few millimeters to 2-3 cm. Leukemids are painless on palpation and sometimes with scaly skin.

There are *cutaneous lymphomas* associated with the skin lymphoid infiltration in patients with chronic lymphocytic leukemia. These are oval or oblong lumps of the solid-elastic texture, a sensitive to palpation. Unlike lymph nodes, cutaneous lymphomas are tightly adherent to the skin.

24.4. Detection of the excessive bleeding

Excessive bleeding (hemorrhagic diathesis) is a tendency to repeated bleeding or hemorrhages in the skin, mucous membranes and some organs, occurring spontaneously or under the influence of physical environmental factors.

Excessive bleeding can be revealed on the basis of the medical history (unexplained nasal or gingival bleeding, prolonged menorrhagia, or prolonged

bleeding after minor injury, tooth brushing, injections, etc.), general and local inspection of the skin, visible mucosa of eyes (conjunctiva), nasal passages, oral cavity, as well as endoscopic examination of the respiratory tract, gastrointestinal tract and abdominal cavity.

Manifestations of the excessive bleeding may be hemorrhagic rashes (e.g., petechiae, ecchymosis), which often occur spontaneously, but they may also appear after a physical impact of the weak force.

Microvascular hemostasis (capillary permeability) clinical tests

No significant skin changes occur with a physical impact in a healthy person. Damage of the blood vessel (e.g., vasculitis, vitamin C deficiency, connective tissue disorders) associates with an increased fragility of the skin small vessels during a weak force of the compression, so that numerous skin rash (petechiae, ecchymosis, purpura) appear. The latter is usable in clinical practice to identify the *disordered microvascular hemostasis* by particular clinical tests – tourniquet test (Fig. 24.7), pinch test, etc.

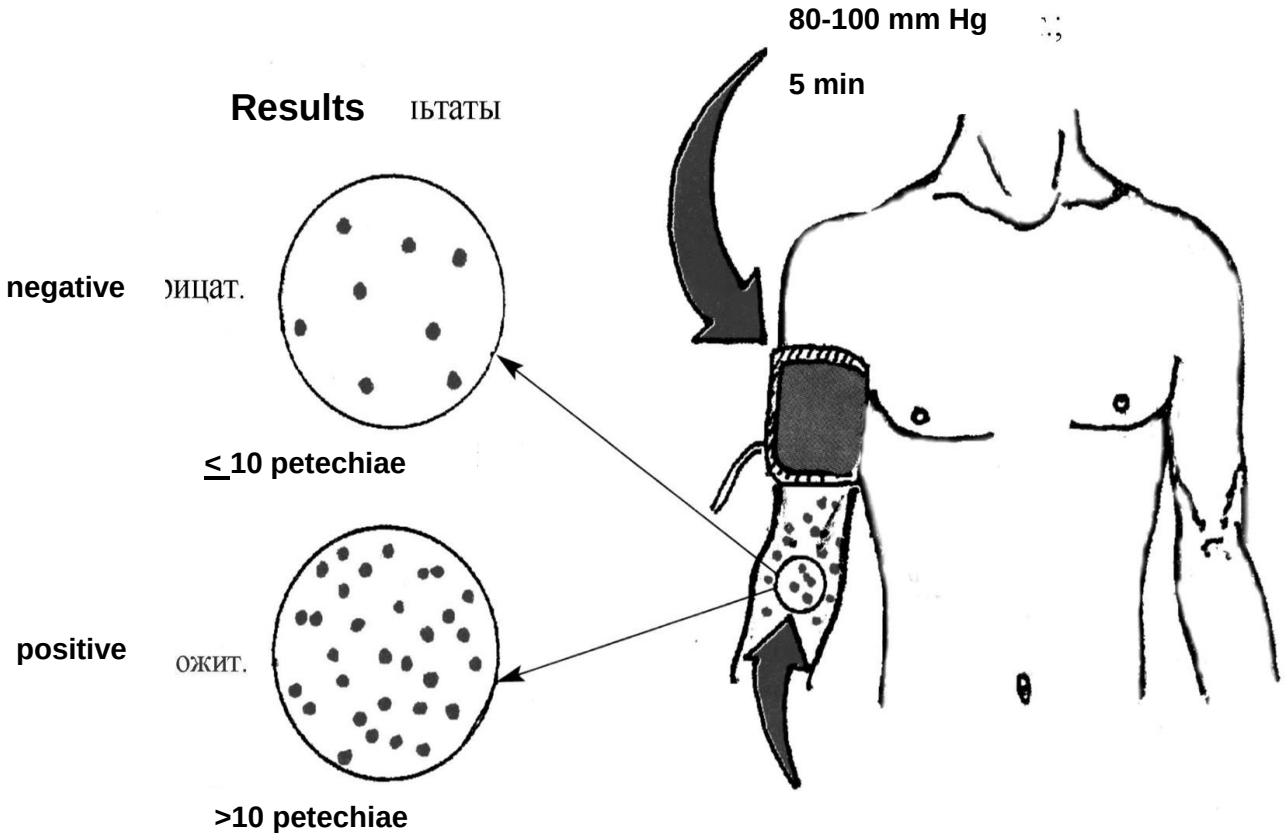


Fig. 24.7. Tourniquet test

Tourniquet test (or *capillary fragility test, or Konchalovsky-Rumpel-Leede sign).* It is a clinical diagnostic test to assess the capillary walls fragility, and it is used to identify thrombocytopenia.

The examiner applies a tourniquet to the forearm. If petechiae appears on the skin below the tourniquet, the test is positive.

The blood pressure cuff can be used for the capillary fragility test. Blood pressure cuff is applied and inflated to the midpoint between the systolic and diastolic blood pressures (about 80-100 mm Hg) for 5 minutes. The test is positive if there are more than 10 to 20 petechiae per square inch.

Cupping glass test. The air is evacuated from the cup applied to the skin (a rarefaction of about 200 mm Hg) for 2 minutes. If the test is positive, petechiae occur on the skin below the cup. The number of the petechiae shows the degree of the vascular wall affection.

Pinch test. The examiner uses his/her fingers to plicate the skin under the clavicle and pinch it. In healthy humans, no skin changes occur either immediately following the pinch or in 24 hours. If the capillary resistance is broken, petechiae or bruising appear at the pinch site, and they gradually increase in size and become more intense in 24 hours.

Mallet sign. Ecchymosis develops on the skin after tapping with a percussion mallet (percussion hammer, or plexor).

The positive tests of the disordered microvascular hemostasis are observed in scurvy (vitamin C deficiency), vasculitis, infective endocarditis, as well as with thrombocytopenic purpura and Waldenstrem's disease (macroglobulinemia), and in certain infectious diseases (e.g., scarlet fever, typhus fever in the first 3-5 days of the illness, epidemic roseola, influenza). However, the positive tests never occur in hemophilia, which allows to distinguish it from the above indicated hemorrhagic diathesis.

24.5. The key points of the theme "Clinical Examination of Patients with Blood diseases"

Specific symptoms of the blood pathology are *bleeding from the nose, gums, intestines, uterus* (due to thrombocytopenia, deficiency of the blood clotting factor, microvascular hemostasis disorders); *perverted appetite* (iron- deficiency anemia), *burning the tongue* (vitamin B_{12}-deficiency anemia), *skin itching* (lymphogranulomatosis, polycythaemia vera), *sore throat and pains in oral cavity* (leukemia), *pain in bones* (ossalgia in leukemia), *fever* (acute and chronic leukemia, lymphogranulomatosis, and agranulocytosis), *lymph nodes enlargement* (acute and chronic leukemia, lymphoma), *heaviness and discomfort in abdomen* (hepato- and splenomegaly in leukemia).

Unspecific complaints (e.g., *general weakness, malaise, fatigue, dizziness, headaches, dyspnea, drowsiness*) can prevail in diseases of the blood system pathology (e.g. anemia, leukemia).

General inspection finds characteristic changes in the color of the skin and visible mucous membranes*: skin pallor* (in anemia), *skin pallor with a golden yellow tint* (prehepatic jaundice in hemolytic anemia), *hemorrhagic rashes* (due to various disorders of the coagulation system, pathology of the platelets or the vascular wall).

Glossitis (inflammation of the tongue) is characteristic of the iron deficiency anemia *(atrophic glossitis)* and vitamin B_{12}- folate deficiency anemia *(Hunter's glossitis).*

Definition of the bleeding type has a certain diagnostic value: *petechiae* are characteristics of the thrombocytopenia, *hematomas* – coagulation factor deficiencies (e.g., hemophilia), *purpura* – hemorrhagic vasculitis, hemorrhagic vasculitis, *ecchymoses* – clotting problems (e.g., von Willebrand's disease), *mixed type* – disseminated intravascular coagulation. *Hemorrhagic telangiectasias* present in *Rendu-Osler-Weber disease* (hereditary arteriovenous malformations in the skin, mucous membranes, and internal organs).

Lymph nodes are not palpable in healthy adults. *Excepted from the rule is a single lymph node of the axillary, cervical, submandibular, inguinal lymph node groups,* which are not larger than 1 cm, soft or elastic, painless, removable during palpation, and not fixed to the adjacent tissue.

Lymphadenopathy *is a palpable enlargement (more than 1 cm) of the lymph nodes.* There are *localized lymphadenopathy* (in only 1 body area) *and generalized lymphadenopathy* (in 2 and more body areas). Lymphadenopathy is a pathology of the peripheral immune system due to a variety of infections, malignancy (metastasis of the malignant tumor, lymphocytic leukemia, lymphoma), autoimmune and metabolic disorders.

Diagnostic biopsy of the lymph nodes is indicated in presence of the warning signs and complicated cases of the lymphadenopathy

The ***positive tests of the disordered microvascular hemostasis (e.g., capillary fragility test, pinch test)*** are observed in scurvy (vitamin C deficiency), vasculitis, infective endocarditis, as well as with thrombocytopenic purpura and Waldenstrem's disease (macroglobulinemia), and in certain infectious diseases (e.g., scarlet fever, typhus fever on the first 3-5 days of the illness, epidemic roseola, influenza).

24.6. Assessment tests on the theme “Clinical Examination of Patients with Blood diseases”

1. Specific symptoms of the blood system pathology are:

1. perverted appetite;
2. fever;
3. gingival bleeding;
4. dizziness;
5. heart pain.

2. Unspecific complaints in patients with the blood system pathology:

1. burning the tongue;
2. malaise;
3. headache;

4. drowsiness;
5. heaviness and discomfort in abdomen.

3. What are typical of patients with the blood system pathology in their past life history?

1. malignant tumors;
2. ionizing radiation;
3. nutritional profile (strict vegan);
4. emotional stress;
5. physical overwork;
6. hereditary predisposition.

4. Characteristic changes of the skin and visible mucosa color in the blood diseases are:

1. cyanosis;
2. skin pallor;
3. skin pallor acquires a greenish tint;
4. skin pallor with a golden yellow tint;
5. brown-yellow;
6. intense red.

5. What are the characteristics of the petechiae?

1. red-purple punctate rash;
2. massive painful hemorrhage;
3. elevated (palpable),
4. due to thrombocytopenia;
5. due to coagulation factor deficiencies.

6. What are the characteristics of the purpura?

1. red-purple punctate rash;
2. red-purple, multiple rash;
3. elevated (palpable),
4. due to thrombocytopenia;
5. hemorrhagic vasculitis.

7. What are the characteristics of the ecchymoses?

1. red-purple punctate rash;
2. red-purple subcutaneous rash >0.5 cm;
3. massive painful hemorrhage;
4. elevated (palpable);
5. due to thrombocytopenia;
6. due to coagulation factor deficiencies.

8. The most considerable splenomegaly is observed in:

1. liver cirrhosis;
2. hemolytic anemia;
3. chronic myeloid leukemia;
4. lymphogranulomatosis;
5. perisplenistis.

9. The characteristics of the lymph nodes in healthy adults are:

1. nonpalpable;
2. all lymph node groups are palpable, > 2 cm in size;
3. Excepted from the rule is a single lymph node of the axillary, cervical, submandibular, inguinal groups, it is not larger than 1 cm;
4. Excepted from the rule is the supraclavicular lymph nodes group;
5. lymph nodes are fixed to adjacent tissue.

10. Causes of the lymphadenopathy are:

1. infections;
2. metastasis of malignant tumors;
3. hemoblastosis (e.g., leukemia, lymphoma);
4. hemolytic anemia;
5. connective tissue systemic diseases;
6. Megaloblastic (vitamin B_{12}- folate deficiency) anemia.

11. The characteristics of the lymphadenopathy in hemoblastosis (hematologic malignancies) are:

1. pain on palpation;
2. soft intradermal nodes;
3. lympn nodes can suppurate and form fistula
4. painless on palpation;
5. dense or rubbery;
6. matted together lymph nodes.

12. A positive test of the disordered microvascular hemostasis (Konchalovsky-Rumpel-Leede sign) presents in:

1. hemorrhagic vasculitis;
2. hemophilia;
3. iron-deficiency anemia;
4. scurvy;
5. thrombocytopenia;
6. decompensated heart failure.

CHAPTER 25. Laboratory and Instrumental Examination of Patients with Blood System Diseases

Goals: to enable students to learn -

1. complete blood count and interpretation of the obtained results in blood diseases;
2. diagnostic value of the bone marrow examination and lymph nodes biopsy in the diagnosis of the impaired hemopoiesis;
3. diagnostic laboratory tests of the pathologic hemolysis and hemostasis.

25.1. Complete blood count

*The **complete blood count (CBC; general blood analysis)*** includes the *red blood cell tests* – an erythrocyte count, blood hemoglobin concentration, an erythrocyte sedimentation test (erythrocyte sedimentation rate, ESR), a reticulocyte count, calculation of the blood color index; *white blood cell tests* – a leucocyte count, a differential blood cell count (leukogram, or leucocyte formula); *a platelet count*, and *an evaluation of the morphology of the peripheral blood cells* (Fig. 25.1).

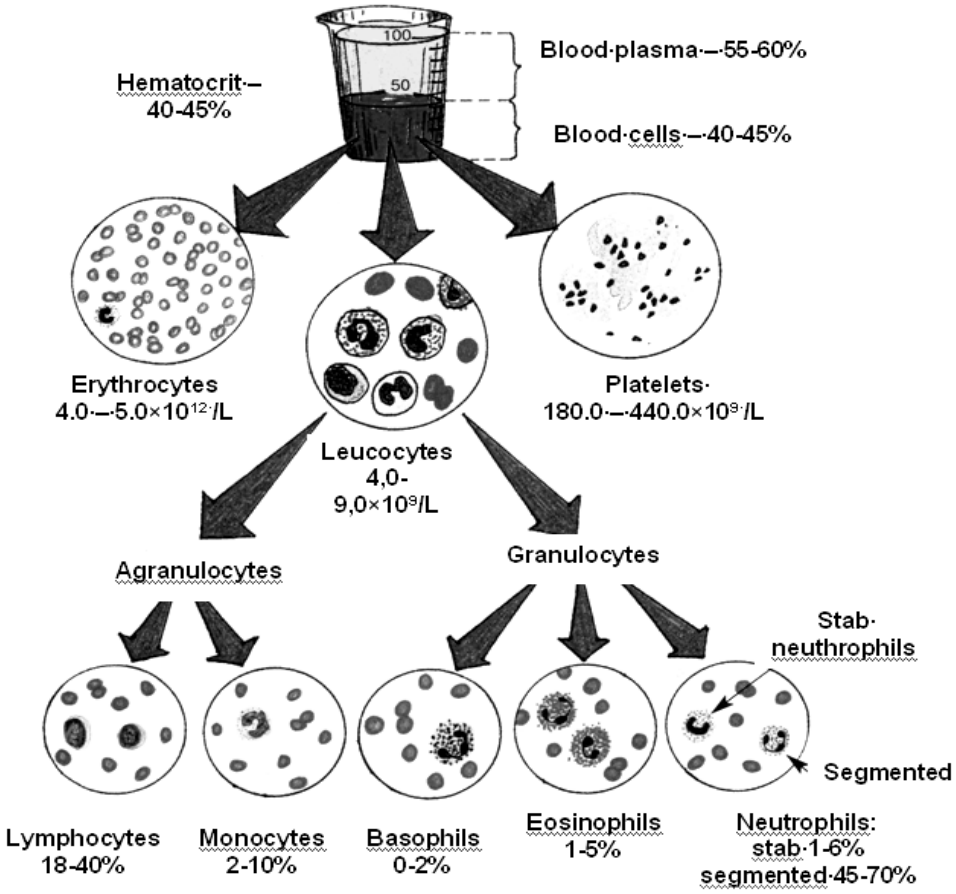


Fig. 25.1. Complete blood count

25.1.1. Erythrocytes (red blood cell, RBC) tests

Hemoglobin. *The c*oncentration of the hemoglobin in healthy people varies within 120-145 g/1 in women and 135-165 g/1 in men (Table 25-1).

Erythrocyte count (RBC count). Normal erythrocyte counts in women are $3.5\text{-}4.7\times10^{12}$/l and in men – $4.0\text{-}5.5\times10^{12}$/l of the blood.

Table 25-1. Erythrocytes conventional tests of the complete blood count

Test	Normal values	Low test result	High test result
Hemoglobin - male - female	 135.0 – 165.0 g/l 120.0 – 145.0 g/l	- anemias; - acute or chronic blood loss; - iron, vitamin B_{12}, folate deficiency; - hemodilution	- polycethemia vera; - symptomatic erythrocytosis (in smoking, COPD) - dehydration
Erythrocytes - male - female	 $4.0 – 5.5\times10^{12}$ / l $3.5 – 4.7\times10^{12}$ / l		
Color index	0.85 – 1.05	- iron deficiency and chronic posthemorrhagic anemias	- vitamin B_{12}-folate-deficiency anemia
Hematocrit (PCV, packed cell volume) - male - female	 0.415–0.504 0.359–0.446	- anemia; - bleeding; - malnutrition; - hemodilution	- dehydration (most commonly); - erythrocytosis
Erythrocyte sedimentation rate (ESR) *Panchenkov method* - male - female *Westergren method* - male (<50 years) - female (<50 years) - male (≥50 years) - female (≥50 years)	 2 – 10 mm/h 2 –15 mm/h ≤15 mm/h ≤20 mm/h ≤20 mm/h ≤30 mm/h	- polycethemia vera; - symptomatic erythrocytosis (in smoking, COPD); -sickle cell disease; -microspherocytosis	- inflammation; -malignant tumors; - hematologic malignancies (leukemia, lymphoma); - anemias; - autoimmune pathology
Reticulocytes	0.5-1.5% or 5 - 15 ‰ or $25\text{-}125\times10^{3}$/μ (muL, microliter)	- hypo- and aplastic anemias); - nutritional deficiency (iron, vitamins B_{12}, folate)	- hemolytic anemia; -acute and chronic blood loss; - response to anemia (iron, B_{12}) treatment; - polycythemia

Anemia is a pathological condition characterized by a decreased number of erythrocytes and/or hemoglobin content in a blood unit volume due to their general deficiency.

In addition to anemias of the various etiology, a *decrease in the level of the hemoglobin is observed in overhydratation* (*due to hemodilution* - a blood thinning that increases a plasma volume relating to the volume of the blood formed elements). A decrease in hemoglobin often occurs in pregnant women.

Erythrocytopenia *is a decrease in the quantity of erythrocytes* due to an acute or chronic blood loss (*posthemorrhagic anemia*), an insufficient blood formation (*iron- deficiency, vitamin* B_{12} *- folate-deficiency, hypo- and aplastic anemia*), and an increased erythrocyte cellular breakdown (*hemolytic anemia*).

The erythrocyte count during pregnancy can decrease by 3.0×10^{12} / l. It is attributable, on the one hand, to the *hemodilution* due to the retention of the water in the body of the pregnant woman, and, on the other hand, to a certain decrease in blood formation due to the iron deficiency.

An *increase in the level of hemoglobin* is noted with *erythremia* (*polycythaemia vera), erythrocytosis* (burns, cardiopulmonary failure), and severe dehydration (due to hemoconcentration).

Erythrocytosis *is an increase in the number of red blood cells.* It is observed in *erythremia (polycythemia vera), and symptomatic erythrocytosis* due to the hypoxia in a chronic respiratory (e.g., COPD, pneumofibrosis) and cardiovascular failure, and in people living in mountainous areas. It is also necessary to exclude tumors producing *erythropoietin*: renal cell carcinoma, tumors of the adrenal glands, pituitary gland, thyroid gland, and ovaries.

Hematocrit (Hct) is the volume percentage (vol %) of the erythrocytes (RBC) in the blood. The normal values are 41.5-50.4 vol % (0.415-0.504 volume fraction), and 35.9-44.6 vol% (0.359-0.446 volume fraction) in women.

Reduced hematocrit levels can indicate anemia, recent or long-term bleeding, malnutrition, and hemodilution.

Elevated hematocrit levels can indicate *erythrocytosis* (e.g. polycythemia vera, chronic respiratory and cardiovascular failure), and dehydration.

Color index. *Color index* is a conventional value of the erythrocytes saturation with hemoglobin. There is a simple formula for calculating the color index:

$$Hb / (Er \times 3),$$

Where Er - first 3 digits of erythrocyte count, excluding comma.

Normally, *the color index is from 0.85 to 1.05 (normochromia*).

An increase in the color index above 1.1 (*hyperchromia*) is observed in hyperchromic anemia (vitamin B_{12}-folate-deficiency anemia - due to the enlarged volume of the red blood cells (*macrocytes and megalocytes*), and a decrease below 0.8 (*hyporchromia*) - with hypochromic anemia (iron deficiency anemia, chronic posthemorrhagic anemia).

The "color index" is outdated in the current context, and it is used today in medical laboratories with limited resources. To assess the erythrocyte hemoglobin

content, modern indices of the automated complete blood count [mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC)] are more informative (see below).

Erythrocytes indices of the automated complete blood count

The average hemoglobin content in one erythrocyte (***mean corpuscular hemoglobin, MCH)*** is a more objective and accurate index than a color index. It is determined by an automatic blood cell counter. ***MCH** is 27.5 – 33.2 pg in norm.*

Reduced MCH can indicate small red cells *(microcytosis)* in iron deficiency anemia and thalassemia. *Elevated MCH* can indicate enlarged red blood cells (*macrocytosis)* in vitamin B_{12}-folate-deficiency anemia (Table 25-2).

***Mean corpuscular hemoglobin concentration (MCHC)** is a calculated average concentration of the hemoglobin inside erythrocytes. MCHC* is *334-355 g/L in norm.*

Reduced MCHC levels occur in iron deficiency anemia and thalassemia. *Elevated MCHC levels* can indicate an increased hemoglobin concentration inside the erythrocytes such as autoimmune hemolytic anemia, hereditary spherocytosis (a rare congenital hemolytic disorder), and in burn patients.

Table 25-2. Erythrocytes indices of the automated complete blood count

Test	Normal values	Low test result	High test result
Mean corpuscular hemoglobin (MCH)	27.5– 33.2 pg (average content of hemoglobin in 1 erythrocyte)	- microcytosis (e.g. iron deficiency anemia, thalas-semia)	- macrocytosis (e.g. vitamin B_{12}-folate-deficiency anemia)
Mean corpuscular volume (MCV)	80-96 μm (average size of erythrocytes)		
Mean corpuscular hemoglobin concen-tration (MCHC)	334-355 g/l (calculated average concentration of the hemoglobin inside erythrocytes)	- iron deficiency anemia; - thalassemia	- autoimmune hemolytic anemia; - hereditary spherocytosis; - burn patients
Red blood cell distribution width (RDW, RDW-SD, or RDW-CV)	12.2 – 16.1% in females; 11.8 – 14.5% in males	erythrocytes are uniform in size (e.g. advanced macrocytic and microcytic anemias)	- anisocytosis (e.g. iron deficiency anemia, vitamin B_{12}-folate-deficiency anemia)

***Mean corpuscular volume (MCV)** is an average size of the erythrocytes. MCV is 80-96 μm (micrometer, or 1×10^{-6}m) in norm.*

Reduced MCV indicates small red cells (microcytosis) caused by iron deficiency anemia or thalassemia. *Elevated MCV indicates macrocytosis,* for example in vitamin B_{12}-folate-deficiency anemia.

Red blood cell distribution width (RDW, RDW-SD, or RDW-CV) *is a variation in the size of erythrocytes.* The *normal range of the RDW is 12.2%-16.1% in women, and 11.8%–14.5% in men.*

Reduced RDW indicates that erythrocytes are uniform in size, for example, in some cases of the macrocytic and microcytic anemias.

Elevated RDW indicates a mixed population of the small and large erythrocytes (anisocytosis), for example, in iron deficiency anemia or in vitamin B_{12}-folate-deficiency anemia.

Morphological changes of the red blood cells.

Changes in the size, shape, color of erythrocytes and the presence of various inclusions in them make it possible to establish the nature of the anemia.

Changes in the size of erythrocytes

The normal average diameter of erythrocytes (MCV) is within the range 80-96 μm in adults.

Anisocytosis is a change in the size of the erythrocytes. *Macrocytes* are erythrocytes with MCV more than 100 μm, *megalocytes* - more than 120 μm, *microcytes* – less than 80 μm. Anisocytosis occur in anemias.

Macrocytosis is observed in vitamin B_{12} - folate deficiency anemia, alcohol abuse. *Microcytosis* is characteristic of the chronic posthemorrhagic anemia, iron deficiency anemia.

Changes in the shape of erythrocytes

Normal erythrocytes have a biconcave discoid shape. The shape of the erythrocyte partially determines its resistance to an osmotic hemolysis, autohemolysis, and mechanical damage.

Poikilocytosis **i**s a change in the shape of the erythrocytes, it indicates a more severe course of the anemia. There are erythrocytes of the irregular shape (oval, pear-shaped, stellate, in the shape of mulberry berries, balls), as well as fragments of the erythrocytes (*schistocytes).*

Erythrocytes are small spheroidal (spherocytes) like small balls in congenital hemolytic anemia (*Minkowski-Shoffard disease, hereditary spherocytosis, or hereditary microspherocytic hemolytic anemia*); and *spherocytosis* may be in autoimmune hemolytic anemia.

There are *oval erythrocytes (ovalocytes)* in patients with thalassemia (congenital ovalocytic hemolytic anemia). *Sickle erythrocytes (drepanocytes*) is a characteristic of the sickle cell *anemia (hemoglobinopathy S).*

Change in the color of erythrocytes

Normochromia is a pink-pink color of the erythrocytes with a *delle* (the central pale dot). Normochromia commonly indicates the normal hemoglobin content in the erythrocyte.

Hypochromia is a pale pink color of the erythrocytes that indicates a decrease in the hemoglobin content in the erythrocyte (e.g. in iron deficiency anemia).

Hyperchromia is an intense red color that appears with an increase in the thickness of the erythrocytes (e.g., in hereditary microspherocytosis, vitamin B_{12}-folate-deficiency anemia). Hyperchromia indicates an increased hemoglobin concentration inside the erythrocytes

Polychromatophilia is a mixing of the normal pink-red erythrocytes and erythrocytes of the blue, purple and transitional colors due to the remnants of the basophilic substance in the young erythrocytes. These erythrocytes are *reticulocytes* in the supravital staining. *Polychromatophilia is a sign of the increased erythropoiesis* (e.g., in posthemorrhagic and hemolytic anemias, during the treatment of the vitamin B_{12}-folate-deficiency anemia). Normally, polychromatophilia occurs only in newborns (up to 1.5 months of age).

Intracellular inclusions in erythrocytes

Intracellular inclusions in erythrocytes indicate a significant erythropoietic hypofunction of the red bone marrow. During maturation of erythrocytes in pathological conditions, nuclear remnants of the normoblasts and erythroblasts can be preserved in the cytoplasm.

Jolly bodies (Howell-Jolly bodies) are the nuclear remnants (round chromatin formations) of the dark purple color in the vitamin B_{12}-folate-deficiency anemia.

Cabot rings are the remnants (thread-like rings) of the pink-colored nucleus membrane in case of the vitamin B_{12}-folate-deficiency anemia.

Basophilic aggregations (basophilic stippling) are degenerative changes of erythrocytes in vitamin B_{12}-folate-deficiency anemia, after splenectomy, and in the lead poisoning.

Normoblasts are nucleated red bone marrow cells which are normally absent in the peripheral blood. Their appearance indicates an extreme enhancement of the erythropoiesis (e.g. in hemolytic, chronic post-hemorrhagic anemias) or extramedullary hematopoiesis (e.g. in chronic myeloid leukemia, myelofibrosis).

Reticulocyte count

Reticulocytes are formed in the bone marrow from erythroblasts. These are young erythrocytes, in which a granular reticular substance is revealed during intravital staining with brilliant cresyl blue.

Normally, most red blood cells pass a reticulocyte stage in the hematopoietic tissue. Some of the reticulocytes leave the bone marrow and morph into mature erythrocytes within the peripheral blood.

The number of reticulocytes in the peripheral blood is normally 5 - 15 ‰ (parts per thousand), or 0.5 - 1.5%.

Reticulocytes are an important indicator of the erythropoiesis intensity.

Reticulocytosis *is an increase of the reticulocyte count.* It is observed in hemolytic anemia, an acute and chronic blood loss, response to treatment (e.g., iron supplementation for iron deficiency anemia; vitamin B_{12} and folic acid – in vitamin B_{12}- folate-deficiency anemia), and polycythemia vera. Persistent reticulocytosis (3-4%) suggests latent bleeding.

Reticulocytopenia (reticulopenia) *is a decrease of the reticulocyte count or complete absence of reticulocytes.* It indicates an impaired erythropoiesis, such as bone marrow disorder or damage (e.g. hypo- and aplastic anemias) or a nutritional deficiency (e.g., iron, vitamins B_{12} or folate).

Erythrocyte sedimentation rate (ESR, in *Russian* – СОЭ)

The ESR test measures the rate of the erythrocytes sedimentation in a sample of the blood to the bottom of the test-tube. ESR depends on the physicochemical properties of the blood (Fig. 25.2).

Fig. 25.2. Panchenkov capillary method of ESR determination.

The negative electric charges on the outside of the cell membrane cause a repulsive interaction of erythrocytes in norm. Plasma proteins with the positive electric charges can neutralize the negative surface charges of the erythrocytes that leads to the *rouleaux formation* of erythrocytes.

Rouleaux formation (and thus the ESR) rises with increased amounts of the immunoglobulins and *acute phase proteins* (*C-reactive protein, fibrinogen, ferritin, hepcidin, haptoglobin, ceruloplasmin, complement proteins C3 / C4*, etc.) that are present in inflammatory conditions, autoimmune pathology, and malignant disease (e.g. cancer, sarcoma), including hematologic malignancies (e.g. leukemia, lymphoma).

Erythrocytosis (an increased number of the erythrocytes) increases blood viscosity and thus causes a reduced ESR. By contrast, *most anemias can*

accelerate ESR due to a decreased blood viscosity. Some congenital hemolytic anemias (such as sickle cell disease and microspherocytosis) can reduce ESR due to the abnormal shape of erythrocytes that impairs the rouleaux formation. Pregnancy and aging may also increase the ESR.

ESR can be estimated by means of the Westergren method, Panchenkov microcapillary method, and with the use of automatic analyzer.

The erythrocyte sedimentation rate (ESR) is expressed in millimeters per hour (mm/h).

The *Panchenkov method of ESR determination* is widely used in Belarus, Russia and some countries of the CIS region (Fig. 25.2). A Panchenkov's capillary graduated in 1 mm (100 divisions) is used for the purpose. The number of millimeters of the 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.*

The International Council for Standardization in Hematology recommended the Westergren test-tube method as the method of choice (1993).

The ESR typically increases with age, and it is higher in females than in males. The higher limits of the reference range for the Westergren ESR test in men and women $\leq$50 years are 15 and 20 mm/h, respectively, whereas for men and women > 50 years – 20 and 30 mm/h, respectively.

25.1.2. Thrombocyte (platelet) tests

Thrombocyte count (platelet count, Plt)

The normal number of platelets is 150×10^9/l - 450×10^9 /l of the blood.

Thrombocytopenia *is a reduced number of platelets in the peripheral blood.* It is observed in Werlhof's disease (autoimmune thrombocytopenic purpura), vitamin B_{12}-folate deficiency anemia, leukemia, poisoning (e.g. benzene, aniline), sepsis, during chemo- and radiation therapy, adverse drug reactions (acetaminophen, quinidine, sulfa drugs), in liver cirrhosis (with the hypersplenism syndrome), viral infections (mononucleosis, measles, hepatitis).

A *significant decrease in platelets (less than 120×10^9/l) in the blood may result in bleeding complications*, the threat of which is great with the thrombocytopenia less than 20×10^9 / l.

Thrombocytosis *in an increase in the number of platelets in the peripheral blood*. It occurs in blood loss, some cases of the iron-deficiency and hemolytic anemias, polycythemia vera, myeloproliferative disorders (myeloid leukemia, myelofibrosis), after splenectomy, as a reaction to a malignant tumor (paraneoplastic syndrome), in systemic autoimmune diseases (e.g. rheumatoid arthritis, lupus erythematosus), acute bacterial infections (pneumonia, osteomyelitis), inflammatory bowel diseases (e.g. ulcerative colitis), chronic alcohol intoxication (Table 25-3).

Thrombocytosis leads to a feebleness (slowdown) of the circulation and tendency to thrombi formation.

Platelet indices of the automated complete blood count:

Mean platelet volume (MPV) is the average size of platelets. MPV commonly is 3.6 -9.3 μm^3 (cubic micrometer).

Reduced MPV may indicate an affected production of platelets by the bone marrow, as the older platelets are generally smaller than young ones. Reduced MPV is associated with thrombocytopenia.

Elevated MPV indicates an increased number of the young platelets due to an intensive thrombocytopoiesis in response to the destruction of platelets (e.g. in autoimmune thrombocytopenic purpura, myeloproliferative diseases).

Table 25-3. Thrombocytes (platelets) tests of the complete blood count

Test	Normal values	Low test result	High test result
Thrombocyte count (platelet count, Plt)	150 - 450×10^9 /l	*Thrombocytopenia* occurs in: - autoimmune thrombocytopenic purpura; - vitamin B_{12}-folate deficiency anemia; - leukemia; - chemo- and radiation therapy; - adverse drug reactions (acetaminophen, quinidine); - liver cirrhosis, - viral infections; - sepsis	*Thrombocytosis* occurs in: - polycythemia vera; - myeloid leukemia; - hemolytic and iron deficiency anemias; - idiopathic thrombocytosis; - after splenectomy - malignant tumors; - rheumatoid arthritis; - acute bacterial infections; - chronic alcohol intoxication
Mean platelet volume (MPV)	3.6-9.3 μm^3	*Reduced MPV* associates with thrombocytopenia	*Elevated MPV* indicates an intensive thrombocytopoiesis (e.g. autoimmune thrombocytopenic purpura, polycythemia vera)
Platelet distribution width (PDW)	9.0-17.0 %	*Low PDF* indicates uniformity in size of platelets	*High PDW* is associated with a risk of the thrombi formation and gastric and ovarian cancer

Platelet distribution width (PDW) is the relative width of the platelets distribution of by volume – 9.0-17.0 % in norm. *A low PDW reflects uniformity of*

the platelets size. A high PDW indicates increased variation in the size of the platelets. *High PDW is a laboratory sign of the platelet activation*, and it is associated with a risk of the thrombi formation and malignancy (gastric and ovarian cancer).

25.1.3. Leukocytes (white blood cell, WBC) tests

Leukocyte count (WBC count)

Leukocyte count is 4.0 - 9.0×10^9/l in healthy adult people (Table 25-4).

***Leukocytosis** is an increase in the number of the white blood cells in the peripheral blood.*

Leukocytosis can be relative (redistributive) and absolute (true).

Relative leukocytosis (10 - 15 ×10^9/l) occurs due to the leukocytes inflow into the blood stream from the blood pool (liver, spleen, skin). It can be found after eating ("digestive" leukocytosis), intense muscular exercise ("myogenic" leukocytosis), hot and cold baths, strong emotions ("vegetovascular" leukocytosis). This is factored into in the rules for the blood sampling.

Absolute leukocytosis can be caused by hyperplasia of the hematopoietic tissue in leukemia and by a reaction to an inflammatory disease (pneumonia, pleurisy, cholecystitis, appendicitis, and peritonitis), a purulent process (abscess, sepsis), the death of the tissues (traumas, burns, a heart attack), exogenous intoxication (carbon monoxide, nitrobenzene, arsenic hydride), bronchial asthma and acute allergy. The *most pronounced leukocytosis (up to and exceeding 500 - 800 ×10^9/l) is observed in leukemia*.

Table 25-4. Leukocyte (white blood cells) count

Test /Normal values	Leukopenia	Leukocytosis
Leukocyte (white blood cell count, WBC) 4,0 - 9,0×10^9 / l	- bone marrow damage (ionizing radiation, toxic substances, chemo-therapy, adverse drug reactions – e.g. acetaminophen, sulfonamides) - autoimmune diseases; - severe infections (e.g. sepsis, HIV/AIDS, COVID-19) - malignancy of the bone marrow; - vitamin B_{12}-folate deficiency anemia)	- bacterial and viral infections, - inflammation and necrosis of the tissues (e.g. trauma, burns, infarction); - leukemia; - polycythemia vera; - acute allergies; - bronchial asthma; - corticosteroid therapy; -intense exercise or severe stress.

***Leukopenia** is a reduced number of the white blood cells in the peripheral blood.*

*Relative (redistributive) leukopenia (*which is not below 3.0×10^9/l) is due accumulation of the leukocytes in the blood pool. It can be for a short time during physical exertion, neurosis, collapse, gastric ulcer and duodenal ulcer.

Absolute leukopenia occurs due to the inhibition of the leukopoiesis in the bone marrow (severe viral and bacterial infections, e.g. sepsis, HIV/AIDS, COVID-19), autoimmune diseases, after taking certain medications (e.g. non-steroidal anti-inflammatory drugs, chloramphenicol, sulfonamides, acetaminophen, cytostatic drugs), toxic substances (e.g. benzene, arsenic*)*, ionizing radiation, dietary deficiencies (in vitamin B_{12}-folate deficiency anemia). Leukopenia in association with thrombocytopenia and anemia is one of the hypersplenism syndrome signs in liver cirrhosis.

If leukopenia is less than 3.0×10^9/l in two consecutive blood tests, the patient should be referred for a consultation with a hematologist.

Leucopenia increases a risk of the potentially life-threatening infections.

Leukocyte formula (white blood cell differential)

*The **leukocyte formula** (white blood cell differential leukogram, differential blood count) is the percentage ratio of every forms of the leukocytes.* It is expressed as the percentage of the each type of the white blood cell per 100 leukocytes. The leukocyte formula is estimated together with the absolute number of leukocytes. It is necessary to focus on the absolute number of each of the leukocyte forms, especially when their total number changes (leukocytosis, leukopenia).

***Granular leukocytes (granulocyte, polymorphonuclear leukocyte)** are represented by **basophils, eosinophils and neutrophils**. In addition, there are **agranular leukocytes (agranulocyte; mononuclear)** – **lymphocytes and monocytes** in the peripheral blood.*

Basophils are cells about 10 μm (micrometer) in size, with a nucleus of an indefinite shape. The cytoplasm of the basophils turns purple. There are large granules with mediators of inflammation and allergic reactions in the cytoplasm of the basophils. There are *0-1% (up to 0.20×10^9/l) basophils in the peripheral blood of healthy adult people (Table 25-5).*

Eosinophils are cells of 12-15 μm in size with a bright yellowish-red (orange) round granularity and a nucleus segmented into two parts. Eosinophils are involved in the antiparasitic immune response and in the development of allergic reactions. *There are 0.5 - 5 % (0.04 - 0.45×10^9/l) eosinophils* in the peripheral blood of healthy adult people.

Neutrophils are round cells from 10 to 12 μm in size, with a pale pink cytoplasm and abundant fine granularity, colored pinkish blue or purple. Properties of neutrophils are migration (*chemotaxis*) to inflammation foci under the influence of the immunity mediators, an intensive phagocytosis of bacteria and cell debris (*microphagocytosis*), and an ability to *degranulation* (release the contents of their granules to the extracellular space), which leads to the death of the surrounding tissues and the formation of pus.

Table 25-5. Leukocyte formula (White blood cell differential)

Test /Normal values	Low test result	High test result
Absolute neutrophil count 1.8-7.8×10^9 / l	- similarly to leukopenia	- similarly to leukocytosis
Stab neutrophils 1 - 6 % (0.04–0.30×10^9/l)	- vitamin B_{12}- folate deficiency anemia; - radiation sickness; - after blood transfusion	- infectious inflammatory disease (e.g. pneumonia, pleurisy, myocarditis, sepsis); - chronic myeloid leukemia
Segmented neutrophils 47 - 72 % 2.0 - 5,5×109 / l	- infectious inflammatory disease (e.g. pneumonia, pleurisy, myocarditis, sepsis); - chronic myeloid leukemia	- vitamin B_{12}- folate deficiency anemia; - liver and kidney failure; - after blood transfusion
Eosinophils 0.5 - 5 % (0.02 – 0.45×10^9/l)	- acute infections (typhoid fever, dysentery, sepsis); - corticosteroid therapy; - myocardial infarction; - burns	- bronchial asthma, allergies ; - parasitic infections; - inflammatory disorders (celiac disease, inflammatory bowel disease); - chronic myeloid leukemia
Basophils 0 - 1 % (0 – 0.02×10^9 / l)	usually not medically significant	- rarely in allergic reactions; - inflammation (rheumatoid arthritis, ulcerative colitis); - chronic myeloid leukemia
Lymphocytes 18 - 40 % (1.2 – 3.5×10^9 /l)	- autoimmune disorders (e.g., lupus, rheumatoid arthritis); - infections (e.g., HIV, viral hepatitis, influenza, Covid-19, sepsis, tuberculosis); - acute and chronic myeloid leukemia; - renal failure; - radiation sickness; - corticosteroid therapy	- acute viral infections (e.g., chicken pox, cytomegalo-virus, Epstein-Barr virus, herpes, rubella); - bacterial infections (e.g., whooping cough, tubercu-losis, toxoplasmosis) ; - inflammatory diseases (e.g., ulcerative colitis); - lymphocytic leukemia, - acute stress
Monocytes 3 - 11 % (0.09–0.60 ×10^9/l)	- severe septic and purulent diseases; - bone marrow damage; - hairy cell leukemia; - aplastic anemia	- chronic infections (e.g., tuberculosis, fungal infections); - infective endocarditis; - autoimmune diseases (e.g., lupus, scleroderma, rheuma-toid arthritis, vasculitis) - monocyte or myelomono-cytic leukemia

There are *stab neutrophils (band neutrophils) and segmented neutrophils* in the normal peripheral blood. The former contain a nucleus in the form of a slightly curved rod, the latter – in the form of separate (from 2 to 5) round-shaped segments connected by the membrane of the nucleus.

In healthy adult people, *the peripheral blood contains 1-6% (0.04 - 0.3×10^9/l) stab neutrophils and 45-72% (2.0 - 5.5×10^9/l) segmented neutrophils.*

Lymphocytes are cells 7-10 μm in size from, with a round, oval or bean-shaped nucleus of blue-violet color and light blue cytoplasm. *Normal number of lymphocytes in the peripheral blood is 18- 40% (1.2 - 3.5×10^9 / l).*

Monocytes are the largest blood cells from 12 to 20 μm in size. They have a round, oval or bean-shaped core of red-violet color and a smoky (grayish-blue) cytoplasm with fine azurophilic granularity. *The normal number of monocytes in the peripheral blood is 3 - 11% (0.08 - 0.6×10^9/l).*

Diagnostic value of the leukocyte formula

The leukocyte formula in pathological conditions can undergo significant changes – an increase or decrease in the content of any type of the leukocytes or an appearance of the leukocyte forms, which are not normally found in the peripheral blood.

An increase in the number of basophils is designated as *basophilia (basophilic leukocytosis)*, eosinophils – as *eosinophilia (eosinophilic leukocytosis)*, neutrophils – as *neutrophilia (neutrocytosis, neutrophilic leukocytosis)*, lymphocytes – as *lymphocytosis (lymphemia, lymphocytic leukocytosis)*, monocytes – as *monocytosis*. A decrease in the number of these types of cells, respectively, is *eosinopenia, neutropenia, lymphopenia and monocytopenia.*

An increase or decrease in the number of certain types of the leukocytes can be absolute and relative. The change in the percentage does not always correspond to the fluctuation in absolute values, which must be taken into account when analyzing the leukocyte formula.

Basophilia is observed in chronic myeloid leukemia, polycythemia, allergic reactions (hives, food allergy), inflammation (rheumatoid arthritis, ulcerative colitis), uremia. Basophilia higher than 0.2×10^9/l in sequential blood tests requires the consultation of the hematologist, as it may be a sign of the onset of myeloproliferative disease.

Eosinophilia (higher than 0.45×10^9/l) occurs in allergic diseases (e.g. bronchial asthma, urticaria, Quincke's edema), parasitic infections (e.g. helminthic infestations, protozoal invasion), chronic myeloid leukemia, inflammatory diseases (e.g., celiac disease, inflammatory bowel diseases), and in infectious diseases (e.g., scarlet fever, tuberculosis, syphilis). A combination of the basophilia and eosinophilia (*basophil – eosinophil association*) may be in chronic myeloid leucosis.

Eosinopenia and eosinophils complete absence (*aneosinophilia*) are observed during the initial period of acute infections (typhoid fever, dysentery

sepsis). Eosinophilia in such cases is a good sign. Eosinopenia also occurs in cases of the corticosteroid therapy, acute myocardial infarction, burns.

Neutrophilia is observed in acute inflammatory and infectious diseases, purulent processes, various intoxications, tumors, acute myocardial infarction.

The right shift (right deviation) in the leukocyte formula is a decrease in the number of the stab neutrophils and an increase in the number of the most mature segmented neutrophils *(segmented neutrophilia)* with *hypersegmented nuclei* (e.g., in vitamin B_{12}- folate deficiency anemia, chronic kidney disease, liver failure, condition after blood transfusion, radiation sickness).

The left shift (left deviation) in the leukocyte formula means an increase in the number of the stab neutrophils and an appearance of the immature neutrophils with a round nucleus, which are normally present only in the bone marrow – *metamyelocytes (juvenile neutrophils) and* their precursors *myelocytes.* The especially strong left shift in the leukocyte formula (to *myelocytes, promyelocytes* and even *myeloblasts*) in combination with a significant leukocytosis is called *leukemoid reaction* as a leukemia is simulated.

A significant neutrophilia with the left shift may indicate the severity of the infectious inflammatory disease (e.g. pneumonia, pleurisy, myocarditis, sepsis). The maximum left shift (to myeloblasts) is observed in myeloproliferative diseases (chronic myeloid leukemia).

Neutropenia (less than 1.8×10^9/l) is observed in a number of infectious diseases (typhoid fever), viral infections (influenza, measles, rubella, viral hepatitis), under the action of the ionizing radiation, chemotherapy, in hemoblastosis (hematologic malignancy), and due to intake of the certain medications (e.g. non-steroidal anti-inflammatory, cytostatic drugs).

Agranulocytosis is a decrease in the level of neutrophils (granulocytes) less than 0.75×10^9/l. It is characterized by a severe clinical picture (ulcerative necrotizing stomatitis and tonsillitis, pneumonia, necrotizing enteropathy, and sepsis). Common causes of the agranulocytosis are immune and toxic reactions to medications (e.g., acetaminophen, metamizole, chloramphenicol, barbiturates, cytostatics), and radiotherapy.

Relative lymphocytosis is often observed in diseases accompanied by neutropenia.

Absolute lymphocytosis (higher than 5.0×10^9/l) occurs in infectious mononucleosis, acute and chronic lymphocytic leukemia, tuberculosis and some infections (adeno- and enterovirus infections, measles, rubella, chickenpox, whooping cough). *Physiological lymphocytosis* may occur in early childhood and due to the low-carbohydrate high-fat diet.

Relative lymphocytopenia (lymphopenia) can occur in patients with neutrophilia.

Absolute lymphocytopenia (less than 1.2×10^9/l) is observed in all diseases accompanied by the replacement of the normal lymphoid tissue with other cellular elements (lymphogranulomatosis, lymphosarcoma, acute and chronic myeloid

leukemia), as well as in uremia, sepsis, tuberculosis, radiation sickness, prolonged use of the glucocorticosteroid hormones.

Monocytosis indicates the development of pathological immune processes in the body. An increase in the number of monocytes with a simultaneous increase in neutrophils is observed in infective endocarditis, suppurative processes.

Absolute monocytosis (higher than 1.0 $\times 10^9$/l) is a characteristic of the infectious mononucleosis, leukemia, a myelodysplastic syndrome and requires a consultation with a hematologist. Minor monocytosis can be with chickenpox, mumps. *Monocytopenia* occurs in severe septic and purulent diseases.

Morphological changes of leukocytes

A microscopic examination of blood smears allows to detect morphological changes of the leukocytes.

An *increased size of the segmented and stab granulocytes* and *hypersegmentation of the neutrophils* (more than 5 segments of the nucleus) are characteristics of the vitamin B_{12}-folate deficiency anemia.

Toxic granulosity (toxic granulation) of neutrophils indicates the increasing severity of the pyoinflammatory and other diseases accompanied by severe intoxication (sepsis, abscess, radiation sickness, lobar pneumonia, etc.).

Vacuolization of the neutrophil's cytoplasm is a kind of "shot" through the cytoplasm due to the fatty degeneration of the cell. It is determined in a severe inflammatory process.

The most significant morphological changes are in leukemia. The leukocyte count can be reduced, normal and increased in patients with acute leukemia. Leukemia is characterized by the presence of the immature parental hematopoietic cells - *blasts (lymphoblasts, monoblasts, myeloblasts, erythroblasts, plasmablasts, megakaryoblasts)* and morphologically unrecognizable progenitor cells (*undifferentiated blasts*).

Blast crisis (leukemic relapse) in chronic leukemia is a rapid increase of the blast cells number in the peripheral blood.

Leukemic gaping (*hiatus leukemicus)* is the absence of maturing cells (e.g., promyelocytes, myelocytes) in the leukocyte formula in the presence of immature (blasts cells) and mature forms. It is a sign of the acute leukemia.

25.2. Study of hemopoietic organs

Bone marrow study

The complete blood count cannot reveal all possible pathology of the hemopoiesis.

The bone marrow study makes available a direct estimation of the blood cell precursors. Bone marrow specimens are taken by a sternal puncture or biopsy from the posterior ileum crest. The latter gives a more accurate information on the cellular composition of the red bone marrow.

The marrow specimen can find abnormal maturation *(dyspoiesis)* of the blood cells, changes in the total number of blood cell precursors, in a number of the juvenile forms, blast cells and primary undifferentiated precursors, and disproportion between the bone marrow red and white blood cells, and presence of the abnormal cellular forms.

A normal number of ***myelocariocytes*** *(bone marrow cells) varies in the wide range from 30-40×10^9 to 200×10^9 and more per 1 mm^3 (μL) of the bone marrow. The myelocaryocyte count less than 30×10^9/μL* may indicate hypoplastic conditions (e.g. hypo- or aplastic anemia, radiation sickness).

The ***leuko-erythroblastic ratio*** *(L/E)* of white blood shoot elements (L) to erythroid lineage (red blood shoot) elements (E) ranges from *2.1 to 4.5 in norm. L/E decreases to 0.3-0.5 in anemia. L/E increases to 6.0-8.0 in leukemia.*

The number of blasts in the bone marrow is 2-4%. An increase in their content up to 5-8% indicates myelodysplastic syndrome, up to 10-20% - low-percentage variants of the acute leukemia, up to 20% or more - typical acute leukemia.

The ***bone marrow biopsy is indicated in case*** of unexplained anemia, a suspected primary damage of the bone-marrow hemopoiesis (e.g, leukemia, lymphoma, aplastic anemia, cancer metastasis), and abnormalities of the two and more cell lineages (e.g., anemia when combined with leukopenia or thrombocytopenia).

Histochemical, cytogenetics and immune tests (to detect the immunophenotype) can be performed on the bone marrow specimens in hematologic malignancies or other tumors, and in congenital hemopoietic diseases.

Lymph node study

The lymph node biopsy is indicated in case of the localized lymphadenopathy when a malignancy is suspected, and if a generalized adenopathy does not resolve in 3 to 4 weeks.

The lymph node biopsy can verify the diagnosis of lymphoproliferative diseases (e.g. lymphoid leukemia, lymphogranulomatosis), and reveal metastases of tumors, etc.

Screening tests required for patients with an unexplained lymphadenopathy are complete blood count, chest x-ray, for generalized lymphadenopathy – a tuberculin skin test, serologic tests for HIV, mononucleosis, toxoplasmosis and syphilis. Patients with arthritis and/or skin rash should pass antinuclear antibody testing for systemic lupus erythematosus.

Internal lymph nodes (e.g., mediastinal, intraabdominal, retroperitoneal) can be examined by imaging studies (X-ray, ultrasonography, CT, MRI, scintigraphy).

Additional biochemical tests for evaluation of anemia:

- serum iron, ferritin, transferrin and iron-binding capacity of the blood serum – for diagnosis of the iron deficiency;
- serum vitamin B_{12} (cobalamine) and folate levels – in case of the macrocytic hyperchromic anemia;
- serum bilirubin (total and unconjugated bilirubin) and serum lactate dehydrogenase (LDH) are elevated in hemolytic anemia and normal in a blood loss; by contrast with the serum haptoglobin decreases in hemolysis. Reticulocyte count increases both in in hemolytic anemia and blood loss.

Immunophenotyping of peripheral blood and bone marrow cells

Immunophenotyping is an identification of cells, based on the types of antigens or markers on the surface of the cell. The process is used to diagnose specific types of leukemias and lymphomas.

Immunophenotyping uses reactions of the antibodies with cell antigens to determine a specific type of the cell in a sample of blood cells, bone marrow cells or lymph node cells. Surface antigenic structures on cells detected by monoclonal antibodies are called *clusters of differentiation (CD, clusters of differentiation)* such as T-lymphocytes (CD3), T-helpers (CD3, CD4), T-cytotoxic lymphocytes (CD3, CD8), activated T-cells (CD25), natural killer cells (CD57), pluripotent hematopoietic stem cells (CD34).

Flow cytometry is a technology that provides rapid multi-parametric analysis of single cells in solution using fluorochrome-labeled monoclonal antibodies that bind to certain CD.

Examples of the diagnostic CDs in leukemias: acute myeloid leukemia (CD13, CD33, CD34, CD117), acute lymphoblastic leukemia (CD19, CD20, and CD22), chronic lymphocytic leukemia (CD20, CD22, CD23). Assessment of the absolute number of CD34+ cells using flow cytometry is the gold standard for counting hematopoietic cells in myelodysplastic syndrome. A minimal residual disease (after treatment of the lymphoproliferative disease or acute leukemia) can be assessed by flow cytometry detection of the leukemia-associated immunophenotype. Flow cytometry helps to detect immunodeficiency (deficiency of cells which are responsible for different immune reactions), AIDS (decreasing of CD4+ cells).

25.3. Evaluation of the hemolysis

Physiologic hemolysis, which completes the life cycle of erythrocytes (about 120 days), occurs continuously in humans. Under physiological conditions, 0.8% of the total mass of erythrocytes undergo daily hemolysis. The final decomposition of the "aging" erythrocytes occurs mainly in the spleen.

Pathologic hemolysis is observed in hemolytic anemias, hemoglobinopathies, under the influence of hemolytic poisons (toxins of some bacteria, lead, arsenic, etc.), due to autoimmune antibodies, during transfusion of incompatible blood, rhesus disease (rhesus-factor incompatibility), exposure to

certain chemical agents, malaria. In pathological hemolysis, destruction of erythrocytes occurs in all cells of the reticuloendothelial system (*extravascular hemolysis* in the liver, bone marrow, lymph nodes, spleen, etc.), and can be in the vascular bed (*intravascular hemolysis*).

Extravascular hemolysis is present in most cases of the pathologic hemolysis. Intravascular hemolysis can be due to autoimmune disorders, disseminated intravascular coagulation, toxins (e.g., clostridial toxins, venomous snake or arthropod bite), mechanic damage (e.g., in defective mechanical heart valves, march hemoglobinuria), and temperature damage (burns, cold) to erythrocytes.

Anemia in combination with reticulocytosis is suspicious for pathologic hemolysis.

Pathologic hemolysis is confirmed by the following laboratory tests:

- elevated levels of the serum LDH and unconjugated bilirubin, reticulocyte count >2%, and decreased serum haptoglobin (Table 25-6).

Laboratory tests in the extravascular hemolysis show *negative urine hemosiderin and urine hemoglobin*; and peripheral blood smear can find *spherocytes (spherocytosis)* in congenital and autoimmune hemolytic anemias. An increased mean corpuscular hemoglobin concentration (MCHC) confirms presence of spherocytes.

Intravascular hemolysis is confirmed by the elevated urine hemosiderin and urine hemoglobin (*hemoglobinuria*), serum free hemoglobin (*hemoglobinemia*). The peripheral blood smear may show *schistocyte*s (erythrocytes fragments).

Table 25-6. Laboratory tests for evaluation of the hemolysis

Confirmation of hemolysis	Extravascular hemolysis	Intravascular hemolysis	Immune hemolysis
- serum LDH ↑; - unconjugated bilirubin ↑; - reticulocyte count ↑; - serum haptoglobin ↓	- spherocytes (+); - osmotic resistance of erythrocytes ↓; - urine hemoglobin (-); - urine hemosiderin (-)	- serum free hemoglobin (+); - schistocytes (+) - urine hemoglobin (+); - urine hemosiderin (+)	direct Coombs test (+)

The note: ↑ – elevated, ↓ – reduced, (+) – positive, (-) – negative.

If spherocytes present, a *positive direct antiglobulin test (DAT, or Coombs test to determine RBC-binding antibody)* identifies autoimmune hemolytic anemia. The negative DAT confirms hereditary spherocytosis (congenital microspherocytic hemolytic anemia). Hereditary spherocytosis is also characterized by a decreased *osmotic resistance* (*osmotic fragility*) test of erythrocytes.

25.4. Study of the hemostasis

Hemostasis *is a complex of the body reactions aimed to at the prevention and control of bleeding.*

Mechanisms of the hemostasis include a combined effect of the vascular factors, platelets and plasma coagulation factors.

A disturbed hemostasis can result in excessive bleeding or thrombosis due to the following abnormalities – platelet (thrombocyte) disorders, coagulation disorders and vascular wall defects.

There are many tests, which can reveal predisposition to bleeding or thrombus formation, to find their causes.

Platelet (thrombocyte) tests

Thrombocyte (platelet) count *associates well with a predisposition of the patients to bleeding.* The normal platelet count is 150.0-450.0×10^9/l (Table 25-7). The platelet count in the range of 50.0-120.0×10^9/l results in a mild prolongation of the bleeding time and a hemorrhage from a serious trauma. The platelet count in the range of 20.0-50.0×10^9/l commonly manifests by the skin purpura after a slight trauma and a contact mucosal bleeding (e.g., oral, nasal, postoperative hemorrhage). Patients with a platelet count less than 20.0×10^9/l, have multiple petechiae and mucosal hemorrhages, and a high risk of the life threatening spontaneous intracranial or other internal bleeding.

Table 25-7. Coagulation tests (coagulogram)

Test	Normal	Hypo-coagulation	Hyper-coagulation
Platelet function tests			
Bleeding time (by Duke's method)	2-4 minutes	↑	↓
Platelet count	150.0-450.0×10^9/l	↓	↑
Coagulation tests			
Coagulation time (Lee and White method)	5-10 minutes	↑	↓
Prothrombin time (PT)	11-16 seconds	↑	↓
International normalized ratio (INR)	0.85-1.35	↑	↓
Prothrombin (time) index (PTI)	93-104%	↓	↑
Activated partial thromboplastin time (APTT, PTT)	30-42 seconds	↑	↓
Thrombin time (TT)	12-16 seconds	↓	↑
Fibrinogen	1.8-4.0 g/l	↓	↑
D-dimer	<0.5 mcg/ml	-	↑

Bleeding time *is a first line test for identifying severe defects of the primary hemostatic plug (blood platelet thrombus) formation*. *The normal bleeding time (by Duke's method) is 2-4 minutes.* The bleeding time depends on the thrombocyte count, functional properties of the platelets, and the ability of the vascular wall to contract in response to the release of the platelet vasoconstrictor factor (serotonin).

The bleeding time is significantly elongated (more than twice as norm) in severe hemostasis defects (e.g., thrombocytopenia, Glanzmann's thrombasthenia, von Willebrand disease).

Thromboelastography (TEG) *is a laboratory technique to test both the platelet function and coagulation* by assaying parameters of the blood clot formation. TEG represents graphically the process of fibrin clot formation as well as fibrinolysis - its destruction. TEG is used to assess the risks of the thromboembolic events in surgical patients before a major operation (e.g. in transplantology, cardiovascular surgery, traumatology).

Coagulation tests (coagulogram)

Coagulation (clotting) time (according to Lee-White) is a measure of the clotting rate of the venous blood in a test tube. The blood coagulation time is the simplest general test for assessing *blood clotting ability on the whole without an estimation of separate coagulation phases.*

In norm, the coagulation time is 5-10 minutes. An increased coagulation time indicates a predisposition to excessive bleeding (e.g., hematomas, hemarthroses). The coagulation time increases due to a deficiency of the clotting factors (e.g., prothrombin, fibrinogen) that are involved in prothrombinase formation, or presence of the coagulation inhibitors in blood, in particular heparin.

Prolonged coagulation time occurs in:

- significant deficiency of plasma clotting factors or their congenital functional incompleteness (e.g., in hemophilias – factor VIII, IX, or XI deficiency);
- diseases of the liver with an impaired liver function (prothrombin and fibrinogen deficiency);
- vitamin K deficiency;
- treatment with heparin, and indirect anticoagulants;
- *DIC (disseminated intravascular coagulation) syndrome* in the hypocoagulable stage.

Decreased coagulation time indicates an increased risk of the thrombosis, and is observed in:

- hypercoagulable stage of the DIC syndrome;
- thrombosis and thrombophilias (conditions with a high risk of the active thrombosis);
- prolonged use of some medicines (contraceptive tablets, corticosteroids, vitamin K, etc.);

- high intake of the vitamin K with the food (liver, broccoli, chickpeas, green tea, kale, turnip and products that contain soybeans).

Prothrombin time (PT) *is a time of the clot formation after adding a tissue factor to the plasma*. PT evaluates the extrinsic and common pathways of the blood clotting (plasma factors VII, X, V, II [prothrombin] and fibrinogen). A *normal PT (11-15 seconds)* indicates that a normal amount of the prothrombin is available.

The increased PT indicates a hypocoagulation and a predisposition to excessive bleeding. *The reduced PT indicates a hypercoagulation* and a risk of the thrombosis.

International normalized ratio (INR) is used to monitor indirect anticoagulants therapy (e.g. warfarin). INR compensates differences in sensitivity of the various PT reagents to the effects of the warfarin. The INR is calculated by the formula:

$$INR = [Patient\ PT : Control\ PT]$$

The normal INR is 0.85-1.35. Therapy with oral anticoagulants (warfarin) requires a higher target INR in the range of 2.0-3.0.

The INR can also be used for monitoring abnormal blood clotting (e.g., in the liver diseases, DIC, vitamin K deficiency).

Prothrombin time index (PTI) is calculated by the formula:

$$PTI = (control\ PT) / (Patient\ PT) \times 100\%$$

PTI is the inverse estimator of the blood clotting ability. PT increases in hypercoagulation, and decreases in hypocoagulation.

Fibrinogen *is a coagulation factor I.* Fibrinogen is produced by the liver, and essential for the proper blood clot formation.

The normal serum fibrinogen is 1.8-4.0 g/l.

The fibrinogen increases in acute phase reactions (infection and inflammation), and decreases in the severe liver diseases and severe DIC.

Activated partial thromboplastin time (APTT, PTT) is used to the plasma for deficiencies of the all coagulation factors excepting factor VII and factor XIII. *The normal APTT is 30-42 seconds*.

Heparin prolongs the APTT, and the APTT is often used to monitor heparin therapy. The target level during the heparin therapy should be 1.5 to 2.5 times over than the patient's APTT before the treatment.

Unlike unfractionated heparin (UFH), the APTT test is not very informative for monitoring low molecular weight heparin (LMWH) therapy. The main way to measure the activity of LMWH is the study of the ***anti-Xa activity*** (reference range – 0.5-1.2 IU/ml). Results below the reference range may indicate insufficient effect, it is advisable to increase the dose. Results above 2 IU/mL may indicate overaction, it is advisable to reduce the heparin dose.

The ***von Willebrand factor (VWF)*** is a large multimeric glycoprotein that is synthesized by vascular endothelial cells, megakaryocytes of the bone marrow

(contained in α-granules of circulating platelets), and the subendothelial connective tissue. The two most important functions of the VWF are associated with hemostasis: 1) as a result of the contact with subendothelial structures (collagen), when vessels are damaged, VWF induces platelets adhesion and aggregation at the site of damage; 2) VWF carries coagulation factor VIII in the blood, protecting it from inactivation. Violation of these functions in VWF deficiency leads to a pathology of the blood clotting and a tendency to bleeding due to a defect in the formation of the platelet thrombus, and in severe cases to secondary factor VIII deficiency (which is clinically similar to hemophilia A).

Willebrand disease is the most common hereditary coagulopathy (with an incidence of 0.5% to 1% of the population) caused by a functional or quantitative deficiency of the VWF, which can be associated with abnormalities both directly in the VWF gene and other genes.

Coagulation factor IX (FIX), also called *antihemophilic globulin B* or *Christmas factor*, is a vitamin K-dependent serine protease. FIX participates in the coagulation cascade along the internal pathway, activating factor X (transfers the inactive form of the factor X into Xa), and thereby taking an active part in the formation of the tenase complex. Congenital FIX deficiency is the cause of the *hemophilia B (Christmas disease).*

Coagulation factor VIII (FVIII), also called antihemophilic globulin, is a plasma glycoprotein that belongs to the factors of the internal pathway of the plasma link of the coagulation cascade. FVIII is synthesized mainly in the liver, circulates in the blood as a complex with VWF, passes into the active form during blood coagulation and acts as a co-factor for FIX, greatly accelerating its activation. Congenital deficiency of the FVIII is the cause of the *hemophilia A.*

Antithrombin III is a glycoprotein synthesized mainly in the vascular endothelium and liver cells. It has the main inhibitory (anticoagulant) effect on the processes of the blood coagulation. This is the main plasma protein in the mechanism of the thrombin inactivation (up to 75% of the thrombin-inhibiting ability). A decrease in the level of the antithrombin III indicates the risk of the thrombosis.

Protein C is one of the most important physiological clotting inhibitors. In its active form, it cleaves and inactivates coagulation factors VIIIa and Va (except factor V Leiden). Protein C exhibits anticoagulant activity, indirectly activates fibrinolysis, and limits the size of the thrombus. Protein C is a vitamin K-dependent protein synthesized in the liver. Protein C deficiency is associated with a tendency to a thromboembolism. A decreased activity of the protein C is observed due to *congenital deficiency of the protein C, liver failure, and an increased consumption of the protein C in syndrome of the disseminated intravascular coagulation (DIC*).

Protein S is a cofactor of the protein C, which enhances its anticoagulant and profibrinolytic effects. It is a vitamin K-dependent protein synthesized in the liver and in endothelium cells. Protein S deficiency manifests as

thromboembolism. A decreased activity of the protein S is observed due to *congenital deficiency or defect of the protein S, liver failure, taking medications (anticoagulants, oral contraceptives), pregnancy, and in acute phase of inflammatory diseases.*

Clotting cascade tests

Thrombin time (TT) measures the final step of the clotting pathway, the conversion of fibrinogen to fibrin. *The normal TT is 12-16 seconds.*

The prolonged TT indicates the late stages of the DIC, the end-stage liver failure, and the heparin therapy.

D-dimer is a protein fragment of the fibrin degradation from the breakdown of a blood clot by fibrinolysis. *The normal plasma concentration of the D-dimer is less than 0.5 mcg/ml.*

An *elevated concentration of the D-dimer indicates an intravascular blood coagulation (e.g., venous thrombosis, pulmonary embolism, DIC).* D-dimer levels may also be elevated in the late pregnancy, inflammation, acute infections, malignancy, trauma, advanced liver diseases, a post-surgical period and in heart diseases (e.g. myocardial infarction, a chronic heart failure).

The *decreasing concentration of the D-dimer indicates an effective anticoagulant treatment*.

Tests in vascular hemostasis disorders

Diagnosis in most vascular bleeding disorders is confirmed by characteristic clinical manifestations (purpura, telangiectasia).

Microvascular hemostasis clinical tests (tourniquet test, pinch test, etc.) are not specific in vascular bleeding disorders (see Chapter 24. Clinical Examination of Patients with Blood System Diseases. Section 24.4. Detection of excessive bleeding)**.** *These tests are positive* in scurvy (vitamin C deficiency), vasculitis as well as with thrombocytopenic purpura and Waldenstrem's disease.

Results of the coagulation and platelet tests are usually normal.

Some laboratory test may help to identify systemic inflammatory and infectious diseases which can be complicated by hemorrhagic vasculitis:

- *elevated erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum immunoglobulins IgG and IgA – in inflammatory disorders of various origin;*

- *reduced complement levels* (total hemolytic complement CH100, CH50, C3, and C4 levels) may be in systemic lupus erythematosus (SLE) or urticarial vasculitis;

- *serologic tests (e.g., antinuclear antibody [ANA]; antineutrophil cytoplasmic antibody [ANCA], rheumatoid factor*) are positive in vasculitis due to autoimmune pathology and connective tissue systemic diseases;

- *anti-streptolysin 0 (ASO) – a* serologic test for a possible streptococcal infection;

- *hepatitis B surface antigen (HBsAg), antibody to hepatitis C virus (anti-HCV) and HCV-RNA* – serologic tests for possible acute and chronic virus hepatitis B and C infection;

- *serum protein electrophoresis* to detect *paraproteinemia* (e.g., in myeloma, acute myeloblastic leukemia, amyloidosis) and *cryoglobulinemia* (e.g., in virus and bacterial infections, autoimmune diseases, lymphoproliferative diseases).

25.5. The key points of the theme "Laboratory and Instrumental Examination of Patients with Blood Diseases"

Anemia is a pathological condition characterized by a decreased number of erythrocytes and/or hemoglobin content in a blood volume unit due to hemopoietic factors deficiency (e.g. iron, vitamin B_{12}, folate deficiency), hemorrhage, hemolysis, and the bone marrow hypo- and aplasia.

Erythrocytosis is an increase in the number of red blood cells (e.g. in polycythemia vera, secondary erythrocytosis due to a chronic hypoxia).

Changes in the size, shape, color of erythrocytes make it possible to establish the nature of the anemia: ***anisocytosis (macrocytosis, microcytosis)*** is a change in the size of the erythrocytes; ***poikilocytosis*** is a change in the shape of the erythrocytes *(e.g., spherocytes, ovalocytes);* changes in the color of erythrocytes *(**hypochromia, hyperchromia, polychromatophilia**).*

Reticulocytosis (an increased reticulocyte count) indicates an intensified erythropoiesis (e.g., in an acute blood loss and hemolysis). ***Reticulocytopenia*** (a decreased reticulocyte count or complete absence of reticulocytes in the blood) shows an inadequate erythropoiesis (e.g., in hypo- and aplastic anemia).

ESR rises with increased amounts of the immunoglobulins and acute phase proteins that are present in inflammatory conditions, autoimmune pathology, and malignant disease (e.g. cancer, sarcoma, leukemia, lymphoma).

Thrombocytopenia is a reduced platelet count in the peripheral blood. A significant thrombocytopenia ($<20\times10^9$/l) may result in bleeding complications.

Thrombocytosis is an increased platelet count. Thrombocytosis leads to a feebleness (slowdown) of the circulation and tendency to thrombi formation.

Leukocytosis is an increased white blood cells count in the peripheral blood (inflammatory and purulent diseases, sepsis, a tissue necrosis, intoxications, bronchial asthma and acute allergy). The most pronounced leukocytosis is observed in leukemia.

Leukopenia is a reduced number of the white blood cells in the peripheral blood. Leucopenia increases a risk of the potentially life-threatening infections.

Leukocyte formula *is the percentage ratio of every forms of the leukocytes.* The leukocyte formula can undergo significant changes in pathological conditions (e.g., in acute inflammation – *neutrophilia and left deviation of the leukocyte formula*, acute allergy and parasitic infections – *eosinophilia,* leukemia - *blast cells)*.

*The **bone marrow study** makes available a direct estimation of the blood cell precursors.* The ***bone marrow biopsy*** is indicated in case of the unexplained anemia, a suspected primary damage of the bone marrow hemopoiesis (e.g., leukemia, lymphoma, aplastic anemia, cancer metastasis), and in abnormalities of the two and more blood cell lineages (e.g., anemia when combined with leukopenia or thrombocytopenia).

The ***lymph node biopsy*** is indicated in case of the localized lymphadenopathy when a malignancy is suspected, and if a generalized lymphadenopathy does not resolve in 3 to 4 weeks.

Pathologic hemolysis is confirmed by elevated levels of the serum unconjugated bilirubin and LDH, reticulocytosis (>2%), and a decreased serum haptoglobin.

Hemostasis is a complex of the body reactions aimed at the prevention and control of bleeding. A disordered hemostasis can result in an excessive bleeding or thrombosis due to the following abnormalities – platelet (thrombocyte) disorders, coagulation disorders and vascular wall defects.

Hypocoagulation characteristic tests include increased coagulation time, bleeding time and prothrombin time (PT); international normalized ratio (INR), activated partial thromboplastin time (APTT), and decreased prothrombin (time) index (PTI),serum fibrinogen, and platelet count.

Hypercoagulation characteristic tests include decreased coagulation time, bleeding time and prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (APTT), and an increased D-dimer, platelet count, PTI, thrombin time (TT), serum fibrinogen.

25.6. Assessment tests on the theme "Laboratory and Instrumental Examination of Patients with Blood Diseases"

1. Hemoglobin value of females in norm is:

1. 90-120 g/l;
2. 100-115 g/l;
3. 120-145 g/l;
4. 145-165 g/l;
5. 180-200 g/l.

2. Hemoglobin value of males in norm is:

1. 80-100 g/l;
2. 100-115 g/l;
3. 120-145 g/l;
4. 135-165 g/l;
5. 165-185 g/l.

3. Leukocyte count varies in norm varies in the following interval:

1. $2.0\text{-}6.0 \times 10^9$/l;

2. 4.0-8.5 × 10^9/l;
3. 5.0-10.0 × 10^9/l;
4. 10.0-14.5 × 10^9/l;
5.15.0-20.0× 10^9/l.

4. Erythrocyte count of males in norm is:
1. 2.5-4.0 × 10^{12}/l;
2. 3.5-5.0 × 10^{12}/l;
3. 4.0-5.5× 10^{12}/l;
4. 5.0-8.5 × 10^{12}/l;
5. 9.0-12.0 × 10^9/l.

5. Erythrocyte count of females in norm is:
1. 2.5-4.0 × 10^{12}/l;
2. 3.5-4.7 × 10^{12}/l;
3. 4.0-5.5× 10^{12}/l;
4. 5.0-8.5 × 10^{12}/l;
5. 9.0-12.0 × 10^9/l.

6. Deviation of the differential blood count (leukocyte formula) to the left is:
1. increased number of the band neutrophils and appearance of the juvenile neutrophils, or their precursors – myelocytes in the leukocyte formula;
2. increased number of the mature neutrophils, i.e. segmented neutrophils;
3. increase in the number of eosinophils and basophils;
4. increase in the number of lymphocytes;
5. increase in the number of monocytes.

7. Deviation of the differential blood count (leukocyte formula) to the right is characterized by:
1. appearance of the juvenile neutrophils, or their precursors - myelocytes in the leukocytic formula;
2. decreased number of the stab neutrophils and an increased number of the segmented neutrophils (segmented neutrophilia) with hypersegmented nuclei;
3. increase in the number of band neutrophils;
4. increase in the number of lymphocytes and monocytes;
5. increase in the number of eosinophils and basophils.

8. Deviation of the differential blood count (leukocyte formula) to the left presents in:
1. radiation sickness;
2. acute inflammatory diseases;
3. purulent infection;

4. chronic myeloid leukemia;
5. vitamin B_{12}-deficiency anemia.

9. Deviation of the differential blood count (leukocyte formula) to the right presents in:

1. acute inflammatory diseases;
2. radiation sickness;
3. condition after blood transfusion;
4. chronic myeloid leukemia;
5. vitamin B_{12}-deficiency anemia.

10. What values of the color index are correct in assessment of anemia:

1. normochromic anemia (0.85—1.05);
2. hypochromic anemia (less than 0.85);
3. hyperchromic anemia (more than 1.1);
4. hypochromic anemia (less than 1.15);
5. hyperchromic anemia (more than 1.25).

11. What is the correct evaluation of the reticulocyte count?

1. reticulocyte count >1,5% indicates highly intense erythropoiesis;
2. reticulocyte count equals 0.5 -1.5% in norm;
3. reticulocyte count <0,2% indicates an impaired erythropoiesis;
4. reticulocyte count >2% indicates an impaired erythropoiesis;
5. reticulocyte count equals 10-25% in norm.

12. What are correct values of the blood tests in anemia?

1. RBC in females $< 3.5 \times 10^{12}$ /l;
2. RBC in males $<4.0 \times 10^{12}$ /l;
3. RBC in both males and females $< 4.5 \times 10^{12}$/l;
4. hemoglobin in females <120.0 g/l;
5. hemoglobin in males <135.0 g/l;
6. hemoglobin in both males and females <140 g/l.

13. What is true of the platelet (thrombocyte) count?

1. normal number of platelets is 50×10^9/l - 450×10^9 /l;
2. normal number of platelets is 150×10^9/l - 450×10^9 /l;
3. platelet count $<20 \times 10^9$ /l has a great risk of bleeding complications;
4. platelet count $<150 \times 10^9$ /l has a great risk of bleeding complications;
5. platelet count $>450 \times 10^9$ /l has a risk of thrombi formation.

14. What are correct values of the erythrocyte sedimentation rate (ESR) by Panchenkov capillary method?

1. normal ESR for men is 2-10 mm/hour;

2. normal ESR for men is 4-15 mm/hour;
3. normal ESR for women is 2-10 mm/hour;
4. normal ESR for women is 4-15 mm/hour;
5. normal ESR for women is 20-30 mm/hour.

15. What is the correct evaluation of the erythrocyte sedimentation rate (ESR) by Panchenkov capillary method?

1. ESR increases with age >50 years, and it is higher in females;
2. ESR decreases with age >50 years, and it is higher in males;
3. ESR increases in erythrocytosis;
4. ESR increases in anemia;
5. ESR increases in inflammatory diseases.

16. What is correct for leukocyte formula in leukemic gaping (hiatus leukemicus)?

1. maturing cells (e. g., promyelocytes, myelocytes) in the absence of immature (blasts) and mature cells (band and segmented neutrophils);
2. no maturing cells (e. g., promyelocytes, myelocytes) in the presence of immature (blasts) and mature cells (band and segmented neutrophils);
3. leukocyte formula contains no band and segmented neutrophils;
4. it is a sign of the acute leukemia;
5. it is a sign of the chronic leukemia.

17. Bone marrow study is indicated for the diagnosis of:

1. unexplained anemias;
2. bone marrow malignancy (e. g., leukemia, lymphoma, cancer metastasis);
3. abnormalities of the two and more cell lineages (e.g., anemia when combined with leukopenia or thrombocytopenia);
4. in any cases of anemias;
5. in bone diseases.

18. Laboratory tests for diagnosis of hemolysis include:

1. anemia;
2. reticulocyte count >2%;
3. elevated level of hemoglobin
4. elevated level of the blood serum unconjugated bilirubin;
5. elevated level of the blood serum LDH;
6. elevated level of the serum haptoglobin.

19. What is true of the bleeding time?

1. bleeding time is <2 minutes in thrombocytopenia;
2. bleeding time is <2 minutes in plasma coagulation factors deficiency;

3. bleeding time is >5-10 minutes in thrombocytopenia;
4. bleeding time is >5-10 minutes in coagulation factors deficiency;
5. bleeding time is >5-10 minutes in thrombocytosis.

20. What is true of the coagulation time?

1. coagulation time is >15 min in platelet disorders (e.g. thrombocytopenia);
2. coagulation time is >15 in plasma clotting factors deficiency (e.g.);
3. coagulation time < 5 min indicates an increased risk of the thrombosis;
4. coagulation time >15 min indicates an increased risk of the thrombosis;
5. coagulation time >15 min indicates a risk of the excessive bleeding.

21. What is correct of the prothrombin time (PT)?

1. PT > 16 sec indicates a hypocoagulation state;
2. PT <11 sec indicates a hypercoagulation state;
3. vitamin K extends PT;
4. vitamin K reduces PT;
5. PT <11 sec is a laboratory sign of the severe liver failure.

22. What are characteristic tests of hypocoagulation conditions?

1. prothrombin index (PTI) <70%;
2. serum fibrinogen < 1.8 g/l;
3. activated partial thromboplastin time (APTT) <30 sec;
4. bleeding time >15-20 minutes;
5. platelet count $<20 \times 10^9$ /l;
6. platelet count $>150 \times 10^9$ /l;

23. What are characteristic tests of hypercoagulation conditions?

1. platelet count <50 × 109 /l;
2. prothrombin index (PTI) >110%;
3. serum fibrinogen > 4.0 g/l;
4. activated partial thromboplastin time (APTT) >70 sec;
5. D-dimer > 0.5-1.0 mcg/ml;
6. coagulation time>15 minutes.

24. Leukemoid reaction characteristics are:

1. a strong left shift in the leukocyte formula (to myelocytes, promyelocytes and even myeloblasts);
2. leukocytosis greater than $40.0\text{-}50.0 \times 10^9$/l;
3. the causes are severe infections, intoxications, malignancies;
4. increased number of the mature (segmented and band) neutrophils;
5. the cause is leukemia.

CHAPTER 26. Clinical Syndromes of the Blood Diseases

Goals: to enable students to learn –

clinical symptoms and laboratory and instrumental signs of the basic clinical syndromes in the blood diseases –anemia, sideropenic and sideroahrestic syndromes, funicular myelosis, myelodysplastic syndrome, hemorrhagic syndrome, and hemoblastosis.

26.1. Syndrome of the anemia

Definition: *Anemia is a pathological syndrome due to a decreased number of erythrocytes and/or hemoglobin content in a volume unit of the blood.*

Anemic syndrome is characterized by general clinical manifestations associated with an inadequate oxygen supply to the organs and the tissues, and compensatory changes in the respiratory and cardiovascular systems including changes in laboratory tests.

Causes. There are three *basic causes of the anemia: (1) blood loss* due to hemorrhages, (2) *disordered erythropoiesis* due to the deficiency of the erythropoetin (in a chronic kidney disease), nutritional deficiency (iron-, vitamin B_{12} and folic acid), in endocrine thyroid and pituitary failure, and red bone marrow damage (hypo- and aplastic anemia), *(3) and excessive hemolysis* (erythrocyte destruction).

Classification of anemia

I. ***According to the causes:***

1. *Posthemorrhagic anemia* - due to the loss of the blood (*acute and chronic*);

2. Anemia due to disordered erythropoiesis:

- *iron-, vitamin B_{12} - , folic acid deficiency anemia,*
- *hypo- and aplastic anemia* due to the inhibition of the bone marrow by toxicosis, radiation, metastasis, hemoblastosis, immunologic abnormalities, infection;
- *sideroachrestic* (iron refractory) anemia;

3. *Hemolytic anemia* - due to excessive hemolysis (*congenital and acquired*)ж

4. Anemia with mixed causes.

II. ***According to a hemoglobin saturation of erythrocytes***:

- *normochromic anemia* (color index – 0.85-1.05; MCH – 27-33 pg) in an acute blood loss and acute hemolysis, anemia of the chronic inflammation;
- *hypochromic anemia* (color index less than 0.85; MCH < 27 pg) in the iron-deficiency and chronic (less acute) posthemorrhagic anemia;

- *hyperchromic anemia* (color index more than 1.1; MCH >33) in vitamin B_{12}-, folic acid deficiency anemia.

III. ***According to the regenerative capacity of the bone marrow:***

- *hyperregenetaive anemia* (reticulocyte count – >20 ‰) in hemolytic anemia, acute and chronic blood loss, response to the treatment of the anemia;
- *regenerative anemia* (reticulocyte count – 5-20 ‰) ;
- *hyporegenerative anemia* (reticulocyte count – <5 ‰) in hypoplastic anemias or a nutritional (e.g., iron, vitamins B_{12} or folate) deficiency;
- *aregenerative, or aplastic anemia* (reticulocyte count – 0 ‰) in bone marrow malignancy, red bone marrow aplasia.

IV. ***According to the erythrocyte size:***

- *microcytic anemia* (MCV < 80 μm);
- *normocytic anemia* (MCV – 80-96 μm);
- *macrocytic anemia* (MCV >96 μm);

V. ***According to the degree of the anemia****:*

- *mild anemia* (hemoglobin 110-90 g/l),
- *moderate anemia* (hemoglobin 90-70 g/l),
- *severe anemia* (hemoglobin <70 g/l).

Common clinical manifestations in all types of anemia

Patient complaints *are due to an inadequate oxygen supply to the peripheral tissues and compensatory changes in the respiratory and cardiovascular systems*: general weakness, dizziness, buzzing in ears (tinnitus), seeing dark spots in one's vision (flickering "flies" in front of the eyes), disorders of an attention and memory, a pronounced drowsiness, irritability, heart palpitations, shortness of breath, fainting spells (syncope).

Certain complaints may indicate causes of anemia. The blood loss is indicated by an epistaxis (nasal bleeding), melena, hematochezia (bloody stool), hematemesis (bloody vomit), pneumorrhagia (cough with bloody sputum), macrohematuria, and menorrhagia. Gastrointestinal complaints (e.g., abdominal pains or discomfort, diarrhea, constipation) can be due to such underlying diseases as peptic ulcer, celiac disease, ulcerative colitis, and others.

Objective examination

A general inspection shows pallor of the skin and mucous membranes. A pale face does not always reflect the degree of anemia, so three areas should be examined – the inferior eyelid conjunctiva, and the skin nail beds and palms of the hands.

There are tachypnoe, tachycardia and arterial hypotension in patients with moderate and severe anemia due to a compensatory response of the respiratory and cardiovascular systems. The heart auscultation can reveal a functional systolic murmur over all points due to a reduction of the blood viscosity. Finally, severe cases of the anemia can result in the heart failure or shock.

Symptoms and signs associated with chronic anemia depend on the age of the patient and the adequacy of the blood supply to critical organs. *Mild anemia is most often recognized by abnormal screening laboratory tests.*

Objective examination can find the signs of the underlying diseases. Severe malnutrition suggests cancer. Jaundice and splenomegaly may suggest hemolysis. Splenomegaly and systemic lymphadenopathy may be in the case of the leukemia, cancer, systemic infections (e.g. sepsis, infective endocarditis, HIV). A considerable hepatomegaly occurs in liver cirrhosis, hepatic cancer, hepatic metastases, myeloid leukemia.

Common laboratory criteria of all types of anemia*:*

- *hemoglobin – female <120,0 g/l, male<130,0 g/l;*
- *RBC (erythrocyte count) – female <3,5×10^{12}/l, male <4,0×10^{12}/l;*
- *leukocytopenia, thrombocytopenia or pancytopenia (a low content of all blood-forming elements) may be in severe anemia*.

Clinical and laboratory features of most common variants of the anemic syndrome are represented in Table 26-1.

Laboratory tests in anemia

Complete blood count shows *erythrocytopenia* and changes of the size, shape and coloration of erythrocytes, *hemoglobinopenia*; and *pancytopenia* (*leukocytopenia, thrombocytopenia*). It can occur in severe anemia. Hemoglobin saturation of erythrocytes is estimated by the colour index and MCH.

Reticulocyte count *increases more than 1,5% in hemolytic anemia and in acute and severe bleeding*. A normal reticulocyte count and reticulocytopenia in anemia indicates a failure of the bone marrow to respond appropriately.

Biochemical tests *are applied for the evaluation of anemia*:

- the *iron deficiency* is confirmed by decreased levels of the serum iron, ferritin and elevated iron-binding capacity of the blood serum ;
- the cause of the *macrocytic hyperchromic anemia* is found by decreased serum vitamin B_{12} (cobalamine) and folate levels;
- *hemolytic anemia* characteristics are elevated serum bilirubin (total and unconjugated bilirubin) and serum lactate dehydrogenase (LDH), and decreased serum haptoglobin.

Bone marrow aspiration and biopsy provide a direct observation of the erythroid activity and maturation of the erythrocyte precursors; abnormal maturity (dyspoiesis) of the cells; and a cellular pattern of the iron content. The *myelocaryocyte count less than 30×10^9 /μL may indicate hypoplastic conditions (e.g. hypo- or aplastic anemia).* The *leuko-erythroblastic ratio (L/E) decreases by 0.3-0.5 in anemia.*

Anemia can develop due to leukemia. *The association of the anemic syndrome with hemoblastosis is recognized after the bone marrow biopsy*. The number of blasts increases in leukemia.

Subsequent laboratory and instrumental studies to identify the possible causes of the anemia should include:

- liver and kidney function tests;
- thyroid hormones (in case of the normochromic and macrocytic anemia);
- biochemical inflammatory markers (e.g., CRP);
- an occult blood stool test;
- chest X-ray, gastrointestinal endoscopy, abdominal ultrasonography;
- pelvic exam for women.

Table 26-1. Clinical and laboratory variants of the anemic syndrome

Variant	Causes	Clinical features	Laboratory tests
Acute posthemorr-hagic anemia	profuse bleeding (trauma, peptic ulcer, etc.)	dizziness, tachypnea, tachycardia, arterial hypo-tension, pulse of the poor volume	normochromia, in 3-7 days hypochrormia, reticulocytosis
Iron deficiency anemia	iron deficiency in food, due to pregnancy, lactation, alimentary tract pathology, and occult bleeding	a sideropenic syndrome	hypochromia, microcytosis, decreased serum iron and ferritin
Sideroachres-tic (iron-utilization, or sidero-blastic) anemia	hereditary, toxic (lead, alcohol. etc.), systemic connective tissue diseases, tumours, infection	hemosiderosis (dark grey skin, diabetes melli-tus, hepatosple-nomegaly, car-diomegaly)	hypochromia, elevated serum iron and ferritin, ring sideroblasts in bone marrow
Vitamin B_{12}-folic acid deficiency anemia (pernicious anemia)	vitamin B_{12} and/or folic acid deficiency in food, alimentary tract pathology (e.g., atrophic gastritis, enteropathy, helminthosis, malabsor-ption syndrome), liver failure	a syndrome of fu-nicular myelosis, Hunter's glossitis	hyperchromia, macrocytosis, megaloblasts in bone marrow, hypersegmented neutrophils
Hemolytic anemia	immune pathology, toxicosis, congenital erythrocytopathy and hemoglobinopathy	a syndrome of hemolytic jaundice, splenomegaly	↑ free bilirubin, reticulocytosis, ↓ RBC osmotic fragility, (+) Coombs test
Hypo- and aplastic anemia	immune pathology, toxicosis, radiation, cancer metastasis, leukemia, chronic kidney disease	hemorrhagic syndrome, tissue necrosis, secondary infection	pancytopenia, reticulocytosis, ↓ erythroid and myeloid precur-sors in marrow

Note: ↑ – increase, ↓ – decrease, (+) – positive test.

26.2. Sideropenic syndrome

Definition: A sideropenic syndrome *is a clinical and laboratory condition of the iron-deficiency.*

Causes of the sideropenic syndrome include iron deficiency in food, pregnancy, lactation, a gastrointestinal tract pathology (e.g., a malabsorption syndrome, inflammatory bowel diseases, a postgastrectomy syndrome), occult bleeding (e.g., a peptic ulcer disease, hemorrhoids, premenopausal women).

Clinical picture

- *an anemic syndrome* represents most manifestations of the iron deficiency;
- *a perverted taste* (*pica* to egg, dirt, paint, etc.) *and smell sense* (pleasure smelling substances with unusual odor as ether, petrol, etc.);
- c*heilosis* (angular stomatitis) - fissures at the corners of the mouth;
- *atrophic glossitis* means that the papillae of the tongue are leveled, burning in the tongue may occur;
- *dryness of the skin*;
- *koilonychia* is a spooning of the fingernails in severe cases of the iron-deficiency. The nails become flat, sometimes spoon-like, opaque, marked by transverse folds;
- *sideropenic dysphagia* (described by Plummer and Vinson) is rarely found.

Laboratory tests

Serum iron (Fe) and iron-binding capacity should both be tested because their relationship is important. ***Serum Fe concentration decreases in the iron deficiency*** *(<13.0 mcmol/l in males, and < 11.0 mcmol/l in females),* and increases in hemolytic anemia and iron overload conditions (>17.0 mcmol/l in males, and < 25.0 mcmol/l in females). The ***iron-binding capacity is increased in the iron deficiency*** *(>81 mcmol/l)* but reduced in anemia of the chronic disease, while the *transferrin saturation decreases < 20%.*

Serum ferritin is an Fe-storage glycoprotein that exists as a tissue-specific isoferritin. Serum ferritin concentrations closely correlate with the total body Fe. The normal range is 30 to 300 mcg/l. ***The low serum ferritin (< 12 mcg/l) is characteristic of the iron deficiency.***

The elevated concentrations serum ferritin presents in the iron overload. Serum ferritin may be falsely elevated in iron deficiency due to hepatocellular injury (hepatitis, liver cirrhosis), malignancy (e.g., acute leukemia, Hodgkin lymphoma, and gastrointestinal tract cancer) or the presence of an acute-phase response in inflammatory and infectious diseases.

A general blood count shows hypochromic and microcytic anemia.

Bone marrow biopsy. Normally 40 to 60% of developing erythroblasts (called *sideroblasts*) have visible ferritin granules. There are few or no sideroblasts in the iron deficiency.

Diagnosis of the sideropenic syndrome is confirmed by;

• *hypochromic and microcytic anemia;*
• *decreased serum iron and ferritin concentrations.*

26.2. Sideroachrestic syndrome

Definition: A sideroachrestic syndrome (*iron-utilization anemia, or sideroblastic anemia*) is caused by abnormal utilization of the intracellular iron for hemoglobin synthesis, despite adequate or increased amounts of iron.

Causes. *The causes are hereditary (due to one of the X-linked or autosomal mutations) and acquired (primary and secondary).*

The *primary cause is the myelodysplastic syndrome* (a group of the bone marrow disorders characterized by hypercellular or hypocellular bone marrow with a dysplasia of the blood cell precursors, pancytopenia in the blood count and a high risk of the acute myeloid leukemia).

Secondary causes are due to drugs (antibiotics, isoniazid, hormones, copper-chelating agents, and cytostatic agents), toxins (e.g. lead), alcohol abuse, copper and pyridoxine (vitamin B_6) deficiencies, chronic inflammatory and neoplastic diseases.

Clinical features. In addition to the common manifestations of the anemic syndrome, there are refractoriness (ineffectiveness) of conventional treatments (iron, vitamin B_{12} and folic acid supplementation), symptoms of the myelodysplastic syndrome (see below Section 26.4. Myelodysplastic syndrome), and (in some of patients) chronic iron overload with by an increased focal or generalized iron deposition in the tissues (*hemosiderosis*).

Hemosiderosis is manifested clinically by a skin hyperpigmentation (dark grey skin,) *bronzed diabetes (or hemochromatosis*), diabetes mellitus, hepatosplenomegaly with abnormal liver function tests, cardiomegaly with a heart failure and arrhythmia.

Laboratory features.

A common blood count shows commonly microcytic or normocytic and hypochromic anemia. Variation in the erythrocytes size (dimorphism) usually results in a high RBC distribution width (RDW). There are red blood cells with iron inclusions (*siderocytes*). Reticulocytopenia presents. *Pancytopenia* may occur in a myelodysplastic syndrome.

Biochemical blood tests show *elevated serum iron and ferritin concentrations.* Serum lead should be examined in an unknown cause of the sideroblastic anemia.

A bone marrow examination is necessary. There is erythroid hyperplasia in the bone marrow. Fe-staining reveals *ringed sideroblasts that contain iron inclusions.*

Diagnosis of the sideroachrestic syndrome is confirmed by:

- *refractory microcytic and hypochromic anemia, reticulocytopenia;*
- *increased serum iron and ferritin concentrations;*
- *ringed sideroblasts in the bone marrow.*

26.3. Syndrome of the funicular myelosis

Definition: Syndrome of the funicular myelosis *(subacute combined degeneration of the spinal cord)* represents neurology manifestations due to the losses of the myelin in the lateral and posterior columns of the spinal cord.

Causes are vitamin B_{12} (cobalamin) deficiency in most cases, and copper or vitamin E deficiency less often. The vitamin B_{12} deficiency may develop due to the dietary deficiency (vegetarian diet), malabsorption in terminal ileum (e.g., Crohn disease, after ileum resection), decreased production of the gastromucoprotein (*Castle's intrinsic factor*) in gastric pathology (e.g., atrophic gastritis, adenocarcinoma of the gastric body, after gastrectomy), intestinal parasitosis (*Diphyllobothrium latum*), chronic administration of some medicines (e.g., ranitidine, proton pump inhibitors, metformin).

Clinical manifestations

A syndrome of the funicular myelosis is usually associated with B_{12}– deficiency anemia. The neurologic symptoms can occasionally precede the hematologic abnormalities (or occur in their absence, particularly if folic acid has been taken). The onset of the syndrome is gradual and uniform.

Clinical signs of the funicular myelosis are:

- numbness (skin anesthesia), tingling and weakness in the extremities (the earliest neurological manifestations);
- sphincter disturbances (urinary and bowel incontinence may occur);
- the gait is often affected due to bilateral spastic paresis (a partial spastic loss of the voluntary movements of lower extremities) and ataxia (a lack of the voluntary coordination of muscle movements);
- reflexes may be diminished or increased, the knee reflex disappears;
- position, pressure, vibration and touch senses are usually diminished;
- vision disorders may occur;
- mental disorders may vary wildly (from mild irritability and forgetfulness to severe anxiety, depression, dementia or psychosis).

Prolonged vitamin B_{12} deficiency leads to irreversible abnormal changes of the nervous system due to an axonal degeneration and eventual neuronal death.

Laboratory and instrumental tests confirm diagnosis of the funicular myelosis by:

- *serum vitamin B_{12} levels <110 pmol/l (or <160 pg/ml);*
- *macrocytic and hyperchromic anemia, anisocytosis, poikilocytosis and hypersegmented neutrophils in common blood count;*
- *an increased mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH);*
- *megaloblasts in the bone marrow;*

- *MRI can show a symmetrical hypersignal lesion in the posterior columns of the spinal cord.*

26.4. Myelodysplastic syndrome

Definition. Myelodysplastic syndrome (MDS) is a group of hematological disorders characterized by cytopenia associated with dysplasia (abnormal morphology) of at least one hematopoietic lineage cells, an ineffective blood cell production, and a risk of transformation to acute myeloid leukemia. MDS is a clonal hematopoietic stem cell disorder leading to impaired cell proliferation and differentiation.

Causes of MDS include exposure to potentially mutagenic factors [e.g., radiation, intoxication (benzene), immunosuppressive treatment, chemotherapy, smoking] and rare genetic abnormalities [e.g., trisomy 21 (Down syndrome), Fanconi's anemia].

Clinical features

MDS mainly occurs in older adult males (> 50 years) with history of the previous chemotherapy or radiation exposure.

Clinical manifestations of MDS are non-specific. The most characteristic symptoms are due to a refractory anemia (see Section 26.1. The Syndrome of anemia). Other manifestation are due to undiagnosed cytopenia: excessive bleeding and hemorrhagic rash – in thrombocytopenia; necrotization of the tissues and recurrent secondary infections (e.g. sepsis, pneumonia, pus formation) – in neutropenia.

A physical examination shows the signs of the anemia. Pyoderma, petechiae and purpura may result from cytopenia. Splenomegaly and lymphadenopathy occur in some cases (about 20% of patients).

Common blood count always detects macrocytic or normocytic anemia associated in the majority of cases with neutropenia and/or thrombocytopenia. *Pancytopenia* (anemia in combination with thrombocytopenia and leukopenia) occurs in up to 50% of cases. Reticulocytopenia is common. Thrombocytopenia is found in one fourth of the patients. Leukopenia due to absolute neutropenia presents in half of the patients, and thrombocytopenia. Myelocytes and myeloblasts (<20%) may be in the peripheral blood.

Blood smears represent features of erythrocytes dysplasia (e.g., polychromatophilia, poikilocytosis, anisocytosis, ovalomacrocytosis, elliptocytosis, intracellular inclusions in erythrocytes – Jolly bodies, basophilic aggregations) and *leukocytes dysplasia* (e.g., dysmorphic or bilobed neutrophils, granulocytes with reduced or absent segmentation).

Bone marrow biopsy commonly reveals *hypercellular bone marrow (myelocaryocyte count > 200×10^9 / μL of the bone marrow)*. The granulocyte precursors number may be increased. There are maturation arrests at the myelocyte stage. *Granulocytic precursors may be with dysplastic features* (e.g., enlarged size, abnormal nuclear size and shape, and granulation changes).

Leuko-erythroblastic ratio (L/E) often decreases to 0.3-0.5 in MCD (in norm 2.1 – 4.5). *Dysplastic features of the erythroid precursors* include a large size, an abnormally enlarged nuclear size and shape; the cytoplasm eosinophilia, basophilia, and vacuolization; and the *ring sideroblasts* containing mitochondria laden with iron.

The *number of blast cells in the bone marrow is increased* (2-4 % in norm) in MSD but with an insufficient level (< 20%) for definite diagnosis of the acute myeloblastic leukemia.

Diagnosis of the MSD should be considered in any patient with unexplained refractory anemia and confirmed by the bone marrow study.

Diagnosis of the MSD is confirmed by:

- *refractory anemia associated with neutropenia and/or thrombocytopenia (cytopenia) in the peripheral blood, and normocellular or hypercellular bone marrow ;*
- *dysplastic features of the RBC and WBC in the blood and the bone marrow;*
- *an increased number of blast cells (5% – 19%) in the bone marrow, but with an insufficient level for definite diagnosis of the acute leukemia.*

26.5. Hemorrhagic syndrome

Definition. Hemorrhagic syndrome (bleeding diathesis; hemorrhagic diathesis) is characterized by the tendency to spontaneous and excessive bleeding, and repeated hemorrhages.

Causes. *Hemorrhagic syndrome develops from the following abnormalities – platelet (thrombocyte) disorders, coagulation disorders and vascular wall defects* (Table 26-2). Hemorrhagic disorders may be acquired or hereditary.

The major causes of *acquired coagulation disorders* are vitamin K deficiency, a liver failure (e.g., in liver cirrhosis, fulminant hepatitis, acute fatty liver of pregnancy), disseminated intravascular coagulation, and a high dose indirect anticoagulants (warfarin).

The most common *hereditary coagulation disorders* are the hemophilias A and B (due to factors VIII and IX deficiency) and von Willebrand disease because of deficiency of von Willebrand factor (VWF; VWF is secreted by vascular endothelium and promotes the platelets adhesion).

An acquired hemorrhagic syndrome due to disorders of vascular hemostasis occurs in hemorrhagic vasculitis (Henoch-Schönein disease), vitamin C deficiency (scurvy), some infections (e.g. sepsis, epidemic typhus, virus hemorrhagic fevers, leptospirosis), allergy, and autoimmune diseases. *Hereditary hemorrhagic diathesis due to vascular wall abnormalities* most common occurs in Rendu-Osler-Weber disease (hemorrhagic telangiectasia) and Ehlers-Danlos syndrome (hereditary collagen disorder).

Disorders of platelets (thrombocytes) results in excessive bleeding because of *thrombocytopenia* [e.g., due to *decreased platelet production* – in leukemias, aplastic anemia; and *increased platelet destruction or consumption* – in hypersplenism, medications (e.g., heparin, quinidine, quinine, sulfonamides), immune thrombocytopenia, infections (sepsis, HIV), and *thrombocytopathy (an inadequate platelet function)* due to antiplatelet medications (aspirin, clopidogrel), uremia, von Willebrand disease, myeloproloferative disorders.

Table 26-2. Basic clinical-laboratory variants of the hemorrhagic syndrome

Charac-teristics	Disorders of plasma factors of coagulation	Disorders of platelets (thrombocytes)	Disorders of vascular hemostasis
Causes	hemophilia A, B, C, von Willebrand disease, liver failure, vitamin K deficiency, indirect anticoagu-lants, DIC	thrombocytopenic purpura; thrombocytopathy; hypersplenism; medications	hemorrhagic vascu-litis; vitamin C deficiency; Rendu-Osler-Weber disease; allergy, infections
Onset of the bleeding	delayed (hours or days) onset of bleeding after trauma	immediate onset of bleeding after trauma	delayed (hours or days) onset of the bleeding after aller-gy, viral infection
Character of the hemor-rhage	deep tissue hemor-rhage (subcutaneous, muscle, brain , retroperitoneum he-matomas), hemarthrosis	multiple skin (petechiae and ecchymoses) and mucosa hemor-rhages (nasal, oral); GI and GU internal bleeding	purpuric skin elevated (palpable) rash at the extensor surfaces; GI and GU bleeding; telangiectasias
History	family history, male, <18 years (in hemophilia A, B); intake of indirect anticoagulants (warfarin)	family history; viral infection; autoimmune patho-logy; medications (e.g. aspirin, clopidogrel), autoimmune diseases	acute infections, supercooling, autoimmune and allergy disease
Laborato-ry features	coagulation time > 15 min; ↓ plasma factors VIII, IX,XI, etc.; bleeding time is normal (3-5 min)	bleeding time>15 min; platelets $<30\times10^9$ /l; capillary permea-bility changes (tourniquet and pinch tests)	capillary per-meability changes (tourniquet and pinch tests); ↑ γ-globulins, im-mune complexes, CRP

Note: ↑ – increase, ↓ – decrease, (+) – positive test, GI – gastrointestinal, GU – genitourinary, DIC - disseminated intravascular coagulation.

Clinical picture

Subjective examination

The general symptoms of the hemorrhagic syndrome are external and internal hemorrhages into various organs and tissues and secondary anemia. There is spontaneous bleeding from mucous membranes (any part of the oral cavity, nose); spontaneous or at little external causes, which otherwise would never provoke bleeding in a normal individual (e.g., a push, mild contusion, pinch, injection), skin hemorrhages and internal bleeding of various localization (e.g., gastrointestinal tract, urogenital region, lungs, uterus, kidneys).

When collecting the *history of the present disease*, it is important to clarify the nature of the bleeding onset of (e.g. localization, duration, immediate onset of the bleeding after injury or delayed, triggering factors - trauma, infection, allergies, prior taking anticoagulants, antiplatelet and some other medications).

A review of the systems allows you to identify not so obvious symptoms of the hemorrhagic diathesis (easy formation of bruises, bleeding gums when brushing teeth, minor nasal bleeding, excessive menstruation, etc.).

Past life history can provide the information about the conditions associated with platelet defects or coagulation disorders, such as severe infections, HIV infection, liver cirrhosis, a malabsorption syndrome, cancer, hematological malignancy (e.g. leukemia, multiple myeloma), systemic connective tissue diseases (e.g. systemic lupus erythematosus), a renal failure, prior excessive or unusual bleeding or blood transfusions, and pregnancy.

Familial predisposition to excessive bleeding is characteristic of the hemophilia and von Willebrand disease.

The *drug history* should be carefully reviewed for medications that may interfere with blood clotting (e.g., heparin, warfarin, direct oral inhibitors of thrombin or factor Xa, such as apixaban, edoxaban, rivaroxaban) or a platelet function (e.g. aspirin, clopidogrel, non-steroidal anti-inflammatory drugs), or cause thrombocytopenia (e.g., heparin, quinidine, quinine, sulfonamides).

Objective examination

The *most common sign is the skin and mucous membranes hemorrhages* (see Chapter 24. Section 24.2. An objective examination of patients in diseases of the blood system, Fig. 24.1, Table 24-2). The bleeding type assessment has a certain diagnostic value. *Petechiae and mucosal (e.g. nasal, gingival) bleeding are characteristics of the thrombocytopenia, hematomas – coagulation factor deficiencies* (e.g. hemophilias A and B), *purpura – hemorrhagic vasculitis*, *ecchymoses – clotting problems* (e.g., von Willebrand's disease), *mixed type bleeding* (petechiae /ecchymoses and hematomas with a predominance of the first) – *disseminated intravascular coagulation*. *Hemorrhagic telangiectasias present in Rendu-Osler-Weber disease* (hereditary arteriovenous malformations in the skin, mucous membranes, and internal organs).

The deeper tissues bleeding may be found by a local swelling and tenderness, a reduced volume of movements. The intracranial bleeding may be

manifested by a headache, confusion, vomiting, stiffness of the neck, loss of vision and other focal neurologic abnormalities.

Clinical features of basic variants of the hemorrhagic diathesis are represented in Table 26-2.

Laboratory and instrumental tests

The most primary screening tests of the primary hemostatic system are (1) bleeding time (a sensitive measure of the platelet function), (2) coagulation time (for assessing blood clotting ability) and (3) thrombocyte count. Patients with normal thrombocyte count need an advanced study of hemostasis (see Chapter 25. Section 25.4. Study of hemostasis*).*

Laboratory diagnosis of the hemorrhagic syndrome is confirmed by*:*

- *bleeding time >15 min* is the first line test for identifying thrombocytopenia and defects of the primary hemostatic plug (blood platelet thrombus) formation*;*
- *thrombocytopenia* $<50.0\times10^9/l$*;*
- *coagulation time (Lee and White method)* > 15 min is the first line test for identifying coagulation factors deficiency*;*
- *coagulogram with indicators of clotting factors:*

- activated partial thrombin time (APTT) > 50 sec;
- prothrombin index (PTI) < 0.7;
- international normalized ratio (INR) > 2;
- thrombin time - > 20 sec;
- fibrinogen < 1 g/l.

The bone marrow (puncture biopsy) study is indicated to confirm the bone marrow cause of thrombocytopenia if the platelet count persists or increases with repeated blood tests.

Diagnosis in most vascular bleeding disorders is confirmed by characteristic clinical manifestations (purpura, telangiectasia).

Microvascular hemostasis clinical tests (tourniquet test, pinch test, etc.) are not specific in vascular bleeding disorders (see Chapter 24. Clinical Examination of Patients with Blood Diseases. Section 24.4. Detection of the excessive bleeding). These tests are positive in scurvy (vitamin C deficiency), vasculitis as well as with thrombocytopenic purpura and Waldenstrem's disease. Results of the coagulation and platelet tests are usually normal.

Some laboratory test may help to identify systemic inflammatory and infectious diseases, which may result in hemorrhagic vasculitis: an elevated erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum immunoglobulins IgG and IgA, and reduced complement levels.

26.6. Syndrome of the hemoblastosis

Definition: Hemoblastosis (hematologic malignancy) – is the term for the definition of the group of tumors originating from the hematopoietic cells.

Hematopoietic system cells of varying degrees of maturity are the substrate for hematologic malignancies.

*Pathogenetic characteristics of the hemoblastosis**:***

- uncontrolled hemopoietic cell growth;
- inhibition of the normal hematopoiesis;
- early metastasis.

Hematologic malignancies include myeloproliferative and lymphoproliferative diseases.

Myeloproliferative diseases are characterized by an increased production of myeloid cells (granulocytes, monocytes, erythrokaryocytes, megakaryocytes) belonging to the tumor clone.

Lymphoproliferative diseases are characterized by an increased production of lymphoid cells (T- and B-lymphocytes) belonging to the tumor clone.

Risk factors for hemoblastosis are an exposure to radiation, intoxication (benzene, some pesticides, polyaromatic hydrocarbons in tobacco smoke), chemotherapy with certain antineoplastic agents (e.g., alkylating agents, topoisomerase II inhibitors, hydroxyurea), virus infections (e.g. Epstein-Barr virus), myelodysplastic syndrome, and rare genetic abnormalities [e.g., trisomy 21 (Down syndrome), Fanconi's anemia].

Classification of the hemoblastosis

Depending on the systemic or regional disorder of the hematopoietic tissue, hematologic malignancies are subdivided into 2 main groups:

1. ***Leukemia (leucosis)*** is a type of the hemoblastosis originating in the bone marrow. Leukemia is characterized by primary or secondary bone marrow involvement with suppression of the normal bone marrow hematopoiesis, and spreading into organs and systems.

Leukemias are classified according to the cellular maturity:

a. ***acute leukemia*** is a disease at which there are a malignant transformation and an explosive growth of the young blast cells. The substrate of the tumor represents cells of the first four classes of the hematopoiesis scheme (blast cells), and mature cells also present.

b. ***chronic leukemia*** is the disease at which there is a development of tumoral cells reaches maturing and differentiated mature forms: leukocytes, erythrocytes (fifth and sixth classes of the hematopoiesis scheme).

2. ***Lymphomas*** are characterized by a primary tumor growth outside the bone marrow in the reticuloendothelial and lymphatic systems.

The major types are Hodgkin lymphoma and non-Hodgkin lymphoma.

Malignant lymphoma (non Hodgkin lymphoma, hematosarcomas) is a group of diseases which belong to the localized tumors in the lymphoreticular sites, including the lymph nodes, the bone marrow, the spleen, the liver, and the gastrointestinal tract.

Hodgkin lymphoma (lymphogranulomatosis, or Hodgkin's disease) is a malignant lymphoma, which affects a lymphatic system with the following tumor changes of the non-lymphatic tissues and organs.

Clinical picture of the hemoblastosis is characterized by a combination of the following syndromes – anemic, hemorrhagic, infectious-toxic, systemic lymphadenopathy, hepatosplenomegaly.

The diagnosis is based on morphological and cytochemical studies of the bone marrow and/or lymph nodes.

***Leukemia is the most common variant of the hemoblastosis*.**

Classification of the leukemia

I. According to hemopoietic abnormalities:

1. Acute leukemia – acute lymphoblastic leukemia;
   - acute myeloid leukemia;
2. Chronic leukemia – chronic myeloid leukemia,
   - chronic lymphocytic leukemia,
   - chronic erythromyelosis,
   - polycythemia vera, and others

II. According to a stage:

- an initial (latency) stage,
- exacerbation (pronounced clinical and hematological symptoms),
- a stage of clinical and hematological remission,
- a terminal stage,
- recovery.

III. *According to quantity of pathological cells in the peripheral blood:*

- a leukemic form - significant increase (>50.0-100.0×10^9 /l);
- a subleukemic form – moderate increase (9.0-50.0×10^9 /l);
- a aleukemic form - normal or decreased quantity of the white blood elements (<9.0×10^9/l).

Clinical picture of the leukemia *is not specific and includes one or more syndromes* (Table 26-3):

Anemic syndrome – hypo-aplastic anemia due to the suppression of the normal blood cell formation and/or bone marrow replacement by leukemic cells.

Hemorrhagic syndrome – skin, nasal, oral hemorrhages, gastrointenstinal bleeding, hemoptysis, metrorrhagia, hematuria due to thrombocytopenia.

Ulceronecrotic syndrome– ulcerogangrenous stomatitis, necrotizing ulcerative gingivitis, necrotic tonsillitis and dermatitis due to agranulocytosis.

Septic syndrome – a high persistent fever, septic foci (abscess, phlegmon, suppurative inflammation), severe bacterial infections (pneumonia, meningitis, pyelonephritis) due to agranulocytosis.

Hepatosplenomegaly syndrome - due to the liver and/or spleen infiltration by leukemic cells.

Systemic lymphadenopathy syndrome – a symmetrical enlargement of ≥2 groups of the lymphatic nodes, painless, elastic, and movable due to the infiltration by the leukemic cells.

Table 26-3. Basic clinical-laboratory variants of the leukemia

Cytology variant	Clinical features	Common blood count	Bone marrow features
Acute myeloid leukemia	- any age; - anemia; - hemorrhagic syndrome; - splenomegaly; - fever	-↑↑WBC; - myeloblasts; -"hiatus leukemicus"; - anemia; - lympho- and -monocytopenia; - thrombocytopenia	↑↑ myeloid precursors, leukemic cell karyotype
Acute lymphoblastic leukemia	- juvenile age; - fever; - anemia; - systemic lymphadenopathy; - hemorrhagic syndrome; - splenomegaly, - central nervous system involvement	- ↑↑WBC; - lymphoblasts; -"hiatus leukemicus"; - anemia; - granulocytopenia; - thrombocytopenia	↑↑ lymphoid precursors
Chronic myeloid leukemia	- adulthood; - anemia; - subfebrile fever; - spleno- and hepatomegaly; - skin leukemic infiltration; infections	- ↑↑WBC (entire myeloid forms series); - basophilic-eosino-phylic association; - anemia; - lympho-, mono-, thrombocytopenia	- ↑↑ myeloid precursors; - Philadelphia (Ph) -chromo-some
Chronic lymphocytic leukemia	- middle and old age; - systemic lymphadenopathy; - splenomegaly; -lymphoid infiltration of skin and etc.; - anemia; - infection	-↑↑ WBC (precursor and differentiated lymphoid forms); - Botkin- Gumprecht cells ("shadows"); - anemia; - granulo-and thrombocytopenia	- ↑↑ lymphoid hyperplasia

Note: ↑↑ – increase.

A laboratory examination includes a general blood count and peripheral blood smear (leukocyte formula), a bone marrow examination (bone marrow biopsy and myelogram), and histochemical studies, cytogenetics, immunophenotyping, and molecular biology studies.

Acute leukemia is characterized by (1) the presence of the blast cells and "hiatus leukemicus" (absence of the premature differentiating cells) in leukocyte formula, (2) anemia, (3) thrombocytopenia, (4) prevalence of the blast cells (>40-60%) in myelogram.

Chronic leukemia is characterized by (1) presence of the blast cells and premature cells of the differentiated hemopoiesis in leukocyte formula, (2) anemia, (3) thrombocytopenia, (4) infiltration of the bone marrow by pathologic premature differentiating cells of the hemopoiesis (lymphoid or myeloid metaplasia of the bone marrow).

Diagnosis of the leukemia

Provisional diagnosis of the leukemia is based on (1) a typical clinical picture and (2) typical changes of the complete blood count (see Table 26-3).

The definitive clinical diagnosis should be confirmed by the results of the bone marrow biopsy and analysis (*myelogram), e.g.* an increase of the blast cells and L/E ratio, lymphoid or myeloid metaplasia of the bone marrow.

Histochemical studies, cytogenetics, immune and molecular biological studies of the bone marrow samples provide an identification of certain variants of the leukemia, which is important for prescribing appropriate therapy.

26.7. The key points of the theme "Clinical Syndromes of the Blood Diseases"

Anemia *is characterized by a decreased number of erythrocytes (female <3.5×10^{12}/l, male <4.0×10^{12}/l)) and/or hemoglobin content (female <120.0 g/l, male<130.0 g/l) in a volume unit of the blood*.

Symptoms and signs of anemia are not specific: fatigue, weakness, pale skin and visible mucous membranes, dyspnea and tachycardia on exercise. *Additional laboratory tests* can determine the cause and type of anemia: *reticulocytosis* – in hemolytic and acute posthemorrhagic anemia; *decreased serum iron and ferritin*– in iron-deficiency anemia; *decreased serum vitamin B_{12} and folate* – in macrocytic hyperchromic anemia; *elevated serum total and unconjugated bilirubin* – in hemolytic anemia; *the bone marrow biopsy* can indicate hypoplastic conditions (e.g. hypo- or aplastic anemia) and confirm the association of the anemic syndrome with hemoblastosis.

Sideropenic syndrome *is a clinical-laboratory condition of the iron-deficiency.* Diagnosis of the sideropenic syndrome is confirmed by hypochromic and microcytic anemia, and decreased serum iron and ferritin concentrations.

Sideroachrestic syndrome is a clinical-laboratory condition of the abnormal iron utilization for hemoglobin synthesis, despite adequate or increased amounts of the iron. *Sideroachrestic syndrome is confirmed* by refractory

microcytic and hypochromic anemia, reticulocytopenia; increased serum iron and ferritin concentrations, and *ringed sideroblasts* in the bone marrow.

Syndrome of the funicular myelosis represents neurology manifestations of the vitamin B_{12} deficiency due to losses of the myelin in the lateral and posterior columns of the spinal cord. The neurologic symptoms can occasionally precede the macrocytic anemia.

Myelodysplastic syndrome is a group of hematological disorders characterized by refractory anemia associated with neutropenia and/or thrombocytopenia in peripheral blood, and dysplastic features of the RBC and WBC in the blood and bone marrow with a risk of transformation to leukemia.

Hemorrhagic syndrome (bleeding diathesis; hemorrhagic diathesis) is characterized by the tendency to spontaneous and excessive bleeding, and repeated hemorrhages due to platelet (thrombocyte) disorders, coagulation disorders and vascular wall defects.

Hemorrhagic syndrome is confirmed by increased bleeding time (>15 min) and coagulation time (Lee and White method > 15 min); activated partial thromboplastin time (APTT> 50 sec), international normalized ratio (INR>2), and a decreased prothrombin index (PTI < 0.7), serum fibrinogen (< 1 g/l.) and platelet count ($<50.0\times10^9$/l). *Diagnosis in most vascular bleeding disorders* is confirmed by characteristic clinical manifestations (purpura, telangiectasia).

Leukemia is the most common variant of the hemoblastosis, which is characterized by the bone marrow involvement with suppression of the normal hematopoiesis, and spreading into organs and systems.

The clinical picture of the leukemia is not specific and it includes one or more syndromes – anemic, hemorrhagic, necrotic, septic, hepatosplenomegaly and system lymphadenopathy.

Diagnosis of the leukemia is based on (a) blast cells and premature cells of the differentiated hemopoiesis in leukocyte formula, and (2) data of the bone marrows study (e.g. an increase of the blast cells and L/E ratio, lymphoid or myeloid metaplasia of the bone marrow).

26.8. Assessment tests on the theme "Clinical Syndromes of the Blood Diseases"

1. Syndrome of the anemia is characterized by:

1. hemoglobin level - female <120.0 g/l, male<130.0 g/l;
2. erythrocyte count - female $<3.5\times10^{12}$/l, male $<4.0\times10^{12}$/l;
3. leukocyte count - $<3.8\times10^9$/l;
4. thrombocyte count - $<160\times10^9$/l;
5. ESR (erythrocyte sedimentation rate) <15 mm/h.

2. It is characteristic of vitamin B_{12}-deficiency anemia:

1. weakness and giddiness;

2. reflexes may be diminished or increased, the knee reflex disappears;
3. paresthesias, paralyses;
4. Hunter glossitis;
5. constipation and diarrhea.

3. The typical syndromes of the leukemia are:
1. anemic;
-2. malnutrition;
3. septic;
4. systemic lymphadenopathy;
5. edema;
6. ulceronecrotic.

4. Basic laboratory differences between vitamin B_{12}-deficiency anemia and iron-deficiency anemia are as follows:
1. microcytosis;
2. decrease of the hemoglobin;
3. hypochromia;
4. hyperchromia
5. macrocytosis.

5. The hemorrhagic syndrome is characteristic of such diseases as:
1. hemophilia;
2. acute leukemia;
3. chronic leukemia;
4. cholecystitis;
5. pyelonephritis.

6. The Following syndromes are characteristic of the hemoblastosis:
1. cerebral syndrome;
2. hemorrhagic syndrome;
3. systemic lymphoadenopathy;
4. anemia;
5. jaundice;
6. infectious-toxic syndrome;

7. What values of the color index are true in the assessment of the anemia:
1. normochromic anemia (0.85—1.05);
2. hypochromic anemia (less than 0.85);
3. hyperchromic anemia (more than 1.1);
4. normochromic anemia (1.05—1.25);

5. hypochromic anemia (less than 1.15);
6. hyperchromic anemia (more than 1.25).

8. Types of anemia according to a regenerative capacity of the bone marrow:

1. regenerative anemia – reticulocyte count>2%;
2. regenerative anemia – reticulocyte count – 25%;
3. hyporegenerative anemia – reticulocyte count equals <0.5%;
4. hyporegenerative anemia – reticulocyte count equals 10-25%;
5. aregenerative anemia - reticulocyte count<10%;
6. aregenerative anemia - reticulocyte count equals 0 ‰.

9. The degree of anemia according to a hemoglobin (Hb) level:

1. mild (Hb >110-120 g/l);
2. mild (Hb is not less 90 g/l);
3. moderate (Hb 70-90 g/l);
4. moderate (Hb 90-110 g/l);
5. severe (Hb<70 g/l);
6. severe (Hb is not less 90 g/l).

10. What are the characteristics of the sideropenic syndrome?

1. decrease of the Serum Iron and Ferritin ;
2. increase of the Serum Iron and Ferritin;
3. decrease of the Total Iron-Binding Capacity of the blood serum;
4. increase of the Total Iron-Binding Capacity of the blood serum;
5. decrease or absence of the ringed sideroblasts in bone marrow;
6. hyperchromic macrocytic anemia;
7. hypochromic microcytic anemia.

11. What are the characteristic clinical manifestation of the sideropenic syndrome?

1. perverted taste;
2. cheilosis (angular stomatitis);
3. atrophic glossitis;
4. koilonychia (spooning of the fingernails;)
5. dysphagia;
6. geographic tongue;
7. funicular myelosis.

12. What are the characteristics of the sideroachrestic syndrome?

1. decrease of the serum Iron and Ferritin;
2. Increase of the Total Iron-Binding Capacity of the blood serum;
3. increase of the serum Iron and Ferritin;

4. ringed sideroblasts in bone marrow;
5. normo- or hyperchromic anemia;
6. hypochromic and microcytic refractory anemia.

13. What are the characteristics of hemorrhagic syndrome in thrombocytopenia?

1. immediate onset of bleeding after trauma;
2. delayed (hours or days) onset of bleeding after trauma
3. mucosa hemorrhages (nasal, gastrointestinal, urinary);
4. bleeding time >15-20 min;
5. platelet count $<30 \times 10^9$ /l;
6. platelet count $>150 \times 10^9$ /l;
7. coagulation time >15-20 min.

14. What are the characteristics of a hemorrhagic syndrome in disorders of the coagulation plasma factors?

1. immediate onset of bleeding after trauma;
2. delayed (hours or days) onset of bleeding after trauma;
3. hematomas;
4. petechiae and ecchymoses
5. coagulation time>15 min;
6. bleeding time is normal (3-5 min);
7. bleeding time >15-20 min.

15. What are the characteristics of a hemorrhagic syndrome in the hemorrhagic vasculitis?

1. delayed (hours or days) onset of bleeding after allergy, supercooling, viral infection;
2. immediate onset of bleeding after trauma;
3. purpuric skin rash at the extensor surfaces;
4. hematomas;
5. capillary permeability changes (pinch test);
6. coagulation time >15-20 min.

16. What platelet count in blood is typical of thrombocytopenic purpura?

1. $<30\times10^9$/l;
2. $60\text{-}120\times10^9$/l;
3. $120\text{-}180\times10^9$/l ;
4. $180\text{-}320\times10^9$/l;
5. $320\text{-}480\times10^9$/l.

Unit VIII. Endocrine System and Locomotor System Examination

CHAPTER 27. Clinical, Laboratory and Instrumental Examination of Patients with Endocrine System Diseases

Goals: to enable students to learn –

1. Subjective examination (inquiry) of patients with endocrine system diseases, and interpretation of the obtained results;
2. Technique of the objective examination in endocrine system diseases, and its diagnostic value;
3. Laboratory and instrumental examination of patients with endocrine system diseases, and their diagnostic value.

27.1. Subjective examination (inquiry) of patients with endocrine system diseases

Complaints. Endocrine system has multiple effects on various body functions, and patient's complaints are therefore varied (a general condition, the central nervous system, the cardiovascular system, the gastrointestinal tract and other organs).

First of all, a patient should be asked about *changes in his/her general condition.* Patients may complain of general weakness, loss of a working capacity, fatigue, sweating, feeling hot or chilly, fever, changes in appetite, thirst, weight loss or weight gain.

The inquiry may reveal *neuropsychiatric features* that are characteristic of some endocrine diseases: e.g., fussiness, rapid movements, hasty speech, excitability, interrupted and superficial sleep, impaired memory, irritability suggest *hyperthyroidism*; while tiredness, weakness, difficulty concentrating and poor memory, feeling cold, impaired hearing – *hypothyroidism*.

A private interview about the sexual function requires a clarification of the following questions:

- a sexual desire (normal, increased, decreased, absent);
- a sexual function in men (normal, increased, decreased, absent);
- a menstrual cycle in women (duration, regularity, pain during menstruation, nature of menstrual discharge - abundant, not abundant, scanty).

This part of the interview requires certain conditions for the conversation (in a separate room in private, or if this is not possible, you can talk in the ward, asking the other patients to leave for a while), a special tact and approach, a trustworthy attitude.

Characteristics of the questioning patients with hyperthyroidism:

In hyperthyroidism, it is easy to notice an agitated state, restlessness, fidgeting and hurrying, which is reflected in the lively, impetuous and stumbling speech of the patients. The patient complains of the intermittent shallow sleep, diminished memory, irritability, ringing of the ears, blood rushes to the head, itching of the skin.

Manifestations of the hyperthyroidism may by a general weakness, sweating, trembling hands, the weight loss despite an increased appetite, heart palpitations, a mood swing (lability), muscle weakness, a subfebrile fever.

The patients with an enlarged thyroid gland may complain of the difficulty in swallowing and food passage via the esophagus (dysphagia), an inspiratory dyspnea, hoarseness of the voice, and a pressure sensation in the neck area.

Sexual weakness may also occur in males, menstrual disorders – in females. Some patients report on an unstable stool with a tendency to diarrhea.

Characteristics of the questioning patients with hypothyroidism:

It is noted an apathy and sluggishness of the patient in hypothyroidism (*myxedema*). There are a monotonicity and a slow delivery of the speech (*bradyphrasia*), and a diminished hearing. The patient's voice is hoarse and deep. Complaints of a general weakness, a constant feeling cold and chills, fatigue, performance degradation, a sharp decrease in memory, drowsiness, a low mood, an indifference to his/her surroundings, mental deficiency are the symptoms of the hypothyroidism. There is a growth and mental retardation in childhood and adolescents. The patients often report on an edema, dry skin, and hair loss, a weight gain despite lack of the appetite, constipation, and a sexual dysfunction.

Characteristics of questioning the patients with diabetes mellitus:

The patients complain of thirst and drinking a lot of fluid (*polydipsia*), an increased appetite (*polyphagia*), an excessive urinary excretion (*polyuria*), persistent furunculosis, skin itching especially in the perineal region.

In severe decompensation of the diabetes mellitus, patients complain of the general and muscle weakness, an increased appetite, followed by a sharp decrease in the appetite. The weight loss occurs in the type 1 diabetes mellitus, an obesity and overweight meanwhile are possible in the insulin-independent diabetes mellitus.

Patients with diabetes insipidus (due to antidiuretic hormone deficiency) characteristically complain of the thirst with drinking large amounts of fluid (up to 15 liters per day), polyuria with large amounts of colorless urine (up to 10-12 liters per day), heaviness in the epigastrium (due to constant overloading of the stomach with water), dry skin, a sharp decrease in sweating and salivation headaches, insomnia, and increased irritability.

Patients with chronic adrenal insufficiency (Addison disease, or *bronzed disease, or hypocorticism)* complain of the persistent progressive weakness, weight loss, decreased appetite, along with a taste for salty foods. Nausea, vomiting, an abdominal pain may occur. The patients may note a brown

pigmentation of the skin with a bronze tint (on exposed areas, in the areas where clothes rub, natural folds, postoperative scars).

In Cushing disease (due to hypersecretion of the adrenocorticotropic hormone; ACTH) and Cushing syndrome (due to glucocorticosteroids excess), complaints of the bone pains, spine pain, headaches, sleep disorders, thirst (in the development of the steroid diabetes) are characteristic. The patients may note changes in appearance and overweight (a moon-shaped face, the excessive development of subcutaneous fat on the trunk, with relatively thin limbs), red stretch marks on the skin of the lateral surfaces of the trunk and hips (*stria*), dry skin, and excessive hair on the face and trunk.

Anamnesis. Special attention should be paid to the past life history of the individual, and to the family and hereditary anamnesis. The course of the physical and mental development from since childhood onwards and the life periods that have already passed (puberty, menopause, and elderly age) must be clarified in sequence. Endocrine diseases often develop during a sexual maturation (puberty), after childbirth, and during menopause. A hereditary factor is also important in endocrine diseases, e.g. in diabetes mellitus.

It is important to identify the immediate factors that precede the onset of the disease. Pathology of some organs can affect endocrine glands function. Chronic pancreatitis leads to diabetes mellitus, and tuberculosis of the adrenal glands is one of the causes of the adrenal insufficiency (Addison disease).

Hyperthyroidism is conventionally characterized by a history of the psychic trauma, infectious inflammatory diseases, craniocerebral injuries and nasopharyngeal diseases.

Hypothyroidism is characterized by a history of the thyroid surgery, radioactive iodine treatment, exposure to ionizing radiation, thyroiditis, goiter, thyroid tumors.

Diabetes mellitus is associated with a genetic predisposition, autoimmune diseases (autoimmune thyroiditis, adrenal insufficiency), viral infections, obesity, alcoholism, diseases of the pancreas (pancreatitis, cystic fibrosis, tumors).

History of patients with Addison disease may reveal such predisposing factors as tuberculosis, malignant tumors, adrenalectomies, a long-term treatment with cytostatics and glucocorticosteroids.

A Cushing disease and a syndrome are characterized by previous craniocerebral trauma, encephalitis, arachnoiditis, pregnancy, prolonged use of high doses of the glucocorticoids.

27.2. Objective examination of patients in endocrine system diseases

General survey

General inspection of endocrine patients is very important. It is often possible even at the first look at the patient to recognize the disease by general appearance or by individual characteristic signs, for example, thyrotoxicosis, myxedema, Addison disease, Cushing syndrome.

Patient's habitus (an external view) is very important for a function evaluation of the endocrine glands. It is necessary to assess the following features:

1. Body characteristics - height, body mass, size and ratios of separate parts of the body, peculiarities of the posture and gait.

2. Nutritional status and peculiarities in deposition of the fat, development of the muscular and fatty tissues.

3. The body hair overgrowth.

4. Condition of the skin.

5. The face, its expression and change in the eyes.

6. Age of the patient, relation between his/her actual age and presumed age according to the examination data.

Body characteristics

In healthy people, anthropometric indicators correspond to the body-build type. There are differences in the height between different ethnic groups: for men it averages 165-180 cm, for women - 155-170 cm. Significant height deviations indicate a possible dysfunction of the pituitary gland, the reproductive glands (*gonadal failure*), and the thyroid gland.

Gigantism (the height is more than 200 cm for men, and more than 190 cm for women) is often due to a hypersecretion of the somatotrophic hormone by the anterior pituitary gland (*acromegalic gigantism*) or a failure of the reproductive glands (*eunuchoid gigantism*).

Dwarfism (the height is less than 145 cm in men, and 135 cm in women) may be a sign of the decreased function of the anterior pituitary gland (*hypopituitarism*), with a preservation of childish body proportions and underdevelopment of sexual characteristics (*pituitary infantilism*). Similar symptoms (*hypothyroid infantilism*) can be observed with a sharp decrease in the thyroid function with a development of the myxedema and mental development disorders (*cretinism*).

Disproportions in some parts of the body and other characteristic features can suggest a pathogenesis of the endocrine disorder. Disproportional enlargement of the distal parts of the body (nose, lips, chin, hands, feet) suggests *acromegaly* (due to hypersecretion of the somatotrophic hormone). *Eunuchoid gigantism* is combined with hypogonadism and disproportionate long femurs. The limbs in this condition are very thin, and X-shaped legs are usually observed.

Nutritional status and peculiarities in deposition of the fat

The fat distribution is a characteristic of the endocrine obesity in typical cases. The excessive fat accumulation in the pelvic girdle (lower abdomen, buttocks, and thigh) and chest is typical of the *hypothalamic and pituitary obesity*. A homogeneous distribution of the fat throughout the body occurs in the *thyroid obesity* (due to hypothyroidism). *Abdominal obesity* is typical of the type 2 diabetes mellitus.

An excessive fat deposition on the face and trunk is one of the signs of the *Cushing syndrome*, which is due to an increased function of the adrenal cortex

(*hyperadrenocorticism*). There is a *moon-shaped face*, a marked dorsocervical fat deposition on the neck and back of the head ("*buffalo hump*"), on the chest and abdomen. A Cushing syndrome is characterized by relatively thin limbs and buttocks (in contrast to the hypothalamic and pituitary obesity).

Severe emaciation (*cachexy*) occurs in hyperthyroidism, some forms of diabetes mellitus, *Addison disease* (*chronic adrenal insufficiency*), and especially in *Simmonds disease (pituitary cachexia)*.

Hair-covering character

The hair-covering character is an important diagnostic sign in case of the endocrine disorders due to dependence of the hair growth on hormonal influence of the reproductive, thyroid, pituitary glands and adrenal cortex. There are peculiar features in a location and development of the hair-covering in men and women. Healthy women have no hair on the face and chest. Poor hair development is noted on the trunk. The pubic hair growth is limited above horizontal line while in men hair grows up to umbilicus.

Hypotrichosis (oligotrichosis) is a thinning and loss of the hair ***(alopecia)*** in the axillary fossa, pubic area, head and eyebrows. It is characteristic of the hypothyroidism (myxedema), a decreased pituitary function (*Simmonds disease, pituitary tumor, pituitary dwarfism*), in men with an insufficient androgen production (eunuchoidism, hypogonadism, liver cirrhosis, anorchia [born testicular absence], Klinefelter syndrome). An early sign of the hypothyroidism may be thinning and loss of the hair in the lateral part of the eyebrows (*Hertoghe's sign*).

Hypertrichosis is overgrowth of the hair and its excessive density. It is observed in hyperthyroidism and acromegaly. Increased hair on the back, around the shoulder blades and umbilicus may occur in patients with diabetes mellitus (*diabetic hypertrichosis*).

Hirsutism is the hair growth in uncharacteristic places in women (face and breasts). Hirsutism can have a constitutional or familial basis. Endocrine hirsutism in most cases is a manifestation of the ***virilism*** (replacement of some female sexual characteristics by male in case of tumors of the reproductive glands or the adrenal cortex). Hirsutism with virilism occurs in hyperplasia and tumors of the adrenal cortex, adrenogenital syndrome, Cushing syndrome, ovarian tumors, Stein-Leventhal syndrome (polycystic ovary syndrome, PCOS). Hirsutism can be drug-induced with a long-term use of the streptomycin, glucocorticoids, estrogens, progesterone, gestagen, diphenin (phenylhydantoin), androgens and anabolic drugs. Hirsutism my occur in some other diseases, e.g. dermatomyositis, multiple sclerosis, porphyria.

Sign of the hirsutism is hair growth on the face, over the upper lip, on the chin, around the nipples or between the breasts. The pubic hair extends in the rhombus shape, and there is a pathological growth of hair in other places (on the hips, back, limbs). *Other characteristics of the virilism* are baldness at the

temples, a low voice, a large *Adam's apple (thyroid eminence)*, broad shoulders, a narrow pelvis, and atrophy of the mammary glands.

Skin

Pale skin with a yellow tint is characteristic of the *myxedema (hypothyroidism)*. The *facial hyperemia* is characteristic of the Cushing syndrome (hyperfunction of the anterior pituitary gland).

Bronze (dark brown) color of the skin occurs in case of the adrenal insufficiency. A more pronounced darkening is seen on exposed parts of the body, areas where clothing rubs, palmar folds and buccal mucosa.

Thick, dense, rough, dry and cold skin is observed in decreased thyroid and parathyroid glands function. The skin is thin, soft, smooth (velvety), moist and hot in thyrotoxicosis. *Thin, brittle, splitting fingernails* are found in hypo- and hyperthyroidism and in hypoparathyroidism.

The *linear skin atrophy (striae*) on the thighs and abdomen in the form of dark red wide stripes is characteristic of the Cushing syndrome, but striae occur in most cases of the rapid-onset obesity.

Diabetes mellitus is often accompanied by skin scratchings, pustular rashes, and an intradermal cholesterol accumulation as yellow plaques *(xanthomatosis*), which are especially frequent on the eyelids and less frequent on the hands, elbows and feet (*xanthelasma, xanthoma*). Xanthomatosis also occur in other disorders of the cholesterol metabolism (atherosclerosis, essential hyperlipidemia, biliary cirrhosis). *Diabetic rubeosis* is a redness of the face due to relatively common microangiopathy associated with diabetes mellitus, Atrophy of the subcutaneous tissue at insulin injection sites (*lipodystrophy*) may occur.

Edema in endocrine disorders. *Myxedema (edema in hypothyroidism)* is not dependent on the position of the body. Myxedema may appear on the neck, eyelids, face and other parts of the body. In myxedema, the swollen skin does not retain the traces of finger pressure, because of the dense swelling.

There is a localized *pretibial myxedema* in the form of well delineated edema over the tibia and on the dorsal surface of the feet in severe forms of the hyperthyroidism.

Bones

Pretibial myxedema may be accompanied by *a clubbed (drumstic, or Hippocratic) fingers (or thyroid acropachy)* in diffuse toxic goiter.

Acromegaly is characterized by sharp thickening bones of the disproportionately developed parts of the skeleton (facial skull, distal phalanges of fingers) and an excessive muscle development of the muscles.

Eunuchoid gigantism is easily recognized by disproportionately long femur bones, due to the delayed bone formation of the epiphysis of the tubular bones.

Convulsions. In *hypoparathyroidism*, patients have tonic convulsions due to a decreased calcium level in the blood. It is a typical involvement mainly flexor muscles of the limbs, usually accompanied by a pain, paresthesia, and sometimes by spasm of the orbicular muscle of the mouth and a throat closing. The patient's

hand is flexed to give a specific appearance of the *"obstetrician hand" (“main d'accoucheur”). Hypocalcemic seizures* may occur in some other conditions (e.g. in violation of the calcium absorption due to persistent vomiting and diarrhea, steatorrhea, vitamin D deficiency, a renal failure, poisoning with fluorine salts and oxalic acid.

Facial expression

The patient’s facial expression and changes in the eyes are an important diagnostic sign of the endocrine pathology.

The typical facial expression in *hyperthyroidism* includes wide bulging and shining eyes (*exophthalmos*), giving a look of the fear or "frozen terror" to the face (Fig. 27.1). When such a patient looks down, a white stripe of the sclera appears between the upper eyelid and iris (*Graefe's sign*). In hyperthyroidism there are also *Mobius sign* (an impaired convergence of the eyeballs: one of them moves aside when looking at an object with a fixed gaze) and *Stellwag's* symptom (infrequent blinking).

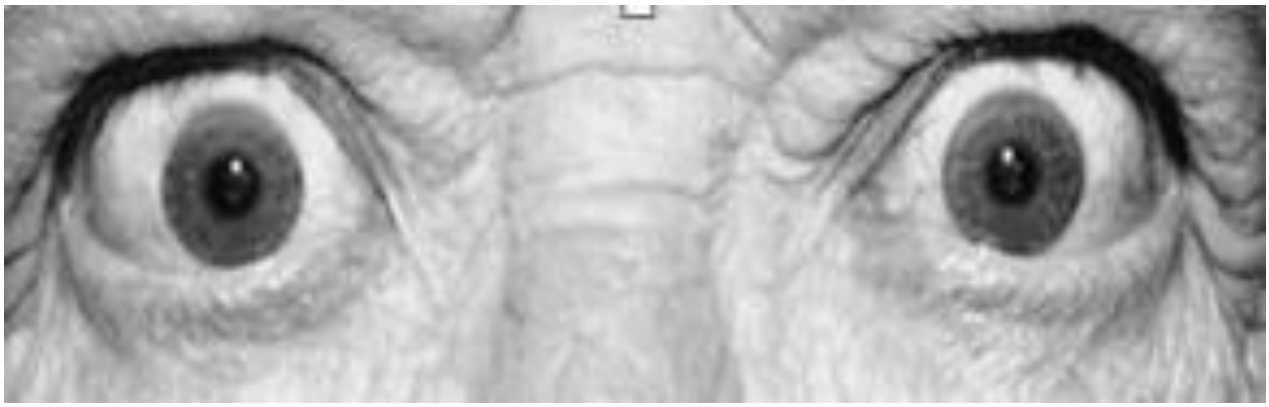


Fig. 27.1. Proptosis (exophthalmos) and lid retraction in thyrotoxic goiter

The face of a patient with *myxedema (hypothyroidism)* is pale, inexpressive, with narrow eye slits, sluggish facial expressions and an indifferent gaze.

A moon-shaped, glossy, red face, with a developed hair cover in the form of the beard and mustache in women is found in *Cushing syndrome* (basophilic adenoma of the anterior pituitary lobe with an increased adrenal cortex function).

In *acromegaly,* there is a sharply enlarged nose, lips, brow arches, lower jaw and tongue. Excessive enlargement of the lower jaw leads to the separation of the teeth (*diastema). Hypofunction of the pituitary gland (hypopituitarism)* is accompanied by obesity, and it gives the face a feminine appearance.

27.3. Thyroid gland examination

Inspection

Thyroid gland normally lies below the thyroid cartilage on the anterior neck (Fig. 27.2). This location allows an examiner to inspect and palpate this bilobular organ, which in the adult human being weighs from 15 to 25 g.

The inspection of the anterior surface of the neck can reveal the size of the thyroid gland. The patient should seat or stand in a comfortable position with the neck in a neutral or slightly extended position. The cross-lighting increases shadows and improves the detection of masses. To enhance the visualization of the thyroid gland, the doctor asks the patient to extend his/her neck, which stretches the overlying tissues, and the patient should swallow a sip of water, watching for the upward movement of the thyroid gland.

After completing anterior inspection of the thyroid gland, the doctor observes the neck from the side, and estimates from the cricoid cartilage to the suprasternal notch.

The thyroid gland in norm is usually invisible on examination.

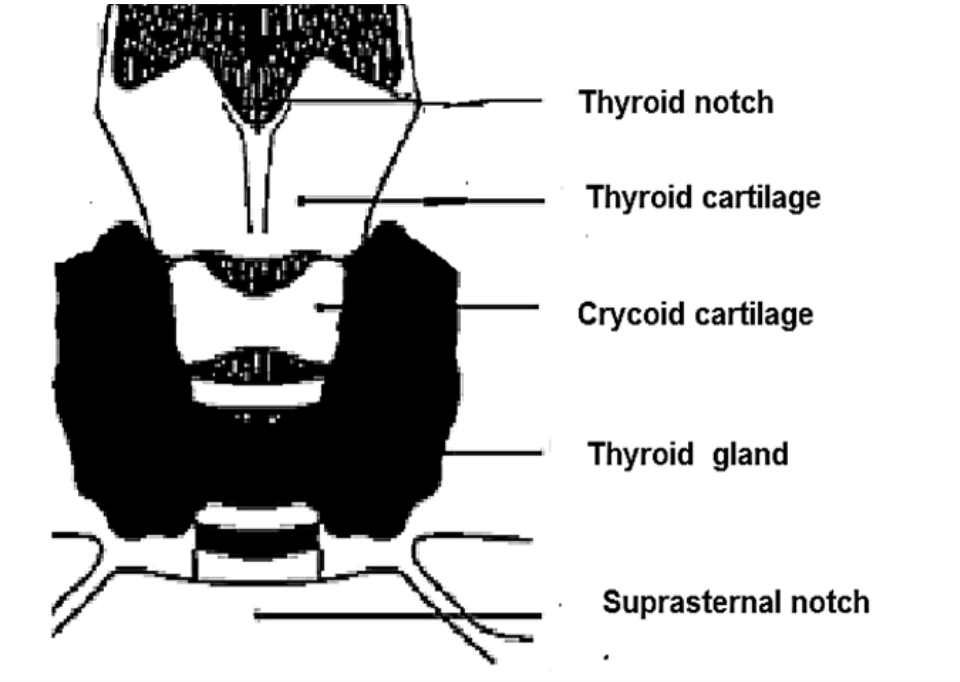


Fig. 27.2. Localization of the thyroid gland

Examination of the thyroid gland area gives an approximate idea of its size and symmetrical or asymmetrical enlargement of its different parts, and points to any surgical scars, obvious masses, or distended veins. It is necessary to pay attention to the character of breathing of patients with thyroid diseases. Breathing may be stridor-like (i.e. noisy, low-pitched, and audible in the distance), when trachea is compressed by benign or malignant tumor of the thyroid gland.

A large retrosternal goiter may cause a venous distention over the neck and difficulty breathing. Hyperemia and facial cyanosis when both arms are raised (*Pemberton's sign*) is possible due to venous occlusion in retrosternal goiter.

In addition to the examination of the thyroid gland itself, the physical examination should include a search for signs of the abnormal thyroid function.

Palpation of the thyroid gland

The thyroid gland is attached to the trachea and moves with it when swallowing. The other cervical masses do not move significantly. In order to successfully palpate the thyroid gland, the neck muscles must be as relaxed as possible. This is done by asking the patient to tilt the head slightly forward, with the chin parallel to the horizontal surface.

The thyroid gland is palpated in an upright position. There are several techniques for palpation of the thyroid gland. Tentative palpation by mild tips of the 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.

The most commonly used techniques for palpation of the thyroid gland.

A. The examiner is in front of the patient (Figure 27.3. A).

Palpation is performed with the thumbs of both hands. The second to fifth fingers of both hands are placed behind the posterior edges of the *m. sternocleidomastoideus*, and the thumbs are placed horizontally at the inferior edge of the thyroid cartilage. The patient is asked to make swallowing motions (swallowing saliva). The thyroid gland (together with the larynx) moves and slips under the examiner's fingers. Palpation of one lateral lobe of the gland can be facilitated by pressing the thyroid cartilage on the opposite side.

This technique allows to identify small changes in the thyroid gland, the mobility of the gland when swallowing, tenderness, and the presence or absence of nodules.

B. The examiner is positioned in front of the patient and slightly to the right (Fig. 27.3. B).

The thyroid gland is palpated by the second-third-fourth fingers of the right hand in a horizontal line over the sternum notch. The left hand holds the neck in place.

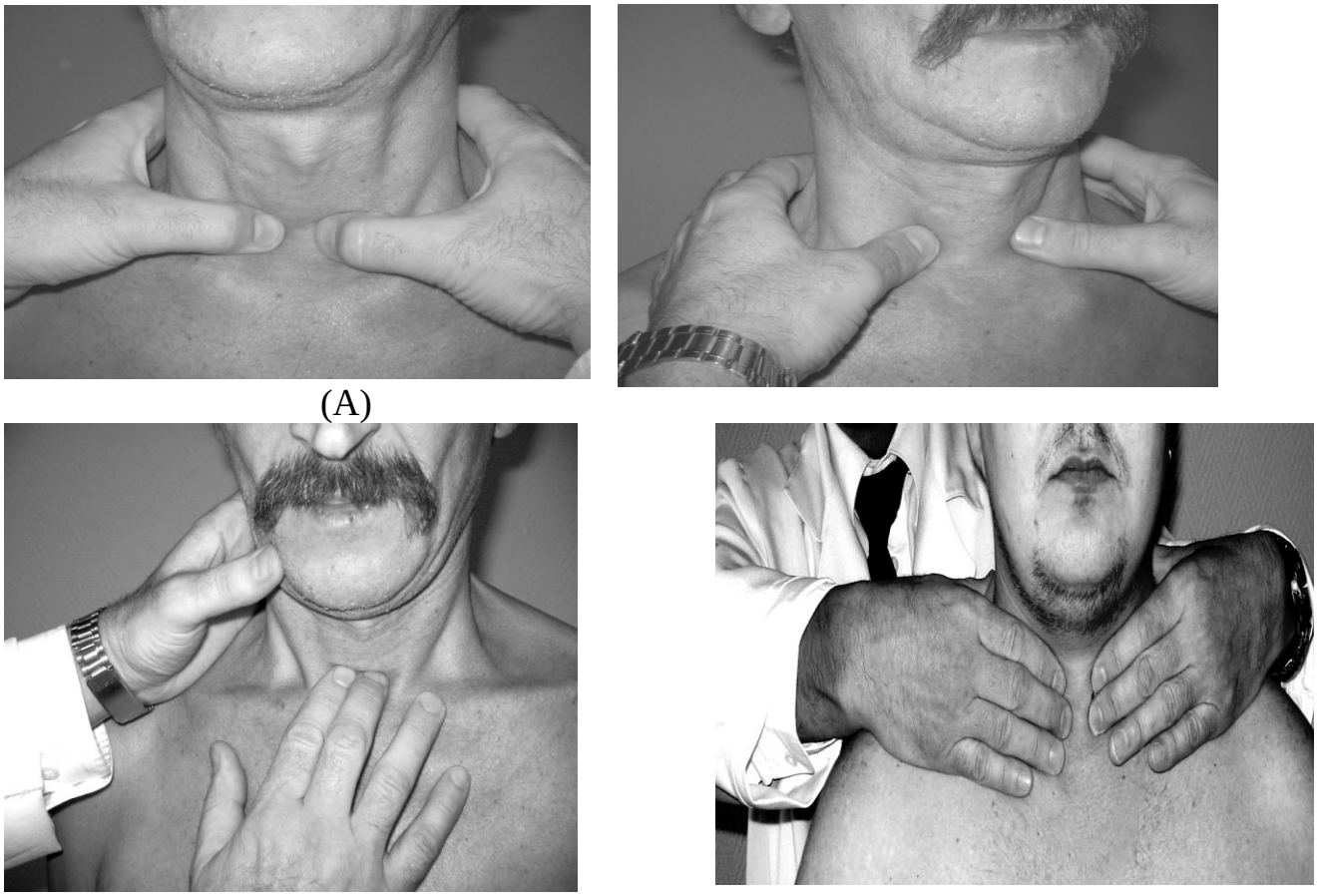
The palpating fingers move up and down in a vertical line. They are then fixed over the sternum, and the patient is asked to make a swallowing movement (a sip of the saliva) at this point. The thyroid isthmus is palpated by the sliding movements of the examining fingers in the direction of the sternal manubrium. While swallowing, the isthmus of the thyroid gland slips under the fingers.

C. If the thyroid gland is significantly enlarged, the doctor palpates it behind the standing or sitting patient (Figure 27.3. C).

The fingers of both hands (except the thumb) are placed over the projection of the thyroid gland. When saliva is swallowed, the fingers slide over the anterior surface of the gland.

Normally, when the thyroid gland is palpated, the volume of its lobes does not exceed the volume of the distal phalanx of the thumb of the patient.

When the thyroid gland is enlarged, it becomes visible. It gives the sensation of a soft or moderately dense roller that rolls over when swallowing. The thyroid gland in most diseases is mobile, and it is not adherent to the underlying tissues.



(A)

(B) (C)

Fig. 27.3. Palpation of thyroid gland (A, B, C - the various techniques of palpation)

In addition to its usual localization (in the area of the anterolateral surfaces of the neck, inside of the *m. sternocleidomastoideus*), the thyroid gland can occupy an atypical position: *intrathoracic goiter (substernal, or retrosternal struma)*, as a ring around the trachea and esophagus (*annular goiter*), *lingual goiter* (in the root of the tongue), *struma sublingualis*, *nasal goiter*. Goiter may develop from an additional lobe or the ectopic tissue of the gland.

According to the form of the enlarged thyroid gland, the presence or the absence of the nodules, it is distinguished *diffuse, nodular and diffuse-nodular (mixed) goiter*.

Diffuse goiter is characterized by a uniform enlargement in the absence of nodes.

Nodular goiter is characterized by an irregular tumor-like overgrowth of the thyroid gland against the background of the absence of the noticeable enlargement of other parts of the thyroid gland.

Diffuse-nodular goiter is diagnosed by nodular growth on the background of the diffuse enlargement of the thyroid gland.

According to the thyroid function, there are *euthyroid (nontoxic, simple), hypothyroid, toxic (hyperthyroid) goiter.*

According to the WHO recommendations (2001), there are the following grades of the thyroid gland enlargement:

Grade 0 - no goiter (volume of the lobes does not exceed the volume of the distal phalanx of the thumb of the patient);

Grade I - the goiter is not visible, but palpable (the size of the lobes is greater than the distal phalanx of the subject's thumb); or there are nodal masses that do not result in an increased volume of the gland;

Grade II - the goiter is visible (with the normal position of the neck) and palpable.

The result of the thyroid gland palpation is influenced by individual anatomical features (the shape of the neck, thickness of muscles and subcutaneous tissue, the position of the thyroid gland).

Palpation cannot be considered a reliable method of the thyroid gland examination. Its findings must be confirmed by an ultrasound, thyroid scintigraphy (in the case of its retrosternal location).

Percussion can find a retrosternal struma (goiter). *Auscultation*. Sounds and murmurs can be heard over the enlarged thyroid in patients with thyrotoxicosis. These are explained by an accelerated flow of the blood and its intensified supply to the thyroid gland.

27.4. Laboratory and instrumental examination in endocrine system diseases

27.4.1. Study of the thyroid function

Laboratory study of the thyroid function includes imunnoassay, radioimunnoassay, and radioassay techniques.

Thyroid hormones. Thyroxine (*tetraiodothyronine,* T_4) contains four iodine atoms. T_4 deiodination leads to production of the potent hormone, *triiodothyronine* (T_3), or the inactive hormone, *reverse* T_3.

Thyroid hormones synthesis is regulated by a classic endocrine feedback loop (Fig. 27.4). Hypothalamic TRH (*thyrotropin-releasing hormone)* stimulates pituitary production of the TSH (*thyroid-stimulating hormone),* which, in turn,

stimulates thyroid hormones synthesis and secretion. Thyroid hormones feed back negatively to inhibit TRH and TSH production.

Serum T3 and T4 levels are increased in hyperthyroidism and decreased in hypothyroidism (Table 27-1).

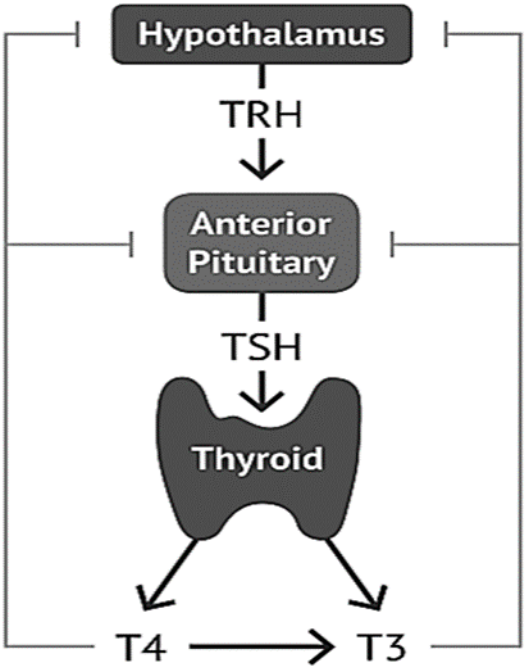


Fig. 27.4. Thyroid hormones regulation:

T3 – triiodothyronine, T4 – thyroxin, TRH – thyrotropin-releasing hormone, TSH – thyroid-stimulating hormone.

Table 27-1. Blood serum thyroid hormones

Tests	Blood levels	Diagnostic value
Triiodothyronine (T_3) free	2.6-5.6 pmol/l >5.6 pmol/l <2.6 pmol/l	- in norm; - hyperthyroidism; - hypothyroidism
Tetraiodothyronine (T_4) free	10-22 mmol/l >22 mmol/l <10-22 mmol/l	- in norm; - hyperthyroidism; - hypothyroidism
Thyroid-stimulating hormone (TSH)	0.3-4.2 мU/l <0.3-4.2 мU/l >4.2 мU/l	- in norm; - hyperthyroidism; - hypothyroidism
Thyroglobulin	≤50 ng/ml >50 ng/ml	- in norm; - toxic and nontoxic goiter

Note: Reference range depends on used test-system

Serum thyroid-stimulating hormone (TSH) is the best test to determine thyroid dysfunction. Normal serum TSH rules out the possibility of the

hyperthyroidism or hypothyroidism, with the exception of the hyperthyroidism secondary to a TSH-secreting pituitary adenoma or pituitary resistance to thyroid hormones, and in some patients with central hypothyroidism due to the 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/l, 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 effect of the elevated free T_4 and free T_3 on the pituitary thyrotrophic cells.

Thyroid autoantibodies. Autoantibodies to the 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 ^{131}I 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.

27.4.2. Thyroid gland imaging

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 (Fig. 27.5-27.6).

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 to determine metastases of tumors.

X-ray (roentgenography) can reveal a retrosternal goiter, deposition of the calcium in the thyroid gland, and displacement and compression of the trachea and esophagus by the thyroid gland.

X-ray is used to detect the enlarged *sella turcica* in patients with pituitary adenoma. These is an indirect evidence of the pituitary affection (usually by tumor).

CT and MRI can be used in the diagnosis of the 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.

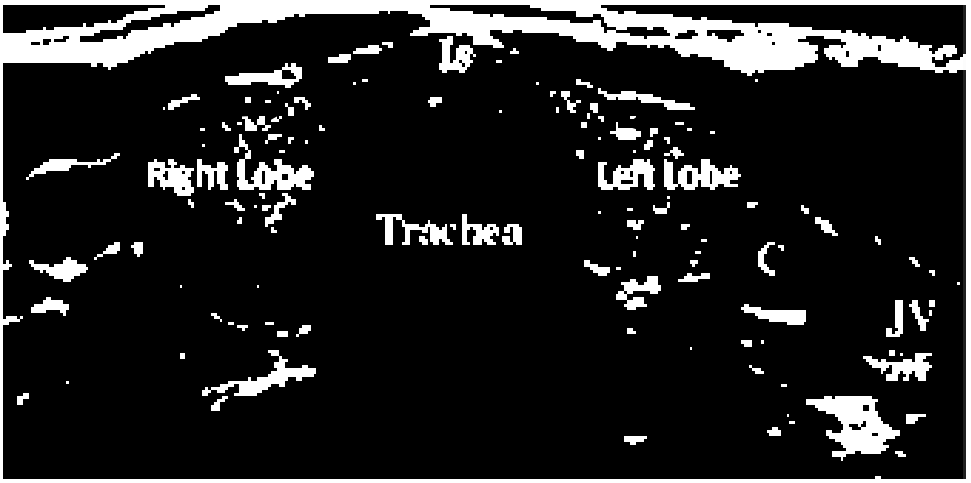


Fig. 27.5. Ultrasonogram of the normal thyroid gland (see arrow):
C – carotid artery, JV – jugular vein

According to ultrasound measurements, normal volume of the thyroid gland in adults: male - up to 24 cm3, female - up to 18 cm3.

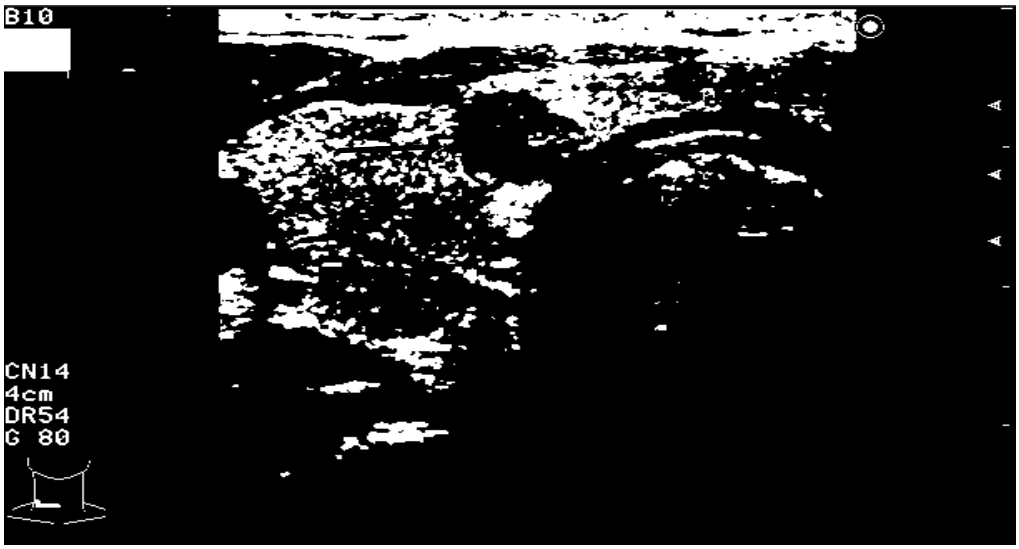


Fig. 27.6. Ultrasonogram of the thyroid gland node on the border of the right lobe and isthmus (see arrow)

27.4.3. 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 glucose) appears to an exceed normal in repeated tests**,** the diagnosis of the diabetes mellitus can be considered proved. After determining blood glucose on a fasting stomach, the patient drinks 75.0 g of the glucose in 200 ml of the water. Then blood specimens are taken.

Assessment of the glucose tolerance test results

- ***Normal blood glucose levels*** *in not over 6.1 mmol/l at fasting levels and 7.8 mmol/1 in 2 hours after intake of the 75.0 g of the glucose (Table 27-2).*
- *The fasting levels between 6.1 and 7.0 mmol/l are borderline of the* ***impaired fasting glycemia****.*
- ***Impaired glucose tolerance*** *is defined as blood glucose levels 7.8-11.0 mmol/l in 2 hours after intake of the 75.0 g of the glucose with a substantial risk for developing type 2 of the diabetes mellitus and cardiovascular disease in the future*.
- ***Diabetes mellitus diagnosis*** *is confirmed by fasting levels of the blood glucose above 7.0 mmol/l and blood glucose over 11.0 mmol/l in 2 hour after intake of 75.0 g of the glucose****.***

Table 27-2. Blood serum carbohydrate metabolism parameters

Tests	Blood levels	Diagnostic value
Glucose		
1) venous blood	4.2-6.1 mmol/l	- in norm;
2) capillary blood	3.88-6.7 mmol/l	- in norm;
3) glucose tolerance test (capillary blood)		
• fasting	≤6.1 mmol/l	- in norm;
	6.1-7.0 mmol/l	-impaired fasting glycemia;
	> 7.0 mmol/l	- diabetes mellitus;
• in 2 hours after oral intake of the glucose 75.0 g	≤7.8 mmol/l	- in norm;
	>7.8 – up to 11.0 mmol/l	- impaired glucose tolerance;
	≥11.1 mmol/l	- diabetes mellitus
Glycosylated hemoglobin (Hb A1c)	4.0-5.6 %	- in norm;
	5.7-6.4%	- prediabetes;
	≥6.5 %	- diabetes mellitus
Insulin	16-160 mcU/ml	- in norm;
	<16 mcU/ml	- type 1 diabetes mellitus;
	> 160 mcU/ml	- type 2 diabetes mellitus, abdominal obesity
C-peptide	0.29-5.3 ng/ml	- in norm;
	<0.29 ng/ml	- type 1 diabetes mellitus;
	>5.3 ng/ml	- type 2 diabetes mellitus, obesity

Insulin. Decreased insulin levels are associated with pancreatic beta cell destruction: e.g. in patients after distal pancreatectomy, chronic pancreatitis, autoimmune destruction, type 1 diabetes mellitus. Elevated insulin levels are associated with an increased insulin resistance (beta cell compensates via hypersecretion of the insulin): e.g. in obesity, steroid hormones administration, acromegaly, Cushing syndrome, type 2 diabetes mellitus.

Glycosylated (glycated) hemoglobin (Hb A1c) is the stable product of the nonenzymatic glycosylation (formation of the glucose-hemoglobin linkage). There is a strong correlation between elevations in the plasma glucose and the HbA1c. Hb A1c indicates the presence of the hyperglycemia. It can be used as a diagnostic test for diabetes mellitus and to estimate plasma glucose control during the preceding 1 to 3 months in diabetes mellitus.

C-peptide. C-peptide is a polypeptide composed of 31 amino acids. It is released from the pancreatic beta-cells during cleavage of the insulin from proinsulin. C-peptide levels are elevated in the insulin resistance conditions, including type 2 diabetes mellitus, obesity, Cushing syndrome. C-peptide levels are suppressed in type 1 diabetes mellitus.

Glucosuria. In the presence of the normal renal function, glucosuria occurs only in an increased concentration of the blood glucose (*hyperglycemia*). The so-called renal glucose threshold (blood glucose concentration) does not usually exceed 8.0-9.9 mmol/1; a higher concentration of the blood glucose indicates glycosuria. In the presence of kidney pathology (nephrosclerosis), glucosuria may be absent even when the blood sugar is abnormally high.

Ketonuria. Ketonuria occurs in decompensated type 1 diabetes mellitus but it can also develop due to carbohydrate deficit (in severe toxicosis with vomiting, long standing gastrointestinal disorders, alcohol intoxication, starvation, etc.).

27.5. The key points of the theme “Clinical and Laboratoryand Instrumental Examination of Patients with Endocrine System Diseases”

Endocrine system has multiple effects on various body functions, and patient's complaints may include a variety of symptoms and signs (a general condition, the central nervous system, the cardiovascular system, the gastrointestinal tract and other organs).

In hyperthyroidism, the patient complains of the intermittent shallow sleep, diminished memory, irritability, general and muscle weakness, sweating, trembling hands, the weight loss despite an increased appetite, heart palpitations, muscle weakness, subfebrile fever. An agitated state is noticed, with restlessness, fidgeting and hurrying, and an impetuous and stumbling speech, wide bulging and shining eyes (exophthalmos), giving a look of the fear,

In hypothyroidism, patients with the complain of a general weakness, constant feeling cold and chills, fatigue, performance degradation, a sharp decrease in memory, drowsiness, and a low mood. There is a monotonicity and slow delivery of the speech (*bradyphrasia*), diminished hearing, hoarse and deep

voice. The face of a patient with *myxedema (hypothyroidism)* is pale, inexpressive, with narrow eye slits, a sluggish expressions and an indifferent gaze.

The patient with a *goiter* (an enlarged thyroid gland) may complain of the difficulty in swallowing and food passage via the esophagus (dysphagia), an inspiratory dyspnea, and a pressure sensation in the neck area.

The patients with *diabetes mellitus* complain of thirst and polydipsia, increased appetite (bulimia), excessive urinary excretion (polyuria), persistent furunculosis, skin itching especially in the perineal region.

The thyroid gland in norm is usually invisible at the examination. Normally, when the thyroid gland is palpated, the volume of its lobes does not exceed the volume of the distal phalanx of the thumb of the patient.

Diagnostic tests in hyperthyroidism are elevated serum T3 and T4, and decreased serum TSH. *Diagnostic tests in hypothyroidism* are decreased serum T3 and T4, and elevated serum TSH.

The diabetes mellitus diagnosis is confirmed by fasting levels of the blood glucose above 7.0 mmol/L and blood glucose over 11.1 mmol/l in 2 hour after intake of 75.0 g of the glucose. Normal blood glucose levels is not over 6.1 mmol/l at fasting levels and 7.8 mmol/1 in 2 hours after intake of the 75.0 g of the glucose.

Impaired glucose tolerance is defined as the fasting glucose levels between 6.1 and 7.0 mmol/l and blood glucose levels 7.8-11.1 mmol/l in 2 hours after intake of the 75.0 g of the glucose with a substantial risk for developing type 2 of the diabetes mellitus and a cardiovascular disease in future.

27.6. Assessment tests on the theme "Clinical and Laboratory and Instrumental Examination of Patients with Endocrine System Diseases"

1. The degree of the thyroid gland hyperplasia (according to WHO):

1. 0 – absence of the goiter;
2. I – the invisible goiter, but the goiter is defined as a lateral lobe with a volume greater than the thumb of the individual being examined;
3. II – the visible and palpable goiter;
4. III – the goiter is visible from a distance;
5. IV - the goiter is visible from a distance>7-10 m.

2. The characteristics of the hypothyroidism are the following:

1. hypersomnia (excessive sleepiness);
2. insomnia;
3. weakness;
4. tachycardia;
5. periodic convulsive contractions of the muscles;
6. face is puffy (edematous).

3. Characteristics of hyperthyroidism are the following:

1. loss of weight;
2. hypotrichosis and alopecia.
3. weakness;
4. tachycardia;
5. exophthalmos (protruded eyeballs);
6. bradycardia.

4. What diseases are characterized by the exophthalmos?
1. nodal struma (goiter) with a hypothyroidism;
2. myxedema;
3. diffuse toxic struma (goiter) with a hyperthyroidism;
4. nodal struma with a hyperthyroidism;
5. thyrotoxicosis.

5. Normal volume of the thyroid gland in adults by ultrasound data:
1. female $\leq$18 $cm^{3;}$
2. female> 18 sm^3;
3. male $\geq$ 24 cm^3;
4. male < 24 cm^3;
5. $\leq$15 cm^3.

6. Laboratory criteria of thyrotoxicosis:
1. increased plasma levels of T_3;
2. decreased plasma levels of T_3 ;
3. increased plasma levels of T_4 ;
4. increased radioactive iodine uptake;
5. decreased serum thyroid-stimulating hormone (TSH);
6. decreased radioactive iodine uptake.

7. Laboratory criteria of primary hypothyroidism:
1. increased radioactive iodine uptake;
2. decreased plasma levels of T_3 and T_4;
3. decreased plasma levels of T_3 and T_4;
4. decreased radioactive iodine uptake;
5. increased serum thyroid-stimulating hormone (TSH).

8. The characteristics of the symptoms of the patients with diabetes mellitus:
1. hypersalivation;
2. thirst;
3. polydipsia;
4. bulimia;
5. oliguria;

6. skin itching in the perineal region.

9. Characteristics of the skin in hypothyroidism:

1. thick and dense;
2. warm and wet;
3. soft and thin;
4. dry and cold;
5. non-pitting edema;
6. pale skin with a yellow tint.

10. Characteristics of the skin in diabetes mellitus:

1. non-pitting edema;
2. icterus;
3. skin scratchings;
4. pustular rashes;
5. xanthomas;
6. atrophy of the subcutaneous tissue at insulin injection sites (lipodystrophy).

11. Types of the goiter according to the form of the enlarged thyroid gland, and presence or absence of nodules:

1. toxic goiter;
2. diffuse;
3. nodular;
4. diffuse-nodular (mixed) goiter;
5. euthyroid goiter.

12. What is true for the evaluation of the radioactive iodine (^{131}I) uptake in the thyroid gland?

1. normal radioactive iodine uptake is 7-12% during 2 hours, and 20-29% during 24 hours;
2. normal radioactive iodine uptake is 12.5-52% during 2 hours, and 20-29% during 24 hours;
3. in hyperthyroidism, radioactive iodine uptake is 9.5-72% during 2 hours, and 11-89 % during 24 hours;
4. in hypothyroidism, radioactive iodine uptake is 1-2% during 2 hours and 2-5 % during 24 hours;
5. in hypothyroidism, radioactive iodine uptake is 9.5-72% during 2 hours, and 20-29% during 24 hours.

13. What is true for the evaluation of the fasting blood glucose levels?

1. fasting blood glucose in not over 4.2 mmol/l in norm;
2. fasting blood glucose in not over 6.1 mmol/l in norm;

3. fasting blood glucose 6.1 – 7.0 mmol/l is the impaired fasting glycemia;
4. fasting blood glucose above 7.0 mmol/L is a diagnostic criterion of the diabetes mellitus;
5. fasting blood glucose above 6.2 mmol/L is a diagnostic criterion of the diabetes mellitus.

14. What is true for the evaluation of the glucose tolerance test?
1. normal blood glucose is not over 7.8 mmol/1 in 2 hours after intake of the 75.0 g of the glucose;
2. normal blood glucose is not over 6.7 mmol/l in 2 hours after intake of the 75.0 g of the glucose;
3. impaired glucose tolerance is the blood glucose 7.8-11.0 mmol/l in 2 hours after intake of the 75.0 g of the glucose;
4. impaired glucose tolerance is blood glucose 6.1-7.8 mmol/l in 2 hours after intake of the 75.0 g of the glucose;
5. diabetes mellitus is confirmed by the blood glucose over 7.8 mmol/l in 2 hour after intake of 75.0 g of the glucose;
6. diabetes mellitus is confirmed by the blood glucose over 11.0 mmol/l in 2 hour after intake of 75.0 g of the glucose.

15. What is the diagnostic value of the glycated hemoglobin (Hb A1c)?
1. >5.6 % in norm;
2. 4.0-5.6 % in norm;
3. 5.7-6.4% in prediabetes;
4. >5.7 % – diabetes mellitus;
5. >6.5 % - diabetes mellitus.

16. What is the diagnostic value of the glucosuria?
1. uremia;
2. gout;
3. diabetes mellitus;
4. impaired glucose tolerance;
5. renal diabetes;
6. myxedema.

17. What is the diagnostic value of the ketonuria?
1. a decompensated type 1 diabetes mellitus;
2. a decompensated type 2 diabetes mellitus;
3. decompensated types 1 and 2 diabetes mellitus;
4. severe toxicosis with vomiting;
5. impaired glucose tolerance;
6. starvation.

18. Gigantism (the height is more than 200 cm for men, and more than 190 cm for women) is haracteristic of:

1. Cushing syndrome;
2. acromegaly;
3. failure of the reproductive glands (eunuchoid gigantism);
4. hyperthyroidism;
5. type 2 diabetes mellitus.

19. Obesity is typical of the following endocrine pathology:

1. Cushing syndrome;
2. hypothyroidism;
3. type 2 diabetes mellitus;
4. hyperthyroidism;
5. Addison disease (primary adrenal Insufficiency).

20. Hypotrichosis (oligotrichosis) is characteristic of:

1. hypothyroidism;
2. hyperthyroidism;
3. decreased pituitary function (Simmonds disease, pituitary tumor, pituitary dwarfism);
4. insufficient androgen production (eunuchoidism, hypogonadism
5. Cushing syndrome.

CHAPTER 28. Clinical Syndromes of the Endocrine System Diseases

Goals: to enable students to learn –

clinical symptoms and laboratory and instrumental signs of the basic clinical syndromes of the endocrine system diseases – hyperglycemia, hypoglycemia, hyperthyroidism (thyrotoxicosis), hypothyroidism (myxedema), obesity, cachexia.

28.1. Syndrome of the hyperglycemia

Definition. A syndrome of the hyperglycemia (hyperglycemic syndrome) is a clinical condition caused by an absolute or relative insulin deficiency, combined with specific angiopathy and neuropathies in chronic hyperglycemia, associated with the elevated concentration of the glucose in the blood plasma.

Causes of the hyperglycemia*:*

(a) *Diabetes mellitus* - hyperglycemia is due to the low insulin levels (*absolute insulin deficiency*) in the *type 1 diabetes mellitus* and/or a reduced tissue sensitivity (insulin resistance) at the cellular level (*relative insulin deficiency*) in the *type 2 diabetes mellitus*.

(b) Hyperglycemia in the absence of the diabetes mellitus may be under the following conditions:

- dysfunction of the endocrine glands (endocrinopathy) - thyroid, adrenal, and pituitary glands (e.g., acromegaly, Cushing disease and syndrome, glucagonoma, pheochromocytoma, hyperthyroidism, somatostatinoma, aldosteronoma);
- diseases of the exocrine part of the pancreas (e.g., acute and chronic pancreatitis, tumors);
- cerebral diseases - encephalitis, brain tumors, meningitis, acute brain stroke, brain hemorrhages;
- due to severe stresses and physical trauma (stress hyperglycemia), severe infections (e.g. sepsis, COVID-19), acute myocardial infarction, convulsions, prolonged major surgery operations;
- at the terminal stages of many diseases.

(c) Certain medications may result in hyperglycemia (e.g., corticosteroids, octreotide, beta-blockers, epinephrine, thiazide diuretics, nicotinic acid, protease inhibitors, and some antipsychotic agents).

Clinical picture

Complaints. The *classic triad of hyperglycemia* includes *polydipsia* (excessive thirst), *polyuria* accompanied nycturia, and *polyphagi*a (increased appetite, or *bulimia*) (Table 28-1).

Table 28-1. Clinical and laboratory characteristics of the hyperglycemia

Characteristics	Syndrome of the hyperglycemia
Causes	- type 1 and type 2 diabetes mellitus; - gestational diabetes mellitus; - diseases of the exocrine part of the pancreas (acute and chronic pancreatitis, tumors); - endocrinopathies (acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma, hyperthyroidism, somatostatinoma, aldosteronoma); - drug- or chemical-induced (e.g., nicotinic acid, glucocorticoids, thyroid hormone, adrenergic agonists, thiazides, alpha interferon, protease inhibitors, beta-blockers) - infections (e.g., sepsis, COVID-19, cytomegalovirus, coxsackie); - severe stresses, acute traumas, acute myocardial infarction, an acute brain stroke, etc.
Symptoms	- excessive thirst (polydipsia); - increased appetite (polyphagia); - polyuria; - wasting, weakness, decreased work capacity; - skin itching, especially in the perineal region; - tachycardia
Capillary blood glucose *(fasting)*	6.1-7.0 mmol/l – impaired fasting glycemia; > 7.0 mmol/l – diabetes mellitus
in 2 hours after meal (or) oral glucose 75.0 g	>7.8 – up to 11.0 mmol/l – impaired glucose tolerance; ≥11.1 mmol/l – diabetes mellitus
Glycosylated hemo-globin (HbA1c)	5.7-6.4% – prediabetes; > 6.5 % – diabetes mellitus
Urinalysis	Glycosuria and ketonuria (the last in type 1diabetes mellitus due to hyperglycemic ketoacidosis)

Patients also complain of weakness, sleepiness, decreased working ability, blurred vision, fatigue, dry skin, skin itching (especially in the perineal region), tingling in feet or heels, decreased libido and sexual potency.

Weight loss and underweight of varying degrees are typical of the type 1 diabetes mellitus, chronic and recurrent pancreatitis. Overweight and obesity present especially in type 2 diabetes mellitus, and in Cushing's syndrome. Increased appetite is typical at the beginning of the type 1 diabetes mellitus and often in the type 2 diabetes mellitus. Decreased appetite and anorexia occur in type 1 diabetes mellitus due to ketoacidosis.

Abdominal pain may be in type 1 diabetes mellitus due to the background of ketoacidosis, and in acute and chronic pancreatitis.

Anamnesis includes episodes of the transient hyperglycemia, gestational diabetes in pregnant women, diseases of the endocrine system (hyperthyroidism, acromegaly, Cushing's syndrome); diseases of the pancreas (acute and chronic pancreatitis, tumors), a poor wound healing, and frequent infections. Hereditary predisposition to diabetes mellitus may occur. A long-term use of the certain medications (corticosteroids, beta-blockers, thiazide diuretics, epinephrine, nicotinic acid, protease inhibitors, and some antipsychotic agents) increases risk of the hyperglycemia in patients with or without diabetes mellitus. It is important to ask patients with diabetes mellitus about factors that can increase the need in insulin and risk of the hyperglycemia (eating more or exercising less than usual, irregular insulin injections, concomitant diseases (e.g., acute respiratory infections, pneumonia), and emotional or physical stresses.

Physical examination:

General survey detects dry mucous membranes, decreased skin turgor, trophic skin changes and scratching.

A typically body mass index (BMI) is over 25 - 30 kg/m^2 (overweight or obesity). Measurement of the ratio of waist circumference to hip circumference (wait-hip ratio) in men more than 0.9 and in women more than 0.8 indicates the abdominal obesity that is characteristic of the metabolic syndrome and type 2 diabetes mellitus.

Percussion of the heart can reveal a possible left shift of the apical impulse and an expansion of the left border of the relative heart dullness. Arterial hypertension is possible. Auscultation of the heart can detect accented II sound above the aorta.

Hepatomegaly develops due to the fat liver mainly against the background of the obesity and type 2 diabetes mellitus.

Complications of the hyperglycemia:

- Acute complications - hyperglycemic (diabetic) ketoacidosis, diabetic comas (hyperglycemic ketoacidosis coma, hyperglycemic hyperosmollar coma);
- *Chronic (late) complications* - ophtalmopathy (retinopathy, macular edema, cataracts, glaucoma); neuropathy sensory and motor, mono- and polyneuropathy, autonomic neuropathy; macroangiopathy (coronary artery disease, peripheral vascular disease, cerebrovascular disease, gangrene of the foot); foot ulcers and joint problems (diabetic osteoarthropathy), gastrointestinal (gastroparesis, diarrhea); diabetic neprhropathy; genitourinary (uropathy/sexual dysfunction); dermatologic (rubeosis, xanthomatosis); risk of infections.

Diabetic angiopathy is characterized by the reduction of the peripheral arterial pulsation.

Diabetic peripheral neuropathy usually affects the feet and legs. Rare cases affect the arms, abdomen, and back. Symptoms include tingling, numbness (which may become permanent), burning (especially in the evening), and pain.

Diabetic osteoarthropathy in the acute phase is usually characterized by the presence of a warm red, edematous foot and ankle, usually the midfoot. In a chronic phase, temperature of the skin and redness gradually subside, while permanent deformities may develop. Plantar pressure ulcers are often associated with bone changes. Detectable foot deformities are mostly an indication of the end stage of the process. Finally, ulcerated areas may become infected and infection may spread to the bone, leading to osteomyelitis.

Hyperglycemic ketoacidosis

Hyperglycemic ketoacidosis occurs primarily in the type 1 diabetes mellitus with the inadequate treatment, or if the disease is complicated by acute infections, injuries, or a nervous stress.

Hyperglycemic ketoacidosis results from a marked absolute insulin deficiency due to a transition from glucose to lipid oxidation and metabolism. In diabetic ketoacidosis, the marked hyperglycemia causes an excessive urinary loss of water, Na, and K, and acidosis resulting from an increased hepatic ketone body synthesis and release. The *ketone bodies* (*acetone, acetoacetic acid and β-hydroxybutyric acid*) induce a metabolic acidosis, a respiratory compensation, and toxic effect on the central nervous system.

Toxic symptoms develop gradually in most cases, and the onset of coma is preceded by its precursors (*precomatose state*). An excessive thirst develops along with polyuria, an epigastric pain, dyspepsia (nausea, vomiting), a headache, and a loss of appetite. The patient's breathe *smells of acetone (odour of rotten apples).*

A precomatose state is followed by the first phase of the *hyperglycemic com*a 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 the diabetic coma: the patient develops dizziness, shows no interest in surroundings, and finally loses consciousness.

The signs of the deep coma: the patient is motionless, the face may be pink or pallid, the skin is 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 the dehydration (dry skin and mucosa) 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.

Principles of the emergency treatment in diabetic (hyperglycemic) ketoacidosis:

- intravenous infusion of the 0.9% isotonic saline solution;

- intravenous infusion of the insulin ;
- correction of the hypokalemia to the level of the serum potassium more than 3.3 mmol/l ;
- intravenous infusion of the sodium bicarbonate may occur if the blood pH is less than 7.0 after 1 hour of the treatment.

Treatment should occur in the intensive care unit. The most urgent goals are rapid intravascular volume repletion, correction of the hyperglycemia, hypokalemia and acidosis, and prevention of the hyperglycemic coma. Identification of precipitating factors is also important.

Laboratory and instrumental diagnosis

The *laboratory diagnosis of the hyperglycemic syndrome is based on the determination of the hyperglycemia with on a fasting stomach and glucose tolerance tests*, and determination of the *glucosuria and ketonuria*.

Hyperglycemia is a fasting plasma glucose level above 7.0 mmol/l and/or postprandial (in 2 hour after meal or oral 75.0 g of the glucose in 200 ml of the water) plasma glucose higher than 11.0 mmol/l, but the symptoms may not start to become noticeable until even higher values such as 15–20 mmol/l. Impaired glucose tolerance (IGT) is defined as plasma glucose levels between 7,8 and 11,l mmol/1 in 2 hour after intake of the 75.0 g of the glucose in 200 ml of the water. Chronic levels exceeding 7.0 mmol/l can produce an organ damage.

Glucosuria is an indirect sign of hyperglycemia. The presence of the glucose in the urine in the absence of hyperglycemia cannot be used as an evidence of diabetes mellitus; since glucosuria can be due to decreased sugar permeability of the kidneys (the renal threshold does not usually exceed 8.0-9.9 mmol/1). In the presence of the nephrosclerosis, glucosuria may be absent even when the blood sugar is abnormally high.

Determination of the acetone and acetoacetic acid (ketone bodies) is obligatory in a suspected hyperglycemia. *Ketonuria (acetonuria)* can also occur in healthy individuals during fasting and in *early pregnancy toxemia (early gestosis)*. Ketonuria occurs in the decompensated type 1 diabetes mellitus but it can also develop due to the carbohydrate deficit (in severe toxicosis with vomiting, long standing gastrointestinal disorders, alcohol intoxication, starvation, etc.).

Glycosylated hemoglobin (Hb A1c) is used to estimate a plasma glucose control during the preceding 1 to 3 months. The normal Hb A1c level is below 5.7%; in poorly controlled diabetics, the level ranges from 9 to 12%. Hb A1c is not a specific test for diagnosing diabetes; however, the elevated Hb A1c often indicates existing diabetes mellitus.

28.2. Syndrome of the hypoglycemia

Definition. Syndrome of the hypoglycemia is a clinical condition characterized by a low plasma glucose level, symptomatic sympathetic nervous system stimulation, and CNS (central nervous system) dysfunction.

Causes:

1. *Symptomatic hypoglycemia is a complication of the drug treatment of the diabetes mellitus* due to the overdose or nontherapeutic administration of the insulin or oral antihyperglycemic agents.

2. *Reactive (postprandial) hypoglycemia*, which happens within a 1-3 hours after eating a meal in –

- prediabetes or being at risk for diabetes mellitus;
- a passed stomach surgery (resection, gastrectomy, gastrointestinal anastomoses), which can accelerate a food passage into the small intestine;
- congenital enzyme deficiencies (fructose intolerance, galactosemia) blocks the hepatic glucose output when fructose or galactose is ingested.

3. *Fasting hypoglycemia*, which may be related to:

- medicines (e.g., salicylates, sulfonamides, quinine, propranolol);
- alcohol abuse;
- renal glycosuria;
- critical illnesses (e.g., a cardiac, hepatic and renal failure; sepsis with multiorgan failure);
- -starvation;
- insulinoma (an insulin secreting tumor of the pancreas);
- endocrine problems - hormonal deficiencies, such as hypoadrenalism (cortisol), hypopituitarism (somatotrophic hormone), glucagon deficiency, and epinephrine deficiency
- exercises (in patients with diabetes mellitus treated with antihyperglycemic agents).

Clinical picture

Complaints

Patients complain of periodically sweating, nausea, warmth, anxiety, tremor, heart palpitations, and possibly hunger and paresthesias due to a burst in the sympathetic autonomic activity in response to a lowering plasma glucose (Table 28-2).

An insufficient glucose supply to the brain causes a headache, blurred or double vision, confusion, speech difficulties, seizures, vertigo, fatigue, somnolence, and sometimes episodes of the syncope (a short-time faintness).

Anamnesis

The patient’s past life history may reveal the following: diabetes mellitus, renal insufficiency/failure, alcoholism, hepatic cirrhosis/failure, other endocrine diseases, or recent surgery, personality changes. Alcohol abuse and nutritional deficiency, weight loss may occur.

History of the reactive (postprandial) hypoglycemia include the following features: more common in patients with metabolic syndrome (overweight and/or abdominal obesity) with a family history of the type 2 diabetes mellitus, or passed stomach surgery (resection, gastrectomy, gastrointestinal anastomoses), which can accelerate a food passage into the small intestine.

Table 28-2. Clinical and laboratory characteristics of the hypoglycemia

Characteristics	Syndrome of the hypoglycemia
Causes	- exogenous hyperinsulinism (overdose of sugar reducing drugs, alcohol; more rarely - salicylates, propranolol, quinine); - endogenous hyperinsulinism (insulinoma); - prolonged fasting; - malabsorption syndrome; - surgical interventions in the gastrointestinal tract; - a severe organ failure (a cardiac, renal, multiple organ failure, and sepsis)
Neuroglycemic symptoms (central nervous system dysfunction)	- asthenia; - speech, visual, and behavioral disorders; - amnesia; - decreased attention span; - headache; - somnolence; - seizures; - paralysis; - coma
Adrenergic symptoms (compensatory activation of the sympathetic nervous system)	- tremor; - tachycardia; - cold sweat; - hunger; - fear; - aggressiveness; - paresthesias; - mydriasis; - nausea; - hypersalivation
Laboratory diagnosis	- fasting blood glucose <2.8 mmol/l in males and <2.3 mmol/l in females; - fasting blood glucose <4.0 mmol/l if patients are treated with insulin or an insulin secretagogue

Physical Examination

Physical findings are nonspecific in hypoglycemia, and generally are related to the central and autonomic nervous system such as hypothermia, tachypnea, tachycardia, and arterial hypertension.

The patient's skin may be sweat and warm or show signs of the dehydration with decrease in turgor.

Cardiovascular signs may include tachycardia, arterial hypertension or hypotension, and arrhythmias.

Respiratory signs may include dyspnea, tachypnea, and acute pulmonary edema.

Possible neurologic manifestations are coma, confusion, fatigue, loss of coordination, psychic excitement and disruptive behavior, tremors, convulsions, and diplopia.

The syndrome of the hypoglycemia is more common in younger people, and occurs at higher plasma glucose threshold levels than in older people.

Classification of the hypoglycemic syndrome:

Degrees of severity:

Mild hypoglycemia– patients feel hunger, weakness, trembling hands, paleness, sweating and irritability, and an impaired ability to concentrate. The patient is capable of self-care: to take 10-20 g of the sugar (or glucose), or a cap of sweet tea, eat a candy.

Moderate hypoglycemia – patients feel a severe headache, problems with vision, speech, inappropriate behavior (agitation, aggression), which in some cases can be combined with mild symptoms. A pain in the region of the heart may be in elderly patients. The patient is pale with a cold sweat, dilated pupils, and tachycardia. It is possible to lose consciousness if the decrease of the blood glucose levels continues. Patients in this state are not able to provide self-help. Surrounding people should get him drink with glucose or sweet tea.

Severe hypoglycemia – signs of the severe hypoglycemia are inappropriate behavior, convulsions, and loss of consciousness or hypoglycemic coma. If the patient does not intake per oral glucose at first symptoms, further provision of the qualified medical care (intravenous glucose solutions and hospitalization) is necessary.

Complications of hypoglycemia are loss of consciousness, coma and death. The short- and long-term complications of the diabetes related hypoglycemia include the precipitation of the acute cerebrovascular disease, myocardial infarction, neurocognitive dysfunction, retinal cell death and loss of vision.

Laboratory and instrumental diagnosis

Symptoms of the hypoglycemic syndrome begin at or beneath a plasma glucose level of about 3.3 mmol/l (and below 4.0 mmol/l for patients treated with insulin or an insulin secretagogue). Symptoms of the central nervous system dysfunction occur at or below a glucose level of the 2.8 mmol/l.

Diagnosis of the hypoglycemic syndrome requires a verification that a plasma glucose level below 2.8 mmol/L in males and <2.3 mmol/l in females (or less 4.0 mmol/l if patients are treated with insulin) exists at the time when hypoglycemic symptoms occur, and that the symptoms are responsive to glucose (dextrose) administration. If a physician is present when the symptoms occur, the blood glucose should be tested. If the blood glucose is normal, diagnosis of the hypoglycemic syndrome is impossible. If the glucose is abnormally low, serum insulin, C-peptide, and proinsulin are tested from the same tube to distinguish the insulin-mediated from non–insulin-mediated hypoglycemia.

A 72-h fasting performed in the controlled conditions is a standard for diagnosis. Patients drink only noncaloric, noncaffeinated beverages, and blood glucose is measured at baseline, whenever the symptoms occur, and every 4 to 6 hours or every1 to 2 hours if the glucose level falls below 3.3 mmol/l.

Oral glucose tolerance test can support reactive (postprandial) hypoglycemia by the lowering of the blood glucose level in 1-2 -3 hours after intake of 75.0 g of glucose with 200 ml of water.

Diagnosis of the hypoglycemic syndrome is based on the collection of three criteria – known as Whipple's criteria (*A.O. Whipple)* – that suggest the individual's signs and symptoms caused by hypoglycemia.

The three criteria of Whipple's Triad are:

- signs and symptoms of the hypoglycemia;
- at the time of the symptoms, a blood test showed low plasma glucose levels $\leq$2.8 mmol/l, and below 4.0 mmol/l if the patients are treated with insulin or an insulin secretagogue;
- when the glucose level is raised to normal levels, symptoms go away.

Principles of the emergency treatment in hypoglycemia:

- Oral sugar or intravenous glucose (dextrose);
- Sometimes - glucagon parenterally.

Immediate therapy for hypoglycemia is limited to providing the patient with glucose. Patients who are still able to eat and drink may drink fruit juice, sweet water, glucose solutions, eat a candy or other sweets, or chew glucose tablets when the symptoms appear. Patients, who are unable to drink or eat, should be given intravenous bolus 50-100 ml of the 40% or 50% dextrose solution at once to relieve the symptoms. It is necessary to continue the infusion of the 5-10% dextrose solution after that.

Glucagon 1 mg subcutaneously or nasal spray with glucagon 3 mg can be also administered in severe hypoglycemia. Efficacy of the glucagon depends on the glycogen stores in the liver. Glucagon has little effect on plasma glucose levels in fasting patients or in the prolonged hypoglycemia.

28.3. Syndrome of the hyperthyroidism (thyrotoxicosis)

Definition. Hyperthyroidism (thyrotoxicosis) is the clinical syndrome, characterized by a hypermetabolism and elevated serum levels of free thyroid hormones.

Causes. Hyperthyroidism may be the result of the increased synthesis and secretion of thyroid hormones (T_4 and T_3) from the thyroid gland, caused by the thyroid gland stimulators in the blood or autonomous thyroid hyperfunction. It can also be caused by the excessive release of the thyroid hormones from the thyroid gland into the peripheral circulation without increased synthesis of the hormones. This is commonly caused by destructive changes in the thyroid gland due to thyroiditis of various etiologies (Table 28-3).

Hyperthyroidism is determined in TSH-secreting anterior pituitary tumor. Chorionic gonadotropin-secreting tumors and pregnancy are conditions involved elevated serum levels of human chorionic gonadotropin, which is a thyroid stimulator.

Hyperthyroidism causes catabolic changes in various tissues and organs, and disturbs various types of metabolism: protein-carbohydrate, fat, mineral, water metabolism, etc. An upset function of the sympathetic-adrenal system is also a very important factor as well, which accounts for many symptoms of the disease.

Etiological classification of the hyperthyroidism

I. Primary hyperthyroidism - due to the 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 the excess thyroid hormone (*thyrotoxicosis factitia*).

II. Secondary hyperthyroidism – due to the 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 an irritability, dysphoria, increased psychic excitability, a non-motivated anxiety, a deranged sleep, tremor of the fingers or in the entire body, a subfebrile fever, the heat intolerance and sweating (*hyperhidrosis*), heart palpitations, fatigue and muscle weakness, weight loss with

an increased appetite, diarrhea, polyuria, frequent defecation, oligomenorrhea, and a decrease in libido.

A general inspection shows special features in the patient's behavior: hyperactivity, irritability and fidgeting, hurried speech. Sometimes the patient quite suddenly drops the topic of the conversation and begins to discuss another topic.

Table 28-3. Clinical and laboratory characteristics of the hyperthyroidism

Characteristics	Syndrome of hyperthyroidism
Causes *Primary hyperthyroidism*	- Graves' disease (diffuse toxic goiter); - toxic solitary or multinodular goiter (Plummer's disease); - metastatic thyroid cancer; - drugs: iodine excess (Jod-Basedow phenomenon); - subacute and autoimmune thyroiditis
Secondary hyperthyroidism	- TSH-secreting pituitary adenoma; - gestational thyrotoxicosis
Symptoms	- hyperactivity, irritability, dysphoria; - heat intolerance and sweating; - heart palpitations; - fatigue and weakness; - weight loss with increased appetite; - diarrhea, polyuria; - oligomenorrhea, loss of libido
Signs *General inspection*	- tremor; - goiter; - warm, moist skin, subfebrile fever; - muscle weakness, proximal myopathy; - lid retraction or lag (signs of Stellwag, Graefe, Kocher)
Cardiovascular system ("thyro-toxic heart")	- percussion - dilation of the heart borders; - auscultation – increased S1 and S2, systolic murmur at the apex; - persistent sinus tachycardia, extrasystoles, paroxysmal or persistent atrial fibrillation; - systolic arterial hypertension, high pulse; - heart failure
Digestive system	- abdominal pain; - diarrhea and liquid stools may occur; - toxic hepatitis (hepatic jaundice and hepatomegaly)
Endocrine disorders	- cystic-fibrosis mastopathy; - impaired glucose tolerance and diabetes mellitus; - gynecomastia may occur; - hypoadrenocorticism (brown skin pigmentation, arterial hypotension) may occur
Laboratory tests	- increased plasma levels of the T_3, T_4, radioactive iodine uptake; - decreased serum thyroid-stimulating hormone (TSH) (in primary hyperthyroidism); - hypocholesterolemia, hyperglycemia; - hypochromic anemia, leukopenia, and lymphocytosis

The tremor involves the hands (*Marie's symptom* - a tremor of the fingers of outstretched hands), eyelids, tongue, and sometimes the whole body ("a telegraph pole symptom"). The skin is warm, moist and soft. The characteristic signs are a subfebrile fever, heat intolerance and hyperhidrosis with warm sweat. The weight loss despite the increased appetite may occur to the point of cachexia.

Hypertrichosis (overgrowth of the hair and its excessive density) occurs in hyperthyroidism. *Pretibial myxedema* (the well delineated edema over the tibia and the dorsal surface of the feet) and *drumstick (Hippocratic) fingers (thyroid acropachy)* may be in severe hyperthyroidism. Gynecomastia in males and brown skin pigmentation may be due to the secondary endocrine dysfunction.

Chronic *thyrotoxic myopathy* occurs with a long course of the hyperthyroidism, characterized by a progressive weakness and fatigue in the proximal muscle groups of the limbs, often the legs. Difficulties in climbing stairs, getting up from a chair, combing hair are noted. The symmetrical hypotrophy of the proximal muscles of the limbs (*proximal myopathy*) gradually develops.

The inspection and palpation of the thyroid gland can find a *diffuse, nodular and diffuse-nodular (mixed) goiter*. The patient's breathing becomes stridorous if the thyroid gland is significantly enlarged.

Ocular signs with hyperthyroidism include wide bulging and shining eyes (*exophthalmos*), giving a look of the fear or "frozen terror" to the face (see Fig. 27.1). When such a patient looks down, a white stripe of the sclera appears between the upper eyelid and iris (*Graefe's sign*). *Kocher's sign* is an 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. A *Mobius sign* is an impaired convergence of the eyeballs: one of them moves aside when looking at an object with a fixed gaze. A *Stellwag's symptom is an infrequent blinking*. These eye signs are mostly due to the excessive adrenergic stimulation and usually go away with a successful treatment.

Circulatory system. "*Thyrotoxic heart*" is a myocardiodystrophy due to the toxic effect of the thyroid hormones on the myocardium. Tachycardia is the most characteristic sign. A pulse rate increases within the range of 90 to 120 and in grave cases to 150 beats per minute. There are predominantly systolic arterial hypertension and the high pulse pressure (the difference between systolic and diastolic pressure). The percussion finds widening the left border of the relative heart dullness. The auscultation of the heart reveals the increased I and II sounds, and systolic murmur at the heart apex which are due to an increased blood flow rate and a low tone of the papillary muscles. A heart failure may develop. ECG detects sinus tachycardia and extrasystoles; and tachysystolic form of the atrial fibrillation is the most frequent variant of the arrhythmia due to toxic effect of the thyroid hormones on the myocardium.

Digestive system. Food intake increases, and some patients have an insatiable appetite. In spite of this, patients are usually thin. Cachexia may occur. Because of an increased intestinal peristalsis, an abdominal pain and frequent

stools are typical, but diarrhea is rare. A hepatic dysfunction may develop from slight disorders (changes of the liver biochemical tests) to toxic hepatitis (hepatic jaundice and hepatomegaly).

Endocrine system. Pronounced hyperthyroidism is attended by a marked dysfunction of the sex glands that can manifest as amenorrhea and cystic-fibrosis mastopathy in female, and gynecomastia and sexual impotence - in male patients. Hypofunction of the adrenal cortex (*hypoadrenocorticism*) manifests by a brown pigmentation of the skin and the arterial hypotension. Diabetes mellitus and impaired glucose tolerance can complicate the hyperthyroidism.

Thyroid storm (thyrotoxic crisis) is a sharp exacerbation of all symptoms of the hyperthyroidism, being a severe complication of the underlying disease (in clinical practice, this is usually a toxic goiter).

A thyroid storm results from untreated or inadequately treated hyperthyroidism. It may be precipitated by an infection, trauma, surgical procedure, embolism, diabetic acidosis, or toxemia of the pregnancy or labor. The pathogenesis of the crisis is the excessive release of the thyroid hormones into the blood and a severe toxic damage to the cardiovascular system, liver, nervous system and adrenal glands. Thyroid storm is a life-threatening emergency condition requiring a specific critical care.

The *clinical picture* is characterized by a sharp agitation (up to psychosis with delirium and hallucinations), which is then replaced by adynamia, drowsiness, muscle weakness, apathy. There are a sharply hyperemic face, pronounced exophthalmos, hot hyperemic skin, profuse sweating later replaced by dry skin due to the marked dehydration and high fever (up to 41-42 °C).

Systolic blood pressure (BP) is high, and diastolic BP is significantly reduced. At the advanced crisis, the systolic BP is sharply reduced. An acute cardiovascular failure may develop. Tachycardia accelerates up to 200 beats per minute and develops into atrial fibrillation.

Dyspeptic disorders (e.g., thirst, nausea, vomiting, liquid stools) are intensified. Hepatomegaly and the development of the jaundice are possible. A further progression of the crisis leads to the loss of the orientation, symptoms of the acute adrenal insufficiency. The clinical symptoms of the crisis often increase within a few hours.

TSH may not be detected in the blood, but T_4 and T_3 levels are very high. Biochemical analysis detects hyperglycemia, high serum urea and potassium levels. Serum sodium level decreases. Leukocytosis with neutrophilic shift to the left is a characteristic of the thyroid storm.

Laboratory and instrumental diagnosis

Laboratory criteria of the hyperthyroidism *are increased plasma levels of T_4 and T_3, and radioactive iodine uptake.*

Decreased serum thyroid-stimulating hormone (TSH) is typical in primary hyperthyroidism. *Increased serum thyroid-stimulating hormone (TSH)* may be in the secondary hyperthyroidism (e.g., in TSH-secreting pituitary adenoma).

Biochemical tests reveal hypocholesterolemia and hyperglycemia.

Complete blood count reveals hypochromic anemia, leukopenia, and lymphocytosis.

28.4. Syndrome of the hypothyroidism (myxedema)

Definition. Hypothyroidism (myxedema) is a pathological clinical syndrome associated with thyroid hypofunction and characterized by a clinical response to thyroid hormone deficiency.

Causes. Factors causing the onset of the primary hypothyroidism are hypoplasia or aplasia of the thyroid gland, an iodine deficiency in the body, subtotal thyroidectomy, overdose of the ^{131}I (which is given in hyperthyroidism) or antithyroid drugs, and iodide; acute (in the past) or chronic thyroiditis (Table 28-4). Hyposecretion of the T_4 and T_3 upsets normal metabolism and causes changes in the tissues, organs, and systems of the body.

Etiological classification of the hypothyroidism

I. Primary hypothyroidism - due to the disorders of the thyroid gland:

- autoimmune hypothyroidism: Hashimoto's thyroiditis;
- iatrogenic: ^{131}I treatment, thyroidectomy, external irradiation of the neck;
- drugs: iodine excess (including iodine-containing contrast media and amiodarone), lithium, antithyroid drugs, p-aminosalicyclic acid, interferon-α;
- congenital hypothyroidism (absent or ectopic thyroid gland);
- iodine deficiency;
- infiltrative disorders (amyloidosis, sarcoidosis, hemochromatosis);

II. Secondary hypothyroidism - due to the 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 the 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 of the thyroid gland occur in hypothyroidism caused by disordered synthesis of the hormones associated with the defective enzyme systems.

Table 28-4. Clinical and laboratory characteristics of the hypothyroidism

Characteristics	Syndrome of the hypothyroidism (myxedema)
Causes *Primary hypothyroidism*	- autoimmune Hashimoto's thyroiditis; - atrophic thyroiditis; - iatrogenic: ^{131}I treatment, thyroidectomy, radiation of the neck; iodine-containing contrast media, amiodarone, lithium, antithyroid drugs, etc.; - congenital: absent or ectopic thyroid gland; - iodine deficiency
Secondary hypothyroidism	hypopituitarism: tumors, pituitary surgery or irradiation, infiltrative disorders, trauma, genetic forms
Tertiary hypothyroidism	hypothalamic disease: tumors, trauma, infiltrative disorders, idiopathic
Hypothermic-me-tabolic syndrome	- increased body weight, obesity; - hypothermia
Myxedema *Hypothyroid dermopathy*	- myxedematous edema (dense non-pitting edema); - dry, thick, dense and cold skin; - puffy face with periorbital edema and large lips; - yellowish skin (due to hypercarotinemia)
Mucous membrane swelling	- tongue with dental impressions along the lateral edges; - nasal breathing problems (due to swollen nasal mucosa); - impaired hearing (due to swelling of the auditory tube and middle ear); - hoarse voice (due to the swelling vocal cords)
Ectodermal abnormalities:	- hair brittleness, loss of hair, including eyebrows; - slow hair growth, alopecia may occur
Myxedematous heart	- bradycardia, systolic arterial hypotension; - low QRS voltage, negative T wave on ECG; - circulatory failure
Digestive system	- constipation, decreased appetite, nausea, atrophic gastritis; - hepatomegaly, cholelithiasis, and biliary dysfunction
Central and peripheral nervous system	- drowsiness, lethargy, memory impairment; - muscle pain, paresthesias, decreased tendon reflexes (due to polyneuropathy)
Endocrine disorders (hyperprolactinemic hypogonadism)	- amenorrhea; - galactorrhea; - a polycystic ovarian syndrome
Laboratory tests	- decreased plasma levels of T_3, T_4, and radioactive iodine uptake; - increased serum thyroid-stimulating hormone (TSH) (in primary hyperthyroidism); - hypercholesterolemia, hypertriglyceridemia; - hypochromic anemia, leukopenia

Clinical picture of the hypothyroidism

The symptoms and signs of the primary hypothyroidism are generally in striking contrast to those of the hyperthyroidism and may be rather unexpressed in their onset.

The main *complaints* are an increased fatigability, slowness, memory impairment, impaired hearing, sleepiness during the day and insomnia at night, weight gain, hypothermia, feeling cold, chills, dry skin, paresthesias (numbness, creeping "goosebumps" on the skin). Changes in the menstrual cycle in women and an impaired potency in men are characteristic.

In severe hypothyroidism, patients complain of the muscle pain, cramps, tightness and the delayed muscle relaxation (*hypothyroid myopathy*).

General inspection. The patient's habitus is quite specific due to myxedema – a puffy ("mask") face with narrow eye slits, and an inexpressive, sluggish facial expressions and indifferent gaze. Skin is dry, cold, pale yellowish, flaky (hyperkeratosis of feet, front surface of shins, knees, elbows are possible). The skin is thick due to myxedema (an accumulation in it of mucopolysaccharides). Myxedema is a dense non-pitting edema, not dependent on the position of the body. The patient’s hair is dry, brittle, sparse (hair deficiency is especially noticeable on the outer third of the eyebrows – *Hertoghe's sign*).

Swelling of the vocal cords and the tongue leads to a slower, slurred, monotonous speech. The timbre of the voice decreases and becomes coarser. The tongue increases in volume (its lateral surfaces show teeth marks).

Cardiovascular system. A myocardial damage (with subsequent development of the *myxedematous heart*) appears at the early stages of the disease. There is dyspnea, increasing even with a minor physical exertion, discomfort in the heart and behind the sternum, not associated with a physical activity and not relieved by nitroglycerin. The height of the apical impulse decreases. The heart sounds S1 and S2 are decreased and muffled. Bradycardia with a small and soft arterial pulse and a decreased systolic blood pressure are often noted. ECG shows low QRS voltage, negative T wave may occur. The heart failure develops in rare cases.

Digestive system. The characteristics are a decreased appetite with a weight gain. Constipation and meteorism develops due to a decreased motor function of the alimentary tract. Cholelithiasis and biliary dysfunction often develops.

Endocrine system. The pronounced hypothyroidism may accompanied by the hyperprolactinemic hypogonadism that results in menorrhagia, later oligomenorrhea or amenorrhea, galactorrhea, and a polycystic ovarian syndrome in female patients.

The central and peripheral nervous system.

Disorders in the peripheral nervous system are manifested by a strong severe radicular pain in the extremities, paresthesia, a muscle pain, cramps, decreased tendon reflexes (due to polyneuropathy), and reeling gait.

Central nervous system disorders are manifested by a drowsiness, lethargy, memory impairment. Psychosis may develop in long-standing hypothyroidism. The clinical symptomatology gradually can develop up to stupor and coma.

Myxedema coma is a life-threatening complication of the hypothyroidism. Precipitating factors of the coma are an exposure to a cold, infections, traumas, and drugs that suppress the central nervous system. It is developed in grave cases on the background of the long-standing hypothyroidism. The coma manifests with extreme hypothermia (body temperature 32.0 – 34.0° C), areflexia (absence of reflexes), seizures, CO_2 retention, and respiratory depression. Severe hypothermia may be missed, unless special low-reading thermometers are used. Rapid diagnosis is imperative because of the high risk of death.

Laboratory criteria of the diagnosis

Primary hypothyroidism is diagnosed by (1) increased serum thyroid-stimulating hormone (TSH); (2) decreased plasma levels of the T_3, T_4, radioactive iodine uptake; (3) a normal serum thyroid-stimulating hormone releasing factor (TSH -RF).

Secondary hypothyroidism is diagnosed by (1) an increased serum thyroid-stimulating hormone releasing factor (TSH-RF); (2) decreased plasma levels of the T_3, T_4, serum thyrotropin-releasing hormone (TRH), radioactive iodine uptake;

Tertiary hypothyroidism is diagnosed by the decreased plasma levels of the T_3, T_4, serum thyroid-stimulating hormone (TSH), serum thyrotropin-releasing hormone (TRH), radioactive iodine uptake.

Biochemical blood analysis: hypercholesterolemia, hypertriglyceridemia; elevated serum creatin phosphokinase (CPK) and aminotransferases.

Common blood count: hypochromic anemia, leukopenia.

28.5. Obesity

Definition. Obesity (adiposis) *is an excess body weight, defined as a body mass index (BMI) of the 30 kg/m^2 and more due to an excessive deposition of fat in subcutaneous and other tissues, which is associated with metabolic disorders.*

Causes. The excessive caloric intake is a leading factor in the development of the obesity. An important role is played by endocrine factors (thyroid, adrenal, pituitary, and ovaries dysfunction); central nervous system diseases (infection, injury, tumour), deficiency of the hypothalamic centers that regulate appetite; genetic factors (more than 20 candidate genes are known to play a major role in the development of the obesity); social factors - high-calorie diet, low physical activity, eating disorders; in women – pregnancy, lactation, and menopause (Table 28-5).

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. A *Binge eating disorder* is characterized by the consumption of large amounts of the food in a short time with a subjective sense of loss of the control during the binge and distress after. *The night-eating syndrome* consists of morning *anorexia, evening hyperphagia, and insomnia*.

An *increased leptin* levels present in the most of the obese people. Leptin is a hormone of the fat tissue. It regulates a feeling of the satiety. The "leptin resistance" is described in obesity.

There are changes of the insulin content in obese patients: hyperinsulinism – at the early stage of the obesity, hypoinsulinemia – in the long-standing obesity (due to exhaustion of the insular apparatus). Hyperinsulinemia impairs the glucose tolerance, which occurs in the metabolic syndrome and abdominal obesity, and often causes diabetes mellitus. Obesity is a prediabetes.

Pathological anatomy. The fat accumulation is more significant in the subcutaneous tissue, omentum, paranephral space, and in the mediastinum. The fat deposits in epicardium are mainly at the heart apex and about the right chambers. The fat can spread into the depths of the heart, separating the muscle fibers, which become thinner as a result. 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. The fat infiltration results in steatosis (fat degeneration) of the liver and pancreas with atrophy of the Langerhans islets.

Classification of the obesity.

I. Causes

1. Primary obesity - alimentary obesity;
2. Secondary obesity:

(a) cerebral (hypothalamic) obesity - due to the affection of the central nervous system,

(b) endocrine obesity- dysfunction of the pituitary, thyroid and adrenal glands, or the ovaries

II. *Body mass index (BMI):* I degree – 30-34.9; II – 35-40; III ->40 kg/m² .

III. Distribution of the fat tissue:

- diffuse obesity, android (male) obesity (waist/hip>1.0), gynoid (female) obesity (waist/hip<0.8), local obesity (lipomatosis).

Table 28-5. Clinical and laboratory characteristics of obesity

Characteristics	Syndrome of obesity
Causes	- excessive caloric intake (alimentary obesity due overeating, hypodynamia); - endocrine diseases (thyroid, adrenal, pituitary, and ovaries dysfunction, impaired glucose tolerance, type 2 diabetes); - central nervous system diseases (infection, injury, tumour); - pregnancy, lactation, and menopause in females; - medication (e.g. steroid hormones, antidepressants. benzodiazepines, lithium, and antipsychotics; - psychologic factors - deviant eating patterns (e.g. binge eating disorder, a night-eating syndrome)
Complaints (mainly in II - III degree of obesity)	- dyspnea (first under a considerable load and later during light exercise), fatigue, impaired memory, hyperhidrosis, flaccidity, constipation, and menstrual disorders
Anthropometry	- body mass index (BMI) >30 kg/m^2 (for South-East Asian >27.5 /m^2); - waist circumference >102 cm in males and >88 cm in females; - waist-to-hip ratio (WHR) >0.90 in males and >0.85 in females; - triceps skin fold (TSF) is >2.5 cm in males and >3.5 cm in females
Skin signs	- striae (on abdomen and thighs); - hyperhidrosis; - often skin diseases (e.g. eczema, pyodermia); - edema of the lower limbs
Joints and bones	an increased risk of the gout and gouty arthritis, osteoporosis, osteoarthrosis, and vertebral osteochondrosis
Respiratory system (in II - III degree of obesity)	sleep apnea, Pickwickian syndrome (severe obesity in combination with pulmonary hypoventilation, sedentary behavior, sleepiness, and a high risk of the cor pulmonale)
Cardiovascular system	often arterial hypertension, left ventricle hypertrophy, coronary atherosclerosis, and a chronic heart failure
Digestive system	- tendency to constipation and meteorism; - fat liver, cholelithiasis, and acute pancreatitis
Urinary system	an increased risk of the nephrolithiasis and urinary infections
Endocrine system	an increased risk of the type 2 diabetes mellitus
Reproductive system	- often male hypogonadism and gynecomastia; - menstrual abnormalities, polycystic ovarian syndrome
Laboratory tests	impaired glucose tolerance test, hyperglycemia, hyperuricemia, hyperlipidemia (increased serum cholesterol, triglycerides, low density lipoproteins)

BMI is not a reliable criterion for assessing the degree of the obesity in people under 20 years old, over 65 years old, athletes with a very muscular build, and pregnant women.

Clinical picture

Complaints. There may be no complaints at the initial stage of the obesity. Complaints present mainly in II - III degree of obesity: e.g., dyspnea (first under considerable load and later during light exercise), heart palpitations, discomfort in the heart area, fatigue, impaired memory, lethargy, apathy, headache, hyperhidrosis, flaccidity, constipation, and menstrual disorders.

General inspection of the patient may be enough to make a diagnosis of the obesity. The skin signs are *striae* (white, red, or violet stripes on abdomen and thighs), often skin diseases due to hyperhidrosis (e.g. eczema, pyodermia), and an edema of the lower limbs. Sometimes the skin fold together with the subcutaneous fat to resemble the "fat apron" on the anterior abdominal wall. There is a type of obesity in which fat is deposited in the tender tumor-like growths (*lipomatosis*).

The *triceps skin fold (TSF) is more than 2.5 cm in males and more than 3.5 cm in females with obesity*.

Characteristics of the body fat distribution are important in the diagnosis of certain disorders, e.g., the *"buffalo hump"* (a marked dorsocervical fat deposition on the neck and back of the head) in *hyperadrenocorticism*.

According to the peculiarities of the fat tissue deposition, there are *abdominal (android, upper type, visceral), gluteofemoral (gynoid, lower type), and mixed obesity.*

The risk of the abdominal obesity increases when the ratio of waist circumference to hip circumference is more than 0.9 in men and more than 0.85 in women. The risk of the greater mortality and morbidity is directly proportional to the size of the waist/hip ratio.

Joints and bones. Obesity leads to an increased risk of the gout and gouty arthritis, osteoporosis, osteoarthrosis, and vertebral osteochondrosis.

Respiratory system. The obese patients often suffer from bronchitis and pneumonia due to a high position of the diaphragm and a reduced ventilation especially in the inferior lobes of the lungs.

Patients with 2-3 degree obesity tend to have *sleep apnea*, a seriously disorder, characterized by moments during sleep when breathing ceases, as often as hundreds of times a night. *Obstructive sleep apnea* develops if excess fat in the neck compresses the airway during sleep. In the *obesity-hypoventilation syndrome (Pickwickian syndrome)*, there are severe obesity combined with pulmonary hypoventilation, sedentary behavior, sleepiness (hypersomnia), hypoxia, hypercapnia, sleep apnea due to the reduced effect of CO_2 in stimulating respiration, *cor pulmonale*, and a high risk of premature death.

Circulatory system. Long-standing and pronounced obesity provokes arterial hypertension, fat myocardiopathy (*cardiomyoliposis*), left ventricle hypertrophy, coronary atherosclerosis, and a chronic heart failure.

Digestive system. Patients with obesity have a tendency to constipation and meteorism, fat liver, cholelithiasis, and acute pancreatitis.

Urinary system. Patients with obesity have an increased risk of the nephrolithiasis, urinary tract infections, and chronic kidney diseases (chronic renal failure).

Endocrine and reproductive systems complications develop due to hyperinsulinemia and insulin resistance increasing with the weight gain and diminishing with the weight loss. Abdominal obesity is a major risk factor for type 2 diabetes mellitus. Obesity has a tendency to male hypogonadism and gynecomastia; and menstrual abnormalities, polycystic ovarian syndrome – in females.

Cancer. Obesity in males is associated with a higher risk and mortality from the colon, rectum, and prostate cancer. Obesity in females is associated with higher mortality from cancer of the gallbladder, bile ducts, breasts, endometrium, cervix, and ovaries.

Laboratory findings include an impaired glucose tolerance test, hyperglycemia, hyperurecemia (increase of the serum uric acid), hyperlipidemia (increase of the serum lipids – cholesterol, fat acids, low density cholesterol).

Diagnosis of obesity is based on BMI not less than 30 kg/m² (for South-East Asian people – not less than 27.5 /m^2). For practical purposes, the "eyeball test" is sufficient: If a person looks fat, the person is fat.

28.6. Cachexia

Defnition. **Cachexia** *(emaciation, protein-energy malnutrition, protein-calorie malnutrition)* is a deficiency syndrome caused by the inadequate intake of the macronutrients (proteins, lipids, carbohydrates). Cachexia is characterized by a general weakness, a sharp decrease in the weight and activity of the physiological processes, as well as changes in the mental state of the patient who is not actively trying to lose weight.

Causes:

- starvation due to social and economic problems (poverty, chronic alcoholism);
- endocrine – in hyperthyroidism, type 1 diabetes mellitus, Addison disease, and in Simmonds disease;
- digestive system diseases with an abdominal pain triggered by food intake (e.g. intestinal ischemia, pancreatitis), maldigestion and malabsorption syndromes due to an alimentary tract obstruction, impaired digestion and absorption, and inflammatory bowel diseases (Crohn's disease, ulcerative colitis);
- malignant tumors (e.g., disseminated cancer, leukemia);
- severe traumas, accidents, burns, major surgery;
- acute or chronic inflammatory and infectious diseases (e.g., tuberculosis, AIDS, chronic obstructive pulmonary disease);
- internal organ failure (liver cirrhosis, chronic kidney disease);

- psychiatric (e.g. anorexia nervosa, depression, dementia).

Risk of the cachexia presents if:

- unintentional loss more 10% of the body mass in the preceding 3 months;
- body mass index (BMI) less than 18,5 kg/m²;
- alcohol intake more 185,0 g ethanol per day;
- no oral food intake for more than 10 days;
- protracted nutrient losses (e.g. malabsorption syndromes, fistulas, diabetes mellitus, renal dialysis, draining abscesses, wounds);
- an increased metabolic needs (e.g. large burns, infections, traumas, sepsis fever, hyperthyroidism, chronic obstructive pulmonary disease);
- intake of the medication with antinutrient or catabolic characteristics (e.g., appetite depressants, corticosteroids, immunosuppressants, cytostatics).

Pathological anatomy. The body utilizes its own tissues as an energy source, leading to atrophy of the visceral organs, muscles and in the fat tissue. Atrophy of the fat and the muscle results in an increased extracellular water, edemas, and an inelastic skin. The loss of the organ weight is greatest in the liver and intestine, moderate – in the heart and the kidneys, and least – in the nervous system.

Classification of malnutrition

1. *Levels of severity:*

(1) body mass index (BMI) less 18.5 kg/m^2 represents a risk of the malnutrition;

(2) BMI within the limits of 17.00-18.49 kg/m^2 – mild malnutrition;

(3) BMI within the limits 16.00-16.99 kg/m^2 – moderate malnutrition;

(4) BMI<16.0 kg/m^2 – severe malnutrition (cachexia) and the risk of death.

2. *Clinical-pathophysiological variants*:

- marasmus (dry form);
- kwashiorkor (wet form),
-combined form (marasmic kwashiorkor).

Clinical picture

Complaints are usually a general weakness, a diminished work capacity, loss of the appetite (anorexia), loss of the weight, digestive disorders (e.g., dysphagia, vomiting, chronic diarrhea), and delayed healing (Table 28-6) .

Taking the patient's history should include the diet and weight change, social and economic conditions that may lead to poverty (e.g., inadequate income, homelessness, and activities that promote diet restriction, such as drug abuse or chronic alcoholism). Strict vegetarianism and inadequate diet may lead to selective deficiencies of some nutrients such as protein, iron, vitamins D and B_{12}. Loss of the appetite may be due to psychiatric disorders (e.g., depression, anorexia

nervosa, and dementia in the elderly patients). Digestive diseases (e.g., tumors, peptic ulcers, gastrointestinal obstruction, malabsorption syndromes, liver cirrhosis, pancreatitis) are common causes of the malnutrition.

Severe malnutrition may be due to endocrine diseases (e.g., hyperthyroidism, type 1 diabetes mellitus, Addison disease, and in Simmonds disease). Cachexia can develop in patients with multiple chronic illnesses that are associated with an increased catabolism and abnormal nutrients metabolism (e.g., renal failure, chronic obstructive pulmonary disease, disseminated cancer, and chronic infections such as AIDS and tuberculosis).

Physical examination

Anthropometry. Anthropometric measurements are necessary for diagnosis and assessment at the severity of the malnutrition, but it is required to exclude the effect of the fluid overload because of the edema and ascites..

The patient's weight (in kg) and height (in cm) should be compared with the normal values given in the tables for males and females. These values should be corrected by ±10 % to account the body constitution of the patient.

Body weight less than 85% of the standard value constitutes malnutrition, or weight loss more than 5% in the past 6 months (unless the patient has no fasting on purpose), or continued loss more than 2% of the body weight.

Values of BMI less 18.5 kg/m^2 represents risk of the malnutrition, BMI less 12 kg/m^2 is incompatible with life.

Using calipers and a measuring tape, the body fat and muscle mass should be estimated (see Propaedeutics of Internal Diseases. Part I / Chapter 2. Objective Examination of a Patient. General Inspection (Survey). 2.6. Skin and mucosa examination, P. 37; and 2.8. Musculoskeletal system examination, P. 41.). *The TSF (triceps skin fold) less 0.5 cm in adult males and less 1.2 cm in adult females are characteristics of the body fat deficiency and protein-energy malnutrition. The body muscle mass depletion (sarcopenia) presents if mid upper arm muscle circumference (MUAMC) less 15.0 cm in male and less 14.0 cm in female.*

General inspection. The emaciation is most obvious in the areas where prominent fat depots normally exist. The skin is thin, dry, non-elastic, pale, and cold. The hair is dry and sparse, and loss of the hair may occur. There are a sharp decrease in the subcutaneous fat tissue and muscles volume. The bones protrude. The mild pitting edema on the lower limbs and ascites may appear due to hypoalbuminemia. Hypothermia may be.

Table 28-6. Clinical and laboratory characteristics of the cachexia

Characteristics	Syndrome of the cachexia
Causes	- starvation; - endocrine – in hyperthyroidism, type 1 diabetes mellitus, Addison disease, and in Simmonds disease; - digestive system diseases with an abdominal pain triggered by food intake (e.g. intestinal ischemia, pancreatitis), maldigestion and malabsorption syndromes due to an alimentary tract obstruction, impaired digestion and absorption, and inflammatory bowel diseases (Crohn's disease, ulcerative colitis); - malignant tumors (e.g., disseminated cancer, leukemia); - severe traumas, accidents, burns, major surgery*;* - acute or chronic inflammatory and infectious diseases (e.g., tuberculosis, AIDS, COPD); - an internal organ failure (liver cirrhosis, chronic kidney disease); - psychiatric (e.g. anorexia nervosa, depression, dementia)
Complaints	weakness, diminished work capacity, loss of appetite (anorexia), loss of weight, digestive disorders (dysphagia, vomiting, chronic diarrhea may be), delayed healing
Anthropometry	- weight loss > 5% in the past 6 months (unless the patient has no fasting on purpose), or continued loss > 2% of the body weight; - BMI < 18.5 kg/m^2 (in severe cases BMI<16.0 kg/m^2); - TSF < 0.5 cm in adult males and < 1.2 cm in adult females; - body muscle mass depletion (sarcopenia) if mid upper arm muscle circumference (MUAMC) <15.0 cm in male and <14.0 cm in female
General inspection	- the skin – thin, dry, non-elastic, pale, and cold; loss of hair; - pitting edema on the lower limbs due to hypoalbuminemia; - atrophy of the subcutaneous fat and skeletal muscles; - hypothermia may be
Signs of the hypovitaminosis and nutrients deficiency	- vitamin A deficiency – papular keratitis ("goose bump rash"), vitamin C - scurvy, vitamin K – ecchymosis and hematoma, vitamin H – skin hyperpigmentation of the sunexposed areas, iron deficiency – spooning nails and cheilosis
Internal organs examination	- respiratory rate and vital capacity decrease; - decreased volume of arterial pulse, arterial hypotension, reduced sizes of the heart; - dysphagia, vomiting, chronic diarrhea
Nervous system	- apathy, memory loss, dementia, peripheral polyneuropathy
Laboratory tests	- hypoproteinemia, hypoalbuminemia; - decreased serum cholesterol, triglycerides, low density lipoproteins, transferrin, glucose (at a lower normal level), serum electrolytes (e.g. potassium, magnesium); - anemia due to iron deficiency, and vitamin B_{12} and folate deficiency, and lymphopenia may be

Signs of hypovitaminosis and nutrients deficiency can be identified by the examination of the patient's skin, hair, nails, and visible mucosa of the conjunctiva and oral cavity. Vitamin A deficiency is found by the *papular keratitis ("goose bump rash")*; vitamin C – skin perifollicular hemorrhages and hypertrophied bleeding gums, vitamin K – ecchymoses and hematomas, vitamin H – skin hyperpigmentation of the sun-exposed areas, iron – spooning nails and cheilosis (*angular stomatitis*), zinc – the *"flaky paint" rash* on the lower limbs, essential fatty acid – *seborrhe*a, protein – transverse nail pigmentation. The *angular stomatitis* can also be due to riboflavin (vitamin B_2) or niacin (vitamin H) deficiency. Glossitis with smooth and red tongue occurs in riboflavin, niacin, cyancobalamin (vitamin B_{12}), and pyridoxine (vitamin B_6) deficiency.

The eye examination can show a pale conjunctiva due to anemia, "Bitot spots" (pericorneal and corneal opacities) – vitamin A deficiency, and nystagmus – vitamin B_1 deficiency.

Examination of the internal organs systems reveals a multiple organ involvement in cachexia. The respiratory rate and vital capacity are usually decreased. There is a decreased rate and volume of the arterial pulse, arterial hypotension, and a reduced size of the relative heart dullness. The digestive system examination can reveal ascites, the abdominal wall tenderness and abdominal masses at palpation, and disordered functions of the alimentary system (e.g. dysphagia, vomiting, and a malabsorption syndrome). The clinical manifestations of severe infections (e.g., pneumonia, chronic diarrhea, pyelonephritis, sepsis) and an impaired wound healing are typical due to immunosuppression.

Central and peripheral nervous system. Mental state may be alert, but an apathy, a memory loss, dementia are common. The examination of the neurologic system may detect a wide-based gait, loss of the distal vibratory and position sense, peripheral neuropathy due to vitamins B group deficiency.

Clinical variants of malnutrition

Marasmus (dry form) refers to a generalized starvation with the loss of the body fat and protein. The marasmus results from starvation with deficiency of the protein and non-protein nutrients. The marasmic patient consumes very little food, and he/she is very thin with atrophy of the muscles and body fat.

Kwashiorkor (wet form) refers to a selective protein malnutrition with an edema and the fatty liver degeneration (hepatic steatosis).

Combined form (marasmic kwashiorkor) is more common for many acute and chronic diseases that lead to depletion of the body fat, muscle wasting, multiple signs of micronutrient deficiencies, decubitus ulcers, and life-threatening infections.

Without the necessary treatment, the progressive cachexia is associated with the heart and renal failure, edemas and ascites, intestinal mucosal atrophy, chronic diarrhea, loss of intracellular minerals (potassium, calcium, zinc,

magnesium, and phosphorus), diminished cell-mediated immune functions, an increased risk of infection, and an eventual death.

Laboratory examination

The biochemical blood analysis usually reveals abnormalities of the protein metabolism (hypoproteinemia, hypoalbuminemia), fat metabolism (hypocholesterolemia, hypotriglyceridemia, decreased serum low density lipoproteins), nitrogen metabolism (increased serum urea and creatinine may be); serum glucose at a lower normal level, decreased serum electrolytes (e.g. potassium, magnesium), decreased serum iron and ferritin.

Common blood count finds hypochromic anemia due to iron deficiency, macrocytic anemia due to vitamin B_{12} and folate deficiency; and leukopenia, and lymphocytosis may be.

***Diagnosis* of the cachexia** is based on anthropometric measurements:

- body weight less than 85% of the standard value constitutes malnutrition;
- or weight loss more than 5% in the past 6 months (unless the patient has no fasting on purpose);
- BMI less 18.5 kg/m^2 (in severe cases BMI less 16.0 kg/m^2); or continued loss more than 2% of the body weight.

Medical and diet histories, a physical examination, and body composition analysis, biochemical blood tests (e.g., serum albumin, glucose, cholesterol, urea, creatinine, ferritin, iron, etc.), common blood count help to assess the severity of the clinical condition, metabolic disorders and prognosis of the patient.

28.7. The key points of the theme "Clinical Syndromes of the Endocrine System Diseases"

Syndrome of the hyperglycemia (hyperglycemic syndrome) is a clinical condition caused by an absolute (the type 1 diabetes mellitus diabetes) or relative insulin deficiency (the type 2 diabetes mellitus), combined with specific angiopathy and neuropathies in chronic hyperglycemia, and associated with elevated concentration of the glucose in the blood plasma. *The laboratory criteria* are the fasting plasma glucose above 7.0 mmol/l and/or postprandial (in 2 hour after meal or oral 75.0 g of the glucose in 200 ml of the water) plasma glucose higher than 11.0 mmol/l.

Syndrome of the hypoglycemia is a clinical condition characterized by the low plasma glucose level (fasting blood glucose less 2.8 mmol/l, or less 4.0 mmol/l if patients are treated with insulin or an insulin secretagogue) and symptoms of the sympathetic nervous system stimulation and central nervous system dysfunction. *The most common causes* are the overdose or nontherapeutic administration of the insulin or oral antihyperglycemic agents.

Hyperthyroidism (thyrotoxicosis) is the clinical syndrome, characterized by a hypermetabolism and elevated serum levels of free thyroid hormones. The

most common causes are Graves' disease (diffuse toxic goiter) and toxic nodular goiter. The *laboratory criteria* are the increased plasma levels of the T_3, T_4, and radioactive iodine uptake.

Hypothyroidism (myxedema) **is** the pathological clinical syndrome associated with thyroid hypofunction and characterized by a clinical response to thyroid hormone deficiency. The *causes of the primary hypothyroidism* are hypoplasia or aplasia of the thyroid gland, an iodine deficiency in the body, subtotal thyroidectomy, overdose of the ^{131}I or antithyroid drugs, and iodide; acute (in the past) or chronic thyroiditis. The *laboratory criteria* are the decreased plasma levels of the T_3, T_4, and radioactive iodine uptake.

Obesity (adiposis) is an excess body weight, defined as a body mass index (BMI) of the 30 kg/m^2 and more (for South-East Asian – more 27.5 $/m^2$) due to an excessive deposition of fat in subcutaneous and other tissues, which is associated with metabolic disorders. The *most common causes of the obesity* are excessive caloric intake and endocrine diseases (thyroid, adrenal, pituitary, and ovaries dysfunction, impaired glucose tolerance, type 2 diabetes).

Cachexia (emaciation, protein-energy malnutrition) is a deficiency syndrome caused by the inadequate intake of the macronutrients (proteins, lipids, carbohydrates). Cachexia is characterized by a general weakness, a sharp decrease in the weight (BMI less 18.5 kg/m^2, in severe cases – less 16.0 kg/m^2) and activity of the physiological processes, as well as changes in the mental state of the patient. The *most common causes* ***a***re starvation, endocrine diseases (e.g., hyperthyroidism, type 1 diabetes mellitus, Addison disease, and in Simmonds disease) and multiple chronic illnesses with an abnormal nutrients metabolism (e.g., a renal failure, a chronic obstructive pulmonary disease, disseminated cancer, and chronic infections such as AIDS and tuberculosis).

28.8. Assessment tests on the theme "Clinical Syndromes of the Endocrine System Diseases"

1. Characteristics of the hypothyroidism are the following:

1. hypersomnia (excessive sleepiness);
2. weakness;
3. bradycardia;
4. subfebrile fever;
5. periodic convulsive contractions of muscles of extremities.

2. Laboratory criteria of the primary hypothyroidism are follows:

1. decreased plasma levels of the T_3, T_4;
2. increased plasma levels of the T_3, T_4;
3. decreased serum thyroid-stimulating hormone (TSH);
4. increased serum thyroid-stimulating hormone (TSH);
5. decreased radioactive iodine uptake.

3. Laboratory criteria of the secondary hypothyroidism are follows:
1. decreased plasma levels of the T_3, T_4;
2. increased plasma levels of the T_3, T_4;
3. decreased serum thyroid-stimulating hormone (TSH);
4. increased serum thyroid-stimulating hormone (TSH);
5. increased serum thyroid-stimulating hormone releasing factor (TSH-RF).

4. Laboratory features of the hypothyroidism are follows:
1. hypocholesterolemia;
2. hypercholesterolemia;
3. hyperglycemia;
4. normocytic-normochromic anemia, leokopenia;
5. leukocytosis.

5. Characteristics of the hyperthyroidism are the following:
1. loss of weight and decreased appetite;
2. apathy;
3. hyperactivity;
4. atrial fibrillation;
5. bradycardia.

6. Laboratory features of the hyperthyroidism are follows:
1. hypocholesterolemia;
2. hyperglycemia;
3. hypochromic anemia and leukopenia;
4. lymphocytosis;
5. leukocytosis.

7. Laboratory criteria of the primary hyperthyroidism are:
1. increased plasma levels of T_4 and T_3, and radioactive iodine uptake;
2. decreased plasma levels of T_4 and T_3, and radioactive iodine uptake;
3. decreased serum thyroid-stimulating hormone (TSH);
4. increased serum thyroid-stimulating hormone (TSH);
5. increased and radioactive iodine uptake.

8. A patient with hyperglycemic syndrome complains of:
1. hypersalivation;
2. dryness in a mouth;
3. skin itching;
4. weakness;
5. polyuria.

9. Complications of the hyperglycemic syndrome include:

1. ketoacidosis;
2. dysphagia;
3. polyneuropathy;
4. nephropathy;
5. hyperglycemic coma.

10. Causes of the hyperglycemic ketoacidosis are:

1. excessive introduction of the insulin;
2. deficient caloric intake of the diurnal diet;
3. sudden cessation of the insulin therapy;
4. insufficient dose of the injected insulin;
5. dehydration as result of the diarrhea;
6. acute infections, injuries, or nervous stress.

11. Principles of the emergency treatment in diabetic (hyperglycemic) ketoacidosis are follows:

1. intravenous infusion of the 0.9% isotonic saline solution;
2. intravenous infusion of the insulin ;
3. intravenous dextrose;
4. glucagon parenterally.
5. correction of the hypokalemia if serum potassium less than 3.3 mmol/l ;
6. intravenous infusion of the sodium bicarbonate if the blood pH less 7.0.

12. Laboratory criteria of the hyperglycemic syndrome are follows:

1. fasting plasma glucose level above 6,0 mmol/l;
2. fasting plasma glucose level above 7,0 mmol/l;
3. plasma glucose higher than 7.0 mmol/l in 2 hours after meal;
4. plasma glucose higher than 11.0 mmol/l in 2 hours after meal;
5. plasma glucose levels between 7,8 and 11,l mmol/1 in 200 ml of the water.

13. A patient with hyperglycemic syndrome complains of:

1. hypersalivation;
2. dryness in a mouth;
3. polyuria;
4. trembling hands;
5. sweating.

14. Criteria of the diagnosis of the hypoglycemic syndrome are follows:

1. signs and symptoms of the hypoglycemia at any blood glucose level;
2. at the time of the symptoms, plasma glucose levels <2.8 mmol/l,

3. at the time of the symptoms, plasma glucose levels below 4.0 mmol/l if patients are treated with insulin;

4. when plasma glucose is raised to normal levels, symptoms go away;

5. When plasma glucose is raised to normal levels, symptoms do not go away.

15. Principles of the emergency treatment in the hypoglycemic syndrome are:

1. intravenous infusion of the 0.9% isotonic saline solution;
2. intravenous infusion of the insulin;
3. oral sugar or intravenous dextrose;
4. sometimes glucagon parenterally.
5. intravenous infusion of glucocorticosteroids.

16. Criteria of the obesity diagnosis are:

1. BMI not less than 30 kg/m² ;
2. for south-east Asian people BMI not less than 27.5 /m^2;
3. BMI more than 25 kg/m²;
4. BMI more than 40 kg/m²;
5. BMI equals 28-33 kg/m².

17. Laboratory features of the obesity include:

1. impaired glucose tolerance ;
2. hypoglycemia;
3. hyperglycemia,
4. hypocoagulation;
5. hyperlipidemia;
6. hyperchromic anemia.

18. Diagnosis of the cachexia is based on the following criteria:

1. Body weight loss more 40% in the past 6 months;
2. body weight less 85% of the standard value constitutes malnutrition;
3. Body weight loss more 5% in the past 6 months (unless the patient has no fasting on purpose);
4. BMI less 18.5 kg/m^2;
5. BMI less 20.0 kg/m^2.

19. Laboratory features of the obesity include:

1. impaired glucose tolerance ;
2. hypoglycemia;
3. hyperglycemia,
4. hypoproteinemia;
5. hyperlipidemia;

6. anemia.

20. Clinical-pathophysiological variants of the cachexia are:

1. asthenic form;
2. marasmus (dry form);
3. kwashiorkor (wet form);
4. combined form (marasmic kwashiorkor);
5. paralytic form.

21. The clinical manifestations of the obesity in systems of the internal organs:

1. Pickwickian syndrome;
2. fat myocardiopathy (cardiomyoliposis);
3. fat liver;
4. chronic gastritis;
5. obstructive sleep apnea.

22. Types of the obesity according to the peculiarities of the fat tissue deposition:

1. abdominal (android, visceral) obesity;
2. gluteofemoral (gynoid) obesity;
3. mixed obesity;
4. cerebral obesity;
5. hypothalamic obesity.

CHAPTER 29. Clinical-laboratory Examination and Clinical Syndromes of the Locomotor System

Goals: to enable students to learn –

1. subjective (inquiry) and objective examination of patients with locomotor (musculoskeletal) system pathology and interpretation of the obtained results;
2. basic laboratory-instrumental methods of the locomotor system examination;
3. clinical symptoms and laboratory-instrumental signs of the basic clinical syndromes of the locomotor system diseases [articular (joint) syndrome, skeletal muscle disorders].

29.1. Concept of the locomotor (musculoskeletal) system

The locomotor (musculoskeletal) system consists of the bony skeleton, skeletal muscles, ligaments, tendons, joints, cartilage, and other connective tissues (Fig. 29-1). These parts work together to allow the body to move.

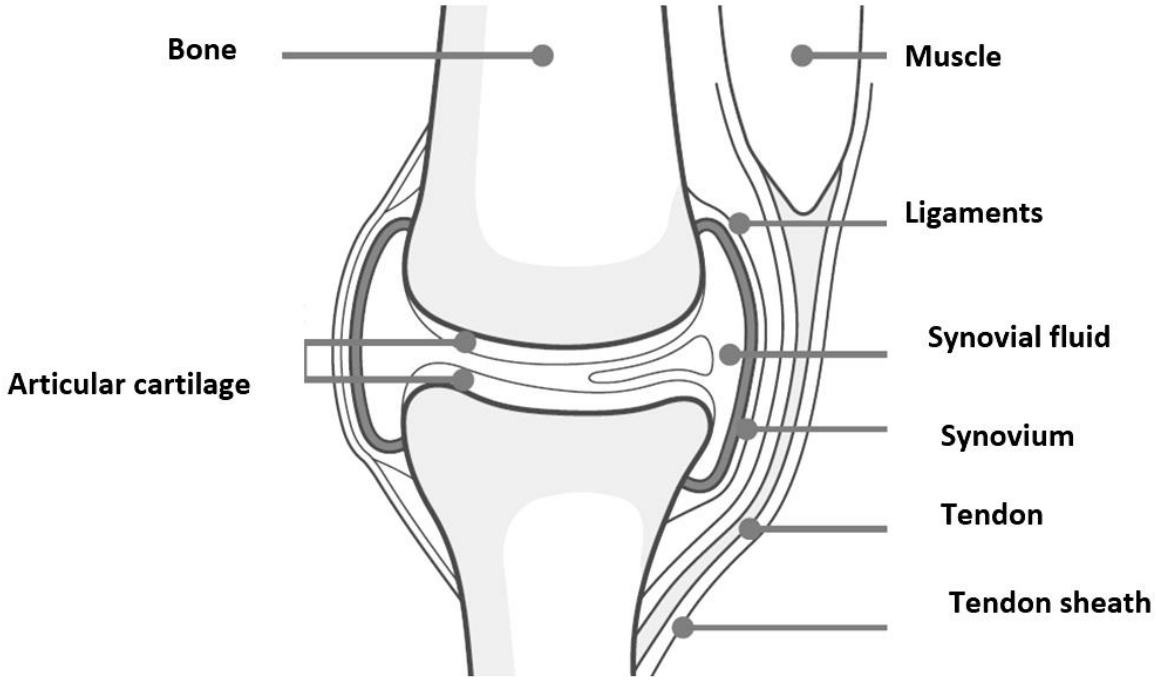


Fig. 29-1. Components of the locomotor (musculoskeletal) system.

29.2. Inquiry of patients with locomotor system pathology

The ***main complaints of the locomotor system diseases*** are joint pain, limitation of joint movements and stiffness, swollen joints, bone pain (ostealgia), muscle pain (myalgia); pain in the ligaments, tendons, in places where they are attached; noise effects from movements in the joints (crackles, clicks, crepitation).

There are three *basic types of the joint pain: inflammatory, mechanical, and functional* (Table 29-1).

Table 29-1. Basic symptoms of the locomotor system pathology

Symptom	Characteristics	Main causes
Inflammatory joint pain	- constant pains, which increase with prolonged immobility (at night, in the morning); - for the relief, the patient has to move	inflammatory processes in joints (arthritis), synovium (synovitis) and periarticular tissues (periarthritis)
Mechanical joint pain	pains are slight to moderate in intensity, appear at mechanical loads (trauma; work with excessive load; sports load) and static (when holding weight, muscle strain) loads, and with movements; intensify at the end of the day, disappear at rest and at night	degenerative-dystrophic joint diseases (e.g. osteoarthritis) due to mechanical irritation with osteophytes and fragments of necrotized cartilage
Functional joint pain	- pains are of uncertain rhythm and variable intensity, increase with psycho-emotional stress, and disappear during sleep; - analgesics are ineffective; - sedatives and tranquilizers relieve the pain	diseases of the nervous system due to hypersensitivity of the pain receptors (hyperalgesia) and transient disturbances in the blood supply to the joints
Pain in ligaments, tendons	- pain is local, painful points near the joints at the tendon attachment to bones and joints; - the pain occurs during the ligament and the tendon contraction; other movements are painless.	inflammatory processes in periarticular tissues (periarthritis), and tendons (tendovaginitis)
Limitation of the joint movements and stiffness	- stiffness in the joints in the morning, lasting from several minutes to several hours, - difficulty in movements	involvement of the periarticular tissues (bursitis, tendovaginitis, etc.), rheumatoid arthritis
Noise effects from move-ments in joints	crackles, clicks, and crepitation during the joint movements	due to articular cartilage irregularities and tendon sheath lesions (e.g. in osteo-arthritis, chronic arthritis, tendovaginitis)

An *acute joint pain* most often indicates an *arthritis and synovitis* (an inflammation in the synovium, the membrane that lines joints), and a *dull pain when moving* – an *osteoarthritis (degenerative joint disease* that results from breakdown of the joint cartilage and underlying bone). The occurrence of the *pain only with certain movements* is characteristic of *bursitis* [an inflammation of one or more synovial bursae (synovial fluid filled sacs)] and *tendovaginitis* (an inflammation of both a tendon and its sheath).

A *night pain with relatively prolonged immobility of the joint is a characteristic of the arthritis.* In the osteoarthritis, the pain also occurs at night, but with a change in the position of the limb while sleeping.

The synovitis in the background of osteoarthritis is characterized by pain at rest, while the periarthritis is characterized by mechanical (at trauma; work and sports with excessive load) and start (at the beginning of the movement) pains.

In diseases of the peripheral nervous system, the pain is localized in the area of one or more nerve trunks. It increases with pressure and strain on the musculature. Radicular pain (the type of pain that irradiates from the spine to the back, thigh, and then to the lower extremity) is "shooting" in nature, localized in strictly limited areas. It intensifies with spinal movements.

Peculiarities of the pain in certain joints. *The shoulder joint pains* after movements and prolonged static loads are observed in scapulocostal syndrome in patients with vertebral column pathology.

Such pains increase sharply after the hand placement behind the lower back of the affected side. The *knee joint deformities* cause the pain due to compression of the injured tibiofemoral articulation. T*he hip joint pain* is localized in the gluteal and inguinal areas, and increases with walking. The temporomandibular joint lesions are characterized by the pain when chewing and inability to fully open the mouth.

General complaints are fever, sweating, general malaise, weakness, weight loss.

Symptoms of lesions of various internal organs may be combined with manifestations of the joint pathology in systemic connective tissue diseases:

- chest pain, which increases with breathing and coughing due to pleurisy and pericarditis (e.g. in systemic lupus erythematosus, acute rheumatic fever);
- muscle weakness with inability to perform basic movements is characteristic of the polymyositis (e.g. in dermatomyositis),
- cutaneous changes (e.g., "butterfly" erythema on the face in systemic lupus erythematosus, ring-shaped erythema in acute rheumatic fever, facial erythema with para-orbital swelling in dermatomyositis; erythema nodosum);
- numbness in the fingers, often with their whitening under the influence of cooling, a consistent change in the color of the skin of the fingers (whitening, blueness, redness) and accompanied by a feeling of tension and painfulness observed in *Raynaud's syndrome*, which may be a sign of the systemic

scleroderma, systemic lupus erythematosus, rheumatoid arthritis, or due to long-term exposure to vibration;

- various types of the eye damage due to uveitis and iridocyclitis, also conjunctivitis, scleritis and episcleritis (e.g. in systemic lupus erythematosus, rheumatoid arthritis);

- diarrhea and dysuric manifestations in reactive arthritis due to genitalia infection (Chlamydia trachomatis) or intestinal infections (Campylobacter, Salmonella, Shigella and Yersinia).

Anamnesis. During the history taking, it is important to assess clinically the peculiarities of the joint syndrome:

- the course of the disease (acute attacks of the arthritis or recurrent);
- triggering factors;
- duration of the joint syndrome;
- consistency and prevalence of the joint involvement (including the involvement of the vertebral column);
- progression of the joint deformity (gradual or rapid).

Careful anamnesis collection helps to link the onset of the joint disease with previous infectious diseases or other triggering factors, for example:

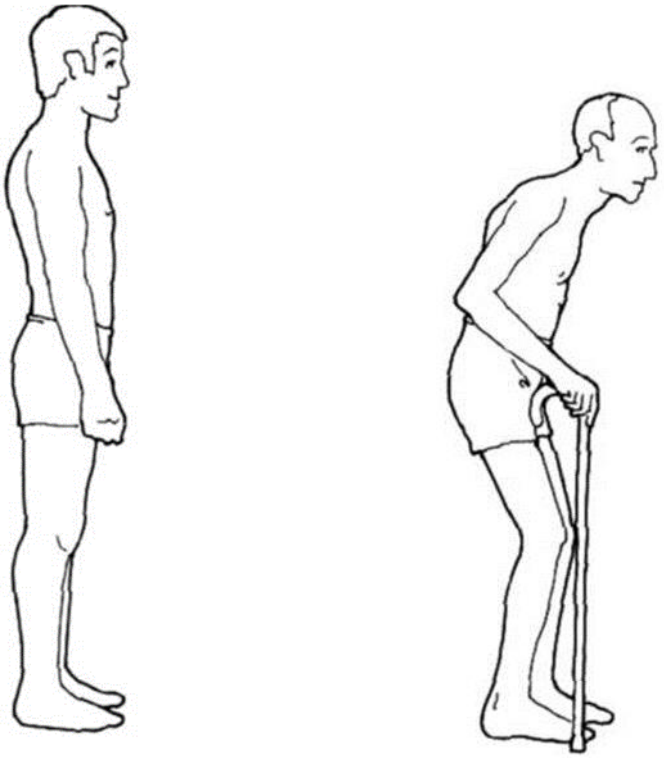
- arthritis may develop after urogenital and intestinal infections;
- tenovaginitis, bursitis, and osteoarthritis are characterized by a history of trauma, especially chronic microtrauma;
- alcohol or eating a lot of the meat can be a trigger factor of the gout attack;
- osteoporosis occurs with a long-term use of glucocorticoids;
- hereditary predisposition to Bekhterev's disease (ankylosing spondylitis) and gout.

29.2. General survey

General examination allows you to assess the condition of the musculoskeletal system as a whole (see CHAPTER 2. Objective Examination of a Patient. General Inspection (Survey). Section 2.8. Musculoskeletal system examination). Attention is paid to the patient's gait, posture, body build, and movements (shaking hands, sitting and standing up from a chair, undressing, etc.), changes of the skin. These are important for identifying signs of musculoskeletal disorders.

Bekhterev's disease (ankylosing spondylitis) characteristically changes the *patient's posture* - the patient's torso is fixed in an oblique *"beggar position"* (due to pronounced kyphosis of the thorax in combination with lumbar lordosis and limited mobility of the spine) (Fig. 29-2).

Unilateral joint damage of the lower limbs causes a *gait disturbance*, forcing the patient to spare the affected limb due to the pain. Unilateral joint damage of the lower limbs causes a gait disturbance, forcing the patient to spare the affected limb due to the pain. Other gait disorders occur with paresis and paralysis of the lower extremities (see below).



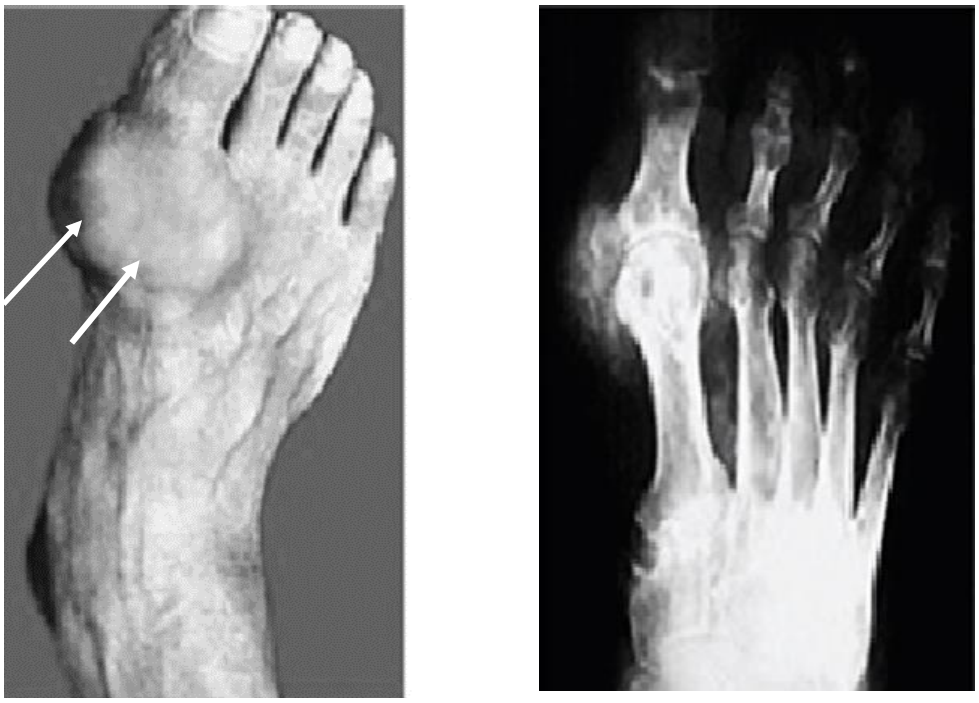
Normal posture *Impaired posture*

Fig. 29-2. Changes of the patient's posture in Bekhterev's disease (ankylosing spondylitis).

Restriction of the patient's mobility and sometimes, complete immobilization can be caused by spinal lesions, joints, and acute inflammation of muscles (myositis).

Examination of the skin and subcutaneous tissue may reveal *ring-shaped erythema (erythema marginatum) and rheumatic nodules* in acute rheumatic fever, *"butterfly" erythema* on the face in systemic lupus erythematosus, *facial erythema with paraorbital swelling* in dermatomyositis. There are an increased dryness and focal sclerotic changes of the skin, edema, and (at later stages of the disease) atrophy of the skin and focal calcinosis of soft tissues, mainly of the fingers and around major joints in systemic scleroderma.

Tophus (gouty pearl) is a whitish nodule in the soft tissues, translucent through thin skin, and containing amorphous masses of the monosodium urate. *Tophi (tophus* in the plural*)* are localized in the subcutaneous tissue above the joints of hands and feet, elbow joints and auricles, on the extensor surface of the forearms, hips, shins, Achilles tendons, on the heels of the feet, and on the forehead (Fig. 29- 3). It is an important diagnostic sign of the gouty arthritis.



(1) (2)

Fig. 29-3. Tophus (gouty pearl) (see arrow) in arthritis of the 1-st metatarsophalangeal joint: (1) – photo, (2) – X-ray.

Psoriatic plaques (flaky papules) help explain the origin of the *psoriatic arthritis*. Psoriatic plaques are typically localized on the scalp and the extensor surfaces of the elbow joints, but can also be found in the groin and gluteal folds.

Mucous membranes lesions can be found in rheumatic diseases - aphthous stomatitis, ulcers in the external genitalia, and eyes, as well as dry mucous membranes of the conjunctiva (xerophthalmia) and oral cavity (xerostomia).

The *muscle consolidation* is observed in systemic scleroderma and dermatomyositis. Muscles are also thickened and tender in regular myositis. Calcium salts (*calcinosis*) can deposit in the subcutaneous fatty tissue and muscles in dermatomyositis and systemic scleroderma. *Muscle cramps (usually flexor muscles)* can be a sign of the contracture development.

Muscular hypotonia (weakness) occurs in prolonged immobilization of the patients, grave diseases, some neurological diseases (myatonia, myasthenia, progressive muscular dystrophy, etc.).

Paresis is the impairment of the active muscle movements, while *paralysis* is the complete loss of the ability to perform movements.

Paresis and paralysis can affect any muscle or muscle group with impaired innervation. Paralysis of only one limb is called *monoplegia*; both legs - *paraplegia*; limbs on one side - *hemiplegia*; in rare cases, paralysis of all four limbs - *tetraplegia*. Paralysis and paresis can develop due to damage to peripheral nerves, the spinal cord and some areas of the brain (trauma, compression, tumor, vascular thrombosis or cerebral hemorrhage).

29.3. Local survey

A detailed examination of the joints is performed by examination and palpation. The joints of superior extremities are examined in a standing or sitting patient position, and the joints of the lower extremities - in a standing or lying position. The involved joints are examined by comparing them with symmetrical healthy joints.

Examination of the joints reveals *changes in their shape and size (swelling, defiguration, deformity*), skin changes and muscle atrophy in the affected joint, as well as restriction of the joint movement.

The joint swelling and defiguration indicate an acute or exacerbated inflammatory process, and the joint deformity indicates a long-term chronic process.

Swelling of the joint and periarticular tissues is an uniform increase in volume and smoothing of its contours due to edema of periarticular tissues and accumulation of effusion in its cavity.

Defiguration of the joint is an irregular change in the shape of the joint due to exudative and proliferative processes (e.g., thickening of the synovial membrane in chronic inflammation, accumulation of effusion in the joint capsule recesses).

Joint deformity, as opposed to swelling and defiguration, is a gross, persistent irregular change in the shape of the joint due to *bony hyperplasia, or the bone overgrowth* (e.g., *Heberden nodules, Bouchard nodules* of the interphalangeal joints in osteoarthritis) (Fig. 29- 4)., destruction of articular bone ends, subluxations, dislocations, ankyloses, etc.

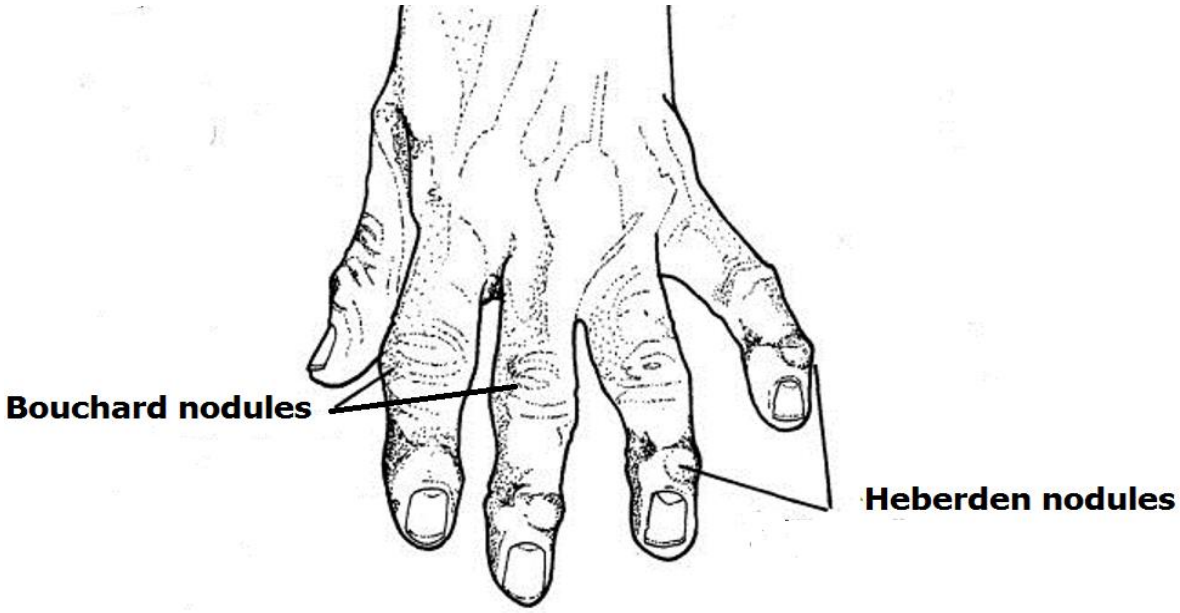


Fig. 29-4. Deformities of the interphalangeal joints (Heberden nodules, Bouchard nodules) in osteoarthritis.

Heberden nodes are dense bone overgrowths (osteophytes) at the bases of the terminal phalanges and the middle trochlea phalangis, detected in the deforming osteoarthritis of the distal interphalangeal joints of hands.

Bouchard nodes are hard formations at the base of the middle phalanges in the deforming osteoarthritis of the proximal interphalangeal joints of hands.

The following deformities are the most common in *rheumatoid arthritis* (all of them are mostly in the hands, less often in the feet):

- *ulnar deviation* of the fingers toward the ulnar bones with an ulnar slippage of the extensor tendons of the metacarpophalangeal joints and the radial wrist deviation (Fig 29-);

- *"swan neck" deformity* is an overextension at the proximal interphalangeal joints of the hand and excessive flexion at the distal interphalangeal joints (Fig. 29- 6);

- *boutonnière (buttonhole) deformity of the fingers* (the finger is bent at the middle interphalangeal joint and straightened at the distal joint.

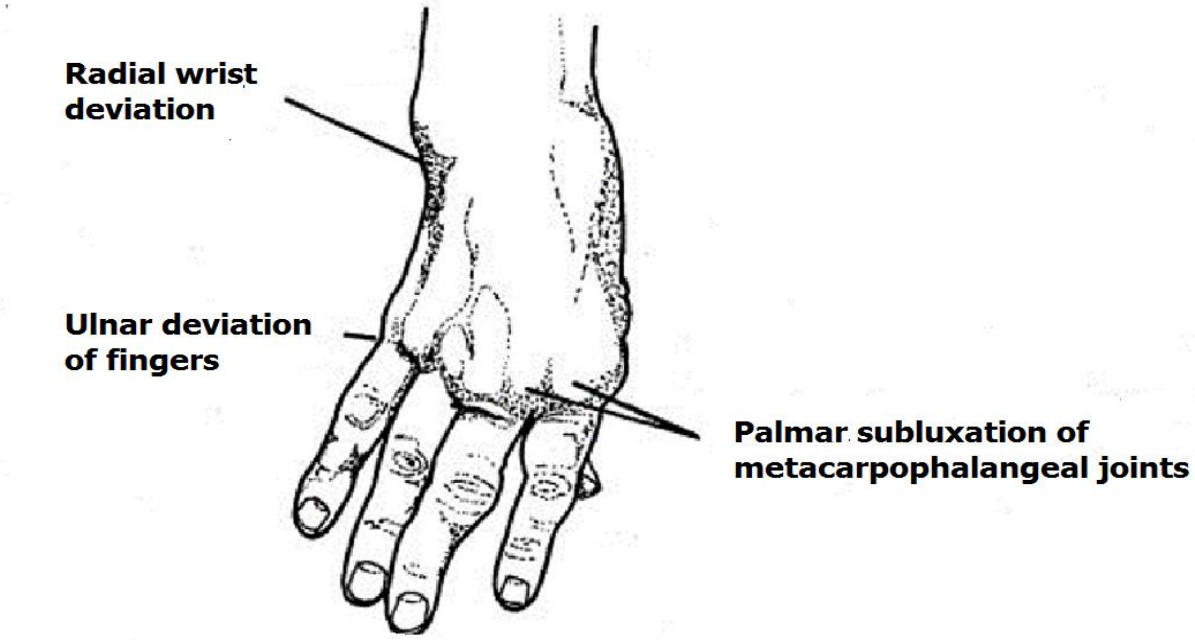


Fig 29- 5. Joint deformities in rheumatoid arthritis.

Enthesopathy includes inflammatory and degenerative changes at the attachment points of the tendons, ligaments, and joint capsules to the bones. Enthesopathy manifests as a spontaneous pain or painfulness on palpation of the tendon attachment sites, such as the Achilles tendon or the plantar fascia that makes it difficult to walk. They occur in *spondyloarthritis*, a group of inflammatory connective tissue diseases that develop in genetically predisposed patients with a lesion of the spine, sacroiliac joints and peripheral joints.

Skin and muscles *over the affected joint* are compared to a healthy symmetrical joint. Skin-articular changes depend on the nature of the pathological process: *skin is hyperemic, shiny and tense in active inflammation*; *skin is dry and thin more often in degenerative-dystrophic joint changes*.

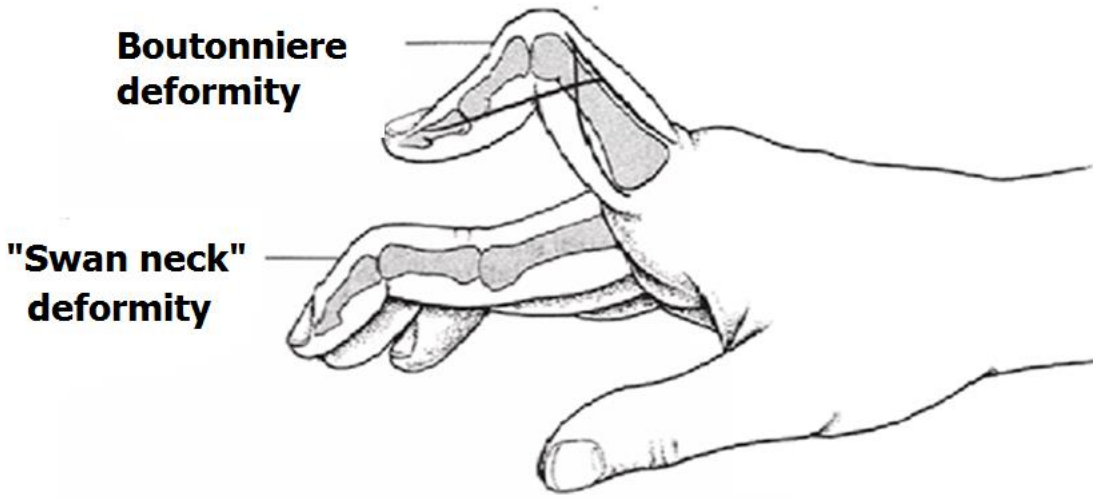
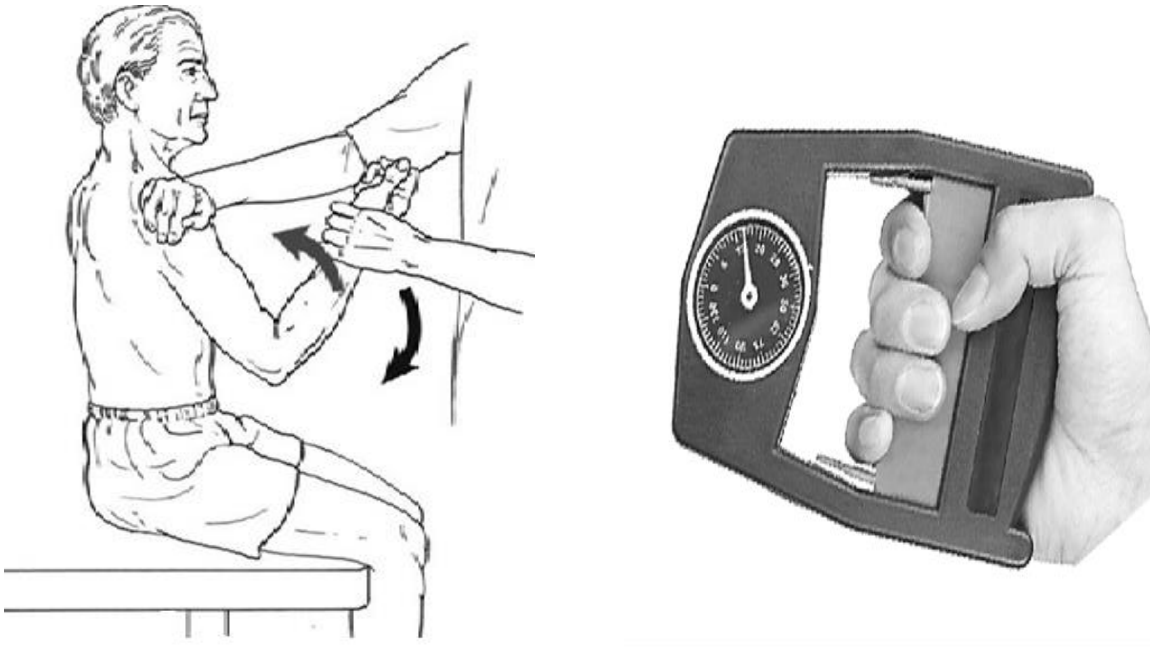


Fig. 29-6. Boutonnière and “swan neck” deformities in rheumatoid arthritis.

Muscles examination notes the muscle tone, strength, and volume, and the presence of local abnormalities (the muscle pain on palpation, swelling, spasm) (see CHAPTER 2. Objective Examination of a Patient. General Inspection (Survey). Section 2.8. Musculoskeletal system examination 2.8.1. Muscular system).

Muscle strength is an ability of the muscle to contract and produce maximum force in a single effort. Muscle strength is measured in two ways. In *manual muscle testing*, the physician assesses the force while resisting the patient's movements (for example, flexing or extending the limbs) (Fig. 29-7).



Manual muscle testing *Dynamometer testing*

Fig. 29-7. Muscle strength testing.

Dynamometer testing measures the tension a muscle during isometric contraction. Distal muscle strength can be measured with a grip force dynamometers) Dynamometer readings in kilograms are compared with the reference (expected) values for the age and sex of the patient.

29.4. Palpation of joints

Joint palpation provides an assessment of the skin temperature in the area of the joints (symmetrical joints are being compared), as well as painfulness, the condition of the joint capsule, swelling, presence of the fluid and additional masses in the joints (nodules, gouty tophi, etc.).

Palpation of joints can be performed both at rest and during movement in the joint. During movement in the joint, a "crackle" (crepitation) may be palpated as well be heard. The painless "crackle" in symmetrical joints may be a physiological.

Depending on the purpose, ***palpation of the joints can be superficial and deep.***

Superficial palpation by briefly (up to 1 second) touching the back of the examiner's hand is used to assess the *skin temperature and moisture on the surface of the joint*.

Superficial palpation by light stroking with fingertips with a slight displacement of the skin and subcutaneous tissue can detect *subcutaneous rheumatic and rheumatoid nodules, tophi, lymph nodes.*

When placing the palm on the joint area at the time of active and passive movements, the examiner can feel a slight gentle crunching in arthritis, and a rough crunching and crackling - in degenerative joint lesions (e.g., arthrosis),

Deep palpation of joints *is performed by two-finger and bimanual methods.*

The two-finger method determines the soreness of the joint capsule along the joint space (gap). Diffuse tenderness at any point of the joint is indicative of the inflammatory lesion (arthritis). Local soreness along the joint space of the knee joint on the medial or lateral side indicates degenerative damage of the articular cartilage. A limited soreness at the site of the tendon-bone attachment indicates a lesion of the ligament apparatus of the joint.

This method allows to assess the painfulness of the metatarsophalangeal and metacarpophalangeal joints when they are affected. To do this, the examiner with two fingers squeezes the patient's foot or hand at the level of the heads of the metatarsal or metacarpal bones.

The bimanual method determines the presence of the free fluid in the joint cavity. The examiner squeezes the sides of the joint with both palms and feels whether fluid is present or absent in the joint cavity with the thumbs.

When examining the knee joint, the examiner places the thumbs on the patient's patella and then uses short strokes to move the patella to the anterior

surface of the articular end of the femur. The *positive floating patella (balloting patella) sign* confirms the presence of the fluid in the knee joint cavity if the examiner's fingers feel a faint push from bumping the patella against the femur.

Examination of the joints sometimes reveals a dense formation that disappears with movement - the so-called "*joint mouse*" (*arthrolith; loose body*), which can cause joint blockages. It is a fragment of the joint cartilage, meniscus or other structures, detached as a result of injury or disease, located in the joint cavity.

A *vertebral soreness and intervertebral discs involvement* are assessed by palpation of the vertebrae and tapping on the spinous processes.

Examination of the *sacroiliac joints* requires squeezing for some time the iliac crests with the palms of the hands. Pain develops in these joints on the affected side in the presence of the inflammation (*sacroiliitis*).

Another bimanual technique of the sacroiliac joints palpation: in the supine position, one of the patient's legs is bent at the knee joint and moved to the side. The heel of the bent leg is placed on the anterior surface of the knee joint of the other straight leg. The examiner presses with one hand on the bent knee joint, pushing it to the couch, and with the other – on the ileum crest of the opposite side. Arthritis of the sacroiliac joint (*sacroiliitis*) causes the pain on the side of the withdrawn inferior limb.

The *functional state of joints* is assessed on symmetrical pairs of joints by the maximum possible range of active and passive movements using a *goniometer* (or *pronometer*, an instrument for measuring the amplitude of the joint movements) (Fig. 29-8).

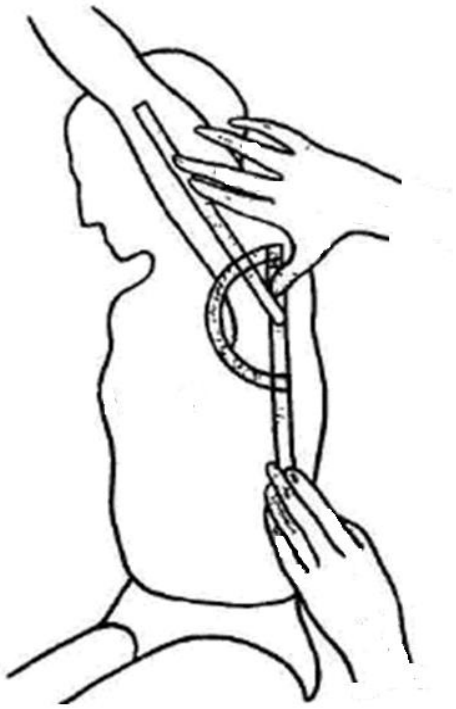


Fig. 29-8. Measurement of the shoulder flexion volume in the sitting position.

29. 5. Laboratory-instrumental methods

29.5.1. Laboratory methods

Laboratory methods are primarily important for assessment the activity of the inflammatory process. Less frequently they have differential-diagnostic value.

Laboratory tests of the inflammatory process activity assessment

Tests that can help determine the inflammatory nature of the musculoskeletal disease are white blood cell count ***(leukocytosis), erythrocyte sedimentation rate (ESR) and serum C-reactive protein***. These tests have no specificity, but are elevated in most diseases of the inflammatory nature. ESR may be accelerated to 50-60 mm/h, and the serum CRP may also increase 5-10 times as compared to norm.

Elevated levels of the serum C-reactive protein and other "acute phase proteins" (e.g., fibrinogen, seromucoid) are usually combined with an increased ESR and dysproteinemia due to increased gamma-globulin content. Severe hypergammaglobulinemia is observed in systemic lupus erythematosus (SLE), rheumatoid arthritis, Sjögren's syndrome.

The serum levels of the CRP and ESR are used to assess the degree of inflammatory activity. However, a large number of non-joint-related diseases (e.g., infections, cancer) can cause an increase of the CRP and ESR.

Laboratory tests that may be useful in the diagnosis of specific joint diseases

Rheumatoid Arthritis

Rheumatoid factor (RF) is a serum autoantibody to the Fc-fragment of IgG. RF has a high sensitivity of about 90%, but a low specificity of about 60% in patients with rheumatoid arthritis.

Anti–cyclic citrullinated peptide antibody (anti-CCP) levels are characteristically elevated in rheumatoid arthritis. They are found in rheumatoid arthritis (65-87%) and have high specificity (over 95%).

There is a 99% chance of the rheumatoid arthritis when RF and anti-CCP titers are combined. Although RF and anti-CCP can be elevated in other arthritis associated with connective system diseases, such as SLE.

Acute rheumatic fever (ARF)

The *anti-streptococcal antibodies (particularly anti-streptolysin-O, or ASL-O)* are markers of a previous streptococcal infection, which causes acute rheumatic fever (ARF). However, a high ASL-O titer only suggests a recent exposure to the infection, and not its presence.

Systemic lupus erythematosus (SLE)

Antinuclear antibodies (ANA) is the first-line test for SLE in patients with relevant symptoms and signs. Positive ANA tests occur in over 98% of people with SLE. However, positive ANA tests can also be found in other connective tissue diseases (e.g. rheumatoid arthritis), autoimmune diseases, malignancy, long-term therapy with certain medications (e.g. hydralazine, procainamide, tumor necrosis factor-alpha antagonists), and even in healthy individuals.

Anti–double-stranded DNA antibodies (anti-dsDNA), a more specific test, is indicated if the ANA is positive. The elevated anti-dsDNA titers are highly specific for SLE, but occur in less than 70% of patients with SLE.

Ankylosing spondyloarthritis (Bekhterev's disease)

HLA-B27 (human leukocyte antigen) is an HLA antigen used in the evaluation of spondyloarthropathies (e.g., when there are symptoms of inflammatory back pain and normal radiological findings or unexplained uveitis and peripheral arthritis). HLA-B27 is a high susceptibility immunogenetic marker for ankylosing spondyloarthritis (sensitivity – 90%, specificity – 92%). The HLA-B27 allele carriers are found in a smaller percentage of cases of the reactive arthritis, psoriatic arthritis, and some other diseases.

Reactive arthritis

Laboratory tests for the detection of infectious agents leading to reactive arthritis in the obtained biological material (blood, urine, scrapings or swabs from the urethra, cervical smears, synovial fluid):

- PCR antigen test for detection of the the urogenitalia infection *Chlamydia trachomatis*;

- immunoassay detection of the *Chlamydia trachomatis* serum antibodies (IgG, IgM, IgA), which are produced in response to *Chlamydia trachomatis* infection entry into the body;

- detection of the *Yersinia enterocolitica* infection by immunoassay (anti-IgA, anti-IgM, anti-IgG);

- detection of the markers of the *hepatitis B and C viruses* – serum hepatitis B surface antigen (HBsAg) and hepatitis C virus (HCVAb) antibody by immunoassay and PCR.

Gouty arthritis

The increased contents of *the uric acid in the blood (hyperuricemia) and in the urine (hyperuricosuria*) is of the great diagnostic value in diagnosing gout. However, the plasma uric acid can be elevated in patients without clinical manifestations of the gout.

Synovial fluid examination

The ***synovial fluid examination is the most reliable way to exclude infection, to diagnose crystal-induced arthritis (from intra-articular deposition of crystals), and to determine the cause of the joint effusion***.

Synovial fluid can be obtained by the *puncture (arthrocentesis)* of the knee joint. Arthrocentesis is indicated for patients with acute or unexplained joint effusions.

In the presence of inflammation, the fluid amount in the joint increases significantly. Normal synovial fluid is a light yellow, slightly opalescent, and moderately viscous.

The ***synovial fluid may change color in some diseases***: cloudy, whitish-green – in purulent arthritis; milky-white (due to a large amount of the urate salts) – in gout; brown – in arthropathies developing in the background of ochronosis

(alkaptonuria); intensely pink or reddish – in hemorrhagic synovitis (e.g due to coagulopathy, trauma, scurvy, tumour).

Biochemical tests of the synovial fluid

Septic arthritis can be distinguished from aseptic arthritis by the the glucose levels in the synovial fluid: *the glucose is undetectable in septic arthritis, whereas it is 2.0-5.5 mmol/L in aseptic arthritis.*

RF (rheumatoid factor) is not normally found in the synovial fluid. The increased RF level is characteristic of the rheumatoid arthritis.

The *CRP* level in inflammatory joint damage increases tenfold or more times higher than normal.

Polarization microscopy of the wet droplet preparation of the synovial fluid for the presence of crystals is necessary f*or the definitive diagnosis of crystal-induced arthritis*, for example: in *gout* - sodium urate, negative birefringent needle-shaped crystals; in *pyrophosphate arthritis* - calcium pyrophosphate, rhomboid or stick-shaped crystals, positive birefringent or non-birefringent.

The ***bacteriologic culture*** **of the fluid** *can identify specific microorganisms in septic arthritis.*

29.5.2. Instrumental methods

Roentgenologic (X-ray, radiological) method allows to reveal *osteoporosis, osteosclerosis, osteophytes, changes in the joint gap, assess the condition of the subscondral bone, the presence of subluxations, ankylosis, et*c. As a rule, pronounced X-ray changes of joints are noted in the presence of clear clinical manifestations of the disease

X-ray signs of the inflammatory joint diseases are an early occurrence of the periarticular osteoporosis (especially in rheumatoid arthritis), and later - narrowing of joint gaps, erosions of the articular surface, cystic remodeling of subchondral bone sections, subluxations and ankylosis (no mobility in the joint). The radiological examination should begin with the joints of the hands and feet in the early stage of the rheumatoid arthritis, and with the sacroiliac joints – in the initial stage of ankylosing spondylitis**.**

X-ray signs of the dystrophic joint lesions (e.g., osteoarthritis) are osteophytes, narrowing of articular gaps, later – a deformation of articular ends of bones. There is no evidence of the bone ankylosis in osteoarthritis.

X-ray signs of the gout are intraosseous cystic masses due to tophi inside or near the joint. These cystic masses may have clear contours ("punched out" lesions). Erosions in the subchondral area of the bone and osteolysis may be found especially in the joints of the great toes, which are more often involved in the process.

CT (computer tomography) *scanning* has the greatest value in the study of the vertebral column. It allows to assess the condition of the intervertebral discs, possible herniated disc protrusion and its direction (into the spinal canal or not), the presence of osteophytes, sequestration of the intervertebral discs and other features.

MRI (magnetic resonance imaging) is now one of the most accurate methods to detect the bone and joint abnormalities. MRI scans of the vertebral column visualize structural changes of the vertebrae and ligamentous apparatus, intervertebral discs, etc. MRI has obvious advantages over CT scanning in the study of large and medium-sized joints. In addition to its high resolution, the method is notable for its safety (compared to X-ray methods. The method is widely used in traumatology practice due to the possibility of creating three-dimensional models.

Arthroscopy is performed by an optical system (arthroscope), which allows to visualize changes inside the joint cavity. It is possible to detect lesions of the meniscus, ligament apparatus, cartilage changes, to assess the synovial membrane condition through biopsy and histological examinations. Arthroscopy is commonly used in traumatology practice, where it has not only diagnostic, but also therapeutic value (arthroscopic operations on damaged joint structures). The knee joint is the most commonly examined by arthroscopy.

Radioisotopic scintigraphy of *bones* is performed with RP (radiopharmaceutical agent). Usually technetium (99mTc) is used as the bone-seeking isotope. The "hot zones" due to a hyperfixation of the RP is found in the sites of the inflammation. The "cold zone" due to a hypofixation of the RP occurs, in particular, in aseptic necrosis of the femoral head.

Densitometry is a useful tool for assessing the density of bone structures and detecting osteoporosis (a decreased bone density). The method provides an evaluation of the degree of the X-ray attenuation of tissues with different densities. The method is based on the photon absorption spectrometry. The darker looks the object, the lower is its density. The bone density gradually becomes less with the older age. The bone density can also be assessed on an ordinary roentgenogram, but such evaluation is a very subjective and inaccurate (as only cases of the marked osteoporosis are identified with a loss at leas30-40% of its original density).

Arthrosonography (a joint ultrasonography) *is a method of visualizing the bony and non-bony structures that form a joint*. The main advantage of ultrasound over other methods of joint examination is its noninvasiveness and harmlessness. The method also describes the soft tissues of the joints well (in contrast to the X-ray method).

Arthrosonography can evaluate changes of the periarticular tissues (e.g. edema), determine the inflammatory fluid in the joint cavity (e.g. synovitis); assess changes of the synovial membrane (e.g. thickening), the articular cartilage (thinning), the ligamentous apparatus of joints (including detection of the torn ligaments), the bone structures that form the joint (osteophytes, erosions), and detect the joint cysts (e.g. Baker's cyst in the knee joint).

The arthrosonography is often used to examine relatively non-deep joints (e.g. knee, and shoulder joints). The ultrasound study can not substitute the radiological examination of the joints, but complements it.

29.6. Basic syndromes (articular syndrome, skeletal muscle damage)

29.6.1. Articular (joint) syndrome

Definition: Articular (joint) syndrome *is a clinical symptom-complex caused by the lesion of the anatomical structures of the joints and periarticular tissues in a variety of the diseases and pathological processes.*

Main causes:

1. Inflammatory joint lesions:
   - infectious arthritis – Gram-positive bacteria (staphylococci, streptococci, and pneumococci); Gram-negative bacteria – (Hemophilus, Neisseria gonorrhoeae; spirochete Borrelia species [in Lyme disease]); tuberculosis; fungi; virus infections - enterovirus, rubella, HIV, hepatitis B and C, parvovirus B19, and COVID-19);
   - reactive arthritis – precipitated by genitourinary (Chlamydia, Chlamydia trachomatis or Ureaplasma urealyticum) or gastrointestinal infections (Escherichia coli, Salmonella, Shigella, Yersinia, Clostridium difficile, and Campylobacter);
   - arthritis in systemic connective tissue diseases (e.g., acute rheumatic fever, rheumatoid arthritis, ankylosing spondylitis [Bekhterev's disease], systemic scleroderma, systemic lupus erythematosus, and systemic vasculitis);
   - microcrystalline arthritis – due to deposition of microctystalls of the uric acid (gout) and calcium pyrophosphate deposition disease (CPPD).
2. Degenerative joint diseases (due to degeneration of the joint cartilage) – osteoarthritis, spondylosis (degeneration of the vertebral column).
3. Other diseases:
   - paraneoplastic arthropathies (in malignant tumours, lymphomas, leukemia);
   - arthropathies associated with endocrine diseases (acromegaly, hypothyroidism, hyperparathyroidism, diabetes mellitus);
   - arthropathies associated with blood diseases (hemophilia, sickle cell anemia, hemochromatosis);
   - soft tissue diseases (e.g., tendinitis, tenosynovitis, bursitis, fibromyalgia).

Clinical manifestation of the joint syndrome are pain, swelling, defiguration (the joint shape change due to exudative and proliferative processes) and deformity (due to bone tissue hyperplasia) of the joint, and limitation of movements in it.

Arthralgia is a joint pain without objective signs of the joint damage (swelling, the local skin hyperemia and hyperthermia, etc.) (Table 29-2).

Table 29-2. Clinical features of the joint syndrome

Symptoms/ Signs	Arthralgia	Arthritis	Degenerative joint diseases
type of the joint pain	pain of the functional or indefinite type	inflammatory pain	mechanical pain
stiffness	does not depend on rest or absent	hours	for a few minutes, after resting
pain on palpation	absent	every time	occasionally
local hyperthermia	absent	frequently	in secondary synovitis
crepitation during the joint movements	absent	soft	pronounced
bony hyperplasia, osteophytes	absent	may be in a chronic disease	frequently
general complaints (subfebrile fever, weakness, weight loss, etc.)	occasionally	frequently	absent
fatigue	usually in the morning	in the second half of the day	absent
depression, emotional lability	frequently	occasionally	absent
X-ray findings	absent	periarticular osteo-porosis; narrowing of articular gaps; erosions of the articular surface; later –subluxa-tions and ankylosis	osteophytes, narrowing of articular gaps; later - deformations articular ends of the bone
Laboratory tests: CRP, ESR	usually normal	significant increase in exacerbations of the disease	more often normal, or there is a slight increase

Arthralgia may be the initial manifestation of a serious pathology. Arthralgia appears due to hypersensitivity of the pain receptors (hyperalgesia) and transient disturbances in the blood supply to the joints. There are *monoarthralgia*

(one painful joint), *oligoarthralgia* (2-4 painful joints), and *polyarthralgia* (5 or more painful joints).

Functional joint pain is a characteristic of an arthralgia (see Sections 29.2. Subjective (inquiry) of patients with locomotor system pathology (Table 29-1). The pain is of the undetermined nature, uncertain rhythm and variable intensity. It increases with psycho-emotional stress, and disappear during sleep. Analgesics may not be effective while sedatives and tranquilizers relieve pain.

Arthritis is characterized by an inflammatory joint involvement. *Monoarthritis, oligoarthritis, and polyarthritis are distinguished.*

The course of arthritis in the absence of proper therapy is usually characterized by an acute onset, with exacerbations and remissions, and progressive deterioration of function (limitation of all movements) of the affected joints. This results in significant deformities, contractures, subluxations, fibrous and bone ankylosis.

Signs of the joint inflammation include a pain, hyperemia (redness), swelling, restriction of movement, and a local increase in the skin temperature. In arthritis, all inflammatory signs are not always found. Three are more common: pain, swelling and limitation of movement in the joint.

Inflammatory joint pains are constant, increased with prolonged immobility. The spontaneous pain in affected joints appears and increases in the second half of the night or in the morning, decreases or disappears in the evening. It is observed both during movements and at complete rest. The pain is accompanied by a feeling of morning stiffness. In some cases, the patient has to move for the relief.

Persistent swelling or defiguration, hyperemia of the affected joint are noted as a result of the inflammatory effusion into the joint cavity and exudative-proliferative changes of periartricular tissues. The palpation finds a diffuse tenderness and an increased skin temperature over the joint.

Rheumatic migratory polyarthritis *is one of the two basic clinical manisfestations of the acute rheumatic fever together with rheumatic carditis (an inflammation of the heart).* It is characterized 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 the pain; pain disappears in one joint and develops in others;
- severe pain, swelling, hyperemia, and hyperthermia of the joints;
- 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;
- salicylates and other anti-inflammatory drugs usually cause prompt resolution of joint symptoms.

The rheumatoid arthritis is a chronic systemic autoimmune disease that primarily involves the joints. It manifests mainly by pain and swelling in various joints, especially in the joints of the fingers and toes. Symmetrical affection of the small joints of the hands and feet is characteristic. Pain increases with movement and at rest. There are morning stiffness (more 60 minutes after rising).

In rheumatoid arthritis, patients may develop fixed joint deformities, especially flexion contractures, *ulnar deviation of the fingers, "swan neck", and boutonnière (buttonhole) deformities* (see Fig. 29-6).

Degenerative joint diseases (e.g. osteoarthritis, spondylosis) are characterized by degenerative-dystrophic changes in the cartilage and bone structures of the peripheral joints and joints of the spine with primary damage of the articular cartilage due to metabolic disorders.

Predominant localization of the degenerative joint diseases are interphalangeal joints, hip joints (*coxarthrosis*), knee joints (*gonarthrosis*), and spinal joints (*spondylosis*).

Mechanical joint pains are slight to moderate in intensity, appear at mechanical (trauma; work with excessive load; sports load) and static (when holding weight, muscle strain) loads, and with movements; intensify at the end of the day, disappear at rest and at night. The pain is caused by the friction of the two mismatched surfaces of the joint cartilage on movement.

Joint deformity as a result of bony overgrowths, thickening and wrinkling of the joint capsule (e.g., *Heberden nodules, Bouchard nodules* in osteoarthritis) is characteristic. The symptoms appear gradually and progress slowly.

Arthropathy is a group of the secondary (not independent) inflammatory or degenerative-dystrophic lesions of the locomotor system, which occur in the course of general-pathological processes (e.g., paraneoplastic arthropathies in malignant tumours; endocrine arthropathies in acromegaly, diabetes mellitus; arthropathies associated in blood diseases – in hemophilia, sickle cell anemia, etc.). It is only one of the manifestations of the disease.

Arthropathies vary in severity from arthralgia with myalgia and ossalgia to chronic arthritis. Their common characteristics are an asymmetric joint involvement, as well as the absence of the joint gap and articular surfaces lesions, parallelism of their course with the dynamics of the basic pathology, and the efficacy of the underlying disease treatment.

Periarticular tissue lesions

Periarticular soft tissues include the muscles, tendons, articular capsule, ligaments, fascia, and aponeurosis. The periarticular tissue lesions include:

- *tenosynovitis* – an inflammation of the tendon sheath;
- *tendinitis* – an inflammation of the tendon;
- *bursitis* – an inflammation of the bursa synovialis;
- *enthesopathy (enthesitis)* – an inflammation of the enthesis (the site of tendon or ligament attachment to bone or joint capsule);
- *capsulitis*, an affection of the joint capsule;

- *fasciitis, aponeurositis* – a lesion of the fascia and aponeurosis;
- *myofascial pain syndrome* - changes in the skeletal muscle and adjacent fascia.

Typical features of patients with periarticular lesions: young and middle-aged people, chronic trauma to the joints, excessive physical strain, and absence of general manifestations (Table 29-3).

Table 29-3. Comparative characteristics of the arthritis and periarticular tissue lesions

Characteristics	Arthritis	Periarticular tissue lesions
Character of the pain	constant	with certain movements
Localization of the pain	diffuse, over the entire joint projection	local pain with the most painful point
Active and passive joint mobility	reduced both active and passive movements	decrease in the volume of active movements, while preserving the volume of passive movements
Swelling of the joint	diffuse swelling; an effusion in the joint cavity	asymmetric swelling associated with certain bursa or tendon sheath

Characteristics of the periarticular pain: the pain is local with the point of the maximum painfulness, and increases with certain movements.

Local survey finds an asymmetric swelling of the affected joint associated with certain bursa or tendon sheath in periarticular tissue lesions. There are a decrease in the volume of active movements of the joint, while the passive movement volume is preserved.

On the contrary, there are a diffuse swelling of the entire joint and effusion in the joint cavity, as well as a limitation of the active and passive mobility of the affected joint in arthritis.

Diagnosis of the articular (joint) syndrome is based on:

(1) ***distinct clinical symptoms and signs*** (*the joint pain, swelling, defiguration and/or deformity, and limitation of movements*);

(2) ***instrumental data*** – *roentgenologic (X-ray, CT) method*s allows to reveal osteoporosis, osteosclerosis, osteophytes, changes in the joint gap, the subscondral bone, subluxations, ankylosis, etc.; *arthrosonography* can evaluate changes of the periarticular tissues (e.g. edema), exudate in the joint cavity, changes of the synovial membrane and the articular cartilage; *MRI* visualize structural changes of the vertebrae, intervertebral discs, etc.

(3) ***laboratory data*** – increase of the *serum CRP and ESR* for assessment of the inflammatory activity in the arthritis; increase of the *serum anti–cyclic citrullinated peptide antibody (anti-CCP)* is diagnostic in rheumatoid arthritis, increase of the *serum anti-streptolysin-O (ASL-O)* – in acute rheumatic fever, an increase of the *serum uric acid* (*hyperuricemia*) and in the urine (hyperuricosuria) – in gouty arthritis; etc.

29.6.2. Skeletal muscle disorders

Definition: Syndrome of the skeletal muscle disorders *refers to the common clinical manifestations of diseases that affect the muscles joined to the bones (skeletal muscles).*

The causes include:

- Trauma or excessive muscle strain, such as sprains, spasms, or tendonitis;
- Hereditary and genetic disease (e.g. muscular dystrophy);
- Malignant tumors;
- Inflammation (myositis, such as polymyositis, dermatomyositis);
- Intoxication (e.g., alcoholism, abuse of narcotics);
- Neuromuscular disorders (nerve diseases that affect the muscles, such as amyotrophic lateral sclerosis, myasthenia gravis);
- Infectious diseases (e.g., virus infections – HIV/AIDS, COVID-19, influenza; bacterial infections – Salmonella typhi, staphylococci; helminthic infection – trichinellosis);
- Certain medications (e.g., glucocorticosteroids, statins, antiviral therapy, chloroquine, tumor necrosis factor-α inhibitors, amiodarone, colchicine);
- Metabolic causes (e.g. severe malnutrition, chronic liver failure, hypokaliemia);
- Endocrine causes (e.g., diabetes mellitus, hyper- and hypothyroidism, hyperparathyroidism, Cushing disease, hyperaldosteronism);
- Vascular diseases, due to conditions of the blood vessels (e.g. peripheral arterial atherosclerotic disease);
- Age (e.g. sarcopenia in older people).

Myositis and endocrine myopathies are the most common skeletal muscle disorders (usually occurring in middle-aged women than in men).

Classification of the skeletal muscle disorders

Skeletal muscle disorders are classified based on the following criteria –

1. *Primary or secondary muscle disorders:*

Primary muscle diseases are direct muscle abnormalities, such as polymyositis, dermatomyositis, myasthenia gravis.

Secondary muscle disorders are caused by diseases of other organs and can lead to muscle damage, such as those caused by endocrine problems, infectious diseases, metabolic disorders.

2. *Genetic or acquired muscle disorders:*

Genetic muscle disorders are due to inheriting abnormal gene mutations (e.g., congenital primary myopathy, mitochondrial myopathy).

Acquired muscle disorders develop over the life of the patient and may be associated with pathologies of other systems and organs, infections, exposure to certain medications, or electrolyte imbalances, etc.

3. *Neuromuscular disorders or myopathies:*

Neuromuscular disorders (e.g. multiple sclerosis, muscular dystrophy, myasthenia gravis) affect the nerves that control skeletal muscles.

Myopathies are muscular disorders that are not due to nervous system abnormalities.

Clinical picture

The most ***characteristic complaints*** are *muscle weakness*, most often in the upper arms, shoulders, and hips; *muscle pain*, possibly with difficulty breathing; *muscle cramps*, *muscle stiffness* (often of the neck), and spasms; and *fatigue on exertion*, and a *fever*.

Other symptoms of the muscular disorders include loss of the muscle mass; movement and gait abnormalities; frequent unexpected falls, dizziness, dysphagia, and swallowing difficulties, sensory disturbances (numbness, tingling, or painful sensations).

Anamnesis. Myopathy usually begins with the appearance of slight muscle weakness in the extremities. Fatigue on walking or other physical exertion occurs more quickly than before the onset of myopathy.

Myopathies, in contrast to neuromuscular disorders, are characterized by progressive difficulty in movement, requiring the use of the proximal muscles of the limbs (getting up from a chair, climbing stairs or lifting heavy weights).

The patient's questioning should include a search for symptoms suggestive of the cause of the myopathy, including:

- skin rash: dermatomyositis, Lyme disease, or syphilis;
- fever: chronic infection;
- muscle pain: myositis;
- dyspnea: heart failure, pulmonary pathology, or anemia;
- anorexia and weight loss: cancer or other chronic disease;
- change in the urine color: liver (due to jaundice) or kidney (due to hematuria) diseases;
- cold or heat intolerance: thyroid disorders (the first is hypothyroidism, the second is hyperthyroidism).
-

Physical examination:

Patients with myopathy are unable by themselves to sit on the support (bed or chair) and get up from it because of the pain and weakness in the muscles of the shoulder girdle, neck, thighs and buttocks (*proximal muscle weakness*). The extensor muscles of the neck may be affected, resulting in difficulty holding the head ("*falling head*" sign). Affection of the oropharyngeal muscles results in impaired swallowing, dysphagia and nasalized speech.

Hyperemia of the skin of the face, neck area, the back of the hands is observed in dermatomyositis. Periorbital reddish purple rash on or around the eyelid (sign of the "heliotrope rash") often occurs against the background of facial hyperemia.

Myalgia and muscle tenderness on palpation is common in ***inflammatory myopathies (myositis)***. An increase in body temperature is a characteristic of the myositis. Decreased muscle force and atrophy (loss of the muscle mass) of the thigh and shoulder girdle muscles are noted. Skeletal muscle damage in the long-term course of the myositis (e.g. dermatomyositis) can result in the formation of the calcified foci (palpable formations of the stony density in the muscle and/or subcutaneous tissue). Dermatomyositis can also affect the joints (arthralgia) and heart (arrhythmias, heart failure).

Endocrine myopathies are secondary muscle disorders due to impaired hormonal secretion of the endocrine glands.

Hyperthyroidism is associated with rapidly increasing muscle weakness and atrophy of the proximal muscles (*thyrotoxic myopathy*). Muscle weakness is observed when walking, getting up from the knees, lifting weights).

Patients in hypothyroidism complain mainly of the proximal muscle weakness, stiffness, and myalgia. Cramps in leg (*gastrocnemius muscles*) are characteristic of the *hypothyroid myopathy*. There may be muscle enlargement (*pseudomuscular hypertrophy*) due to myxedema.

Drug-induced myopathy is due to drug administration in a patient without previous muscle disease. The most common myotoxic medications are glucocorticoids, and statins.

Symptoms of the myopathy (proximal muscle weakness, myalgia, fatigue) usually appear a few weeks or months after starting the treatment and usually resolve within a few weeks after stopping the drug.

Administration of the myotoxic medications (e.g. high dose statins) can be complicated by *rhabdomyolysis (muscle breakdown). Rhabdomyolysis* is an acute necrotizing myopathy that presents with severe pain, muscle swelling, and weakness, and well as a rise of the serum CK up to 2000 times higher than the upper limit of norm. It is associated with *myoglobinuria* (dark brown urine due to the presence of the myoglobin), which can lead to an acute kidney injury.

Neuromuscular disorders are characterized by predominantly a distal muscle weakness – a weak hand grasping, handwriting problems, difficulty walking, a flapping kind of the gait.

Table 29-4. Clinical features of skeletal muscle disorders

Symptoms/ Signs	Myositis (inflammatory myopathy)	Non-inflammatory myopathy	Neuromuscular disease
Muscle weakness	proximal symmetric (muscles of the neck, shoulder and pelvic girdles)	proximal symmetric predominantly	distal symmetric predominantly (muscles of the forearm, hand, foot and leg); generalized or local asymmetric may be
Muscle pain, fever	frequently	occasionally	absent
Decrease of muscle-stretch reflexes	in the late stages of the disease	occasionally	typical
Sensation and mental disorders	absent	occasionally	numbness, paresthesia; reduced sensations (tactile, pressure, temperature, etc.); mental disorders
Muscle biopsy	myofiber necrosis, myophagocytosis, inflammatory infiltrate; in long-standing disease – muscle atrophy and calcification	muscular dystrophy; minimal myofiber necrosis or absent	neurogenic changes; muscular atrophy
Serum creatine kinase (CK)	High (> 10 times than normal)	from mildly elevated to high levels	Normal or mildly elevated levels
Blood inflammatory tests: CRP, ESR	increase	more often normal	more often normal

There are a decrease of the muscle-stretch reflexes (the muscle contraction in response to its passive stretching), sensation disorders in the affected areas (numbness, paresthesias – prickling and tingling sensations, reduced sensations –

tactile, pressure, temperature, etc.). *Diplopia* (double vision) and *blepharoptosis* (drooping eyelids) may occur in some cases of the neuromuscular disorders.

Laboratory-instrumental examination

Serum creatine (CK; cretinphosphokinase, CPK) is a protein enzyme that present in greater amount in the mitochondria and cytoplasm of skeletal muscles.

Normal levels of the CK are 55-170 units/L in males, and 30-135 units/L in females. CK levels are elevated in myositis, myopathies (infectious, drug-induced, endocrine, etc.). Extremely high CK levels occur in rhabdomyolysis. It is not common for serum CK to rise in neuromuscular diseases.

CK may be elevated in the absence of the myopathy. Total serum CK can rise in any condition causing muscle injury (e.g., recent intense physical activity, intramuscular injections, muscle trauma, epileptic seizure, high fever accompanied by tremors), diseases of the myocardium (e.g. acute myocardial infarction, myocarditis), liver (e.g. hepatitis, liver cirrhosis) and kidney (e.g. acute kidney injury, acute glomerulonephritis).

Myoglobinuria is the presence of myoglobin in the urine, which usually results from rhabdomyolysis or muscle injury. Myoglobulinuria is associated with an increase in levels of the CK.

Blood inflammatory tests CRP and ESR are high in myositis.

Evaluation of anti-muscle antibodies, rheumatoid factor and antinuclear antibodies (ANA) is useful for the diagnosis of the autoimmune myositis and association with systemic connective tissue diseases.

Needle electromyography (EMG) is an electrophysiological technique that examines the electrical activity of muscles as well as motor units consisting of several muscle cells, nerve fibers, and spinal cord cells. Electromyography (EMG) shows different results in myopathies and neuromuscular disorders that may be useful in distinguishing between them.

Muscle biopsy can help determine whether a patient has a neurogenic or a myogenic disorder. The biopsy reveals specific features for each type of the skeletal muscle injury: myositis (e.g., polymyositis, dermatomyositis), non-inflammatory myopathies (e.g., endocrine, drug-induced, toxic, metabolic myopathy), and neuromuscular diseases.

Magnetic resonance imaging (MRI) demonstrates signal intensity abnormalities of the muscle due to inflammation, edema, or scarring. MRI can be used to assess the volume of the muscle involvement and to target the muscle biopsy.

Genetic testing is necessary to identify hereditary causes of myopathy (e.g., *Duchenne and Becker muscular dystrophy*) due to mutations in genes encoding proteins critical for muscle structure and function.

Diagnosis of the skeletal muscle disorders syndrome is based on *clinical manifestations* (muscle weakness, muscle pain, muscle stiffness and spasms; and fatigue on exertion), *instrumental data* (e.g., needle electromyography, muscle biopsy, MRI), and *laboratory data* (e.g. increase of the serum CR in inflammatory

and non-inflammatory myopathies, CRP and ESR in the myositis; myoglobinuria in rhabdomyolysis; genetic testing in congenital muscle dystrophy).

29.7. The key points of the theme "Clinical-laboratory Examination and Clinical Syndromes of the Locomotor System"

The ***basic complaints in the locomotor system diseases*** are joint pain, limitation of the joint movements and stiffness, swollen joints, noise effects from movements in the joints (crackles, clicks, crepitation), the bone pain (ostealgia), and muscle pain (myalgia) and weakness.

Inspection of joints reveals changes in their shape and size, such as a *swelling* (due to edema of periarticular tissues and an effusion in the joint cavity), *defiguration* (due to exudative and proliferative processes in the joint), and *deformity* (due to bony hyperplasia – *Heberden nodules, Bouchard nodules* in the interphalangeal joints in osteoarthritis, etc.), skin changes and muscles atrophy in the area of the affected joint, and restriction of the joint movements.

Joint palpation provides an assessment of the skin temperature in the area of the joints (symmetrical joints are being compared), as well as painfulness, the condition of the joint capsule, swelling, presence of the fluid and additional masses in the joints (nodules, gouty tophi, etc.).

Muscles examination notes the muscle tone and strength, atrophy, and the muscle local abnormalities (the muscle pain on palpation, swelling, spasm).

Tests that can help determine the inflammatory nature of the musculoskeletal disease are white blood cell count ***(leukocytosis),*** and an increase in ***erythrocyte sedimentation rate (ESR) and serum C-reactive protein (CRP)***.

Tests that confirm the muscle damage*: an* ***elevated serum creatine (CK; cretin phosphokinase, CPK)*** *and* ***myoglobinuria*** *are the result of the muscle injury, myositis, and myopathies (infectious, drug-induced, endocrine, etc.).*

Roentgenologic (X-ray) method, CT (computer tomography), MRI scanning, and arthrosonography can detect the bone and joint abnormalities, structural changes of the vertebral column, periarticular tissues, and muscles.

Articular (joint) syndrome **is** a clinical symptom-complex caused by the lesion of the anatomical structures of the joints and periarticular tissues in a variety of the diseases and pathological processes.

Diagnosis of the syndrome is based on *clinical manifestations* (pain, swelling, defiguration and deformity of the joint, and limitation of the movements in the joint), *instrumental data* (X-ray, CT, arthrosonography, etc.), and *laboratory data* (e.g. increase of the serum CRP and ESR in the arthritis; an increase of the *serum uric acid* – in gouty arthritis).

Syndrome of the skeletal muscle disorders refers to the common clinical manifestations of diseases that affect the muscles joined to the bones.

Diagnosis of the syndrome is based on *clinical manifestations* (muscle weakness, muscle pain, muscle stiffness and spasms; and fatigue on exertion),

instrumental data (e.g., needle electromyography, muscle biopsy, MRI), and *laboratory data* (e.g. increase of the serum CK in inflammatory and non-inflammatory myopathies, CRP and ESR in the myositis; myoglobinuria in rhabdomyolysis; genetic testing in congenital muscle dystrophy).

29.8. Assessment tests on the theme "Clinical-laboratory Examination and Clinical Syndromes of the Locomotor System"

1. What is true for the inflammatory type of the joint pain?

1. constant pain which increases with prolonged immobility (at night, in the morning);
2. pain intensifies at the end of the day, and disappear at rest and at night;
3. for the relief, the patient has to move;
4. in degenerative-dystrophic joint disease (osteoarthritis), due to mechanical trauma;
5. in arthritis, synovitis, and periarthritis.

2. What is true for the mechanical type of the joint pain?

1. pains are slight to moderate in intensity, appear at mechanical loads;
2. for the relief, the patient has to move;
3. the pain disappears at rest and at night;
4. in arthritis and periarthritis;
5. in degenerative-dystrophic joint disease (osteoarthritis).

3. What is true for pains in ligaments and tendons?

1. pain in the whole joint;
2. for the relief, the patient has to move;
3. pain is localized near the joints at the tendon attachment to bones and joints;
4. the pain occurs during the ligament and the tendon contraction; other movements are painless;
5. in periarthritis and tendovaginitis.

4. Signs of the joint disease on inspection include:

1. changes in the joint shape and size (swelling, defiguration, deformity);
2. restriction of the joint movement;
3. proximal muscle weakness;
4. changes in laboratory blood values (increased serum CK and myoglobinouria)
5. hyperemia of the skin on the joint.

5. What are characteristics of the gouty tophi?

1. flaky papules on the scalp and the extensor surfaces of joints
2. whitish nodules in the subcutaneous tissue above the joints and auricles;
3. masses of the monosodium urate;
4. masses of the cholesterol and triglycerids;
5. in rheumatoid and psoriatic arthritis;

6. in gouty arthritis.

6. What are characteristics of the joint swelling?

1. an irregular change in the shape of the joint;
2. the bone overgrowth;
3. an uniform (regular) increase in volume of the joint;
4. smoothing of the joint contours due to edema of periarticular tissues
5. an accumulation of the effusion in the joint cavity.

7. What are characteristics of the joint defiguration?

1. an irregular change in the shape of the joint;
2. the bone overgrowth;
3. exudative and proliferative processes (chronic inflammation) in the joint;
4. uniform (regular) increase in volume of the joint;
5. smoothing of the joint.

8. What do you understand by the joint deformity?

1. an irregular change in the shape of the joint due to exudative and proliferative processes;
2. persistent irregular changes in the shape of the joint due to the bone hyperplasia;
3. Heberden and Bouchard nodules of the interphalangeal joints;
4. an uniform (regular) increase in volume of the joint;
5. smoothing of the joint contours due to edema of periarticular tissues.

9. Most common joint deformities in rheumatoid arthritis:

1. ulnar deviation of the fingers toward the ulnar bones;
2. Heberden and Bouchard nodules of the interphalangeal joints;
3. “swan neck” deformity is an overextension at the proximal interphalangeal joints of the hand;
4. boutonnière deformity of the fingers;
5. drum stick fingers (clubbing in the nailbed).

10. Which tests can help determine the inflammatory nature of the musculoskeletal disease?

1. hypercreatininemia;
2. increased white blood cell count (leukocytosis);
3. increase in erythrocyte sedimentation rate;
4. elevated level of the serum C-reactive protein (CRP);
5. hypoproteinemia;
6. decrease in hemoglobin and red blood cell count (anemia).

11. What is true for arthralgia?

1. the joint pain without objective signs of the joint damage;
2. the joint swelling;
3. a local skin hyperemia and hyperthermia;
4. the joint stiffness;
5. the joint is painless on palpation.

12. What are characteristics of the arthritis?

1. pains are constant, increased with prolonged immobility;
2. the pain disappears at rest and at night;
3. local hyperthermia;
4. significant increase in CRP and ESR;
5. the joint is painless on palpation;
6. the joint stiffness.

13. What are characteristics of the degenerative joint diseases?

1. the joint is painless on palpation
2. mechanical joint pain;
3. pronounced crepitation during the joint movements;
4. bony hyperplasia, osteophytes
5. significant increase in CRP and ESR.

14. What are clinical features of the rheumatic migratory polyarthritis?

1. symmetrical arthritis of large joints (ankles, wrists, knees, elbows);
2. symmetrical affection of the small joints of the hands and feet;
3. fixed joint deformities and other clinical manifestations are completely or partially non-reversible
4. migrating character of the pain; pain disappears in one joint and develops in others;
5. severe pain, swelling, hyperemia, and hyperthermia of the joints;
6. all clinical findings are completely reversible.

15. What are clinical features of the rheumatoid arthritis?

1. acute symmetrical arthritis of large joints (ankles, wrists, knees, elbows);
2. chronic symmetrical arthritis in various joints, especially in the joints of the fingers and toes;
3. migrating character of the pain; pain disappears in one joint and develops in others;
4. all clinical findings are completely reversible;
5. fixed joint deformities and other clinical manifestations are completely or partially non-reversible.

16. Which laboratory tests are of the diagnostic value in rheumatic migratory polyarthritis?

1. rheumatoid factor (RF) is positive;
2. increased CRP;
3. leukocytosis and increased erythrocyte sedimentation rate (ESR);
4. high ASL-O (anti-streptolysin-O) titer;
5. increased anti–cyclic citrullinated peptide antibody (anti-CCP) levels.

17. Which laboratory tests are of the diagnostic value in rheumatoid arthritis?

1. increased CRP;

2. increase in the blood uric acid (hyperuricemia) and in the urine (hyperuricosuria);
3. leukocytosis;
4. rheumatoid factor (RF) is positive;
5. increased anti–cyclic citrullinated peptide antibody (anti-CCP) levels;
6. high ASL-O (anti-streptolysin-O) titer.

18. What are clinical features of patients in the periarticular tissue lesions?

1. young and middle-aged people with chronic trauma to the joints and an excessive physical strain;
2. local pain with the point of the maximum painfulness, and increases with certain movements;
3. decrease in the volume of active movements of the joint, while the passive movement volume is preserved;
4. limitation of the active and passive mobility of the affected joint
5. diffuse swelling of the entire joint;
6. asymmetric swelling of the affected joint.

19. What are clinical features of skeletal muscle disorders?

1. distal symmetric muscle weakness;
2. local or asymmetric muscle weakness;
3. proximal symmetric muscle weakness;
4. muscle pain;
5. sensory and mental disorders.

20. Which laboratory tests are of the diagnostic value in skeletal muscle disorders?

1. increase in serum creatine kinase (CK);
2. myoglobinuria;
3. muscle biopsy;
4. increase in serum creatinine and urea;
5. increase in the blood uric acid (hyperuricemia) and in the urine (hyperuricosuria).

21. What are clinical-laboratory features of the myositis inflammatory myopathy (myositis)?

1. distal muscle weakness (forearm, hand, foot) and muscle pain rarely;
2. proximal symmetric muscle weakness (muscles of the neck, shoulder and pelvic girdles) and muscle pain frequently;
3. normal body temperature;
4. increase in CRP and ESR;
5. muscle biopsy finds muscular dystrophy;
6. normal serum creatine kinase (CK).

22. What are clinical-laboratory features of the non-inflammatory myopathy?

1. proximal symmetric muscle weakness ((muscles of the neck, shoulder and pelvic girdles);
2. muscle pain and fever;
3. increase in CRP and ESR;
5. muscle biopsy finds muscular dystrophy;
6. mild increase in serum creatine kinase (CK).

23. The most important causes of drug-induced myopathy:
1. antibiotics;
2. statins;
3. glucocorticosteroids;
4. thiamin;
5. tocopherol.

24. What are clinical-laboratory features of the neuromuscular disease?
1. proximal symmetric muscle weakness (muscles of the neck, shoulder and pelvic girdles);
2. distal symmetric muscle weakness (forearm, hand, foot and leg);
3. muscle pain and fever;
4. numbness, paresthesia, reduced sensations (tactile, pressure, temperature, and mental disorders;
5. muscle biopsy finds muscular necrosis;
6. high increase in serum creatine kinase (CK).

Application

Answers to the test questions for supervised students' individual work

Standards of the assessment tests on the theme “Subjective and Objective Examination of Patients with Gastrointestinal Diseases” Chapter 14

Number of question	Variant of answers	Number of question	Variant of answers
1	2,3	**11**	1,2,3
2	1	**12**	2,3
3	1,2,3,4	**13**	1,5
4	1,2,3,5	**14**	2,5
5	2,3,5	**15**	1,2,3,4,5
6	1	**16**	3
7	3	**17**	1,2
8	1	**18**	3
9	1,2,3,4	**19**	3,4,5
10	1,2,3,4	**20**	1

Standards of the assessment tests on the theme “Palpation of the Abdomen” Chapter 15

Number of question	Variant of answers	Number of question	Variant of answers
1	1,2,3,4	**11**	1
2	2,3	**12**	2,3,4,5
3	1	**13**	2,3,5
4	3	**14**	1,2,3,4
5	1	**15**	1,4
6	4,5	**16**	2,3,4
7	1,2,3,4,5	**17**	1,3,4,5
8	1,2,3,4	**18**	1,3,4
9	1,4,5	**19**	2,3,5
10	5	**20**	1,2,3,5

Standards of the assessment tests answers on the theme "Laboratory and Instrumental Examination of the Gastrointestinal tract" Chapter 16

Number of question	Variant of answers	Number of question	Variant of answers
1	5	**11**	1,4
2	1	**12**	1,2,3
3	2	**13**	2,5
4	2	**14**	1,2,4,5
5	2,4,5	**15**	2
6	2,4	**16**	1
7	1,3	**17**	1
8	1,2,5	**18**	1,3
9	2,3	**19**	4
10	1,3,4,5	**20**	2

Standards of the assessment tests answers on the theme "Clinical-laboratory Syndromes of the Gastrointestinal Tract Diseases" Chapter 17

Number of question	Variant of answers	Number of question	Variant of answers
1	1	**13**	1,3,4
2	1,2,5	**14**	1,4
3	2,3,4	**15**	1,2,3
4	1,2,3,4	**16**	2,3
5	1,2,3,4	**17**	2,3,4
6	3,4,5	**18**	2,3,4,5
7	1,2,3,4,5	**19**	2,3,5
8	1,3	**20**	3,4,5
9	1,3,4	**21**	1,4
10	2	**22**	2,3,4
11	1,2,4,5		
12	1,2		

Standards of the assessment tests answers on the theme "Subjective and Objective Examination of Patients with Diseases of the Liver and Biliary Tract" Chapter 18

Number of question	Variant of answers	Number of question	Variant of answers
1	1,3	**13**	1,2,4
2	1,2,3,4	**14**	1,2,3,4,5
3	1,3	**15**	2,4
4	2,4	**16**	1,2,3,4,5
5	1	**17**	5
6	1,2,3	**18**	5
7	2,3,4	**19**	3
8	2	**20**	2,4,5
9	1	**21**	1,2,3
10	4	**22**	2
11	1	**23**	1,2,3,4,5
12	3		

Standards of the assessment tests on the theme "Laboratory and Instrumental Examination of Liver and Biliary Tract" Chapter 19

Number of question	Variant of answers	Number of question	Variant of answers
1	1,3,5	**12**	1,2,3,4
2	1,2	**13**	2,4,5
3	4	**14**	2,3
4	2,3,5	**15**	1,2
5	1	**16**	1,2,3,4
6	1	**17**	1,2,3
7	1,2	**18**	2,3,4,5
8	2	**19**	2,3,4,5
9	4	**20**	4,5
10	1,2	**21**	1,3,5
11	2,3,4		

Standards of the assessment tests on the theme "Clinical-laboratory Syndromes of the Liver and Biliary System Diseases" Chapter 20

Number of question	Variant of answers	Number of question	Variant of answers
1	2,5	**13**	1,4
2	1,2,3,4	**14**	1
3	1,3,4	**15**	2,3,4
4	2,3,5	**16**	2,3,5
5	2,3,4	**17**	1,2,3
6	3,4	**18**	1, 2
7	2,3,4	**19**	1,2,3,4
8	2	**20**	2,3,5
9	3,4,5	**21**	3,4
10	1,3,4,5	**22**	1,2
11	1,2,3,4	**23**	4,5
12	1,2,3,4		

Standards of the assessment tests on the theme "Subjective and Objective Examination of Patients with Diseases of the Urinary System" Chapter 21

Number of question	Variant of answers	Number of question	Variant of answers
1	1,2,3	**13**	5
2	1,2,3	**14**	2
3	1	**15**	1,2
4	1,2	**16**	1,3
5	1,3,5	**17**	4
6	1,2	**18**	1,3
7	5	**19**	3,5
8	2	**20**	1,2,4,5
9	3	**21**	2,4
10	4	**22**	1,2,3,5
11	2	**23**	1
12	1	**24**	1,2,4

Standards of the assessment tests on the theme "Laboratory - Instrumental Examination of the Urinary System" Chapter 22

Number of question	Variant of answers	Number of question	Variant of answers
1	4	**12**	1,2,3
2	3	**13**	2,3
3	1,2,3	**14**	2,3,4
4	1,4,5	**15**	1,3,5
5	1,3,4	**16**	1,2,3,4
6	1	**17**	3,4,5,6
7	1	**18**	1,4,5
8	2	**19**	1,4
9	2,3,5	**20**	2,5
10	1,4,5	**21**	1,3
11	3	**22**	2,3,4

Standards of the assessment tests on the theme "Basic Clinical-Laboratory Syndromes of the Kidneys and Urinary Tract Diseases" Chapter 23

Number of question	Variant of answers	Number of question	Variant of answers
1	1,2,3	**12**	1,2,4
2	2,3,4,5	**13**	2,3,4,6
3	2,3	**14**	2,4,5,6,
4	1,2,3,4	**15**	1,3,4
5	1,2,5	**16**	1,3,5
6	3,4	**17**	2,3,4
7	1	**18**	2,3,6
8	2,3	**19**	3,4,5
9	1	**20**	1,3,5
10	1,2	**21**	1,3,4,6
11	4,5	**22**	1,2,5

Standards of the assessment tests on the theme "Clinical Examination of Patients with Blood System Diseases" Chapter 24

Number of question	Variant of answers	Number of question	Variant of answers
1	1,2,3	**7**	2,6
2	2,3,4	**8**	3
3	1,2,3,6	**9**	1,3
4	2,3,4,6	**10**	1,2,3,5
5	1,4	**11**	4,5,6
6	2,3,5	**12**	1,4,5

Standards of the assessment tests on the theme "Laboratory and Instrumental Examination of Patients with Blood System Diseases" Chapter 25

Number of question	Variant of answers	Number of question	Variant of answers
1	3	**13**	2,3,5
2	4	**14**	1
3	2	**15**	1,4
4	3	**16**	2,4
5	2	**17**	1,2,3
6	1	**18**	1,2,4,5
7	2	**19**	3
8	2,3,4	**20**	2,3,5
9	2,4,5	**21**	1,2,4
10	1,2,3	**22**	1,2,4,5
11	1,2,3	**23**	2,3,5,6
12	1,2,4,5	**24**	1,2,3

Standards of the assessment tests theme "Clinical Syndromes of the Blood System Diseases" Chapter 26

Number of question	Variant of answers	Number of question	Variant of answers
1	1,2	**9**	2,3,5
2	2,3,4	**10**	1,4,5,7
3	1,3,4,6	**11**	1,2,3,4,5
4	4,5	**12**	3,4,6
5	1,2,3	**13**	1,3,4,5
6	2,3,4,6	**14**	2,3,5,6
7	1,2,3	**15**	1,3,5
8	1,3,6	**16**	1

Standards of the assessment tests answers on the theme "Clinical and Laboratory and Instrumental Examination of Patients with Endocrine System Diseases" Chapter 27

Number of question	Variant of answers	Number of question	Variant of answers
1	1,2,3	**11**	2,3,4
2	1,3,5,6	**12**	1,3,4
3	1,3,4,5	**13**	2,3,4
4	3,4,5	**14**	1,3,6
5	1,4	**15**	2,3,5
6	1,3,4,5	**16**	3,4,5
7	2,4	**17**	1,4,5
8	2,3,4,6	**18**	2,3
9	1,4,5,6	**19**	1,2,3
10	3,4,5,6	**20**	1,3,4

Standards of the assessment tests answers on the theme "Assessment tests on the theme "Clinical Syndromes of the Endocrine System Diseases" Chapter 28

Number of question	Variant of answers	Number of question	Variant of answers
1	1,2,3,5	**12**	2,4
2	1,4,5	**13**	1,4,5
3	1,3,5	**14**	2,3,4
4	2,4	**15**	3,4
5	1,3,5	**16**	1,2
6	1,3,4	**17**	1,3,4,5
7	1,3,5	**18**	2,3,4
8	2,3,4,5	**19**	2,4,6
9	1,3,4,5	**20**	2,3,4
10	3,4,6	**21**	1,2,3,5
11	1,2,5,6	**22**	1,2,3

Standards of the assessment tests answers on the theme "Assessment tests on the theme Clinical-laboratory Examination and Clinical Syndromes of the Locomotor System" Chapter 29

Number of question	Variant of answers	Number of question	Variant of answers
1	1,3,5	**13**	2,3,4
2	1,3,5	**14**	1,4,5,6
3	3,4,5	**15**	2,5
4	1,2,5	**16**	2,3,4
5	2,3,6	**17**	1,4,5
6	3,4,5	**18**	1,2,3,6
7	1,3	**19**	3,4
8	2,3	**20**	1,2,3
9	1,3,4	**21**	2,4
10	2,3,4	**22**	1,5,6
11	1,5	**23**	2,3
12	1,3,4,6	**24**	2,4

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