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ОСНОВЫ СИСТЕМНОЙ ПАТОМОРФОЛОГИИ

Учебно-методическое пособие
по патологической анатомии для студентов 3 курса
факультета по подготовке специалистов
для зарубежных стран медицинских вузов

BASIC OF SYSTEMIC PATHOMORPHOLOGY

Teaching workbook on pathological anatomy
for 3rd year English-speaking students
of faculty on preparation of experts for foreign countries
of medical highest educational institutions

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SYSTEMIC PATHOLOGY

I. DISEASES OF CARDIOVASCULAR SYSTEM

Atherosclerosis

Atherosclerosis (AS) is a multifactorial disease that affects the intima of elastic arteries. The disease is characterized by intramural deposits of lipids, proliferation of vascular smooth muscle cells and fibroblasts, and accumulation of macrophages.

Basic lesion is the patchy deposition of yellow lipid in plaques deep in the intima with overlying fibrosis up to 1,5 cm in diameter, protruding into the vessels lumen. It is called atheroma, i.e. it is essentially an intimal disease.

The term AS derives from the combination of athero — («porridge»), referring to the soft, lipid-rich material in the center of a typical intimal plaque, and sclerosis (scarring), referring to the connective tissue components.

The major clinical syndromes are related with ischemia, which is produced by narrowing of the vascular lumen (coronary heart disease, peripheral vascular disease, cerebral infarction), or from weakening of the arterial wall leading to aneurysm.

Atherosclerosis begins early in life and develops progressively over years, it is rarely symptomatic in the first three decades, but thereafter the frequency of clinical atherosclerotic events increases logarithmically. Because of its prevalence, as can be considered epidemic in industrialized nations.

Every year approximately 1 million persons in the world experience either a myocardial infarct or sudden cardiac death. Nearly all of them are the result of atherosclerotic coronary disease.

Background etiological factors influencing the rich of or susceptibility to atheroma are multiply and interrelated. The major background factors may be grouped into two main categories:

I. Endogenous (not modifiable):

1. Sex.

Atherosclerotic coronary heart disease is predominantly a disease of men. Especially in younger ages; *the prevalence in men in the fourth decade is three times that in women.* Possible explanations for the sex differences include levels of estrogenic hormones and higher levels of high-density lipoprotein, which is known to be antiatherogenic, in premenopausal women then in men.

2. Genetic factors (Heredity).

Evidenced in cases with clearly defined abnormalities of lipid metabolism. Apparent genetic roles in familial predisposition to AS may be related to genetic effects on other risk factors, especially hyperlipoproteinemia, hypertension and diabetes mellitus.

II. Environmental (modifiable):

1. Diet.

Many studies have demonstrated the specific effects of diet on lipid and lipoprotein levels, including the amount of dietary cholesterol ingested, the total number of calories from carbohydrates, protein and fat, and the intake of alcohol and concentrated sweets (anti-oxidants including red wine reduce the risk).

2. Metabolic diseases.

There are diabetes mellitus, myxedema, nephrosis, xanthomatosis, familial hyper cholesteronemia:

— *hypertension;*

— *cigarette smoking.*

The component of cigarette smoking responsible for the acceleration of atherosclerotic events is not known. It may be related to effects of the cigarette smoking on thrombosis or to increased concentration of carboxygemoglobin in the blood of smokers.

3. Lack of physical exercise.

4. Other risk factors.

Other risk factors suggested being associated with AS obesity, physical activity, hyperglycemia, stress, and coffee consumption.

These factors may act as increased blood lipids-cholesterol and lipoproteins. The risk is correlated with elevated low-density lipoprotein (LDL), formed from the catabolism of very-low-density lipoprotein (VLDL) to a cholesterol ester-protein core that carries some 70 % of the total serum cholesterol. Atheroma is specifically associated with high blood low-density lipoprotein levels (as well as total cholesterol levels). Risk is inversely related to the high-density lipoprotein (HDL) levels, perhaps because HDL helps clear cholesterol from vessel lesion.

Pathogenesis of AS has three stages:

1. Endothelial injury is accompanied by the attachment of monocytes, platelets, and thrombus formation.

2. Macrophages in the intima phagocytise lipid and transform into foam cells. Macrophages also secrete growth factors that stimulate the proliferation of smooth muscle cells.

3. Ruptured atheromas release thrombogenic material into the circulation, causing thrombus for intimal ulceration.

Classification AS has the following microscopically stages (phases):

1. **Pre-lipid stage** is characterized by mucoid swelling of intima and accumulation of plasmaproteins, and glycosaminoglycanes, the destruction of endothelium and elastic and collagen fibers of intima's basal membrane.

2. **Stage of fatty stripes (lipoidois).** Fatty stripes appear on intima due to its lipid infiltration, lipoproteins and proteins fixation. Lipids impregnate intima and are accumulated in macrophages. Macrophages that have accumulated lipid in their cytoplasm appear histologically as ***csantomic or foam cells.*** Elastic membranes become swollen, their destruction occurs.

3. **Stage of liposclerosis.** Macrophages secrete growth factors and cytokines, which recruitadditional monocytes, macrophages and other cells. Cyto-

kines and growth factors also stimulate the proliferation of smooth muscle cells and their ingrowth into the intima from the tunica media. Lipid accumulates not only in macrophages but also in smooth muscle cells. From dead and dying cells, cholesterol is released into interstitial spaces. In the areas of lipidosis a young connective tissue grows and forms ***a fibrous cap.*** On the luminal side, atheromas typically covered with an intimal fibrous cap, consisting of fibroblasts, surrounded by collagen, which replaces the normal intimal cells. Macroscopically dense, oval, white formations are observed there.

4. **Stage of atheromatosis** is characterized by necrosis of the central part of fibrous cap withforming of amorphous substance (atheromatouse detritis). ***Atheromas*** consist of amorphous lipid-rich material and are soft. Cholesterol clefts are recognized by their typical needle-shaped appearance.

5. **Stage of ulceration** is characterized by the break of the fibrous cap cover and forming of ulcerwith small hemorrhage into plaque.

6. **Stage of atherocalcinosis** is characterized by deposition of calcium in ulcerative plaque. Denseand fragile cap is formed due to the cap of connective tissue infiltration with calcium. The calcification of vessels leads to hardening of arteries. Atheromas weaken the arteries and predispose to formation of aneurysm.

Complicated plaques develop from preexisting fibrous plaques as a result of one of a combination of several pathologic changes that include calcification; ulceration, thrombosis and hemorrhage. The complicated lesion is the most common type of atherosclerotic lesion that produces significant circulatory change and clinical disease.

Clinical-morphological appearances:

1. **Atherosclerosis of aorta** — the most common form. Usually it is not complicated by thethrombosis, thromboembolism and embolism to legs. Development of aortal aneurysm is possible.

2. **Atherosclerosis of coronary arteries** of heart lead to ischemic heart disease (IHD). May becauses acute infarction.

3. **Atherosclerosis of arteries of cerebrum.** It's possible the development of thrombosis. Theresults are ischemic infarctions of brain, less often the haemorrhage in brain occurs. Dystrophy and atrophy of the brain cortex may develop as result of the long-term ischemia. General chronic ischemia of brain leads to senile dementia. Atherosclerosis of carotides leads to acute local ischemia and cerebral softening (infarction).

4. **Atherosclerosis of renal arteries** leads to atrophy of parenchyma, or infarction. Outcome isatherosclerotic nephro-cirrhosis.

5. **Atherosclerosis of arteries of an intestine** is complicated by the thrombosis, leading to the gangrene.

6. **Atherosclerosis of arteries of extremities**, very often this process is located in femoralarteries. The thrombosis with gangrene of leg is possible. Col-

lateral circulation is usually good; atheroma must be very severe before chronic ischemia with intermittent claudication/or gangrene develops.

Aneurysms

These are localized abnormal dilatations of vascular wall. Most common (and significant) are aortic aneurysms. Morbidity and mortality are secondary to:

— Rupture.

— Impingement on adjacent structures.

— Occlusion of proximate vessels by either extrinsic pressure or superimposed thrombosis. Embolism from mural thrombosis.

Etiologies of aneurysms include atherosclerosis, cystic medial necrosis (the two most common causes), syphilis, trauma, congenital defects, and infections (mycotic aneurysms).

Morphologically, aneurysms are classified as follows:

Berry aneurysm. Spherical dilatation due to congenital wall weakness, generally less than 1.5 cm in diameter, typically in the circle of Willis.

Saccular aneurysm. Large spherical dilatation up to 20 cm in diameter, often at leastpartially filled with thrombus. The etiology is usually atherosclerosis.

• **Fusiform (cylindroid) aneurysm.** Gradual lumen dilatation generating a spindle-shapedlesion up to 20 cm in diameter, and to the full length of the aorta. AS is the most common cause.

• **Dissecting aneurysm.** Blood enters the arterial wall through a tear, usually in the aorticarch, and dissects the layers-typically between the middle and outer thirds of the media.

Hypertension

In medically advanced countries, hypertension is the most common serious chronic disease, affecting about a half of the *population* over 50 years of age. Arterial hypertension is defined clinically as borderline when it riches 140/90 mm Hg and hypertensive when 165/95 mm Hg.

There is elevation of systolic pressure alone, (systolic hypertension) or elevation, of both systolic — and diastolic pressure (diastolic hypertension), both have an increased risk of serious complications, but diastolic hypertension is more dangerous.

Hypertension is classified into two types:

1. In 90–95 % of all cases of hypertension, no cause can been established — such cases are called ***essential or idiopathic or primary.***

2. In only 5–10 % of all cases of hypertension is any disease, which may be associated with disturbance of these mechanisms detectable — such cases are ***secondary hypertension***. Examples:

— Kidney diseases.

— Hyperfunction of adrenal cortex (Cushing's syndrome — corticosteroid excess).

— Tumor of adrenal medulla (pheochromocytoma) — catecholamine excess.

— Hypertension occurs in toxemia of pregnancy.

— This hypertension comprises 5–10 % causes of disease.

If these causes of secondary hypertension were eliminated, hypertension disease would be cure.

According to the clinical course, both types of hypertension may ***be benign or malignant.***

1. ***Benign hypertension***is moderate elevation of blood pressure and the rise is slow as the years pass.About 90 % of patients of hypertension have benign disease.

2. ***Malignant hypertension***is marked and rapid increase of blood pressure to 200/140 mm Hg or moreand the patients have papilledema, hemorrhages and hypertensive encephalopathy.

All the above mechanisms are essentially vaso-constrictor. The possible roles of vaso-dilator mechanisms — for example the effect of nitric oxide on vascular smooth muscle — are being currently researched.

The increased peripheral resistance resulting in sustained hypertension may arise from:

- Increased sympathetic tone.
- Increased release of renin and generation of angiotensin.
- The presence of vasoconstrictive substances in the circulation.
- Increased sodium load and extracellular fluid load, and finally.
- A postulated excessive responsiveness to the other factors.

Morphology

- It is important to realize that the central lesion in most cases of hypertension is a decrease in the size of the lumen in small muscular arteries and arterioles, the resistance vessels that control the flow of blood through the capillary bed.
- The lumen may be restricted by active contraction of the vessel wall, an increase in the structural mass of the vessel wall, or both.
- The morphologic changes associated with moderate elevations of blood pressure are too subtle to be detected by simple histological studies. Small muscular arteries show segmental dilatation as a result of necrosis of smooth muscle cells.
- The combination of cell necrosis and deposition of plasma proteins in the vessel wall is termed fibrinoid necrosis.
- The period of acute injury is rapidly followed by smooth muscle proliferation and a striking increase in the number of layers of smooth muscle cells, which yields the so-called **onion-skin appearance**. Taken together, these changes are labeled malignant arteriosclerosis ormalignant arteriolosclerosis, depending on the size of the vessels affected.

Clinical-morphological stages:

1. Subclinical stage occurs by hypertrophy of muscular layer and elastic structures of arterioles and small-sized arteries, spasm of arterioles. At this stage the hypertrophy of the left ventricle of heart begins.

2. A stage of general changes of arteries begins as arterial pressure increases. Arteriolar walls permeability is increased, it results in plasmatic impregnation and hyalinosis. Elastic, muscular-elastic and muscular arteries walls undergo *elastofibrosis and atherosclerosis. Elastofibrosis* is characterized by a hyperplasia and breaking of internal elastic membrane and spreading of connective tissue. Atherosclerotic changes in case of hypertension are more extensive, the process reaches small-sized arteries of muscular type, plaques are more often circular, that cause acute mechanical stenosis of the vessel.

3. The stage of secondary changes of organs is developed in connection with changes of arteries and insufficiency of the intraorganic blood circulation. These changes develop slowly, that results in atrophy of parenchyma and sclerosis (*it's characteristic of benign hypertension*), quickly (spasm, thrombosis, fibrinoid necrosis) and causing infarctions and hemorrhages (*it'scharacteristic of malignant hypertension*).

The main clinical-morphological forms of essential hypertension:

1. Cardiac form:

• Hypertensive heart disease or hypertensive cardiomyopathy is the disease of the heart resulting from systemic hypertension of prolonged duration and manifesting by left ventricular hypertrophy.

• Often hypertension predisposes to atherosclerosis. The arterial changes and vascular complications increase with the severity and duration of the hypertension, but are modified by genetic factors, environmental factors, sex (females tolerate hypertension better), and associated diseases.

• Macroscopically, the most significant finding is marked hypertrophy of the heart, especially of the left ventricle. Weight of heart reaches 1 kg, thickness of left ventricle walls is up to 3 cm, the papillary muscles are rounded and prominent, and the cardiac chamber is small **(concentric hypertrophy)**. But when decompensation and cardiac failure develop, there is **eccentric hypertrophy (myogenic dilation)** with thinning of the ventricular wall anddilation of the left ventricular and atrial cavities.

• There may be dilatation and hypertrophy of right heart as well. Heart is called **«corbovinum»**.

2. Cerebral form (Cerebrovascular diseases.

It is characterized first of all as impairment of cerebral blood circulation. This hypertension can result in two main types of parenchymal diseases of the brain:

1) Ischemic brain damage (hypoxic encephalopathy and cerebral infarction):

• The pathologic appearance of the brain in hypoxic encephalopathy varies depending on the duration and severity of hypoxic episode and the length of survival.

• Macroscopically, there is focal softening. The area supplied by distal branches of the cerebral arteries suffers from the most severe ischemic damage and may develop border zone or watershed infarcts in the adjacent zones between the territories supplied by major arteries.

• Microscopically, the nerve cells die and disappear and are replaced by reactive fibrillary glia.

• Cerebral infarction is a localized area of tissue necrosis caused by local vascular occlusion.

• Cerebral infarction may be anemic or hemorrhagic.

• Macroscopically, an anemic infarct becomes evident 6–12 hours after its occurrence. The affected area is soft and swollen and there is blurry of junction between gray and white matter. Within 2–3 days, the infarct undergoes softening and disintegration.

• A hemorrhagic infarct is red and superficially resembles a hematoma. It is usually the result of fragmentation of occlusive arterial emboli or venous thrombosis.

2) Intracranial hemorrhage (intracerebral and subarachnoid hemorrhage):

• Hemorrhage into the brain of patient with hypertension is intracerebral hemorrhage, which is usually of hypertensive origin due to rupture of microaneurysm.

• The common sites of hypertensive intracerebral hemorrhage are the region of the basal ganglia, medulla and cerebellum cortex.

• About 40 % of patients die during the first 3–4 days of hemorrhage, mostly from hemorrhage into the ventricles.

•The outcome of intracerebral hemorrhage is cyst formation. Patients can be paralyzed.

2. Renal form:

• Renal form is characterized by chronic arteriolo-sclerotic nephrosclerosis.

• Kidneys have a term **«primary shrunken kidneys».**

• Macroscopically, both kidneys are affected equally and are reduced in size and weight, often weighting about 6 gm. The capsule is connected densely to the cortical surface. The surface of the kidney is finely granular and shows V-shaped areas of scarring. The cut surface shows firm kidney and narrowed cortex.

• Microscopically, there are primary diffuse vascular changes, which produce parenchymal changes and secondary as a result of ischemia. There is variable degree of atrophy of parenchyma; these include glomerular shrinkage, deposition of collagen in Bowman's space, periglomerular fibrosis.

• Clinical features are variable, elevation of the blood pressure with headache, dizziness, and palpitation.

• Renal failure and uremia may occur.

• In case of malignant hypertension can develop as hypertonic crisis — acute increase of arterial pressure in communication (connection) with spasm of arterioles.

• Morphological appearance of hypertonic crisis: plasmatic impregnation or fibrinoid necrosis of arteriolar walls.

The causes of death among hypertensive patients are the following:

• Congestive heart failure.

• Coronary artery disease.

• Cerebrovascular accidents.

• Uremia.

• Causes unrelated to hypertension. The cardiac complications therefore account for 36 % of the death.

Ischemic heart disease

Ischemic heart disease (IHD) is the generic designation for a group of closely related syndromes resulting from ischemia — an imbalance between the supply and demand of the heart for oxygenated blood. Ischemia comprises not only insufficiency of oxygen (hypoxia, anoxia) but also reduced availability of nutrient substrates and inadequate removal of metabolites. Because coronary artery narrowing or obstruction owing to atherosclerosis underlies myocardial ischemia in the vast majority of cases, IHD is often termed coronary artery disease (CAD) or coronary heart disease (CHD).

The etiology and pathogenesis

Etiology of IHD is identical to the one of atherosclerosis and hypertension. Direct reasons of development of the myocardial infarctions are spasms of vessels, thrombosis or thromboembolism of coronary arteries of heart. Pathogenic factors (factors of risk) are:

Hyperlipidemia:

1) arterial hypertension;
2) steatosis;
3) hypodynamia;
4) smoking;
5) impairments of tolerance to carbohydrates;
6) diathesis;
7) genetic predisposition;
8) sex-binded.

Depending on the rate of development and ultimate of the arterial narrowing and the myocardial response, *four ischemic syndromes* may result:

Angina pectoris:

1. Myocardial infarction.
2. Sudden cardiac death.
3. Chronic ischemic heart disease. **Acute Ischemic Heart Disease (AIHD) Angina pectoris.**

It is a symptom complex of IHD characterized by paroxysmal attacks of substernal or pericordial chest discomfort (variously described as constricting, squeezing, choking, or knife-like) caused by transient (15 sec. to 15 min.) myocardial ischemia that falls short of inducing the cellular necrosis that defines infarction.

There are three somewhat distinctive patterns of angina pectoris, differentiated on the basis of the provocation and severity of the pain:

1. **Stable (typical) angina pectoris** appears to be reduction of coronary perfusion to a criticallevel by chronic stenosing coronary atherosclerosis; this

renders the heart vulnerable to further ischemia whenever there is increased demand, such as that produced by physical activity, emotional excitement, or any other cause of increased cardiac workload.

2. **Prinzmetal's variant** refers to a pattern of episodic angina that occurs at rest and has beendocumented to be due to coronary artery spasm.

3. **Unstable angina** refers to a pattern of pain that occurs with progressively increasingfrequency, is precipitated with progressively less effort, often occurs at rest, and tends to be of prolonged duration. This syndrome is sometimes referred to as preinfarction or acute coronary insufficiency. Unstable angina is induced by fissuring, ulceration, or rupture of an atherosclerotic plaque with superimposed partial thrombosis and possibly embolization or vasospasm.

Acute myocardial infarction

Acute myocardial infarction (MI) also known as «heart attack», is overwhelmingly the most important form of IHD in industrial nations.

Pathogenesis. At least 90 % of transmural acute MI are caused by an occlusive intracoronarythrombus overlying an ulcerated or fissured stenotic plaque. Occlusion of a major coronary artery results in ischemia throughout the anatomic region supplied by that artery, most pronounced in the subendocardium. The function becomes strikingly abnormal within 1 min after ischemia, but myocardial coagulation necrosis occurs only after 20 to 40 min of severe ischemia.

Classification of myocardial infarction:

I. According to localization: left ventricle, right ventricle, and right atrium, left atrium.

Infarctions are most frequently located in the left ventricle. Besides it may be located in other parts of heart, but this is observed rarely. The region of infarction depends upon the area of obstructed blood supply by one or more of the three coronary arterial trunks:

— Stenosis of the left anterior descending coronary artery is the most common (40–50 %) — the infarctions of the anterior wall of left ventricle near apex or anterior two-thirds of interventricle septum:

1) stenosis of the right coronary artery is the next most frequent (30–40 %) — interior/posterior wall of left ventricle; posterior one-third of interventricular septum, posterior right ventricular free wall in some cases;

2) stenosis of the left circumflex coronary artery is seen least frequently (15–20 %) — lateral wall of left ventricle.

II. According to the anatomic region of the left ventricle: anterior, posterior, lateral, septal and circumferential.

III. According to the degree of thickness of the ventricular wall:

1. *Full-thickness or transmural*, in which the ischemic necrosis involves

the full or nearly fullthickness of the ventrical wall in the distribution of a single coronary artery. As a result the rupture of cardiac wall, endocarditis with thrombus and fibrinous pericarditis can develop.

2. *Subendocardial or lamina* constitutes an area of ischemic necrosis limited to the inner one-third or at most one-half of the ventricular walls, often extending laterally beyond the perfusion territory of a single coronary artery.

3. *Subepicardial* is rare infarction. In region of it fibrinous inflammation of pericardium develops.

It is called reactive pericarditis.

IV. According to the duration of infarctions:

1. ***Acute myocardial infarction*** develops in the first time (during 8 weeks from beginning ofischemic necrosis).

2. ***Repeated myocardial infarction*** develops after 8 weeks of acute infarction.

3. ***Recurring (recidivic) myocardial infarction*** develops during 8 weeks of acute infarction.

Morphology

The macroscopic and microscopic changes in the myocardial infarction correspond to the age of the infarct.

In 6–12 hours the lesion may have a slight pallor but may be inapparent; however, changes in as early as 3 to 6 hours may be accentuated by use histochemical techniques.

By 18–24 hours infracted tissue is pale to cyanotic.

During first week the lesion becomes progressively more sharply defined, the color of infarction is charged from cyanotic red to bright yellow or yellow-green. The consistency of infarct in this period is soft.

A circumferential rim of hyperemic granulation tissue that progressively expends may be seen by 7 to10 days.

Fibrous scar is well established by 6 weeks. It is thin, gray-white, hard, shrunken fibrous scar.

Microscopically, within one hour of ischemic injury, there is intercellular edema, and myocytesbecome wavy and buckled. This is attributable to stretching of noncontractile dead fibers by adjacent viable contracting myocytes. In addition, border-zone viable cells show fine lipid droplets and large cytoplasmic vacuoles called vacuolar degeneration or myocytolysis. At this stage, typical coagulative necrosis is not yet evident.

In 12 to 72 hours a neutrophilic infiltrate into necrotic tissue with progressive evolution of characteristic eosinophilic coagulative necrosis can occurs.

Between 3 and 7 days dead myocytes begin to disintegrate and are resorbed by macrophages and enzyme proteolysis.

At 7 to 10 days granulation tissue appears and progressively replaces necrotic tissue, ultimately generating a dens fibrous scar.

In fourth to sixth week increased fibrous tissue, decreased blood supply, fewer pigmented macrophages, lymphocytes and plasma cells are seen.

Complications of infarction

Complications of infarction depend on the size and location of the necrosis, as well as the reserve of functional myocardium.

Arrhythmias are the most common form of complication in acute myocardial infarction (75 to 95 %).

1. Left ventricular congestive failure and mild-to-severe pulmonary edema (60 %).
2. Cardiogenic shock (10 %).
3. During the first weak the heart rupture may develop, which is often fatal. Rupture of the free wall causes pericardial hemorrhage and tamponade. Rupture of the septum produces a left-to right shunt with right heart volume overload.
4. Fibrinous pericarditis appears on the second day of myocardial infarction.
5. About 3–4 % of patients who suffered from acute myocardial infarction develop post-myocardial infarction syndrome, which is characterized by pneumonitis.
6. Mural thrombosis and thromboembolism from intracardiac thrombi and thrombosis in the leg veins is observed in 15–45 % cases of acute myocardial infarction.
7. Cardiac aneurysm often occurs in the left ventricle, it impairs the function of the heart and is the site for mural thrombi.
8. Dressler's syndrome. It is immunocomplexis reaction to decomposition's products of the necrotic tissue with formation pericarditis and right-side pleurisy.

The main causes of death in this case are complications:

1. Cardiogenic shock.
2. Tamponade of heart.
3. Thromboembolism.
4. Acute cardiac insufficiency.

Sudden cardiac death (SCD):

• Defined as unexpected death from cardiac causes early after or without the onset of symptoms. In the vast majority of cases in adults SCD is a complication and often the first clinical manifestation of IHD. Infrequently, it is a consequence of myocarditis, mitral valve prolapse, or hypertrophic cardiomyopathy.

• The ultimate mechanism of death is almost always a lethal arrhythmia, presumably triggered by previous conduction system scarring, acute ischemic injury, or electrical instability due to electrolyte imbalance.

•Morphology. Marked coronary atherosclerosis with critical (greater than 75 %) stenosis involving more than one of the three major vessels is present in 80 to 90 % of victims; only 10 to 20 % of cases are of nonatherosclerotic origin.

Chronic ischemic heart disease

• The designation of Chronic ischemic heart disease (CIHD) is used for the heart of patients often but not exclusively elderly, who individuously develop congestive heart failure (CHF), sometimes fatal, as a consequence of ischemic

myocardial damage.

- Most cases of CIHD constitute simply postinfarctional cardiac decompensation or slowly ischemic myocyte degeneration.
- Cardiosclerosis can be local postinfarctional and diffuse atherosclerotic.
- Macroscopically*:* on section white foci of sclerosis or brown coloration of the heart, hypertrophy of left ventricle or, in contrary, some reduction in heart size, moderate to severe multivessel stenosing coronary atherosclerosis and sometimes total occlusions resulting from organized thrombi.
- Microscopically: diffuse or local perivascular and interstitial fibrosis. In some cases the hypertrophy of adjacent myocytes occurs, in others cases myocytic atrophy with perinuclear deposition of lipofuscin appears.
- Due to postinfarctional cardiosclerosis the chronic heart's aneurysm may develops.
- The pericardial surface of the heart in CIHD may have adhesions as the result of healing of pericarditis also associated with post myocardial infarctions.
- Cardiosclerosis leads to chronic cardiac insufficiency, which is characterized by congestion: edema, cyanosis, petechias; indurations of organs (lungs, kidneys, spleen) and development of the «nutmeg» liver.
- Patients may die due to cardiacdecompensation or thromboembolism.

Cardiac hypertrophy and dilation

The heart may undergo compensatory enlargement in the form of hypertrophy, dilation, or both, so as to prevent or postpone heart failure.

Compensatory hypertrophy

Hypertrophy of the heart is defined as an increase in size and weight of the myocardium. It generally results from increased pressure load while creased volume load (e.g. valvular incompetence) results in hypertrophy with dilatation of the affected chamber due to regurgitation of the blood through incompetent valve. The atria may also undergo compensatory changes due lo increased workload.

It appears that stretching of myocardial fibers in response to stress induces the cells to increase in length. The elongated fibers receive better nutrition and thus increase in size.

Causes:

1. Left ventricular hypertrophy. The common causes of left ventricular hypertrophy are:

a) systemic hypertension;
b) aortic stenosis and insufficiency;
c) mitral insufficiency;
d) coarctation of the aorta;
e) occlusive coronary artery disease;

f) congenital anomalies like septal defects and patent ductus arteriosus;

g) conditions with increased cardiac output: thyrotoxicosis, anemia, and arteriovenous fistulae.

2. Right ventricular hypertrophy. Most of the causes of right ventricular hypertrophy are due topulmonary arterial hypertension. These are:

a) pulmonary stenosis and insufficiency;

b) tricuspid insufficiency;

c) mitral stenosis and/or insufficiency;

d) chronic lung diseases: chronic emphysema, bronchiectasis, pneumoconiosis, pulmonary vascular diseases, etc.;

e) left ventricular hypertrophy.

Compensatory dilation. Quite often, hypertrophy of the heart is accompanied by cardiac dilation.

Causes:

▪ Valvular insufficiency (mitral and/or aortic insufficiency in left ventricular dilatation, tricuspid and/or pulmonary insufficiency in right ventricular dilatation).

▪ Conditions with high cardiac output e.g. thyrotoxicosis, arteriovenous shunt.

▪ Myocardial diseases: cardiomyopathies, myocarditis.

▪ Systemic hypertension.

Hypertrophy of the myocardium without dilatation is referred to as concentric, and when associated with dilatation is called eccentric. The weight of the heart is increased above the normal, often over 500 gm.

Macroscopically, the thickness of the left ventricular wall above 15 mm is indicative of significant hypertrophy. In concentric hypertrophy, the lumen of the chamber is smaller than usual, while in eccentric hypertrophy the lumen is dilated. In pure hypertrophy, the papillary muscles and trabeculae cameae are rounded and enlarged, while in hypertrophy with dilatation these are flattened.

Microscopically, there is increase in size of individual muscle fibres. There may be multiple minute foci of degenerative changes and necrosis in the hypertrophied myocardium.

II. RHEUMATIC DISEASES

• Rheumatic diseases are group of collagen or systemic connective tissue diseases including rheumatic fever, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, dermatomyositis and polyarteriitis nodosa, and Bechterew's disease.

• They are characterized by affect of collagen or connective tissue due to disturbances of immune homeostasis.

• Disturbances of immune homeostasis, development of autoimmune reactions, formation of the toxic immune complexes and sensibilizated cells, injury of microcirculation with following systemic progressive disorganization of con-

nective tissue are main links of pathogenesis of rheumatic diseases.

General characteristic of rheumatic diseases:

- Presence of chronic infectious focus.
- Presence of early systemic changes of microcirculation.
- Presence of hypersensitivity of immediate type with development of exudative — necrotic reactions and hypersensitivity of delayed type with formation cellular infiltration.
- Systemic progressive disorganization of connective tissue includes mucoid swelling, fibrinoid changes, cellular reactions, sclerosis. Combination of different phases of connective tissue disorganization, which indicates the chronic character of the diseases.
- Chronic recurrent diseases with alternation of periods of exacerbation and remission.
- Genetic and environmental factors are important for development of these diseases. Thus, rheumatic arthritis has less severe course in the residents of Africa than in those of Europe, Lupus erythematosus is more frequent in Europian countries and USA than in Great Britain.

Rheumatic fever and rheumatic heart disease

- **Rheumatic fever (RF)** is an acute, inflammatory, recurrent disease mainly of children (ages 5 to 15) that typically occurs 1 to 5 weeks after a group A streptococcal infection (usually sore throat).
- Acute RF occurs after the infection with beta-hemolytic streptococci group A. The various manifestations of the disease in the heart and other regions of the body, excluding the initial infection (tonsillitis, nasopharyngitis), are not the result of a direct infection.
- Most evidence suggests is secondary to host antistreptococcal antibodies that are cross-reactive to cardiac antigens, but microbe initiated autoimmune reactivity is not ruled out.
- Rheumatic Fever is thus a disease that involves many regions of the body, but it is not serious import to the patient unless it involves the heart. It has been said, «rheumatic fever licks the joints but bits the heart».
- Death is rare during acute RF, being secondary usually to the myocarditis. Typically, the myocarditis and arthritis are transient and largely resolve, but the valvular involement may lead to deformed, scarred valves with permanent dysfunction (chronic **rheumatic heart disease (RHD)**) and subsequent CHF.
- Chronic RHD is more likely to occur when the first attack is in early childhood, when the first bout of RF is severe, or with recurrent attacks.

Diagnosis rests on the clinical history and the presence of five major

(Jones) criteria:

1. **Erythema marginatum.** Seen in children more often than adults. There is specific skin «rush», typically in a bathing suit distribution, macular lesions with erythematous rims and central clearing.

2. **Sydenhams chorea.** A neurologic disorder with rapid, involuntary, purposeless movements.

3. **Carditis.** It may be myo-, endo-, or pericarditis.

4. **Subcutaneos nodules.** Seen in children more often than adults. Histologically, giant aschoff bodies are noted.

5. **Migratory large joint polyarthritis.**

Minor criteria:

1. Fever.
2. Arthralgia.
3. Longer PR interval in the ECG.
4. Leukocytosis.

Also may develop:

- Rheumatic glomerulonephritis, rheumatic pneumonia is visceral changes.
- Hyperplasia of lymphatic tissue, marked plasmatization is observed in the immune system.
- Rheumatic vasculitis with fibrinoid changes of the walls. In the capillaries, there is endothelium proliferation followed by desquamation, so-called rheumatic endotheliosis. Vascular permeability increases sharply. The disease results in vascular sclerosis (arteriolosclerosis, arteriosclerosis, capillarosclerosis).

Pathogenesis and Morphology of RF

A widely accepted concept of the nature of RF is that it is one of the so-called immune disorders of connective tissue, the principal lesions being in the connective tissues throughout the body, especially in the heart. RF has four stages.

Mucoid swelling. In the early phase of development of the lesions, edema of the connectivetissues is associated with an increase of mucopolysaccharide. The collagen fibers are pushed apart by the accumulating of basophilic ground substance, and subsequently they undergo swelling, fraying, fragmentation, and disintegration.

Fibrinoid changes. The affected areas, including collagen fibers and the ground substance,are altered considerably and take on a deeply eosinophilic appearance resembling fibrin; thus, the change is referred to as fibrinoid degeneration or necrosis.

Cellular reactions. The early exudative and degenerative features are followed byproliferation, that is, an infiltration by lymphocytes, plasma cells, histiocytes, and fibroblasts. The most distinctive proliferative lesion is the granulematous phase of the Aschoff body.

Sclerosis. Aschoff bodies or diffuse inflammatory cellular infiltration are slowly replacedby fibrous scar mainly about the vessels.

Pathognomonic focal inflammatory nodules called **Aschoff bodies** are the

most characteristic in the heart, but similar lesions may occur elsewhere. Three phases or stages in the development of the Aschoff body are recognized:

Early (exudative, degenerative, or alterative) phase. These constitute foci of fibrinoidnecrosis, initially surrounded by lymphocytes, macrophages and a few plasma cells. The early phase of the life cycle of the Aschoff body occur up to the fourth week of acute RF.

1. ***Intermediate (proliferative or granulematous) phase.*** In the intermediate phase, which isevident during the fourth to the thirteenth week of the disease, cellular proliferation is the dominant feature. Distinctive plump histiocytes *(Aschoff or Anitschkow cells)*, some of which are multinucleated *(Aschoff multinucleated giant cells with abundant basophilic cytoplasm),* appear in periphery of nodules. *Anitschkow cells* are mononuclear cells. They have a moderate amount of faintly stained cytoplasm with vaguely defined borders. Their nuclei are large and vesicular and contain a prominent central chromatin mass that longitudinal section is serrated (caterpillar-like). In cross section a halo is observed about the chromatin bar so that the nucleus has an *«owl-eye» appearance*.

2. ***Late (senescent, fibrous, healing, or healed) phase.*** In 3 to 4 months, the healing phase isreached, characterized by regression and fibrosis of the nodule. The collagenous fibers fuse to form dense collagenous bindles, resulting in small scars between the muscle bundles, frequently perivascularly.

Clinical-anatomical forms of Rheumatic Fever:

1. **Cardiovascular form** occurs endocarditis, myocarditis, pericarditis.

2. **Polyarthritic form** occurs migratory large joint polyarthritis (knee, cubital, humeral, hip joint, ankle-joint). It is characterized by serous or serous-fibrinous inflammation. In the synovial membrane the mucoid swelling develops. Articular cartilage is safe, therefore deformation and ankylosis is absent.

3. **Nodular** (nodules around vessels) form occurs deposition of giant Aschoff bodies under skinand may develop perivascular sclerosis.

4. **Cerebral form occurs chorea.** The damage of the brain is connected with rheumaticvasculitis. Nervous cells degeneration, brain destruction and hemorrhages occur in the brain. If these changes are clearly marked, they may cause chorea minor (in children).

Cardiovascular form

The cardiac involvement in RF is that of a pancarditis; that is, there is endocarditis, myocarditis, and pericarditis.

Endocarditis (valvulitis)

- The most prominent changes develop in mitral and aortic valves. Lesions may also be present on the chordae tendineae, particularly at their attachment to the leaflets, and are rarely on the papillary muscles of the left ventricle.
- According to A. I. Abrikosov, valvular endocarditis is classified as follows:

1. **Diffuse or valvulitis.** In the active acute stage of the disease the valve leaflets or cusps arethickened and lose their transparency. Edema with swelling of the leaflet, an increased number of capillaries, and an infiltration by lymphocytes and occasionally by neutrophils are seen. Plasma cells and fibroblasts may be present. In some instances, this nonspecific inflammatory reaction may be all that occurs. Usually, however, there is also an increase in acid mucopolysaccharide, with alteration of collagen and the fibrinoid change near the surface of the valve and with surface deposition of fibrin from the blood in the ventricular cavity.

2. **Acute verrucous endocarditis.** This is followed by the appearance of characteristic wartlikenodules (verrucae) ranging from 1 to 3 mm in diameter, mainly along the line of closure of the cusps. It may lead to thickening, shortening, and blunting of valvular leaflets. Microscopically: fibrinoid necrosis with thrombotic masses.

3. **Fibroblastic or healing of the rheumatic valvulitis.** The following changes take place:

a) fibroblastic proliferation and collagen formation throughout the valve with scarring, thickening, and rigidity of the leaflets;

b) organization of the vegetations, with greater thickening along the line of closure. Adhesions between the lateral portions of the cusps, particularly in the region of the commisures;

c) thickening, shortening, and fusion of the chordae tendineae;

d) frequently, calcification, with contributes to the rigidity of the valve.

4. **Relapsing verrucous endocarditis:**

- The result is deformity of one or more valves, especially mitral or aortic.
- In the chronic or recurrent condition, the functionally important lesions are those of the valves, which result in heart failure because of the increased work of the heart caused by the valvular stenosis of insufficiency.

Mitral insufficiency

- The pathophysiology of mitral regurgitation is complex.
- Proper closure of the mitral valve depends not only on the mitral valve leaflets by themselves but also on several additional functional components of the mitral valve apparatus, namely, the chordae tendineae, the papillary muscles, and the left ventricle.
- Valvular insufficiency may result because of retraction of the scarred leaflets in the vertical direction leading to shortening of the cusps.
- Changing hemodynamic conditions may dramatically improve or worsen the degree of mitral regurgitation.
- Mitral insufficiency and stenosis are commonly combined.
- When mitral insufficiency is the main alteration, the effects are the follows:

a) dilatation and hypertrophy of the left ventricle;

b) dilatation and hypertrophy of the left atrium, often greater than in mitral

stenosis;

c) effects on the right side of the heart as in mitral stenosis after left-sided failure.

Mitral stenosis

- The most characteristic type of deformity causes mitral stenosis.
- Mitral stenosis is the result of rheumatic endocarditis or bacterial endocarditis.
- The gross appearance of the stenotic valve varies greatly according to the degree of involvement.
- Fibrous adhesion at the comissures may be slight or extensive.
- The leaflets are fibrotic and thickened, especially toward the closing edges.
- Contraction of scar tissue takes place, the valve leaflets become more rigid, and calcification of the mitral cusps and ring frequently is present to a greater or lesser degree.
- Ulceration of the thickest part of deformed valve is a common occurrence.
- The orifice becomes considerably narrowed.
- When the valves are less extensively involved and the bases of the leaflets are still somewhat pliable, the narrowed opening is surrounded but puckered, thickened tissue, so-called purse-string puckering. As the entire valve becomes more rigid it takes on appearance of a fixed diaphragm with a narrow oval or curved opening, ***a «buttonhole» or «fish-mouth» orifice.***
- The effects of mitral stenosis develop as a consequence of obstruction to the outflow of blood from the left atrium and include the following:

a) dilatation and hypertrophy of the left atrium, which occasionally appears as a huge saclike structure (so-called giant left atrium);

b) endocardial fibrous thickening of the left atrium;

c) pronounced chronic passive congestion of the lungs; eventual pulmonary-arteriolar thickening;

d) hypertrophy and dilatation of the right ventricle as a result of pulmonary hypertension;

e) dilatation of the right atrium as a right-sided heart failure develops;

f) a normal-sized left ventricle or, in prolonged mitral stenosis, atrophic left ventricle caused by reduced inflow of blood, with possible hypertrophy of this ventricle if mitral insufficiency or aortic stenosis is present.

- One of the complications that may occur in mitral stenosis and the consequent atrial dilatation is atrial fibrillation. Atrial fibrillation contributes to blood stasis and predisposes to development of thrombosis, especially in the left atrial appendage; systemic embolism may result.

Myocarditis

Rheumatic myocarditis is characterized by the presence of

1. Granulematous myocarditis. It is characterized by the presence of spe-

cific Aschoff bodies. There is gradual subsidence of the inflammatory reaction, and the Aschoff bodies are converted into small scars.

2. Nonspecific exudative interstitial myocarditis. It is characterized by diffuse or focal lymphohistiocytic infiltration and vasculitis. In the later stages of the disease may diffuse small-focal cardiosclerosis.

3. Parenchymal damage may lead to acute cardiac insufficiency and to death in early stages of disease or to chronic ischemic heart disease.

Pericarditis

- The tendency to affect serous membranes is one of the distinctive features of RF, and fibrinous pericarditis is a prominent part of the picture of acute rheumatic heart disease.
- The exudate varies from a thin film of fibrin to a shaggy coat with adhesions between the layers of the pericardium, thus the designation of «shaggy» heart, or «cor villosum».
- Microscopically, fibrin is seen as a shaggy layer on the surface of the epicardium and an infiltrate of lymphocytes, plasma cells, histiosytes, and occasionally neutrophils are present.
- Subsequently, organization of the fibrin by vascularized connective tissue may be observed. This may lead to fibrous thickening and adhesions of the visceral and parietal layers, to partial or complete obliteration of the pericardial cavity, and to a «chronic adhesive pericarditis».
- Although pericarditis may be the most prominent gross manifestation of the acute disease, it is usually a little physiologic significance and does not usually affect the clinical course of the patient.

Postmorten diagnosis of old rheumatic disease is based on the following marks:

1. Chronic adhesive pericarditis, especially circumscribed obliteration of the cardiac sac nears the apex.
2. Fibrous thickening of the valve leaflets, especially at the line of closure.
3. Valvular deformities, especially aortic or mitral stenosis of insufficiency and, more significantly, involvement of both the aortic and mitral valves.
4. Thickening, shortening, and adhesions of the chordal tendineae.
5. Microscopic changes, including foci of perivascular interstitial fibrosis and vascularization of the valves.
6. The chief causes of death in RF patients are cardiac failure, infective endocarditis, and embolism. Death may, however, be attributable to various conditions such as pneumonia.

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic progressive inflammatory arthritis of unknown origininvolving multiple joints and characterized by disorganization of connective tissue of the synovial membrane and articular cartilarge and de-

velopment of their deformation. RA is likely an autoimmune disease.

RA is basically a severe form of chronic synovitis that can lead to destruction and ankylosis of affected joints. The small joints of hands and feet are usually the first and most common to be involved, with lesions of the large joints appearing later in the course of the disease.

Although the skin, eyes, heart, lungs, spleen, lymph nodes, sceletal muscle, central and peripheral nervous system, and other organs can be affected.

Females are affected three times more often than males and there is peak prevalence in the third to fourth decades of life.

Pathogenesis of RA

Rheumatoid disease is often accompanied by characteristic immunoglobulin (often IgM), called rheumatoid factosr (RF), in affected person serum. These factors are against the own immunoglobulins (often IgG) and are of considerable complexity; they are capable of acting as antiglobulins and of forming complexes with abnormal antigenic gammaglobulins in vivo and in vitro.

RF forms locally in joint fluid; an immune complex binds complement and forms the intra-articular chemotactic factors C3a and C5a. The resultant accumulation of neutrophils contributes to the pathogenesis of the joint disease.

Other autoantibodies are also found in RA, and in addition to circulating immune complexes, cell-mediated immune systems also contribute to the pathogenesis of the articular and extra-articular manifestations of RA.

The cells and mediators that likely play a role in the RA include neutrophils, synovial lining cells, lymphocytes, and macrophages. The last-mentioned produce IL-1 and tumor necrosis factor, cytokines known to stimulate release of collagenases and other lytic enzymes.

The trigger for these immunologic reactions remains unknown; some authors have suggested Epstein-Barr virus (EBV) infection.

Morphology of RA

Main morphological appearance of RA is synovitis

RA generally first affects the small, proximal joints of the hands and feet, but then may involve, usually symmetrically, the wrists, elbows, ankles, and knees.

Stages of synovitis:

1. First stage:

• Acute inflammatory reaction with development of edema, hyperemia, and infiltration by small and large lymphocytes, plasma cells, plasmoblasts, mast cells, and macrophages, indicating the presence of both humoral and cellular immune response arises.

• There often are small areas of superficial necrosis of synovial lining cells with formation of superficial erosions covered by fibrinoid deposits; these de-

posits are composed of fibrin and small amounts of gamma globulin and complement components.

• An exudate containing polymorphonuclear leukocytes, may with ingested immune complexes, accumulates in joint cavity.

• Not infrequently, 2 to 3 mm **«rice» bodies**, composed of fibrin, fibronectin, collagen and immunoglobulin are present in joint cavities of seropositive patients.

2. Second stage:

• Hypertrophy of the synovium, synoviocytic hyperplasia, and an intense lymphoplasmacytic and hystiocytic infiltrate take place.

• Granulation tissue composed of synovial fibroblasts and capillaries causes grossly recognizable villous thickening of the synovium, whose lining cells become hypertrophic and hyperplastic.

• In some of these lining cells as well as lymphocytes and plasma cells of the synovium and in leukocytes of the synovial fluid occur.

• This exuberant synovium is known **as pannus**, which eventually fills the joint space, encroaching upon the articular surfaces.

• Release of destructive enzymes (proteases and collagenases) and cytokines (particularly IL-1) and pannus formation destroy cartilage, leading to changes very reminiscent of degenerative joint disease.

3. Third stage:

• Fibrous and bony ankylosis can result.

• As the pannus ages, vascularity decreases, the fibrosis and collagenization lead to shrinkage of the capsule, progressive narrowing of the joint space, and displacement or increasing approximation of the ends of the bones.

• Closely opposing bones may become fused by bone bridges developing in the scar tissue, or they may be telescoped into each other, with complete elimination of the joint.

• Other features include rheumatoid nodules (or rheumatoid granuloma) in subcutaneous tissues (areas of necrosis surrounded by palisade of fibroblasts and white cells at pressure points such as elbows), acute vasculitis (in patients with high rheumatoid factors), and nonspecific, fibrinous inflammatory lesions of lungs, pleura, pericardium, myocardium, peripheral nerves, and eyes.

The most common extra-articular lesion

• The most common extra-articular lesion is the subcutaneous nodule, a granuloma of a few millimeters to several centimeters in size, developing usually in areas close to the joints and subject to minor mechanical insults.

•Vasculitis associated with deposition of immune complexes in vessel walls is seen especially in patients with high serum titers of IgM-RF complex; occlusion of the vessel may result in ischemia and microinfarcts. Occlusion of the large vessels can cause gangrene of the terminal phalanges of fingers or toes.

• Cardiac lesions may involve the pericardium, myocardium, and endocardium, with focal accumulation of lymphocytes and plasma cells, vasculitis, granulomas, fibrosis, and amyloidosis.

• Pulmonary lesions may be focal and granulematous or diffuse, interstitial, or intraalveolar. The result is focal fibrosis.

• Lymph nodes show hyperplasia and, less commonly, granulomas. Several types of scleritis and retinopathy have been described in about 1 % of patients with rheumatoid disease.

• Amyloidosis is a late complication of RA with data on the frequency varying from 25 to 60 %.

Clinical features

• Variable. Most patients experience a prodrome of malaise, fever, fatigue, and musculoskeletal pain before joint involvement occurs.

• The lucky patient experiences mild transient disease without sequelae, but most has fluctuating disease with the greatest progression during the initial 4 to 5 years. In a minority the onset in acute, with rapidly progressive development of joint deformities.

• Characteristic deformities are radial deviation of the wrist with ulnar deviation of the fingers.

• Extra-articular manifestations (mentioned above), although infrequent, are rarely the presenting features of the disease, and tend to develop in patients with high RF titers.

• Some of the total morbidity of RA is caused by GI bleeding from long-term aspirin therapy, infections from steroid use, or amyloidosis in long-term severe disease.

• The death is caused by uremia.

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) *(Libmnan-Sacks disease)* is the classic prototype of the multisystem disease of autoimmune origin, characterized by a bewildering array of autoantibodies, particularly antinuclear antibodies. Acute or insidious in its onset, it is chronic, remitting and relasping, often febrile illness characterized principally by injury to the skin, joints, kidney, and serosal membranes.

Likely most autoimmune diseases, SLE is predominantly a disease of women, with frequency of 1 in 700 among women between ages of 20 and 64 and female to-male ratio of 9:1.

The cause of SLE remains unknown, but the existence of a seemingly limitless number of antibodies in these patients against self-constituents indicates that the fundamental defect in SLE is a failure of the regulatory mechanisms that sustain self-tolerance. Some authors consider that RNA virus may cause it.

Antibodies have been identified against an array of nuclear and cytoplasmic components of the cell that are either organ or species specific. Apart from their value in the diagnosis and management of patients with SLE, these antibodies are of major pathogenetic significance, as, for example, in the immune complex-mediated glomerulonephritis so typical of this disease.

Antinuclear antibodies are directed against several nuclear antigens and can be grouped into four categories: (1) antibodies to DNA, (2) antibodies to histones, (3) antibodies to nonhistone proteins bound to RNA, and (4) antibodies to nuclear antigens.

SLE appears to be a complex disorder of multifactorial origin resulting from interactions among genetic, hormonal, and environmental factors acting in concert to cause activation of helper T cells and B cells that results in the secretion of several species of autoantibodies. In this complex web, each factor may be necessary but not enough for clinical expression of the disease; the relative importance of various factors may vary from individual to individual.

Morphology

The morphologic changes in SLE are extremely variable, reflecting the variability of the clinical manifestations and the course of the disease in individual patients. It can also be said that none of these morphologic changes is pathognomic. The constellation of clinical, serologic, and morphologic changes is essential for diagnosis.

SLE is characterized by different cellular and tissue changes which can be divided into 5 groups:

1. Acute necrotic and degenerative changes of the connective tissue (all stages of disorganization).

2. Subacute interstitial inflammation of all organs including nervous system with involvement of microcirculation (capillaritis, arteriolitis, vasculitis).

3. Changes of sclerotic character caused by the above changes. This group is characterized by onion-like sclerosis in the spleen.

4. Changes of the immune system. Focal accumulations of leukocytes with marked plasmatization are present in the central and peripheral organs. Macrophagic activity is increased.

5. Nuclear pathology in the cells of all organs and tissues, particularly in the lymph nodes. The shape of the nuclei does not change but they gradually lose DNA and look pale after stain. After the death of the cell, the nucleus disintegrates into granules, i. e. ***hematoxylin bodies***. This phenomen characterizes LSE. Neutrophils and macrophages phagocytize hematoxylin bodies and form so-called ***«lupus cells».*** Their presence in the blood is a significant sign of SLE. Except for the blood, they can be found in the bone marrow, spleen, lymph nodes and the vascular walls.

Visceral manifestations of LSE

The most characteristic lesions result from the deposition of immune com-

plexes and are found in the blood vessels, kidneys, connective tissue, and skin.

An acute necrotizing vasculitis involving small arteries and arterioles may be present in any tissue although skin and muscles are most commonly affected. Fibrinoid deposits characterize the vessel walls of arteries. In chronic stages, vessels undergo fibrous thickening with narrowing lumen. In the spleen, these vascular lesions involve the central arteries and are characterized by marked perivascular fibrosis, producing so-called **«onion-skin» lesions**.

Kidney. On light microscopic examination, the kidney appears to be involved in 60 to 70 % of cases, but if immunofluorescence and electron microscopy are included in the examination of biopsy material, almost all cases of SLE show some renal abnormality. According to WHO morphologic classification of lupus nephritis, five patterns are recognized:

1. Normal by light, electron, and immunofluorescent microscopy (class 1), which is quite fare.
2. Mesangial lupus glomerulonephritis (class 2).
3. Focal proliferative glomerulonephritis (class 3).
4. Diffuse prolirefative glomerulonephritis (class 4).
5. Membranous glomerulonephritis (class 5).

It should be noted, however, that none of these patterns are specific for lupus.

Skin. The skin is involved in the majority of patients. Characteristic erythema in the bridgeof the nose and cheeks **(facial «butterfly»)** occurs, but a similar rash may also be seen on the extremities and trunk. Urticaria, bullae, maculopapular lesions, and ulcerations also occur. Exposure to sunlight incites or accentuates the erythema. Histologically, the involved areas show liquefactive degeneration of the basal layer of the epidermis together with edema at the dermal junction. In the dermis, there is variable edema and perivascular mononuclear infiltrates. Vasculitis with fibrinoid necrosis of the vessels may be prominent.

Joints. Joint involvement is frequent, the typical lesion being a nonserosive synovitis withlittle deformity. The latter fact distinguishes this arthritis from that seen in rheumatoid disease. In the acute phases of arthritis in SLE, there is exudation of neutrophils and fibrin into the synovium and a perivascular mononuclear cell infiltrate in the synovial tissue.

Serosal cavities. Inflammation of the serosal lining membranes may be acute, subacute, orchronic. During the acute phase, the mesothelial surfaces are sometimes covered with fibrinous exudate. Later they become thickened, opaque, and coated with a shaggy fibrous tissue that may lead to partial or total obliteration of the serosal cavity.

Cardiovascular system. Involvement is manifested primarily in the form of pericarditis.Valvular endocarditis may occur, but it is clinically insignificant. In the era before the widespread use of steroids, so-called **Libman-Sacks endocarditis** was more common. The nonbacterial verrucous endocarditis takes the form of single or multiple irregular 1-to3-mm warty deposits on any valve in the

heart, distinctively on either surface of the leaflets. Myocarditis, manifested as non-specific mononuclear cell infiltration, may also be present but is less common.

Spleen. The spleen may be moderately enlarged.

Lungs. In lungs the pneumanitis, fibrosing alveolitis and diffuse interstitial fibrosis arefound out.

The most common **causes of death** are renal failure (uremia) and intercurrent infections, followed by diffuse central nervous system disease. Patients treated with steroids and immunosuppressive drugs incur the usual risks associated with such therapy.

Bechterew's disease

• ***Bechterew's disease*** is a chronic disease involving joints and ligaments of the spine causingits immobility. Involvement of peripheral joints and inner organs is possible.

• ***Etiology:*** infectious-allergic factor, spine injury and hereditary factors. The disease mainly occurs in men with antigen histocompatibility HLA-B27.

• ***Morphology.*** Destructive inflammatory changes in the tissues of small joints of the spinal column resembling those in rheumatoid arthritis with destruction of articular cartilages, growth of stroma in the cavity of the joint and its-bony metaplasia with development of bone ankylosis and limitation of their mobility. The same process with bone formation develops in intervertebral disks, which results in complete immobility of the spinal column. Visceral changes: chronic inflammation and sclerosis of aorta, heart, lungs; amyloidosis in kidneys.

Systemic scleroderma

• ***Systemic scleroderma*** is chronic disease with skin involvement and visceral manifestations.

• ***Etiology.*** Viruses, genetic factors causing disturbances in collagen synthesis cannot be excluded. Abnormal collagen disintegrates quickly and is followed by sclerosis.

• ***Morphology.*** All stages of connective tissue disorganization against the background of slight cellular reaction are noted in the skin and internal organs. The condition results in sclerosis and hyalinosis. The skin becomes dense; its mobility is poor. Cortical necrosis may develop when the vessels of the kidneys are involved. It manifests by acute renal failure, termed «true sclerodennic kidney». Development of large-focus cardiosclerosis, fibrosis of the lungs and subpleural cavities (basal pneumosclcrosis) are possible.

• The complications and the causes of death depend on the visceral lesions (kidneys, heart, lungs).

Dermatomyositis

• ***Dermatomyositis*** is a chronic rheumatic disease involving striated and in rare cases smoothmuscles and skin. If the skin is not damaged, the disease is called polymyositis. It may occur at any age, mainly in women.

• ***Morphology.*** Striated muscles, the muscles of the pharynx, larynx, and diaphragm, ocular muscles are involved. Degeneration, calcinosis, necrosis, edema, cellular reactions are observed. Degenerative, inflammatory and sclerotic changes are observed in the heart, lungs, and alimentary tract. Hyperplasia against the background of plasmatization is observed in the immune organs.

• Clinico-morpholbgical forms:

1) Primary (idiopathic). Primary form in children is caused by genetic factor.

2) Secondary (tumor). Secondary form is frequently observed in cancer of ovaries, stomach, lungs, and breast.

• Each form may be acute, subacute, constantly relapsing and chronic.

III. DISEASES OF RESPIRATORY SYSTEM. ACUTE BACTERIAL INFECTIONS OF THE LUNGS

• Occur when normal lung or systemic protective mechanisms are impaired. Pulmonary protective mechanisms include nasal, tracheobronchial, and alveolar mechanisms to filter, neutralize, and clear inhaled organisms and particles.

• Important factors interfering with normal lung defenses are:

1. Decreased cough reflex leading to aspiration (seen in coma, anesthesia, drug effects).

2. Injury to mucociliary apparatus (as with cigarette or other smoke / gaseous inhalations).

3. Decreased phagocytic/bactericidal function of the alveolar macrophage (as a result of alcohol, tobacco, oxygen toxicity).

4. Edema/congestion (CIHD).

5. Accumulation of secretions.

• There are a lot of diseases, of pulmonary system as well as the etiologic factors, which cause these diseases. Acute and chronic bronchitis, pneumonia, destructive processes (abscess and gangrene), bronchial asthma, chronic nonspecific pulmonary diseases and cancer of lungs are the most common.

• Pathogenic organisms gain access to the lung through the airways, through the bloodstream, by traumatic implantation, or by direct spread across the diaphragm from the subphrenic source, probably through the lymphatics. The most common route is the airways.

Pneumonias

• Pneumonia is acute inflammation of the respiratory tract with deposition

of intraalveolar exudates.

• Etiologic classification of pneumonia:

1. Bacterial pneumonia.
2. Viral and mycoplasmal pneumonia.
3. Other types of pneumonias:

a) pneumocystis carini pneumonia;
b) legionella pneumonia;
c) aspiration pneumonia;
d) hypostatic pneumonia;
e) lipid pneumonia.

• Clinical-morphological classification:

4. Lobar pneumonia.
5. Bronchopneumonia (lobular pneumonia).
6. Interstitial pneumonia.

Lobar pneumonia

• Synonyms: crupous, lobular, fibrinous, pleurapneumonia.

• **Croupous pneumonia** is infectious-allergic infection and involves a lobe of lung.

• Most lobar pneumonias are caused by pneumococci and Klebsiella pneumonia which enter the lungs via the airways.

• The pneumococcus continues to be responsible for 30 to 80 % or more of community-acquired pneumonias.

• Groups at particular risk include the very young and very old, alcoholics, diabetics, spleenectomized subjects, and patients with multiple myeloma or circle cell disease.

• Hypersensivity of immediate type plays an important role in pathogenesis.

• Pleural involvement occurs commonly in lobar pneumonia Pneumococcal pneumonia typically presents the picture of lobar pneumonia. One or occasionally several lobes of the lung are involved. Fibrinous exudates in alveoli are presence.

• Traditionally the progress of the disease is divided into four stages:

1. **Congestion and Edema** predominates in the first 24 hours. The initial response to theorganism is edema, which spreads throughout the lobe through pores of Kohn and bronchioles. At this stage an involved lobe appears distended, moist, and deep red of purple. The pleura are shiny, and fluid exudes from the cut surface.

2. **Red hepatization** (2 days) describes lung tissue with confluent acute exudate containingneutrophils and red cells, giving a red, firm. Lobe is liver-like.

Gray hepatization (4–6 days) follows, as the red cells disintegrate and the remainingfibrinous-suppurative exudates persist, giving a gray-brown gross appearance.

3. **Resolution** (9–11 days) is the favorable final stage in which consolidated exudatesundergoes enzymatic and cellular degradation and clearance. Normal structure is restored.

• Complications:

1. ***Carnification*** is organization of fibrinoid exudate.
2. Abscess formation. Lung abscess results from the breakdown of alveolar walls.

3. Empyema (spread of infection to pleural cavity).

4. Gangrene.

5. Bacteremic spread leads to purulent meningitis, bacterial endocarditis, arthritis, pericarditis and other organs.

• Causes of death are acute cardiac-respiratory insufficiency and purulent complications.

Bronchopneumonia (focal pneumonia)

• **Bronchopneumonia** is marked by patchy exudative consolidation of lung parenchyma.

• Polyetiologic. The most often agents are bacterias: pneumococci, staphylococci, streptococci, hemophylus influenzae, pseudomonas aeruginosa, and coliform bacteria.

• Bronchopneumonia often arises due to autoinfection. Depending pathogenesis autoinfectional bronchopneumonia may be aspirationous, hypostatic, postoperative, immunodificiency.

• Bronchopneumonia often is a complication of others disease.

• According to extent may be acynous, lobular, segmental, and miliary.

Morphology

• Initially bronchi are affected. Then, inflammation spreads to parenchyma of lungs with accumulation of exudates in the alveoli.

• Grossly, the lungs show dispersed, elevated, focal areas of palpable consolidation and suppuration.

• Histological features consist of acute (neutrophilic) suppurative, serous, hemorrhagic or mixed exudates filling airspaces and airways, usually about bronchi and bronchioles.

• Outcomes and complications: resolution of the exudates usually restores normal lung structure, but organization may occur and result in fibrous scarring in some cases. Aggressive disease may produce abscess, pleurisy, and empyema.

Streptococcal pneumonia

• Beta-hemolytic streptococci are an uncommon cause of pneumonia at the present time. In adults streptococcal pneumonia like other pneumonias usually occurs in elderly, severely debilitated patients. Diabetes is also a risk factor. Infections caused by this microbe in the newborn are discussed elsewhere.

• The lower lobe is usually the site of major involvement.

• The airways appear thickened and are filled with a hemorrhagic or purulent exudate.

• The pneumonia is lobular with consolidated patches clearly centered on terminal bronchioles. The distinctive microscopic feature of streptococcal pneumonia is greater interstitial involvement than in other bacterial pneumonias.

There is necrosis of the epithelium of distal airways with infiltration of the bronchial walls by neutrophils and mononuclear cells. The interstitial infiltrate also extends into the adjacent alveolar walls.

Staphylococcal pneumonia

• Staphylococcal pneumonia usually occurs either in the presence of a source of bacteremia or after viral infection.

• Hematogenous pneumonia is seen in those with soft-tissue infections, in patients undergoing long-term dialysis. The lesions may appear as septic infarcts that are yellow and purulent but preserve to some degree the wedge-shaped configuration of infarcts and are associated with thrombosed vessels, or they may be rounded patches of necrotizing pneumonia that break down, giving rise to abscesses.

• Staphylococcal pneumonia also results from spread of organisms from the colonized nasopharynx. The lesions are those of bronchopneumonia accompanied by a hemorrhagic and necrotizing bronchitis. Purulent exudate fills the bronchioles and spreads into the adjacent acini.

Staphylococcal bronchopneumonia is not rare in children less than 6 months of age. A notable feature of staphylococcal pneumonia in small children is development of abscesss.

Local complications of staphylococcal pneumonia include empyema and bronchopleural fistula.

Aspiration pneumonia

Aspiration pneumonia results from inhaling different agents into the lungs. These substances include food, gastric contents, infected material from oral cavity, amniotic fluid or meconium in infants, etc.

Hypostatic pneumonia

Hypostatic pneumonia is the term used for the collection of edema fluid and secretions in the dependent parts of the lungs in bed-patients.

Interstitial pneumonia

Infections by viruses, mycoplasma pneumonia, pneumocystis carinii, etc. result in varied clinical and pathologic patterns, ranging from relatively mild upper respiratory tract involvements to severe lower respiratory tract disease.

Morphology

• Patchy or lobar areas of congestion without the consolidation of bacterial pneumonias.

• A predominance of interstitial pneumonitis with widened, edematous alveolar walls containing a mononuclear inflammatory cell infiltrates.

• The formation of hyaline membranes, reflecting diffuse alveolar damage.

• Pneumocystic pneumonia is characterized by desquamation of alveolar epithelium. Alveoli filled by foamy fluid and pneumocysts, and also hyperemia and inflammatory infiltration of the alveolar septs. It may pattern in AIDS.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

The term chronic obstructive pulmonary disease (COPD) refers to a group of conditions that share a major symptom — dyspnea- and are accompanied by chronic or recurrent obstruction to air flow within the lung.

Obstructive diseases are characterized by increased resistance to airflow because of chronic or recurring expiratory obstruction.

In their prototypical forms, these individual disorders — chronic bronchitis, bronchiectasis, asthma, emphysema — have distinct anatomic and clinical characteristic.

Hypertension of pulmonary circulation and «cor pulmonale» develops in all Chronic Obstructive Pulmonary diseases.

Amyloidosis of kidneys and chronic renal insufficiency may develop often. Death of the most patients with COPD is due to:

1) respiratory acidosis and coma;
2) right-sided failure;
3) massive collapse of the lung secondary to pneumothorax.

Chronic Bronchitis

The widely accepted definition of **chronic bronchitis** is a clinical one — chronic bronchitis (CB) is present in any patient who has persistent cough with sputum production for at least 3 months in at least 2 consecutive years.

This disorder, so common among habitual smokers and inhabitants of smog-laden cities, is not nearly so trivial as was once thought.

The role of infection appears to be secondary. It is not responsible for the initiation of CB but is probably significant in maintaining it and may be criterial in producing acute exacerbations.

Pathogenesis. Two sets of factors are important in the genesis of chronic bronchitis: 1. Chronic irritation by inhaled substances.

2. Microbiologic infections.

Morphology

• The hallmark and earliest failure of CB is hypersecretion of mucus in the large airways, and is associated with hypertrophy of the submucosal glands in the trachea and bronchi.

• As CB persists, there is also a marked increase in goblet cells of small airways — small bronchi and bronchioles — leading to excessive mucus production that contributes to airway obstruction.

• Although mucus hypersecretion in large airways is the cause of sputum

overproduction, it is now thought that accompanying alterations in the small airways of the lung can result in physiologically important and early manifestations of the chronic airway obstruction.

- Histological features of the small airways:

1. Goblet cell metaplasia with mucus plugging of the lumen.
2. Clustering of pigmented alveolar macrophages.
3. Inflammatory infiltration.
4. Fibrosis of bronchiolar wall.

Outcomes and complications

- Lead to «cor pulmonale» and heart failure.
- Cause atypical metaplasia and dysplasia of the respiratory epithelium, providing a possible soil for cancerous transformation.
- Amyloidosis of kidneys.
- Lead to bronchiectasis.

Bronchiectasis

Bronchiectasis (BE) is chronic necrotizing infection of the bronchi and bronchioles leading to or associated with abnormal dilation of these airways.

BE has many origins and usually develops in association with following conditions:

1. Bronchial obstruction, due to tumor, foreign bodies, and occasionally mucous impaction, in which the BE are localized to the obstructed lung segment; or due to diffuse obstructive airway disease, most commonly atopic asthma and chronic bronchitis, measles.
2. Congenital or hereditary conditions, including congenital BE, cystic fibrosis, intralobar sequestration of the lung states, and immune cilia and Kartagener's syndromes.
3. Necrotizing pneumonia, most often caused by tubercle bacillus or staphylococci or mixed infections.

Morphology

- BE usually affects the lower lobes bilaterally, particularly those air passages that is most vertical, and is most severe in the more distal bronchi and bronchioles.
- When tumors or aspiration of foreign bodies leads to BE, the involvement may be sharply localized to a single segment of the lungs.
- The pleura is usually fibrotic and thickened with adhesions to the chest wall. Cut surface has honey-combed appearance. The walls of bronchi are thickened and the lumen arc filled with mucus.
- The airways are dilated; sometime up to four times normal size. These dilations may produce:

1. Long, tube-like enlargements (cylindroid BE) in 1 to 4 type of bronchus.

2. May cause fusiform or even sharply saccular distention (saccular BE) in 6–10 types of bronchus.

• The histologic findings vary with the activity and chronicity of the disease:

3. In the full-down active case, there in an intense acute and chronic inflammatory exudation within the walls of bronchi and bronchioles, associated with desquamation of the lining epithelium and extensive areas of necrotizing ulceration. There may be squamous metaplasia of the remaining epithelium.

4. In some instances, the necrosis completely destroys the bronchial or bronchiolar walls and forms a lung abscess.

5. Fibrosis of the bronchial and bronchiolar walls and peribronchial fibrosis develop in the more chronic cases.

Outcomes and complications

1. Obstructive ventilatory insufficiency can lead to marked dyspnea and cyanosis.
2. Pulmonary hemorrhage.
3. Pulmonary abscess.
4. Empyema of the pleura.
5. Metastatic brain abscess.
6. «Cor pulmonale» and chronic cardiac-pulmonary insufficiency.
7. Amyloidosis are less frequent complications of BE.

Emphysema

Emphysema is a condition of the lung characterized by abnormal permanent enlargement ofthe airspace distal to the terminal bronchiole, accompanied by destruction of their walls, and without obvious fibrosis. In contrast, the enlargement of airspaces unaccompanied by destruction is termed overinflation, for example, the distention of airspaces in the opposite lung following unilateral pneumonectomy.

Pathogenesis

While details of the genesis of the two common forms of emphysema — centiacinar and panacinar — remain unsettled, the most plausible hypothesis to account for the destruction of alveolar walls is the protease-antiprotease mechanism. Thus, emphysema is seen to result from the destructive effect of the high protease activity in subjects with low antiprotease activity.

The protease-antiprotease hypothesis also explains the deleterious effect of cigarette smoking:

1. Smokers have greater numbers of neutrophils and macrophages in their alveoli. The increased recruitment of neutrophils into the lung is likely to result, in part, from the release by activated alveolar macrophages of neutrophil chemotactic factors, this release being stimulated by smoking. In addition, nicotine is chemotactic for neutrophils, and cigarette smoke activates the alternative compliment pathway.

2. Smoking stimulates release of elastase from neutrophils.

3. Smoking enhances elastolytic proteases activity in macrophages; macrophage elastase is not inhibited by alpha-1-AT and, indeed, can proteolytically digest this enzyme.

4. Oxidants in cigarette smoke and oxygen free radicals secreted by neutrophils inhibit alpha-1-AT and thus decrease net antielastase activity in smokers.

It is thus postulated that impaction of smoke particles in the small bronchi and bronchioles, with the resultant influx of neutrophils and macrophages, and increased elastase and decreased alpha-1-AT activity causes to the centriacinar emphysema seen in smokers.

Classification

Although the term «emphysema» is sometimes loosely applied to diverse conditions, there are four types:

1. Centriacinar (cenrolobular) emphysema. The distinctive feature of this type is the pattern ofinvolvement of the lobules; the central or proximal parts of the acini, formed by respiratory bronchioles, are affected, whereas distal alveoli are spared. The walls of the emphysematous spaces often contain large amount of black pigment. Inflammation around bronchi and bronchioles and in the septa is common. Moderate-to-severe degrees of emphysema occur predominantly in heavy smokers, often in association with chronic bronchitis. In addition, some lesions of so-called coal workers' pneumoconiosis bear a striking resemblance to centriacinar emphysema.

2. Panacinar (panlobular) emphysema. In this type the acini are uniformly enlarged from the level atthe respiratory bronchiole to the terminal blind alveoli. This type of emphysema is associated with alpha-1-antitrypsin deficiency.

3. Paraseptal (distal acinar) emphysema. In this type the proximal portion of the acinus is normal, but the distal part is dominantly involved. The emphysema is more striking adjacent to the pleura, along the lobular connective tissue septa, and at the margins of the lobules. This type of emphysema probably underlies many of the cases of spontaneous pneumothorax in young adults.

4. Irregular emphysema, so named because the acinus is the irregularly involved, is almost invariablyassociated with scarring. Thus, it may be the most common form of emphysema, as careful search of most lungs at autopsy shows one or more scars from a healed inflammatory process. In most instances, these foci of irregular emphysema are asymptomatic.

Types of emphysema according to cause

1. Compensatory E. This term is sometimes used to designate dilation of alveoli but not destruction ofseptal walls in response to loss of lung substance elsewhere. It is best exemplified by the hyperexpansion of the residual lung parenchyma that follows surgical removal of a diseased lung or lobe.

2. Obstructive overinflation refers to the condition in which the lung expands because air is trappedwithin it.

3. Senile E. refers to the overdistended, sometimes voluminous lungs found in the aged.

Bullous E. Refers merely to at any form of E. that produces large subpleural blebs or bullae (spacesmore than 1 cm in diameter in the distended state).

4. Interstitial E. The entrance of air into the connective tissue stroma of the lung, mediastinum, orsubcutaneous tissue is designated interstitial emphysema.

Morphology

- The diagnosis and classification of the emphysemas are based on naked eye (or hand lens) examination of lungs fixed in a state of inflation.
- Panacinar emphysema, when well developed, produces voluminous lungs, often overlapping the heart and hiding it when the anterior chest wall is removed.
- The macroscopic signs of centriacinar emphysema are less impressive. The lungs may not appear particularly pale or voluminous unless the disease is well advanced.
- Generally, the upper two-thirds of the lungs are more severely affected.
- Large apical blebs or bulla are more characteristic of irregular emphysema secondary to scarring.
- Microscopical examination is accessory to visualize the abnormal fenestrations in the walls of the alveoli, the complete destruction of septal walls, and the distribution of damage within the pulmonary lobule. With advance of the disease, adjacent alveoli fuse, producing even larger abnormal airspaces and possibly blebs or bulla. Often the respiratory bronchioles and vasculature of the lung are deformed and compressed by the emphysematous distortion of the airspaces, and, as mentioned, there may or may not be evidence of bronchitis or bronchiolitis.

Bronchial asthma

Bronchial asthma (BA) is a disease characterized by hyper-reactive airways, leading to episodic,reversible bronchoconstriction, owing to increased responsiveness of the tracheobronchial tree to various stimuli. A severe and unremitting type of the disease termed status asthmaticus may prove fatal.

Pathogenesis

- Chronic airway inflammation involving many cell types and inflammatory mediators accompanies the bronchial hyper-responsiveness of asthma.
- Nevertheless, the relationship of the inflammatory cells and their mediators to airway hyper-reactivity is not fully understood.

Classification

1. **Extrinsic BA** is initiated by a type 1 hypersensitivity reaction induced by exposure to an extrinsicantigen. Subtypes include atopic (allergic), BA, occupational BA (many forms), and allergic bronchopulmonary aspergillosis (bronchial colonization with aspergillus organisms followed by development of IgE antibodies).

2. In contrast, **intrinsic BA** is initiated by diverse, nonimmune mechanisms, including aspirin, pulmonary infections; especially those caused by viruses, cold, inhaled irrigants (pollutants such as sulfur dioxide), stress, and exercise.

Morphology

The morphologic changes in asthma have been described principally in patients dying of status asthmaticus, but it appears that the pathology in nonfatal cases is similar.

Grossly, the lungs are overdistended because of overinflation, and there may be small areas of atelectasis.

The most striking macroscopic finding is occlusion of bronchi and bronchioles by thick, tenacious mucous plaques.

Histologically, the mucous plaques whorls of shed epithelium, which give, rise to the well-known Curschmann's spirals.

- Numerous eosinophils and Charcot-Leyden crystals are present.
- The other characteristic histologic findings of BA include:

— Thickening of the basement membrane of the bronchial epithelium.

— Edema and inflammatory infiltrate in the bronchial walls, with a prominence of eosinophils, which form 5 to 50 % of the cellular infiltrate.

— An increase in size of the submucosal glands.

— Hypertrophy of the bronchial wall muscle, a reflection of prolonged bronchoconstriction.

— Emphysematous changes sometimes occur, and if chronic bacterial infection has supervened, bronchitis may occur.

The classic ***asthmatic attack*** lasts up to several hours and is followed by prolonged coughing; the raising of copious mucous secretions provides considerable relief of the respiratory difficulty. In some patients, these symptoms persist at a low level all the time. In its most severe form, status asthmaticus, the severe acute paroxysm persists for days and even weeks, and, under these circumstances, ventilatory function may be so impaired as to cause severe cyanosis and even death.

Chronic lung abscess

The term «**Chronic Lung Abscess» (LA)** describes a local suppurative process within the lung characterized by necrosis of lung tissue.

Oropharyngeal surgical procedures, bronchial infections, dental sepsis, and bronchiectases play important roles in their development.

The causative organisms are introduced by the following mechanisms:

— Aspiration of infective material.
— Antecedent primary bacterial infection.
— Septic embolism.
— Obstructive tumors.
— Direct traumatic punctures.
— Miscellaneous.

When all these causes are excluded, there are still cases in which no reasonable basis for the LA formation can be identified. These are referred to as «primary cryptogenic» LA.

Morphology

Abscesses vary in diameter from lesions of a few millimeters to large cavities of 5 to 6 cm. They may affect any part of the lung and may be single or multiple.

The cavity may or may not be filled with suppurative debris, depending on the presence or absence of a communication with one of the air passages.

When such communications exist, the contained exudate may be partially drained to create an air-containing cavity.

Superimposed saprophytic infections are prone to flourishing within the already necrotic debris of the abscess cavity.

Continued infection leads to large, fetid, green-black, multilocular cavities with poor demarcation of their margins, designated gangrene of the lung.

The cardinal histologic change in all abscesses is suppurative destruction of the lung parenchyma within the central area of cavitation.

A reactive fibrous wall often surrounds chronic abscesses.

Complications include extension of the infection into the pleural cavity, hemorrhage, thedevelopment of brain abscesses or meningitis from septic emboli, and rarely reactive secondary amyloidosis.

Idiopathic pulmonary fibrosis

Diffuse interstitial fibrosis occurs as a result of different pulmonary diseases. It is so called «idiopathic pulmonary fibrosis» or «cryptogenic fibrosing alveolitis» or «chronic interstitial pneumonitis».

Morphology

- Pathological changes are bilateral and widespread.
- Macroscopically the lungs are dense, reduced volume.

Honey-combing (i.e. enlarged, thick-walled air spaces) develops in parts of lung. Microscopically, changes vary according to the stage of the disease with formation of hyaline membranes.

- There is edema and cellular infiltrate in the alveolar septa in early stage.
- There is organization of the alveolar exudate and replacement fibrosis in

the alveoli and in the interstitial septal wall with variable amount of inflammation in advanced stage.

IV. DISEASES OF ALIMENTARY SYSTEMS

Tonsillitis

• Tonsillitis is infectious disease and is characterized by inflammatory changes in the crypts of the adenoids and the tonsils on the anterior wall of the pharynx.

• Tonsillitis can be acute and chronic.

Etiophathogenesis

• Infectious agents are staphylococcus, streptococcus, adenovirus and bacterium's assotiations.

• Transephithelial, hematogenic pathways are responsible for the transmission. Autoinfection is most often cause of tonsillitis against a background the cooling and trauma.

• Acute edema and erythema, and sometimes purulent exudates and abscesses, may develop in the crypts of the adenoids and the tonsils on the anterior wall of the pharynx.

• Lymphoid tissue is distributed on the posterior pharyngeal wall and under the tongue, but not as masses of nodes with crypts such as composes the palatine adenoids and facial tonsils.

• Tonsils and adenoids are usually unapparent in early infancy, but gradually undergo hypertrophy and hyperplasia to rich their relatively greatest mass between 2 and 5 years of age.

• Their location is such that they are exposed to inspired air and food and whatever antigens may be carried in either one. These tissues are part of the bursal system of immunity and consist mostly of B cells.

Classification

Acute tonsillitis:

• Cattharal tonsillitis is characterized by hyperemia and serous or mucous leucocytic infiltration.

• Fibrinous tonsillitis the deposition of whitish-yellowish fibrinous films (in diphtheria) occurs.

• Purulent tonsillitis is characterized by phlegmonous inflammation or the formation of abscesses. Tonsils are enlarged due to edema and leucocytic infiltration.

• Follicular tonsillitis is characterized by hyperplasia of tonsils. Leucocytic infiltration and necrosis of follicles take place. Tonsils are enlarged and hyperemic.

• Cryptous tonsillitis is characterized by the deposition of the serous, mu-

cous or purulent exudates, which are located in crypts.

• Necrotic tonsillitis the ulceration occurs and can be in leukemia and scarlet fever.

• Gangrenous tonsillitis the ulceration and hemorrhages occurs also.

Chronic tonsillitis

• Chronic tonsillitis is characterized by the persistence of infection or due to relapse of acute tonsillitis.

• Hyperplasia and sclerosis of lymphoid tissue, sclerosis of tonsil's capsule, increasing of crypts, ulceration of the epithelium are morphological features of chronic tonsillitis.

• Chronic infection can present as anorexia, failure to gain weight, low-grade fever, or recurrent sore throats with high fever. Hypertrophy can be considerable and lead to mouth breathing, or even upper airway obstruction, retention, sleep apnea, and, rarely, cor pulmonale.

• Ersistent anterior and posterior cervical adenopathy in the absence of generalized lymphadenopathy is evidence of chronic or recurrent infection. Inspection of the tonsils is of limited help during acute episode.

Complication of tonsillitis

·Extension of tonsillar infection can take place in the surrounding tissues and is called peritonsillar abscess or quinsy. The retropharyngeal nodes drain both the adenoids and the nasopharynx and can become chronically infected. This is known as retropharyngeal abscess.

·These complications of tonsillitis are usually caused by B-hemolytic streptococci, which are almost sensitive to penicillin. Consequently, the widespread use of antibiotics to treat streptococcal pharingitis has been associated with less suppuration in the peritonsillar of retropharyngeal spaces.

·Peritonsillar cellulitis and abscess are characterized by an extremely sore throat and often high fever. If the condition is untreated, it may lead to significant swelling and even occlusion of the oral pharynx.

·Retropharyngeal abscess is virtually limited to infants in the first 2 years of life. The characteristic findings and fever, hyperextension of the neck, dysphagia, and noisy respirations. There is prominence of the infected pharyngeal wall but swelling is almost always unilateral.

·The importance of this disease is that it is commonly a precursor of rheumatic fever or one form of glomerulonephritis.

Gastritis

Gastritis is an inflammation of gastric mucosa and can be acute and chronic.

Acute gastritis

Acute inflammation develops due to injury of the mucosa by the alimentary, drugs, toxic and bacterial agents.

Morphologic classification of acute gastritis:

1. Catarrhal gastritis.
2. Fibrinous gastritis.
3. Phlegmonous gastritis.
4. Necrotic (or Corrosive).
5. Hemorrhagic gastritis.
6. Pseudomembranous.

Chronic gastritis

- Chronic inflammatory changes in the mucosa of the stomach, with various degrees of loss of the specialized glandular tissue, are extremely common, although often clinically silent.
- Collectively constitute a morphologic continuum of increasingly intense inflammation of mucosa accompanied by progressively more marked atrophy of the mucosa glands.
- Glandular atrophy is often accompanied by metaplasia, dysplasia and atypia of the surface epithelium.
- Our understanding of the etiology and mechanism of gastritis and gastroduodenal ulceration has been radically altered by the discovery of specific infective agent Helicobacter pylori.
- The Sidney System is a new classification based on this recent new knowledge. It incorporates two separate divisions: histological and endoscopic.

Clasification

The histological classification incorporates three main positions:

1. Etiology.
2. Topography (i.e. — site affected: antrum, body or both).
3. Morphology (including information about activity, intestinal metaplasia — graded as mild, moderate or severe).

The three main types of chronic gastritis are examples of this classification **according totopography** use:

I. Autoimmune associated chronic pangaslritis with severe atrophy (Type A fundal gastritis):

- Associated with circulating antibodies to parietal cells and intrinsic factor and complete loss of parietal cells.
- Loss of parietal cells leads to hypo- or achlorhydria, hypergastrinemia, inadequate synthesis of intrinsic factor and vitamin B_{12} absorption.

• Overt pernicious anemia develops in 10 %.

• Associated with Hashimoto's thyroiditis and Addison's disease, hence the term autoimmune gastritis.

• Intestinal metaplasia and dysplasia may occur and possibly resulting in gastric carcinoma.

II. Helicobacter pylori associated chronic gastritis of the antrum with moderate activity (Type B gastritis):

• The most common form of gastritis in all age groups.

• Background factors are environmental such as intoxication, abnormal dietary, and alcohol.

• Associated with gastric atrophy, intestinal metaplasia, gastric polyps, and gastric cancer.

• Initially superficial, gradually becomes deeper to affect the entire mucosa with glandular atrophy, leading to «chronic atrophic gastritis».

• Colonization of mucous layer and surface of mucosal cells with curved organisms, with little to no tissue invasion, confined to areas of gastric mucosa.

• Small foci of neutrophils, some passing to surface or into superficial crypt lumen occur, superimposed on a variable background of chronic gastritis (active chronic gastritis with abundant neutrophils).

III. Reflux-gastritis (formerly known as Type C gastritis):

• Associated with reflux of duodenal contents in stomach.

• May occur after gastric surgery, or with weakened pyloric sphincter tone.

• Localization is antrum.

• Achlorhydria and hypergastrinemia is absent.

According to topography:

1. Antral gastritis.
2. Fundal gastritis.
3. Pangastritis.

According to morphology

• Chronic superficial gastritis (early stage): lymphocytes and plasma cells in the upper third of the lamina propria, some mucosal flattening.

• Chronic atrophic gastritis (later stage): flattening of rugal folds, mucosa thinned and flattened, chronic inflammation of full thickness of the mucosa, loss of glands, metaplasia of mucosa to the intestinal type.

Peptic ulcer disease

Ulcerative disease is chronic disease with development chronic recurrent peptic ulcer.

Background factors:

Age. Often diagnosed in middle-aged to elder adults, but may appear in young adult life.

Common in industrialized nations.

Sex. Mail-female ratio 3:1.

Familial tendency and genetic factors for duodenal ulcer.

Environmental and geographical factors.

Dietary habits.

The ingestion of drugs (especially aspirin, corticosteroids).

Stresses may be important.

Cigarette smoking and alcohol.

Pathogenesis

Hypersecretion of gastric juice and emotional factors have been considered to be important in the pathogenesis of peptic ulcers. The gastroduodenal mucous membrane is protected against digestion of normal gastric secretions not only by its mucus coating but also by dilution and neutralization with swallowed food, saliva, and regurgitated duodenal fluids. This is considered to be the result of vagal stimulation and can be abolished by section of the vagus nerve. The spiral bacterium Helicobacter (campylobacter pylori) has been frequently isolated from patients with gastritis or peptic ulcer disease, but its pathogenic role remains to be determined. Prostaglandin deficiency has also been implicated as a possible cause of peptic ulcer disease.

For duodenal ulcers, the most important cause is excess exposure to acid and pepsin. Major influences for duodenal ulcers:

- Hypertone of vagus with increasing of acid-peptic factors.
- Abnormally rapid gastric emptying, exposing the duodenum to a greater acid load. Increasing of the level of ACTG and glucocorticoids.
- Duodenal ulcer has been associated with tension, stress, and anxiety but this is by no means always the case and there is no agreement on the importance of stress in its pathogenesis.

For gastric ulcers, breakdown in mucosal defenses appears to be most important. Major influences for gastric ulcers:

- Suppression of hypothalamic and hypophysic functions.
- Hypotone of vagus and decreasing of gastric secretion.
- May involve decreased pyloric sphincter tone, and reflux of bile acids.
- Weakening of protective factors of gastric mucosa.
- Exogenous agents that damage the mucosa are more likely to cause gastric ulcers than duodenal ulcers (alcohol, drugs, chemical substance).
- Possible defect in gastric mucus with the presence of Helicobacter.

Morphogenesis and morphology

I. **Erosion** is superficial necrosis of mucosal epithelial elements:

— These are tiny ulcers, a few millimeters in diameter, which are formed

by the digestion of the mucosal membrane overlying small hemorrhage.

— They are usually multiple and affect all parts of the stomach.

— They occur mostly on the apex of mucosal folds and involve only the mucosa.

— Note that the changes are superficial so that restoration to normal can very quickly occur.

II. Acute ulcer:

— Loss of tissue penetrating into the submucosa.

— Location: single or multiple lesions throughout the stomach and duodenum.

— Circular and small, less than 1 cm in diameter.

— Inflammatory reaction absent initially, develops secondarily.

— Massive hemorrhage may be fatal.

— Perforation can lead to peritonitis.

— This type of ulcer usually heals without a visible scar.

III. Chronic peptic ulcer:

— The term «chronic» is applied when the pathological changes have penetrated and destroyed the muscle coat; they are also, of course, of much longer duration than acute ulcers.

— Gastric ulcers are located along the distal lesser curvature, usually within about 5 cm of the pylorus.

— Duodenal ulcers usually occur in the first centimeter or two distal to the pylorus on the anterior or posterior wall rather that laterally (kissing ulcers).

— Classic peptic ulcer is small (about 1 cm in the duodenum; 1 to 2,5 cm in the stomach), round-to-oval. It is characteristically «punched out», with sharply defined margins, and has overhanging mucosa producing a flashlike appearance. Its edges are not raised, and the mucosal folds covering on the ulcer are distinct to its edge. Frequently it has a terraced structure.

— Malignant gastric ulcers are generally bowel shaped, with margins that are usually sloped and generally without overhanging mucosa. The edges are raised and indurated, and nodular mucosal or submucosal thickening interrupts the mucosal folds toward the crater.

Microscopically:

1. The bed of the ulcer is covered by fibrinous exudate containing fragmented leukocytes.
2. Fibrinoid necrosis.
3. Granulation tissue with plasma cell and lymphocytic infiltration.
4. Fibrous tissue.

The principal complications of peptic ulcer

I. Ulcerative-destructive:

• **Perforation.** Anterior duodenal ulcers may perforate into the free peritoneal cavity, withresultant peritonitis. The peritonitis from perforated peptic ulcer is initially a chemical inflammation, but bacterial contamination soon follows. After successful surgical treatment of the perforation, there is a risk that infected

material lodged between the liver and diaphragm may become sealed off by fibrinous exudate and cause an abscess that may later infect the pleura.

• **Penetration.** Extension of the inflammation to the serous coat may result in adhesion to theadjacent organs. Perforating posterior ulcers more often penetrate the pancreas, producing intractable pain. Posterior perforation also may occur into the lesser peritoneal sac, leading to localized peritonitis. The omentum or adhesions to adjacent organs may also serve to localize peritoneal inflammation.

• **Hemorrhage.** Both gastric and duodenal ulcers are subject to massive hemorrhage.Duodenal ulcers are especially prone to perforation. Any ulcer, but especially those located posterior, may bleed in smaller amounts, producing melena or evidence of occult blood in the stool. It may be abundant and give rise to «coffee-grounds» vomit. Sometimes a major artery may be eroded and a large, even fatal, hemorrhage takes place.

II. Ulcerative- cicatricial (obstruction or healing and scarring):

• Pyloric obstruction may be a complication of an ulcer, gastric or duodenal, situated near the pylorus. It usually results from a combination of cicatricial narrowing and spasm.

• Scarring in the duodenum may lead to serious stricture (pyloric stenosis). The stomach becomes greatly dilated and hypertrophied and lead to chronic vomiting with alkalosis and malnutration.

III. Malignization:

• The development of carcinoma has been reffered to as one of the complications of peptic ulcer. It seems probable that carcinoma can develop in a preexisting ulcer, but it is equally probable that it is a rare event. It is extremely difficult to establish the occurrence of such a sequence of events in any particular case.

IV. Inflammatory (gastritis, perigastritis, duodenitis, periduodenitis).

V. Mixed.

Appendicitis

Appendicitis results in severe acute or chronic inflammation of the vermiform appendix.

Acute appendicitis

• Acute appendicitis is the most common acute abdominal condition requiring surgery.

• Acute appendicitis is uncommon at the extremes of age and it is most frequently seen in elder children and young adults.

• The most important factor in its pathogenesis is obstruction of the lumen, with the most frequent cause being a fecalith, a molded mass of inspissated fecal material that may develop rock-hard consistency.

• Other causes of obstruction are scars representing a residuum of previous attacks of appendicitis, tumors, external bands, and adhesions, rarely masses of para-

sites, foreign bodies, and possibly spasm of the muscle at the base of the appendix.

• The immediate cause of acute appendicitis is bacterial infection from the intestinal lumen, though bacterial invasion from the bloodstream in systemic disease is possible.

• The appendix may be involved in diseases primarily affecting other portions of the gastrointestinal tract, such as Crohn's disease, typhoid fever, and amebiasis, and in certain systemic diseases (such as measles).

Clinical-morphological classification of acute appendicitis

1. **Simple appendicitis** is characterized by hyperemia; small hemorrhages and primary affectincluding small foci leucocytes.

2. **Superficial appendicitis** is characterized by focus of suppurative inflammation in mucosa andedema. Serous membrane is dim.

3. Destructive forms:

• ***Flegmonous appendicitis*** occurs the diffuse infiltration of leucocytes in wall of appendix.Gross appearance: appendix is increased, swollen; tense and markedly congested and covered by fibrinous exudate.

• ***Flegmonous-ulcerative appendicitis*** is characterized by flegmonous inflammation withnecrosis and ulceration in mucosa.

• ***Apostematous appendicitis*** the formation of small abscesses occurs. The primaryinflammatory lesion may increase in intensity and lead to a small abscess in the wall, and this may perforate.

• ***Gangrenous appendicitis*** occurs large areas of necrosis, the immediate antecedent ofrupture and may has two causes:

a) thrombosis and thromboembolism of mesentery artery (primary gangrene of appendix) due to obstraction of the lumen by fecoliths;

b) thrombosis due to development of periappendicitis (secondary gangrenous appendicitis).

The complications of acute appendicitis

1. Necrosis of appendix wall (gangrenous appendicitis), leading to perforation, with subsequent generalized peritonitis.

2. Involvement of adjacent bowel loops, causing perforation of small bowel.

3. The omentum may become adherent, localizing the peritonitis to the right iliac fossa. Fibrosis and continued inflammation cause development of a mass in the right iliac fossa. This may resolve with scarring, may form an abscess that drains to the surface, or may rupture, with development of generalized peritonitis.

4. Empyema of appendix due to obstruction of proximal parts.

5. Spread of infection by portal vein branches may propagate to the liver; this was formerly an important cause of portal pyemic abscesses in the liver.

Chronic appendicitis

Chronic appendicitis is characterized by sclerosis and atrophy, lipomatosis and diffuseinfiltration by lymphocytes and hystiocytes.

Obliteration of part or all of the appendiceal lumen by a mixture of fibrous tissue, lymphocytes, lymphoid follicles, and nerve bundles is common.

In the fibrosis causes complete of the lumen, continued mucous secretion might result in cystic dilatation — **mucocele**.

Such a cyst may rupture, giving rise to myxoma peritonei: the mucus-secreting epithelium is spilled into the peritoneal cavity and loculations of mucin and adhesions result.

Surgically removed appendix may be histologically normal (false-positive clinical diagnosis). If the appendix is normal, but clinical cymptomes took place is called ***«false appendicitis».*** It may be due to mimicking acute appendicitis some diseases: salpingitis, ectopic pregnancy, Meckel's diverticulitis, peptic ulcer, and pain cause by trivial pelvic bleeding at the time ovulation.

V. DISEASES OF THE LIVER

- There are various diseases of the liver.
- In some instances, the disease is primary to the liver, as in viral hepatitis and hepatocellular carcinoma.
- More often the hepatic involvement is secondary, often to some of the most often diseases in humans, such as cardiac decompensation, disseminated cancer, alcoholism, and extrahepatic infections.
- Some general aspects of liver disease are reviewed.

Morphologic patterns of hepatic injury

The liver is an inherently simple organ, with a limited repertoire of responses to injurious events. Regardless of cause, five general reactions may occur.

I. Necrosis:

- Virtually any significant insult to the liver may cause hepatocyte necrosis.
- In ischemic necrosis, poorly stained mummified hepatocytes remain (coagulative necrosis).
- Necrosis of scattered hepatosytes, clumps, or an entire lobule. Isolated necrotic hepatocytes appear as eosinophilic rounded — up, shrunken cells and are called Councilman Bodies or apoptotic bodies).
- Alternatively, hepatocytes may osmotically swell and rupture so-called hydropic degeneration.
- Necrosis may be limited to scattered cells within the hepatic lobules (focal necrosis) or involve particular regions of the lobule (zonal necrosis), entire lobules (submassive necrosis), or the whole liver (massive necrosis):

a) Focal necrosis is most characteristic of microbial infections, particularly smoldering forms of viral hepatitis.

b) Centrilobular necrosis is characteristic of ischemic injury and many drug and toxic chemical reaction.

d) Midzonal necrosis is a rare pattern, seen in yellow fever. Strictly periportal necrosis is seen primarily in phosphorus poisoning and eclampsia.

e) Massive necrosis is most commonly caused by severe chemical and drug toxicity or viral hepatitis.

• In other conditions, such as typhoid fever, tularemia, brucellosis, and herpes or adenovirus infection, expanding regions of the parenchyma are destroyed (geographic necrosis). With disseminated candidal or bacterial infection, macroscopic abscesses may occur.

II. Degeneration:

• Short of outright necrosis, hepatocytes may take on a swollen, edematous appearance (ballooning degeneration) with irregularly clumped cytoplasm and large, clear spaces.

• Alternatively, retained biliary material may impart a diffuse foamy swollen appearance to the hepatocyte (cholestasis).

• Accumulation of specific substances in viable hepatocytes, such as iron, copper, and viral particles, may be of particular diagnostic value.

III. Inflammation:

• Inflammation is defined as the influx of acute or chronic inflammatory cells intothe liver and is termed hepatitis.

• Although inflammation may be secondary to hepatocellular necrosis, lymphocytic attack of viable antigen-expressing liver cells is a common cause of liver damage.

• Inflammatory cells may be limited to the site of entry (portal tracts) or spill over into the parenchyma.

• In the case of focal hepatocyte necrosis, scavenger macrophages quickly generate scattered clumps of inflammatory cells in an otherwise innocuous parenchyma.

• Foreign bodies, organisms, and a variety of drugs may incite a granulomatous reaction.

IV. Regeneration:

• The liver has enormous reserve, and regeneration occurs in all but the most fulminant diseases. Regeneration is signified by thickening of the hepatocyte cords (the result of hepatocyte proliferation) and some disorganization of the parenchymal structure.

• When massive hepatocellular necrosis occurs and leaves the connective tissue framework intact, almost perfect restitution can occur.

V. Fibrosis:

• Fibrous tissue is formed in response to inflammation or direct toxic insult to the liver.

• Deposition of collagen has lasting consequences on hepatic patterns of blood flow and perfusion of hepatocytes.

• In the initial stages, fibrosis may develop around portal tracts or the central vein or may be deposited directly within the space of Disse.

• With continuing fibrosis, the liver is subdivided into nodules of regenerating hepatocytes surrounded by scar tissue, termed ***cirrhosis***.

Classification of the liver diseases:

1. Hepatosis (when degeneration and necrosis inflammation in the hepatocytes prevail).
2. Hepatitis (when inflammation in the liver prevails).
3. Cirrhosis (when disregeneration is observed).
4. Hepatic tumors.

Hepatosis

• The term hepatosis is used to describe degeneration and necrosis in the liver caused by infectious, toxic, circulatory or traumatic agents.

• Hepatosis may be inherited and acquired. Inherited hepatosis develops in storage diseases or enzymopathy. Acquired hepatosis may be acute and chronic.

• The massive necrosis is the most common acute hepatosis.

• The steatosis (fat hepatosis) is the most common chronic one.

Massive necrosis (toxic degeneration of the liver)

Massive necrosis (toxic degeneration of the liver) is acute (rarely chronic) diseasecharacterized by massive necrosis of the hepatocytes with development of the hepatic insufficiency.

Etiology. It is most commonly caused by viral hepatitis, drug or mushroom toxicity.

Morphology

There are 2 stages in this hepatosis:

1. ***Stage of yellow degeneration***, when liver becomes enlarged, dense and yellow. Then it size increases; it consistency becomes flabby; capsule is shrunken. The cut surface is grey. Microscopically fat degeneration, necrosis and autolysis of hepatocytes are observed.

2. ***Stage of red degeneration*** is characterized by progressive reduction of liver size and mass.Macroscopically the liver is red due to necrosis end autolysis of hepatocytes with appearance of plethoric blood vessels. Jaundice, hyperplasia of lymph nodes and spleen, numerous hemorrhages in the skin and mucous, necrosis of the renal epithelium, degenerative and necrotic changes in pancreas, myocardial, CNS are observed in the patients with massive necrosis of the liver.

Steatosis

• It is a chronic disease, which is characterized by increase of fat amount in the cytoplasm of the hepatocytes.

• Etiology of steatosis is similar to massive necrosis of the liver. But in this pathologic agent has less toxicity and, as a rule, compensatory and adaptive processes are higher.

• Macroscopically the liver is enlarged, flabby. Fat drops are seen on the incision. The color is yellow. This is called «goose» liver.

• Microscopically — dust-like, small and large drop in the liver cells are observed.

Viral hepatitis

Viral hepatitis is reserved for infection of the liver caused by a small (but growing) group ofviruses having a particular affinity for the liver: Hepatitis A Virus (HAV), Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), Hepatitis D Virus (HDV), and Hepatitis E Virus (HEV).

I. Hepatitis A virus (HAV) causing a fecally spread self-limiting disease. Hepatitis A is responsiblefor 20–25 % of clinical hepatitis in the developing countries of the world. The disease occurs in epidemic form as well as sporadically. The spread is related to close personal contact such as in overcrowding, poor hygiene and sanitation. An incubation period carries on 15–45 days. HAV does not cause chronic hepatitis. The fatality rate associated with HAV is about 0.1 %.

II. Hepatitis B virus (HBV), causing a parenterally transmitted disease that may become chronic. Anincubation period carries on 4 to 26 weeks. HBV can produce:

1. Acute hepatitis.
2. Chronic nonprogressive hepatitis.
3. Progressive chronic disease ending in cirrhosis.
4. Fulminant hepatitis with massive liver necrosis.
5. An asymptomatic carrier state with or without progressive disease.

Further more HBV plays an important role in the development of hepatocellular carcinoma. Transfusion, blood products, dialysis, needle-stick accidents among health care workers, intravenous drug abuse, and homosexual activity constitute primary risk categories for HBV.

III. Hepatitis C virus (HCV), also tenned non-A, non-B (NANB) hepatitis virus involved chiefly intransfusion-related hepatitis. HCV has a high rate of progression to chronic disease and eventual cirrhosis, exceeding 50 %.

IV. Delta hepatitis virus (HDV) is acute coinfection by exposure to serum containing both HDV andHBV. Hepatitis may be mild to fulminant, with fulminant disease somewhat more likely than with HBV alone; chronicity rarely develops.

Morphological patterns of Acute Viral Hepatitis

• Any one of the hepatotropic viruses can cause acute viral hepatitis. Whatever the agent, the disease is more or less the same and can be divvied into four phases:

1. An incubation period.
2. A symptomatic preicteric phase.
3. A symptomatic icteric phase.
4. Convalescence.

• The morphologic changes in acute viral hepatitis are virtually the same regardless of the causative agent and can be mimicked by drug reactions.

• Grossly, the liver is slightly enlarged: more or less green depending on the phase of the acute disease and the degree of jaundice.

• Histologically the major findings are:

Hepatocellular injury:

— Necrosis of scattered hepatocytes, clumps, or an entire lobule.

— Isolated liver cells or small cell clusters appear as eosinophilic rounded-up cells **(apoptoticbodies, Councilman's bodies)**.

— Degenerated hepatocytes may also appear ballooned. Fatty change is unusual except with HCV.

— Macrophages may phagocytize the necrotic hepatocytes; and may accumulate clumps of lymphocytes and macrophages.

— Confluent necrosis may lead to **bridging necrosis** connecting portal-to-portal, central- to-central, or portal-to-central regions of adjacent lobules, signifying a more severe form of acute hepatitis.

Inflammation is a characteristic, usually prominent feature of acute hepatitis

The portal tracts are usually infiltrated with a mixture of inflammatory cells; this infiltrate consists of lymphocytes with a touch of leucocytes and may spill over into the parenchyma, particularly where adjacent hepatocytes have undergone necrosis.

Reactive changes in Kupffer's cells

Kupffer cells and sinusoidal lining cells undergo hypertrophy and hyperplasia and are often laden with lipofuscin pigment owing to phagocytosis of hepatocellular debris.

Cholestasis is biliary stasis

An inconstant finding is bile stasis within the lobule. The bile duct epithelium may proliferate, particularly in cases of HCV hepatitis, forming poorly defined ductular structures (cholangioles).

Regeneration

• In the recovery phase of acute hepatitis, the lobule remains somewhat dis-

organized because hepatocytes can proliferate faster than normal cord-sinusoid-cord relationships can be established.

• Regenerating hepatocytes lack uniformity in size and are pale, the result of diminished numbers of cytoplasmic organelles.

• Double and triple nuclei in regenerating cells are commonly observed. Residual clumps of inflammatory cells may persist for some time.

• Lobular disarray results from the cellular swelling (ballooning), necrosis, and regeneration of cells producing compression of the vascular sinusoids and loss of the normal, more or less radial array. Disruption of lobular architecture by necrosis is called lobular disarry.

Morphological patterns of Chronic Viral Hepatitis

• Symptomatic, biochemical, or serologic evidence of continuing or relapsing hepatic disease for more than 6 months, optimally with histologically documented inflammation and necrosis, is taken to mean **chronic hepatitis.**

• Although the hepatitis viruses are responsible for most cases of chronic hepatitis, there are many other etiologies: Wilson's disease, alpha-1-antitrypsin deficiency, chronic alcoholism, drugs (isoniazid, alpha-methyldopa, methotrexate), and autoimmunity.

• Since 1968, chronic hepatitis has been classified according to the extent of inflammation:

1. Chronic persistent hepatitis, in which inflammation is confined to the portal tracts.

2. Chronic active hepatitis, in which portal tract inflammation spills into the parenchyma and surrounds regions of necrotic hepatocytes.

3. Chronic lobular hepatitis, in which persistent inflammation is confined to the lobule.

• It is now apparent that the primary determinant of disease progression, and therefore prognosis, is the etiologic form of hepatitis. Therefore, although histologic information may provide information helpful for patient management, classification of chronic hepatitis strictly by histologic criteria is obsolete and should not be used. This is particularly important because therapy that is effective for one cause of chronic hepatitis may be ineffective, or potentially detrimental, in other forms of the disease.

• The likelihood of chronic hepatitis following acute viral infection can be summarized:

1. HAV: Extremely rare.

2. HBV: Develops in more than 90 % of infected neonates and 5 % of infected adults, of whom one-fourth progress to cirrhosis.

HCV: Develops in more than 50 % of infected patients, half of whom progresses to cirrhosis.

3. HDV: Rare in acute HDV/HBV coinfection; a more severe chronic hepatitis is the most frequent outcome of HDV superinfection.

4. HEV: Does not produce chronic hepatitis.

• Chronic hepatitis with HBV, and apparently with HCV, contributes significantly to the development of primary hepatocellular carcinoma.

Morphology

The morphology of chronic hepatitis ranges from exceedingly mild to severe, to eventual cirrhosis.

The diagnosis **of chronic persistent hepatitis** is confirmed by needle biopsy of the liver, which is invaluable in distinguishing it from more serious form of chronic active hepatitis.

Microscopically:

There is portal triad characterized by expansion of the portal tract by mononuclear inflammatory cells, consisting of lymphocytes, macrophages, occasional plasma cells, and an occasional rare neutrophiles or eosinophiles.

The lobular architecture of hepatic parenchyma is usually preserved.

There is absence of piecemeal necrosis.

Chronic active (aggressive) hepatitis is defined as a progressive form of chronic necrotisingand fibrosing disease involving portal tracts as well as hepatic parenchyma.

Microscopically:

The histologic hallmark of progressive disease is piecemeal necrosis, where by the chronic inflammatory infiltrate spills out from portal tracts into adjacent parenchyma, with associated necrosis of hepatocytes in the limiting plate.

There may be formation of lymphoid follicles.

There may be lobular inflammation with focal necrosis of hepatocytes.

As with acute hepatitis, bridging necrosis may connect adjacent **portal-portal, central-central, and portal-central zones.**

Although piecemeal and bridging necrosis do not imply inevitable progression of disease, continued loss of hepatocytes results in fibrous septum formation, which, accompanied by hepatocyte regeneration, results in cirrhosis.

The aforementioned features are common to all forms of chronic hepatitis (viral or otherwise). In patients with chronic HCV hepatitis, lymphoid aggregates in portal tracts and mild fatty change are seen in about 50 % of cases, and bile duct damage is seen in more than 90 %. Conversely, *«ground-glass»* hepatocytes are sometimes present in chronic HBV hepatitis. Despite use of immunohistochemical techniques, it is frequently impossible to identify the etiology of chronic hepatitis on tissue samples, so great reliance must be placed on clinical, virologic, and serologic observations.

The clinical features of chronic hepatitis

• The clinical features of chronic hepatitis are extremely variable and are not predictive of outcome.

• In some patients, the only signs of chronic disease are persistent elevations of serum transaminases, hence the facetious designation «transaminitis».

• The most common symptom is fatigue; less common symptoms are malaise, loss of appetite, and occasional bouts of mild jaundice.

• Physical findings are few, if any, the most common being spider angiomas, palmar erythema, mild hepatomegaly, hepatic tenderness, and mild splenomegaly.

• Laboratory studies may reveal prolongation of the prothrombin time and, in some instances, hyperglobulinemia, hyperbilirubinemia, and mild elevations in alkaline phosphatase.

• Occasionally in cases of HBV, and rarely in HCV, immune-complex diseases may develop secondary to the presence of circulating antibody-antigen complexes, in the form of vasculitis (subcutaneous or visceral, i.e., polyarteritis nodosa) or glomerulonephritis.

• The major causes of death are hepatic insuffisiency and hepatic encephalopathy or massive hemorrhage from esophageal varicose and, in those with long-standing HBV (particularly neonatal) or a HCV infection, hepatocellular carcinoma.

Cirrhosis of liver

Cirrhosis is the final stage of liver disease and is defined by three characteristics:

1. Fibrosis is present in the form of delicate bands or broad scars replacing multiple adjacent lobules.

2. The parenchymal architecture of the liver is divided by interconnecting fibrous scars.

3. Parenchymal nodules are created by regeneration of hepatocytes. The nodules may vary from micronodules (less than 3 mm in diameter) to macronodules (3 mm to several centimeters in diameter).

Several features should be understood:

The parenchymal injury and consequent fibrosis are diffuse, extending throughout the liver; focal injury with scarring does not constitute cirrhosis.

1. Nodularity is requisite for the diagnosis and reflects the balance between regenerative activity and constrictive scarring.

2. The fibrosis, once developed, is generally irreversible; some regression has been observed in humans with treated schistosomiasis and hemochromatosis.

3. Vascular architecture is recognized by parenchymal damage and scarring, with formation of abnormal interconnections between vascular inflow and hepatic vein outflow.

Classification

Morphological types of cirrhosis:

1. Micronodular(the nodules are usually regular and small, less than 3 mm in diameter).

2. Macronodular(the nodules are of variable size and are generally large than 3 mm in diameter).

3. Mixed (some part of the liver show micronodular appearance while other parts show macronodularpattern).

Each of these forms may have an active and inactive form:

— Hepatocellular necrosis and inflammatory reaction, a process that closely resembles chronic active hepatosis characterizes an active form.

— An inactive form, vise verse, has no evidence of continuing hepatocellular necrosis and has sharply-defined nodules of surviving hepatic parenchyma without any significant inflammation.

Etiologic types of cirrhosis:

1. Infectious (often viral).
2. Toxic and toxic-allergic (Alcoholic cirrhosis, the most common, 60–70 %; allergen, drugs, etc.).
3. Biliary cirrhosis (5–10 %).
4. Metabolic-alimentary (Cirrhosis in Wilson's disease, Cirrhosis in α-l antitrypsin deficiency, Pigment cirrhosis in hemochromatosis (5 %), etc.).
5. Cardiac cirrhosis.
6. Cryptogenic cirrhosis (10–15 %).

Types according to morphogenesis:

1. Postnecrotic cirrhosis.
2. Portal (septical) cirrhosis.
3. Mixed cirrhosis.

Morphological patterns of cirrhosis:

- Morphological changes of all types of cirrhosis are similar.
- Macroscopically the liver is small, having distorted shape with irregular and coarse scars and nodules of varying size. The cut surface shows scars and nodules varying in diameter from 3 mm to a few centimetres.
- Microscopically, the features are following:

Abnormal lobular architecture can be identified and central veins are hard to find.

The fibrous septa dividing the variable-sized nodules are generally thick.

Active liver cell necrosis is observed. Fibrous septa contain prominent mononuclear inflammatory cell infiltrate even with follicles. Often there is extensive proliferation of bile ductules derived from collapsed liver lobules.

Liver cells vary considerably in size and multiple large nuclei are common in regenerative nodules. Fatty degeneration may be present.

Postnecrotic cirrhosis

- This pattern of cirrhosis is characterized by irregularly sized nodules separated by variable but mostly broad scars.

• The most common known cause is previous viral infection; in about 20 to 25 % of cases it evolves from chronic HBV infection; the contribution of chronic HCV may be even greater.

• In a small number of instances, there is a well-documented history of acute liver damage caused by some hepatotoxin, such as phosphorus; carbon tetrachloride; mushroom poisoning; or a drug such as acetaminophen, oxyphenisatin, or alpha-methyldopa. Undoubtedly some cases represent end-stage alcoholic cirrhosis, readily misinterpreted as postnecrotic cirrhosis in the absence of a history of chronic alcoholism.

• After all these possibilities have been excluded, there remains a large residual of uncertain origin.

• A single attack of massive hepatic necrosis only infrequently gives rise to postnecrotic cirrhosis because either it is fatal, or regeneration of the liver cells permits survival with little or no residual scarring.

Morphology

• Typically some time after an acute event or following years of chronic hepatitis, the liver exhibits nodules of varying size (some several centimeters in diameter) and broad bands or areas of depressed scarring.

• Severe collapse may leave a shrunken liver less than 1 kg in size.

• Microscopically tubular architecture may be completely lost in the developing nodules and scar.

• Alternatively, progressive chronic hepatitis of any etiology inexorably transforms a more normalized liver into a patchwork of variably sized nodules alternating with broad septal scars.

• Eventually active liver cell necrosis becomes inconspicuous.

• Residua of portal tracts may be evident; bile stasis is variable.

• Ltimately the diagnosis rests on excluding other bases for cirrhosis

Biliary cirrhosis

Biliary cirrhosis is defined as a chronic disorder characterized by clinical, biochemical andmorphological features of long-continued cholestasis of extrahepatic or intrahepatic origin. There is primary and secondary biliary cirrhosis.

Primary biliary cirrhosis

• Primary biliary cirrhosis (PBC) is autoimmune disorder focused on intralobular bile ducts and holangioles, this disease causes chronic inflammation of intrahepatic bile ducts, leading to their destruction and, in time, cirrhosis.

• The primary feature of this disease is a nonsuppurative, granulomatous destruction of medium-sized intrahepatic bile ducts; cirrhosis appears only late in the course.

• This is primarily a disease of middle-aged women, with a female-to-male

predominance in excess of 6:1. Age of onset is between 20 and 80 years, with the peak incidence between 40 and 50 years.

• The onset is insidious, usually presenting with pruritus. Jaundice develops late in the course.

• Hepatomegaly is typical. Xanthomas and xanthelasmas arise as a result of cholesterol retention. Stigmata of chronic liver disease are late features.

• The disease may be asymptomatic for years, running its course over two or more decades.

• PBC is the prototype of all conditions leading to small-duct biliary fibrosis and cirrhosis.

• Historically, four histologic stages have described:

1) ***The duct lesion (granulomatous destruction of interlobular bile ducts).*** There israndom, focal destruction of interlobular and septal bile ducts by granulomatous inflammation, named the florid duct lesion. Affected portal tracts exhibit a dense infiltrate of lymphocytes (including lymphoid follicle formation), histiocytes, plasma cells, and a few eosinophils. Parenchymal holestasis may be present.

2) ***Ductular proliferation with periportal hepatitis.*** With more global hepaticinvolvement, normal interlobular bile ducts become infrequent, and secondary obstructive changes develop, similar to those seen in extrahepatic obstruction. *Mallorybodies (alcoholic hyaline)* may be present in hepatocytes adjacent to portal tracts.Initially portal tract inflammation may be marked and spill over into the parenchyma, causing destruction of adjacent hepatocytes (piecemeal necrosis).

3) ***Fibrosis.*** With time, inflammation decreases; granulomas and duct lesions becomeinfrequent and are replaced by fibrous septa. Bile ducts are reduced; holestasis is prominent.

4) ***Cirrhosis.*** Hepatocyte loss, fibrosis, and nodular regeneration lead to the gradualdevelopment of true cirrhosis. Macroscopically the liver does not at first appear abnormal, but as the disease progresses, bile stasis stains the liver green. The capsule remains smooth and glistening until a fine granularity appears, culminating in a well developed, uniform micronodularity. Liver weight is at first normal to increased (owing to inflammation); ultimately liver weight is slightly decreased. In most cases, the end-stage picture may be difficult to distinguish from secondary biliary cirrhosis or the cirrhosis that follows chronic active hepatitis.

Secondary biliary cirrhosis

• Develops with prolonged extrahepatic biliary tract obstruction.

• The most common cause of obstruction is an impacted gallstone in the common bile duct; other conditions include biliary atresia, malignancies of the biliary tree and head of the pancreas, and strictures resulting from previous surgical procedures.

• Retained bile leads to inflammation initiating periportal fibrosis and eventual cirrhosis.

• Secondary bacterial infection («ascending cholangitis») may contribute to the

damage; enteric organisms such as coliforms and enterococci are common culprits.

• Macroscopically, the liver is of yellow -green color and is accompanied by marked icteric discoloration of body tissues and fluids. On cut surface, the liver is hard, with a finely granular appearance.

Microscopically:

• Large and small bile ducts are distended and frequently contain inspissated bile.

• Portal tracts are interconnected by inflamed fibrous septa and appear edematous; there is frequently a narrow zone of edema and ductular proliferation at the junction of parenchyma and septa.

• Cholestatic features may be severe, with cytoplasmic and canalicular accumulation of bile, extensive feathery degeneration of hepatocytes, and the formation of bile lakes (see earlier discussion of cholestasis).

• Once the regenerative nodules of cirrhosis have formed, however, bile stasis may become less conspicuous.

• Ascending bacterial infection incites a supervening robust neutrophilic infiltration of bile ducts and cholangitic abscesses.

Cardiac cirrhosis

• ***Cardiac cirrhosis*** is uncommon complication of severe right-sided congestive heart failureof long-standing duration.

• The common causes culminating in cardiac cirrhosis are «cor pulmonale», tricuspid insufficiency or constrictive pericarditis.

• Microscopically, the hepatic sinusoids are dilated and congested with hemorrhagic necrosis of centrolobular hepatocytes.

• Then fibrous strands radiating from the central veins are observed.

Alcoholic liver disease

Alcohol abuse constitutes the major form of liver disease in many countries.

Chronic alcohol consumption has a variety of adverse effects. Of greatest impact, however, there are three distinctive, albeit overlapping, forms of liver disease:

1. Hepatic steatosis.
2. Alcoholic hepatitis.
3. Cirrhosis referred to as alcoholic liver disease.

Hepatic steatosis

• Following even moderate intake of alcohol, small (microvesicular) lipid droplets accumulate in hepatocytes.

• With chronic intake of alcohol, lipid accumulates to the point of creating large clear macrovesicular spaces, compressing and displacing the nucleus to the periphery of the hepatocyte.

• This transformation is initially centrolobular, but in severe cases, it may involve the entire lobule.

• The liver is often grossly enlarged, up to 4 to 6 kg, and is a soft, yellow, greasy organ.

• Although there is little or no fibrosis at the outset, with continued alcohol abuse, fibrous tissue develops around the central veins and extends into the adjacent sinusoids.

• Up to the time that fibrosis appears, the fatty change is completely reversible if there is further abstention from alcohol.

Alcoholic hepatitis

Alcoholic hepatitis exhibits the following:

Liver cell necrosis, single or scattered foci of cells undergo swelling (ballooning) and necrosis, more frequently in the centrolobular regions of the lobule.

Mallory bodies (alcoholic hyaline), scattered hepatocytes accumulate tangled skeins of cytokeratin intermediate filaments and other proteins, visible as eosinophilic cytoplasmic inclusions.

Neutrophilic reaction. Neutrophils permeate the lobule and accumulate around degenerating liver cells, particularly those having Mallory bodies. Lymphocytes and macrophages also enter portal tracts and spill into the lobule. Potentially reversible, this lesion may smaller on long after cessation of alcohol intake.

Fibrosis. Alcoholic hepatitis is almost always accompanied by a sinusoidal and perivenular fibrosis; occasionally periportal fibrosis may predominate, particularly with repeated bouts of heavy alcohol intake. Fat may be present or entirely absent. Deranged iron processing in the alcoholic typically leads to a modest accumulation of hemosiderin in hepatocytes and Kupffer's cells. The outcome is unpredictable. The condition may resolve in the absence of further alcohol exposure or may lead to cirrhosis, but there is significant risk of death with each bout.

Alcoholic cirrhosis

• The final and irreversible form of alcoholic liver disease usually evolves slowly and insidiously.

• At first the cirrhotic liver is yellow-tan, fatty, and enlarged, usually weighing more than 2 kg.

• Over the span of years, it is transformed into a brown, shrunken, nonfatty organ, and sometimes less than 1 kg in weight.

• Cirrhosis may develop within 1 to 2 years in the setting of alcoholic hepatitis.

• Initially the developing fibrous septa are delicate and extend from central vein to portal regions as well as from portal tract to portal tract.

• Regenerative activity of the entrapped parenchymal acini generates fairly uniformly sized «micronodules».

• With time, the nodularity becomes more prominent; scattered nodules may be-

come quite large, and occasionally nodules more than 2 cm in diameter may develop.

• As fibrous septa dissect and surround nodules, the liver becomes more fibrotic, loses fat, and shrinks progressively in size.

• Parenchymal islands are engulfed by ever wider bands of fibrous tissue, and the liver is converted into a mixed micronodular and macronodular pattern.

• Further ischemic necrosis and fibrous obliteration of nodules eventually create broad expanses of tough, pate scar tissue, leaving residual parenchymal nodules that protrude like «hobnails» from the surface of the liver («Laennec's cirrhosis»).

• By microscopy, the septa contain variable amounts of scattered lymphocytes and some reactive bile duct proliferation. Bile stasis often develops; Mallory bodies are only rarely evident at this stage.

• Thus, end-stage alcoholic cirrhosis comes to resemble, both macroscopically and microscopically, postnecrotic cirrhosis.

Complications of cirrhosis

Complications of cirrhosis are subdivided into 2 groups: hepatic and non-hepatic.

I. Hepatic complication:

— Progressive hepatic insufficiency.

— Development of hepatocellular carcinoma.

— Steatorrhea due to reduced hepatic bile secretion.

— Gall stones usually of pigment type, are seen twice more frequently in patients with cirrhosis than in general population.

II. Non hepatic complication

1. ***Portal hypertension*** (increased resistance to portal flow) and its effects such as:

— ascites;

— the formation of portosystemic venous shunts through variceal chanells in the esophagus rectum, and periumbilical abdominal wall;

— congestive splenomegaly;

— hepatic ehcephalopathy.

2. Chronic relapsing pancreatitis, especially in alcoholic liver disease.

3. Infections are more frequent in patients with cirrhosis due to impaired phagocytic activity of reticuloendothelial system.

4. Hematological derangements such as bleeding disorders and anemia due to impaired hepatic synthesis of coagulation factors and hypoalbuminemia are present.

5. Cardiovascular complications such as atherosclerosis of coronaries and aorta and myocardial infarction are more frequent in these patients.

6. Hypertrophic osteoarthropathy.

7. Endocrine disorders such as gynecomastia, testicular atrophy and impotence, whereas in cirrhotic women amenorrhoe is a frequent abnormality.

8. Hepatorenal syndrome leading to renal failure may occur in late stages of cirrhosis.

Causes of death:

1. Hepatic coma.
2. Massive gastrointestinal hemorrhage from esophageal varice.
3. Intercurrent infections.
4. Hepatorenal syndrome.
5. Development of hepatocellular carcinoma.

Cholelitiasis (Gallstones)

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

• Accordingly, the gallstones commonly contain cholesterol, bile pigment and calcium salts in varying proportions.

• They are usually formed in the gall bladder, but sometimes may develop within extrahepatic biliary passages, and rarely in the larger intrahepatic bile duct.

• The incidence of gallstones varies markedly in different geographic areas, age, sex, diet and various other risk factors.

• The mechanism of cholesterol gallstone formation or lithogenesis is determined by 3 major factors:

1) namely supersaturation of bile with cholesterol;
2) cholesterol nucleation;
3) the hyperfunction of gallbladder.

• Types of gallstones. As stated before, gallstones contain cholesterol, bile pigment and calcium carbonate, either in pure form or in various combinations. Gallstones are of 3 major types:

1) pure gallstones;
2) mixed gallstones;
3) combined gallstones.

• In general, gallstones are formed most frequently in the gall bladder but may occur in exlrahepatic as well as intrahepatic biliary passages.

• Numerous complications develop in cholelithiasis. They are cholecystitis, choledocholithiasis, mucocele or hydrops of the gallbladder, biliary fistula, gallstone ileus, and gallbladder cancer.

Cholecyscitis

Cholecyscitis or inflammation of the gallbladder may be acute, chronic, or acute superimposedon chronic.

Acute cholecystitis

• In many ways, acute cholecystitis is similar to acute appendicitis. The condition usually begins with obstruction, followed by infection later.

• Based on the initiating mechanisms, acute cholecystitis occurs in two types of situations — acute calculous and acute acalculous cholecystitis.

• In majority of cases, acute cholecystitis is caused by obstruction in the neck of the gallbladder or in the cystic duct by a gallstone. The commonest location of impaction of a gallstone is in Hartman's pouch. After that secondary bacterial infection, for instance E. coli and Streptococcus facialis, supervenes.

• Acute calculous cholecystitis. The remaining 10 % cases of acute cholecystitis do not contain gallstones. In such cases, a variety of causes have been assigned such as previous non-biliary surgery, multiple injuries, bums, severe sepsis, diabetes mellitus, etc.

Morphology

• Except for the presence or absence of calculi, the two forms of acute cholecystitis are morphologically similar.

• Macroscopically, the gall bladder is distended and tense. The serosal surface is coated with fibrinous exudate with congestion and hemorrhages. The mucosa is red. The lumen is filled with pus mixed with green bile. In calculous cholecystitis, a stone is generally impacted in the neck or in the cystic duct. When obstruction of the cystic duct is complete, the lumen is filled with purulent exudate and the condition is known as empyema of the gall bladder.

• Microscopically, wall of the gall bladder shows marked inflammatory edema, congestion and neutrophilic exudate. There may be frank abscesses in the wall and gangrenous necrosis with rupture into the peritoneal cavity (gangrenous cholecystitis).

Chronic Cholecystitis

• Chronic cholecystitis is the commonest type of clinical gallbladder disease.

• The association of chronic cholecystitis with mixed and combined gallstones is virtually always present.

• Macroscopically, the gall bladder is generally contracted but may be normal or enlarged. The wall of the gall bladder is thickened which on cut section is grey-white due to dense fibrosis or may be even calcified. The mucosal folds may be intact, thickened, or flattened and atrophied. The lumen commonly contains multiple mixed stones or a combined stone.

• Microscopically, the following signs, may be observed: thickened and congested mucosa but occasionally mucosa may be totally destroyed; penetration of the mucosa deep into the wall of the gall bladder up td muscular layer to form Rokitansky-Aschoff sinuses; variable degree of chronic inflammatory reaction, consisting of lymphocytes, plasma cells and macrophages, present in the lamina propria and subserosal layer; variable degree of fibrosis in the subserosal and subepithelial layers.

Pancreatitis

Pancreatitis is inflammation of the pancreas with acinic cell injury. It is classified into acuteand chronic forms both of which are two distinct entities.

Acute pancreatitis

- Acute pancreatitis is an acute inflammation of the pancreas.
- The severe form of the disease associated with macroscopic hemorrhages and fat necrosis in and around the pancreas is termed acute hemorrhage pancreatitis or acute pancreatic necrosis.
- The condition occurs in adults between the age of 40 and 70 years and is commoner in females than in males.
- The onset of acute pancreatitis is sudden, occurring after a bout of alcohol or a heavy meal. The patient presents with abdominal pain, vomiting and collapse and the condition must be differentiated from other diseases producing acute abdomen such as acute appendicitis, perforated peptic ulcer, and acute cholecystitis.
- ***Etiology.*** The two leading causes associated with acute pancreatitis are alcoholism and cholelithiasis, both of which are implicated in more than 80 % of cases. Less common causes of acute pancreatitis include trauma, ischemia, shock, extension of inflammation from the adjacent tissues, blood-borne bacterial infection, viral infections, certain drugs, etc.

Morphology

- The morphology of acute pancreatic necrosis stems directly from the action of activated pancreatic enzymes that are released into the pancreatic substance.
- The basic alterations are proteolytic destruction of pancreatic substance, necrosis of blood vessels with subsequent hemorrhage, necrosis of fat, and an accompanying inflammatory reaction.
- Amorphous basophilic calcium precipitates may be visible within the necrotic focus.
- Grossly, foci of pancreatic necrosis are blue-black hemorrhages and grey-white necrotic softening alternates with sprinkled foci of yellow-white, chalky fat necrosis.

Complications

A patient of acute pancreatitis who survives may develop a variety of systemic and local complications:

1. Systemic complications are chemical and bacterial peritonitis, endotoxic shock, and acute renal failure.
2. Local complications are pancreatic abscess, pancreatic pseudocyst, and duodenal obstruction.

Chronic pancreatitis

Chronic pancreatitis is the progressive destruction of the pancreas due to repeated mild andsubclinical attack of acute pancreatitis.

Most patients present with recurrent attacks of severe abdominal pain at intervals of months to years.

Weight loss and jaundice are often associated. Later manifestations include associated diabetes mellitus and steatorrhea.

Etiology. Most cases of chronic pancreatitis are caused by the same factors as for acutepancreatitis.

Morphology

- Chronic pancreatitis is distinguished by irregularly distributed fibrosis, reduced number and size of acini with relative sparing of the islets of Langerhans, and variable obstruction of pancreatic ducts of all sizes.
- The lesions have a macroscopic lobular distribution and may involve portions or the entire pancreas.
- A chronic inflammatory infiltrate around lobules and ducts is usually present.
- The ductal epithelium may be atrophied or hyperplastic or may show squamous metaplasia.
- Macroscopically, the gland is hard and exhibits foci of calcification and may developed pancreatic calculi. These concretions vary from calculi invisible to the naked eye, to stones 1 cm to several centimetres in diameter, giving rise to the term **«chronic calcifyingpancreatitis»**.

With chronic ductal obstruction, the distribution of lesions is irregular, and the ductal epithelium generally is less severely damaged. Protein plugs and calcified stones are rare.

Complications

Last stage of chronic pancreatitis may be complicated by diabetes mellitus, pancreatic insufficiency with steatorrhea and malabsorption and formation of pancreatic pseudocysts.

VI. DISEASES OF KIDNEY AND URINARY TRACT

Diseases of the kidney are characterized by the injury basic morphologic components: glomeruli, tubules, interstitium, and blood vessels. The clinical manifestations of renal diseases can be grouped into reasonably well-defined syndromes.

We can now turn to a brief description of the major renal syndromes:

1. **Acute nephritic syndrome** is a glomerular syndrome dominated by the acute inset of usuallygrossly visible hematuria (red blood cells in urine), mild to moderate proteinuria, and hypertension; it is the classic presentation of acute poststreptococcal glomerulonephritis (GN).

2. **The nephrotic syndrome** is characterized by heavy proteinuria, hypoalbuminuria, severeedema, hyperlipidemia, and lipiduria.

3. **Asymptomatic hematuria or proteinuria**, or a combination of them, is

usually manifestationof subtle or mild glomerular abnormalities.

4. **Acute renal failure** is dominated by oliguria or anuria, with recent onset of azotemia. It canresult from glomerular injury, interstitial injury, or acute tubular necrosis.

5.**Chronic renal failure**, characterized by prolonged symptoms and signs of uremia, is the finalresult of all chronic renal diseases.

6. **Renal tubular defects** are dominated by polyuria, nocturia, and electrilyte disorders. They arethe result of either diseases directly affecting tubular structure or defects in specific tubular infection. The latter may be inheridited or acquired.

7. **Urinary tract infection** is characterized by bacteriuria and pyuria. The infection may besymptomatic or asymptomatic, and it may affect the kidney or the bladder only.

8. **Nephrolitiasis (renal stone)** is manifested by renal colic, hematuria, and recurrent stoneformation.

Glomerular Diseases

Glomerular injury is a major cause of renal disease and may be primary and secondary.

Primary glomerular diseases are characterized by primary injury of the glomeruli (acute andchronic glomerulonephritis (GN), lipoid nephrosis, etc.).

1. *In secondary glomerular diseases* the kidney is one of many organs and systems damaged by asystemic disease (Systemic lupus erythematous, diabetes mellitus, amyloidosis, etc.).

Pathogenesis of glomerular injury

The consequences of injury at different sites within the glomerulus can be assessed when compared with the normal physiologic role of the main cells involved, i.e. *endothelial, mesangial,visceral epithelial, and parietal epithelial cells as well as of the GBM.*

There are two basic mechanisms of glomerular injury: immune and nonimmune.

Immune mechanisms

A. Antibody-mediated glomerular injury 1. Immune complex disease.

The deposition of Ag-Ab complexes in glomeruli is a major mechanism of glomerular injury, whether they are formed «in situ» with glomerular antigens or are trapped circulating complexes.

Immunologic mechanisms underlying glomerular injury are primarily antibody-mediated (immune- complex disease). More recently there has been evidence to suggest that cell-mediated immune reactions in the form of delayed type hypersensitivity can cause glomerular injury.

Glomerular deposits are formed by one of the following *two mechanisms:*

Local immune complex deposits. Formation of glomerular deposits of

immune complex «in situ» occurs as a result of combination of antibodies with autologous non-basement membrane antigens or nonglomerular antigens planted on glomeruli. Classic experimental model of «in situ» immune complex GN is Heymann nephritis. The examples of planted nonglomerular antigens are cationic proteins, lectins, DNA, bacterial products (e.g. a protein of group A streptococci), viral and parasitic products and drugs.

Circulating immune complex deposits. Circulating immune complexes cause glomerulardamage under certain circumstances, e.g. their presence in high concentrations for prolonged periods, or when they possess properties that cause their binding to glomeruli, or when host mechanisms fail to eliminate immune complexes. The antigen-antibody complexes are trapped in the glomeruli where they produce glomerular injury after combining with complement.

Immune complex GN is observed in the following diseases:

1. Primary GN, e.g. acute diffuse proliferative GN, membranous GN, membranoproliferative GN, IgA nephropathy and some cases of rapidly progressive GN and focal GN.

2. Systemic diseases, e.g. glomerular disease in SLE, malaria, syphilis, hepatitis, Henoch-Schonlein purpura and idiopathic mixed cryoglobulinemia.

2. Anti-GBM disease.

Less than 5 % cases of human GN are associated with anti-GBM antibodies. The component of GBM acting as antigen appears to component of collagen IV of the basement membrane.

Anti-GBM disease is classically characterized by homogeneous linear deposits of anti-GBM antibodies (mostly IgG; rarely IgA and IgM) and complement (mainly C3) along the glomerular basement membrane.

Anti-GBM disease is characteristically exemplified by glomerular injury in Goodpasture's syndrome. About half to two-third of the patients with renal lesions in Goodpasture's syndrome have pulmonary hemorrhage mediated by cross-reacting autoantibodies against alveolar basement membrane.

3. Alternative pathway disease.

The complement system, in particular C3, contributes to glomerular injury in the majority of forms of GN.

The deposits in alternate pathway of the disease are characteristically electron-dense, glomerular lesions in such cases are referred to as dense-deposit disease.

Alternate pathway disease occurs in most cases of type II membranoproliferative GN, some patients of rapidly progressive GN, acute diffuse proliferative GN, IgA nephropathy and in SLE.

4. Other mechanisms of antibody-mediated injury.

A few autoantibodies have been implicated in some patients of glomerulonephritis:

Anti-neutrophil cytoplasmic antibodies (ANCA). About 40 % cases of rapidly progressiveGN are deficient in immunoglobulins in glomeruli and are positive for ANCA against neutrophil cytoplasmic antigens in their circulation.

ANCA causes endothelial injury by generation of reactive oxygen radicals.

Anti-endothelial cell antibodies (AECA). Autoantibodies against endothelial antigens havebeen detected in circulation are several inflammatory vasculitis and glomerulonephritis.

B. Cell-mediated Glomerular Injury:

Recent evidence suggests that cell-mediated immune reactions in the form of delayed hypersensitivity may be involved in causing glomerular injury, particularly in cases with deficient immunoglobulins.

C. Secondary pathogenetic mechanisms:

Secondary pathogenetic mechanisms are a number of mediators of immunologic glomerular injury, such as: neutrophils, mononuclear phagocytes, complement system, platelets, mesangial cells, and coagulation system.

Nonimmune mechanisms

Though most forms of GN are immunologically mediated, a few examples by non-immunologic mechanisms are found:

1. Metabolic glomerular injury, e.g. diabetic nephropathy.
2. Hemodynamic glomerular injury, e.g. systemic hypertension.
3. Deposition diseases, e.g. cryoglobulinaemia, amyloidosis.
4. Infectious diseases, e.g. HBV, HCV, HIV.
5. Inherited glomerular diseases, e.g. Alport's syndrome, nail-patella syndrome.

These diseases destroy sufficient functioning nephrons. Adaptive changes in glomeruli to the increased workload cause epithelial and endothelial injury and resulten proteinuria. The mesangial response, involving mesangial cell proliferation and matrix deposition, and intraglomerular coagulationcause the glomerulosclerosis.

Acute Glomerulonephritis

- The first group of glomerular diseases are characterized anatomically by inflammatory alterations in the glomeruli and clinically by a complex of findings classically reffered to as the syndrome of acute nephritis.
- Nonrenal features, such as: arterial hypertension, hypotrophy of right heart, disproteinemia, edema, hypernitrogenemia and uremia are presence.
- It is infectious-allergic or unknown etiology disease with double nonsuppurative glomerulitis.
- The nephritic patient usually presents with hematuria, red cell casts in the urine, azotemia, oliguria, and mild to moderate hypertension.
- The patient also commonly has proteinuria and edema, but these are not as several those encountered in the nephrotic syndrome. The acute nephritic syndrome may occur in such multisystem diseases as SLE and polyarteritis nodosa. Typically, however, it is characteristic of acute proliferative GN and is an im-

portant component of crescentic GN.

Principles of glomeluronephritis classification

- Gomerulonephritis may be primary or secondary.
- According to the etiology it may be bacterial, viral, unclear.
- According to the pathogenesis there are 2 types of glomeluronephritis: immuno-associated and non-immunoassociated.
- According to the course GN may be classified into acute, sub-acute, chronic.
- According to the histological pattern of damage seen on renal biopsy; hence knowledge of this aspect of histopathology is needed to understand disease. In morphological classification, topography, character, propagation of pathological process are accounted:

1. According to topography: iner- and extracapillary GN.
2. According to character of inflammation: nonsuppurative exudative and proliferative.
3. According to propagation: diffuse and local.

Acute poststreptococcal glomerulonephritis

- It usually appears 1 to 4 weeks after streptococcal infection of the pharynx or the skin.
- In occurs most frequently in children of six to ten years of age, but adults of any age can be affected.
- Duration of disease may 1,5 to 12 monthes.
- Gross appearance: Kidney enlarged; cortex broad, pale, without markings; medullary rays congested; glomeruli just visible as grey avascular dots.
- The classic diagnostic picture is one of enlarged, hypercellular, relatively bloodness glomeruli.
- The most often the histological type is **intracapilary proliferative GN:**

Proliferation of endothelial and mesangial cells and, in many cases, epithelial cells.

Infiltration by leukocytes, both neutrophils and monocytes. The proliferation and leukocytes infiltration are diffuse, that is, involving all lobules of all glomeruli.

There is also swelling of endothelial cells, and the combination of proliferation, swelling, and leukocytic infiltration obliterates the capillary lumen.

Special stains can demonstrate small deposites of fibrin within capillary lumina and mesangium.

There may be interstitial edema and inflammation, and the tubes often contain red cell coasts and may show evidence of degeneration.

By immunofluorescence microscopy there are glandular deposits of IgG, IgM, and C3 in the mesangium and along the basement membrane. Although present, they are often focal and sparse. The characteristic electron microscopic findings are the discrete, amorphous, electron-dense deposits on the epithelial

side of the membrane, often having the appearance of «humps», presumably representing the antigen- antibody complexes at the epithelial cell surface. Subendothelial and intramembranous deposits sometimes seen, and there is often swelling of endothelial and mesangial cells.

Rapidly progressive (crescentic) glomerulonephritis

It is a syndrome characterized by the accumulation of cells in Bowman's space in the form of ***«crescents»*** accompanied by a rapid, progressive decline in renal function, frequently with severeoliguria or anuria, usually resulting in irreversible renal failure in weeks or months.

Morphoplogy

According to histological picture there is extracapillary proliferative GN.

The kidneys are enlarged and pale, often with petechial hemorrhages on the cortical surfaces.

Depending on the underlying cause, the glomeruli may show focal necrosis, diffuse or focal endothelial proliferation.

The syndrome is characterized histologically by the accumulation of cells in Bowman's space in the form of «crescents».

The histologic picture, however, is dominated by the formation of distinctive crescents, which are formed by proliferation of parietal cells and by migration of monocytes and macrophages into Bowman's space. Neutrophils and lymphocytes can be present. The crescents eventually obliterate Bowman's space and compress the glomerular tuft. Fibrin strands are prominent between the cellular layers in the crescents.

Electron microscopy may disclose subepithelial deposits in some cases, but in all cases shows distinct ruptures in the GBM.

In time, most crescents undergo sclerosis.

This syndrome may occur in the course of three broad disease groups:

1. Postinfectious rapidly progressive (crescentic) glomerulonephritis, complicating acute GN.
2. Systemic diseases (SLE, Goodpasture's syndrom, polyarteritis nodosa, etc.).
3. Idiopathic.

Nephrotic syndrome

Membranous glomerulonephritis (MGN):

- It is a major cause of nephrotic syndrome in adults.
- It is characterized by the presence of electron-dense, immonoglobulin-containing deposits along the epithelial side of the basement membrane.
- In situ formation and deposition of circulating immune complexes, involving intrinsic glomerular antigens or endogenous and exogenous or planted

antigens, are postulated to account for the subepithelial electron-dense deposits.

• Early in the disease, the glomeruli may appear normal by light microscopy, but well-developed cases show diffuse thickening of the capillary wall.

• MGN may occur in association with known disorders or etiologic agents. These include the following:

1. Malignant epithelial tumors, particularly carcinoma of the lung and colon and melanoma.
2. Systemic lupus erythematosus (SLE).
3. Exposure to inorganic salts (gold, mercury).
4. Drugs (penicillamine, captopril).
5. Infections (chronic hepatitis B, syphilis, schistomiasis, malaria).
6. Metabolic disorders (diabetes mellitus, thyroiditis).

• In about 85 % of patients, the condition is truly «idiopathic».

Morphology

• By light microscopy, the glomeruli appear normal in the early stages of the disease or exhibit uniform, diffuse thickening of the glomerular capillary wall, hence the term «membranous».

• By electron microscopy the apparent thickening is caused by irregular dense deposits between the basement membrane and the overlying epithelial cells, the latter having lost their foot processes.

• Basement membrane material is laid down between these deposits, appearing as irregular spikes protruding from the GMB.

• In time, these spikes thicken to produce dome-like protrusions and eventually close over the immune deposits, burying them within a markedly thickened, irregular membrane.

• Immunofluorescence microscopy demonstrates that the granular deposits contain both immunoglobulins and complement.

• Others changes: protein and fatty droplets in the tubular epithelium and stroma. Foamy macrophages and giant cells form granulomas is association with cholesterol deposits.

• With progress of the disease, narrowing of the glomerular capillaries causes ischemic atrophy of the tubules and interstitial fibrosis.

Membranoproliferative glomerulonephritis (MPGN)

• As the term implies, this group of disorders is characterized histologically by alteration in the basement membrane and proliferation of glomerular cells. Because the proliferation is predominant in the mesangium, a frequently used synonym is **mesangiocapillary GN.**

• Like many other GN, histologic MPGN either can be associated with other systemic disorders and known etiologic agents (secondary MPGN) or may be primary, without known cause (idiopathic) in the kidney.

• Patients have hematuria or proteinuria demonstrate a combined nephritic-nephrotic picture.

Morphology

Primary MPGN is devided into two major types on the basis of distinct ultrastructural, immunofluorescent, and probably pathogenic findings.

By light microscopy both types are similar. The glomeruli are large and hypercellular.

The hypercellularity is produced by proliferation of cells in the mesangium, although infiltrating leukocytes and parietal epithelial crescents are present in many cases.

The glomeruli have a «lobular» appearance accentuated by the proliferating mesangial cells and increased mesangial matrix.

The GBM is clearly thickened, often focally, most evident in the peripheral capillary loops. The glomerular capillary wall often shows a «double-contour» or «tram-track» appearance, especially evident in silver or PAS stains.

This is caused by «splitting» of the basement membrane because of the inclusion within it of processes of mesangial cells extending into the peripheral capillary loops, so-called «mesangial interposition».

Injury of tubular structures and stroma take place.

Minimal change disease (MCD) (Lipoid nephrosis)

• Nephrotic syndrom in children can be often; characterized by normal glomeruli on light microscopy but uniform and diffuse effacement of the foot processes of visceral epithelial cells on electronic microscopy.

• Etiology is unknown.

• Immunofluorescence shows no immune deposits.

• The most characteristic feature of this condition is the good response to corticosteroid therapy.

• Proteinuria is usually selective and is associated with loss glomerular filtration (negative changes) and a hyperpermeable capillary wall.

Morphology

• GBM isn’t changes.

• Tubules are dilated; their epithelium is swelling, conteining hyaline and fatty droplets.

• Fatty degeneration, necrobiosis, atrophy, desquamation in tubular epithelium take place.

• Gross appearances («big white kidneys»): kidneys enlarged, flabby, yellow color.

Chronic glomerulonephritis (CGN)

• CGN is the final stage of GN when sclerosis has eliminated many glomeruli and their associated tubules.

• This is often the late result of membranous or membranoproliferative GN, less commonly postinfectious acute nephritis.

• At the final stage, it is difficult to determine the etiology of the pathological lesion.

Morphology

The kidneys are symmetrically contracted and have diffusely granular, cortical surfaces. Pieces of renal tissue adhere to stripped capsule; capsule is adherent and strips with difficult. Weight is 50 gm each. On section, the cortex is thinned and irregular, pelvis dilated and they're in an increasing peripelvic fat. Such kidneys are called **«secondary shrinkage ofkidneys».**

The glomerular histology depends on the stage of the disease. In early cases, the glomeruli may still show evidence of the primary disease.

Kidneys from the patients with end-stage disease on long-term dialysis exhibit a variety of so-called «dialysis changes» that are unrelated to the primary disease. Histological feature is nephrosclerosis.

These include arterial intimal thickening caused by accumulation of smooth muscle-like cells and a loose, proteoglycan-rich stroma; calcification, most obvious in glomerular tufts and tubular basement membranes; extensive deposition of calcium oxalate crystals in tubules and interstitium; acquired cystic disease; and increased numbers or renal adenomas and borderline adenocarcinomas.

Patients dying with chronic GN also exhibit pathologic changes outside the kidney that are related to the uremic state and are also present in other forms of chronic renal failure. Often clinically important, these includes uremic pericarditis, uremic gastroenteritis, secondary hyperparathyroidism with nephrocalcinosis and renal osteodystrophy, left ventricular hypertrophy due to hypertension, and pulmonary changes of diffuse alveolar damage often ascribed to uremia (uremic pneumonitis).

Uremia, hypertensive cardiac failure or cerebral hemorrhage may cause death.

Tubulopathy

Acute renal failure

Acute renal failure (ARF) is a syndrome associated with acute suppression of renal function, often accompanied by oliguria, and rarely anuria or polyuria. ARF is caused by:

1. Organic vascular obstruction.
2. Severe glomerular disease.
3. Acute tubulointerstitial nephritis.
4. Massive infection.
5. Disseminated intravascular renal coagulation.

6. Urinary obstructions.
7. Acute tubular necrosis.

Acute tubular necrosis

Acute tubular necrosis (ATN) is characterized by destrucrion of renal tubular epithelial cells either from ischemia or nephrotoxins.

Ischemic ATN is called tubulorrhectic ATN or shock kidney, occurs due to hypoperfusion ofthe kidneys resulting in focal damage to the tubules.

Etiopathogenesis

Ischemia may result from following causes:

— Shock (post-traumatic, surgical, burns, dehydration, obstetrical and septic). Crush injuries.

— Non-traumatic rhabdomyolysis induced by alcohol, coma, muscle disease or extreme muscular exertion (myoglobinuria nephrosis).

— Mismatched blood transfusions, black-water fever (hemoglobinuric nephrosis). The *pathogenetic mechanism* of ischemic ATN is explained on the basis of:

— Arteriolar vasoconstriction induced by renin-angiotensin system. Tubular obstruction by casts in the lumina or by interstitial edema. Back-leak of tubular fluid into the interstitium.

Morphology

• The kidneys are enlarged and swollen. On cut section, the cortex is often widened and pale, while medulla is dark.

• Predominant changes are seen in the tubules, while glomeruli are normal. Interstitium shows edema and mild chronic inflammatory cell infiltrate. Tubular changes are as follows:

a) dilatation of the proximal and distal convoluted tubules;

b) focal tubular necrosis at different points along the nephron;

c) flattened epithelium lining the tubules;

d) eosinophilic hyaline casts or pigmented hemoglobin and myoglobin casts in the tubular lumina;

e) disruption of tubular basement membrane (tubulorrhexis).

Nephrotoxic ATN occurs as a result of direct damage to tubular cells by ingestion, injection orinhalation of a number of toxic agents.

Etiopathogenesis

The toxic agents causing toxic ATN are:

— General poisons such as mercuric chloride, carbon tetrachloride, ethylene glycol, mushrooms and insecticides.

— Heavy metals (mercury, lead, arsenic, phosphorus and gold).

— Drugs, such as sulfonamides, certain antibiotics (gentamycin, cephalosporin), anaesthetic agents (methoxyflurane, halothane), barbiturates, salicylates.

— Radiographic contrast material.

— The *pathogenetic mechanism* producing ARF in toxic ATN is in principle similar to that for ischemic ATN.

Morphology

• The kidneys are enlarged and swollen. On cut section, the cortex is pale, while the medulla is slightly darker than normal.

• In general it involves the segment of tubule diffusely. In mercuric chloride poisoning, the features are as follows:

a) epithelial cells of mainly proximal convoluted tubules are necrotic and desquamated into the tubular lumina;

b) the desquamated cells may undergo dystrophic calcification;

c) tubular basement membrane is generally intact;

d) the regenerating epithelium, which is flat and thin with few mitoses, may be seen lining the tubular basement membrane.

The clinical course of ATN may be devided into stages:

1. **The initiating stage (shock),** lasting for about 36 hours, is dominated by the inciting medical, surgical, or obstetric event in the ischemic form of ATN. Macroscopically, kidneys are diffusely swollen and edematous. It is characterized by ischemic cortex and congestion of pyramids. Acute renal failure and oliguria, hyperkalemia and fluid overload in patients develop.

2. **The maintenance stage (Oliguric phase, 2–9 days)** is characterized by sustained decreases in urine output to between 40 to 400 ml per day, with salt and water overload, rising blood urea nitrogens, hyperkaliemia, metabolic acidosis, and other manifestations of uremia dominating this phase. There is blockage of renal tubules by necrotic cells, and a secondary reduction in glomerular blood flow (caused by arteriolar constriction) reduces glomerular filtration. It stage may be fatal.

3. **The recovery stage (Polyuric phase, 10–21 days)** is ushered by a steady increase in urine volume that may reach up to 3 liters per day. Regeneration of renal tubular epithelium takes place, with removal of dead material by phagocytic cells, as well as in the form of casts in urine. As tubules open up and glomerular blood flow increases, patients develop polyuria. This is because the regenerated tubular cells are undifferentiated and have not developed the specializations necessary for resorption of electrolytes and water. Replacement of fluid and electrolytes is needed to compensate for excessive loss from urine. Hypokalemia, rather than hyperkalemia, becomes a clinical problem.

The prognosis of ATN depends on the clinical setting surrounding its development.

Tubulointerstitial Disease

The term tubulointerstitial nephritis is used for inflammatory process that predominantly involves the renal interstitial tissue and is usually accompanied by some degree of tubular damage. The term *interstitial nephritis* is reserved for those cases where there is no primary involvement of glomeruli, tubules or blood vessels. A number of bacterial and non-bacterial, acute and chronic conditions may produce tubulointerstitial nephritis.

Pyelonephritis

Pyelonephritis (PN) *is a renal disorder affecting tubules, intrestitium, and renal pelvis and is one of the most common diseases of the kidney.* The term urinary tract infection (UTI) implies involvement of eitherthe bladder (cystitis) or the kidney and their collecting system (pyelonephritis), or both. UTIs are extremely common disorders. It occurs in two forms:

1. Acute PN is acute pyogenic infection.
2. Chronic PN is a more complex disorder: bacterial infection plays a dominant role, but other factors (vesicoureteral reflux, obstruction) are involved in its pathogenesis.

Etiopathogenesis

- The dominant etiologic agents are the gram-negative bacilli that are normal inhabitants of the intestinal tract: E.coli (Proteus, Klebsiella and Enterobacter), Str. fecalis etc.
- In most patients with UTI, the infecting organisms are derived from the patient's own fecal flora. This is thus a form of endogenous infection.
- There are two routs by which bacteria can reach the kidneys:

a) through the bloodstream (hematogenous);

b) from the lower urinary tract (ascending infection).

- Although obstruction is an important predisposing factor in the pathogenesis of ascending infection, it is incompetence of the vesicoureteral orifice that allows bacteria to ascend the ureter into the pelvis.

Acute Pyelonephritis

Morphology:

- The hallmarks of acute PN are patchy interstitial suppurative inflammation and tubular necrosis.
- Macroscopically, the kidneys show variable numbers of small, yellowish white cortical abscesses, which are usually spherical, under 2 mm in diameter, and are sometimes surrounded by a zone of hyperemia; the cortical abscesses are often most prominent on the sub-capsular surface, after the capsule has been

stripped away. In the medulla the abscesses tend to be in the form of yellowish white linear streaks that converge on the papilla. The pelvicalyceal mucosa is hyperemic or covered with a fibrinopurulent exudate.

• Histologically: the neutrophilic infiltration is limited to the interstitial tissue. Some tubules destroyed: abscesses formed; other tubules filled by puss cells. Glomeruli usually unaffected.

• Clinical features. Classically, acute pyelonephritis has an acute onset with chills, fever, loin pain, lumbar tenderness, dysuria and frequency of micturition. Urine will show bacteria, pus cells and pus cell casts in the urinary sediment.

• Three complications of acute PN are encountered in special circumstances.

1. *Papillary necrosis* is seen mainly in diabetics and in those with urinary tractobstruction. Papillary necrosis is usually bilateral, but may be unilateral.

2. *Pyonephrosis* is seen when there is total or almost complete obstruction, particularlywhen it is high in the urinary tract (pelvis filled with puss).

3. *Perinephric abscess* implies extension of suppurative inflammation through the renalcapsule into the perinephric tissue.

• At the acute phase of PN, healing occurs. The neutrophilic infiltration is replaced by macrophages, plasma cells, and (later) lymphocytes. The inflammatory foci are eventually replaced by scars. The pyelonephritic scar is almost always associated with inflammation, fibrosis, and deformation of the underlying calyx and pelvis.

• Uncomplicated acute PN usually follows a benign course, and the symptoms disappear within a few days after the institution of appropriate antibiotic therapy. In the presence of unrelieved urinary obstruction, diabetes mellitus acute PN may be more serious, leading to repeated septicemic episodes.

Chronic Pyelonephritis

Chronic Pyelonephritis (CPN) is a chronic tubulointerstitial renal disorder in which chronic tubulointerstitial inflammation and renal scarring are associated with pathologic involvement of the calyces and pelvis.

Etiopathogenesis

Two types of chronic pyelonephritis are described:

Reflux nephropathy. Reflux of urine from the bladder into one or both the ureters during micturition is the major cause of chronic pyelonephritis. Vesicoureteric reflux is particularly common in children, especially in girls, due to congenital absence or shortening of the intravesical portion of the ureter so that ureter is not compressed during the act of micturition. Reflux results in increase in pressure in the renal pelvis so that the urine is forced into renal tubules, which are eventually followed by damage to the kidney and scar formation.

Obstructive pyelonephritis. Obstruction to the outflow of urine at different levels predisposes the kidney to infection. Recurrent episodes of such obstruction and infection result in renal damage and scarring.

Morphology

• Gross examination. The kidneys are usually small and contracted (weighing less than 100 gm) showing unequal reduction; if bilateral, the involvement is asymmetric. The surface of the kidney is irregularly scarred; the capsule can be stripped off with difficulty due to adherence to scars. There is generally dilatation of pelvis and blunted calyces. This contrasts with chronic glomerulonephritis, in which the kidneys are diffusely and symmetrically scarred.

• The microscopic changes involve predominantly tubules and interstitium.

• **The tubules** show atrophy in some areas and hypertrophy in others, or dilatation. Dilatedtubules may be filled with colloid crystals, producing thyroidisation of tubules (thyroid-like).

• **Interstitium.** There is chronic interstitial inflammatory reaction, chiefly composed oflymphocytes, plasma cells and macrophages with pronounced interstitial fibrosis. *Xanthogranulomatous pyelonephritis* is an uncommon variant characterised by collection offoamy macrophages admixed with other inflammatory cells and giant cells.

• **Pelvicalyceal system.** The renal pelvis and calyces are dilated. And show marked chronicinflammation and fibrosis.

• **Blood vessels.** Blood vessels entrapped in the scarred areas show obliterative endarteritis.

• **Glomeruli.** There is often periglomerular fibrosis. In advanced cases, there may behyalinisation of glomeruli.

• **Clinical features.** Chronic pyelonephritis often has an insidious onset. The patients present with clinical picture of chronic renal failure or with symptoms of hypertension.

• Chronic obstructive PN may be insidious in onset or may present the clinical manifestations of acute recurrent PN with back pain, fever, frequent pyuria, and bacteriuria.

Infections of the lower urinary tract

• Infections in the lower urinary tract are predisposed by obstruction and stasis.

• Lower urinary tract infection is usually due to Gram-negative coliform bacilli, e.g. E. coli and Proteus, which are normally in the large bowel; because they have a short urethra, women are particularly prone to developing ascending infections.

• In men, lower urinary tract infection is usually associated with structural abnormalities of the lower urinary tract and stasis due to obstruction.

• Diabetes mellitus also predisposes to infection.

Morphology

• The pelvicalyceal system is dark reddish brown as a result of acute inflammation of the usually smooth creamy mucosal lining due to bacterial infection.

• The kidney is also congested and some small scattered abscesses are pre-

sent in the cortex and medulla (acute pyelonephritis).

• Obstruction of the drainage of urine from the kidney causes hydronephrosis.

• Obstruction, one of the most important consequences of disease of the lower urinary tract, may occur at any place in the tract: renal pelvis (calculi, tumors), pelviureteric junction (stricture, calculi, extrinsic compression), ureter (calculi, extrinsic compression -pregnancy, tumor, fibrosis), bladder (tumor, calculi); urethra (prostatic hyperplasia or carcinoma, urethral valves, urethral stricture).

If obstruction occurs in the urethra, the bladder develops dilatation and secondary hypertrophy of muscle in its wall. This predisposes to development of out pouching of the bladder mucosa (diverticulae).

If obstruction occurs in a ureter, there is dilatation of the ureter (megaureter), with progressive dilatation of the renal pelvicalyceal system, termed hydronephrosis. Fluid entering the collecting ducts cannot empty into the renal pelvis and there is intrarenal resorption of fluid. At this stage, if the obstruction is relieved, renal, function returns to normal. However, if obstruction persists, there is atrophy of renal tubules, glomerular hyalinization, and fibrosis. As an end-stage, the renal parenchyma becomes severely atrophic and renal function is permanently impaired.

Urinary tract obstruction also predisposes to infection and stone formation.

Urolithiasis

• Urolithiasis or formation of urinary calculi at any level of the urinary tract is a common condition. It is estimated that approximately 2 % of the population experiences renal stone disease at sometime in their life with male-female ratio of 2:1.

• Renal calculi are characterized clinically by colicky pain (renal colic) as they pass down along the ureter and manifest by hematuria.

• Sites of formation. Two suggestions have been made:

1. Precipitates form in the collecting tubules and pass into renal pelvis where they enlarge.

2. Deposits are formed in the lymphatic vessels of the renal papillae and are extruted into the renal pelvis.

Types of Urinary Calculi

There are 4 main types of urinary calculi:

Calcium stones. Calcium stones are the most common comprising about 75 % of all urinarycalculi. They may be pure stones of calcium oxalate (50 %) or calcium phosphate (5 %), or mixture of calcium oxalate.

1) **Mixed (Struvite) stones.** About 15 % of urinary calculi are made of magnesium-ammonium-calcium phosphate, often called struvite. «Staghorn stone» which is a large, solitary stone that takes the shape of the renal pelvis where it is often formed is an example of struvite stone.

2) **Uric acid stones.** Uric acid calculi are radiolucent unlike radio-opaque calcium stones. Uricacid stones are smooth, yellowish-brown, hard and often multiple.

3) **Cystine stones.** Cystine stones are small, rounded, smooth and often

multiple. They are yellowish and waxy. They are seen in heritable tubular transport defects causing cystinuria. **Complications:** pyelonephtitis, hemorrhage, hydronephrosis.

Hydronephrosis

• Hydronephrosis is the term used for dilatation of renal pelvis and calyces due to partial orintermittent obstruction to the outflow of urine.

• Hydroureter nearly always accompanies hydronephrosis

• Hydronephrosis may be unilateral or bilateral.

• Unilateral hydronephrosis. This occurs due to some form of ureteral obstruction at the levelof periureteric junction (PUJ). The causes are:

a) Intraluminal, e.g. a calculus in the ureter or renal pelvis.

b) Intramural, e.g. congenital PUJ obstruction, atresia of ureter, inflammatory stricture, trauma, neoplasm of ureter or bladder.

c) Extramural, e.g. obstruction of upper part of ureter by inferior renal artery or vein, pressure on ureter from outside such as carcinoma cervix, prostrate, rectum, colon or cecum and retroperitoneal fibrosis.

• Bilateral hydronephrosis. This is generally the result of some form of urethral obstruction but can occur from the various causes listed above if the lesions involve both sides.

Congenital, e.g. atresia of the urethral meatus, congenital posterior urethral valve.

a) Acquired, e.g. bladder tumor involving ureteric orifices, prostatic enlargement, prostatic carcinoma and prostatitis, bladder neck stenosis, inflammatory or traumatic urethral stricture and phimosis.

Morphology

• The kidneys may have moderate to marked enlargement.

• Initially, there is extrarenal hydronephrosis characterised by dilatation of renal pelvis medially in the form of a sac.

• Eventually, the dilated pelvi-calyceal system extends deep into the renal cortex so that a thin rim of renal cortex is stretched over the dilated calcyes and the external surface assumes tabulated appearance. This advanced stage is called as intrarenal hydronephrosis.

• The wall of hydronephrotic sac is thickened due to fibrous scarring and chronic inflammatory cell infiltrate.

Cystic disease of the kidney

• There are several cystic diseases of the kidney, some of which produce renal failure by causing disturbance of renal structure. Importantly, some conditions are heritable.

• Adult polycystic disease is inherited in an autosomal dominant trait, gen-

erally becoming clinically manifest in adult life. Increasingly, disease is detected in childhood, with family screening and ultrasound examination.

• Cysts develop and progressively enlarge over a number of' years, but remain asymptomatic until the number and size of the cysts is so great that the patient becomes aware of abdominal masses.

• At about the same time, the replacement and compression of functioning renal parenchyma by the cysts leads to slowly progressive impairment of renal function, and patients develop chronic renal failure and hypertension.

• Patients with adult-type polycystic renal disease may also develop cysts in the liver, lung and pancreas. There is an association with berry aneurysms of the cerebral arteries, which, with development of hypertension, predisposes to intracranial hemorrhage.

• Infantile polycystic disease is uncommon and is encountered at birth. Children develop severe renal failure, with compression of the lungs due to massive enlargement of the kidneys.

• Simple renal cysts are the most common form of renal cystic disease and must be distinguished from the congenital types discussed above. They are widely held to be acquired abnormalities, incidence increasing with age. They contain clear, watery fluid and have a smooth lining.

• Simple cysts may be single or multiple and vary in size, generally being no larger than 5–6 cm. They have no effect on renal function, but may rarely become infected or develop hemorrhage.

• Acquired cystic disease is seen in kidneys left in situ while patients are treated by dialysis or transplantation for chronic renal failure. The kidney is converted into a mass of large cysts. Hemorrhage into cysts is common, leading to bloodstained contents.

Chronic renal failure

• ***Nephrosclerosis*** is morphologic basis of chronic renal failure.

• Uremia is a syndrome encompassing a group of clinical and biochemical sings derived essentially from the retention of waste products and the failure to control fluid and electrolyte balance.

• Uremia is final stage of chronic renal failure, which is characterised by:

1. Hypernitrogenemia.
2. Metabolic acidosis (accumulation of sulphates, phosphates, and organic acids).
3. Hyperkaliemia, hypercalcemia.
4. Anemia.
5. Depression of immunological reaction. Infections are common and will in turn affect renal function.
6. Arterial hypertension.
7. Hemorrhagic syndrome (petechias, hemorrhagic erosions and ulcer in mucosa).
8. Fibrinous inflammation:

a) Fibrinous pericarditis («cor vilosum»).

b) «Uremic pneumonitis» with pleural exudates.

c) Uremic gastritis, enteritis, colitis.

d) Edema of lungs.

• The prognosis of final stage renal failure has been greatly improved by dialysis, renal transplantation.

VII. GENITAL TPACT DISEASES

Diseases of Cervix

• The cervix is an important site of pathology, particularly in women of reproductive age.

• The ectocervix is covered by squamous epithelium, and the endocervical canal is covered by mucus-secreting columnar epithelium, which shows glandular down growth.

• At various stages in a woman's reproductive life, the junction between the squamous and columnar epithelium migrates into the convexity of the ectocervix, then back into the endocervical canal. This squamocolumnar junction is the seat of most of the epithelial diseases that occur in the cervix.

Cervical erosion (endocervicosis)

• It represents an unfolding and eversion of the distal endocervix into an ectocervix. The term «cervical ectopia» is preffered.

• Etiology: increased uterine bulk, in pregnancy, hormonal stimulation.

• According to duration the endocervicosis classified:

1. **Simple endocervicosis** is characterized by metaplasia of the squamous epithelium intocolumnar epithelium without proliferation of reserve cells, presence of the cervical glands in ectocervix and papillary formation.

2. **Progressive endocervicosis** is characterised by proliferation of reserve cells andpresence of the various size glands. Zone transformation is dilated.

3. **Healing endocervicosis** is characterized by recovery of normal structure of ectocervixor formation of Naboti's cysts. Due to impairment of differentiations the dysplasia can take place.

Dysplasia

Dysplasia refers as *cervical intraepithelial neoplasia (CIN)* and it has 3 grades of differentiation:

1. **CIN 1 or mild dysplasia:** cells of basal third have high nucleocytoplasmic ratioand pleomorphic nuclei.

2. **CIN 2 or moderate dysplasia:** basal cells occupy lower half of squamous epithelium.

3. **CIN 3 or severe dysplasia or cancer in situ:** almost complete loss of stratification, loss of polarity of the cells, variation in nuclear size with increase in nuclear/cytoplasmic ratio and mitotic figures.

Cervicitis

- Cervicitis may be specific and non-specific.
- Acute and chronic cervicitis results from infection by any number of microorganisms, particulary Streptococcus, staphylococcus, or Enterococcus, and, less commonly, Neisseria gonorrhoeae and Chlamydia trachomatis.
- Some of these microorganisms are sexually transmitted, whereas others may be introduced by foreign bodies, such as residual fragments of tampons and pessaries.
- Purulent inflammation is a clinical sign of acute cervicitis. The inflamed cervix becomes congested and edematous.
- Since biopsy samples from the cervix frequently exhibit some degree of nonspecific chronic inflammation, the diagnosis of chronic cervicitis should be made only when numerous lymphoid cells are present. Leukoplakia may develop (it means the white patches of hyperkeratosis).

Diseases of endometrium

Dysfunctional Bleeding

- Dysfunctional uterine bleeding is denned as abnormal bleeding in the absence of an organic lesion of the endometrium.
- It is one of the most common gynecologic disorders of women of reproductive age, but one that is still poorly understood.
- The bleeding may be due to anovulatory cycles related to excessive and prolonged estrogenic stimulation.
- Without ovulation, a corpus luteum does not develop and progesterone is not secreted.
- The endometrium, therefore, fails to proceed through the normal secretory phase, and an abnormal menstrual cycle results.
- Organic lesions of the uterus must be excluded before the diagnosis of dysfunctional bleeding can be made. Examples of organic disorders are carcinoma, hyperplasia, polyps, endometritis, and complications of intrauterine or ectopic pregnancy.

Anovulatory Bleeding

- Anovulatory bleeding is the most common form of dysfunctional uterine bleeding, particularly during adolescence and the climacteric period.
- It is believed that estrogen maintains the stromal fluid turgescence that supports the blood vessels.
- Anovulatory bleeding is caused by a fall in estrogen levels, which results in loss of fluid from the stroma and hence loss of vascular support. The vascular collapse leads to compression of the vessels, which in turn leads to stasis, thrombosis, infarction, and hemorrhage.
- On microscopic examination the glands are disordered and appear

crowded because of severe stromal necrosis and collapse of the proliferative endometrium.

Abnormalities of the Normal Menstrual Cycle

- Dysfunctional bleeding may also be associated with abnormalities of the normal menstrual cycle.
- Ovulatory oligomenorrhea (cycle longer than 45 days) is almost always due to a long follicular phase and may be the prelude to ovarian failure.
- Ovulatory polymenorrhea, in which cycles are less than 18 days in length, is caused by short follicular phases (seen generally in adolescence) or short luteal phases (inadequate luteal phase). The latter may be due to defects in factors that maintain the corpus lutein.

Endometritis

Acute endometritis

- This is almost confined to infection associated with partirition and abortion.
- A mixed bacterial flora, pyococci, coliform organisms and proteus are usual.
- Suppurative inflammation is usual.
- Presence of polymorphonuclear leukocytes, results when an infection ascends from the cervix.
- Curettage is both diagnostic and curative because it removes the necrotic tissue that serves as the nidus of infection.
- Complications may follow endometritis: myometritis, parametritis, salpingitis, peritonitis, subsequent tubal blockage and infertility.
- Pyometra, pus in the endometrial cavity, is associated with any lesion that causes cervical stenosis, such as a tumor or scarring from surgical treatment (conization) of the cervix. Long-standing pyometra may be associated with the development of squamous cell cancer of the endometrium.

Chronic endometritis

- Chronic endometritis is usually associated with recent gestation, pelvic inflammatory disease, intrauterine contraceptive devices (IUD) use, and retained products of conception after an abortion or delivery, menstrual irregularities, but is also found in women who are being investigated for infertility.
- Chronic endometritis may be caused by gonococcal or chlamydial infection, or tuberculosis.
- Clinically, patients usually complain of bleeding, pelvic pain, or both.
- Histologically: stroma infiltrated by plasma cells and lymphocytes; glands small and infrequent; epithelium atrophied.

Hyperplasia of endometrium

Endometrial hyperplasia usually results with conditions of prolonged estro-

gen excess and can lead to metrorrhagia (uterine bleeding at irregular intervals), menorrhagia (excessive bleeding with menstrual periods), or menometrorrhagia.

It is classified into following 3 types:

1. **Simple hyperplasia (cystic glandular hyperplasia)** is characterised by the presence of largeand cystically dilated, varying-sized glands, which are lined by atrophic epithelium. Simple endometrial hyperplasias can cause bleeding, but are not thought to be premalignant.

2. **Adenomatous hyperplasia (complex hyperplasia without atypia).** This shows distinctproliferative pattern. The glands are increased in number, exhibit variation in size and are irregular in shape. Multiple layers of tall columnar epithelial cells with large nuclei, which have not lost basal polarity, line the glands and there is no atypia. Adenomatous hyperplasia is premalignant.

3. **Atypical hyperplasia (complex hyperplasia with atypia)** is characterised by the presence ofatypical cells in the hyperplastic epithelium. The glands are enlarged and irregular with columnar cells that have some atypia (loss polarity, large size, irregular and hyperchromic nuclei, prominent nuclei, and altered nucleocytoplasmic ratio).

Endometriosis

- When endometrial glands and stroma are found outside the uterus, the condition is known as endometriosis.
- Up to 10 % of women may have this condition. It can be very disabling and painful, even when just a few foci are present.
- Typical locations for endometriosis may include: ovaries, uterine ligaments, rectovaginal septum, pelvic peritoneum, fallopian tubes and laparotomy scars. Endometriosis may even be found at more distant locations such as appendix and vagina.
- Grossly, in areas of endometriosis the blood is darker and gives the small foci of endometriosis the gross appearance of ***«powder burns».*** Such areas of endometriosis can be seen and obliterated by cauterization via laparoscopy. Sometimes the old dark brown blood collects over time from repeated hemorrhage in a cystic space in the ovary and produces a so-called «chocolate cyst» (endometriotic cyst).
- Histologically: foci of endometrial glands and stroma, old or new hemorrhage, hemosiderin-laden macrophages and surrounding zone of inflammation and fibrosis.

Diseases of fallopian tubes

- Acute and chronic salpingitis usually results from an ascending infection from the lower genital tract.
- The most common causative organisms are E. coli, N. gonorrheae, Chlamydia, and Mycoplasma. Clostridia perfringens and various other anaerobes are less commonly encountered.

• A fallopian tube damaged by prior infection is particularly susceptible to reinfection.

Acute Salpingitis

The host responds with a brisk granulocytic infiltrate and vascular engorgement, and edema of the involved tubal layers ensues. As the lumen fills with granulocytes, the tube distends and **pyosalpinx** develops.

Chronic Salpingitis

• Chronic salpingitis usually results from repeated episodes of acute salpingitis.

• The acute episodes, particularly those associated with chlamydial infection, may be asymptomatic.

• Complications may be caused by either destruction of epithelium or deposition of fibrin on the mucosal plicae; the fibrin bridges cause the plicae to adhere to one another.

• Fibrinous adhesions between the serosa and surrounding peritoneal surfaces may organize into thin, fibrous adhesions («violin string» adhesions).

• In severe chronic salpingitis, the adhesions may be dense and the fimbria adhere to each other to form a blunted; clubbed end.

• Ovarian involvement leads to the formation of a tubo-ovarian abscess.

• The consequence of the blocked lumen may be a hydrosalpinx or pyosalpinx. Because of destruction of the tubal epithelium and fibrosis, chronic salpingitis may lead to infertility and ectopic pregnancy.

Diseases of ovaries

Ovarian changes of functional origin.

1. **Follicilar cysts** are cysts arising from Graafian follicles and are lined by granulosa cells,with an outer coat of thecal cells. They filled with clear serous fluid and may attain a diameter up to 2 sm. They may be single or multiple. Multiple follicular cysts, usually small, are associated with endometrial hyperplasia.

2. **Luteal cysts** are cysts from which the granulosa cells have disappeared, leaving cysts surrounded by luteinised tissue. Cysts are typically 2–3 cm in diameter, with a thick, yellow lining of luteinized granulosa cells. There is continued production of progesterone, resulting in menstrual irregularity.

3. **Theca lutein cysts** are usually seen as multiple bilateral cysts, up to 1 cm in diameter, filledwith clear fluid. They are caused by high levels of gonadotropin, which precipitates follicle development (e.g. in hydatidiform mole and drug treatment).

4. **Polycystic ovary disease (Stein-Leventhal Syndrome)** is associated with obesity, hirsutism, oligomenorrhea, anovulation, and infertility.

• The pathogenesis of this syndrome is still uncertain. Patients have a per-

sistent anovulatory state, high level of estrogen, low level of progesteron with high levels of circulating androgen produced by the ovary. The high estrogen levels may cause endometrial hyperplasia and increase the risk of development of endometrial carcinoma.

- The ovaries are usually involved bilaterally and are at least twice the size of the normal ovary. They are grey-white color and studded with multiple small bluish cysts just beneath the cortex.
- Histologically. The outer cortex is thick and fibrous. The subcortical cysts are lined by prominent luteinised theca cells and represent follicles in various stages of maturation but there is no evidence of corpus lutein.

Obstetric pathology

Pre-eclampsia and eclampsia

- **Pre-eclamptic toxemia syndrome** is characterised by hypertension, proteinuria andperipheral edema.
- Seen particularly in association with multiple pregnancies, primigravidae and women over the age of 35 years.
- Most cases are mild, with the blood pressure under 100 mmHg diastolic and no proteinuria; in severe cases the diastolic pressure is consistently above 100 mmHg, and there is proteinuria and severe peripheral edema.
- A feature of pre-eclampsia is reduced placental blood flow; this may lead to fetal hypoxia in late pregnancy, particularly during labour, with increased risk of perinatal mortality. The fetus may also suffer intrauterine growth retardation and have low birth weight.
- Placental ischemia takes place.
- In the kidney, endothelial cells become swollen, with deposition of fibrin in glomeruli, leading, to proteinuria. If untreated, severe hypertension and intravascular coagulation occur with development of cerebral ischemia and fits.
- **Eclampsia** is now a fare complication of pregnancy. Patients develop severe systemicdisturbance, rapid and sustained rise in blood pressure, shock, anuria and fits.
- Complications and causes of death: patients develop disseminated intravascular coagulation, with widespread occlusion of blood vessels, fibrinoid necrosis of vessel wails, and, in fatal cases, widespread microinfarcts in brain, liver, kidney and other organs.

Ectopic Pregnancy

Ectopic pregnancy refers to any gestation that develops outside the endometriun.

Over 95 % occur in the tube (ampullary implantation, interstitial implantation and tubal wall).

Ovarian pregnancy is presumed to result from the rare fertilization and trapping of the ovum within the follicle just at the time of its rupture.

Abdominal pregnancies may develop when the fertilized ovum drops out of the fimbriated end of the tube.

Etiology of tubal pregnancy: salpingitis, leading to partial blockage of the tube; in women fitted with intrauterine contraceptive devices, endometriosis. Other factors are peritubal adhesions owing to appendicitis, leiomyomas, and previous surgery.

In all abnormal locations, the fertilized ovum undergoes its usual development with the formation of placental tissue, amniotic sac, and fetus, and the host implantation site develops decidual changes and syncytio-trophoblasts.

Abdominal pain is the most common symptom.

The appearance of ectopic pregnancy resembles that of placenta increta and percreta of the uterus. Because the tubal mucosa has a limited ability to undergo decidualization, the trophoblast readily penetrates the mucosa and wall, a situation, which results in an abnormal implantation.

The wall of the fallopian tube is thin and unless the ectopic pregnancy is discovered, the wall usually ruptures by the 12th week of gestation.

Tubal rupture with subsequent hemorrhage is a life-threatening complication. The direction of rupture varies:

1. Rupture into the lumen of the tube and leakage into perinatal cavity (tubal abortion). Exceedingly rarely the whole pregnancy — ovum and placental tissue — aborts into peritoneal cavity where it reimplants. Usually development is limited and the fetus dies.

2. Rupture directly into the peritoneal cavity. If the implatation is interstitial, there may be a further complication — damage to the uterine arteries with arterial bleeding.

3. Rupture into the broad ligament lead to extraperitoneal hematoma.

Gestational Trophoblastic Disease

The clinical term «gestational trophoblastic disease» include of hydatidiform mole (complete and partial mole), invasive mole, gestational choriocarcinoma, and placental site trophoblastic tumor.

Hydatidiform Mole

1. Complete type.

In complete hydatidiform mole, grossly swollen chorionic villi, which resemble a bunch of grapes, show varying degrees of trophoblastic proliferation.

There is no embryo.

Complete mole results from fertilization of an egg in which the maternal chromosomal material has been lost or inactivated by a single sperm with a 23X set of chromosomes, which duplicate to 46XX.

The embryo dies at an early stage before the placental circulation has developed, and chorionic villi then contain few, if any, blood vessels.

Complications of complete hydatidiform mole include uterine hemorrhage, coagulopathy, uterine perforation, trophoblastic embolism, and infection. The most important complication is the development of choriocarcinoma.

2. Partial type.

In partial hydatidiform mole two populations of chorionic villi exist, some of which show hydropic swelling.

Trophoblastic proliferation is focal and usually less pronounced than in the complete mole. In partial hydatidiform mole, unlike complete mole, there is frequently an associated embryo.

Partial hydatidiform mole is generally the result of fertilization of an egg by two paternal sets of chromosomes, with the maternal chromosomes remaining. This results in triploidy.

The fetus associated with a partial mole usually dies at approximately 10 weeks of gestation, and the mole is aborted shortly thereafter.

Microscopically, partial hydatidiform mole resembles complete mole, being composed of seemingly normal small villi along with villi that have accumulated considerable fluid. Blood vessels are typically found within the chorionic villi and contain fetal (nucleated) red blood cells. The villous outlines commonly have a scalloped appearance.

It is difficult to determine the relative frequency of complete and partial moles, since the entity of partial mole has only recently been recognized. Partial moles have a lower malignant potential than complete moles.

3. Invasive type.

The invasive mole, also called chorioadenoma destruens, is a hydatidiform mole that has invaded the underlying myometrium.

Uterine perforation from the locally infiltrative disease is the major complication.

Theca lutein cysts (hyperreactio luteinalis) may occur with any form of trophoblastic disease and may be prominent with invasive moles.

Microscopically, invasive moles show less hydropic change than complete moles; trophoblastic proliferation is usually prominent.

Benign diseases of the breast

Fibrocystic disease

• **Fibrocystic disease** is the most common disorder of the female breast.

• The cause of fibrocystic disease is uncertain. Most believe that it is due to disturbances of cyclical ovarian estrogen and progesterone levels, accompanied by altered responsiveness of breast tissues in women approaching the menopause.

• Fibrocystic change is characterized by hyperplastic overgrowth of com-

ponents of the mammary unit, i.e. lobules, ductules and stroma.

• In this condition there are four characteristic features, and the form, which the disease takes varies according to the relative proportions of these features:

1. **Fibrosis.** This is mainly an increase in the amount of collagen rather a true growth of fibrous tissue.

2. **Adenosis:**

• This is an increase in the number of lobules and in the size of existing lobules.

• Sclerosing adenosis (fibroadenomatoid hyperplasia or fibroadenosis) is localised condition, which may simulate carcinoma.

• There is proliferation of acini and stroma, and mitotic activity can be marked but there is no danger of malignancy.

• This presents as palpable thickening and nodularity of breast tissue, but may also result in the development of single breast lumps.

3. **Cyst formation:**

• Cysts are a prominent component, increasing in incidence with the approach of the menopause.

• Obstruction of ducts leads to dilatation on the ducts and acini.

• They range in size from those detectable only by histology to palpable lesions 1–2 cm in diameter.

• **Histologically:** cysts are lined by flattened epithelium derived from the lobular-ductal unit and are filled with watery fluid. As some carcinomas of the breast may be associated with cysts, it is not safe to assume that a lesion is benign because it has a fluid-filled cyst. The lining epithelium may show apocrine metaplasia.

4. **Fibrocystic change:**

• Epithelial hyperplasia is the most important component because it forms a link between simple proliferation and malignant change.

• *Macroscopically,* areas of fibrocystic changes appear as firm, rubbery replacement of breasttissue, in which cysts may be visible.

• There are many *histological variations* within fibrocystic disease, such as:

a) proliferation of myoepithelial layer;

b) proliferation of ductal epithelium forming an irregular network (atypical ductal hyperplasia);

c) uniform proliferation of acinar epithelium without acinar expansion (atypical lobular hyperplasia).

Fibroadenoma

• **Fibroadenoma** is a bening nodular proliferation, now considered to be a component offibrocystic changes and not a true neoplasm. The fibroadenoma is therefore best regarded as a form of hormone-dependent nodular hyperplasia, rather than a true benign tumor.

• Fibroadenoma presents as a mobile lump in the breast of young women.

• Macroscopically, fibroadenomas are typically 1–3 cm in diameter, ap-

pearing as firm, rubbery, well-circumscribed, elastic consistency, glistening, greish cut surface.

• *Histologically:*

a) small acinar and duct structures resembling normal brest.

b) fibrous tissue arranged around acini.

c) epithelium forms clefts: these are due to pressure from the projecting fibrous tissue.

Diseases of male genitalia

Prostatitis may be acute, chronic and granulomatous types.

Acute prostatitis

• Acute prostatitis is characterised by acute focal or diffuse suppurative inflammation of the prostate.

• It occurs most commonly due to ascent of bacteria from the urethra, less often by descent from the upper urinary tract or bladder, and occasionally by lymphogenous or hematogenous spread from a distant focus of infection.

• The infection may occur spontaneously or may be a complication of urethral manipulation such as by catheterization, cystoscopy, etc.

• Macroscopically, the prostate is enlarged, swollen and dense. Cut section shows multiple abscesses and foci of necrosis.

• Histologically, the prostatic acini are dilated and filled with neutrophilic exudate. There may be diffuse acute inflammatory infiltrate. Edema, hyperemia and foci of necrosis frequently accompany acute inflammatory involvement.

Chronic prostatitis

• Macroscopically, the prostate may be enlarged, fibrosed and shrunken.

• Microscopically, the diagnosis of chronic prostatitis is made by foci of lymphocytes, plasma cells, macrophages and neutrophils within the prostatic substance. Prostatic calculi and foci of squamous metaplasia in the prostatic acini may accompany inflammatory changes.

Granulomatous prostatitis is a variety of chronic prostatitis, probably caused by leakage ofprostatic secretions into the tissue, or could be of autoimmune origin. Macroscopically, the gland is firm to hard, giving the clinical impression of psoriatic carcinoma on rectal examination. Microscopically, the inflammatory reaction consists of macrophages, lymphocytes, plasma cells and some multinucleated giant cells.

Bening prostatatic hyperplasia (Nodular hyperplasia)

Nodular prostatic hyperplasia has been suggested by some as precursor for

development of prostatic cancer.

Morphology

Macroscopically:

The enlarged prostate is nodular, smooth and firm.

The appearance on cut section varies depending upon whether the hyperplasia is predominantly of the glandular or fibromuscular tissue.

In primarily glandular benign nodular hyperplasia the tissue is yellow-pink, soft, honey-combed, and milky fluid exudes.

In mainly fibromuscular benign nodular hyperplasia the cut surface is firm, homogeneous and does not exude milky fluid.

The hyperplastic nodule forms a mass mainly in the inner periurethral prostatic gland so that the surrounding prostatic tissue forms a false capsule, which enables the surgeon to enucleate the nodular masses.

Microscopically:

Hyperplasia of all tissue elements in varying proportions — glandular, fibrous and muscular take place.

Glandular hyperplasia predominates in most cases and is identified by exaggerated intra-acinar papillary infoldings with delicate fibrovascular cores.

Fibromuscular hyperplasia when present as dominant component appears as aggregates of spindle cells forming an appearance akin to fibromyoma of the uterus.

Complications:

- Chronic retention of urine.
- Cystitis and pyelonephritis.
- Hydronephrosis.
- Bladder stone.

Gynecomastia of male breast

- Gynecomastia of male breast is most commonly idiopathic, but may be a sign of underlying endocrine disturbance.
- The male breast is normally rudimentary and inactive, consisting of fibroadipose tissue containing atrophic mammary ducts.
- Enlargement of the male breast, which is termed gynecomastia, may be unilateral (70 % of cases) or bilateral.
- In most cases it is idiopathic. Other causes include: Klinefelter's syndrome. Estrogen excess (cirrhosis, puberty, adrenal tumor, exogenous estrogens), gonadotropin excess (testicular tumor), prolactin excess (hypothalamic or pituitary disease), drug-related (spironolactone, chlorpromazine, digitalis).
- Macroscopically, there is enlargement of the breast as a firm, raised, rubbery mass beneath the nipple.

VIII. ENDOCRINE PATHOLOGY

• The endocrine system consists of a highly integrated and widely distributed group of organs whose primary function is the control of homeostases.

• All peripheral endocrine glands (thyroid, adrenal, pancreas, sexual, parathyroid) are closely connected with each other as well as with the central endocrine glands (pituitary, epiphysis) and neuronal (hypothalamus).

• All diseases of the endocrine system are divided into 1) congenital, 2) acquired.

• They may be represented by:

1. Hypofuniction.
2. Hyperfunction.
3. Dysfunction.

• In this case, dystrophy, atrophy, dysplasia, sclerosis and tumors may develop.

• A practical classification of endocrine pathology is based on the damage of the main (primary) gland. The most frequent are endocrinopathy of:

4. Pituitary body.
5. Adrenal glands.
6. Thyroid gland.
7. Pancreas.
8. Parathyroid gland.
9. Sexual glands.

Diseases of pituitary body

Diseases of pituitary body may occur the symptoms of hyperpituitarism or hypopituitarism. **Hyperpituitarism** is characterised by oversecretion of one or more of the pituitary hormones due to the development of a hormone-secreting pituitary adenoma. The most frequent diseases of pituitary body associated with hyperfunction are Itsenko-Cushing disease, acromegaly, and gigantism.

1. Itsenko-Cushing disease.

Itsenko-Cushing disease occurs in adenomas from basophilic cells of anterior lobe of the pituitary or adenocarcinoma in rare cases. Increased ACTH production causes cortex hyperplasia as well as increased production of glucocorticoids.

It results in obesity of face and body, elevation of arterial pressure, diabetes mellitus, and sexual gland dysfunction. Osteoporosis, nephrolithiasis and chronic pyelonephritis may also develop.

The disease should be differentiated from Itsenko-Cushing syndrome. Its clinical manifestations (so called Cushingoid) are the same as in the disease (obesity of the upper part of the body), but the other signs are not clearly marked.

The causes of these states are adrenals damage (tumor of zona fasciculata), the administration of hormones (cortisole, prednisolone, hydrocortisone).

2. Acromegaly and gigantism

Excess of STH stimulates all mesenchymal derivatives (bones, cartilages,

connective tissue). If the disease occurs in adults, it is called acromegaly (the bones does not grow but ears, nose, lower jaw, feet and hands enlarge). The term «acromegaly» means increased growth of extremities.

If the disease occurs in prepubertal boys and gerls, it is called gigantism.

The other glands also involve by the process (goiter, atrophy of insulin apparatus of pancreas, thymus and epiphysis hyperplasia, adrenal cortex hyperplasia, sexual glands atrophy occur).

Hypopituitarism is characterised by less secretion of one or more of the pituitary hormones dueto destraction of the anterior lobe (by metastases, ischemic necrosis) and the development of a nonsecretory adenoma or others tumors. The most frequent diseases of pituitary body associated with hypofunction are hypophyseal nanism, cerebro-hypophyseal cachexia, and diabetes insipidus.

1. Pituitary dwarfism (nanism) develops in congenital hypoplasia of the pituitarybody or its necrosis in children. General underdevelopment of the organism with preserved proportions is observed.

2. Simmonds' disease (cerebro-hypophyseal cachexia) is caused by necrosis ofpituitary anterior lobe. It may occur after childbirth due to vascular embolism as well as due to syphilis, tuberculosis, and tumor. It manifests by cachexia, inner organ atrophy, and sexual dysfunction.

3. Diabetes insipidus is caused by tumors, inflammation, sclerosis, and trauma of the posterior lobe of pituitary. It manifests itself by increased urine excretion due to deficiency of Antidiuretic hormone.

Diseases of adrenal glands

• Adrenal glands consist of cortex and medullar substance. There are 3 zones in the cortex: glomerular zone which produces mineralocorticoids e.g. aldosterone, zona fasciculata which produces glucocorticoids, reticular zone which produces sexual hormones.

• The most frequent disease associated with hypoadrenalism is Addison's disease.

• In 1849 Addison described the so-called bronze disease, which develops in bilateral lesion of adrenal cortex with the development of acorticism (absence of hormones) or hypoadrenocorticosis.

• The causes of Addison's disease are divided into two groups:

1. One of them causes primary Addison's disease (genetic autoimmune disturbances).

2. Secondary Addison's disease is caused by metastases in the adrenal glands, amyloidosis, hemorrhage, tuberculosis; necrosis due to vascular thrombosis, damage of the pituitary body (decreases ACTH or corticotropin releasing factor).

Morphology

• Hyperpigmentation of the skin and mucous membrane due to excessive production of melanin stimulating hormone.

• Myocardial atrophy.

• Changes of the lumen in the aorta and large vessels.

• Hyperplasia of the cells of islets of Langerhans in the pancreas (hypoglycemia).

• Gastric mucosa atrophy.

• Hyperplasia of thymus and lymphatic peripheral tissue.

The cause of death:

• Acute adrenal failure.

• Cachexia (suprarenal cachexia).

• Cardiovascular insufficiency.

Diseases of the thyroid gland

Two significant functional disorders characterised by distinct clinical syndromes are discribed. There are: ***hyperthyroidism (thyrotoxicosis) and hypothyroidism (mixedema).***

Hyperthyroidism

Hyperthyroidism (thyrotoxicosis) is a hypermetabolic clinical and biochemical state byexcess production of thyroid hormones.

Many diseases may cause hyperthyroidism, but three most common causes are:

1. Graves' disease (diffuse toxic goitre).
2. Toxic multinodular goitre.
3. Toxic adenoma.

Less frequent causes are thyroiditis, metastatic tomors of thyroid, struma ovarii, congenital hyperthyroidism.

Goitre

Goitre is defined as thyroid enlargement caused by compensatory hyperplasia and hypertrophy of the follicular epithelium is response to thyroid hormone deficiency.

Goitre is classified according to their morphology and epidemiology, course, functional and clinical peculiarities.

I. According to the morphology goitre may be:

1. Simple goitre (diffuse nontoxic or colloid goitre).
2. Nodular goitre (multinodular goitre or adenomatous goitre).
3. Diffuse nodular (mixed).

II. According to the histology there are 2 types of goitre:

1. **Colloid.** Colloid goitre may be macrofollicular and microfollicular as well as mixed type. Itconsists of follicles. In case of epithelial proliferation the disease is termed proliferating colloid goitre, which is usually nodular.

2. **Parenchymal.** Parenchymal goitre is characterized by epithelium prolif-

eration with formationof small follicle-like structures without colloid. In the majority of cases the disease is diffuse.

III. According to the epidemiology goiter is classified into:

1. **Endemic.** Endemic goitre develops in the areas with iodine deficiency in the drinking water (the Urals, Siberia, Middle Asia, Switzerland). The thyroid gland has the structure of colloid or parenchymal goitre. The functional activity is decreased. In children, endemic cretinism may develop (physical and mental retardation).

2. **Sporadic.** Sporadic goitre manifests in young and old age. This may be colloid; diffuse ormixed. It does not influence the organism as a whole, but it can cause compression of the esophagus, trachea, larynx, etc. with disturbance of their function. This goitre may be the cause of Basedow's disease.

Graves' disease

• **Graves' disease** (or diffuse toxic goiter, Basedow's disease, primary hyperplasia,exophthalmic goitre)

• Diffuse toxic goiter is an autoimmune disease.

• Morphology: prismatic epithelium turns into cylindrical, epithelium proliferation with formation of papillae, colloid vacuolization, lymphoid plasmocytic infiltration of the stroma, formation of lymphoid follicles with germ centers are observed.

• In the other organs, hypertrophy of the left ventricle of the heart, serous edema and lymphacytic infiltration myocardial interstitial spaces develop (thyrotoxic heart). The outcome is diffuse interstitial sclerosis. In the liver, there is serous edema causing thyrotoxic liver fibrosis. Thymus enlargement causes lymphoid tissue hyperplasia and adrenal hypertrophy. Exophthalmus takes place.

•The causes of death are cardiac insufficiency and cachexia.

Hypothyroidism (mixedema)

Hypothyroidism is a hypometabolic clinical state resulting from inadequate production ofthyroid hormones of prolonged periods of, or rarely, from resistance of the periferal tissues tj the effects of thyroid hormones. The clinival manifestations of hyperthyroidism are divided to into group:

I. Cretinism or congenital hyperthyroidism.

It produces the clinical syndrome, which occurs a puffy face and enlarged tongue (coarse features), a protuberant abdomen, and delayed physical and mental developmental milestones. The main causes of cretinism are:

Untreated maternal hypothyroidism. This is now rare, due to better prevention, recognition and treatment of maternal hypothyroidism but it is still a problem in some areas of the world where endemic goiter due to dietary iodine deficiency is seen.

Inherited enzyme defect. This produces sporadic cretinism and is due to failure of normal T3 and T4 synthesis.

II. Myxedema

It is the adult hypothyroidism, which is due to reduced metabolic rate. The

term «myxedema» connotes non-pitting edema due to accumulation of hydrophilic micopolysaccharides in the ground substence of dermis and others tissues. There is progressive slowing of physical and mental activity, increasing lethargy and sensitivity to cold, puffy face, coarse dry skin, thinning of hair (particularly of the eyebrows), hoarseness and deepening of voice, and various internal abnormalities, particularly heart failure and a predisposition to hyperlipidemia and hypothermic coma.

The main causes of myxedema are:

Surgical ablation of the thyroid gland, which is usually as a result of total thyroidectomy for malignant disease, or aggressive subtotal thyroidectomy for hypothyroid Graves' disease.

Hashimoto's thyroiditis. Some drug e.g. lithium.

Thyroiditis

Thyroiditis is classified into the following types: 1. Hashimoto's thyroiditis.

2. Infectious thyroiditis.

3. Granulomatous thyroiditis (de Quervain's thyroiditis or giant cell thyroiditis).

4. Riedel's thyroiditis (or invasive fibrous thyroiditis, Riedel' struma).

Hashimoto's thyroiditis

Hashimoto's thyroiditis is a destructive autoimmune thyroiditis leading to hypothyroidism. It is most common in middle age, affecting women more often than men, a good example of organ-specific autoimmune disease.

The following autoantibodies against different thyroid cell antigens are detectable in the sera of most patients:

1. Thyroid microsomal thyroiditis.

2. Thyroglobulin autoantibodies.

Morphology

• Two varieties of Hashimoto's thyroiditis are seen: classic from (more common), and fibrosing variant (only 10 % cases).

• Macroscopically, the classic form is characterised by diffuse, symmetric, firm and rubberyenlargement of the thyroid which may weigh 100–300 gm. Sectioned surface is fleshly with accentuation of normal lobulations but with retained normal shape.

• Microscopically, the classic form shows the following features:

• There is extensive infiltration of the gland by lymphocytes, plasma cells, immunoblasts and macrophages, with formation of lymphoid follicles having germinal centres.

• There is decreased number of thyroid follicles, which are generally atrophic and are often devoid of colloid.

• The follicular epithelial cells are transformed into their degenerated state

termed **Hurthle cells (Askanazy cells).** These cells have abundant oxyphilic or eosinophilic and granular cytoplasm due to large number of mitochondria and may cantain large nuclei.

• There is slight fibrous thickening of the septa separating the thyroid lobules.

• Hashimoto thyroids proceed to primary atrophic thyroiditis or lead to carcinoma.

Riedel's thyroiditis

• Riedel's thyroiditis is characterised by stony-hard thyroid that is densenly adherent to the adjacent structures in the neck.

• The etiology is inknown.

• Macroscopically, the thyroid gland is contracted, stony-hard, assemetric and adherent to the adjasent structures. Cut section is hard and devoid of lobulations.

• Microscopically: extensive fibrocollagenous replacement, atrophy of thyroid tissue, locally scattered lymphocytic infiltration and invasion of the adjusent muscle by the process.

Diabetes mellitus

Diabetes mellitus is a chronic clinical syndrome characterised by hyperglycemia due todeficiency or defective response to insulin.

This is classified into:

1. ***Spontaneous diabetes mellitus*** is an independent disease and can be of 2 types:

— Type I (insulin- dependent).

— Type 2 (insulin-independent).

2. ***Secondary diabetes*** may occur in pancreatic diseases, acromegaly, Itsenko-Cushing disease, and complicated genetic syndromes, at administration of some «drugs».

3. ***Diabetes of pregnant*** occurs during pregnancy.

4. ***Latent (subclinical) diabetes*** is not evident.

Etiopathogenetic factors:

• Genetically determined disturbances of the number and structure of beta-cells.

• Environmental factors, which disturb beta-cell nutrition (bacteria, viruses, autoimmune reactions), increase of activity of adrenergetic nervous system.

• Risk factors of different kinds of spontaneous diabetes are different.

Pathogenesis

Insulin insufficiency increases blood glucose amount because cellular

membranes are closed for glucose — hyperglycemia and glucosuria develop. Considerable amount of sugar is formed from the fats and proteins causing hyperlipidaemia, aceton- and ketonemia.

Morphology

- The pancreas is diminished with lipomatosis and sclerosis.
- Degeneration and hyalinosis are observed in the islets, some of them are hypertrophic.
- The liver is enlarged, glycogen is absent, fat degeneration is observed.
- Diabetic macro- and microangiopathy is seen in the vessels.
- Macroangiopathy is arterial atherosclerosis.
- Microangiopathy is characterized by plasmatic saturation, hyalinosis, and sclerosis with lipohyalin.
- Vasculitis takes place.
- There is generalized microangiopathy in the kidneys, retina, skeletal muscles, digestive tract mucosa, pancreas, brain, and nerves.
- In the kidneys, diabetic glomerulonephritis and glomerulosclerosis develop.
- Microscopically proliferation of mesangial cells in response to mesangium clogging with «ballast» metabolic products and immune complexes are observed. Mesangium hyalinosis and glomerulosclerosis take place.
- Diabetic glomerulosclerosis may be diffuse and nodular as well as mixed type. Its clinical manifestations are Kimmelstiel-Wilson syndrome (proteinuria, edema, increased arterial pressure).
- In the lungs, lipogranulomas consisting of macrophages and gigantic cell of foreign bodies are present in the walls of the arteries.
- In the spleen, liver, lymphatic glands: infiltration of brstiomacrophagal system and skin with cell lipids (xantomatosis) develop.

Complications:

- Diabetic coma.
- Accompanied with macroangiopathy: gangrene of extremities, myocardial infarction.
- Diabetic nephropathy (acute and chronic renal failure).
- Diabetic retinopathy is a leading cause of blidness.
- Infectious sepsis.
- The death is caused by coma, diabetic glomerulosclerosis, gangrene.

IX. PRENATAL PATHOLOGY

- The period of fetus development beginning with the moment of fertilization to the birth of the child is called **Prenatal period.**
- Duration of the prenatal period is 40 weeks (280 days) or 10 lunar months

or 9 calendar's months.

• Fetal pathology, which occurs in this period, is called **prenatal pathology**.

• The case of fetal death before the 14th week of gestation is called **abortion** that within the period of 14–22 weeks is called **late abortion**. If the fetus dies on the 22nd week or later (until the delivery or during it), the case is called **mortinatality.**

• The normal and pathologic development and growth can be divided into the following stages:

1. Progenesis is characterised by gametogenesis, i.e.formation and maturation of the gametes. It stageoccurs before the fertilization of the ovum. *Pathology of gametogenesis is called gametopathy.*

2. Development after fertilization is called **kymatogenesis.** This intrauterine phase can be divided into:

a) **Blastogenesis** from Day 1 to Day 15 of gestation. Pathology of blastogenesis iscalled ***blastopathy.***

b) **Embryogenesis** from Day 16 to the end of the 3rdmonth (75thday). Pathology ofembryogenesis is called ***embryopathy.***

c) **Fetogenesis** from the 4rd month of gestation to delivery (from 76th to 280th day).Pathology of fetogenesis is called ***fetopathy.***

Gametopathy

• Gametopathy is an injury of formation and maturation of the gametes during ovo- and spermatogenesis until fertilization.

• Gametopathy occurs in gene mutations and chromosomal aberrations. At present about 150 autosomal recessive genetic defects and 200 defects with autosomal dominant inheritance are known. There are also defects connected with sex X chromosome.

• Chromosome mutations are called **chromosomal aberrations**. Virtually all the chromosomal syndromes are characterized by congenital anomalies.

• Genetic injuries in origin can be deviled into three groups:

a) Those associated with karyotypic aberrations.

b) These arising in single gene mutations.

c) Those suspected of resulting from multifactorial inheritance, a term that implies the interaction of two or more genes of small effect with environmental factors.

• The most frequent is trisomy 21 (Down syndrome) and trisomy 13 (Patau's syndrome), trisomy 18 (Edward's syndrome), Klinefelter's syndrome, Turner's syndrome.

Down's syndrome

• **Down syndrome** is the most common of the chromosomal disorders and a major cause ofmental retardation.

• The risk of the development of Down syndrome increases with maternal age.

• It is a disorder associated with autosomes.

• Trisomy 21 type — 47XXC2 or 47XXYC1. The majority of cases of Down's syndrome are due to nondisjunction of maternal meiosis.

• Currently more than 80 % survive to age 30 or beyond.

• The most causes of death are interrcurrent infections or cardiac insufficiency.

• **Gross appearance:**

Short stature.
Muscle hypotonia.
Hyperflexibility of joints and lack of Maro reflex. Short crooked fifth finger.
Short broad hands with a single simian crease on the palm. Flat facial profile.
Low-bridged nose. Dysplastic ears.
Reduced interpupillary distance. Oblique palpebral fissures.
Epicanthic folds.
Brushfield spots (the iris may be speckled).
The mouth is often open and protruding tongue.

• **Clinical significances:**

Mental retardation is usually severe. Low intelligence.
May be leukemia.
Patients with Down syndrome have abnormal immune responses that predispose them to serious infections, particularly of the lungs.
Virtually all patients with trisomy 21 older than 40 years of age develop neuropathologic changes characteristic of Alzheimer disease, a form of senile dementia.
Thyroid dysfunction: hyperthyroidism, goiter, and hypothyroidism. Congenital heart defects.
Gastrointestinal anomalies.

Edward's syndrome

• Trisomy 18E – 47XXE or 47XYE.

• May die in the neonatal period, and the majority do not survive beyong 1 year.

• Survivors have severe mental retardation and failure to thrive.

• **Characteristics:**

Hypertonicity.
Prominent occiput.
Micrognathia and low-set ears.
Flexion of fingers (index over third). Short sternum and small pelvis.
Abnormalities of the hips and feet (syndactyly), rocker-bottom feet.
Cardiac defects: patent, ductus arteriosus and interventricular septal defects. Renal malformations.
Meckel's diverticulum.
Absence of the corpus callosum and incomplete development of the cerebellum.

Patau's syndrome

• Trisomy 13D — 47XXD or 47XYD occurs at frequency of 1 in 20000 births.
• Most children die in the first month, and those who survive have severe mental retardation.

• **Characteristics:**

Microphaly and archinencephaly. Scalp defect.
Coloboma of the iris. Microphtalmos.
Anophtalmos. Cleft palate. Hair lip.
Polydactyly.
Hemangiomas of the head. Neck and lower back.
Rocker-bottom feet.
Apneic spells and myoclinic seizures.
Cardiac dextraposition and interventricular septal defect.
Extensive visceral defects: polycystic of kidneys, ectopia of spleen into pancreas; double uterus and vagina.

Turner's syndrome

• It is gonadal dysgenesis (defective second X chromosome — 45 X0).

• **Somatic anomalies:**

Short stature.
Primary amenorrhea. Webbing of the neck.
Cubitus valgus (an increase in carrying angle of the arm). Shield — like chest with widely spaced nipples.
Coarctation of the aorta.
Webbing of the digits or of the axillae. Senile facies.
High-arched palate. Low-set ears.
Peripheral lymphedema at birth. Pigmented nevi.
Low posterior hairline.
Uterus, ovarium and fallopian tubes are infantile. Secondary sex characteristics are absent.

• **Characteristic laboratory and morphologic findings are:**

Negative sex chromatin test.
Ovaries are replaced by white «streaks» of fibrous stroma devoid of follicles. Reduced levels of ovarian estrogenes.
Increased gonadotropin.

• **Clinical significans:**

It is an important cause of sterility in the female. Normal intelligence.

Blastopathy

• Blastopathies occur during the first 15 days from the moment of fertilization.
• The most frequent cause of blastopathy is chromosomal aberration in

combination with harmful effect of environmental factors.

• **Manifestations of blastopathies** are different:

a) Superficial or deep implantation of blastocyst (causes defects of development, shape, localization of placenta).

b) Disturbance of embryo orientation (umbilical-cord defects are the most frequent).

c) Empty embryo sacs (blastocytes without an embryo).

d) Double malformations are reduplicated embrional primordial that are either primary or the result of later devision. They may be independent of each other, i.e. they may be connecting only by the placenta or the umbilical cord, or they may be in direct bodily contact. Usually they cannot live.

• ***Double malformations may be free and conjoined:***

I. Free double malformations are designated as twins (gemini). They may be identical and fullydeveloped (monosigotes twins), or they may be malformed. ***Holocardius Acephalus*** is the most frequent of the free double malformations in which only the trunk and lower extremities are clearly identifiable, while the head is absent.

II. Conjoined double malformations occur:

1. Asymmetric (parasitic) or heteropagus (one of the twins is underdeveloped).Asymmetrical double monsters have one well developed and one rudimentary or hypoplastic twin. The rudimentary twin is always abnormal, and is either externally attached to or internally included in the body of the better-developed sibling *(fetus infetu).* Some of the congenital teratomas, especially those in the sacrococcygeal area, areactually asymmetrical monsters. *Teratomas* are regarded as asymmetric monsters.

2. Symmetric forms or diplopagus represent two equally well developed embrionalprimordial that are connected to each other by a partial fusion of tissues. *They may be:*

a) Incomplete individuals result from extensive fusion i.e., there is only anincomplete reduplication of the body axis. This type of malformation includes the dicephalus (to spinal columns but only one pelvis).

b) Complete symmetrical double malformations show a partial fusion betweentwo generally mature fetuses. The important feature is the reduplication of the body axis (head, trunk, or spinal column). It is called cephalopagus, diprosopus (reduplication of the face), craniopagus, thoracopagus, and ischiopagus («Siamese twins»).

Embryopathy

• Embryopathy is a pathology developed within the period of 16–75 days and occurs by the development of the congenital malformations.

Congenital malformations are morphologic defects that are present at birth, although theymay not become clinically apparent until later in life. The term congenital does not imply or exclude a genetic basis for malformations. It is estimated that about 3 % of newborns have a major malformation, defined as a malformation having either cosmetic or functional significance.

Pathologic development is connected with the termination period in which the causative agent acts. Each organ has its own period of teratogenic factor action. This period is called teratogenic termination period.

Causes of the congenital malformations

I. Environmental influences, such as viral infections, drugs, and irradiation, to which the mother was exposed during pregnancy, may induce malformations in the fetus and infant.

TORCH infections are caused by Toxoplasma (T), rubella (R), cytomegalovirus (C), herpesvirus (H), and a number of other (O) bacterial and viral agents. The latter include fever, encephalitis, chorioretinitis, hemolytic anemia, hepatosplenomegaly, pneumonitis, myocarditis, and vesicular/hemorrhagic skin lesions. Such infections, occurring early in gestation may also cause chronic sequelae in the child, including growth and mental retardation, cataracts, congenital cardiac anomalies, and bone defects.

A variety of drugs and chemicals have been suspected to be teratogenic. The list includes thalidomide, folate antagonists, androgenic hormones, alcohol, anticonvulsants, warrafin (oral anticoagulant).

Radiation.

II. Genetic factors.

Any congenital defect may manifest as one of the following changes:

Agenesis is the complete absence of an organ pri-mordium.

Aplasia is absence of the organ coupled with persistence of the organ anlage or a rudimentthat never developed completely.

Hypoplasia refers to reduce size due to the incomplete development of the organ.

Dysraphic anomalies are defects caused by failure to fuse. Spina bifida is an anomaly inwhich the spinal canal has not closed completely and the overlaying bone and skin have not fused, thus leaving a midline defect.

Involution failures are defects due to the persistence of embryonic or fetal structures thatshould involute at certain stages of development.

Division failures are defects caused by incomplete cleavage, when that process depends onthe involution and programmed death of cells. Fingers and toes are formed at the distal end of the limb bud through programmed death of cells between the primordia that contain the cartilage. If these cells do not die in a predetermined manner, the fingers will be conjoined or incompletely separated («syndactyly»).

Atresia refers to defects caused by incomplete formation of a lumen. Many hollow organsoriginate as strands and cords of cells, the centers of which are programmed to die, thus forming a central cavity or lumen. Atresia of the esophagus is characterized by partial occlusion of the lumen, which was not fully established in embryogenesis.

Dysplasia is a defect caused by abnormal organization of cells into tissues, a situation thatresults in abnormal histogenesis.

Ectopia or heterotopia is an anomaly in which an organ is outside its normal anatomicalsite. Thus, ectopic heart is located outside the thorax. Heterotopic parathyroid glands can be located within the thymus in the anterior mediastinum.

Classification of congenital defects

1. According to the character of involvement.
Isolated (one organ).
Systemic (several organs of one system).
Multiple (in different organs and systems).
2. According to localization.
Central nervous system. Cardiovascular system. Alimentary tract.
Urinary system, etc.

Central nervous system, and cardiovascular system are most frequently involved because these systems have the longest teratogenic terminal period, from the 18th day to the 50th day.

Malformations of the nervous system

I. Errors of fusion

1. **Craniorachischisis** totalis due to failure closure of the neural tube the convexity of the skull isabsent and the spine is represented only by it's bodies with no posterior covering.

2. **Spina bifida occulta** due to the failure of closure of the sacral bones (rachischisis):

a) Meningocele, diverticulum — like bulging of an arachoid sac filled with clear spinalfluid.

b) Meningomyelocele in which the arachnoidal sac also contains parts of the spinalcord, the cauda equna or the area medullovasculosa (see above), which protrudes because of the accumulation of fluid.

c) **Meningomyelycystacele or syrengomyelocele**, a combination of meningocele andhydromyelia (ballooning of the spinal cord due to a hydrophic accumulation of the fluid in the central canal).

3. Anencephally is an absence of the cranial vault (acrania) and of the brain (anencephaly) and a short neck.

4. Microcephaly is decrease of the brain's size.

5. Amyelia, or total aplasia of the spinal cord.

6. Diplomyelia (Each half of the spinal cord develops separately over many segments).

7. Diastematomyelia (each half has only one dorsal and one ventral horn with a intervening cystic cavity to represent the central canal).

8. Arnold-Chiari malformation is a group of different combinations (the full deformity is a herniation of the posterior cerebellum, the medulla and the fo-

ramen magnum, with an added sharp curvature of the neuraxix at the cervicomedullary junction).

9. Congenital stenosis of the aqueduct.

10. Cyclopia (one eye in the middle of a deformed forehead).

11. Arrhinencephaly (the olfactory buld and tracts are absent in the mildest form of the disorder).

12. Agenesis of the corpus callosum is a component of arrhinencephaly.

13. Hydrocephalus is meant an increased amount of cerebrospinal fluid in the ventriculosubarachnoid pathways of the brain.

II. Errors of migration (Heterotopies, Ectopias)

1. **Status verrucosus** is a wart-like appearance of the cortex produced by a disorderlyarrangement of the neuroblasts so that fissuration and sulcation are irregular and unpredictable.

2. **Pachygyria** is the appearance of large gyri in the cortex due to inadequate differentiation ofsulci.

3. **Microgyria** (secondary fissures are lacking).

Congenital malformations of the heart

Congenital malformations of the heart represent structural changes that originate during the development of the septa and the rotation of the arterial heart, during the first 3 months of gestation.

Congenital heart defects are the most common forms of heart disease in children. They occur in about 1 % of neonates and in 18 % of spontaneous aborted and stillborn fetuses.

Most defects manifest themselves within the first year of life, such as large ventricular septal defects and tetralogy of Fallot.

Others, like bicuspid aortic valve, remain silent until middle age, when degenerative changes of the abnormal valve cause stenosis.

Still other defects, like a small ventrical septal defects (VSD) or patent foramen ovale may never cause any difficulty at all.

The most important malformations are:

I. Septal defects

Patent foramen oval (Atrial septal defect). Ventricular septal defects (Roger's disease).

Complete absence of the ventricular septum, with or without septal defect (cor bilocular or cor triboculare

II. Transposition defects

Dextraposition of the aorta (Eisenmenger's syndrome, tetralogy Fallot). Dextraposition of the heart.

III. Stenoses

Tricuspid stenosis or atresia. Pulmonary stenosis.

Mitral stenosis or atresia. Aortic stenosis or atresia. Aortic coarctation.

IV. Valvular insufficiency

Congenital tricuspid insufficiency (or Ebstein's anomaly). Congenital mitral insufficiency.

V. Persistent fetal vessels

Patent ductus arteriosus (with many congenital cardiac defects).

Anomalies of the pulmonary veins include openings into the superior or inferior vena cava or the coronary sinus.

VI. Combined heart defects

A.**Trialogy of Fallot** consists of
Ventricular septal defect.
Stenosis or atresia of the pulmonary outflow tract.
Right ventricular hypertrophy.

B. **Tetralogy of Fallot** consists of:
Stenosis or atresia of the pulmonary outflow tract.
Ventricular septal defect.
Aorta overriding the right ventricle (aorta dexraposition).
Right ventricular hypertrophy.

C. **Pentalogy of Fallot** consists of:
Ventricular septal defect.
Stenosis or atresia of the pulmonary outflow tract.
Hypertrophy of the right heart.
Aorta dexraposition.
Defect of interatrial septum.

Classification anomalous development of the heart (by Ebbott)

I. Acyanotic shunt (left-right):
1) Patent ductus arteriosus.
2) Atrial septal defect.
3) Ventricular septal defect (Roger's disease).

II. Cyanotic shunt (Right-left):
1) Tetralogy of Fallot.
2) Eisenmenger's complex (variant of the tetralogy of Fallot).
3) Transposition of great vessels.

III. No shunt
1) Coarctation of the aorta.
2) Aortic stenosis.

Examplies of some heart defects

Patent ductus arteriosus (PDA)

• Before birth the ductus arteriosus (DA) is the only route by which blood in the right ventricle (RV) can reach the systemic circulation.

• The DA is located superior to the bifurcation of the pulmonary arteries and enters the aorta just distal to the left subclavian artery. It is invested with

spirals of smooth muscle, which contract at birth in response to high tension (coming from the newly aerated lungs). Within a day or two, the DA is usually functionally closed.

• Not infrequently and often in premature infants, the DA fails to close, hence a PDA. With the drop in pulmonary arterial pressure, which occurs following lung inflation after birth, blood shunts from the aorta across the PDA and into the main pulmonary artery.

• The RV responds to increased flow and pressure with either dilatation (congestive heart failure) or hypertrophy.

• If pulmonary resistance exceeds systemic resistance (due to hypoplastic lungs, for instance), blood is shunted right-to-left and cyanosis may ensue.

Atrial septal defects (ASD)

• The most common ASD is a secundum ASD or ASD II. A secundum ASD means that the ASD is reminiscent of the ostium secundum i.e., the ostium secundum is not covered over. An ASD II may form in any of four ways:

1. Deficient formation of septum primum.
2. Deficient formation of septum secundum.
3. Combination of both.
4. Dilation of the atria, thereby pulling septum primum and septum secundum apart.

• After birth, the blood shunts from left to right atrium. This shunt may be large if the septal defect is large.

• In atrial septal defects, the pulmonary artery pressure falls to normal or near normal levels soon after birth. However, the resulting atrophy of the right ventricle makes this chamber more distensible than the left ventricle.

• With a sizable atrial defect, pressures in the two atria are similar and the right ventricle fills more easily than the left.

• Consequently, not only does the vena caval blood enter the right ventricle but also much of the pulmonary venous blood from the left atrium enters the right ventricle as well.

• Pulmonary blood flow is greatly increased while oxyhemoglobin saturation in the systemic arterial system is normal.

• The pulmonary arterial bed responds to this «over circulation» with smooth muscle hyperplasia and hypertrophy.

• If the septal defect is operatively closed at this stage, the pulmonary arterial muscle will atrophy and a normal circulatory pattern will be established. If a large defect is not closed in time, diastolic overloading of the right ventricle continues and both the right ventricle and atrium dilate and hypertrophy.

• Left ventricular output is usually near normal so that these infants develop normally.

• Over the course of several decades, pulmonary vascular obstruction takes place within the pulmonary arterial bed.

• This progressively narrowed bed offers greater and greater resistance to pulmonary blood flow. Resistance in the pulmonary arterial bed may eventually equal or exceed that in the systemic bed.

• When this occurs, shunts are reversed and cyanosis appears or becomes more prominent.

• If the normal cardiac anatomy is now restored through surgery, such patients will develop right-sided cardiac failure since the right ventricle is incapable of forcing all of the caval blood through the restricted pulmonary vascular bed.

Ventricular septal defects (VSD)

• These are the most common of the cardiac defects. The ventricles are separated by the growth of the muscular septum and by the growth and fusion of the endocardial cushions near the atria. VSD's can be located near the atrioventricular valves or nearer to the apex (i.e. tip) of the heart.

• Before birth, VSD's are of little consequence since the pulmonary arterial pressure is equal to the systemic pressure and thus, most of the blood enters the systemic circulation.

• After birth, VSD's may be of little consequence if they are small. But, if they are large, they allow significant left-to-right shunting, since now (after birth) the pulmonary (right) pressure is lower than the systemic (left) pressure.

• Thus, the pulmonary vascular bed is faced with abnormally high pressures, as is the RV. The pulmonary vessels become thicker by undergoing smooth muscle hyperplasia/hypertrophy.

• The RV may also hypertrophy. These changes reflect the presence of pulmonary hypertension.

• Because of this left-to-right shunting, pulmonary blood flow may be greatly increased, leading to pulmonary congestion, edema, hemorrhage, pneumonia and congestive heart failure.

• After a long time, pulmonary pressure may equal or even exceed systemic resistance. In the latter situation, blood shunts from right-to-left, resulting in cyanosis.

Common atrioventricular canal (CAVC)

• In this cardiac malformation, the endocardial cushions fail to separate the atrioventricular canal into right and left sides.

• Because the atrioventricular valves (mitral and tricuspid) are also formed by the endocardial cushions, they are malformed as well.

• Thus, blood from the right atrium (RA) and the left atrium (LA) enters into a common, undivided atrioventrical (AV) canal above the incompletely divided RV and left ventricle (LV). Much mixing of blood occurs.

• This defect is commonly associated with Down's syndrome (Trisomy 21).

Transposition of the great arteries (TGA)

• This is a fairly common defect and it is important to recognize it early since surgical correction is possible and successful.

• It is thought to be due to abnormal development of the conal muscle beneath the two semilunar valves.

• In this defect the aorta arises from the right ventricle and the pulmonary artery arises from the left ventricle. In utero, this defect causes no trouble, since venous blood (from the placenta) is oxygenated.

• After birth, however, the pulmonary and systemic circulations are disconnected.

• Venous blood enters the RA, then the RV and then out the aorta. Pulmonary venous blood enters the LA, then the LV and then out the pulmonary arteries back to the lungs.

• Survival is dependent on any kind of mixing of oxygenated and unoxygenated blood whether through an ASD, a VSD or a patent ductus arteriosus.

• Whatever mixing of the two systems there is, it is usually inadequate and these neonates have marked cyanosis.

• If the communication between the two circulations is adequate for oxygenation, then problems of cardiac failure and pulmonary hypertension will inevitably develop.

Combined heart defects:

Tetralogy of Fallot

• It was Etienne-Louis Arthur Fallot in 1888 who well described this form of cyanotic heart disease. Fallot did not actually coin the term, «tetralogy of Fallot». He used the term la maladie bleu, i.e., the blue disease. It was E. Maude Abbott who first used this term tetralogy of Fallot in 1924.

• What comprises tetralogy of Fallot?

1. Stenosis or atresia of the pulmonary outflow tract.
2. Ventricular septal defect.
3. Aorta overriding the right ventricle.
4. Right ventricular hypertrophy.

• Actually, the basic abnormality is underdevelopment of the subpulmonary cone of muscle (conus), resulting in stenosis/atresia of the pulmonary outflow tract.

• This underdevelopment of the conus results in malaligament of a band of muscle (the parietal band) that lies beneath the pulmonic valve.

• In tetralogy, this band of muscle shifts anteriorly, superiorly and to the left, which obstructs the pulmonary outflow tract. This opens up a «hole» in the interventricular septum (hence a VSD).

• With this leftward shift, the aorta is «looking down into» the RV (hence an «overriding» aorta).

• Finally, with the narrowed pulmonary outflow tract, there is obstruction (hence right ventricular hypertrophy).

• The VSD also contributes to right ventricular hypertrophy.

• So, in essence, Fallot's congenital anomaly could be called «monology of Fallot» with the single underlying abnormality being an underdeveloped conus resulting in a stenotic or atretic pulmonary outflow tract. The other three abnormalities are a result of this one abnormality.

The degree of cyanosis depends on the degree of pulmonary outflow obstruction. This obstruction can be at the level of the pulmonic valve or in the right ventricle just beneath the pulmonic valve.

The right ventricle hypertrophies, in response to the increased resistance and because of the large VSD. With severe right ventricular outflow obstruction, right to-left shunt occurs across the VSD and the patient suffers from severe cyanosis.

Surgical repair is now highly effective; complete repair usually being done within the first two years of life.

Despite the nearly unbelievable variety of cardiac malformations that are possible, the net result of these abnormalities can be reduced to a mercifully short list of clinical signs and symptoms.

Congenital anomalies of the kidneys and the lower urinary tract

- Agenesis.
- Hypoplasia.
- Displacement.
- Polycystic kidney disease.
- Horseshoe kidney.
- Accessory (Additional) kidneys.
- Reduplication of the urachus.

Congenital anomalies of the genital system

I. Male:
- Phimosis.
- Hipospadias and epispadias.
- Cryptorchidism.

II. Female:
- Septate uterus.
- Double uterus with double cervix.

Congenital anomalies of the gastrointestinal tract

- Agenesis (esophagus, intestinum).
- Atresia.
- Fistulous tract of the esophagus with the trachea or main stem bronchi.
- Stenosis.
- Megaesophagus.
- Diaphragmatic Hernias.

• Pyloric stenosis.
• Meckel's Diverticulum.
• Megacolon (dilation of bowel) in **Hirschprung's disease**. Hirschsprung's disease results from a failure of migration of neuroblasts that form the myenteric plexus. In all patients, ganglioncells are absent in the region of the anorectal junction. The result is intestinal obstruction in affected neonates. The incidence is 1 per 5000 live births.

Congenital Cystic liver disease:

• Agenesis, hypoplasia, hyperplasia, total reduplication of the qallbladder.
• Ectopia of the pancreas.

Congenital anomalies in the face (8th to 10th week of the embryonal period)

1. Lateral facial clefts:
a) cheiloschisis or cleft lip (limited to the upper lip).
b) gnathoschisis (extend to the maxilla).
c) palatoschisis (extend to the hard palate).
2. **Median facial clefts** may also be limited to the upper lip, maxilla, or palate. The nose is troguentlyflat due to the aplasia of the vomer.
3. **Oblique facial clefts** extend from the upper lip to the corner of the eye.

Congenital malformations of the bone-cartilage system

• Hondrodysplasias is characterized by the shortening and thickening of the legs.
• Achondroplasia is a derangement in epiphyseal cartilaginous growth resulting in dwarfism.
• Hondrodysplasia of fetus (lethal micromelia):
a) Chondrodysplasia.
b) Increase of the head.
c) Open mouth.
d) Saddle-like nose.
e) Thickening of the tongue.
f) Short neck.
g) Hypoplasia of the thorax and lungs.
h) Thickening of vertebra.
• Sirenomelia. The term comes from «siren» or «mermaid» because of the characteristic fusion of the lower extremities that results from a failure of normal vascular supply from the lower aorta in utero.
• Aplasia (Amelia) of legs.
• Phocomelia is underdevelopment of the proximal parts of legs, when the foot and arm growth from trunk.
• Polyductyly is a malformation consisting of supernumerary finger development.
• Syndactyly is partial or complete fusion of several fingers.

Defects of placental development

• Placental hypoplasia (normal mass is 0.5–0.7 kg), placenta/fetus ratio is 1/5–1/7. When the mass of the placenta decreases, fetus hypoplasia develops.

• Defects of placenta localization are marginal and central placenta presentation in respect to internal uterus orifice. This develops as a result of Mastopathy, its causes are unknown, and it presents a risk of placenta detachment during the delivery and intranatal death of the fetus.

• Defects of placenta detachment are placenta adhesion (caused by deep implantation of blastocyst). The placenta does not detach after the delivery. Hemorrhage may occur.

• Placenta abruption. This occurs at extragenital and genital maternal pathology. It may result in intranatal fetus asphyxia.

• Umbilical cord defects (its normal length is 0.5–0.7 m). If the length is less than 0.5 m, the cord is short, more than 0.7 in it is long.

• Disturbance of the umbilical cord attachment to the placenta:

1. Central and eccentric are normal types of attachment.

2. Membranous is pathological one, when the umbilical cord is attached to the membranes, its vessels may be compressed with the parts of the fetus and amniotic fluid, which may cause their rupture, ante-, and intranatal fetus death may occur.

• Amnion development defects: — hydramnion (2000 ml and more), oligoamnios (500 ml and less).

Fetopathy

• Fetopathy is characterised by the combination of the impairment of tissue morphogenesis and reactive processes.

• In early period the impairment of tissue morphogenesis predominates.

• In late period the reactive processes such as the disturbance of the blood circulation, degenerations, necrosis, inflammation, presence of immune reactions, compensative and adaptative processes, regeneration.

• Fetopathies may be infectious and non-infectious.

Infectious fetopathies

• Infectious fetopathies can be connected with the influence of viruses and bacterium.

• Inflammation in placenta takes place.

• Pathologic morphology of fetopaties:

a) Necrosis of parenhymatous organs and brain (rubella, cytomegaly, chickenpox, toxoplasmolis).

b) Formation of granulomas (syphilis, tuberculosis).

c) Hemorrhagic syndrome.

d) Immune reactions.
e) Hepato- and splenomegaly.
f) Jaundice.
The main infectious fetopathies are cytomegaly and congenital toxoplasmosis.

Cytomegaly

• **Cytomegaly** (from cytos — cell and megaios — large) is a virus infection involving salivaryglands. The disease is characterized by formation of giant cells with intranuclear inclusions.

• Generalized form of infection develops in the newborns. DNA-containing virus enters the organism of the fetus from the mother through the placenta.

• Generalized infection in children is characterized by central nervous system (CNS) involvement, which is not observed in acquired cytomegaly. Encephalitis with formation of cytomegalic cells, perivascular infiltration and calcinosis foci in the subependymal zone are observed in children. These phenomena cause hydrocephalia.

• Cytomegalic cells contain intranuclear formation resembling **«owl's eye».** They can be found in the lungs, kidneys, liver, intestine, pancreas, adrenal gland, and thymus.

• Hemorrhages and necroses can also be observed in these organs.

• The disease lasts several days (sometimes weeks). It ends with death caused by damage to vitally important organs.

Congenital toxoplasmosis

• **Congenital toxoplasmosis** is a disease caused by toxoplasma. It develops as a result ofhematogenic transfer from the mother's organism.

• Toxoplasma is a protozoic microorganism from tripanosomid family. The source of human infection is dogs and cats. The fetuses are infected through the maternal placenta.

• During teratogenic termination period, embryopathy incompatible with life occurs.

• Early period is characterised by microcephalia of brain, porencephalia with gliosis (consolidation of the remained brain tissue) and calcinosis. Microscopic examination demonstrates cysts filled with granular spheres.

• Late period occurs the foci of necrosis, and calcinosis in the brain, pseudocysts and free parasites, encephalitis in the whole brain, meningopathy, ependymatitis, and hydrocephalus. Productive necrotic rhinitis and uveitis in the retina. Generalized form: besides GNS involvement there is hepato- and splenomegaly, jaundice, ulcers of the intestine, myocarditis, interstitial pneumonia. Microscopic examination demonstrates erythroblastosis in the liver and spleen, necrosis, calcinosis and lymphohistiocytic infiltration in the liver, myocardium, kidneys, cholestearosis in the liver.

• Outcome: death of fetuses and newborns or complication (paralysis, mental retardation, hemorrhage).

Noninfectious fetopathies

• The main noninfectious fetopathies are hemolytic disease of the newborn, fetal mucoviscidosis, fibroelastosis of myocardium and diabetic fetopathy.

• Early fetopaties occur by the isolated congenital defects (pylorostenosis, megacolon, megaloureter, agenesia, cystosis) and systemic congenital defects of the bone and muscular tissues, skin.

Diabetic fetopathy

• Diabetic fetopathy is the disease of the fetus due to maternal prediabetes and diabetes.

• As a rule, the body mass is 4–6 kg.

• The skin is purple cyanotic with small point hemorrhages, the neck is short, and the face as well as the soft tissues of the back and chest are swollen.

• The signs of immaturity are observed in the mature fetus.

• Hepatomegaly and cardiomegaly can be seen.

• Microscopic examination demonstrates hypertrophy of islets of Langerhars, increased amount of B-cells, fat degeneration of the liver, glycogen accumulation in the tubular epithelium in the kidneys, hydropic degeneration of the myocardium.

• During the delivery of the child with fetopathy, hypoxia due to placenta vascular sclerosis and disturbance of placental circulation may occur.

• Hyaline membrane disease may develop because synthesis of surfactant is disturbed due to disturbed lipid exchange (lipoproteid).

The death is caused by antenatal and intranatal asphyxia, respiratory insufficiency, birth injury, and hypoglycemia after birth stress.

Cystic fibrosis (Fetal mucoviscidosis)

• A disorder of exocrine glands, affecting both mucus-secreting and eccrine sweat glands throughout the body, leading to viscid mucinous secretions and obstructive disease in lungs, pancreas, liver.

• A simple autosomal recessive syndrome; heterozygotes are unaffected.

• The mutant gene may code for abnormal protein that affects chloride transport channels across epithelial membranes.

• General morphologic feature: obstruction by viscous mucoid secretions.

• Pancreas: plugging and dilatation of ducts, atrophy of acini, and progressive fibrosis.

• Liver: bile ducts plugged by mucus with biliary obstruction and fibrosis.

• Lung: Obstruction and secondary infection of air passages, hyperplasia and hypertrophy of mucus -secreting cells.

• Salivary glands: progressive dilatation of ducts, squamous metaplasia, glandular atrophy, and fibrosis.

• Intestinum: obstruction by mucus (meconium ileus).

Endocardial Fibroelastosis

- Primary myocardial metabolic/enzymic defect and congenital malformations take place.
- It is characterized by focal to diffuse, cartilage-like fibroelastic thickening of the myocardium, cardiomegaly due to hypertrophy of left ventricle.
- Death can be due to acute cardiac insufficiency in first days of life or due to chronic cardiac decompensation at connection (intercurrent) of the others diseases (pneumonia).

Alcogolic syndrome of fetus

- Alcogolic syndrome of fetus occurs by signs of embryofetopathy.
- Prematurity, small weight of fetus.
- Tight forehead, flat bridge.
- Narrow palpebral fissures.
- Hyperthelorism, ptosis, epicanthus.
- Cleft palate, short fingers.
- Malformations of the heart, kidney, hip-joint.
- Small cerebellum.
- Decreased pulmonary surfactant.
- Frequent mental retardation.

X. PERINATAL PATHOLOGY

Perinatal period means the period before and after the delivery, begining from the 22th weekof gestation (196th day) to the 1st week of extrauterine life.

Perinatal period and the respective pathology and mortality is divided into:

1. Antenatal period (from the 22ndweek of gestation to the delivery).

2. Intranatal period (during the delivery) begins in the moment of the delivery until the birth.

3. Postnatal (neonatal) period (from birth to 7thday after birth).

In the 22nd week of gestation the fetus must have the weight more than 500 g and the length of the body — 25–30 cm. This fetus can live a life of independence.

Delivery of a smaller fetus and until the end of 22 week of the gestation is called abortion. Stillborn is fetus without breathing and palpitation in the moment of the delivery. Liveborn is infant with signs of the breathing and palpitation.

Perinatal mortality is stillborn and infant mortality within the first 7 days of the life.

Causes and morphological features of prematurity and overmaturity of newborns

Features of the prematurity

1. Premature infant is defined as those when the term of gestation is until 37 week.
2. Body weight is less then 500 gramms.

3. Body length is less then 25 cm.
4. Lanugo hair on the face.
5. Underdeveloped nails.
6. Soft lobe of the ear.
7. In girls the labia minora and clitoris are not covered by labia majora.
8. In boys the testes are not descended, scrotum isn't wrinkled.
9. Soft cranial bones.
10. Beclard's nucleus of the distal femoral epiphysis is absent (in mature children it is 5–7 mm).

Microscopic examination of the organs in premature fetus allows determining the degree of prematurity:

1. Embryonic glomeruli are noted in the superficial layer of the cortical substance of the kidneys.
2. Erythroblastosis foci are observed in the kidneys and liver.
3. Thickening of interalveolar septa in the lungs.
4. Sprout zone in the brain is widened.

Main causes of the prematurity:

1. Diseases of the genital tract of the pregnant women.
2. Placental insufficiency.
3. Early agein of placenta.
4. Placental infections.
5. Acute and chronic infections of the pregnant women.
6. Severe toxicosis of pregnancy (nephropathy, eclampsia).
7. Rh antigens incompatibility.

Features of the overmaturity

1. Overmaturity infant is defined as termination from the 41st week of gestation and later.
2. Epidermis is dry, peeling, macerated, yellow or yellow-greenish color.
3. Very dense cranial bones.
4. Dense long lobe of the auricle.
5. Long nails.
6. General hypotrophy of fetus.
7. Decreased amount of amniotic fluid.
8. Amniotic fluid, umbilical cord, amniotic membranes are usually staining with meconium (yellow-greenish color) as the fetus experiences intrauterine hypoxia.
9. Beclard's nucleus has 8 mm and more).
10. Signs of the placenta's agening (placental infarction, petrification of the placenta).

Main cause of the overmaturity is late prime-gravide.

Overmaturity may lead to antenatal and intranatal death of the fetus due to hypoxia.

The most important diseases of perinatal period Asphyxia (anoxia)

• Asphyxia means lack of oxygen and excess of carbon dioxide in the blood suppling.

• Asphyxia may be:

1. **Antenatal asphyxia** is called the intrauterine asphyxia of the fetus (fetal asphyxia)and arises during pregnancy.

2. **Intranatal asphyxia** (asphyxia neonatorum) arises during delivery.

3. **Postnatal asphyxia** (asphyxia neonatorum) is called asphyxia of the newborn andarises after delivery in result of illnesses of newborn.

Causes of asphyxia

I. Causes of antenatal asphyxia associated with maternal factors resulting in decreased placental blood flow and placental insufficiency, such as:

Maternal cardiovascular diseases. Late toxemia of the pregnancy.

Chronic renal and pulmonary diseases of the mother. Endocrine diseases (diabetes mellitus, thyreotoxicosis). Accidental hemorrhage.

Severe infections of the mother.

Social causes (narcomania, alcohol, heavy cigarette smoking).

II. Causes of intranatal asphyxia associated with defects of the placenta and complications of thedelivery:

Pretermed placental separation. Placental abruption.

Placenta previa.

Prolaps of the umbilical cord. Cord knots.

Multiple gestations.

Complications of the delivery: weakness of the delivery processes, fetus breech presentation, disproportion between the fetus' head and delivery tract of mother (narrow pelvis, large fetus), rupture the short umbilical cord, umbilical cord winding round the neck of fetus.

III. Causes of postnatal asphyxia associated with disturbance of the breathing.

As a rule, postnatal asphyxia is a continuation (or consequence) of intranatal asphyxia.

When during the delivery CNS (including respiratory center) is damaged or under the influence of intrauterine hypoxia, the fetus makes the first inspiration intrauterinally (carbon dioxide stimulates the respiratory center) and amniotic content is aspirated. In this case the alveoli cannot spread after the delivery; postnatal asphyxia develops.

Brain trauma or edema with suppression of the respiratory center. A birth injury of the spinal cord and central nervous system.

Infections of newborn. Aspiration pneumonia.

Background: progressive fetal asphyxia.

Besides, fetal factors import for all types of asphyxia, because they lead to an inadequate supply of nutrients from the mother, to inadequate of the delivery

and may lead to birth injury. Prominent among such fetal conditions are chromosomal disorders, congenital anomalies, and congenital infections.

The main clinical-morphological syndromes of asphyxia

- Hemorrhagic syndrome: petechial hemorrhage in brain, adrenal glands, serous membranes and mucosa, congestion, dark fluid blood in the heart chambers, development of syndrome's disseminated intravascular coagulopathy on the other hand, resulting in fibrin thrombi in the microcirculatory vesells.
- Edematous syndrome in inner organs and cavities.
- Degenerative changes in the liver, kidneys, myocardium, brain.
- Aspiration of amniotic fluid containing skin epithelium, lanugo, meconium.
- If such children survive, the disturbance of the psychomotor development and cardiosclerosis may develop.

Pneumopathies

Pneumopathies are noninflammatory pulmonary diseases, which lead to asphyxia of newborn.They occur as a rule in preterm children. There is atelectasis, development of the hyaline membranes, edematous-hemorragic syndrome.

Atelectasis

- Atelectasis in the newborn or **primary atelectasis** is defined as incomplete expansion of a lung or part of a lung.
- Stillborn infants have total atelectasis, while the newborn infants with weak respiratory action develop incomplete expansion of the lungs and clinical atelectasis.
- The common causes are prematurity, cerebral birth injury, CNS (central nervous system) malformations and intrauterine hypoxia.

Macroscopicall appearance of atelectasis:

- Large plural space.
- Small and collapsed lungs against vertebral column and are of cyanotic color.
- Slitlike air spaces.
- Heart and great vessels fully exposed.

Microscopic examination demonstrates collapsed alveoli.

- While pulmonary collapse or primary atelectasis is the term used for reduction in lung size of a previously expanded and well-aerated lungs.
- Secondary atelectasis in children and adults may occur from various causes such as compression, obstruction, contraction and lack of pulmonary surfactant. Collapse may be of the following 3 types:

1. **Compressive collapse.** Pressure from outside causes compressive collapse e.g. bymassive pleural effusion, hemothorax, pneumothorax, intrathoracic tumor, high diaphragm and spinal deformities.

2. **Obstructive/absorptive collapse.** Obstruction of a bronchus or many bronchiolescauses absorption of oxygen in the affected alveoli followed by collapse e.g. by viscid mucus secretions in bronchial asthma, chronic bronchitis, bronchiectasis, bronchial tumors and aspiration of foreign bodies.

3. Contraction collapse. This type occurs due to localised fibrosis in lung causingcontraction followed by collapse.

Edematous hemorrhagic syndrome

- It is associated with asphyxia when the lung capillaries are overfilled with the blood, vascular permeability increases due to hypoxia.
- Diffuse edema and large intra- and extraalveolar hemorrhages develop.
- Difficulty of the breathing takes place; the children die because of respiratory insufficiency.
- The disease of hyalin membranes often accompanies this condition.
- Autopsy demonstrates large lungs with hemorrhages.
- Microscopic examination shows intraalveolar pink fluid, hemorrhages.

Respiratory distress syndrome of newborn (RDS)

- RDS is one of the most common life threatening complications to confront the newborn infant.
- RDS is also known as hyaline membrane disease (HMD), highlighting one of the major pulmonary anatomic findings in this disease.
- Lungs are involved, asphyxia develops quickly, and the newborns die within the period of 24.
- 36 hours.
- It can have many origins, including:

1. Excessive sedation of the mother with consequent depression of respiration in the infant.
2. Brain injury with failure of the central respiratory centers.
3. Feeble respiratory efforts secondary to immaturity of the lungs and sceletal muscles (primary atelectasis).
4. Aspiration during birth of blood clot and amniotic fluid when the amniotic debris (i.e., desquamated keratotic squames, mucus, lanugo hairs, proteinaceous precipitate, and blood) blocks ventilatory function.
5. Asphyxiating coils of umbilical cord about neck of the infant. But more important than all these by an order of magnitude is the idiopathic RDS.

The fundamental defect in RDS is a deficiency of pulmonary surfactant. Surfactant reducessurface tension within the alveoli so that less pressure is required to hold alveoli open, and it maintains alveolar expansion by varying surface tension with alveolar size. It is synthesized by type 2 alveolar cells most abundantly after the 35 week of gestation in the fetus. At birth, the first breath of life requires high inspiratory pressures to expand the lung. With deficiency of surfactant the lungs collapse with each successive breath as it did with the first.

Surfactant synthesis is modulated by a variety of hormones, including cortisol, insulin, prolactin, and thyroxin. The role of glucocorticoids is particularly important. Corticosteroids induce the formation of surfactant lipids and apoproteins in fetal lung. Surfactant synthesis may be suppressed by the infants of diabetic mothers' compensatory high blood levels of insulin, which counteracts the effects of steroids. This may explain why infants of diabetic mothers have a higher risk of developing RDS.

Morphological features of RDS

Gross examination of the lungs. Although of normal size, they are solid, airless, reddishpurple like the liver, and they usually sink in water. Autopsy demonstrates stiff, congested and heavy

lungs **Microscopic examination:**

The alveoli are poorly developed, and those that are present are collapsed. The atelectasis results from the clearance of the fluid without its replacement by air.

Interstitial and intraalveolar edema.

In early stage of RDS the necrotic cellular debris is present in the terminal bronchioles and alveolar ducts.

Later, the necrotic material becomes incorporated within pink hyaline membranes that line the respiratory bronchioles, alveolar ducts, and random alveoli, mostly the proximal alveoli.

The membranes are largely made up of fibrinogen and fibrin admixed with cell debris derived chiefly from necrotic alveolar-lining pneumocytes.

In infants who survive more than 48 hours reparative changes are seen in the lungs. The alveolar epithelium proliferates under the surface of the membrane, which may be desquamated into the airspace, where it may undergo partial digestion or phagocytosis by macrophages.

Infants who recover RDS are at increased risk for developing a variety of other complications stiff, as well. Most important among these are patent ductus arteriosus, intraventricular hemorrhage, and necrotizing enterocolitis. Thus, although the high technology of today saves many infants with RDS, it also brings to the surface the exquisite fragility of the immature neonate.

Pneumonia in newborn

• Pneumonia of newborns may occur in uterus (in ante- and intranatal periods) as well as after the birth. The etiology is different. The most frequent are coccal pneumonias, klebsiella, and colon bacillus. The disease often develops against the background of amniotic fluid aspiration both infected and not infected.

• The most often in newborn the aspiration pneumonia develops.

• Aspiration syndrome is the first inspiration done in uterus. Amniotic fluid may be infected or may contain meconium.

• The syndrome is due to hypoxia, and is often observed at overmaturation.

• If the child survives for 3–5 hours, small-focal pneumonia develops, in 24 hours it turns into confluent pneumonia.

• In massive aspiration, total or disseminated atelectasis of the lungs (primary) may develop as the lungs are filled with aspiration masses and do not spread.

• Microscopically, leukocytic and monocytic infiltration of alveolar tissue involving the bronchioles and bronchi are observed. Elements of amniotic fluid are determined in the exudate.

• It is considered that intrauterine pneumonia is responsible for the death during the first 1–3 days of life.

Birth injury

• Birth injuries constitute important causes of illness or death in infants as well as in children during the first years of life.

• Morbidity associated with birth injury may be acute or the result of later-appearing sequels.

• Birth injuries are damage to the fetal tissues and organs with mechanical forces during the delivery. Birth injury should be differentiated from obstetric injury, which occurs when obstetric manipulations are carried out.

Causes of birth injury are due to:

1. The state of the fetus:

a) embryopathy;

b) fetopathy;

c) prematurity (the tissues are easily ruptured) and overmaturity (hypoxia increased vulnerability of the fetus).

2. The state of the maternal passages:

a) rigidity of the birth canal tissue;

b) pelvis defects (narrow pelvis, rachitic pelvis, anomalies, tumors, wounds);

c) tumors of maternal passages;

d) oligoamnios, hydramnion.

3. The state of failure of the delivery's dynamic:

a) precipitated delivery;

b) prolonged delivery;

c) a lot or little of amniotic fluid.

Pathology

• Cephalogematoma is produced by an effusion of blood between the pericranium and one of the bones of the head.

• It disappears slowly. When infected, it may become a source of purulent meningitis. The most severe intracranial injury is hemorrhage to the meninges and brain substance.

• All hemorrhages are divided into:

1. ***Epidural hemorrhages*** are located between the bones of the skull and the dura mater(inner cephalohematoma).

2. ***Subdural cephalohematomas*** occur in rupture of the falciform process andcerebellum tentorium. The blood is accumulated under the dura mater on the brain substance.

3. ***Subarachnoid cephalohematoma*** is localized between the arachnoid and pia mater.It occurs in rupture of the falciform process, cerebellum tentorium, veins.

4. ***Intracerebral cephalohematomas*** are the hemorrhages to the vascular plexi of thebrain, under the ependyma of the lateral ventricles with rupture to the ventricles.

- The most frequent course of the death in intracranial injury is rupture of the falciform process and cerebellum tentorium.
- Caput succedaneum and cephalhematoma are also so common, even in normal uncomplicated births, that they hardly merit the designation «birth injury». The first refers to progressive accumulation of the interstitial fluid in the soft tissues of the scalp, giving rise to a usually circular area of edema, congestion, and swelling at the site where the head being to enter the lower uterine canal. Because the fluid accumulates in the subcutaneous tissue, it may extend across the suture lines.
- Hematoma of the sternomastoid muscle may follow traction on the head during the birth of the shoulders, or the extraction of the after-coming head.
- Visceral hemorrhages: subcapsular hematomas and hemorrhage from spleen, liver, stomach due to fracture.
- The most often fractures of the spine (often fatal to the life), fracture of the clavicle, bone's skull, femoral and humerus bones occurring in large fetuses.

Hemolytic disease of the newborn (HDN) or Erythroblastosis fetalis

- **Erythroblastosis fetalis** is defined as a hemolytic disease in the newborn caused by ABO-group and Rh incompatibility between mother and child.
- When the fetus inherits red cells antigenic determinations from the father that are foreign to the mother, a maternal immune reaction may occur, leading to the hemolytic disease in the infant. Basis to such a phenomenon are leakage of fetal red cells into the maternal circulation and, in turn, transplacental passage of the maternal antibodies into the fetus.
- Any of the numerous red cell antigenic systems may theoretically be involved, but the major antigens known to induce clinically significant immunologic disease are the ABO and certain of the Rh antigens (Rh negative mother and Rh positive fetus).
- The resultant fetal hemolytic reaction may cause mild-to-severe disease in the newborn, or even death.
- A hemoliyic disease that may appear during gestation or shortly after delivery.

Classification of erythroblastosis fetalis

1. Congenital hydrops (edematous form) is characterised by edema of skin, subcutaneous fat, meninges and brain substance, there is transudation in the cavities. Microscopically: erythroblastosis in the liver, spleen, lymphatic nodes, and kidneys. Signs of immaturity of organs in mature newborns can be found.

2. Anemia neonatorum (hemolytic anemia) is frequent in immature fetuses. The skin and mucousmembranes are pale. Jaundice is absent. Hepatosplenomegaly take place. In the mildest form, the anemia may be only slight, and the child may survive without further complications. More severe hemolysis dives rise to jaundice and other features associated with hemolytic anemias.

3. Icterus gravis (severe jaundice of the newborn) is evident by the end of the first day. The diseasedevelops quickly. The most serious threat in this disease is central nervous system damage known as *kernicterus.* In jaundiced infants, the unconjugated bilirubin appears to be particularly toxic to thebrain tissue. The brain is enlarged and edematous and, when sectioned, is found to have a bright yellow pigmentation *(kernicterus).* The cells stain by yellow color. The liver and spleen are enlarged; they have the signs of erythroblastosis and hemosiderosis. There are bilirubin infarcts in the kidneys.

a) Histologically in all forms, the diagnosis of erythroblastosis depends on the identification of abnormally increased erythropoetic activity in the infant. The red cells series in the marrow is hyperactive and extramedullary hematopoesis is almost invariably present in the liver, spleen, and possibly other tissues, such as lymph nodes, kidneys, lungs, and even in the heart.

b) In early massive immunization of the mother, early fetopathy develops. The fetus dies before the birth, on the 5^{th}–7^{th} month of gestation.

c) When the mother's immunization is later and more moderate, the child is born alive with one of the forms of HDN.

d) In children who survived HDN, defects of CNS development (including complete idiopathy) may occur in future.

Sudden infant death syndrome (SIDS)

• Included here since some cases of SIDS may be related to congenital cardiac disorders. Defined as sudden and unexpected death in a previously basically well infant, when the cause of death cannot be explained even after autopsy.

• Probably a multifactorial entity or common end point of diverse derangements.

• Ninety per cent of SIDS deaths occur in the first 6 months of life, most between the ages of 2 and 4 months. The deaths occur without a struggle during the night after a period of sleep.

• Often there are minor antecedent respiratory tract infections.

• Causes of death are unknown. Among innumerable hypotheses, those favored are:

— Cardiac arrhythmias.

— Disturbed regulation of respiration, «the apnea hypothesis».

— Inherited disorders of fat oxidation.

— Unsuspected intestinal infection with Clostrium botulinum.

— Defective regulation of body temperature with resultant acute malignant hyperthermia.

Morphology

A variety of changes of uncertain significance.

Abnormalities in the myocardial conduction system have been observed, not always present and of diverse nature.

Subtle medial thickening of small pulmonary arteries and brain-stem gliosis suggests chronic hypoxia.

Right ventricular hypertrophy may be secondary to pulmonary vascular changes or a primary anomaly.

Also seen are retention of fetal hemoglobin, extramedullary.

XI. INFECTIOUS DISEASES

Infectious diseases are those caused by infectious agents (viruses, bacteria, fungi). Protozoaand helminths cause invasive diseases. Infectious diseases have a number of common features.

Clinical-morphological characteristics of infectious diseases

- Each infectious disease has its own causative agent, which can be isolated from the blood or excreted materials of the patient.
- In infectious, one can observe formation of a primary infectious complex consisting of a primary affect, lymphangitis and lymphadenitis.
- The route of the infection from the primary focus or complex may be lymphogenic, hematogenic, intracanalicular, and perineural, contact.
- Each infectious disease is characterized by local changes in the portal of entry of infectious agent.
- A number of common changes (rash, vasculitis, hyperplastic processes in the lymphatic nodes, spleen, bone marrow, inflammatory processes in the interstitial tissue and degenerative changes in the parenchymatous organs) are observed in infectious diseases.
- Infectious diseases are chiefly cyclic. The course of the infectious disease is divided into incubative and prodromal periods and the period of main manifestations of the disease (phases of increase of the signs, climax and extinction).
- Infections can be either exogenic or endogenic.
- Infectious diseases are classified according to a number of signs.

Biological classification:

- Anthroponoses — infectious diseases typical only for people.
- Antropozoonoses — infectious diseases that can develop both in people and animals.
- Biocenoses — a group of anthroponoses and anthropozoonoses transmitted through the bites of insects, which become the place of causative agent multiplying.

According to the etiology they are divided into:

- Viral.
- Rickettsiosis.
- Bacterial.
- Fungal.
- Protozoal.
- Parasitogenic.

Classification according to the mechanism of transmission:

- Intestinal.
- Respiratory.
- Blood (transmissive) transmitted by blood-sucking insects.
- Infections of the external integument, (subcutaneous fat and muscles).
- Infections with different mechanisms of transmission.

According to the duration there are

- Acute.
- Chronic.
- Latent.

Viral diseases

Respiratory disorders are caused by a wide variety of viruses, of different families, species, and serotypes. These include:

1.	Orthomyxoviruses (influenza A, B, and C – RNA virus).
2.	Paramyxoviruses (respiratory syncytial virus, parainfluenza viruses, measles virus, mumps virus)
3.	Adenoviruses.
4.	Herpesviruses (varicella-zoster virus).
5.	Cytomegalovirus.
6.	Herpes simplex virus (HSV).
7.	Picornaviruses (rhinoviruses, echoviruses, and coxsackieviruses).
8.	Human respiratory coronaviruses.

The peculiarities of viral diseases

1. Being highly contagious, viruses cause epidemics and pandemic.

2. The variety of viruses determines the lesion of specific cells due to the virus trophism. The character of the cell receptors determines trophism.

3. The duration of the disease depends both on the type of the virus and the reactivity of the macroorganism and can be acute, chronic, slow.

4. The morphological manifestations of cell-virus interrelations are:

a) Cytolytic effect of the virus on the cell (influenza).

b) Formation of inclusions in the cell (influenza, adenovirus infection).

c) Integration of the virus and the cell genome without considerable destruction of the cell (hepatitis B, HIV infection).

d) Proliferation of target cells (smallpox).

e) Giant-cell transformations (measles).

Acute respiratory viral infection (ARVI)

The term denotes a group of acute inflammatory diseases caused by pneumotropic viruses (Influenza, parainfluenza, adenovirus infection, respiratory sincitial virus, rhinovirus, reovirus).

Influenza

• Influenza is a disease characterized by abrupt onset, fever, sore throat, headache, muscle pains, and acute toxic state. Dry cough and nasal discharge are present but usually are overshadowed by systemic symptoms. In uncomplicated cases the illness lasts a few days, but pulmonary complications such as influenza pneumonia and secondary bacterial infection of the lung may complicate and prolong course.

• Influenza viruses are highly contagious and afflict people of all ages and have 3 types:

a) Influenza A virus, the most common cause of viral pneumonia in adults, infects animals and man and produces pandemics.

b) Influenza B virus is apparently restricted to man, causes epidemics, and is associated with Reye's syndrome in children and pneumonitis and croup in infants.

c) Influenza C virus causes sporadic upper respiratory infections, but not epidemic influenza. Influenza has significant mortality and morbidity, and may have long-term sequelae.

• Patients with viral influenza during the third trimester of pregnancy, the aged, and persons with valvular heart disease or chronic bronchopulmonary disease all have increased susceptibility to bacterial superinfection. Superinfection usually occurs 1 to 5 days after the onset of the viral illness, while the patient appears to be getting well.

• At present differential diagnosis of ARVI is not difficult. Immunomorphological study with antisera to the definite strain of viruses is performed in the smears from the mucous membrane of the upper respiratory tract or in the tissue (if it is autopsy material). In this case bright fluorescence is seen under the microscope.

• Influenza viruses are transmitted by aerosols generated by coughing and sneezing.

• The incubation period is 2–4 days.

• The virus invades the bronchial and alveolar epithelium and endotheliocytes of the capillaries and multiplies there causing primary viremia. The epithe-

lial cells die, the virus leaves them and invades ones more the bronchial and alveolar epithelium. At this stage acute bronchitis or tracheitis develops. These are the first clinical signs of the disease.

- The development of the virus in the cells causes degeneration, necrosis and desquamation of the bronchial epithelium, which in turn causes secondary viremia.
- Its manifestations are vasoparalytic action (plethora, stasis, hemorrhage) and immune-depressive action (phagocytosis inhibition, chemotaxis, etc.), which contributes secondary (often bacterial) infection.

Morphology

Clinical-morphological forms of influenza

1. Slight influenza is characterized by the lesion in mucosa of the upper respiratory tract (edema, hyperemia, serous inflammation). Laringitis, tracheitis and bronchitis occur. These are microcolonies of the virus; they also can be determined with immunomorphological method. The duration of the disease is 5 - 6 days with following convalescence.

2. Mild influenza is characterized by involvement of the pathological processes in mucosa of thebronchi, bronchioles and lungs.

The histopathologic features include a necrotizing tracheitis and bronchitis; diffuse hemorrhagic necrotizing pneumonitis with pulmonary edema.

Ciliated epithelial cells are destroyed and goblet cells and mucous glands disrupted. Individual cells show pycnosis of the nuclei and loss of cilia.

Interstitial pneumonia develops. Interalveolar septa are thickened due to proliferation with lymphocytes and macrophages.

Bronchioles become thickened, distended, and infiltrated with mononuclear cells. There is often severe inflammatory edema, and a fluid exudate in the alveolar spaces has a hyaline membrane appearance.

Desquamation of the alveolocytes lead to decrease of surfactant and development surfactant-depending atelectases in the lungs.

The duration of the disease is 3–4 weeks.

3. Severe influenza is characterized by the complicated duration of disease and occurs by:

1. Severe toxicosis.

Besides serous hemorrhagic bronchitis and pneumonia, hemorrhagic lung edema may develop. Hemorrhage to the brain and internal organs develop.

The patients die on, the 4th–5th day of hemorrhage to vital centres and of acute respiratory and cardiovascular insufficiency.

2. Pulmonary complications.

If bacterial superinfection occurs, the picture is indistinguishable from that of ordinary bronchopneumonia or lobar pneumonia.

Lungs are dark red and firm with interstitial emphysema (pink color) that may extend into the mediastinal tissue. Necrotic foci, abscesses are presence also. Lungs appear as («large variegated (motley) influenza lung»).

Microscopically, there is pronounced sloughing of the bronchial epithelium into the bronchial lumens.

Encephalitis, serous meningitis, brain edema, trunk dislocation develop in the brain.

Obliterating bronchitis, bronchiolitis, bronchiectasis, pneumofibrosis and other chronic lung diseases develop.

Degeneration and inflammation in the nodes of the vagus and sympathetic nerves cause neuritis.

Myocarditis and pericarditis, as well as encephalitis, might be found as postmorten examination of fatal cases, but they are uncommon.

The death is caused by intoxication, cerebral hemorrhages, brain edema, brain trunk dislocation, pulmonary complications (pneumothorax, empyema), and cardiovascular and pulmonary insufficiency.

Paramyxoviruses

• Paramyxoviruses (parainfluenza viruses, respiratory syncytial virus, measles virus, mumps virus) are important causes of respiratory disease in infants and young children.

• Paramyxoviruses are spherical enveloped viruses that contain single-stranded RNA.

• They are transmitted by inhalation of droplets of aerosols.

Parainfluenza viruses infection (Types l–4)

• Type 3 parainfluenza is the most prevalent of the parainfluenzas, occurring endemically throughout the year.

• Infants are especially susceptible.

• Parainfluenza viruses are spread principally by direct contact or by large droplets (in contrast to the spread of influenza virus by inhalation of small droplets).

• Replication is restricted to the respiratory tract and moderate intoxication.

• The infection involves only the upper respiratory tract, except in some infants in whom the primary infection may also involve the larynx, trachea, and bronchioles.

• The pathology of the disease resembles slight influenza.

• The characteristic signs are tracheal and bronchial epithelium proliferation, appearance of polymorphic cells with one or several picnotic nuclei (multinucleated cells).

• Edema in larynx may lead to development of the **«false croup»** and asphyxia.

• Complications are secondary infection, bronchopneumonia, asphyxia, angina, sinusitis, and otitis.

Respiratory Syncytial Virus infection

• The respiratory syncytial virus is the most common cause of viral pneumonia in children under 2 years of age and is a common cause of death in infants aged 1 to 6 months.

• This agent accounts for about one-third of hospital admissions for pneumonia and for up to 90 % of those admitted for bronchiolitis.

• Susceptibility is also increased in elderly or immunocompromised patients.

• In temperate climates of the northern hemisphere, annual epidemics occur in midwinter (January-March).

• Histopathologic features include necrotizing bronchitis, bronchiolitis, and interstitial pneumonia.

• The infiltrate is purely mononuclear (predominantly lymphocytes). In many cases irregular intracytoplasmic inclusion bodies are seen in alveolar and bronchiolar epithelial cells, but intranuclear inclusions are not present.

• The death is caused by asphyxia and pulmonary complications.

Adenovirus infection

• Adenovirus infection (AVI) is caused by DNA-containing adenovirus. This is characterized by invasion of the upper respiratory tract, lymphoid tissue of the intestine, abdominal lymphatic nodes as well as conjunctivitis.

• Adenoviruses (subgroup B, types 4 and 7) are common causes of acute respiratory disease and adenovirus pneumonia in military recruits coming together for the first time for basic training.

• Adenoviruses (subgroup C) are also important causes of chronic pulmonary disease in infants and young children.

• The course may be slight and severe.

1. **Slight AVI** is characterized by acute rhinitis, laryngitis, tracheobronchitis, acute pharyngitis,conjunctivitis and regional lymphadenitis. Histopathologic features of adenovirus pneumonitis include necrotizing bronchitis and bronchiolitis, with necrosis and desquamation of the epithelium Sloughed epithelial cells are subsequently mixed with mononuclear cells, mucus, and cell debris, so that the damaged bronchiole resembles a thrombosed blood vessel. There is interstitial pneumonia, with areas of consolidation showing extensive necrosis, hemorrhage, edema, and mononuclear inflammatory infiltrate. Two distinctive types of intranuclear inclusions — smudge cells and Cowdry type A intranuclear inclusions — are scattered throughout the lesions but primarily involve bronchiolar epithelial cells and alveolar lining cells.

2. **Severe AVI** is caused by generalization of the virus and secondary infections. In generalizedinfection, the viruses multiply in the epithelium of the intestine (diarrhea), kidneys, liver, pancreas, ganglious cells of the brain with development of inflammation and hemorrhages. Secondary infection is characterized by suppuration and sepsis.

• Complications: otitis, sinusitis, tonsillitis, pneumonia due to the secondary infection. The cause of death is pneumonia, sepsis.

Measles

Measles is an acute highly contagious infectious disease characterized by catarrhalinflammation of the mucous membranes of the upper respiratory tract, conjunctiva and spotted papular eruption on the skin.

Etiology and pathogenesis

• The causative agent of measles is an RNA-containing virus transmitted by inhalation (air-droplets).

• The virus enters the upper respiratory tract and eye conjunctiva.

• Degenerative changes in the epithelium of the mucous membrane and hematogenous spread are accompanied by short viremia resulting in dissemination of the virus in the lymphoid tissue, which in turn causes immune reconstruction.

• Viremia becomes more expressed and prolonged, the eruption appears. When the eruption disappears, the virus cannot be found in the organism.

• Incubation period is 9–11 days. The duration of the disease is 2–3 weeks.

• The disease produces stable immunity.

Morphology

Catarrhal inflammation in the mucous membrane of the mouth, trachea, bronchi, conjunctiva develops.

The mucous membrane is swollen, plethoric; the mucous secretion is increased, which is accompanied by rhinitis, cough, and lacrimation.

Severe cases are accompanied by necroses; the mucosa becomes dull, greyish-yellow; small lumps are seen on its surface.

The edema and necrosis of the laryngeal mucosa can develop reflex spasm of its muscles with asphyxia (so called «false croup»).

Measles is characterized by metaplasia of mucosa epithelium into multilayer squamous epithelium observed in early periods (5^{th}–6^{th} days of the disease), which decreases the barrier function of the epithelium.

Varies from pure interstitial (viral) pneumonia to lobar (bacterial) pneumonia. There are often pathognomonic multinucleated giant cells (Warthin-Finkeldey cells), intranuclear and intracytoplasmic inclusions, and hyperplasia of distal bronchial cells. In immunocompromised patients measles pneumonia may occur without rash and is often fatal.

Viremia and generalization of the process result in enanthema and exanthema:

1. ***Enanthema*** is noted on the mucous membrane of the cheeks against the lesser lowermolars. It looks like whitish spots called Belsky-Filatov-Koplik spots, which develop before the eruption on the skin. They are of great diagnostic significance.

2. ***Exanthema*** in the form of large-spot papular eruption first appears on the skin behindthe ears, then on the face, neck, body, and inner surface of the extremities.

Complications is accompanied with the secondary viral and bacterial infection.

Destructive (necrotic or purulent- necrotic) panbronchitis can occur.

The disease involves internal membrane of the bronchi (endobronchitis), middle layer (mesobronchitis), and external layer (peribronchitis).

On incision, the involved lungs look like grey-yellow foci resembling tuberculosis ones. Such panbronchitis is the source of bronchiectasis, lung ab-

scess, and purulent pleurisy. The involvement of peribronchial lung parenchyma causes the development of peribronchial pneumonia and chronic disease of the lungs resulting in pneumosclerosis.

Moist gangrene of the soft tissue of the face (noma) is rarely observed at present.

The death of the patients with measles is associated with pulmonary complications and asphyxia in «false croup». Modern seroprophylaxis and vaccination have resulted in considerable reduction of the frequency of disease and death rate.

Mumps

- Mumps virus causes a transient inflammation of the parotid glands and rarely of the testes, pancreas and central nervous system. Mumps viruses are spread by inhalation (air-droplets) and multiply within respiratory epithelial cells, salivary glands, and T-cells in lymph nodes.
- A transient viremia spreads the mumps virus to other glands and the central nervous system via the choroid plexus.

Morphology

- In mumps (parotitis), which is bilateral in 70 % of cases, affected glands are enlarged, have a soft consistency, and are moist, glistening, and reddish brown on cut-section.
- Microscopically, the gland interstitium is edematous and diffusely infiltrated by histiocytes, lymphocytes, and plasmocytes that compress acini and ducts. Neutrophils and necrotic debris may fill the ductal lumen and cause focal damage to the ductal epithelium.
- In mumps orchitis, testicular edema, mononuclear cell infiltration, and focal hemorrhages has been revealed.
- **Complications:** atrophy of testis with azoospermia development, serous meningitis andmeningoencephalitis.
- **The death** of the patients with mumps is associated with central nervous systeminvolvement.

Acquired immune deficiency syndrome (AIDS)

Etiology and pathogenesis

- Human immunodeficiency virus (HIV) is the causative agent for AIDS.
- HIV is a retrovirus that contains only RNA. HIV is a sexually transmitted disease.
- Infection is aided by Langerhans cells in mucosal epithelial surfaces, which can become infected.
- Infection is also aided by the presence of other sexually transmitted diseases that can produce mucosal ulceration and inflammation.
- The CD4+ T-lymphocytes have surface receptors to which HIV can attach to promote entry into the cell. The infection extends to lymphoid tissues

which contain follicular dendritic cells that can become infected and provide a reservoir for continuing infection of CD4+ T-lymphocytes.

• HIV can also be spread via blood or blood products, most commonly with shared contaminated needles used by persons engaging in intravenous drug use.

• Mothers who are HIV infected can pass the virus on to their fetuses in utero or to infants via breast milk.

• The source of HIV is a sick person or a virus carrier. The patients are infective during all the life.

• When HIV infects a cell, it must use its reverse transcriptase enzyme to transcribe its RNA to host cell proviral DNA. It is this proviral DNA that directs the cell to produce additional HIV virions, which are released.

• When the CD-4 lymphocyte count drops below 200/microliter, then the stage of clinical AIDS has been reached. This is the point at which the characteristic opportunistic infections and neoplasms of AIDS appear.

Clinical picture

Incubative period of HIV-1 at sexual way of infection lasts from 2–3 weeks to 2–3 months, sometimes I year.

The early signs of the disease are increase of temperature, cough, nausea, vomiting, diarrhea, presence of antibodies to HIV infection with simultaneous loss of body mass (20 kg during the last 2–3 years).

After those lymphatic nodes of different localization as well as the liver and spleen enlarge, lymphopenia and hypergammaglobulinemia develop. The signs of the disease also depend on the lesion in the definite system, i.e. meningoencephalitis, pneumonia, gastritis, duodenitis, nephritis.

Next stage is appearance of oncological diseases or generalized infection. The clinical spectrum of HIV infection is now recognized to comprise:

1. Acute viral infection sometimes associated with immune complex disease.
2. Persistent generalized lymphadenopathy.
3. Chronic active viral infection with constitutional symptoms or AIDS related complex.
4. Immunodeficiency leading to opportunistic infections or tumors (AIDS).
5. Chronic encephalopathy caused by HIV
6. Chronic active viral infection with immunocomplex disease (such as thrombocytopenic purpura).

The signs of suspected AIDS (according to WHO)

• Prolonged fever of unclear origin.
• Chronic diarrhea (not less than 2 months).
• Unexplainable body weight loss (by 10 % or more).
• Pneumonia of unclear origin resistant to standard therapy.
• Lymphopenia.

There are AIDS-ihdicating diseases (according to WHO)

- Candidosis of the esophagus, trachea, bronchi, lungs.
- Extrauterine cryptococcosis.
- Cryptosporiosis with diarrhea for more than 1 month.
- Pneumocyst pneumonia.
- Cytomegalovirus lesion of some organs (except for the liver, spleen, lymphatic nodes in the patients over 1 month).
- Infection caused by herpes simplex, persisting more than I month in the patients aged over 1 month.
- Toxoplasmosis of the CNS in the patients aged over 1 month.
- Malignant lymphomas seen with AIDS are typically of a high grade and extranodal, often in the brain. They are very aggressive and respond poorly to therapy.
- Kaposi's sarcoma (KS) produces reddish purple patches, plaques, or nodules over the skin and can be diagnosed with skin biopsy. Visceral organ involvement eventually occurs in 3/4 of patients with KS.

Morphology

At autopsy the gross pathology of AIDS can be split into three general categories as follows:

1. The morphologic manifestations of profound lymphoid depletion.
2. Infections caused by opportunistic pathogens.
3. Unusual neoplasms such as Kaposi's sarcoma and high-grade lymphoma.

The early stage of HIV is characterized by enlarged lymph nodes and the follicular hyperplasia.

With disease progression, the frenzy of B-cell proliferation subsides and gives way to a pattern of severe follicular involution. The follicles are depleted of cells; and the organized network of follicular dendritic cells is disrupted. The germinal centres may even become hyalinised. These «burnt-out» lymph nodes are atrophic and small and may harbor numerous opportunistic pathogens. In the empty-looking lymph nodes and in other organs, the presence of infectious agents may not be readily apparent without the application of special stains.

In later stages of AIDS, spleen and thymus also appear to be «wastelands».

Non-Hodgkin's lymphomas, involving the nodes as well as extranodular sites, such as the liver, gastrointestinal tract, and bone marrow, are primarily high-grade diffuse B-cell neoplasms.

Neurologic complications, especially the AIDS-dementia is an important cause of morbidity in patients in advanced stages of infection. The pathologic abnormalities in patients with AIDS-dementia complex are variable. Multinucleated cells in the brain are found in a subgroup of patients with severe disease. These cells are derived from macrophages and support viral replication. These are thus markers of productive infection. All histopathlogic abnormalities are

most prominent in the subcortical structures, and besides multinucleated cells they include diffuse pallor of the white matter and vacuolar myelopathy.

Lymphocytic meningitis is seen in patients around the time of seroconversion and is defined as occurring in the absence of any demonstrable opportunistic pathogens.

HIV encephalitis is a multifocal process characterized by inflammatory foci including multinucleated giant cells, mainly seen in white matter, basal ganglia and brain stem.

Diffuse poliodystrophy is the term applied to neuronal loss, microglial activation and gliosis in CNS grey matter.

Cerebral vasculitis is seen most prominently in childhood HIV disease of the brain.

Bacterial infections of childhood

Diphtheria (D)

Diphtheria is an acute infectious disease characterized by fibrinous inflammation in the focusof primary fixation of the causative agent and general intoxication due to exotoxin absorption.

Etiology and pathogenesis

• **Diphtheria** is caused by a slender, gram-positive rod Corynebacterium diphtheria, which ispassed from person to person via aerosols or traumatic skin.

• Diphtheria is amenable to virtually complete eradication by routine immunization with diphtheria toxoid. Even in medically advanced countries, however, diphtheria may occur when immunization procedures break down because of war, complacency, or cultism.

• Transmission to nonimmune individuals usually occurs by the respiratory route.

• Diphtheria is a composite of a local inflammation and a systemic intoxication. Toxic produced locally by toxigenic strains of C. diphtheriae is responsible for an inflammatory reaction on body surfaces at the site of infection (usually the oral pharynx, from which the process often extends to the nose or larynx).

• Occasionally the tracheal, esophageal, or gastric mucosa is involved as well.

• Less commonly, but particularly in the tropics, cutaneous trauma or burns may be the site of diphtheria.

• The umbilical cord (in diphtheria neonatorum), the genital tract, and the conjunctivae are rare sites.

• Incubation period is 2–10 days.

• The diphtheria bacillus multiplies at the site of attachment on the mucosa and excretes exotoxin. The exotoxin causes local necrosis of the epithelium, paretic dilatation of the vessels with disturbance of their permeability, edema of the tissues and release of fibrinogen from the vascular bed. Fibrinous films are formed on the surface of the damaged mucous membrane.

• Exotoxin affects cardiovascular, nervous systems and adrenal glands. This simultaneous damage causes hemodynamic disturbances in the organism; excretion of the exotoxin from the organism is accompanied by the damage of tubular epithelium of the kidneys.

• The disease is more common in children; at present the disease is more frequent in children over 7 years.

Morphology

Clinical-morphological classification:

1. Diphtheria in the pharynx.
2. Diphtheria in the respiratory tract.
3. Rarely forms of diphtheria.

Diphtheria in the pharynx Local changes:

• Cervical adenopathy seems out of proportion to the pharyngeal lesion.

• Soon small gray or white patches of exudate appear on the pharyngeal mucosa, usually over the tonsils. These enlarge and coalesce and, with the accumulation of blood, become gray or black. This exudate constitutes the characteristic diphtheritic inflammation, which consists of leukocytes and numerous bacteria enmeshed in a dense network of fibrin.

• The lymphoid tissues both in regional lymph nodes and systemically (as in the spleen) undergo hyperplasia with the development of prominent germinal centers that are often centrally necrotic.

• The soft tissue of the neck is swollen. In severe toxic forms, the edema is considerable and can involve the anterior surface of the chest.

General changes are accompanied with toxinemia and appear:

1. Diphtheria toxin is particularly toxic to myocardium.

• Toxic myocarditis develops in the heart. Alterative and interstitial forms of myocarditis are distinguished. The cavities of the heart are dilated; the muscle is dull, flabby, variegated. Parietal thrombi can be observed.

In the early stages, interstitial edema, cloudy swelling of myocardial fibers, and the accumulation of fine cytoplasmic granules of lipid are seen microscopically. The changes of cardiomyocytes are characterized by fat degeneration and small foci of myolysis.

• If myocarditis develops at the beginning of the 2nd week of the disease and the death is caused by acute cardiac failure and an arrhythmia, the condition is called early cardioplegia. Due to diphtheritic myocarditis the cardiosclerosis and congestive heart failure develop.

1. Diphtherial toxin has a special affinity for peripheral nerves (often in glossopharyngeal nerve, diaphragmatic nerve, vagus, sympatic nerves).

• Toxic effects are manifested in degeneration or even destruction of myelin membrane. Axis cylinders undergo swelling and rarely necrosis.

• Parenchymatous neuritis with dvelopment of the late paralysis of the palate, diaphragm, and heart develops. The paralytic effects of diphtheritic neuropathy are often sharply localized.

• Paralysis of the voluntary muscles of the palate may produce a peculiar nasal quality of the voice and a tendency to regurgitate fluids through the nose.

• Paralysis of the diaphragm may lead to aspiration pneumonia.

• Late paralysis of the heart may lead to acute cardiac failure.

• Involvement of extraocular muscles may produce diplopia, and involvement of the ciliary body may result in defective visual accommodation.

• Clinically apparent weakness or paralysis of limbs is rare. Neuropathic manifestations of diphtheria are usually temporary and disappear within 2 or 3 months if the patient survives.

2. Hemorrhages, degeneration and necrosis of the cells are observed in the medullary layer of the adrenal glands, foci of necrosis and disappearance of lipids are seen in the cortical layer. Acute adrenal insufficiency may develop.

3. A nonspecific, nonsuppurative interstitial nephritis is frequent in diphtheria and is believed to be responsible for the proteinuria often observed. Necrotic nephrosis and massive necroses of the cortical layer in the severe cases of toxic diphtheria are observed in the kidneys. The renal lesion usually resolves completely in patients who recover.

4. The liver is characteristically enlarged; hepatocytes exhibit cloudy swelling and less commonly focal necrosis.

Diphtheria in the respiratory tract

• Diphtheria of the respiratory tract is characterised by croupous inflammation of the larynx, trachea, and bronchi with formation of fibrinous films, which can be discharged at cough.

• The epithelial surface becomes necrotic and easily adherent to the overlying membrane; this adherence explains why raw bleeding, points are exposed when the membrane is forcibly removed. If particularly extensive, the local process may produce mechanical respiratory obstruction, stridor, and even asphyxia.

• Croupous inflammation of the larynx in diphtheria is called **true croup,** propagation of the process in the small branches of the bronchial tree is called descending croup, which may be accompanied by development of focal pneumonia.

• Complications in diphtheria of the respiratory tract are caused by:

— Asphyxia due to obstruction of fibrinous films.

— Intubation or tracheotomy, which can result in decubitus.

— Secondary infection in decubitus causes purulent perichondritis of the cartilages of the larynx, phlegmon, and purulent mediastinitis.

• Death is caused by:

— Asphyxia (spasm of the larynx in true croup or occlusion of the respiratory tract with fibrinous films) or by accompanying pneumonia and purulent complications.

— Early cardioplegia in myocarditis and late cardioplegia or paralysis of the diaphragm due to parenchymatous neuritis when antitoxic serum is not administered in time.

Scarlet fever

Scarlet fever (SF) is one of the forms of streptococcal infection, it is an acute infectious diseaseaccompanied by local inflammatory changes mainly in the pharynx and typical generalized rash. The disease is common in children (3–12 years old), but it can also be observed in the adults.

Etiology and pathogenesis

The causative agent is beta-hemolytic streptococcal group A of different serological types.

The patients are infected by inhalation (air-droplets rout), but the disease can also be transmitted through personal belongings and foodstuffs (mainly milk).

- Incubation period is 3–7 days.
- Pathogenesis of scarlet fever is complicated and explained by third factors: erythrogenic toxin, microbial invasion and allergic reactions.
- The duration of the disease is divided into two periods, toxic (first) and infectious allergic (second) ones.
- In the early stages there is rather severe pharyngitis and tonsillitis. These, combined with fever, vomiting, and headache, make up the cardinal prodromal symptoms of scarlet fever. Because there is no specific strain of beta-hemolytic streptococci responsible for scarlet fever, bacteriologic studies do not provide a means for early diagnosis; in other words, a diagnosis of throat infection caused by S. pyogenes is not a diagnosis of scarlet fever. The diagnosis cannot be positively made until the second stage of the disease, which is reached 1 to 5 days after the onset.

Morphology

1. Toxic period (1–2 weeks).

Local changes appear the inflammatory process in the site of the primary fixation (tonsils, skin,lungs, seldom-genital tract), which is accompanied by regional lymphangitis and lymphadenitis. This is called **«primary scarlatinic affect» and «primary scarlatinic complex». «Primary scarlatinicaffect»** is characterized by catarrhal or necrotic tonsillitis.

Catarrhal tonsillitis (during the first few days) is manifested by hyperemia of pharynx **(«flaring pharynx» or «burning faucet»)** with involvement to oral cavity and tongue. Itpresents a **«strawberry»** appearance because of the erythematous papillae that project from a gray-coated background. When peeling occurs, the tongue becomes beefy red and glistening.

Necrotic tonsillitis is characterized by coagulative necrosis and ulceration. Microscopically, there is a characteristic acute, edematous, neutrophilic inflam-

matory reaction within the affected tissues. Necrosis may involve the soft palate, pharynx, auditory tube (Eustaphian tube), middle ear; it can pass from the lymphatic nodes to the subcutaneous fat of the neck. Rejection of the necrotic masses results in ulcers. Cervical lymphatic nodes are plethoric, juicy, enlarged, with foci of necrosis and marked myeloid infiltration.

2. General changes.

The general changes depending on toxemia are first of all rash.

A punctate erythematous rash that is most abundant over the trunk and inner aspects of the arms and legs manifests **exanthema.** The face is also involved, but usually a small area about the mouth (nasolabial triangle) remains relatively unaffected, to produce a circumoral pallor.

Microscopically, there is a characteristic acute, edematous, neutrophilic inflammatory reaction surrounding the affected tissues (skin and lymph nodes).

The inflammatory involvement of the epidermis is usually followed by hyperkeratosis of the skin, which accounts for the scaling during defervescence. The hyperemia and resultant red coloration of skin are manifestations of toxic injury (atony and dilatation) of vascular endothelium. This hyperemia blanches on pressure and disappears on death; thus little of the characteristic skin reaction is evident at autopsy.

3. The second period (allergic).

• The second period may develop on the 3^{rd}–5^{th} week of the disease rarely. The second period begins with moderate catarrhal tonsillitis.

The most significant is development of acute or chronic glomerulonephritis with possible nephrosclerosis development.

• Skin rash, vasculitis, serous arthritis, verrucous endocarditis can be observed. Complications are divisible into three major categories:

1 The results of bacterial disseminations locally — otitis media, sinusitis, cervical adenitis, phlegmon of the neck, acute suppurative mastoiditis, and retropharyngeal abscess.

2. The result of bacterial dissemination generally — metastatic foci of infection throughout the body, or trunk septicemia.

3. The manifestation of extraordinary reactions to toxins (this may be brought about by hypersensitivity) — interstitial nephritis or myocarditis, pericarditis, nonsuppurative arthritis, and glomerulonephritis.

The death is caused by toxemia or septic complications.

Meningitis (M)

Meningitis (leptomeningitis) is an acute or chronic inflammatory process chiefly affecting the pia and arachnoid mater, cerebrospinal fluid (CSF) and may be caused by bacteria, fungi, or parasites.

It is usually caused by an infection, but chemical meningitis may also occur in response to a nonbacterial irritant introduced into the subarachnoid space.

Infectious M. can be broadly classified as acute pyogenic (usually bacterial), aseptic (usually viral), and chronic (bacterial or fungal).

Meningococcal infection is an acute infectious process which has three main forms: nasopharyngitis, purulent meningitis and meningococcemia.

This is characterized by periodic epidemics, the disease is more common in children under 5 years, but the disease may occur in persons of any age.

The typical patient with acute pyogenic meningitis has general signs of infection with the added symptoms and signs of meningeal irritation: headache, photophobia, irritability, clouding of consciousness, and neck stiffness.

Etiology. The causative agent is meningococcus (Neisseria meningitidis), which discharges the endotoxin.

Morphology

Meningococcal nasopharyngitis

- It is characterized by catarrhal inflammation of the mucosa with marked hyperemia, edema of the posterior wall of the pharynx and hyperplasia of lymphatic follicles.
- This form is of great epidemiological importance as clinical diagnosis is often difficult. Bacteriologic investigation is necessary for diagnose.

Meningococcal meningitis

- It is characterized by the hyperemia of the pia mater, saturated with dull serous exudate during the first days of the disease.
- By the end of the 2^{nd}–3^{rd} day the exudate becomes thicker, green-yellow, purulent. By the 5^{th}–6^{th} day it becomes denser due to fibrinous effusion.
- The process begins with basal surface and passes through, the perivenous spaces to the convex surface mainly of anterior portion of the brain, locating there in the form of a **yellow-green «cap».**
- The purulent process involves the meninges of the spine.
- The meningeal vessels are enlarged and stand prominently.
- The infection may extend into the ventricular system through the foramina of Magende and Luschka causing ventriculitis.
- Other complications of meningitis include hydrocephalus resulting from ventricular obstruction or meningeal fibrosis, subdural effusion caused by fluid leading into the subdural space through defects in the arachnoid and occuring most commonly in children, and cranial nerve palsies probably related to inflammatory involvement of nerve roots crossing the subarachnoid space.
- The death may occur from the brain swelling with wedging of the cerebellum tonsils to the great foramen and strangulation of the oblong brain during the acute period.

• Later the cause of death is meningoencephalitis, purulent ependymitis or general cerebral cachexia due to hydrocephalia and atrophy of the brain hemispheres during the following periods.

Meningococcemia

• Duration is 24–48 hours.

• Bacteriemia and endotoxinemia lead to endotoxic shock with the development of syndrome of disseminated intravascular coagulation.

Changes on the organs are characterized by generalized damage of microcirculation, skin rash, changes in the joints, vascular membrane of the eyes, adrenal glands and kidneys. Changes in the serous layers of the pericardium are observed.

• The changes of the microcirculation are characterized by vasculitis and necrosis.

• The rash is hemorrhagic, star-like, located mainly on the buttocks, lower extremities, eyelids and scleras. There may be vesicles or dull dryish foci of necrosis in the centre of the skin elements. Purulent arthritis is observed in the small joints of the extremities.

• Focal necroses and hemorrhages or bilateral massive hemorrhages with the development of acute adrenal insufficiency (Waterhouse-Friderichsen syndrome) are noted in the adrenals.

• Necrosis of nephrothelium of the tubules (necrotic nephrosis) is observed in the kidneys.

• Serous meningitis and hemorrhage may occur.

• The death of the patients is caused by bacterial shock, its severity is aggravated by hemorrhages to the adrenals; acute renal insufficiency is not so common (in the adults). When the duration of the disease is prolonged, the death occurs from septicemia or purulent meningitis.

Gastrointestinal infections

Shigella bacillary dysentery (D)

• Dysentery refers to diarrhea with abdominal cramping and tenesmus in which loose stools contain blood, pus, and mucus.

• Bacillary D. is caused by Shigella dysenteriae, S. flexneri, S. boydii, and S. sonnei as well as certain O-type enterotoxic E. coli.

• Transmission occurs by the fecal-oral route.

• Symptoms appear 2 to 5 days after the ingestion of bacteria. The dose of organisms and the status of host defenses influence the incubation period and severity.

• The key to the pathogenicity of Shigella is its ability to invade and multiply in the epithelium and lamina propria of the terminal ileum and colon, and destroy host cells.

• Endotoxin probably adds to necrosis, but the role of enterotoxin produced by some species of Shigella in the pathogenesis of dysentery is uncertain.

• While clearly secondary to invasion, Shiga toxin probably contributes to the profuse diarrhea that precedes dysentery in some patients.

• This enterotoxin, which is related antigenically to the enterotoxin of enteropathogenic E. coli, activates membrane-associated adenyl cyclase. Thus, shiga toxin, like cholera toxin and E. coli enterotoxin, induces hypersecretion of fluid and electrolytes from the mucosa of the terminal ileum. Water and electrolyte balance must be maintained to prevent dehydration, prostration, and impaired mental status.

Morphology

Colitis has 4 stages:

1. Catarrhal colitis. The mucosa becomes edematous and hyperemic, and is covered by pus and mucus.

2. Fibrinous colitis. Within the course of 24 hours, a fibrinosuppurative exudate first patchily, then diffusely covers the mucosa and produces a dirty gray-to-yellow pseudomembrane, consisting of necrotic mucosa, neutrophils, fibrin, and erythrocytes. Sloughed pseudomembrane, together with blood-tinged mucus, comprises the characteristic dysenteric stool of shigellosis.

3. Ulcer formation (ulcerative colitis).

4. Healing of the wound. The epithelium persists only in the depths of the crypts, and goblet cells contain no mucus in the acute stage. Epithelial regeneration is rapid and healing is complete in 2 ^{weeks}Histologically, there is predominantly mononuclear leukocytic infiltrate within the lamina propria, but the surfaces of the ulcers are covered with an acute, suppurative, neutrophilic reaction accompanied by congestion, marked edema, fibrin deposition, and thromboses of small vessels. As the disease progresses, the ulcer margins are transformed into active granulation tissue. When the disease remits, this granulation tissue fills the defect, and the ulcers heal by regeneration of the mucosal epithelium.

In case of solitary follicle cell hyperplasia, they enlarge and protrude over the surface of the mucous membrane (follicular colitis and follicular-ulcerative colitis).

Lymphadenitis develops in the regional lymphatic nodes. Common changes are spleen hyperplasia, fatty degeneration in the heart and liver, small-focal necroses in the liver, necrosis of renal tubular epithelium.

Complications of dysentery are:

— Perforation (microperforation) of the ulcer with development of. paraproctitis or peritonitis, intestinal phlegmon.

— Intraintestinal hemorrhage

— Scar stenosis of the intestine is less common.

— Extraintestinal complications are bronchopneumonia, pyelonephritis, serous (toxic) arthritis, and pylephlebilic abscesses of the liver, amyloidosis, intoxication, and cachexia.

The death may cause by intestinal or extraintestinal complications.

Amebiasis

The protozoan parasite Entamoeba histolytica infects approximately 500 million persons in developing countries. The disease is common in India, Mexico, and Colombia. Amebae cause dysentery — bloody diarrhea, intestinal pain, fever — when they attach to the colonic epithelium, lyses colonic epithelial cells, and invade the bowel well.

Morphology

- Amebiasis most frequently involves the cecum and ascending colon, followed in order by sigmoid, rectum, and appendix. In severe, full-blown cases, however, the entire colon is involved.
- Amebae invade the crypts of the colonic glands, burrow through the tunica propria, and are halted by the muscularis mucosae. As the lesion progresses, the overlying surface mucosa is deprived of its blood supply and sloughs. The earliest amebic lesions show neutrophilic infiltrates in the mucosa, which later develop into ulcers that contain few host inflammatory cells and areas of extensive liquefactive necrosis.
- The mucosa between ulcers is often normal or midly inflamed.
- In about 40 % of patients with amebic dysentery, parasites penetrate portal vessels and embolize to the liver to produce solitary, or less often multiple, discrete abscesses, some exceeding 10 cm in diameter. Amebic liver abscesses have a scant inflammatory reaction at their margins and a shaggy fibrin lining. Because of hemorrhage into the cavities, the abscesses are sometimes filled with a chocolate-colored, odorless, pasty material likened to anchovy paste. Secondary bacterial infection may make these abscesses purulent. As the amebic abscesses enlarge, they produce pain by pressing on the liver capsule and can be visualized with ultrasound. Amebic liver abscesses are treated with drainage and drugs or with drugs alone.
- Rarely, amebic abscesses reach the lung and the heart by direct extension or appeared through the blood into the kidneys and brain.

Salmonellosis and typhoid fever

- Salmonellae are flagellated, gram-negative bacteria that cause a self-limited and water-borne gastroenteritis or a little-threatening systemic illness marked by fever.
- Salmonellas invade nonphagocytotic interstitial epithelial cells as well as tissue macrophages.

Typhoid fever

- **Typhoid fever (enteric fever)** is an acute intestinal infectious disease caused by Salmonellatyphy abdominalis. Epidemics are possible but at present the disease is rare, its course is not severe. The infection is parenteral.

• The source of infection is a sick person or a human carrier whose excretions (faeces, urine, sweat) contain the microbes.

Pathogenesis

• The bacteria multiply in the lower portion of the small intestine and produce endotoxins.

• On penetrating the intestinal mucosa, the organisms enter Peyer's patches and solitary follicles, quickly enter lymphatic vessels and mesenteric nodes, whence they reach the liver and then, by the thoracic duct, the bloodstream. All this occurs in the incubation period, usually 10 to 14 days. This is the first stage of the disease; in which generalization of the infection occurs before localizing lesions draw attention to the intestine.

• Bacteremia develops (1st week of the disease); the bacillus can be isolated from the blood (homoculture). Bacteremia is associated with generalization of the infection.

• Beginning with the 2nd week antibodies to the causative agent are determined in the blood with agglutination reaction (Widal's reaction).

• Bacteremia is also associated with elimination the causative agent that is excreted with the sweat, milk, urine, faeces, and bile. The patient is especially infective during this period.

• The most favourable conditions for the life of the bacteria are in the bile where they intensively multiply (bacteriocholia).

• They are excreted with the bile to the small intestine and cause hyperergic reaction in the previously sensibilized lymphatic follicles. The condition results in necrosis of the intestine lymphatic system.

Morphology

The changes in typhoid fever can be local and generalized.

Local changes occur in the mucous membrane and lymphatic system (group and solitaryfollicles of the intestine). The most prominent changes develop in the Peyer's patches of the ileum (ileotyphus).

These changes develop in 5 stages. Each stage takes approximately one week.

1. **Medullar swelling**is acute proliferative granulematous inflammation in lymphoid apparatus ofintestine with development macrophagal granulomas («typhoid granuloma»). They consist of large macrophages with pail-pink cytoplasm, containing bacteria. In mucosa the catarrhal inflammation is found out. Proliferation of phagocytes with enlargement of reticuloendothelial and lymphoid tissues throughout the body develop. Peyer's patches in the terminal ileum become sharply delineated, plateau-like elevations up to 1 cm in diameter, with enlargement of draining mesenteric lymph nodes. Follicles are protruded in intestine lumen. Their surface is striated and like brain.

2. **Necrosis.** After 7 to 10 days, the picture in the intestine is complicated by necrosis and ulceration ofareas that formerly exhibited lymphoid hyperplasia.

3. **Ulcer formation («unclear ulcers»)**. In the second week, the mucosa over the swollen lymphoidtissue is shed, resulting in oval ulcers with their long axes in the direction of bowel flow. In the colon, ulcers are smaller and punctate, corresponding to the smaller lymphoid follicles there. Edges of ulcer are irregular with necrotic tissue. Macrophages, lymphocytes and plasma cells, whereas neutrophils are present near the ulcerated surface.

4. **«Clean ulcer» has regular shape without necrotic tissue**. In this stage the perphoration candevelop.

5. **Healing (recovery)**. Granulomas are sclerosed, necroses undergo to petrification.

General changes. The changes in typhoid fever may be typical only for this disease as well ascharacteristic for any infection.

Roseolar-papular rash and typhoid granuloma in different organs occurs.

The latter are the processes in the organs of the lymphatic system and degenerative changes in the parenchymal organs.

The spleen is enlarged, soft, and bulging, with uniformly pale red pulp, obliterated follicular markings, and prominent sinus histiocytosis and reticuloendothelial proliferation.

The liver shows small, randomly scattered foci of parenchymal necrosis in which the hepatocytes are replaced by a phagocytic mononuclear cell aggregates, called «typhoid nodule».

These distinctive nodules also occur in the bone marrow and lymph nodes.

Gallbladder colonization, which may be associated with gallstones, causes a chronic carrier that may require cholecystectomy to eliminate bacterial shedding.

Atypical forms are pneumotyphus, cholangiotyphus.

Complications

- Intestinal (intraintestinal hemorrhages, ulcer perforation, peritonitis).
- Extraintestinal (pneumonia, purulent perichondritis of the larynx, Zenker' s necrosis of the abdominal muscles, osteomyelitis, intramuscular abscesses).
- The death is caused by the complications.

Salmonellosis

- Salmonellosis is an intestinal infection caused by salmonellas. It is anthropozoonosis and occurs both in human beings and animals.
- The most often pathogenic organism is Salmonella typhi murium, salmonella enteritidis, salmonella cholera suis.
- Incubation's period is 12–36 hours.
- Clinical symptoms are accompanied with endotoxin and endotoxinemia: fever, diarrhea and hypotony and endotoxic shock.

• **Pathology.** Salmonellas cause three types of human disease (salmonellosis): interstitial(toxic), septic, typhoid.

1. **Interstitial salmonellosis** (gastroenteritis) develops in food poisoning. It ischaracterized by acute gastroenteritis causing severe-dehydration of the organism. The disease resembles cholera that is why it is called «home cholera».

2. **Septic salmonellosis** (septicemic diseases without specific organ-system localization)differs from interstitial one in hematogenic generalization of the causative agent with formation of metastatic abscesses in different organs while the changes in the small intestine are not significantly pronounced.

3. **Typhoid salmonellosis** (specific enteric fevers) resembles typhoid fever.

Complications. Toxicoinfectious shock, purulent complications, dysbacteriosis when thetreatment is inadequate.

Cholera

• Cholera is an acute gastrointestinal infectious quarantinic disease and is characterized by diarrhea and exicosis.

• The vibrios never invade the enteric epithelium but instead remain within the lumen and secrete their endotoxin.

• Secretory diarrhea is caused by released of an endotoxin, called cholera toxin, which is nearly identical to E.coli endotoxin.

• This is due to the exotoxin of the Vibrio cholera, which evokes an intense outpouring of watery fluid and electrolytes into the gut lumen, resulting in severe diarrhea and hypovolemic shok.

• Vibrio cholera is comma-shaped, gram-negative bacteria that have been caused of seven great long-lasting epidemics (pandemics) of diarrheal disease. Vibrio cholera locates in water often.

• The only significant natural reservoir of cholera appears to be humans, and the only clinically significant portal of entry is the alimentary tract by the fecal-oral route. V. cholera are appreciably sensitive to normal gastric acidity.

• The incubation period is usually 1 to 5 days, after which a profuse watery diarrhea occurs usually without tenesmus or abdominal distress.

• Fluid loss can exceed 10 liters per day. Prostration is therefore rapid and profound.

• The disease is ordinarily self-limited, with death or recovery occurring within a few days. An asymptomatic convalescent carrier state is uncommon but can occur.

• Drinking water contaminated with V. cholera and food prepared with contaminated water is infectious. Those with a normal gastric acidity are much less susceptible than those with low levels of stomach acid as a result of a gastrectomy or other cause. Vibrios traverse the stomach, enter the small intestine and propagate.

Clinical-morphological stages of cholera

1. **Choleric enteritis** is characterized by the hard diarrhea. Morphologically: swelling ofenterocytes, serous edema of the intestine mucosa.

2. **Choleric gastroenteritis** is characterized by the hard diarrhea and vomit, increase ofdehydration. The loss of sodium and water causes severe diarrhea, called **«rice-water stool».** Fluid loss may exceed 1 liter per hour.

3. **Choleric exicosis (algid):**

• Acute dehydration, hypovolemic shock, and metabolic acidosis follow quickly.

• The patient exhibits dry skin, sunken eyes, lethargy, cyanosis, a weak pulse, faint heart sounds, hemoconcentration, and elevation of serum proteins. The hematocrit may rise to 55–65 and the plasma specific gravity to 1.035–1.050. Patients are usually a febrile; body temperature may be subnormal.

• Rigor mortis develops quickly and persists for several days. The outlines of the muscles are well pronounced **(«gladiator posture»).**

• The skin is dry, creasy (especially on the fingers, **«beef-steak hands»**). Due to rapid development of rigor mortis, resembles **«goose's skin».**

• The mucous membranes, subcutaneous fat and muscles are dry; the muscles become dark red. The blood in the veins is thick, dark. The serous membranes are also dry, covered with sticky transparent mucus, which is stretched out in the form of threads.

• Changes in different organs due to dehydration (spleen, liver, gallbladder, kidneys, myocardium, brain) can be.

• The spleen diminishes, its capsule becomes creasy, the follicles are atrophic, and pulp hemosiderosis is observed.

• Degeneration and focal necroses in the liver develop. Bile formation is disturbed. The gallbladder is not distended, filled with clear light bile **(«white bile»).**

• Necrotic nephrosis of the main portions of nephron (the changes observed in oliguria and acute renal failure) is noted in the kidneys.

• There are degenerative and necrobiotic changes in the brain and myocardium.

• Treatment is prompt rehydration, and under such circumstances most patients survive. After the onset of diarrhea, urine production ceases, but renal function improves when fluid and electrolytes are replaced. Inadequate replacement, however, leads to prolonged renal failure, with acute damage of tubules and the vacuolar lesions of hypokalemia.

Complications

There are nonspecific and unspecific complications of cholera. Cholera typhoid and post-cholera uremia are specific complications. Nonspecific complications are pneumonia, abscesses, phlegmon, erysipelas, and sepsis.

The death occurs in algid period and is caused by dehydration, coma, uremia, and intoxication.At present owing to early adequate treatment (administration of water and salts, antibiotics) the death rate has been considerably decreased.

Escherichia coli Infection

Escherichia coli, a gram-negative bacillus that is part of the intestinal flora, is also an importantopportunistic pathogen, causing diarrhea and dysentery, urinary

tract infections, pneumonia, and neonatal meningitis. E. coli causes at least three patterns of human enteric diseases: enterotoxigenic,enteroinvasive, and enteroadherent.

1. Enterotoxigenic E. coli causes a diarrheal disease by elaborating two plasmid-mediatedenterotoxins. The heat-labile toxin is antigenically, structurally, and functionally related to the cholera toxin, although the toxin of E. coli is less potent than that of cholera. As in cholera, the resulting activation of adenylcyclase produces a hypersecretory diarrhea. The heat-stable toxin of E. coli is different from cholera toxin and apparently acts to impair sodium and chloride absorption and to reduce the motility of the small intestine. Dehydration and electrolyte imbalance is a significant cause of morbidity and mortality when appropriate rehydration is lacking — a common combination among infants in less developed countries. Enterotoxigenic E. coli is also responsible for 50 % of traveller's diarrhea.

2. Enteroinvasive E. coli produces a dysentery-like disease resembling shigellosis, although itis less severe and requires a much larger infecting dose of organisms. Enteroinvasive E. coli invades the intestinal mucosa and causes local tissue destruction and sloughing of necrotic mucosa. Bloody mucoid stools contain neutrophils.

3. Enteroadhesive E. coli has only recently been associated with diarrheal diseases.Enteroadhesiveness is plasmid-dependent and is apparently mediated by pili, which bind tightly to receptors on the intestinal epithelial cells. The mechanism of diarrhea is unknown.

About 80 % of all infections of the urinary tract in humans, ranging from mild cystitis to fatal pyelonephritis, are caused by E. coli. In addition, E. coli is the etiologic agent in many cases of nosocomial pneumonia, most often in elderly patients with underlying chronic disease. Aspirates of endogenous oral flora containing E. coli appear to be the cause of this bronchopneumonia, although in bacteremic patients pneumonia may result from seeding by septic emboli. Empyema is a common complication, especially in patients with disease lasting more than a week.

Only rarely does E. coli cause meningitis in adults, but it is a major cause of neonatal meningitis. Between 40 and 80 % of infants with E. coli meningitis die, and the survivors frequently suffer from neurologic or developmental anomalies.

Tuberculosis

- Tuberculosis is a chronic communicable disease with specific granulomatous inflammation caused by a variety of tubercle bacilli, especially Micobacterium tuberculosis hominis and M. t. bovis.
- The organism is a strict aerobe and thrives best in tissues with high oxygen tension like in the apex of the lung.
- The lungs are the prime target, but any organ may be infected. The characteristic lesion is a specifical granuloma with central caseous necrosis.
- Tuberculosis still continues to be worldwide in distribution, more common in poorer countries of Africa, Latin America and Asia. Other factors contributing to higher incidence of tuberculosis are malnutrition, inadequate medi-

cal care, poverty, crowding, chronic debilitating conditions like uncontrolled diabetes, alcoholism and immunocompromised states like AIDS.

Mode of transmission

Human beings acquire infection with tubercle bacilli by one of the following routes:

By inhalation into the respiratory tract.

Ingestion. Through ingestion into GI tract leads to development to tonsillar or intestinal tuberculosis.

Inoculation. Through mucous membranes of mouth and throat, skin.

Transplacental route results in development of congenital tuberculosis in fetus from infected mother and is a rare mode of transmission.

Spread of tuberculosis

1. **Local spread.** This takes place by macrophages carrying the bacilli into the surrounding tissues.

2. **Lymphatic spread.** Tuberculosis is primarily an infection of lymphoid tissues. Primarycomplex is primary focus with lymphangitis and lymphadenitis.

3. **Hematogenous spread.** This occurs either as a result of tuberculous bacillemia because of the drainage of lymphatics into the venous system or due to caseous material escaping through ulcerated wall of a vein. This produces millet seed-sized lesions in different organs of the body like lungs, liver, kidneys, bones and other tissues and is known as miliary tuberculosis.

4. **By the natural passages.**

Infection may spread from:

Lung lesions into pleura (tuberculous pleurisy).

Transbronchial spread into the adjacent lung segments.

Tuberculous salpingitis into peritoneal cavity (tuberculous peritonitis). Infected sputum into larynx (tuberculous laryngitis).

Swallowing of infected sputum (ileocecal tuberculosis). Renal lesions into ureter and down to trigone of bladder.

Hypersensitivity and immunity in tuberculosis

Hypersensitivity or allergy, and immunity or resistance, plays a major role in the development of lesions in tuberculosis.

Tissue changes seen in tuberculosis are not the result of any exotoxin or endotoxin but are instead the result of host response to the organism, which is in the form of development of cell-mediated hypersensitivity (or type IV hypersensitivity) and immunity.

Tissue reaction to tubercle bacilli is different in healthy organism not previously infected (primary infection) from an organism who is previously infected (secondary infection).

1. In the primary infection, intradermal injection of tubercle bacilli into the skin evokes no visible reaction for 10–14 days. After this period, a nodule develops at the inoculation site, which subsequently ulcerates and heals poorly. This process is a manifestation of delayed type of hypersensitivity and is comparable to primary tuberculosis in children.

2. In the secondary infection, the tubercle bacilli are injected into the skin who has been infected with tuberculosis 4–6 weeks earlier. In 1–2 days, the site of inoculation is indurated and dark, attaining a diameter of about 1 cm. The skin lesion ulcerates which heals quickly and the regional lymph nodes are not affected. This is called **Koch'sphenomenon** and is indicative of hypersensitivity and immunity in the host.

Hypersensitivity and immunity are closely related and are initiated through T lymphocytes sensitised against specific antigens in tuberculin.

Tuberculin (Mantoux) skin test. This test is done by intradermal injection of 0.1 ml of tuberculoprotein, purified protein derivative (PPD). Delayed type of hypersensitivity develops in individuals who are having or have been previously infected with tuberculous infection which is identified as an indurated area of more than 15 mm in 72 hours. However, patients having disseminated tuberculosis may show negative test due to release of large amount of tuberculoproteins. A positive test is indicative of cell-mediated hypersensitivity to tubercular antigens but does not distinguish between infection and disease. The test may be false positive in atypical mycobacterial infection and false negative in sarcoidosis, some viral infections, Hodgkin's disease and fulminant tuberculosis.

Immunisation against tuberculosis. Protective immunisation against tuberculosis is induced by injection of attenuated strains of bovine type of tubercle bacilli, Bacilli Calmette Guerin (BCG). Cell-mediated immunity with consequent delayed hypersensitivity reaction develops with healing of the lesion, but the cell-mediated immunity persists, rendering the host tuberculin-positive and hence immune.

Evolution of tubercule

- The sequences of events, which take place when tubercle bacilli are introduced into the tissue, are as under:
- The inhaled organism enters the alveolus and is ingested by the alveolar macrophage. The M. tuberculosis can either be killed by the macrophage; its growth inhibited or multiplies inside the macrophage.
- It behaves more like a parasite and lives in symbiosis with the cell.
- The macrophages start phagocytosing the tubercle bacilli. In 2–3 days, the macrophages undergo structural changes as a result of immune mechanisms — these modified macrophages resemble epithelial cells and are called **epithelioid cells.**
- The macrophages continue to enter the tissue either from circulating monocytes or from local proliferation. Release of cytokines in response to sensitised CD 4 + T cells and some constituents of mycobacterial cell wall play a role in formation of granuloma.

• Some of the macrophages form **multinucleated giant cells** by fusion of adjacent cells. The giant cells may be Langhans' type or they may be foreign body type. The giant cells may have 20 or more nuclei. These nuclei may be arranged at the periphery like horse-shoe or ring or clustered at the two poles, or they may be present centrally (foreign body giant cells).

• Around the mass of epithelioid cells and giant cells is a zone of lymphocytes, plasma cells and fibroblasts. The lesion at this stage is called **hard tubercle** due to absence of central necrosis.

• Within 10–14 days, the centre of the cellular mass begins to undergo caseation necrosis. This stage is called **soft tubercle**, which is the hallmark of tuberculous lesions.

• Acid-fast bacilli are difficult to find in these lesions and may be demonstrated at the margins of recent necrotic foci and in the walls of the cavities.

•In granuloma enclosed by fibrous tissue, calcium salts may get deposited in the caseous material (dystrophic calcification) and sometimes the lesion may even get ossified over the years.

Types of tuberculosis

I. Primary tuberculosis
II. Post primary tuberculosis
a) Secondary tuberculosis
b) Hematogenous tuberculosis

Primary Tuberculosis

• The infection of an individual who has pot been previously infected or immunised is called primary tuberculosis or Ghon's complex or childhood tuberculosis.

• Primary complex or Ghon's complex is the lesion produced at the portal of entry with foci in the draining lymphatic vessels and lymph nodes. Commonly involved tissues for primary complex are lungs and hilar lymph nodes.

• The incidence of disseminated form of progressive primary tuberculosis is particularly high in immunocompromised host (in patients of AIDS).

• The primary complex in lungs is located in the lower part of the right upper lobes or the upper part of the lower lobes in 3, 8, 9, 10 segments usually. The initial infection produces only slight abnormalities and may cause only slight malaise and mild fever.

• **Primary complex or Ghon's complex** in lungs consists of 3 components:

1. **Pulmonary component** (Primary affect or primary focus or Ghon's focus) is 1–2 cmsolitary area of tuberculous pneumonia surrounding by perifocal serous inflammation. It is located under the pleura, in the lower part of upper lobe and has white-yellow color and firm consistence.

2. **Lymphatic vessel component.** The lymphatics draining the lung lesion containphagocytes containing bacilli and may develop beaded, miliary tubercles

along the path of hilar lymph nodes. Tuberculous lymphangitis the lymphostasis and tuberculi along the edematous perivascular tissue occurs.

3. **Lymph node component.** This consists of enlarged hilar and tracheobronchiallymph nodes in the area drained. The affected lymph nodes are matted and show caseation necrosis.

• In the case of primary tuberculosis of alimentary tract due to ingestion of tubercle bacilli, a small primary focus is seen in the intestine with enlarged mesenteric lymphnodes producing tabes mesenterica. The enlarged and caseous mesenteric lymphnodes may rupture into peritoneal cavity and cause tuberculous peritonitis.

Fate of primary Tuberculosis

Primary complex may have one of the following sequelae:

I. Heal by fibrosis and in time undergo calcification and even ossification. In over 90 % of normaladults the infection follows this self-limited course, because the cellular immune response is sufficient to control the multiplication of bacilli. Therefore, in both the lung and the lymph nodes the lesions of the Ghon complex heal, undergoing shrinkage, fibrous scarring, and calcification. Most of the organisms die, but a few remain viable for years. Later, if immune mechanisms wane or fail, the resting bacilli may break out and cause serious tuberculous infection.

II. In some cases, the primary focus in the lung continues to grow called **progressive primarytuberculosis.**

1. Growth of primary parenhymal injury:

• The primary Ghon focus in the lung is characterized by enlargement of caseous necrosis, erodes the bronchial tree, and spreads, a sequence that results in adjacent «satellite» lesions.

• The lesion may enlarge in size and liquefy with a cavity formation (so called **«primarytuberculous caverna»**) as in an adult or produce an area of consolidation. The caseousmaterial can enter into a bronchus and then spread to other parts of the lung or the opposite lung, resulting in a tuberculous bronchopneumonia. When this happens the caseous material is discharged leaving an acute cavity. It must be differentiated from lung abscess caused by other conditions.

• A subpleural focus can involve the pleura and cause pleuris followed by pleural effusion.

• The infected material can by a retrograde spread, cause bronchial lesion and result in endobronchial ulceration and stenosis, which can produce either a complete or partial obstruction. This may lead to a segmental collapse, with compensatory emphysema or an obstructive emphvsema. If the collapse persists for a long time, the affected lung may become bronchiectactic.

2. Lymphogenous spreading:

• Lymphogenous spreading is characterized by involvement the new groups of lymph nodes, such as: paratracheal, supraclavicular, subclavian, cervical and development of tuberculous mezadenitis.

• The enlargement of the bronchial lymph nodes may cause extrinsic compression on the bronchus or erode into the adjacent structures. This leads to a variety of clinical symptoms and pathological changes and form the spectrum of progressive primary tuberculosis.

• The effect of external compression of the Iymph nodes on the bronchus is similar to what happens in the retrograde involvement from the parenchyma of the lung, complete or partial obstruction.

• The enlargement of the lymph nodes may produce a wheeze by compressing the bronchus.

The lymph node enlargement persists for a longer period and may cause further lymphatic or hematogenous spread.

3. Hematogenous spreading:

• The most serious immediate complication is miliary tuberculosis, in which there is invasion of the bloodstream by M. tuberculosis and dissemination throughout the body.

• The name «military» derives from their supposed resemblance to millet seeds.

• This occurs when the parenchymal part of the Ghon complex involves a pulmonary artery or vein and discharges its infected contents into the blood.

• Multiple minute granulomas develop in many organs of the body. The lesions are classically mm to 2 mm in diameter, yellowish white, and evenly distributed through the affected organ. A punctate area of necrosis may be seen in the center.

• Microscopically, the lesions of miliary tuberculosis consist of small granulomas, usually with a central necrotic portion in which numerous organisms are seen.

• Few organs are spared; those most often involved are the lung (mainly by recirculation of the organisms), spleen, liver, kidney, meninges, and bone marrow.

• Miliary tuberculosis used to be found most often in young children, but in industrialized countries it has become more common in the elderly and debilitated, in alcoholics, and in high-risk racial groups.

Postprimary Tuberculosis

Hematogenous Tuberculosis

The healed lesions of primary tuberculosis may get reactivated. The bacilli lying dormant in acellular caseous material are activated and cause progressive hematogenous tuberculosis.

Hematogenous tuberculosis appears after primary tuberculosis under following conditions:

The presence of sensibilization to tuberculin. Strongly pronounced immunity.

The presence of foci is healed after hematogenous generalization of primary tuberculosis (sifting).

Hematogenous tuberculosis is characterized by proliferative reaction or formation of the granulomas and hematogenous spreading.

Classification of Hematogenous tuberculosis:

1. Generalized hematogenous tuberculosis is more serious form with dessimenation of granuloms:

a) The most acute tubercular sepsis.

b) Acute general miliary tuberculosis.

c) Acute general large-focal tuberculosis. d) Chronic miliary tuberculosis.

2. Hematogenous pulmonary tuberculosis

a) Acute miliary tuberculosis. b) Chronic miliary tuberculosis.

c) Chronic large-focal tuberculosis or hematogenous-disseminative.

Features of hematogenous-disseminative tuberculosis:

- May by in adults only.
- Prevalence apex-plural localization.
- Proliferative tissue reaction.
- Development of the pneumosclerosis and emphysema of lungs.
- Cor pulmonale (hypertrophy of right ventricle of heart).
- Presence of unpulmonary tubercular foci.

2. Hematogenous tuberculosis with unpulmonary lesions or organic tuberculosis is characterizedby acute and chronic destruction and insufficiency of organs. It may be:

- Bone-articular. In tuberculosis of bones and cartilages tuberculous osteomyelitis-espccially spondylitis, coxitis (hip joint disease), gonitis develop.
- Tuberculosis of the kidneys.
- Tuberculosis of genital tract.
- Tuberculosis of skin.
- Tuberculosis of endocrine organs and others.

Tuberculosis of the brain is most important hematogenous localization. May cause meningitis or abscess. Meningitis is characterized by numerous granulomas in the leptomeninges, with features of chronic meningitis. Infection is most marked around the base of the brain and, even when infection is treated, there is often development of meningeal fibrosis to cause hydrocephalus. Tuberculous abscess, (tuberculoma) forms with infection of the brain parenchyma. A tuberculoma is typically a firm, lobulated mass of granulomatous inflammation with central caseous necrosis, up to several centimeters in diameter, and walled off by fibrous tissue. Lesions occur within the cerebral hemispheres, but are most common in the cerebellum. Treatment with antibiotics is usually ineffective and surgical excision is required.

Secondary Tuberculosis

Secondary tuberculosis usually results from reactivation of dormant, endogenous tubercle bacilli in a sensitized patient who has had previous contact with the tubercle bacillus. In some cases, the disease is caused by reinfection with exogenous bacilli.

Secondary tuberculosis may develop any time after primary infection, even decades later.

Reactivation typically begins in the apical or posterior segments (often 1-st and 2-nd segments) of one or both upper lobes **(«Simon's foci»)**, where the organisms were seeded during the primary infection. Only Pulmonary localization takes place.

Contact and intracanalicular spreading. Shifts of the clinical-morphological forms.

The symptoms of secondary tuberculosis begin with cough, which may be erroneously attributed to smoking or to a «cold». Low-grade fever develops, with general malaise, fatigue, anorexia, weight loss, and often night sweats. As the disease progresses, the cough worsen and the sputum may be streaked with blood. The rupture of a branch of the pulmonary artery in the wall of a cavity leads to massive hemoptysis and asphyxiation or exsanguination.

Forms or stages of the secondary tuberculosis

1. Acute local tuberculosis is characterized by specific endo-, meso-, and panbronchitis. During the treatment the exudative process is replaced by proliferative process. Foci of caseous necrosis are incapsulated and petrificated.

2. Fibrous-local tuberculosis forms due to intensification of acute local tuberculosis withformation of fibrous capsule.

3. Infiltrative tuberculosis is characterized by extension of perifocal inflammation.

4. Tuberculoma consists of focus necrosis surrauded by fibrous capcule. Size of tuberculomamay be near 2–5 cm. It must be differentiated from tumor of the lungs.

5. Caseous pneumonia develops due to progression of infiltrative tuberculosis. The caseousmaterial from a case of secondary tuberculosis in an individual with high degree of hypersensitivity may spread to rest of the lung producing caseous pneumonia. The caseous changes prevail over perifocal inflammation.

6. Acute cavernous tuberculosis develops due to lyses of caseous necrosis and characterizedby formation of the round cavity. It must be differentiated from primary cavernous tuberculosis.

7. Fibrous — cavernous tuberculosis is most frequent form. Macroscopically, the lesions arespherical and cavitary — the so-called coin lesions. A fibrous capsule surrounds a caseous, acellular center, which contains numerous tubercle bacilli. From these cavitary nodules the organisms can spread through the lungs and be discharged into the air during bouts of coughing. Microscopically, the wall of cavity shows eosinophilic, granular, caseous material, which may show foci of dystrophic calcification. Widespread coalesced tuberculous granulomas composed of epithelioid cells; Langhans' giant cells and peripheral mantle of lymphocytes and having central caseation necrosis are seen. The cuter wall of cavity shows fibrosis.

The wall of cavern has three membranes:

Internal membrane occurs by necrotic tissue.

Medium membrane occurs by special granular tissue. External membrane occurs by fibrous tissue.

Internal surface may be to connect with bronchus; therefore process spreads along bronchi into others sites of the lungs.

Complications of cavitary secondary tuberculosis

• Aneurysms of patent arteries crossing the cavity producing hemoptysis. Extension to pleura producing bronchopleural fistula.

Tuberculous empyema from deposition of caseous material on the pleural surface.

Thickened pleura from adhesions of parietal pleura.

8. Cirrhotic tuberculosis is a progressive variant of fibrous — cavernous tuberculosis. Lungsare deformed due to development of the diffuse pneumosclerosis.

These pulmonary lesions of secondary tuberculosis are often complicated by a variety of secondary effects, including

1. Scarring and calcification.
2. Spread to other areas.
3. Pneumothorax, pleural fibrosis and adhesions, with associated pleurisy, sharp pleuritic pain, and shortness of breath.
4. Rupture of a caseous lesion, which spills bacilli into the pleural cavity.
5. Erosion into a bronchus, which seeds the mucosal lining of bronchioles, bronchi, and 6. Implantation of bacilli in the larynx, which causes laryngitis, hoarseness, and pain on swallowing. Lesions of secondary tuberculosis acquired through the gastrointestinal tract (usually with M. t. bovis) can lead to entrapment of bacilli in lymphoid patches of small and large bowel.

Causes of death

• Chronic respiratory-cardiac insufficiency due to development cor pulmonale.
• Acute hemorrhage due to arrosion of vessels.
• Chronic renal insufficiency due to development of amiloidosis of kidneys.
• Due to intoxication and sepsis.

Syphilis

Syphilis (lues) is a sexually transmitted disease of mankind caused by the spirochetteTreponema pallidum.

Stages of syphilis:

1. Primary (the chancre).
2. Secondary (disseminated).
3. Tertiary (with lesions of deep organs following a latent period of 2 to 20 years or more).

The chancre develops at the site of inoculation in 10 to 90 days (average 21 days) and has a characteristic «luetic vasculitis», in which endothelial cells proliferate and swell, and the walls of the vessels become thickened by lymphocytes and fibrous tissue.

Morphology

In primary Syphilis, the ***chancre*** is a slightly elevated, firm, reddened papule, up to severalcentimeters in diameter that erodes to create a clean-based,

shallow ulcer. Histologically, the chancrecontains an intense infiltrate of plasma cells, with scattered macrophages and lymphocytes and an obliterative endarteritis. The regional nodes are usually enlarged and may show nonspecific acute orchronic lymphadenitis, plasma cell-rich infiltrates, or focal epithelioid granulomas. The combination of chancre, lymphangitis, and lymphadenitis is called **primary syphilitic complex.**

Secondary Syphilis. It presents as a widespreadskin rash (pox) of varying appearance,ulceration of mucous membranes, generalized lymphadenopathy, damage to various individual organs and tissues. There are constitutional effects — particularly fiver and anemia.

The essential pathology is the presence of very numerous spirochaetes accompanied by focal infiltration of lymphocytes, plasma cells and macrophages with mild arteritis. Infectivity is very high. Tissue destruction is minimal and healing occurs without scarring. A latent stage of long duration is followed in 35 % of cases by tertiary syphilis.

Tertiary (Late) Syphilis. The lesions, which may occur at any time for many years afterhealing of the secondary phase, offer striking contrasts. This stage is characterized mainly by local destructive lesions, the result of cell-mediated immune reactions (T-cells) causing necrosis of tissue. It occurs years after the initial infection and most frequently involves the aorta, the central nervous system, and the liver, bones and testes (gummas).

The main forms are:

1. Gumma.

This is a localized area of necrosis, which may affect large parts of any organ or tissue but particularly bones, testis and liver and looks like white-gray and rubbery formation.

In the liver, gumma may produce the coarsely nodular pattern of cirrhosis, termed hepar lobatum because of the simulation by the deep scars of multiple lobes.

Bone and joint gummas lead to areas of cortical and articular destruction. Pathologic features and joint immobilization may result.

Testicular gummas often cause painless enlargement of the affected testis, thus simulating a tumor.

Histologically, the gummas contain a center of coagulated, necrotic material and margins composed of plump or palisaded macrophages and fibroblasts surrounded by large numbers of mononuclear leukocytes, chiefly plasma cells.

2. Syphilitic aortitis. The aorta is affected by an infiltration of lymphocytes and plasma cellsbeginning around the vasa vasorum and extending into the media, causing weakening due to focal destruction (windowing) of the specialized elastic tissues. There is compensatory irregular thickening of the intima (tree-bark appearance), but the important effect is expanding aneurysm formation.

3. Neurological Syphilis. Neurosyphilis takes one of several forms, designated meningovascularSyphilis, tabes dorsalis, and general paresis.

Meningovascular — mainly affects the meningeal blood vessels and causes neurological impairment secondary.

Parenchymatous:

a) General paralysis of the insane — severe destruction of cerebral tissue, atrophy of convolutions, enlargement of ventricales;

b) Tabes dorsales — the damage specifically affected the posterior roots and columns of spinal cord — is associated with characteristic clinical symptoms due to lose of proprioceptive sensation in the legs.

Congential syphilis is most severe when the mother's infection is recent. In perinatal andinfantile Syphilis, a diffuse rash develops. Syphilitic osteochondritis and periostitis affect all bones. Destruction of the vomer causes collapse of the bridge of the nose and, later on, the characteristic saddle nose deformity. Periostitis of the tibia leads to excessive new bone growth on the anterior surfaces and anterior bowing, or saber shin. The liver is often affected severely in congenital syphilis. Diffuse fibrosis permeates lobules to isolate hepatic cells into small nests. Gummas are occasionally found in the liver, even in early cases. The lungs may be affected by a diffuse interstitial fibrosis.

The late-occurring form of congenital syphilis is distinctive for the triad of interstitial keratitis, Hutchinson's teeth, and eight-nerve deafness.

XII. SEPSIS

Sepsis is general infectious disease caused by infections getting into the organism and differsfrom other infectious diseases.

Sepsis is severe disease with high lethality. The death rate in sepsis is very high. The incidence of sepsis has increased recently which is associated with the appearance of antibiotic-resistant strains of bacteria and administration of cytostatic preparations causing immune system insufficiency.

Epidemiological feature is polyetiology (except viruses), not infectious illness. Sepsis may be cause by different causative agents (staphylococci, streptococci, pneumococci, meningococci, blue pus bacilli, tuberculosis mycobacteria, typhoid bacilli, fungi and other agents, except for viruses).

Sepsis is not contagious; it cannot be reproduced experimentally.

Clinical features irrespective of the character of the activator displays of illness are stereotyped, are stipulated by generalization of infection and inadequate reaction of organism on the infection.

The course of the disease is not cyclic, as it is observed in many infections.

There is no certain incubate period. The duration of the disease is different (from some days to several months and even years), that is why some forms of the disease may be defined, i.e. very acute, acute, subacute, and chronic.

Immunologic peculiarity of the sepsis is that immunity is not formed at this disease; inadequate reaction on the activator develops, hyperergic reaction prevails.

Morphological feature is the fact that the local and general changes have no specific features as it is observed in many infections.

Pathogenesis

• Sepsis is a special form of interaction of macro- and microorganism, significance of which is equivalent.

• Hyperergic reaction of the organism on infects and absence of immunity stimulates generalization of infection, acyclic course, prevalence of general reaction and losses of the ability to locate infection.

Morphology

1. Local changes:

• Local changes occur by the primary focus of infection (portal of entry) or at some distance, in some cases it is absent.

• Usually it is a focus of purulent inflammation, sometimes with no changes.

• The infection propagates from the focus through the lymph and blood vessels.

• Lymphangitis, lymphothrombosis and lymphadenitis, but also phlebitis and thrombophlebitis quickly develop.

• There is purulent thrombophlebitis, progressing to thrombobacterial embolism.

2. General changes:

• General changes at sepsis have degenerative, inflammatory and hyperplastic character.

•Degenerative changes develop in parenchymatous organs and often finish by the necrosis.

• The inflammatory processes in parenchymatous organs and vessels occur.

• Inflammatory changes are represented by interstitial septic nephritis, hepatitis, myocarditis, and acute polypous-ulcerative endocarditis with the tissue melting and tearing off of the valve.

• Vasculitis, intoxication, increasing of vascular permeability, anemia stimulates the hemorrhagic syndrome.

Hyperplastic processes develop in blood-creating and lymphatic tissues.

• Hyperplastic processes in sepsis are observed mainly in the hemopoietic and lymphoid tissue.

• Bone marrow hyperplasia occurs in the flat bones. The yellow bone marrow of the tubular bones becomes red.

• In blood leukocytosis and, sometimes, immature leukocytes are found, the so-called leukemoid reaction develops.

• Peripheral lymphonodes are increased; spleen is acutely increased, flabby on cut and of red color. Spleen produces large scrap of pulp **(«septic splenitis»).**

• Hyperplastic processes in histiocyte-macrophage system are the cause of the liver enlargement.

• Hemolytic jaundice may result from hemolytic action of some bacterial toxins.

Classification of sepsis

A number of features are taken into account in classification.

According to the etiology: staphylococcal, blue pus bacillus and association of these microorganisms, meningococcal, pneumococcal, gonococcal, colibacillary, anthracic, tuberculous.

II. According to portal of entry of infectious agent (location of the septic focus).

— Therapeutic (parainfectious).
— Tonsilogenic sepsis.
— Surgical.
— Uterine.
— Otogenic.
— Odontogenic.
— Umbilical.
— Pulmonary.

Septicemia

- It is a form of sepsis, for which toxicosis (high temperature, delirium) are characteristic, increased reactivity of organism (hyperergia), absence of purulent metastases and rapid course.
- The etiology is frequently streptococcus.
- Primary septic focus is frequently absent.
- The skin and sclera are usually yellow (hemolytic jaundice).
- Hemorrhagic syndrome is well pronounced (petechial rash, hemorrhages to the serous and mucous membranes and internal organs).
- Hyperplasia of lymphoid and hemopoietic system is typical: the spleen is enlarged, with pulp scraping («septic spleen»). The lymph nodes are also enlarged.
- Proliferation of lymphoid and reticular cells as well as accumulation of mature and immature blood cells are found in the spleen and lymph nodes.
- Increased hemopoiesis with formation of a large number of immature forms is noted in the bone marrow of the flat bones and in the diaphyses of the bones.
- The foci of extramedullar hemopoiesis appear.
- Interstitial inflammation develops in the parenchymal organs (heart, liver, kidneys). The stroma of the organs is edematous; infiltration by neutrophils, lymphocytes, and histiocytes is noted.
- Septicemia is also characterized by increased vascular permeability, fibrinoid changes in the vessels, allergic vasculitis that is responsible for hemorrhagic syndrome.

Septicopyemia

- It is the form of sepsis, main attributes of which are purulent processes in the entrance of infection and bacterial embolism with formation of abscesses in many organs and tissues.

• In contrast to septicemia, hyperergy signs are moderate; the course of the disease is not very acute.

• The development is assosiated with staphylococcus and blue pus bacillus.

• At the dissection there is primary septic focus, it is usual in the entrance of infection with purulent lymphangitis and lymphadenitis.

• The purulent thrombophlebitis in the primary septic focus is a source of thrombobacterial embolism, which causes the creation of metastatic abscesses in organs.

• At first metastatic abscesses appear in the lungs, then in the liver, kidneys (apostematous nephritis), subcutaneous fat, bone marrow (purulent osteomyelitis), synovial membranes (purulent arthritis), the heart valves (acute septic polypous-ulcerative endocarditis).

• Besides, purulent pleuritis and pericarditis develop in the cases of lung abscess. In liver abscess, purulent peritonitis develops. Kidney abscesses are complicated with peri- and paranephritis; skin abscess is complicated with phlegmon.

• Hyperplastic processes in blood-creating lymphatic tissue are expressed more poorly. The lymphatic nodes are not increased.

• Spleen is septic.

• Interstitial inflammation in parenchymatous organs is moderate or is absent.

Septic (bacterial) endocarditis

• It is the form of sepsis, for which septic lesion of valves of the heart is characteristic.

• Hyperergia occurs and it can be considered to be bacterial septicemia.

• The presence of primary septic focus on valves of the heart stimulates hyperergic damage of cardiac — vascular system.

• The most often causative agents are staphylococcus albus, aureus, streptococcus viridian, and enterococcus.

• In the basis of hyperergia reactions of hypersensitivity lays, stimulated by toxic immune complexes circulating in the blood, containing antigen of activator and causing to generalized vasculitis.

• Increasing of vascular pemerability, thromboembolic syndrome, cellular reactions of stroma are marked.

Classification

According to the character of course:

Acute (about 2 weeks). Subacute (till 3 months).

Chronic (months and years).

Depending on the presence of the background disease, septic endocarditis (especially subacute and acute) is divided into 2 types:

On unchanged valves (intact valves) — primary septic endocarditis (Chernogybov's disease), in 20–30 % of cases.

Developed on changed valves (defective) — secondary septic endocarditis in 70–80 % of cases.

Morphology

- Polypous-ulcerative endocarditis develops on both sclerotic and intact valves.
- Large thromboembolic polyp-shaped plaques appear on sclerotic valves.
- The plaques are easily crumbled and are saturated with calcium, which is characteristic for the disease.
- After removal of the plaques, ulcerative defects are seen in the sclerotic and deformed cusps of the valves.
- Thrombotic plaques are located not only on the cusps but also on the parietal endocardium.
- When the aortic valves are injured, the disease involves the aortic intima.
- The spleen is enlarged due to prolonged pulp hyperplasia; there are infarcts in the organ.
- Immune-complex diffuse glomerulonephritis develops in the kidneys. Infarctions and postinfarction scars are frequently observed.
- Interstitial inflammatory processes, vasculitis, hemorrhages, infarctions are observed in different organs.
- The foci of softening and hemorrhages are observed in the brain due to vascular changes (vasculitis, aneurysm) and thromboembolism.
- The so-called peripheral signs of septic endocarditis are:

a) Petechial hemorrhages in the conjunctiva near the internal angle of the lower eyelid («Lukin-Libman spots»).

b) Nodular thickening on the palm surface of the hand («Osler's nodes»).

c) Thickening of the nail phalanges («drum sticks»).

d) Necrotic foci in the subcutaneous fat. Hemorrhages to the skin and subcutaneous fat (Jeinway's spots).

e) Jaundice.

- Thromboembolic complications are frequent, as the source of thromboembolism; thromboendocarditis is most commonly localized in the left heart.
- Thromboembolism frequently becomes generalized and dominates in the clinical picture of the disease.
- The embolisms give the rise to infarctions in the lungs, spleen, kidneys, retina, and skin necrosis, gangrene of the extremities, intestine, foci of softening in the brain.
- In spite of the presence of streptococci in the thrombi, suppuration in the tissue is absent which suggests hyperergic reaction of the organism in septic endocarditis.

Chronic septicemia

- This form of sepsis is characterised by durably availability, not healing primary septic focus.

• These septic foci can be found in carious teeth, tonsils but more frequently they are large suppurations resulting from wounds.

• Extensive purulent processes, causing to intoxication, progressing exhaustion (cachexia) and amyloidosis take place.

• In organs and tissues there is atrophy, dehydration are expressed.

• Brown atrophy is found in the liver, myocardium, and striated muscles.

• The spleen is decreased.

Septic shock

Septic shock is currently the most common cause of death in intensive care units.

It results from the spread of microbes from severe localized infections (e.g., abscess, peritonitis, pneumonia) into the bloodstream.

The majority of cases are caused by endotoxin-producing gram-negative bacilli — E. coli, Klebsiella pneumonia, Proteus species, Pseudomonas aeruginosa, Serratia, and Bacteroides — hence the term endotoxic shock.

Endotoxins are bacterial wall polysaccharides, consisting of a toxic lipid A core component and a complex polysaccharide coat. Gram-positive cocci, such as pneumococci and streptococci, and certain fungi, as well as gram-positive bacterial toxins produce a similar syndrome.

Shock is a progressive disorder that may lead to death.

Shock tends to evolve through three stages:

1. An initial nonprogressive phase during which reflex compensatory mechanisms are activated and perfusion of the vital organs is preserved.

2. A progressive stage characterized by tissue hypoperfusion and onset of an ever-widening circle of circulatory and metabolic imbalances.

3. In finally, an irreversible stage that sets in after the body has incurred cellular and tissue injury so severe that even if therapy corrects the hemodynamic defects survival is not possible.

Morphology

• These reactive features are nonspecific and are present in most bacterial septicemias.

• Shock is characterized by hypoxic failure of multiple organ systems, and hence the cellular changes may appear in any tissue. They are particularly evident in the brain, heart, lungs, kidneys, liver, spleen, adrenals and gastrointestinal tract.

• In the **brain** the so-called ischemic encephalopathy may develop.

• The **heart** may undergo a variety of changes. Subendocardial hemorrhages and necrosis, or «zonal lesions», sometimes appear in all forms of shock. The term zonal lesions refers to apparent hypercontraction of a myocyte, including shortening and scalloping of the sarcomere, fragmentation of the Z band,

distortion of the myofilaments, and displacement of the mitochondria away from the intercalated disc.

• The **kidneys** may be severely affected in shock, and that is why oliguria, anuria, and electrolyte disturbances constitute major clinical problems. The renal changes are referred to as acute tubular necrosis.

• The **lungs** are seldom affected in pure hypovolemic shock because they are resistant to hypoxic injury, but when the vascular collapse is caused by bacterial sepsis or trauma, changes may appear that are referred to as «shock lung». They are referred to as the acute respiratory distress syndrome.

Splenomegaly of moderate degree (250 to 350 g) is common in acute systemic infectionsand is referred to as «acute reactive hyperplasia» or «septic splenitis». The spleen is enlarged and soft, and the cut surface demonstrates an equal prominence of the red and white pulp. Lymphoid hyperplasia with germinal center formation is pronounced, and plasma cell hyperplasia is present in the marginal zone of the white pulp and in the cords. Histiocytic hyperplasia is equally prominent.

The abscesses of the **liver** may take place also.

The **adrenal** alterations encountered in shock comprise in essence those common to all forms of stress and so might be referred to as «the stress response».

The **gastrointestinal tract** may suffer patchy mucosal hemorrhages and necroses referred to as «hemorrhagic enteropathy».

Virtually all of these organs changes may revert to normal if the patient survives. However, loss of neurons from the brain and of the myocytes from the heart is, of course, irreversible. However, most patients who suffer shock so severe as to produce irreversible changes succumb before these alterations become well developed.

It is evident that postshock course of the patient does not lack for threats to life. The prognosis varies with the origin of shock and its duration.

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