**PATHOPHYSIOLOGY OF DIGESTION AND LIVER**

Insufficiency of digestion is such a state of the gastrointestinal tract when it does not ensure assimilation of the food entering in the organism.

This state results in negative nitrogen balance, hypoproteinemia, exhaustion of the organism, hypovitaminoses, disturbances in the reactivity, etc.

Activity of all parts of the digestive system is regulated by the same neurohumoral mechanisms. Therefore, functionally various parts of the gastrointestinal tract constitute a single system, and disturbances in one part cause disorders also in the function of another parts. The compensatory resources of the digestive system are great. For instances; dog may preserve its viability after removal (gradually, in many stage operation) of stomach, a great part of small intestine, large intestine (except its initial part and rectum).

Observation of changes that accompany removal of different parts of the gastrointestional tract in this type experiments permits to study their functions and compensatory potential. Removal of cardiac part of the stomach in dogs causes polyphagia. After stomach resection part of small intestine widens and undertakes reservoir function of stomach. In people after stomach resection postgastrectomy syndrome or dumping syndrome is observed: general weakness nausea, tachycardia, increased sweating, dizziness, warm sensation. The changes in the organism during dumping syndrome are explained by reflex processes resulted from rapid filling of the small intestine. The main etiologic factors of the digestive system diseases are the following:

1. Disorders in nutrition, lack of appetite, reaction of food in irregular feeding, long intake of low quality, dry, harsh, hot or cold food, disorders of mastication.
2. Infections affecting digestive system (abdominal typhoid, paratyphoids, dysentery, alimentary, toxoinfections), helminths, protozoa;
3. Alcoholic drinks and smoking;
4. Poisonous substances (heavy metal salts, plant poisons).
5. Injurious conditions of production (in chemical and printing industry, hot shops).
6. Psychic trauma, negative emotions, endocrine disturbances.
7. Congenital defects of the digestive organs.

Disturbances in appetite are the following:

1. Hyperorexia (bulimia)- pathologically increased appetite,
2. Insatiable hunger results in polyphagia (sharp increase in food consumption). It is observed as a result of increased or perverted metabolism, thyrotoxicosis, diabetes mellitus, some functional and organic diseases of the central nervous system (neuroses , tumors of the brain , certain lesions in the subcortical region , especially in hypothalamius). In experiment hyperorexia is reproduced by destruction of ventromedial hypothalamic nuclei.
3. Hyporexia (decreased appetite) or anorexia (lack of appetite) are one of the main symptoms of the diseases of the gastrointestinal tract that are accompanied by diminished secretion of digestive juices. Besides, they are caused by a number of infectious diseases, avitaminoses, negative emotions, etc. In experiment anorexia is reproduced by destruction of lateral hypothalamic nuclei.
4. Parorexia (perverted appetite) is characterized by the tendency to consume nonalimentary substances (chalk, coal). It is caused by central and peripheral disturbances in the functions of the gustatory analyzer.
5. Rapid satiety - is characterized by disappearance of appetite shortly after beginning of taking a food. It is observed in postresection syndrome (after stomach resection), alcoholic intoxication, neurotic states, etc.

Frequently disturbances in digestion begin in oral cavity. Since mastication of food cause reflex secretion of gastric and pancreatic juices, disturbances in the processing of food in the oral cavity affect the function of lower parts of the digestive tract. Besides, poorly ground food causes disorders of gastric digestion which often give rise to gastritis.

The following factors cause disturbances in mastication:

1. lesion (caries parodontosis) or absence of a large number of teeth;
2. lesions to the masticatory mucles or disturbances in their innervation;
3. lesions to jawbones or temporomandibular joints;
4. inflammatory processes in the oral mucosa and gingiva (stomatitis, gingivitis).

Disorders in salivary secretion are the following:

1. hypersalvation – increased secretion of saliva;
2. hyposalivation – depression of salivary secretion.

Hypersalivation carries out some defensive function, that is, certain toxic metabolites and poisons are excreted from the organism in saliva.

But loss of large amounts of saliva (5-14 litres instead of the normal 1-2 litres) leads to emaciation of the organism.

Increased salivation overlubricates the alimentary bolus; the swallowed saliva neutralizes the gastric juice with the result that digestion in the stomach diminishes and processes of fermentation and putrefaction develop. Protracted influense of saliva causes necrosis and maceration in the skin of lips.

Hypersalivation results from the direct or reflex stimulation of salivary center in medulla oblongata or secretory nerves of the salivary gland:

1. some lesions to the central nervous system (bulbar paralysis);
2. inflammatory processes in the oral mucosa (stomatitis, gingivitis);
3. diseases of the esophagus;
4. inflammatory processes in the gastric mucosa (gastritis);
5. helminthic invasion;
6. toxicosis of pregnancy;
7. intoxication by some vegetative poisons, especially in cholinomimetics (pilocarpine, physostigmine–eserine).

Hyposalivation impedes chewing, swallowing and speech, promotes lesions to the oral and gastric mucosa. Favourable conditions (decreased amount of lysozyme) for reproduction of microorganisms and inflammatory processes in the oral cavity come into being.

Hyposalivation is observed in the following cases:

1. dehydration of the organism (increased sweating , diarrhea);
2. feverish diseases;
3. emotional stress and pain;
4. diseases of the salivary glands (parotitis tumors) and calculi in the salivary ducts;
5. intoxication by some vegetative poisons, especially m– cholinoblockers (atropine, scopolamine).

Dysphagia, that is, disturbances in deglutiton, may result from central and peripheral lesions of the V (trigeminal ), IX (glossopharyngeal) , X (vagus), XII ( hypoglossal) cranial nerves. Paresis of the muscules of the tongue and some psychic diseases cause disturbances in the voluntary phase of swallowing. Congenital and acquired defects of the hard and soft palate, tonsillitis, diseases of the mucous membrane of the throat result in dysphagia . Disturbances in the involuntary phase of deglutition may be caused by paresis or spasm of muscules of the esophagus (in the tetanus, rabies, hysteria).

Pathological changes in the esophagus consist mainly in impeded movement of the alimentary bolus towards the stomach. This is usually result of constriction of the esophagus due to anatomic changes in its wall, (tumors, scars), its mechanical compression (tumors, aneurysm of the aorta, abscesses in the tissues surrounding the esophagus) or spastic contraction (neurogenic causes, for instance, hysteria). Paralysis of motor activity of the esephagus arises as a result of affection of the nerves which innervate it.

 As a result of stretching of the esophageal wall a by a foreign body or trauma diverticula are formed. These are local dilatations of the esophagus in which the part of the wall protrude like a hernia. Food is retained in this part and an inflammatory process arises ; the process is accompanied by regurgitation and pain sensation. Sometimes the diverticula rupture , their contents come in contact with surrounding tissues ; the result is ichorous mediastinitis which often leads to death .

Disturbances in the process of digestion in stomach may result from changes in its secretory, motor, reservoir, absorptive and excretory functions.

In pathological states hypersecretion and hyposecretion of gastric juice occur which are usually accompanied by corresponding qualitative changes , that is, hyperacidity and hypacidity , as well as achlorhydria (complete absence of hydrochloric acid) and achylia (absence of hydrochloric acid and enzymes).

 In the hyperacidity (excessive acidity of gastric juice) in terms of units (number of ml of 0.1 N solution of NaOH which neutralizes 100 ml of gastric juice) the total acidity rises above 60 (normally – 40-60 ) and the free hydrochloric acid – above 50 (normally 20-40), whereas PH of gastric juice becomes lower than 1,5.

 In hypersecretion passage of acid gastric contents into duodenum causes reflex spasm of pyloric sphincter, and emptying of the stomach slows down. Pyrosis, eructation, vomiting and constipation (as a result of weakened peristalsis of intestine) are observed . Increased acidity and digestive activity of the gastric juice causes lesions of the gastric mucosa.

 Hypersecretion of gastric juice is observed in the following cases:

1. peptic ulcer of the stomach and duodenum;
2. some types of the chronic gastritis (hyperacid gastritis);
3. pylorospasm and pylorostenosis ;
4. some drugs (asetylsalicylic acid,cortisone);
5. alcoholic drinks;
6. high and low temprature.

In decreased acidity of gastric juice (hypacidity) or complete absence of hydrocloric acid (anacidity or achlorhydria) the total activity is below 30 and may drop to 2-10, whereas free hydrochloric acid is absent.

Hyposecretion of the gastric juice and hypacidity are observed in the following cases:

1. some types of the chronic and acute gastritis(subacid gastritis, anacid gastritis);
2. tumors of stomach;
3. psychic trauma and some neurotic states;
4. dehydration of the organism.

Achylia may be functional and of organic character. In functional achylia after elimination of the etiologic factor(for instance, negative emotion)the gastric secretion recovers, whereas organic achylia is connected with irreversible changes in gastric mucosa. Achylia is observed in the following cases:

1. some types of the chronic atrophic gastritis;
2. carcinoma of the stomach;
3. malignant anemia.

In hyposecretion of the gastric juice accompanied by hypacidity or anacidity digestive function of the gastric juice is disturbed (without hydrochloric acid pepsin is not activated), emptying of the stomach is accelerated (pyloric sphincter is open), secretion of the pancreatic juice is also decreased (in absence of hydrochloric acid secretin is not synthesized), insufficiently processed chyme passes into lower parts of the intestine, irritates its walls and causes diarrhea.

Disturbances in intestinal absorption cause disorders in metabolism, hypovitaminoses, anemia.

Disturbances in motor function of the stomach manifest themselves as changes in the tone and peristalsis of the gastric muscles which occur usually simultaneously. That is, increased tone (hypertension) is observed together with intensified peristalsis (hyperkinesis), whereas decreased tone (hypotension) is accompanied by weakened peristalsis (hypokinesis) .

Hypertension of the gastric muscles may be complete or partial. Complete hypertension is observed in acute gastritis, gastric ulcer or is resulted from reflex influences (in renal or hepatic colics). The main types of the partial hypertension are congenital or acquired cardiospasm and pylorospasm. Acquired pylorospasm develops as complication of gastric ulcer, polyposis gastrica, pyloroduodenitis.When the pylorospasm is accompanied by pylorostenosis, at first peristalsis is intensified. But during protracted stenosis gastric wall is gradually atrophied and loses its tone; peristalsis is also weakened.

Increased peristalsis may be caused by coarse food, alcohol, lactic acid (increased vagus nerve tonicity ). Hyperkinesis is usually accompanied by hyperacidity. Acid chyme, getting into duodenum, causes contraction of pylorus ,and emptying of the stomach is delayed.

Hypotension or complete loss of tone (atonia) may be caused by paresis of gastric muscles, tumors, scars, as well as psychic factors (negative emotions, mental depression). Sometimes excessive dilatation of the stomach during atonia results in severe disturbances in the process of digestion. Gastric perstalsis may decrease in gastritis.

Disturbances in the motor function of the stomach are manifested as pyrosis (heartburn ), eructation (belching ), singultus (hiccough ), nausea, vomiting.

Pyrosis is characrerized by burning sensation in the epigastric and retrosternal areas. It arises when the acid content of the stomach is forced into the esophagus by gastric antiperistalsis (especially in the persons with increased hydrochloric and lactic acids in gastric juice) .

Eructation is ejection of swallowed air from the stomach and gases (hydrogen sulfide, carbon dioxide, methane) if they have been formed in the stomach as a result of impaired digestion. It is observed in disturbed secretory and motor functions of the stomach. Eructation occurs as follows: in case of an open cardia and spasm of the pylorus the diaphragm, which lowers on inhalation, and the tense abdominal muscles press on the stomach; some part is also played by the contraction of the stomch walls. These phenomena are most probably produced by reflexes originating in the stomach or the peritoneum.

Singultus is reflex act which results from irritation of receptors in diaphragm and abdominal cavity organs. Diaphragm, abdominal press muscles and stomach contract and air goes out rapidly through true glottis.

Nausea is often a prodrome of vomiting. It is the conscious recognition of subconscious excitation in an area of the medulla oblongata closely associated with or part of the vomiting center. Nausea can be caused by irritative impulses coming from the gastrointestinal tract, originating in the lower brain associated with motion sickness or impulses from the cerebral cortex to initiate vomiting. But occasionally vomiting occurs without the prodromal sensation of nausea. So, only certain portions of the vomiting centers are associated with the sensation of nausea. Nausea is accompanied by hypersalivation, general weakness, paleness, cooling of extremities, decreased blood pressure (vagus nerve stimulation).

Vomiting is defence reaction serving for removal from the organism of harmful substances getting into the stomach. But in a number of diseases (peritonitis, meningitis, acute infectious diseases, hyperthermia, tumors of the brain, cerebral hemorrhage) vomiting is of pathological character and exhausts the organism. Frequent and excessive vomiting (toxic dyspepsia in infants, toxicosis of pregnancy) causes severe changes in the organism:dehydration, loss of a large amount of electrolytes and hydrochloric acid, disturbances in the acid- base equilibrium, changes in the blood circulation and activity of the respiratory system, etc.

Frequently vomiting occurs as a result of chemical or mechanical irritation of receptors of the stomach (inferior food- stuffs and toxins, excessive filling and overdistension of the stomach). Reflexogenic zones of the vomiting are localized also in the posterior wall of the throat, in the ileocecal area. Besides, impulses from peritoneum, uterus, kidneys, liver and other organs to the central nervous system may cause vomiting. Vomiting also may be of central (increased intracranial pressure, uremia) or conditioned reflex character.

Once the vomiting center (in the medulla oblongata )have been sufficiently stimulated, the vomiting act begins-a deep inhalation, strong contraction of the abdominal muscles, sharp descent of the diaphragm (with closure of the pylorus, contraction of the stomach and opening of cardia)and ejection of the food from the stomach through the esophagus into the oral cavity and to the exterior. The lowering of the epiglottis, rise of the larynx and closure of the rima glottidis prevent the vomit from gaining entrance into the respiratory tract. Contraction of the muscles which raise the soft palate prevent the vomit from entering the nasal cavity. Severe vomiting is accompanied by excessive intestinal peristalsis, sometimes in the opposite direction (antiperistalsis).In such cases the ejected food may contain bile from the duodenum.

Reservoir function of the stomach is closely connected with its tone and peristalsis. All the processes resulting in weakened tone and peristalsis, as well as operations on the stomach (stomach resection, formation of the artificial anastomosis between stomach and intestine) cause disturbances in the reservoir function. The gastric wall becomes thinner, its cavity is dilated, evacuation of the food and gases from the stomach into duodenum is impeded, the processes of fermentation and putrefaction are intensified, the amount of gases in the stomach is increased, pyrosis and eructation become frequent.

Normally absorptive function of the stomach is weak. Atonia and lesion to the gastric wall, gastritis are accompanied by increased absorptive function; high - molecular substances (polypeptides) and toxins easily pass into the blood.

Pathological processes in the stomach cause also disturbances in its excretory function.

In the chronic purulent inflammatory processes secretion of the gastric juice continues ceaselessly, content of hydrochloric acid in it is decreased (or it is absent), but it contains a large amount of nitrogen - bearing organic substances which in intestine are repeatedly absorbed into the blood. However, the absorption rate lags behind the rate of excretion. Loss of nitrogen - containing substances by this way is one of the main pathogenetic mechanisms of cachexia connected with chronic inflammatory processes .

Peptic ulcer of the stomach and duodenum is caused by the following factors;

1. neuregenic agents (psycho – emotional strain, negative emotions, hard brain-work);
2. alimentary factors (disorders in the dietary regimen, coarse food);
3. pharmacological agents –sodium salisylate (damages gastric mucosa directly and causes formation of necrotic foci in it), corticosteroids (promote development of the ulcer, acting on the gastric secretion and formation of the protective mucus), aspirin, cinchophen, pilocarpine, etc.;
4. bad habits (alcholism, smoking).

 In the etiology of the peptic ulcer hereditary and constitutional predisposition plays a certain part. It is assumed that morphofunctional properties of the digestive system and their regulation mechanisms are inherited . So, heriditary predisposition to the peptic ulcer is connected with the weakness of the protective properties of stomach and duodenum.

To reproduse peptic ulcer in experiment the following methods are used:

1. Damage to gastric mucosa by physical or chemical irritants (hot water, argentic nitrate, croton oil, acids).
2. Disturbances in blood circulation in the wall of stomach or duodenum (ligation, embolism or sclerosing of vessels).
3. 3.Long administration of substances increasing gastric secretion (cinchophen , histamine, pilocarpine, physostigmine , pentagastrin).
4. Chronic stimulation of the vagus nerve.
5. Disturbances in the cortical control mechanisms of the gastric function in experimental neuroses.

In comparison with other theories the corticovisceral theory comes closest to truth. After all, the disturbances that form the basis of the preceding theories, also may be explained from the standpoint of the changes in the corticovisceral interrelations.

According to modern concepts peptic ulcer of the stomach and duodenum results from disturbed equilibrium between "damaging" and "protective" factors. Damaging factors include disturbances in motor activity of the stomach and duodenum, increased activity and proteolytic activity of the gastric juice. Protective factors are: mucus which is secreted by the gastric wall and protects the gastric mucosa from the influence of the hydrochloric acid; ability of the mucous membrane to regenerate; the state of the local blood circulation in the gastric wall and nervous trophicity. Frequent psychoemotional strain increases the damaging factors and weakens the protective factors. Hormonal factors also play a part in the development of this disease. For instance in stress situations the peptic ulcer develops as a result of influence of corticosteroids which increase secretion, acidity and activity of the gastric juice but decrease secretion of mucus.

So, in the pathogenesis of the peptic ulcer neurogenic and humoral changes play a part. Besides, it is assumed that peptic ulcer results from local immune reaction against some microorganisms in the mucous membrane of the stomach and duodenum.

Gastric and duodenal ulcers are local manifestations of the general state of the organism, that is, peptic ulcer is a disease of the whole organism - an ulcer disease.

The following types of pathological processes in intestine are distinguished which may be of complex character (disturbances in one function of the intestine cause changes also in other functions):

1. disturbances in the secretion of the pancreatic and intestinal juices and that of bile;
2. disturbances in the process of intestinal absorption;
3. disturbances in the parietal digestion;
4. disturbances in the motor functon of intestines;
5. changes in the intestinal microflora.

Inflammatory processses (duodenitis, enteritis, colitis) and peptic ulcer of duodenum may be accompained by increasing secretory activity of intestines .In the inflammatory processes content of mucus in the intestinal juice is also increased. Sometimes changes in secretory and motor activity of intestines result from disturbances in the nervous system .

 Increased vagus nerve tonicity causes accelerated intestinal secretion and increased enzymatic activity. Increased acidity of the gastric juice and accelerated emptying of the stomach result in disturbances in duodenal digestion;

The following factors cause disturbances in exocrine activity of pancreas;

1. obstruction or squeezing of the pancreatic duct (calculi in duct or tumors in the surrounding tissues);
2. acute and chronic pancreatites;
3. tumors and allergic diseases of pancreas;
4. duodenitis (decreased synthesis of secretin);
5. disturbed innervation (lesion to vagus nerve, poisoning by atropine).

Pancreatic hyposecretion results in the sharp disturbances of fats 60-80 of which is not digested and is excreted in feces (streatorrhea). Absence of pancreatic juice in the intestine causes also disturbances in digestion of proteins and starch. Motor function of intestines and process of absorption are disturbed.

Trauma and inflammation of the pancreas, penetration of bile into its duct may cause activation of its enzymes in the gland itself which results in pancreatitis and pancreone - crosis , as well as necrosis in other organs and tissues (especially in omentum). Absorption of the activated pancreatic juice into the blood causes general intoxication, vascular wall paralysis and sharp decrease in arterial pressure (pancreatic collapse).

Decrease (hypocholia) or absence (acholia) of biliary secretion is one of the main result of parenchymatous diseases of the liver and diseases of the biliary tracts .They cause in the first place disturbances in digestion and absorption of fats. In acholia more than 60% of fats is not assimilated by the organism .

 In the hypocholia and acholia digestion of proteins is also disturbed (fats in intestine settle on the chyme and prevent action of trypsyn). Decrease of bile acids promote fermentation and putrefaction; meteorism (accumulation of gases) and constipation (as a result of weakened peristalsis) develop. Feces contains a large amount of fats, organic acids and their salts, and becomes of bolus alba colour. Besides, in hyposecretion of bile absorption of fat – soluble vitamines is impeded, and symptomps of hypovitaminoses develop.

 The following factors cause disturbances in the parietal digestion:

1. lesion to intestinal villi (dysenteria cholera, sprue, high doses of some antibiotics especially those of neomycin sulfate);
2. decreased amount and activity of enzymes participating in parietal digestion;
3. disturbances in absorptive function of enterocytes;
4. disturbed motor function of intestines;
5. insufficient splitting of food in the intestinal cavity.

 Intestinal absorption may be decreased in the following cases:

1. distirbances in the secretory and motor functions of the digestive organs (especially hyposecretion of the digestive juices);
2. diarrhea;
3. decreased blood circulation in intestines;
4. disturbed flow of lymph.

When the permeability of the intestinal mucosa is increased high – molecular substances (particularly proteins) and products of the vital activity of the intestinal microorganisms pass into the blood and cause intoxication . Proteins of antigen nature may cause sensibilization of the organism. Increased intestinal absorption is frequent in infants whose intestinal permeability is comparatively higher.

 Deseases of the digestive system are accompanied also by disturbances in the excretory function of the intestine. Disturbances in motor function of intestine include excessive and diminished peristalses. Excessive peristalsis is observed in the following cases:

1. inflammatory processes (enteritis, colitis);
2. mechanical influence of the coarse food;
3. chemical irritants and microbic;
4. toxins in the inferior food;
5. changes in the activity of the endocrine and nervous systems (agitation, fear).

 Excessive intestinal peristalsis results in diarrhea – increased frequency of stool. Increased secretion of the mucosa and diminished absorption of water also play some part in the increased frequency of the stool. Diarrhea is usually caused by excessive peristalsis of the large intestine, especially when associated with similar phenomena in the small intestine. The reason for excessive peristalsis of the large intestine in addition to neurogenic factors is poorly digested contents of the small intestine which irritate the large intestine. As a result of diarrhea the organism loses a large amount of water and electrolytes, the blood is concentrated. Frequent diarrheas lead not only to digestive disorders, but also to general nutritional disturbances.

 Diminished intestinal peristalsis causes constipation. An important part in the pathogenesis of constipation is played by the large intestine where the fecal masses are consolidated and formed .Depending on the mechanism of constipation its two forms are distinguished:

1. Atonic constipation –is due to relaxation of the muscular layer of the intestinal wall and diminution in peristalsis in the upper parts of the large intestine.
2. Spastic constipation- is the result of prolonged spasm of the circular muscles of the intestinal wall.

Protracted constipation is one of the main symptoms of the Hirschprung’s diseases (congenital megacolon). Disturbed innervation of the intestines, weakness of their muscular layer, vitamine B1 deficiency may result in development of the atonic constipation . Constipation may result from decreased stimulation of the receptors of the mucosa, especially when there is no cellulose in the intestinal contents or there are too much fats or too little organic acid and monosaccharides which stimulate peristalsis. Psychic strain, increased vagus nerve tonicity, intoxications (lead poisoning) play a part in the development of the spastic constipation .

Long constipation leads to hyposecretion of the intestinal juices and disturbances in the digestive process As a result of constipation the intestine absorbs more water, the fecal masses become consolidated, coproliths are formed; the appetite diminishes, general weakness develops, meteorism occurs.

Meteorism is the result of diminished intestinal, peristalsis, increased process of fermentation and putrefaction and accumlation of gases in the intestine. As a result of high position of the diaphragm activity of the heart and lungs is impeded.

Stimulation of the mechano- and chemoreceptors in the intestinal wall cause a number of reflex changes in the organism (changes in the arterial pressure, decreased diuresis, etc). Secretory function of the digestive glands diminishes.

The foregoing disturbances in intestinal functon are particularly marked in intestinal obstruction (ileus), two forms of which are distinguished :

1. mechanical ileus - is caused by mechanical closure of the intestinal lumen (obstruction by extrinsic volvulas , intussusseption);
2. dynamic ileus – is caused by paralysis or (less frequently) spasm of the intestinal muscles.

The part of the intestine situated above the obstruction becomes considerably dilated. Antiperistaltic movements appear and lead to vomiting.

As a result of compression of the mesenteric vessels circulatory disturbances develop with subsequent mortification of the corresponding portion of the intestine.

Intestinal obstruction leads to development of deep general changes in the organism particularly manifested in general circulatory disturbances and characteristic alteration of the blood composition. The organism becomes dehydrated and hemoconcentration , hypochloremia , azotemia and alkalosis develop. These changes are in large measure due to increased secretion of digestive juices and their discontinued reabsorption , intractable vomiting and corresponding disturbances in renal function.

In the pathogenesis of the disorders observed in ileus an important part is played by intoxication due to absorbtion of the poisons formed and retained in the intestines; the reflex influences of the affected intestine on the blood circulation and other vitally important functions are also of some importance.

Diminished intestinal peristalsis and decreased secretion result in acceleration of the processes of fermentation and putrefaction. Therefore, protracted constipation and ileus are accompanied by autointoxication. Liver cannot decontaminate a large amount of toxic substances which spread by the blood all over the organism. Increased permeability of intestinal mucosa, decreased barrier function of liver, disturbed excretory function of kidneys also play a part in development of the intestinal autointoxication.

As a result of reflexes originating in the intestines abnormally distended by gases, as well as influence of toxins on the vascular wall receptors and nerve centers headache appears, arterial pressure decreases, changes occur in metabolism, heart contractions and respiration become weaker, inhibitory processes in the cerebral cortex are strengthened; in severe cases coma develops. In chronic cases anemia, disturbances in appetite and emaciation are also observed.

Disorders of defecation arise as a result of lesion of defecation center (in the lumbar and sacral segments of the spinal cord) or higher centers which control the voluntary act of defecation (in the medulla oblongata , hypothalamus, cerebral cortex). This causes decreased tonicity of the rectal sphincters and incontinence of feces. Dissection of the spinal cord higher than the defecation center causes increased tonicity of sphincters, feces remains in the rectum for a long time, but defecation acquires involuntary character. Emotional overstrain (especially fear) may cause involuntary decrease of tonicity of sphincters and defecation . In inflammation of the mucosa in the region of the sphincters the sensibility of the mucosa increases causing tenesmus, that is, frequent false urges to defecate.

 In view of multiplicity and complexity of the hepatic functions, battery of liver function tests are employed for accurate diagnosis , to assess the severity of damage , to judge prognosis and to evaluate therapy .

1. Tests for manufacture and excretion of bile .
2. Bilirubin pigment can be detected in serum , feces and urine :

a) serum bilirubin estimation is based on van den Bergh diazo reaction by spectrophotometric method. Water- soluble conjugated bilirubin gives direct van den Bergh reaction with diazo reagent within one minute , whereas alcohol – soluble free bilirubin is determined by indirect van den Bergh reaction. Addition of alcohol to the reaction mixture gives positive test for both conjugated and unconjugated bilirubin pigment . The free bilirubin level is then estimated by subtracting direct bilirubin value from this total value. Bilirubin level rises in diseases of hepatocytes, obstruction to biliary excretion into duodenum, in hemolysis and defects of hepatic uptake and conjugation of bilirubin pigment such as in Gilbert’s disease (hereditary non –hemolytic hyperbilirubinemia);

b) In feces excretion of bilirubin is assessed by inspection of stools. Clay coloured stools due to absence of fecal excretion of the pigment indicates obstructive jaundice.

c) Free bilirubin is not excreted in the urine Bilirubinuria occurs only when there is raised level of conjugated bilirubin. This is not protein found in plasma and therefore.is available for glomerular filtration.Bilirubinuria appears in patients of hepatitis before the patient becomes jaundiced.

2. Bile acids(bile salts ). The primary bile acids are formed from cholesterol in the hepatocytes, on secretion into the gut come in contact with colonic bacteria and undergo deconjugation with production of secondary bile acids. Most of these bile acids are reabsorbed through enterohepatic circulation and reach the liver. Only about 10%of the total bile acids are excreted in the feces normally as unabsorbable toxic lithocholic acid. Hepatobiliary diseases with cholestasis are associated with raised levels of serum bile acids which are responsible for produsing itching (pruritis).

II. Serum enzyme assays.

1. Serum alkaline phosphatase- is produced by many tissues (bone, liver, intestine, placenta) and is excreted in the bile. In the absence of bone disease and pregnancy an elevated serum alkaline phosphatase levels generally reflect hepatobiliary disease, slight to moderate increase is seen in pparenchymal liver diseases (hepatitis, cirrhosis, metastatic liver diseases), whereas the greatest (3-10 times normal) elevation occurs in biliary tract obstruction.

2. γ-glutamyl traspeptidase(γ-GT).

Its serum level parallels serum alkaline phosphatase and is used to confirm that the elevated serum alkaline phosphatase is of hepatobiliary origin. But its level is high in patients with alcohol abuse even without liver disease.

1. Transaminases (aminotransferases):
2. AST(aspartate transaminase) or(formerly)SGOT(serum glutamic oxaloacetic transaminase);
3. ALT (alanine transaminase) or ( formerly) SGPT (serum glutamic pyruvic transaminase).

Serum levels of AST and ALT are increased on damage to the tissues producing them. Thus serum estimation of ALT which is fairly specific for liver tissues is of greater value in liver cell injury, whereas AST level may rise in acute necrosis or ischemia of other organs (myocardium) ,besides liver cell injury.

 Transaminase estimations are useful in the early diagnosis of viral hepatites. Very high levels are seen in extensive acute hepatic necrosis (severe viral hepatitis, acute cholestasis).Alcoholic liver disease and cirrhosis are associated with mild to moderate elevation of transaminases.

III. Test for metabolic function.

1. Based on metabolic functions of the liver,serum estimation of proteins, immunoglobulins, ammonia and aminoaciduria are employed to assess the liver cell damage.

a) Hypoalbuminemia may occur in liver diseases having significant destruction of hepatocytes. Hyperglobulinemia may be present in chronic inflammatory disorders (cirrhosis, chronic active hepatitis).

b) The levels of serum immunoglobulins produced by lymphocytes and plasma cells show nonspecific abnormalities in liver diseases and represent inflammatory or immune response rather than liver cell dysfunction. IgA is predominant immunoglobulin in bile and its level is raised in cirrhosis, IgG is markedly raised in chronic active hepatitis and IgM- in primary biliary cirrhosis.

c) Prothrombin time and partial thromboplastin time ,both of which reflect the activities of various clotting factors, are prolonged in patients with hepatocellular disease.

1. High blood levels of ammonia are found in acute fulminant hepatitis,cirrhosis, hepatic encephalopathy. The rise in serum ammonia is due to inability of severely damaged liver to convert ammonia to urea. Thus ,urea synthesis is reduced in chronic liver disease.
2. Estimation of total serum cholesterol, triglycerides and lipoprotein are frequently done in patients with liver disease .There is rise total serum cholesterol in cholestasis (due to retention of cholesterol which is normally excreted in the bile).Serum triglyceride is also elevated. Values are lowered in acute and chronic diffuse liver diseases and in malnutrition.
3. Blood glucose level is lowered in fulminant acute hepatic necrosis . In chronic liver disease , there is impaired glucose tolerance and relative insulin resistance.
4. Immune tests.

 Liver diseases are associated with various immune abnormalities which may be nonspecific immune reactions or antibodies against specific etiologic agents.

 1.Nonspecific immune reactions:

1. Smooth muscle antibody to actin component of muscle is formed in certain hepatic necroses. It appears that hepatocytes have a protein which is immunologically similar to actin.
2. Mitochondrial antibody develops in patients with primary biliary cirrhosis.
3. Antinuclear antibody is present in some patients of chronic active hepatitis.

2.Antibodies to specific etiologic agents:

1. Hepatitis B surface antigen (HBs Ag) can be demonstrated in cases of serum hepatitis.

Confirmed positive test for HBs Ag is definite proof of hepatitis B infection.

b) Hepatitis B core antibody (HBc) can be detected in all patients with hepatitis B.

c) Hepatitis Be antigen (HBe Ag) can be found in chronic varieties of hepatitis B.

1. Amoeba antibodies to Entamoeba histolytica develop in patients with amoebic liver abcess.

Various agents which may damage the hepatic tissue play a part in the etiology of the diseases of the liver;

 1) pathogenic bacteria (staphylococci, streptococci, typhoid bacillus, etc.);

2) viruses (virus of infectious hepatitis);

3) spirochaeta;

4) parasites (echinococcus)

5) industrial poisons (carbon tetrachloride, combinations of phosphorus, lead, mercury, derivatives of benzene);

6) plant poisons;

7) toxic metabolites;

8) vital activity products of the pus- producing bacteria(in cases of increased processes of putrefaction in intestines);

9) some drugs ( barbiturates, sulfanilamides, antibiotics);

10) the substances of the antigenic nature which are administered into the organism by the parenteral way;

11) disturbances in the dietary regimen (vitamin and protein deficiency, intake of excessively fatty food, alcoholic drinks, etc.)

To understand the mechanisms underlying biliary pathology, it is important to understand normal bilirubin metabolism. About 80-85% of the bilirubin is derived from the catabolism of hemoglobin of senescent erythrocytes which are destructed (at the end of their normal life span of 120 days ) in the reticuloendothelial system in the bone marrow, spleen and liver . The remaining 15-20 % of the bilirubin comes from non-hemoglobin hem-containing pigments (myoglobin, catalase, cytachromes) and ineffective erythropoiesis. In either case, hem moiety is formed which is converted to biliverdin, and bilirubin is formed from biliverdin. Bilirubin on release from macrophages circulates as unconjugated (free) bilirubin in plasma tightly bound to albumin. Certain drugs (sulfonamides, salicylates) compete with bilirubin for albumin binding and displace bilirubin from albumin, this facilitating bilirubin to enter into the brain in neonates and increase the risk of kernicterus (nuclear jaundice). Bilirubin is found in body fluids in proportion to their albumin content.

On coming in contact with the hepatocyte surface, free bilirubin is metabolized which in -volves 3 stages; hepaic uptake, conjugation and secretion in bile.

Free bilirubin is not water- soluble but is alcohol- souble and is converted into water- soluble compount by conjugation. Conjugation involves conversion to bilirubin diglucuronide by the action of microsomal enzyme, bilirubin glucuronyl transferase. The process of conjugation can be induced by drugs like phenobarbital.

 In intestine bilirubin is separated from the glucuronic acid ,reduced and converted into urobilinogen (mesobilinogen ). The main part of the urobelinogen passes into large intestine, is reduced by the participation of the anaerobic microflora and converted into stercobilinogen. In the lower parts of the large intestine stercobilinogen is oxidized, and stercobilin is formed which is excreted in the stool and imparts to it normal yellow colour.

A small part of the stercobelinogen is absorbed in the lower parts of the large intestine, enters the system of the inferior vena cava (by –passing the liver ) and is exreted by kidneys .

Urobelinogen may appear in urine as a result of damage to the hepatic parenchyma .

Free bilirubin does not pass into urine , conjugated bilirubin is excreted in urine and is almost absent in blood .

Normal blood serum contains less than 1mg/dl of total bilirubin, out of which less than 0.25 mg/dl is conjugated bilirubin. Increased content of the conjugated bilirubin in blood serum is pathological symptom.

Pathogenic agents enter the liver by different ways. Frequently they are brought into liver by the portal vein system from intestines. The liver may also be reached through its arterial system and bile ducts, and sometimes from the surrounding tissues through the lymphatic vessels .

In the liver inflammatory and dystrophic processes are observed , though frequently they are in the mixed form, that is, dystrophy occurs in the hepatocytes, and at the same time infiltrative changes appear in the mesenchymal elements.

Inflammatory diseases of the liver (hepatites) may be acute and chronic. One of the most frequent forms of the acute hepatites is infectious hepatitis (Botkin’s disease). Noninfectious acute hepatitis is observed in some intoxications (poisoning by carbon tetrachloride, compounds of mercury). Acute hepatitis is characterized by diffuse lesion of the liver; diffuse dystrophy of the hepatic cells is accompanied by infiltration of the mesenchymal elements. The most severe form of the diffuse hepatic lesions is characterised by autolysis of the hepatic tissue , severe jaundice, intoxication and coma.

One of the frequent chronic diffuse lesions of the liver are cirrhoses. Their various forms differ from the etiological standpoint, but there are common features in their pathogenesis: in all forms of the cirrhosis in liver chronic cellular dystrophy is observed, and elements of the connective tissue develop. This results in decrease of the parenchymal elements of the liver and they are replaced by cicatricial tissue. Gradually these changes cause hepatic insufficiency. Though liver has a marked regenerative capacity and a large functional reverse ,hepatic failure may develop from severe acute and fulminant liver injury with massive necrosis of liver cell(acute hepatic faillure), or from advanced chronic liver disease (chronic hepatic failure).

Two groups of causes of the hepatic insufficiency are distinguished:

1. Pathological processes that are localized in the liver and biliferous tract: hepatitis (virus, bacterial, toxic), hepatosis (dystrophy), cirrhosis, tumor and parasitogenic affection of the liver, genetic defects of hepatocytes; calculi, tumors, inflamation of biliferous tracts with marked cholestasis.
2. Pathological processes outside the liver: schock(including postoperative),cardiac insufficiency, general hypoxia, renal insufficiency, protein deficiency, hypo-avitaminosis E, selenium deficiency, endocrinopathies (on particular, acute adrenal insufficiency), metastases of tumors into the liver.

 Since functions of the liver and the spleen are closely connected, disturbed functions of the liver cause changes also in the spleen: it is increased, monocytosis is observed. In the pathology simultaneous disturbance in the liver and spleen is called hepatolienal syndrome.

 Hepatic insufficiency manifests itself in disturbances in barrier function of the liver and changes in all types of the metabolism.

In severe lesions of the liver its detoxicating function is disturbed; organism’s sensibility to the toxic substances and drugs is increased. In the diseases that are accompanied by damage to the hepatic parenchyma (acute virus hepatitis, intoxication by hepatotropic poisons, cirrhosis) a large amount of underoxidized metabolites, ammonia and vital activity metabolites of intestinal bacteria are accumulated in the organism. They disturb the function of the nervous system and in severe cases cause hepatic coma.

 The reaction of the liver to stimuli manifests itself primarily in changes in carbohydrate metabolism. Damage to hepatic cells cause disturbances in synthesis and breakdown of glycogen. Since the enzymes participating in glyconeogenesis are synthesized only in the liver , this process is also disturbed. So, in hepatic insufficiency regulation of the blood sugar is disturbed and hypoglycemia occurs easily.

Decreased synthesis of proteins is also one of the main manifestations of the hepatic insufficiency. Damage to the hepatic parenchyma causes quantitative (hypoalbuminemia) and qualitative (paraproteins) changes in the plasma proteins. Blood content of free amino acids and residual nitrogen is increased. At the same time processes of transamination in the liver are disturbed, and the amino acids that are necessary for synthesis of proteins, are not synthesized. Part of amino acids are used for synthesis of the fatty acids and ketone bodies; a large amount of free amino acids is excreted in urine. Ammonia is accumulated in the organism which cannot be detoxicated by the liver: synthesis of the urea in the damaged hepatic cells is disturbed. Blood content of uric acid is also decreased.

In hepatic insufficiency oxidation of organic acids, as well as synthesis of lipoproteids from neutral fats and organic acids, are disturbed. This results in impeded excretion of lipides from the liver, and its fatty degeneration develops. Formation of ketone bodies is increased which leads to hyperketonemia. Owing to disturbed bile secretion the total cholesterol in the blood increases, while in parenchymatous affections of the liver it noticeably diminishes.

In hepatic diseases acid-base equilibrium, as well as heat balance of the organism are also disturbed. Vitamin (A, B, C, D, E, K) deficiency is observed. Since surplus of hormones, circulating in the blood, is oxidized in the liver, in hepatic insufficiency blood content of hormones is increased.

Disorders in the exocrine activity of the liver, that is, in bile secretion, may be caused by the following factors:

1. functional disturbances in the motor function (dyskinesia) of the biliary tracts (disturbances in the contractions of the muscles of the gallbladder and ducts, strong contraction of the sphincter of Oddi as a result of stimulation of the parasympathetic nervous system, impeded egress of bile as a result of relaxation of the galbladder due to stimulation of the sympathetic nervous system;
2. obstruction of the biliary tracts by gallstones or narrowing as a result of inflammatory processes;
3. compression of bile ducts by tumor in the surrounding tissues.

One of the important manifestations of impaired bile production and bile secretion is jaundice.

Jaundice (icterus) is pathological condition characterized by yellow pigmentation of the skin, mucous membranes and sclerae (as well as blood serum) due to deposition of bilirubin. Jaundice may be accompanied also by accumulation of bile acids and other bile components in the blood (cholemia). Jaundice becomes clinically evident when the total serum bilirubin exceeds 2 mg/dl. A rise of serum bilirubin between the normal (0.2 - 0.8 mg/dl, most of which is free) and 2 mg/dl is generally not accompanied by visible jaundice and is called latent jaundice.

Jaundice may result from one or more of the following mechanisms (hyperbilirubinemia due to the first three mechanisms is mainly unconjugated, and the last variety - conjugated):

1. increased bilirubin production;
2. decreased hepatic uptake;
3. decreased hepatic conjugation;
4. decreased excretion of bilirubin into bile.

Accordingly, a simple classification of jaundice includes 3 predominant types:

1. prehepatic (hemolytic or dynamic) jaundice - due to intensified breakdown of blood erythrocytes and increased bile production;
2. hepatic (parenchymal or retention) jaundice due to impaired function of the hepatic parenchyma;
3. cholestatic (mechanical, obstructive, congestion or resorption) jaundice - due to impaired bile secretion caused by mechanical obstruction in the extrahepatic bile ducts.

Although the skin is tinged yellow in all types of jaundice, but its shades are different: lemon-yellow in the hemolytic jaundice, saffron - yellow in the parenchymal jaundice and olive-green in the mechanical jaundice.

The hemolytic jaundice may be caused by all factors that result in hemolytic anemia. The hemoglobin liberated in hemolysis is transformed into bilirubin which forms so large an amount that the liver fails to excrete it; bilirubin is retained in the blood; passes into the tissues and is responsible for the appearance of jaundice. Hyperbilirubinemia develops when the capacity of the liver to conjugate large amount of bilirubin is exceeded. Therefore, it is free bilirubin's blood content that is increased. Since free bilirubin is not excreted by kidneys, in hemolytic jaundice there is no bilirubin in urine, but its large amount passes into intestine. This leads to increased excretion (in feces), and there is dark brown colour of stools.

Unlike other forms of jaundice, the pure cases of hemolytic jaundice are not accompanied by retention of bile acids and cholesterol in the blood.

In unconjugated hyperbilirubinemia, the free bilirubin, being a toxic sunstance, disturbs the function of hepatocytes. So, disorders in the hepatic function also play a part in the pathogenesis of the hemolytic jaundice.

Some types of jaundice of the newborn belong to this group.

Parenchymal jaundice is connected with separate or combined disturbances in hepatic uptake, conjugation and secretion of the bilirubin into bile. The following factors may cause different types of the parenchymal jaundice:

1. The large doses of some (antihelminthic) drugs - weaken hepatic uptake of bilirubin; blood content of free bilirubin increases.
2. Glucuronyltransferase deficiency - causes enzymopathic jaundice which may be congenital (jaundice of newborn, Gilbert's syndrome) or acquired (hepatitis, cirrhosis). It is accompanied by increase of free bilirubin in the blood.
3. Infectious hepatitis, leptospiral jaundice, sepsis, pneumonia, intoxication by hepatotropic poisons (carbon tetrachloride, compound of phosphorus, arsenic) - cause cholestatic jaundice (intrahepatic cholestasis) which is connected with disturbances in passage of the bile from hepatocytes into the biliary capillaries.

This is the most frequent and characteristic type of the parenchymal jaundice. Part of hepatocytes is necrotized, biliary capillaries are inflamed, their internal surface is destructed and obstructed by thick bile. All of these chages impede the movement of bile by its natural way, and a large amount of conjugated bilirubin and bile acids pass into the blood. Besides, ability of hepatocytes to conjugate the bilirubin is decreased and blood content of free bilirubin is also increased. Damaged hepatocytes cannot break down the urobilinogen (mesibilinogen) which is absorbed from intestines. Urobilinogen passes into blood and is excreted in the urine which contains also bilirubin. But content of stercobilinogen in the urine and that of stercobilin in the feces are decreased.

Since in parenchymal jaundice the blood contains bile acids, all signs of cholemia (itch, bradycardia, decreased arterial pressure) are observed.

Mechanical jaundice (extrahepatic cholestasis) results from mechanical obstruction to large bile ducts outside the liver or within the porta hepatis. The common cause are gallstones, inflammatory strictures, carcinoma head of pancrease, tumors of bile duct, congenital atresia of extrahepatic ducts. The obstruction may be complete and sudden with eventual progressive obstructive jaundice, or partial resulting in intermittent jaundice.

Above the obstruction the bile ducts are distended by bile. Owing to proximity of their terminal parts to the walls of the lymph capillaries of the liver, bile is absorbed into the lymphatic system, bile constituents gain entrance into the general circulation through the thoracic duct with resultant phenomena of general intoxication.

Hyperbilirubinemia (both free and conjugated), bilirubinuria are observed, but stercobilinogen (in urine) and stercobilin (in feces) are decreased.

When the biliary tracts are completely obstructed bile cannot enter the intestines (acholia), and the stools of such patients become clay - coloured. The general changes in the organism caused by the passage of the bile into the blood are called syndrome of cholemia: bradycardia and decreased arterial pressure (reflex and humoral influences of the bile acids on the vagus nerve toncity), intense pruritus (itch) (influence of bile acids on the sensory nerve ends in the skin), headache, predominance of the excitation in the nervous system activity which then is replaced by depression.

Since the obstruction is in the extrahepatic bile ducts, there is progressive retrograde extension of bile stasis into intrahepatic duct system. This results in dilatation of bile ducts and rupture of canaliculi with extravasation of bile, producing bile lakes. Since bile is toxic, the regions of bile lakes are surrounded by focal necrosis of hepatocytes. Stasis of bile predisposes to ascending bacterial infections (ascending cholangitis).

The mechanical jaundice is accompanied by acholic syndrome: without bile in the intestines the process of digestion is disturbed, steatorrhea occurs, activity of the trypsin and amylase are decreased, decreased tonicity and peristalsis of intestines cause constipation.

Absorption of the fatty acids and fatsoluble vitamins is impeded. As a result of decreased vitamin K in the organism, synthesis of prothrombin in the liver is slowed down. Blood coagulability is disturbed.

So, some symptoms of extrahepatic cholestasis (mechanical jaundice) and intrahepatic cholestasis (parenchymal jaundice) are alike, morever, mechanical jaundice may damage the hepatic tissue and cause parenchymal jaundice. But there are certain features which help to distinguish them. Prolonged protrombin time in extrahepatic cholestasis shows improvement following parenteral administration of vitamin K, whereas hypoprothrombinemia due to intrahepatic cholestasis does not show such improvement.

To produce the mechanical jaundice in experiment, dog's common bile duct is ligated.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Types of jaundice** | **Blood** | **Urine** | **Feces** | **Cholemia and itch** |
| bilirubin | biliary pigments | colour |
| free | conjugated | free | conjugated |
| Hemolytic | + | - | - | - | + | Dark brown | - |
| Parenchymal | + | + | - | + | + | Greenish-pale | + |
| Mechanical | + | + | - | + | - | Clay-coloured | + |
| Normally | + | - | - | - | + |  | - |

Cholelithasis is characterized by formation of stones (gallstones) in the gallbladder and bile ducts. The main causes of cholelithiasis are the following:

1. disturbances in the metabolism (increased content of cholesterol and bile pigments in the bile);
2. stagnation of bile;
3. infectious- inflammatory processes.

The incidence of gallstones varies markedly in different geographic areas, genetic factors, age, sex, diet and other risk factors. These factors which largely pertain to cholesterol stones can be summed up in the old saying that gallstones are common in 4 F's - "fat, female, fertile (multipara) and forty".

Gallstones are formed from constituents of the bile (cholesterol, bile pigments, calcium salts) along with other organic components.

Gallstones are of 3 major types:

1. pure gallstones (10% of all gallstones) - pure cholesterol, pigment or calcium carbonate gallstones;
2. mixed gallstones (80%) - on section have distinst laminated structure with alternating dark pigment layer and pale - white layer revealing different combinations of cholesterol, bilirubin, pigment and calcium carbonate, laid down in layers in different times;
3. combined gallstones (10%) - are usually solitary, large and smooth - surfaced; they have a pure gallstone nucleus (cholesterol, bile pigment or calcium carbonate) and outer shell of mixed gallstone, or a mixed nucleus with pure shell.

Portal hypertension is symptom - complex connected with increased pressure in the portal system usually follows obstruction to the portal blood flow anywhere along its course. Portal veins have no valves and thus obstruction anywhere in the portal system raises pressure in all the veins proximal to the obstruction.

The normal portal venous pressure is quite low (10-15 mm saline). Portal hypertension occurs when the portal pressure is above 30 mm saline.

Unless proved otherwise, portal hypertension means obstruction to the portal blood flow by cirrhosis of the liver. About 30-60% patients of cirrhosis develop significant portal hypertension.

Based on the site of obstruction to portal venous blood flow, 4 types of portal hypertension are distinguished:

1. Prehepatic portal hypertension - results from blockade of portal flow before portal blood reaches the hepatic sinusoids (thrombosis and neoplastic obstruction of the portal vein before it ramifies in the liver, compression of the portal vein by tumor of the surrounding tissues, myelofibrosis, congenital absence of portal vein).
2. Intrahepatic portal hypertension - cirrhosis, metastatic tumors, non-cirrhotic nodular regenerative conditions, hepatic venous obstruction (Budd - Chiari syndrome), veno-occlusive disease, schistosomiasis, diffuse granulomatous diseases, extensive fatty change. There is obstruction to the portal venous flow by fibrosis, thrombosis and pressure by regenerative nodules.
3. Posthepatic portal hypertension - is uncommon and results from obstruction to the blood flow through hepatic vein into inferior vena cava (neoplastic occlusion, thrombosis of the hepatic or of the inferior vena cava). Prolonged congestive heart failure and constrictive pericarditis may also cause portal hypertension by transmitting the elevated pressure through the hepatic vessels into the portal vein.
4. Mixed type of portal hypertension.

Irrespective of the mechanisms involved in the pathogenesis of portal hypertension, there are 4 major clinical consequences:

1. ascites;
2. varices (collateral channels, portosystemic shunts);
3. splenomegaly;
4. hepatic encephalopathy.

Ascites is accumulation of excessive volume of fluid within the peritoneal cavity. It frequently accompanies cirrhosis and other diffuse liver diseases. The development of ascites is connected with hemodilution, edema and decreased urinary output. Ascitic fluid is generally transudate with specific gravity of 1. 010, protein content below 3 g/dl. The ascites becomes clinically detectable when more than 500 ml of fluid has accumulated in the peritoneal cavity. The following factors favour formation of ascites:

1. Systemic factors:
2. decreased plasma oncotic pressure - impaired hepatic synthesis of plasma proteins, as well as loss of albumin from the blood plasma into the peritoneal cavity cause hypoalbuminemia which, in turn, results in reduced plasma oncotic pressure and leads to loss of water into extravascular space;
3. hyperaldosteronism - due to reduced renal blood flow, impaired hepatic metabolism and excretion of aldosterone;
4. impaired renal excretion - reduced renal blood flow and excessive release of antidiuretic hormone results in renal retension of sodium and water and impaired renal excretion.
5. Local factors:
6. portal hypertension - in combination with other factors contributes to the formation and localization of the fluid retention in the peritoneal cavity;
7. increased hepatic lymph formation - obstruction of hepatic vein and increased intrasinusoidal pressure in cirrhosis stimulates hepatic lymph formation that weeps through the surface of the liver.

As a result of rise in the portal circulation within or outside the liver, the blood tends to bypass the liver and return to the heart by development of porto-systemic collateral chanels (or shunts or varices). These varices develop at sites where the systemic and portal circulations have common capillary beds. The principal sites are:

1. esophago-gastric varices which is frequently manifested by massive hematemesis and is important consequence of portal hypertension;
2. collaterals between the superior, middle and inferior hemorrhoidal veins resulting in hemorrhoids bleeding from which is not as serious a complication as hematemesis from esophageal varices;
3. anastomoses between the portal and systemic veins may develop between the hilum of the liver and the umbilicus along the paraumbilical plexus of veins resulting in abdominal wall collaterals which appear as dilated subcutaneous veins radiating from the umbilicus and are termed caput medusae;
4. retroperitoneal anastomoses - are portocaval anastomoses established in the retroperitoneum.

In prolonged portal hypertension congestive splenomegaly occurs. The spleen is larger in young people and in macronodular cirrhosis than in micronodular cirrhosis.

Portosystemic venous shunting may result in a complex metabolic and organic syndrome of brain characterized by disturbed consciousness, neurologic signs and flapping tremors. Hepatic encephalopathy is particularly connected with advanced hepatocellular disease (in cirrhosis).