abortus it uses to be associated with sepsis, so with disseminated intravascular coagulation. **Acute renal failure after the delivery** occurs as consequence of acute haemorrhage. In some cases diffuse necrosis is found in renal cortex accompanied usually with disseminated intravascular coagualtion.

The impairment of renal functions can appear also **during hepatic diseases** in absence of known renal or other cause. It is manifested by oliguria associated with a modest finding in urine sediment. It occurs usually during the liver cirrhosis associated with icterus, ascites and hepatic encephalopathy.

4.7 Chronic renal failure

Renal diseases are dangerous because of destructive process progression resulting in lost of nephrones. These are: glomerulonephritis, tubulo-interstitial diseases, diabetic nephropathy, nephrosclerosis and futher renal diseases leading to an extensive reduction of renal nephrones and resulting in chronic renal failure with clinical picture termed uraemia. This term emphasizes the most important finding: the increased plasmatic level of urea. Nevertheless, it implies the deterioration of several mechanisms, causing alterations in the whole organism. The resulting condition depends on extent of nephron reduction and on the speed of its progression.

Kidneys have the capability to maintain body functions unchanged also during decreased glomerular filtration rate. This can be decreased to 35 to 55 per cent of the physiologic values and the patient will be asymptomatic. Except for glomerular filtration decrease no other changes have to be found. **However, when the glomerular filtration falls to 20 to 35 per cent of physiological values, the azotaemia appears with other pathologic signs signalizing the renal failure manifestation**. Systemic arterial hypertension and anaemia are appearing first and most frequently. Later, carbohydrate intolerance, hyperuricaemia, hypertriglyceridaemia and inability to concentrate the urine may be observed. Polyuria and nycturia appears thereafter. This condition can persist during variably long time. Later, a further decrease of nephron number occurs, anaemia and hypertension becomes more severe, renal failure becomes manifest, the metabolic acidosis, gastrointestinal, cardiovascular and nervous disturbances appear. Even in this situation are the kidneys capable to excrete potassium. Clinically important hyperkalaemia does not occur.

It has been known long ago that the serum from an uraemic patient has toxic effects on many biological systems. This fact led to searching after responsible toxins. Substances with toxic effect are protein- and aminoacid-metabolites. Lipids and carbohydrates are metabolized to CO_2 and H_2O and easily excreted by exhalation and through the skin. The waste products of protein metabolism, however, are excreted almost exclusively by kidneys. In patients with chronic renal failure urea represents about 80 per cent of nitrogen excreted by urine. The guanidine compounds are on the second place of importance among the nitrogenous substances being the end - product of protein metabolism: guanidine, methyl- and dimethyl-guanidine, creatinine and guanidine-succinic acid. Further, the metabolites of nucleic acids and derivates of aromatic aminoacids as tryptophan, tyrosine and phenylalanine exhibit toxic effects. It is not possible to decide which substance is responsible for a given symptom. The plasmatic level of urea reflects, to some degree, appearing of anorexia, malaise, nausea, vomiting and headache. Very probably not urea alone is the underlying cause of these symptomes. The guanidine-succinic acid impairs the thrombocyte functions by affecting the thrombocyte factor 3. Some metabolites are not directly toxic (e.g. creatinine), they can however influence other substance which change under their influence into the toxic ones.

In uraemia are nitrogenous substances with high molecular weight retained in the body. Analysing the plasma of uraemic patient, however, molecules of intermediate size were prevailing. The kidneys catabolise many plasmatic proteins and polypeptides. When the functional parenchyma is lost, plasmatic levels of polypeptide hormones: parathormone, insulin, glucagon, growth-hormone, luteinizing hormone and prolactin raise. Not only the renal impairment participates in this increase of proteins, but also the elevated secretion of mentioned hormones during chronic renal failure.

4.7.1 Cell – organ – and metabolic alterations due to uraemia

Uraemia is associated with changes in intracellular and extracellular fluids. These alterations affect the ion transport mechanisms across the cell membranes. It is very probable that **the transport of ions across the membranes is impaired by uraemic toxins**. At the first place is the sodium transport. Sodium is permanently present in higher concentration in extracellular than in intracellular space. The cell requires energy and oxygen to maintain this state. The sodium efflux is necessary for the maintenance of membrane resting potential, by this process is concominantly also the potassium influx ensured. **The uraemic toxins inhibit sodium efflux**. Most outstanding alterations can be found in erythrocytes, leucocytes, skeletal muscles but also in other tissues. The changes in sodium efflux and potassium influx are, of course, mainly affecting the membrane potentials of excitable tissues. During uraemia a fall in Na^+ –K^+ –ATP-ase activity has been observed in several types of cells. This is why the transport of mentioned ions falls.

As mentioned, uraemia causes **the sodium efflux decrease** from the cells. Impaired sodium transport out of the cell leads to an elevated sodium concentration in cells. Sodium causes consequently osmotic hyperhydrations of cells. This alteration can affect all cells, of course, it can be developed to various degree. During uraemia progression, untill the terminal stage, a tendency of sodium and water retention persists. The successful haemodialysis is manifested by an outstanding fall of body weight – due to decrease of cells hyperhydration. The success of transplantation becomes evident by very important body weight gain caused by regeneration of body mass and of lipid deposits reaching the status before the uraemia.

The potassium concentration in uraemia can be unfavorably affected by diet, vomiting, diarhea and diuretics. The potassium loss can be increased in uraemic patient if the volume of excreted urine remains relatively normal, in addition, it can rise due to high aldosterone level in uraemia. Aldosterone can increase the potassium loss into the colon. In spite of the low cell potassium level kalaemia is usually normal or increased due to metabolic acidosis inducing the potassium efflux from cells.

In uraemia, **urea and other toxic substances** cause hypothermia. The active sodium transport across membranes is proportional to the basal energy production. An inverse relation between the body temperature and azotaemia is due to the inhibition of sodium pump mechanism by accumulation of toxic substances during uraemia.

The capability to metabolise the exogenous glucose load is in uraemic patients impaired. The disturbance becomes manifest by slower decrease of glucose plasmatic level after glucose intake. The fasting plasmatic level of glucose is normal or moderately elevated. Hyperglycaemia and ketosis are commonly present in uraemia. The glucose intolerance do not require specific treatment. During uraemia the secretion of total insulin impairs, resp. its degradation is also impaired. Therefore the plasmatic insulin level is moderately increased. The glucose load, on the other hand, leads to delayed return of glucose level to the initial value. The glucose intolerance is caused by insensitivity of peripheral tissues to insulin effects.

Intracellular potassium deficiency contributes to the **carbohydrate intolerance**. A similar condition can be induced in patients by treatment with thiazide diuretics. The carbohydrate intolerance is impaired by metabolic acidosis. Disorders of acid-base balance inhibit the glycolysis and the glucose utilisation and influence the peripheral insulin effect. The plasmatic glucagon level uses to be elevated in chronic renal failure. Glucagon plays a role in hepatic glycogenolysis. Hyperglucagonaemia depends from the functional parenchyma of kidneys. The reduced nephron number results in impaired glucagon excretion. In the pathogenesis of glucose intolerance participate also catecholamines, growth hormone, prolactin and further potential toxic substances.

In chronic renal failure **the renal capability to excrete nitrogen and products of protein metabolism is extremely reduced**. This condition can be designated also as protein intolerance. The retention of nitrogenous substances is the cardinal underlying cause of uraemic symptoms. In addition the hypertriglyceridaemia with simultaneous decrease of HDL level. The plasmatic cholesterol level is usually normal. It is not clear if uraemia induces an increased triglyceride production in liver and in intestine. Insulin could participate in triglyceride synthesis. As mentioned, the plasmatic level of insulin during uraemia is increased. Its lipogenetic effect could contribute to the hypertriglyceridaemia. Insulin enhances the synthesis of triglycerides and inhibits the lipoprotein

lipase. The metabolic alterations concerning lipids are irreparable by haemodialysis. Thus, in patients with chronic renal failure cardio-respiratory disturbances appear as consequence of atherosclerosis.

4.7.2 Pathophysiology of symptoms in uraemia

Chronic renal failure and its terminal stage – uraemia – represent a very complex disturbance affecting almost, every organ or system. In all patients with uraemia **retention of sodium and water occur**. Expansion of the extracellular fluid volume needs not to be evident. The sodium retention contribute to development of heart failure, systemic arterial hypertension, ascites and oedemas. Hyponatraemia can be observed if the water retention prevails. No other symptoms are present in this situation. Decrease of extracellular water volume (during fever, vomiting, diarrhea) impairs the still preserved renal function and gradates the manifestations of uraemic symptoms.

Potassium level is moderately changed in the initial phases of uraemia owing to adaptation of distal tubules and colon. Aldosterone and other factors increase the potassium excretion. In this situation can oliguria lead to hyperkalaemia. The fall of blood pH can result also in hyperkalaemia. Acidosis leads to the potassium leak from intracellular space into the extracellular fluid. Between potassium and pH values is a reciprocal relation.

Concentration of phosphates in plasma raises if glomerular filtration becomes impaired to such a degree, that its value falls to less than 25 per cent of normal value. Increase in plasmatic phosphates facilitates the intake of calcium into the bones, leading to hypocalcaemia. The hypocalcaemia induces the rise of parathyroid hormone plasmatic level. In chronic renal failure is hypocalcaemia caused by incapability of kidneys to synthesise the active form of vitamin D (1,25 dihydroxycalciferol). When the level of active vitamin D is low, the reabsorption of calcium from gut is reduced. In patients with very advanced renal failure is the resorption of calcium salts from bone by parathormone reduced. In spite of various causes of hypocalcaemia the hypocalcemic tetania and similar syptoms are not observed in uraemic patients.

In uraemia severe bone diseases like **uraemic osteodystrophy** are appearing. This term includes conditions differing significantly from each other. The uraemic osteodystrophy comprises osteomalacia, osteosclerosis, osteofibrosis and growth disorders in children. Clinical symptoms of these disturbances are present in about 10 per cent of uraemic patients with advanced chronic renal failure. Histological alterations in bones are nevertheless found in 35-95 per cent of uraemic patients. Renal osteodystrophy occurs more frequently in children with renal anomalies, mostly with a slow progression of renal failure. The underlying causes are the elevated parathyroid hormone production, **disturbance of vitamin D metabolism**, chronic metabolic acidosis and severe calcium losses by stool. Renal osteodystrophy can be classified according radiological skeletal findings. In patients spontaneous fractures may occur without tendency to heal. Joint pain can dominate, caused by calcium deposits in bursae and periarticular structures. A severe pain of bone or joint is sometimes accompanied with proximal myopathy. Following renal transplantation with secondary hyperparathyroidism aseptic femoral necrosis can occur. Responsible for it could be the disturbance of vitamin D metabolism and the treatment with corticoids. Extraosseal metastatic calcification appears in middle sized vessels, in joints and periarticular structures, in myocardium and in lungs.

The progression of chronic renal failure is accompanied with elevated plasmatic levels of uric acid and magnesium.

4.7.3 Consequences of alterations occuring in chronic renal failure

Fluid retention represents a **large preload for the heart**. Pulmonary congestion occurs not inevitably accompanied with overload of circulation. Pulmonary oedema is developing during normal intracardiac and pulmonary pressure. Radiological examination of uraemic lungs reveals a peripheral, vascular congestion in shape of butterfly wings. Uraemic lungs and cardiopulmonaly alterations associated with preload of circulation recover quickly following haemodialysis.

A very frequent complication of end-stage renal diseases, including chronic renal failure is **the systemic arterial hypertension**. The absence of hypertension may have several underlying causes: the patient receives antihypertensive drugs, or the patient

has evidently large fluid losses through gastrointestinal system. Diuretic treatment can lead to fluid loss, and so does a salt wasting renal disease with chronic pyelonephritis. The major cause of hypertension in uraemic patient is the hypervolemia. In spite of this the blood pressure improves during the haemodialysis even without regulation of circulating blood volume.

Systemic arterial hypertension can be present also in absence of salt and water retention. Under these circumstances, elevated renin plasmatic activity is found almost regularly. More seldom, but not exceptional is the progression of the hypertension to so-called malignant hypertension. The systolic and diastolic blood pressure is elevated, plasmatic renin activity use to be increased, the hypertensive encephalopathy is developing, retinal alterations and oedema of optic papilla appear. Haemodialysis and drug treatment have no effect. Only bilateral nephrectomy results in a rapid fall of elevated blood pressure. Progressive uraemia is often accompanied with pericarditis. In chronic renal failure atherosclerosis is developing, in spite of successful haemodialysis, affecting coronary, cerebral and peripheral arteries. More accelerating factors participate in the atherosclerosis progression: hypertension, hyperlipidaemia, glucose intolerance and metastatic vascular calcifications.

Chronic renal failure progresses to such a degree that **kidneys are unable to synthesize erythropoietin**, thus a normochromic, normocytic anaemia develops. Its appearence is facilitated by erythropoiesis depression induced by retained toxins, in addition, to above mentioned absence of erythropoietin. Toxic substances induce premature haemolysis of erythrocytes. Certain amount of blood is lost through the gastrointestinal tract. The heparin administration to haemodialysed patients potentiates the blood loss. Larger haemorhage into the gastrointestinal tract, pericardial cavity; subdural and intracerebral bleeding may be observed. In chronic renal failure the bleeding time is prolongated, caused by diminished thrombocytic factor 3 activity which corresponds with the rise of guanidinylsuccinic acid plasmatic level.

In chronic renal failure **the production and function of leucocytes becomes deteriorated**. Lymphopenia and atrophy of lymphatic tissue appear. The neutrophils are less affected, being more resistent. The deterioration of all types of leucocytes is caused by toxins present in uraemic serum. The chemotaxis of leucocytes is also depressed. The reactions to infection are in uraemic patients reduced, even during severe infection the fever does not rise to substantial degree. This can lead to underestimation of infection severity. In addition, the resistance towards infection of uraemic patients is impaired, due to leucocytes deterioration. The presence of acidosis, hyperglycaemia, azotaemia and the decreased immunoglobulin and complement level contribute to infection development progression.

At the initial stage of uraemia only moderate **disorders of central nervous system** are found: minor sleep- and behavioral disturbances. Lack of concentration, amnesia and signs of neuromuscular irritability appear later. Hiccups, convulsions, twitchings of large muscles mainly are frequently present. Peripheral neuropathy affecting more the lower than the upper extremities arises being the sign of severe impairment and progression of disease. It uses initiate the treatment by haemodialysis or renal transplantation. These interventions are evidently not riskless. At the beginning of dialysis the plasmatic urea level falls rapidly. This fall use to be associated with nausea, vomiting, headache and cramps. The underlying cause of these symptoms are rapid changes in extracellular fluid. Retarded sequential alterations in intracellular space follow. Cerebral oedema may develop. During chronic dialysis, the syndrome of dialysis dementia occurs. It is thought to be related with elevated aluminium level and is manifested by dysarthria, myoclonus and dementia. In addition, the patients are threatened with viral infections, as hepatitis B or AIDS.

Anorexia, frequently **singultus, nausea and vomiting** occur in patient with uraemia. High plasmatic level of urea leads to its excretion by saliva. Urea is in saliva decomposed to ammonia causing the uraemic foetor ex ore. Along the whole gastrointestinal system mucosal ulcerations, or extensive, less demarcated lesions termed uraemic gastritis can appear. Ulcerations and enteritis lead to blood loss from gastrointestinal tract. Peptic ulcers are particularly frequent, occuring in every forth uraemic patient. Gastric hyperacidity, enhanced gastrin secretion or the secondary hyperparathyroidism could contribute to their formation.

In chronic renal failure anaemia associated with

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