ЗМІСТ

Pathomorphology: textbook

Про книгу

The textbook is written by a group of authors of the pathological anatomy department of Kharkiv National Medical University. The modern actual information on general and special pathomorphology is presented in English. The textbook consists of two parts. The first part is devoted to general pathological processes: damage of cells and tissues, regeneration and adaptation, circulation disorders, inflammation, immune pathology, basics of oncology and tanatology. The second part covers the pathomorphology of diseases according to the nosological principle. The morphological manifestations of pathological processes are described using the newest research methods at the organ, tissue, cellular and subcellular levels, with high-quality illustrations (see colour inserts) of macro- and microspecimens. The edition is supplemented with the chapter Oral Pathology, which allows it to be of use for students of the dentistry faculty. For English-speaking students of higher medical education establishments of Ukraine in the specialties “general medicine”, “dentistry”.

Pathomorphology

TEXTBOOK

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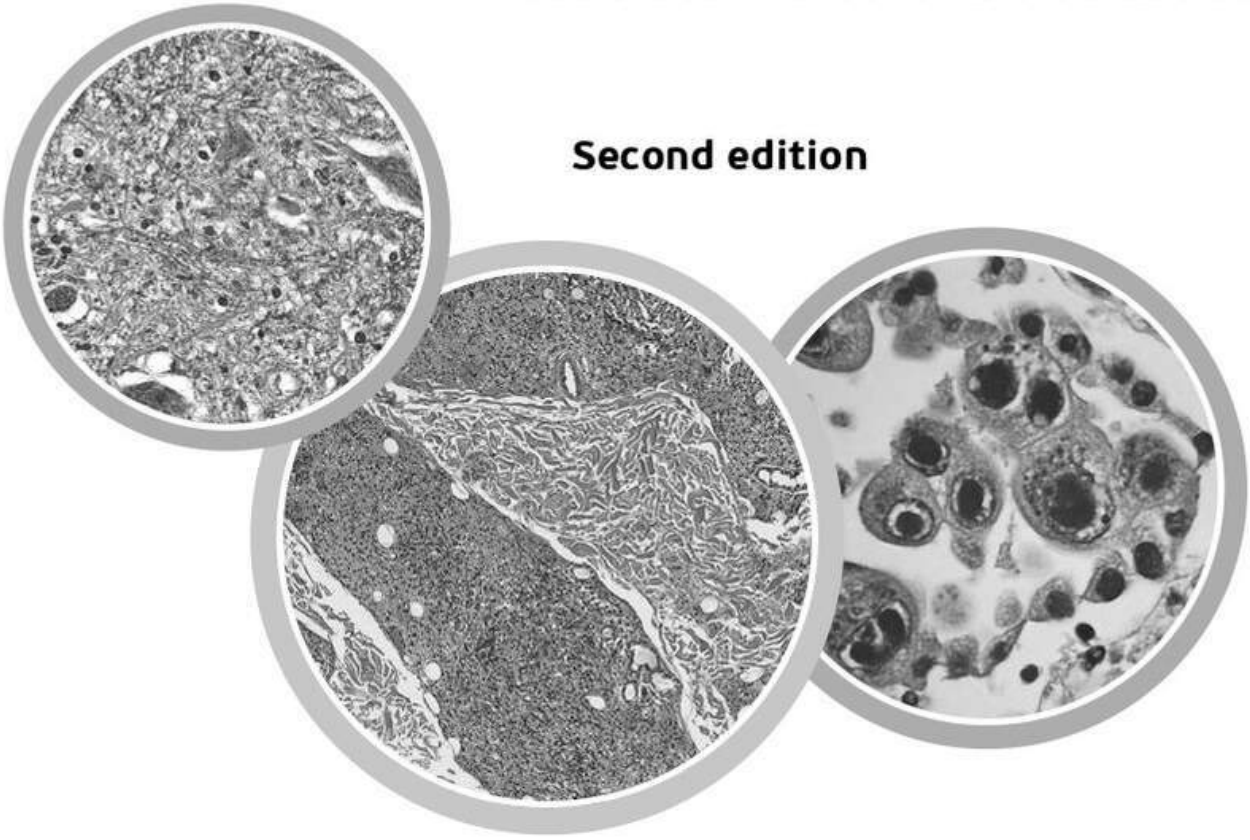

Second edition

APPROVED
by the Academic Council of Kharkiv National Medical University as a textbook

Kyiv
AUS Medicine Publishing
2020

UDC 616-091(075.8)
LBC 52.5ya73
P31

Approved by the Academic Council of Kharkiv National Medical University as a textbook (minutes No. 2, 22 February 2018)

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Pathomorphology : textbook / I.V. Sorokina, V.D. Markovskyi, D.I. Halata
P31 et al. ; edited by I.V. Sorokina, V.D. Markovskyi, D.I. Halata. — 2nd edition. — Kyiv : AUS Medicine Publishing, 2020. — 328 p. + 2 colour inserts (8 p. + 12 p.).
ISBN 978-617-505-790-2

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CARDIOVASCULAR PATHOLOGIES

1

ATHEROSCLEROSIS

> **ATHEROSCLEROSIS** is a chronic disease affecting primarily the intima of the large and medium-sized arteries and is characterised by fibrolipid plaques or atheromas. Atherosclerosis is the most common vascular disease.

Epidemiology. It is known that the most frequent cause of death (40 %) is cardiovascular pathology, most of which are related to atherosclerosis. Epidemiologic investigations on living populations have revealed a number of *risk factors*, which are often acting in combination rather than singly.

The first of them is *age*. However, early atherosclerotic lesions may be present in childhood. In scientific research, which has been performed at the Pathological Anatomy department of Kharkiv National Medical University, morphological signs of atherosclerosis were found in the foetus's and newborn's aortas.

The second risk factor is *sex*. The incidence and severity of atherosclerosis is higher in men than in women.

Genetic factors play a significant role in atherosclerosis. There is family predisposition to atherosclerosis, which may be related to other risk factors like diabetes, hypertension and hyperlipoproteinaemia.

Geographic factors also play a role. There is a high incidence of atherosclerosis in Europe, Australia and the USA. Many studies have demonstrated specific effects of diet including the amount of dietary cholesterol ingested on the lipid and lipoprotein levels.

Hypertension is a major risk factor in atherosclerosis development. It acts probably by mechanical injury of the arterial wall due to increased blood pressure. Other factors are diabetes mellitus, smoking, obesity etc.

Pathogenesis. There are several pathogenesis theories of atherosclerosis: Virchow's, Rokitansky's, Anychkow's, Benditt's. Historically, two hypotheses of atherogenesis were dominant: one emphasised cellular proliferation in the intima as a result of accumulation of plasma proteins and lipids from the blood, whereas the other postulated that organisation and repetitive growth of thrombi resulted in plaque formation. The contemporary view of the pathogenesis of atherosclerosis incorporates elements of both older

theories and is called the response to injury hypothesis. Formulated in 1973 and modified in 1986 and 1993, it states that atherosclerotic lesions are initiated as a response to some form of injury of the arterial endothelium. The injury is a form of endothelial dysfunction, which increases permeability to plasma components, including lipids and permits monocytes and thrombocytes to adhere to the endothelium. Monocytes adhere and subsequently enter the intima, transform into macrophages and accumulate lipid to become foam cells, contributing to the evolution of the lesion. Factors released from activated thrombocytes at the surface or monocytes then cause migration of smooth muscle cells from media into the intima, followed by proliferation and synthesis of extracellular matrix components by smooth muscle cells, leading to the accumulation of collagen and proteoglycans. Endothelial function can be recovered after single or short-term injuries. Repeated or chronic injury, however, results in the development of an atheromatous plaque, probably due to increased permeability, ingress of monocytes or thrombocytes interactions.

Morphology. Atherosclerosis passes through certain stages of development, which have some definite *gross* (*macroscopic*) and *microscopic* characteristics.

Grossly, there are the following types of atherosclerotic changes (Fig. 8-1).

(1) *Intimal thickening* of arteries may be a part of atherosclerotic process, particularly rapid during the first two decades of life. Macroscopically the lesions may appear as small white areas of intimal cushion at the bifurcation and branching of arteries, or may appear as "diffuse intimal thickening". Microscopically, the lesions consist of smooth muscle cells, fibrous tissue, some collagen but no lipid and thrombus.

(2) *Intimal xanthoma* ("fatty streak") is especially prominent in the aorta and major arteries, more often on the posterior wall than the anterior wall. Grossly, the lesions may appear as flat or slightly elevated and yellow. They may be either in the form of small (about 1 mm in size) or elongated streaks. Microscopically, fatty streaks are composed of closely-packed foam cells, lipid-containing elongated smooth muscle cells and a few lymphoid cells. A small amount of extracellular lipid, collagen and proteoglycans is also present. The cholesterol esters in foam cells of fatty streaks differ chemically from those in the lipid core of atheromatous fibrous plaque. These dissimilarities might be explained on the basis of two types of fatty streaks, which differ in morphology, cellular genotype and lipid content, with one type related to the fibrous plaque and the other type not related.

(3) *Fibrous Plaque (Atheroma).* The lesions are raised, pearly white to grey, smooth-surfaced, plaque-like structures in the intima but may extend into the media, may encroach considerably on the vascular lumen, especially in muscular arteries such as coronary arteries. On cross section a typical lesion has a soft, yellow central zone with gruel-like material covered on the luminal aspect by a layer of dense fibromuscular tissue (fibrous cap).

In general, plaques are found most often in the abdominal aorta, large arteries of the lower limbs, carotid arteries, coronary arteries.

The histologic appearance of lesions varies considerably depending on the relative amounts of different components. The central atheroma of an uncomplicated fibrous plaque consists of acellular, amorphous, electron-dense material that contains lipids, cellular debris, fibrin and other plasma proteins. The fibrous cap is composed of avascular connective tissue and elongated smooth muscle cells covered with endothelium. In-

flammatory cells, including macrophages, may be present. In older and more advanced lesions the collagen in the fibrous cap may be dense and hyalinised, smooth muscle cells may be atrophic and foam cells are fewer.

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

Complications include:

a) *Calcification:* the intima is brittle and cracks like an eggshell when the vessel is opened (Fig. 8-2). Microscopically, the dystrophic calcification process involves both the fibrous cap and the atheromatous portion of the plaque.

b) *Ulceration and Thrombosis*. Advanced fibrous plaques with calcification may ulcerate as a result of mechanical or haemodynamic forces. With ulceration, cholesterol or lipid debris from the atheroma may be discharged and leads to embolism. Mural thrombi may form on the ulcer or at sites of endothelial damage. Such thrombi also may become organised and incorporated within the intimal plaque. Mural thrombi in medium-sized arteries may progress to occlusive thrombi, which can be recanalised.

c) *Haemorrhage* into atherosclerotic plaque is a common finding in advanced lesions, especially in the coronary arteries. The blood may reach the lesion from the vascular lumen through surface ulcerations or from the rupture of capillaries that have vascularised the atheroma from the adventitial vasa vasorum.

d) *Secondary Changes in the Media*. Fragmentation of the internal elastic lamina with atrophy of the smooth muscle cells that can lead to aneurysmal dilatation, especially in elastic arteries.

Microscopically, the following states of atherosclerosis are distinguished:

- *pre-lipidosis,*
- *lipidosis* (Fig. 8-3),
- *liposclerosis,*
- *atheromatosis,*
- *ulceration,*
- *atherocalcification.*

The **clinical effects** result from the following:

- Slow luminal narrowing causing ischaemia and atrophy.
- Sudden luminal occlusion causing infarction necrosis.
- Propagation of plaque by thrombi and emboli formation.
- Formation of aneurysm and eventual rupture.

Clinico-morphological types of atherosclerosis are distinguished in accordance with the localisation. There are:

- atherosclerosis of the aorta,
- atherosclerosis of the coronary arteries (Fig. 8-4),
- atherosclerosis of the cerebral artery,
- atherosclerosis of the arteries of the lower extremities,
- atherosclerosis of the arteries of the small intestine,
- atherosclerosis of the renal arteries.

The symptoms of atherosclerotic disease involve most often the heart, brain, kidneys, small intestine and lower extremities. Some of the important effects are listed be-

low: *aorta* — aneurysm formation, thrombosis and embolisation to other organs; *heart* — myocardial infarction, ischaemic heart disease; *brain* — ischaemic or haemorrhagic stroke, cerebral haematomas, atherosclerotic dementia; *small intestine* — haemorrhagic infarction or gangrene; *lower extremities* — intermittent claudication, gangrene; *kidney* — atherosclerotic nephrosclerosis. Most of them may be a cause of death.

2
ISCHAEMIC HEART DISEASE

Ischaemic heart disease is a group of diseases due to lack of coronary circulation. Depending on the suddenness of onset, duration, degree, location and extent of the area affected by myocardial ischaemia, there are two types of ischaemic manifestation:

- Myocardial infarction.
- Non-infarct effects of myocardial ischaemia, which include: angina pectoris, chronic ischaemic heart disease and sudden cardiac death.

MYOCARDIAL INFARCTION

Myocardial infarction (MI) is the most significant in human pathology. In industrialised countries myocardial infarction accounts for 10–25 % of all deaths. About 5 % heart attacks occur in young people under the age of 40, especially with hypertension, diabetes mellitus, cigarette smoking etc. The usual cause of sudden blockage in the coronary artery is thrombus formation. The blood clot typically forms inside the coronary artery that already has been narrowed by atherosclerosis.

Sometimes MI is caused by non-atherosclerotic factors, such as coronary vasospasm, arteritis, embolism or trauma.

MI classification:

- According to the anatomic region of the left ventricle:

— *anterior*,
— *posterior*,
— *lateral*,
— *septal*,
— *circumferential*.

- According to the degree of thickness of the ventricular wall:

— *transmural* (when it involves the entire thickness of the ventricular wall),
— *subepicardial* (when it occupies the outer subepicardial part of the myocardium),
— *intramural* (when it occupies the medium part of the ventricular wall),
— *subendocardial* (when it occupies the inner subendocardial part of the myocardium).

- According to the moment of MI occurrence:

— *acute*: 8 weeks from the moment of ischaemia attack until complete scarring,
— *relapsing*: if one more MI develops during 8 weeks of present acute MI,
— *repeated* (recurrent): if MI occurs 8 weeks after acute MI.

MI is most frequently located in the left ventricle. The region of infarction depends on the area of obstructed blood flow by one or more of the three coronary arterial trunks. Stenosis of the left anterior descending coronary artery is the most common (40–50 %). Stenosis of the right coronary artery is the next most frequent (30–40 %). Stenosis of the left circumflex coronary artery is seen least frequently (15–20 %).

Morphology. The macroscopic and microscopic changes in MI depend on the morphologic stage of the MI. The first stage is ***necrotic*** (lasts for 30 min to 3–7 days) (Fig. 8-5) and the second stage is ***organisation*** (from 3–7 days to 8 weeks) when macrophages and young fibrocytes replace leucocytes and a scar forms (Fig. 8-6) (Table 7).

TABLE 7

Morphologic Changes in MI

Time	Macroscopic Changes	Microscopic Changes
Reversible Injury		
0–30 min	None	None
Irreversible Injury		
30 min – 4 h	None	None; sometimes waviness of fibres at the border
4–12 h	Occasionally dark mottling	Beginning coagulation necrosis; oedema; haemorrhage
12–24 h	Dark mottling	Coagulative necrosis; nuclear pycnosis; increased eosinophilia of cardiomyocytes; marginal contraction band necrosis; beginning neutrophilic infiltrate
1–3 days	Mottling with yellow-tan infarct centre	Coagulative necrosis with loss of striations and nuclei; interstitial neutrophilic infiltration
3–7 days	Hyperaemic border (haemorrhagic rim) with yellow-tan softening of infarct	Beginning disintegration of dead myofibres, with dying leucocytes; early phagocytosis of dead cells by macrophages at infarct margins
7–10 days	Maximally yellow-tan and soft, with depressed red-tan margins	Prominent phagocytosis of dead cells; beginning of granulation tissue formation at margins
10–14 days	Red-gray depressed infarct borders	Well-developed granulation tissue with new blood vessels and collagen deposition
2–8 weeks	Grey-white scar, progressing from margins toward the centre of infarct	Maturation of the connective tissue with decreased cellularity and increased collagen deposition
> 2 month	Scarring complete	Mature collagenous scar

Using special methods such as electron microscopy, chemical and histochemical studies, the changes can be demonstrated in early infarcts before detectable light microscopic alterations appear: 0–30 min (relaxation of myofibrils; glycogen loss; mitochondrial swelling); 30 min — 4 h (sarcolemmal disruption; mitochondrial amorphous densities).

Complications. About 10 % patients with acute MI develop *cardiogenic shock*, which is characterised by hypotension with systolic blood pressure of 80 mm Hg or less for many days. Shock may be accompanied by peripheral circulatory failure, oliguria and mental confusion. A lot of patients with MI suffer from *congestive heart failure*, which may be in the form of right ventricular, left ventricular failure or both. This complication is responsible for about 40 % of deaths from acute MI. *Arrhythmias* are the most common form of complication in acute MI. *Mural thrombosis and thromboembolism* are observed in 15–45 % cases of acute MI. Sometimes *heart rupture* may develop in the first week. It is often fatal. Cardiac aneurysm often develops in the left ventricle. It impairs the function of the heart and is a site for mural thrombi. *Fibrinous pericarditis* appears on about the second day of MI. As a rule, this complication develops in patients with transmural MI. About 3–4 % patients who suffered from acute MI develop *post-myocardial infarction syndrome* characterised by pneumonitis.

Non-Infarct Effects of Myocardial Ischaemia

Non-infarct effects of myocardial ischaemia include angina pectoris, chronic ischaemic heart disease and sudden cardiac death.

Angina pectoris is a clinical syndrome of coronary artery disease. Dystrophy and necrobiosis are revealed in the myocardial cells, due to which transient myocardial pain in the substernal or pericardial region of the chest occurs.

Chronic Coronary Artery Disease (myocardial fibrosis). Myocardial fibrosis (sclerosis) may be focal or diffuse. The mechanism of the development of myocardial fibrosis can be different. Grossly, the heart with diffuse myocardial sclerosis contains many little whitish areas of fibrous tissue, especially around the small blood vessels in the interstitial tissue of the myocardium. Focal cardiosclerosis develops due to previous myocardial infarction.

Sudden cardiac death is defined as sudden death within 24 hours of the onset of cardiac symptoms. In the majority of cases it is caused by coronary artery disease, coronary vasospasm, calcific aortic stenosis, myocarditis, hypertrophic cardiomyopathy, hereditary and acquired defects of the conduction system. The autopsy in such cases reveals most commonly critical atherosclerotic coronary narrowing.

3
HYPERTENSIVE VASCULAR DISEASE

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

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

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 hypertension, but are modified by genetic factors, environmental factors, sex (females tolerate hypertension better) and associated diseases.

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

– increased tonus of the sympathetic nervous system,
– increased release of renin and generation of angiotensin-2,
– the presence of vasoconstrictive substances in the circulation,
– increased sodium load and extracellular fluid load.

In a given individual, hypertension may be attributable to a combination of these factors.

Hypertension is classified into two types:

• *Primary or essential hypertension,* in which the cause of increase in blood pressure in unknown. This hypertension constitutes about 90–95 % patients of hypertension.

• *Secondary hypertension*, in which the increase in blood pressure is caused by diseases of the kidneys, endocrine or some other organs. This hypertension comprises 5–10 % causes of the disease.

According to the clinical course, both types of hypertension may be *benign* or *malignant.* Benign hypertension is moderate elevation of blood pressure and the rise is slow as the years pass. About 90 % patients of hypertension have benign disease. Malignant hypertension is marked and has a rapid increase of blood pressure to 200/140 mm Hg or more. Usually patients have papilloedema, haemorrhages and hypertensive encephalopathy.

PRIMARY (ESSENTIAL) HYPERTENSION

The cause of essential hypertension is unknown. But there are a lot of factors related to its development: genetic factors (the evidences in support are familial aggregation); racial and environmental factors (surveys in the US have revealed a higher incidence of primary hypertension in blacks than in whites). A number of environmental factors have been implicated in the development of this type of hypertension including salt intake, obesity, skilled occupation, higher living standards and patients in high stress.

There are some factors modifying the course of essential hypertension:

• age — younger age, at which hypertension is first noted but untreated, reduces life expectancy,
• sex — females tolerate hypertension better than males,
• atherosclerosis — as a rule, accompanies essential hypertension.

Pathogenesis:

• high plasma level of catecholamine,
• increase in blood volume, i. e. arterial overfilling (volume hypertension) and arteriolar constriction (vasoconstrictor hypertension),

- increased cardiac output,
- low-renin essential hypertension found in approximately 20 % patients due to decreased responsiveness to renin release,
- high renin essential hypertension due to decreased adrenal responsiveness to angiotensin 2.

Morphology. The morphologic effects of systemic hypertension are manifested as lesions in the heart, peripheral vessels, kidneys and brain. There are three clinical and morphological types of essential hypertension: *cardio-vascular*, *renal* and *cerebral*.

Hypertensive heart disease is an important and common form of heart disease all over the world.

Changes in the blood vessels involve arterioles and arteries.

There are two types of these changes:

- *hyaline arteriolosclerosis* that results in homogeneous eosinophilic thickening of the wall of small blood vessels, with narrowing of the vascular lumen,
- *intimal thickening* due to proliferation of smooth muscle cells in the intima.

The most significant gross feature is marked hypertrophy of the heart, especially of the left ventricle. The weight of the heart increases (cor bovinum) to 500–700 g (may be 1000 g) vs normal weight (about 300 g). The weight of the heart is directly related to the severity of hypertension, but there is no correlation between the weight of the heart and the duration of hypertension. The left ventricular wall is thickened (up to 20 mm or more), the papillary muscles are rounded and prominent and the cardiac chamber is small (concentric hypertrophy). However, when decompensation and cardiac failure develop, there is eccentric hypertrophy with thinning of the ventricular wall and dilation of the left ventricular and atrial cavities. There may be dilation and hypertrophy of the right heart as well. Atherosclerosis usually develops in the large blood vessels.

Renal type of hypertension may be benign and malignant. "Benign nephrosclerosis" is the term used to describe the kidney of benign phase of hypertension. Grossly, both kidneys are affected equally and are reduced in size and weight, often weighing about 100 g or less. The capsule is often adherent to the cortical surface. The surface of the kidney is finely granular (primary "shrunken" kidney). The cut surface shows firm kidney and narrowed cortex. Microscopically, there are primarily diffuse vascular changes, which produce parenchymal changes secondarily as a result of ischaemia (Fig. 8-7). There is a variable degree of atrophy of the parenchyma, which include glomerular shrinkage, deposition of collagen in Bowman's space, periglomerular fibrosis. Clinical features are variable: elevation of blood pressure with headache, dizziness, palpitation. Renal failure and uraemia may occur.

Cerebrovascular Diseases (Cerebral Type). Hypertension can result in two main types of parenchymal diseases of the brain:

- ischaemic brain damage (hypoxic encephalopathy and cerebral infarction),
- intracranial haemorrhage (intracerebral or subarachnoid).

The pathologic appearance of the brain in hypoxic encephalopathy varies depending on the duration and severity of the hypoxic episode and the length of survival. Grossly, there is focal softening. The area supplied by distal branches of the cerebral arteries suffers from the most severe ischaemic damage and may develop a border zone or watershed infarctions in the adjacent zones between the territories supplied by major ar-

teries. Microscopically, the nerve cells die and disappear and are replaced by proliferative glia.

Cerebral infarction (stroke) is a localised area of tissue necrosis caused by local vascular occlusion. Clinically, the signs and symptoms associated with cerebral infarction depend on the region infarcted. Cerebral infarcts may be ischaemic or haemorrhagic.

Grossly, an ***ischaemic infarction*** becomes evident 6–12 hours after its occurrence. The affected area is soft and swollen and there is a blurred junction between the grey and white matter. Within 2–3 days, the infarct undergoes softening and disintegration. A ***haemorrhagic infarction*** is red and usually the result of fragmentation of occlusive arterial emboli or venous thrombosis.

Intracerebral haemorrhage is presented by a cavity with blood in different areas of the brain and usually has hypertensive origin. A lot of patients with hypertension at middle age have a microaneurism in very small cerebral arteries in the brain tissue. The common sites of hypertensive intracerebral haemorrhage are the region of the basal ganglia, pons and cerebellar cortex. About 40 % patients die during the first 3–4 days of haemorrhage, mostly from haemorrhage into the ventricles. The outcome of intracerebral haemorrhage is cyst formation.

The causes of death among patients with hypertension are progressive heart failure; coronary artery disease; cerebrovascular accidents; uraemia. The cardiac complications therefore account for 36 % deaths.

SECONDARY HYPERTENSION

Like primary hypertension, secondary hypertension usually has no specific signs or symptoms, even if blood pressure has reached dangerously high levels. A number of conditions can cause secondary hypertension. These include:

1. Renal:
- vascular diseases (atherosclerosis, arteritis, thrombosis, embolism, tumours),
- parenchymal renal diseases (glomerulonephritis, pyelonephritis, amyloidosis, polycystic kidney disease, tumours),
- perinephric diseases (perinephritis, tumours, haematoma).

2. Cerebral:
- increased intracranial pressure (trauma, inflammation, tumours),
- anxiety states,
- sleep apnoea.

3. Cardiovascular:
- coarctation of the aorta.

4. Endocrine:
- pheochromocytoma,
- adrenocortical adenomas,
- pituitary adenomas,
- hyperthyroidism,
- diabetic nephropathy.

5. Pregnancy-induced hypertension or preeclampsia.

If these causes of secondary hypertension are eliminated, hypertension disease can cure.

4

SYSTEMIC DISEASES OF THE CONNECTIVE TISSUE WITH IMMUNE DISTURBANCES (RHEUMATIC DISEASES)

Rheumatic (collagen) diseases are a group of diseases including rheumatism, systemic lupus erythematosus (SLE), rheumatoid arthritis, scleroderma, nodular periarteritis, dermatomyositis as well as Bechterew's disease (spondylitis deformans).

As connective tissue involvement is the main link in the morphogenesis of these diseases, "systemic diseases of the connective tissue with immune disturbances" or "rheumatic diseases", which are also frequently used, replaced the term "collagen diseases" suggested by G. Klemperer in 1942.

This group of diseases is characterised by involvement of the connective tissue of a particular organ: heart in rheumatism; joints in rheumatic arthritis; joints and ligaments of the spinal column in Bechterew's disease; skin in scleroderma; vessels in nodular periarteritis; skin, vessels and kidney in lupus erythematosus; striated muscles in dermatomyositis;

Genetic and environmental factors are important for the development of these diseases. Thus, rheumatic arthritis has a less severe course in the residents of Africa than in those of Europe. Lupus erythematosus is more frequent in continental Europe and the USA than in Great Britain.

Morphologic features of rheumatic diseases:

1) early systemic changes of microcirculation,

2) systemic and progressive disorganisation of the connective tissue consisting of four phases: (a) mucoid swelling, (b) fibrinoid changes, (c) cellular reactions, (d) sclerosis,

3) combination of different phases of connective tissue disorganisation, which indicated the chronic character of the disease,

4) marked disturbance of immune homeostasis with immune organ hyperplasia,

5) involvement of the synovial membranes,

6) visceral disturbances.

RHEUMATISM

> **RHEUMATISM** (Sokolsky–Bouillaud disease) is an acute relapsing chronic disease of infectious allergic character, which involves mainly the heart and vessels.

Aetiology. Beta-haemolytic streptococcus of group A is a causative agent of rheumatism.

Pathogenesis. The pathogenesis is very complicated and is not clear. However, it is known that streptococcus invades the tonsils causing angina. Body sensitisation occurs and antibodies to streptococcus antigens are produced. Gradually under the influence of streptococcus antigens and their enzymes, immune reaction becomes inverted (autoaggression), because the antigenic properties of the human connective tissue are similar to