urochrome retention cause the typical coloration of the skin. Urea is excreted also by sweat and may contribute to the uraemic itching.

The patients, if in good care, die most commonly of cardiovascular complications (50 per cent) and of sepsis (25 per cent).

4.8 Inflammatory processes of kidneys due to immunopathogenic mechanisms

Etiopathogenesis of several inflammatory processes in kidneys is due to immune mechanisms activation. Immunopathologic mechanisms may result in inflammatory process of kidneys by three ways:

1. by heterologue antibodies against the basement membrane
2. by soluble immune complexes not containing the renal antigen originating in kidneys, but a different antigen
3. by autoimmune mechanism following streptococcal (group A), or other infection.

In the first type is the underlying cause the reaction between the circulating antibodies and the antigen in kidneys. The antigen may be a natural constituent (component) of kidneys, or it can be an antigen bound with the tissue by biological or immunological reactions. The primary components of immune-pathological mechanism leading to the damage of tissue are the antigens in the basement membrane of glomerular capillaries or renal tubules and the antibodies against basement membranes.

In the second, more frequent type, the macromolecular immune complexes composed of antigens and antibodies are deposited in kidneys, mainly in glomeruli. In this case are kidneys a passive participant, a victim of this process which can start at any time. The antigen can be of autologous or heterologous type. It is never a component, or constituent of kidneys.

In the third type the autoantibodies are involved, arising following streptococcal, staphylococcal, or pneumococcal infections or following malaria. The most frequent cause are the streptococci of group A. In contrast to the rheumatic fever the poststreptococcal glomerulonephritis is not caused by all, but only by some serotypes. These nephritogenic cocci produce a lipoprotein with a molecular weight of about 120 000 daltons, which is an component of cytoplasmatic membrane and is an efficient immunogene. Antibodies produced against this lipoprotein can cross-react with antigenic determinants of renal tissue, mainly of the basement membrane. Following this interaction arise histologically well identificable immune complexes activating the complement. The basement membrane, or other tissues are than damaged by cytotoxic effects of terminal complement, components and of neutrophil leucocytes attracted by chemotactic factors produced during complement activation. Above all, the free oxygen radicals and hydrolytic lysosomal enzymes released from neutrophiles have cytotoxic effects. Apart from neutrophils, the macrophages and monocytes may participate in this process by mechanism of ADCC (antibody-dependent cell-mediated cytotoxicity).

Recently, a further autoimmune mechanism significantly participating in the pathogenesis of human glomerulonephritis was described, represented by autoantibodies against some lysosomal enzymes of neutrophiles, especially against myeloperoxidase and elastase.

4.8.1 Renal damage due to antibodies against basement membrane

This type of renal damage is in men uncommon. Under experimental conditions a model of this disease may be elaborated. The nephritis induced by nephrotoxic serum may be considered to be the prototype of this disease. In the classical experiment (Masugi's nephritis) the antibodies against the glomerular basement membrane of rabbits are obtained by immunization of ducks. The nephrotoxic serum is than injected into rabbits. The heterologous antibodies are rapidly bound to relevant antigen in glomerular basement membrane. The antigen is a glycoprotein evenly dislocated in the basement membrane of glomerular capillaries. On immunofluorescent examination the reactive immunoglobulin will

be therefore equally dispersed in the capillary wall of glomeruli. If a sufficient amount of heterologous antibodies has been applied and they were bound to the antigen, various mechanisms and reactions will be activated. First, are the complement and the haemocoagulation cascade activated. Vasoactive polypeptides, polymorphonuclear neutrophiles and macrophages are activated subsequently. The phagocytes and some lymphocytes may operate by mechanism termed antibody-dependent cytotoxicity (ADCC). By action of these factors is the functional and anatomic integrity of capillary wall deteriorated to such a degree,that proteinuria appears. The proliferation of cellular elements in capillaries appears simultaneously resulting in development of progressive capillary obstruction. Reduction of capillary lumen leads to reduced renal blood flow and glomerular filtration rate. Released local hormones can cause the disintegration of glomerular capillary basement membrane. Macromolecular substances - like fibrinogen and cellular elements as macrophages and erythrocytes may get from capillaries into the Bowman's capsule. If the injury of glomerular capillary walls is severe extracapillary proliferation also appears. It is dependent on fibrin polymerisation in the Bowman's capsule. The complement activation enhances the injury induced by chemotactic and cytolytic effect. The glomerular damage however, can develop also independently from the complement activation.

This phase of glomerulonephritis is termed the heterologous phase. The antibodies bound to the basement membrane operate, at the same time, as antigen. Therefore anti-antibodies against it begin to be produced. The duration of their production is 1 to 2 weeks. They affect subsequently the antibodies already bound to the basement membrane. The so-called autologous phase begins. Virtually, only now the condition becomes to be glomerulonephritis.

Several drugs have the ability to bind on renal structures, forming conjugated antigens. This is e.g. penicillin. This could be considered to be an analogy to the heterologous phase of nephrotoxic nephritis. Later, the production of antibodies may begin. A similar situation may occur following the renal transplantation. Some structures of renal transplant may become antigenic for the recipient.

In a classical case the glomerulonephritis induced by antibodies is developing according the following principle. A component of non-collagenous constituent of glomerular basement membrane with high content of sialic acid, fucose, mannose, galactose and glucose is the most frequently occuring antigen. Its molecular weight is about 26 000 to 58 000 daltons. The highest concentration of this antigen is found in lamina rara interna of the glomerular basement membrane. Less is found in tubular basement membranes and in Bowman's capsule. The antigen is equipped with epitopes similar to the basement membrane of lungs, eye, cochlea and plexus chorioideus epitopes. The antigen of basement membrane termed nephritogenic antigen is excreted by urine. The underlying cause, giving rise to of glomerulonephritis is thought to be the penetration of this antigen into the circulation and its contact with immunocompetent cells. Some conditions facilitate these processes: viral infections, toxins, drugs and renal ischaemia. The helper T-cells distinguish the released nephritic nephritogenic antigen. Primarly activated T-cells produce interleukin-2 (IL-2) and create new receptors for it. Binding of IL-2 on receptors stimulates lymphokines production and the proliferation of specific clones of helper T-cells which releasing activating factors stimulate the specific B-cell clones. These activated B-cell clones begin to produce specific antibodies. These antibodies binding with antigen cause its destruction. Together with amplification systems of immunity they destruct also the relevant tissues. Antibody - mediated glomerulonephritis appears. The basement membrane destruction leads to further antigen release. A circulus vitiosus develops – being the underlying cause of rapid progression of this type of glomerulonephritis. The antibodies against glomerular capillary basement membrane can bind to the cross-reacting epitopes of other organ capillary membrane antigens. In the Goodpasture's syndrome the antibodies bind to the pulmonal capillaries. Haemoptysis appears with rapidly progressing glomerulonephritis.

Antibodies against glomerular capillary basement membrane IgG are bound to antigen determinants. They activate the phagocytosis and the complement system. The chemotactic components of complement attract the leucocytes, the neutrophils, above all. The neutrophils bind to the glomerular structures and release the lysosomal enzymes like proteases, collagenases and other hydrolases. The activated leucocytes, in the same time, produce toxic oxygen metabolites, mainly the hydroxyl rad-

icals (OH), superoxid anion (O_2^-) and the hydrogen peroxide (H_2O_2), arachidonic acid metabolites (prostaglandins and leukotriens) kinins, angiotensin II and histamine. These processes occur with participation of complement, mainly its components – C5a6789 forming the membrane attacking complex (MAC). The MAC perforates the biologic membranes and thereby disturbs their selective permeability. The perforation of the cellular cytoplasmatic membrane may result in the cytolysis. Owing to these processes are the endothelial cells of capillaries damaged. The capillaries are narrowed and obstructed by cells and thrombi. The integrity of the basement membrane is considerably impaired. In basement membrane and the capillary walls appear perforations. This impairs the blood flow and enhances the permeability of glomerular capillary walls. The plasmatic proteins including fibrinogen and other coagulation factors penetrate through the perforated capillary walls into the Bowman's capsule. The negative charge of Bowman's capsule epithelial cells induces the Hageman factor activation. Through the gaps penetrate into the Bowman's capsule also the monocytes containing prothrombinase, activating the thrombin. This all results in rapid activation of haemocoagulation processes during which fibrin polymers are produced. The epithelial cells of glomeruli and the monocytes phagocytise the produced fibrin. The phagocytised fibrin stimulates the cell proliferation. The extracapillary space is therefore rapidly filled by cells. In addition, the monocytes release mitogenic factors for fibroblasts. It results in collagen deposition and forming of scars, replacing the functional renal parenchyma.

4.8.2 Renal damage induced by immune complexes

The deposition of circulating immune complexes in kidneys is the underlying cause in more than **75 per cent of all renal disturbances** induced by immunopathologic processes. The immune complexes may circulate in blood and form subsequently deposits in the basement membrane. The antigen component of immune complexes may be of exogenous origin – e.g. the antigens of some bacteria, hepatitis B virus, foreign proteins. The endogenous antigens of immune complexes are most commonly the components of tumors, myeloma immune complexes in plasmacytoma (multiple myeloma), DNA in lupus erythematosus nephritis and the tubular antigen in Heymann nephritis.

The **immune complexes** are usually, immediately after their appearence, bound to the complement which solubilises them and enables their transport to the cells of phagocytic and macrophage-system. Here are immune complexes continously decomposed. Immune complexes are transported mainly by erythrocytes. Every disturbance of immune complex decomposition results in immune complex-mediated disease. In this way can arise the immune complex-mediated glomerulonephritis.

Soluble circulating immune complexes without any relations to the glomeruli may be retained in glomerular capillaries. This form of glomerulonephritis may be induced, experimentally, by intravenous application e.g. of bovine serum albumin to rabbits immunised before by this antigen and having circulating antibodies against it. Antibodies of recipient are bound to antigen and the immune complexes formed are deposited in various tissues, including the glomerular capillaries - where they activate the complement. This induces the chemotactic effects of C5a and C3a complement fragments to neutrophylic leucocytes. The leucocytes release proteolytic enzymes and kinins and with complement components damage the basement membrane in glomeruli, breaches arise in it and system of haemocoagulation becomes activated. The inflammatory mediators are released and the glomerulonephritis is developing.

When the immune complexes are deposited in glomerular capillaries develops most frequently the chronic proliferative glomerulonephritis.

The specific configuration of kidneys facilitates the **deposition of immune complexes**. In glomerular capillaries, in comparison with other capillaries, the blood pressure is higher. In addition, there takes place only the filtration, the reabsorption occurs at another site. An important contribution has the state of immune system. If it is perfect, the immune complexes are completly removed, by the monocyte-macrophage system in the liver, spleen and other organs. Immune system defect can be manifested also by forming of small, soluble immune complexes, which are most dangerous for causing glomerulonephritis.

The glomerular basement membrane is negatively charged, hence repelling the majority of protein

molecules, including the immune complexes. The loss of electric charge may be the cause of immune complex deposition in glomeruli and vice versa – the immune complex deposition leads to the loss of basement membrane electric charge. This may be one of proteinuria causes.

In Heymann nephritis the immune complexes pass through the basement membrane and form deposits at its outer side. These immune complex deposits lead to forming the epithelial cell processes.

The circulating immune complexes are not per se the cause of pathologic process in kidneys. They occur in circulation without any renal alterations.

In some cases the antibodies against the antigens of epithelial cell pedicles may be produced. These antibodies pass through the glomerular basement membrane and can be bound to antigen. Immune complexes are formed which are situated outside the basement membrane.

4.9 Glomerulopathies

If the integrity of glomerular capillaries is structurally or functionally damaged disturbances of renal functions may appear. The renal function alterations are the underlying cause of findings occuring isolated or in combination: haematuria, proteinuria, reduction of glomerular filtration rate and hypertension. From pathophysiological point of view some disturbances of glomeruli may be distinguished relatively well: acute forms of glomerulonephritis, rapidly progressive glomerulonephritis, chronic glomerulonephritis, nephrotic syndrome and asymptomatic abnormalities. The clinical classification by itself is considerably variable. It was several times changed untill the contemporary classification has been elaborated by WHO (World Health Organization) which takes into consideration mainly the clinical aspects. Thus, the effort of morphologists to adapt it to the morphologic classification is not surprising. The description of single clinical pictures and the precise classification is left to the clinicians.

4.9.1 Acute glomerulonephritis

Acute glomerulonephritis is characterised by an abrupt onset. Haematuria and proteinuria associated with azotaemia appear, due to reduced glomerular filtration. Retention of salt and water is present. If it is considerable, oliguria arises. The salt and water retention causes congestion of circulation, hypertension and oedemas. The fluid retention is the consequence of glomerular filtration decrease and of exaggerated water and salt absorption, mainly in the distal renal tubules. Oedema is located at sites with low oncotic pressure (e.g. periorbital oedema), but if it progresses it can lead to ascites or pleural exsudation. The congestion of circulation is manifested by elevated systemic arterial or pulmonal blood pressure associated with normal or enhanced ejection volume per minute and with shortened circulation time. If ischaemic heart disease or valvular defect are not present it is not probable that the right ventricular failure will develop. If the filling pressure in the left heart atrium rises considerably, pulmonal oedema may develop. The arterial diastolic hypertension is caused by several factors: increased volume of extracellular fluid, enhanced heart volume per minute and moderate increase in peripheral resistance. The plasmatic renin activity, aldosterone and the activity of the sympathetic nervous system are rather depressed. The systemic arterial hypertension may be, mainly in younger children associated with encephalopathy.

The most frequent and very remarkable symptom of acute glomerulonephritis is the macroscopic haematuria. The microscopic haematuria can be overlooked. In this case, the fluid retention and hypertension may be incorrectly considered to be symptoms of a different disease. Haematuria is often associated with occurence of erythrocytic casts in urine. In the definitive urine are found frequently leucocytes and leucocytic cylinders. They are the evidence of inflammatory processes in glomeruli. The degree of proteinuria varies according the glomerular damage extent. Proteinuria may be sometimes severe. In persistent severe proteinuria the nephrotic syndrome is developing.

The course of glomerulonephritis depends on the character of glomerular lesion. In some cases the fluid retention and systemic arterial hypertension may improve. In other cases renal failure develops