holics, and uremic patients. This condition always carries bad prognosis.

Septicemia with **disseminated intravascular coagulation** is usually accompanied by acrocyanosis and necrosis of the peripheral sites of the body. In some patients we may notice an initial nausea, vomiting, diarrhea or ileus. An upper GIT bleeding may appear.

If septic shock takes place in patients with another serious disease the prognosis is always bad. Mortality due to septic shock is about 25 %. The highest mortality occurs within the first 48 hours, and is caused by the irreversible shock with all its drawbacks.

3.20 Etiopathogenesis of atherosclerosis

In the last 40 years **cardiovascular diseases** are in all economically developed countries of the world the major cause of morbidity and mortality. Their substantial part is due to atherosclerosis. In our country the number of these diseases continues to increase in contrast to countries such as USA or Sweden where this number has been already decreasing for several years. The consequences of atherosclerosis in our country cause about 56 % of all deaths in the age between 35 to 65 years, i.e. in the working productive population. Furthermore, their occurence is shifting towards younger age groups. From the point of view of **pathological anatomy** the basis of atherosclerosis is a focal accumulation of lipid substances and an increased amount of connective tissue components within the arterial intima resulting in a subsequent oringin of focuses of pulpy fat-tissue debris known as atheromatous plaques. These plaques protrude into the arterial lumen and cause its narrowing. Within the atheromatous calcium salts may be deposited later (calcificated plaques). The consequence is a substantial loss of the arterial wall elasticity so that the arteries are no more able to allow for an increased blood flow during higher oxygen demands of the tissues.

The endothelium damage and the blood flow turbulence in the place of atheromatous plaques create conditions for **the mural trombus formation**. This trombus gets organized with time but with the repeated occurence of this process it in fact extends and progressively narrows or acutely occludes the artery.

In advanced stages of atherogenesis the atheromatous plaques undergo some relevant changes, e.g. disruption ulceration (cell necrosis on the top of the plaques), or intraplaque haemorrhage and intramural haemorrhage into the surrounding artery wall. Plaque disruption and ulceration considerably increase the disposiotion to the formation of superficial thrombi. Intramural haemorrhage also produces acute narrowing of the artery lumen. Advanced plaques affected by these changes, i.e. **calcification, ulceration, haemorrhage and thrombosis** are so-called "complicated atheromatous lesions". Only in this stage of atherosclerosis a clinically significant occlusion of the artery followed by ischaemia of the supplied region originates. Complicated atheromatous lesions may crumble and the pulpy fat-tissue debris and other constituents of the plaques may get loosened into the lumen of the artery and may be a source of microembolisation.

Atherosclerosis affects mostly aorta, elastic and elastic-muscular type of arteries (large and medium size arteries). Atherosclerotic lesions may develop separately only in one vessel region (e.g. in aorta, in coronary carotid, cerebral, legs, renal, or mesenterial arteries), or it may be a diffuse affection of the whole arterial system (generalized atherosclerosis). The affections of the coronary (ischaemic heart disease followed by myocardial infarction), cerebral (haemorrhage or encefalomalacy) and lower extremities (gangrene) arteries are the most frequent occurances with serious clinical consequences.

In conclusion, atherosclerosis is a long-term, very complicated and complex pathological process causing lesions of the arterial wall. It is asymptomatic for a long period of time and gets clinically manifest only when complicated atheromatous lesions occur. **Clinical consequences** of atherosclerosis appear particulary because of the occlusion of the corresponding artery, or sometimes because of the aneurysmatic dilation of the artery (an atheromatous lesion of the arterial wall leads to its weakening, which causes an aneurysm formation). Clinical symptoms differ according to the affected organ, or part of the vascular region.

In the past as well as at the present time great attention was focused upon the research of the **pathogenesis of atherosclerosis**. According to present knowledge atherosclerosis is not caused only by one pathogenetic stimulus, but undoubtedly by more factors of the internal and external environment which participate in its origin and development. Thus, atherosclerosis has a **multifactorial genesis**. According to the currently accepted hypothesis the first step at the beginning of the long-term developing process of atherogenesis is **the damage of the endothelial layer** of the arterial wall (the hypothesis of a repeated or chronic microtrauma of the endothelium). The most important **atherogenic factors** today are considered to be hemodynamic stress, low-density lipoproteins (LDLs), very low-density lipoproteins (VLDLs), vasoactive substances (mainly catecholamines and angiotensin), immunocomplexes, endo- and exo-toxins, hypoxia and viruses. The atherogenic factors may act separately or in combination. Their atherogenicity is multiplied by increasing their number. They damage the endothelium of the arteries by their mechanical, cytotoxic or metabolic effects.

Focal endothelial damage provokes in the place of its origin two processes which have very important role in atherogenesis:

- **increased endothelial permeability** to plasma macromolecules, especially lipoproteins (LDLs and VLDLs), which are increasingly transported into the intima.
- response of the arterial wall, which leads to **interactions between cellular blood** elements (platelets, leucocytes, monocytes and lymfocytes) and the **arterial wall**.

From the pathogenetic point of view the most important are adhesion and aggregation of platelets in the place of endothelial damage, and adhesion and penetration of circulating monocytes into the intima. So the atherosclerotic lesion develops as a reaction of the arterial wall to endothelial damage. This response has many signs of an inflammatory process (increased permeability, neutrophils and monocytes adhesion, monocytes migration).

The atherogenic factors can cause several types of a focal injury of the arterial endothelium. There are conected with breaking of the functional or morphological integrity of the endothelium. **A disorder of endothelial function** causes increase of transcellular transport of plasma lipoprotein macromolecules and may be manifested by:

1. An increasing number of pinocytic vesicles in the endothelial cells.
2. Formation of bigger pinocytic vesicles at the luminal pole of the endothelial cells.
3. Joining of the vesicles in the endothelial cell cytoplasm and forming big transport vesicles.
4. Forming transcellular channels after the fusion of pinocytic vesicles at the luminal and basal ends poles of the endothelial cells.

There are also several types of **disorders of the endothelial morphological integrity**:

1. A partial damage of compact intercellular junctions caused by intensive endothelial-cell contraction (vasoactive substances provoke the contraction of actin fibres in endothelial cells), or by the the direct demage of intercellular material by the atherogenic factor itself. Plasma is cumulating in these gaps and its components get into the cells by endocytosis not only through the luminal pole of the endothelial cells but also through their side wall.
2. A complete opening of the intercellular junctions. Blood components get straight into the subendothelial space through these intercellular ductuli, but also by endocytosis through the side wall of the endothelial cells.
3. Death of the endothelial cells (necrosis and desquamation). At the beginning there is a higher transport of plasma components through the anatomically damaged cells. Later, after their desquamation, there is a straight connection between blood and the subendothelial tissue.
4. Endothelial cells can flatten, and so, because of a path shorthening, an increase of transcellular transport of plasma macromolecules may occur.

Many observations from the last years showed that the relationship between endothelial injury and atherogenesis is not as simple and straight as it had been believed initally. It was concluded that for the

origin and development of the atherosclerotic lesion the status of the morphological integrity of the endothelium is not so decisive as the actual **functional status of the endothelial cells**. Crucial is the functional integrity disorder of the endothelium, i.e. a dysfunction of endothelial cells. When trying experimentally to deendothelize the artery it was found that in places with a new endothelial layer there was a thicker intima and an accumulation of larger amount of lipids in the subendothelial space than in those parts of the artery wall which were still noncovered by the endothelium. This means that at the beginning of reendothelization the function of the new endothelium is not fully recovered. So, for the lipid accumulation in the intima the endothelial functional status is more important than its anatomical presence. That shows that for atherogenesis the **transcellular transport of plasma lipoprotein macromolecules into the intima** of the artery is more important than their intercellular transport. It means that it is not the absence of the endothelium, but rather its dysfunction that will cause a higher lipid accumulation in the intima and its thickening.

Although we gained much new information there is still missing an exact definition of **the endothelial dysfunction**, the presence of which is a crucial condition for the development of arterial wall atherosclerotic lesion. It seems that the dysfunction may manifest itself not only by a higher transendothelial transport of lipoprotein macromolecules, but also by decreased prostacyclin synthesis, increased synthesis of the endothelial cells growth factor, glycosaminoglycans and by decreased tissue plasminogen activator synthesis in endothelial cells. The presence of other changes of metabolism and function of endothelial cells are also presumed.

In the place of endothelial damage (caused by atherogenic factors) **adhesion and aggregation of platelets** and the release of the content of their granules occur immidiately. This is the next important step in pathogenesis of atherosclerosis. There is evidence that the adhesion of platelets can occur also on a morphologically intact surface of endothelium, e.g. during a decreased synthesis of endothelial cell prostacyclin (PGI_2) and an increased synthesis of platelets tromboxan A_2(TXA_2), which result from hypercholesterolemia and hyperlipoproteinemia.

The substances released from the granules of the activated platelets potentiate the agreggation of more platelets, damage endothelial cells, increase endothelium permeability, iniciate the inflammatory reaction of the damaged arterial wall and stimulate the migration and proliferation of media smooth muscle cells. From the platelet factors the most important for atherogenesis are:

1. ADP and tromboxan A_2 – powerful potentiating factors of platelets aggregation.

2. Serotonin, which increases the permeability of the endothelium.

3. Lysosome enzymes – destructing the surrounding tissue and thus further increasing the endothelial permeability.

4. The **platelet-derived growth factor** which is of the greatest importance for the patogenesis of atherosclerosis. It iniciates migration of smooth muscle cells from the media through the openings in internal elastic lamina into the intima and also stimulates their proliferation.

There is evidence that vascular myocytes proliferation is stimulated also by some plasma components, which get into the subendothelial area because of the endothelium permeability disorder. These are low density lipoproteins (LDLs), fibrinogen and insulin. It seems though that the platelet-derived growth factor plays a crucial role in the initial state of atherogenesis. It acts as a starter of myocytes migration and proliferation. The above-mentioned plasma components cumulating in the intima below the place of the endothelium damage have only a supporting role in stimulating of the proliferation of migrated myocytes.

What is the **role of monocytes in the pathogenesis of atherosclerosis** – that was the question mainly for intensive recent studies. It was demonstrated that on the luminal surface of the artery, at the place of endothelial damage, margination and adhesion of circulating monocytes occur very soon. It is followed by their penetration between the endothelial cells and so they become localized subendothelialy where they undergo conversion into macrophages.

The migration mechanism of blood monocytes into the subendothelial space of the arterial intima is not exactly known yet. It seems that their adhesion to the vascular endothelium is initiated by platelets, which are the first from the blood cells ahering to

the arterial wall in the damaged part of endothelium. The platelet-derived growth factor is chemotactic not only for media smooth muscle cells, but also for circulated monocytes. It is presumed that in migration of blood monocytes also participate the chemotactic factor of the damaged endothelial cells, the smooth muscle cells chemotactic factor and the chemotactic factor of macrophages cumulated in the intima. In the last years the attention of experts is concentrated especially on the oxidized LDLs. They study not only their participation in monocytes migration but mainly their role and mechanisms of action in the pathogenesis of atherosclerosis. During a long-lasting hypercholesterolemia and hyperlipoproteinemia the molecules of plasma LDLs circulate for a longer time, so there is a higher probability that their molecules will be oxidized, acylated, or otherwhise modified. Oxidized LDL molecules are not only very cytotoxic, but when transported into the intima they can be chemotactic for monocytes and in that way induce their migration.

Clinical and experimental studies have shown that **monocyte – macrophages** may participate in atherogenesis by several mechanisms the most important of which are:

1. Synthesis and release of the growth factor, which stimulates the proliferation of myocytes in the arterial wall.
2. Accumulation of lipids followed by formation of macrophage-derived "foam cells" of the atherosclerotic lesion.
3. Production of reactive forms of oxygen.
4. Release of some types of proteases.
5. Modulation of the arterial wall imune reaction.
6. Chemotactic factor production.

It seems that in the proliferation of arterial wall myocytes **the macrophage-derived growth factor** is at least as important as the platelet factor. Platelets adhesion to the arterial wall and the release of the content of their granules is most intensive in the first 24 hours after the endothelial damage. Therefore, some authors presume that a continuous presence of monocyte-macrophages in the intima below the damaged endothelium could be important not only at the beginning, but mainly in the subsequent phases of atherosclerotic lesion development. The interaction between blood monocytes and neutrophils, and the arterial endothelium already from the first hours after endothelium damage as well as the following accumulation of monocyte-macrophages in the intima below the damaged place are signs of inflammatory mechanisms participating in atherogenesis.

A subject for intensive studies is also the role of participation of **the endothelial cell growth factor** in the proliferation of arterial wall myocytes. Beside the fact that this factor is released from the undamaged cells around the place of the endothelial desquamation (the aim is the reendothelisation), its production can probably be stimulated also when a dysfunction of endothelial cells due to hypercholesterolemia and hyperlipoproteinemia occures.

In connection with the participation of arterial wall myocytes in atherogenesis it is important to mention the hypothesis **of benign neoplastic origin of** the myocytes population with the **autonomous proliferation** in the atherosclerotic lesion. Several methods have shown that myocytes of the atherosclerotic lesion have a monoclonal origin (are derivated from one cell or one clone of myocytes). This hypothesis presumes that it is a reaction of media myocytes to unnown mutagenic factors, e.g. chemical substances or viruses. On the other hand there are some findings showing that early atherosclerotic lesions are not monoclonal but polyclonal. And so it seems that the monoclonal lesions develop only later due to the selection of cell subpopulations during the development of atherosclerotic lesion. Some scientists see the basis for monoclonal origin of atherosclerotic lesion myocytes in the fact that some media myocytes are tetraploic or more polyploic. It is especially this genoma instability which is brought into relationship with the greater proliferation readiness. The hypothesis of monoclonal origin of atherosclerotic lesion myocytes is not in contradiction to the hypothesis of the crucial role of endothelial dysfunction and growth factors production in atherogenesis. It is only its supplementation - though in another type of the mechanism of arterial wall myocytes proliferation. Smooth muscle myocytes of the arterial wall have preserved the characteristics of multipotent mesenchyma cells. **After the myocyte migration from the media into the intima** their contractile status changes to a synthetic status. After having migrated into intima and having lost their contact with other media myocytes

they get very sensitive to the effect of growth factors, which stimulate them to intesive proliferation. In the intima proliferated accumulated myocytes begin **an intensive synthesis and a production of connective tissue matrix**, i.e. collagen, elastin and glycosaminoglycans, mainly dermatan sulfate and heparan sulfate. There is evidence that a higher content of glycosaminoglycans in the subendothelial space is caused by their higher synthesis and production by damaged endothelial cells. Glycosaminoglycans and mainly dermatan sulfate have a high affinity to low-density lipoproteins and together they create a nonsoluble complex. That is why their higher production is supposed to play an important role in lipoprotein accumulation in arterial intima.

Smooth muscle cell multiplication, and collagen, elastin and glycosaminoglycans accumulation in the intima result in the formation of the **fibromuscular plaque** which is considered to be an early atherosclerotic lesion.

Recent imunohistochemic studies have shown that not only in the early but also in the advanced atherosclerotic lesions T-lymphocytes and imunocomplexes are often present beside monocyte-macrophages. Their presence in an atherosclerotic lesions hints at imune mechanism participation in atherogenesis. An accelerated development of atherosclerosis was observed in patients with a high concentration of circulating imunocomplexes and also in patients with a heart transplantation (a very fast development of coronary arteries atherosclerosis).

From the early stages of atherogenesis, i.e. when a fibromuscular plaques aris, the arterial wall lesions may continue to develop in two directions. **If the atherogenic factor will not be effective any more** the endothelial cells will regenerate and restore their normal function. The result of the previous lesion is only a mild local thickening of the intima having one ore two layers of myocytes. Smooth muscle cells are normally not present in the intima there. During the lifetime the vascular system of everyone probably undergoes many such microtraumas of the endothelium. Under favourable circumstances these always regenerate and the result is only a cellular fibrous thickening of the arterial intima.

On the other hand, if the effect of **the atherogenic factor operates repeatedly or continuously**, the atherosclerotic process progresses. In the place of the early atherosclerotic lesion myocytes proliferation and production of connective tissue components continue. The intimal myocytes accumulate large amounts of lipids, mainly cholesteryl esters. This process of intracellular lipids deposition is followed by formation of **myocyte-derived "foam cells"**. However, in progressing atherosclerotic lesions lipids are mainly accumulated in mono- cyte-macrophages of the intima and these are transformed into **macrophage- derived "foam cells"**. The amount of foam cells in intima is progressively increasing. Later many of these lipid overloaded foma cells rupture and necrotize and release their lipids droplets into the surrounding extracellular space. So besides the continuous intracellular lipid accumulation there is present also their extracellular deposition. These progressing atherosclerotic lesions of the arterial wall are spreading and deepening. This process results in the formation of advanced atherosclerotic lesions called **"atheromatous plaques"**. The core of this advanced plaques contains fat-cellular debris (necrotic foam cells, extracellular lipid droplets, cholesterol crystals and later also deposits of calcium salts). This central core of atheroma is at the luminal side of the artery covered by a fibromuscular layer (collagen and elastin fibrils and smooth muscle cells), called a **"fibromuscular cap"**.

As mentioned above, the terminal stage of atherogenesis results in **complicated atheromatous lesions**. Their characteristics are ulceration, superficial thrombosis, haemorrhage and/or calcification. Only these complicated lesions cause the origin of serious clinical symptoms of atherosclerosis.

Recently the investigators have focused on the study of **the mechanism of lipid accumulation in monocyte-macrophages** and their transformation into foam cells of the atherosclerotic lesion. It is well-known that under physiological circumstances there is a continuous transendothelial lipid transport from blood into intima and media, and so the nutrition of these two layers is provided directly from the vessel lumen. On the contrary, the nutrition of the adventitia is provided by its own capillaries – vasa vasorum. Under physiological conditions there is a balance between the supply and the consuption of lipids in vessel cells, respectively their removing from arterial wall. One of the crucial pathogenetic mechanism of atherogenesis is breaking this balance followed by

lipid accumulation in intima cells (macrophages and myocytes).

The most important plasma cholesterol-carriers are LDLs. LDLs transport cholesterol mainly from the place of its synthesis (in the liver) to tissues (also to the arterial wall), and that is why they are such an atherogenic factor. High density lipoproteins (HDLs) contain less amount of cholesterol than LDLs, and they are the main transport system of cholesterol from the extrahepatic tissues (that means also from the arterial wall) to the liver, where cholesterol is degraded into bile acids. To a certain extent HDLs protect the arterial wall from the devepolment of atherosclerosis and so they are called "antiatherogenic lipids".

Most tissues, including arterial wall smooth muscle cells can take up plasma LDLs with the help of **membrane LDL-receptors**. After a LDL-molecule links with a cell receptor, an endocyte vacuole arises and is hydrolysated by lysosome enzymes. LDLs are catabolised according to the needs of the cell. The interaction between LDLs and membrane LDL-receptors has the basic influence on intracellular cholesterol metabolism. An increase of intracellular cholesterol concentration inhibits its synthesisin the cell, increases its esterification and inhibits the number or the activity of the membrane LDL-receptors. This LDL catabolism regulation through a feedback mechanism protects cells against uncontrolled uptake and intracellular cumulation of cholesterol. A disability of cells to degrade LDLs is due to a complete lack or a great insufficiency of membrane LDL-receptors, as it is e.g. in familial hyperlipoproteinemia (type II.).

In various pathological conditions the plasma level of **oxidized** or otherwise **modified LDLs** can increase. In contrast to native LDLs, modified LDL-molecules are not well recognized by membrane LDL-receptors. Therefore their catabolism is not regulated by the feedback mechanism, but by compensatory way, when especially monocyte-macrophages come into play and these become progressively transformed into foam cells. The alternative way of taking up chemically modified LDLs is provided via a mediation of monocyte-macrophages specific membranereceptors, known as **scavenger receptors** (acyl-LDL-receptors). Owing to the mediation of these receptors, but also to beta-VLDL-receptors the arterial intima macrophages are able to accumulate a great amount of lipids (mostly cholesteryl esters) because these receptors do not respond to the feedback regulation. It leads to their transformation into fat-laden foam cells.

Thus, it can be concluded that pathologically increased modification, especially the oxidation of LDL molecules plays the key role in the development of intima foam cells and, therefore, also in pathogenesis of atherosclerosis. Oxidized LDLs may be involved in atherogenesis also due to their cytotoxic effect upon endothelial and smooth muscle cells of the arterial wall.

In recent years a great deal of scientifical activity has been focused on the study of **the role of long-chain polyunsaturated fatty acids** in atherogenesis. There are several experimental and clinical observations, which indicated that the esential fatty acids participate in the development of atherosclerotic lesions, as well as in their thrombotic complications. It was shown that cause of low mortality from ischaemic heart disease in Eskimos and partly also in Japanese is due to a regular consuming of large quantitis of sea fish. In the fish oil there is a high ratio of polyunsaturated fatty acids to saturated fatty acids. Further it was found that among the polyunsaturated fatty acids of seafood the majority is represented by omega-3 (eicosapentaenoic acid – $C_{20:5}$,n-3 and docosahexaenoic acid – $C_{22:6}$,n-3) and not omega-6 fatty acids (linoleic acid – $C_{18:2}$,n-6, arachidonic acid – $C_{20:4}$,n-6 and docosapentaenoic acid – $C_{22:5}$,n-6). There is evidence that **omega-3 fatty acids** have a protective effect in atherogenesis. Meals prepared from fish (mainly mackerel and carp) are highly recomended as an important part of the anti-atherogenic diet. On the contrary, vegetable oil contains mainly **omega-6 fatty acids**, in particular $C_{18:2}$,n-6 and $C_{20:4}$,n-6. But some vegetable oils (walnut, rape-seed, soya beans and flax-seeds) contain also a bigger amount of linolenic acid ($C_{18:3}$,n-3) which is one of omega-3 fatty acids.

It was found that **the eicosapentaenic acid** ($C_{20:5}$,n-3) is a false substrate for prostaglandins synthesis. Instead of TXA_2 which is (synthetized from $C_{20:4}$,n-6) and causes aggregation and vasoconstriction, in platelets is syntetized TXA_3 which has reduced platelet aggregatory effect. On the other hand, the arterial wall endothelial cells synthesize from eicosapentaenoic acid prostacyclin PGI_3 that is biologically fully active – antiaggregating and vasodi-

lating features are the same as those of PGI_2 which is synthesized from arachidonic acid – $C_{20:4}$,n-6. PGI_3 so increases the total antiaggregating activity of prostacyclins. Besides that, it seems, that eikosapentaenoic acid competitively inhibits cyclooxygenase, which also results in the reduced TXA_2 production. Recent observations showed that omega-3 fatty acids have also other beneficial effects. They reduce triacylglycerides and VLDLs plasma concentrations, they inhibit the production of reactive oxygen forms in neutrophils and monocytes, they inhibit the production of the growth factors in trombocytes, endothelial cells, monocytes and fibroblasts, they mildly decrease blood pressure, they significantly inhibit the synthesis of an important inflammatory mediator – leukotriene LTB_4 (synthetized from arachidonic acid) and stimulate the production of LTB_5, which has a much smaller inflammatory effect. From the therapeutic point of view and especially from the point of prevention of atherosclerosis the presented results of experimental and clinical studies pointed out the importance of regular intake of substances inhibiting the oxidized-LDLs production (antioxidants). These characteristics are already known in vitamines E,C and A, but there is an intensive search for other such substances. An adequate regular fish meal consuming has also protective effect. From the clinical point of view it may be useful to look for specific growth factor antagonists, or drugs that could inhibit their production in platelets, monocyte-macrophages and endothelial cells of the arterial wall.

Finally, according to the present knowledge, the **process of atherogenesis** comprises 5 main stages:

1. **A disorder** of functional and/or morphological integrity of the endothelium (the origin of endothelial dysfunction).

2. **Cumulation of cells** (myocytes, monocyte-macrophages, T-lymphocytes) in the intima of the artery wall.

3. **Production of connective tissue components** (collagen, elastin, glycosaminoglycans) in the intima which leads to the origin of the fibromuscular plaque.

4. **Accumulation of lipids** in the intima monocyte-macrophages and myocytes, and their successive **transformation** into foam cells. Later, necrosis of foam cells and extracellular lipid deposition occur which result in the origin of the atheromatous plaque.

5. The origin of **complicated atheromatous lesions** (ulceration, superficial thrombosis, calcification and haemorrhage) which are conected with the manifestation of serious clinical symptoms of atherosclerosis.

3.20.1 Atherosclerosis of important vascular regions

3.20.1.1 Atherosclerosis of lower extremities

Atherosclerotic changes in vessels may cause a **stenosis** (narrowing) or an **obliteration** (complete closure) of the vessel lumen.

In the stenotic portion there is acceleration of the blood flow with laminar flow changing to turbulent (this is the basis for a vascular murmur). Also the endothelium distal to the stenosis is being damaged. The collagen thrombogene structures are naked, a thrombus arises and further deteriorates the arterial stenosis.

From the clinical point of view we distinguish a **proximal** stenosis or obliteration - above the popliteal artery branching (to this group belong also patients with ischaemic disease of the lower extremities due to an affection of the iliac arteries or the abdominal aorta), a **distal** stenosis (the affected place is below the popliteal artery branching) and a **combined** stenosis, when both areas are affected. Distal and combined occlusions of the limb have a much worse prognosis and risk of a gangrene. If atherosclerosis gets manifested after 45 years of age, more often a proximal affection occurs, with a better prognosis.

A more progressive stage of the atherosclerotic process is characterized by a complete arterial occlusion. As the whole process takes usually a long time, during the continuous artery narrowing there is enough time to develop a collateral system to provide at least a limited blood supply behind the complete occlusion of the main artery. Patients with a complete arterial stop is typically suffered from **intermittent claudication**. The pain appears when the blood flow through the narrowed artery is insufficient to cope with the metabolic demands of the working muscles. This pain is sharp or blunt and relieves after 2 or 3 minutes of rest. A lower pain intensity

depends in some cases on the ability of the circulation to increase hyperaemia in the affected limb and to eliminate the substances which are causing pain. According to the pain location we can predict the level of the arterial occlusion. Later on, nerve trunks hypoxia develops resulting in ischaemic neuropathy with resting pain, in supine position, or at night. In later stage of the disease trophic defects, mainly painful ulcerations and gangrene, appear on the skin. They often result from minor injuries.

The absence of the pulse on one of the limb arteries and the decreased skin temperature of the affected area can be very helpful for estimating the diagnosis. Important are the functional tests of the blood flow in lower extremities, the reflectory vasodilatation test, the measurement of the distal pressure with Doppler ultrasound method and angiography.

3.20.1.2 Closure of the abdominal aorta

is usually caused by atheroma located in the aortic bifurcation followed by thrombosis. This process sometimes has its origin in the iliac artery and is continuing to the abdominal aorta and also to the contralateral iliac artery.

It may be manifested by pain in the thigh and in the gluteal muscles. The closure of the abdominal aorta can continue proximally and may lead to an occlusion of the renal or mesenteric arteries causing abdominal angina.

To verify the diagnosis translumbal aortography is needed.

Similar clinical signs may be observed when a closure of the iliac artery is present, however the pain in the thigh and in the gluteal muscle may be one-sided. A vasculogenuous impotence may be present.

3.20.1.3 The aortic arch syndrome

The aortic arch is the most frequent location where atherosclerotic lesions occur. A closure of the arterial branches arising from the aortic arch can also be found, manifesting with clinical signs of the upper limb, face, central nervous system or the eyes.

3.20.1.4 Closure of carotid arteries

The affection of the external carotid is manifested by claudication pain of the chewing muscles, face atrofia, severe paradentosis. An isolated closure is rare.

The closure of the internal carotid in its extracranial part plays a major role in 1/3 of cerebral strokes.

3.20.1.5 Closure of the subclavian artery and the upper limb arteries

The subclavian artery closure is manifested as the ischaemic disease of the upper limb. If the occlusion is located before the origin of the vertebral artery a so called "steal" phenomenon may occur. The CNS circulation receives less blood, while this is flowing according to a pressure gradient through the vertebral artery to a vasodilated upper limb circulation (the vasodilatation as a result of ischaemia). Clinical signs are headache, sight disturbance, vertigo or syncope during working with the upper limb.

Atherosclerotic occlusions of the upper limb itself are extremely rare.

3.20.1.6 Acute arterial closures

Acute arterial closures are sudden events. The limb survival, but often also patient's life depends on the earliest possible therapeutic intervention.

Most often they are caused by thrombosis or embolism, more rarely by dissecting aneurysm or by ileofemoral venous thrombosis.

Acute arterial thrombosis usually develops in the place of intimal damage, most often due to a sclerotic process.

About 50 % of patients feel a pain like a lash of a whip. The affected limb is pale and cold. After the vasospasm remission the pain relieves and changes to ischaemic neuralgia with paresthesia. The colour of the extremity changes to marbly with ecchymoses. Ischaemia of the nervous trunks may cause limb plegia and anesthesia. A gangrene may follow.

3.20.2 Aorta diseases

The aorta as an outflow vessel is heavily loaded with changing blood pressure depending on heart output. Aorta is an elastic vessel. During the systole it distends according to the blood output volume, in diastole it recoils to its previous position so that blood is ejected to the periphery. Aortic damage most often occurs in places of the greatest mechanical stress.

The most common aorta diseases are pathological dilations – aneurysms. It is a dilation of a particular

aortic segment. The real aneurysm is a pathological dilation of all three aortic layers. In a pseudoaneurysm there is a tear in intima and media, while adventia is dilated. In a fusiformed aneurysm the aorta is dilated all around its circumference. In a saccular aneurysm only a part of the circuit is affected. Aneurysms of the aorta are usually caused by atherosclerosis. The most common location is the abdominal aorta. The ascending aorta is affected by cystic medial necrosis. Aortic aneurysms are most often clinically silent. Sometimes pain occurs. Troubles may be caused also by compression or by erosion of the surrounding tissues. In the dilated area thrombi may occur and may cause a peripheral embolisation. Aneurysms may get perforated. A perivascular bleeding is accompanied with a pain and tension feeling.

3.20.2.1 Atherosclerotic aneurysms

are usually located in the abdominal aorta below the origin of the renal arteries. Most often they are asymptomatic. During abdominal palpation a pulsation may be discovered. The ultrasound examination will establish the diagnosis. The prognosis depends on the extent of the aneurysm. One half of the very big aneurysms end-up lethally in two years when not treated surgically.

Cystic medial necrosis is a degenerative process when collagenous and elastic fibres of the aorta change into a mucoid matherial. Affected is the proximal aorta. A fusiformed aneurysm develops. It often occurs in Marfan's syndrome but also in pregnacy and with hypertension.

Intimal disruption of the aorta. It's origin is not exactly known but basicaly it occurs in places of the greatest mechanical load. Most often the external part of the aortic arch is affected. The disruption continues to the descending aorta. Under the disrupted intima a false duct can be found. The predisposing factors are hypertension, cystic medial necrosis and congenital defects of the aortic valve. In the latter case the disruption begins near the valve. The clinical sign is pain between the scapulae. With a dramatic onset fatigue, dyspnea and syncope may occur. Aortic regurgitation may result in pulmonary edema. The prognosis is very bad.

Atherosclerotic occlusion of the aorta begins most often in the distal part of the abdominal aorta below the origin of the renal arteries. The occlusion is distending slowly in both directions. The presence of symptoms depends upon the development of collaterals.

Syphilitic aortitis is the best known inflammatory process of the aorta. The ascending aorta and the aortic arch are affected most often. An aneurysm often occurs. Sometimes a rheumatic aortitis may develop.

3.21 Coronary circulation disturbances

The heart has the action of a valvular pump. This means that the *pumping of blood* takes place by filling and expulsion in the direction determined by its anatomic structure and the functioning valves. The physiological outcome of the heart function is the cardiac output. Both the ventricles have the same cardiac output otherwise there will be an accumulation of blood ahead from the ventricle that expels less blood. The cardiac function is both pressor and volumetric work. This work is provided when the heart changes the speed of blood flow, which takes place from the heart to vessels. The cardiac output is expression of the heart function, and its effectiveness. We may have an idea about the cardiac function by measuring its energetic expenditure. The requirement of O_2 in the myocardium per minute equals three times the O_2 needed by the brain and ten times the O_2 needed by the skeletal muscles. As blood flows through the myocardium the oxygen is maximally extracted from it. That is the reason why the difference between the arterial and the venous oxygen is the largest in the body. The exchange of substances in the heart takes place in aerobic conditions. The heart cannot work with oxygen deficit (debt.), and that is why it needs a very effective arterial blood supply.

The myocardial blood supply is provided by the coronary arteries. The coronary circulation actually represents a junction between the aorta and the right atrium. It is hence the shortest circulation in the body with the highest pressure gradient. The coro-