4.5 Disturbances of glomerular functions

4.5.1 Decrease of glomerular filtration rate

Reduced glomerular filtration rate is one of the most important consequences of glomerular function disturbances. Decreased glomerular filtration rate occurs mainly:

1. during the fall of systemic arterial blood pressure (anatomic restriction of blood flow to glomeruli e.g. in renovascular diseases)
2. when the intrarenal tissue pressure is elevated (during the obstruction of ureters, oedema renis, in perinephritis with stiffened capsula renis etc.)
3. when the oncotic pressure of plasma is increased (during dehydratation)
4. if the filtration surface is reduced (destruction of glomeruli, partial nephrectomy)

Decrease of glomerular filtration rate of **renal origin** is usually due to destruction of glomeruli being replaced by connective tissue. During the progressive glomerular destruction (chronic glomerulonephritis, pyelonephritis, nephroangiosclerosis etc.) functional and morphologic compensation is developing by the hypertrophy of remaining functioning nephrons. Decrease of glomerular filtration rate can occur owing to the fall of effective filtration pressure even if the number of functioning nephrons is not reduced. This functionally caused reduction of glomerular filtration rate is distinguishable from the anatomically caused decrease of glomerular filtration connected with irreverisible elimination of a larger number of glomeruli. During the glomerular filtration decrease from functional causes are the fluctuations of glomerular filtration values usually retained. The fluctuation of glomerular filtration values during the day is a physiologic sign of well functioning kidneys.

Decreased glomerular filtration rate is manifested by **retention of nitrogenous substances in organism**. The most outstanding is the rise of plasmatic concentration of substances with renal excretion depending chiefly on their filtration (urea, creatinine). Between the clearance value of creatinine and its plasmatic concentration is not a linear, but a hyperbolic relation. If the glomerular filtration values are low, even a small further decrease of filtration results in relative high creatinine plasmatic concentration. Thus, in progressive renal failure yet a small reduction of filtration leads to a rapid raise of creatinine plasmatic concentration. Vice versa the normal value of creatinine plasmatic concentration does not exclude disturbance of glomerular functions. Similar relation between the glomerular filtration and plasmatic concentration counts also for urea. If the decrease of glomerular filtration is caused haemodynamically the urea plasmatic concentration raises more rapidly than the creatinine concentration. In addition, the urea plasmatic concentration depends more on protein turnover than the creatinine concentration. During the protein katabolism rises the urea plasmatic concentration already when the glomerular filtration rate has yet normal values and vice versa in patients with chronic renal failure during low protein intake may the plasmatic urea concentration decrease without alterations of glomerular filtration. Therefore is the plasmatic creatinine concentration a better indicator of glomerular filtration than the urea concentration.

When the glomerular filtration decreases more than to one quarter of the normal value, in addition to the progressive creatinine and urea retention, phosphate retention, and in terminal stage occurs also retention of sodium, chlorides, sulphates, magnesium, potassium, uric acid, phenols and other substances.

4.5.2 Alterations of glomerular membrane permeability

Glomerular disturbance can be manifested by increased permeability of glomerular membrane. Under physiological circumstances less than 200 mg of proteins are excreted daily by urine. The very small amount of proteins leaking across the glomerular capillary wall into the ultrafiltrate are removed in tubules by pinocytosis. One part of proteins occuring in the definitive urine originate directly from kidneys. In the cells of Henle's loop a glycoprotein

(uromucoid), an alfa-globulin with molecular weight more than 70 000 daltons is formed. 25 mg of this protein are excreted into the urine in 24 hours. It is produced also in cells of distal tubules and collecting tubules. This glycoprotein (Tamm-Horsfall's mucoprotein) constitutes the main component of urinary casts occuring under pathologic circumstances. When the permeability of glomerular membrane is increased larger amount of plasmatic proteins passes into the urine than the tubules are capable to reabsorbe. This is the way the proteins are passing into the urine, first albumins, and if the impairment of glomerular basement membrane is more severe the globulins.

The glomerular permeability to proteins is determined by the structure of single capillary layers. Substances with molecular weight less than 70 000 daltons can cross the glomerular capillaries. The basement membrane operates as a **gross filter** and the epithelial cells as **fine filter**. In addition to this the permeability of glomerular filter to a given substance depends not only on its molecular weight, but also on the configuration of its molecule. So can some polysaccharides cross the glomerular filter and get into the urine, if they are sufficiently flexible. The electric charge of these structures participates, to some degree, in the filtration process in glomeruli. The endothelial cells, basement membrane, epithelial cells have in the region of pores a strong negative charge repulsing the negatively charged proteins.

The glomerular permeability is partly influenced by the glomerular filtration rate. If the glomerular fitration rate is decreased the contact time of protein molecules with the capillary wall becomes prolonged. Decrease of filtration pressure may cause enlargement of pores through which the blood plasma ultrafiltration occurs. In pathologic alterations can these factors concomitantly exert their influence, or can combine with furhter factors.

4.5.2.1 Proteinuria

The condition where **the amount of proteins appearing in urine exceeds 0,2 g daily** is named proteinuria. This finding signalizes a potential renal disease and initiates a thorough examination of renal functions. Nevertheless, the proteinuria per se need not indicate a renal disease. It may be observed also in healthy subjects. These so called functional or **innocent** proteinurias and are explained by enhanced filtration of plasmatic proteins or by a transient increase in glomerular membrane permeability due to hypoxia. In these cases is the composition of protein fractions in urine similar with that in plasma. This type of proteinuria can be observed following hard physical exertion, long lasting exposure to cold and after s.c. vegetative crises (colics, epileptic seizures etc.). A transient, reversible glomerular damage and proteinuria may occur during febrile conditions.

Preglomerular proteinuria is a condition without presence of renal disturbance. The underlying cause is the filtrating of atypical proteins with smaller molecular weight which may appear in blood (myoglobin, haemoglobin, products of fibrin degradation etc.). In multiple myeloma the light chains of immunoglobulins occur in urine, exhibiting positive reaction in protein determination in urine by boiling (s.c. Bence Jones protein with molecular weight 45 000 dalton).

The lowmolecular proteinuria occurs also in amyloidosis. Proteinurias due to haemodynamic alterations are considered to be of preglomerular character, because of true renal disturbance absence (proteinuria in heart failure). Also the haemoglobin can be excreted by urine without presence of pathologic alterations in glomeruli. The renal threshold for haemoglobin is about 150 mg/dl. By exceeding this plasmatic concentration haemoglobin passes into the primordial urine. During a massive damage of skelatal muscles myoglobin may occur in urine.

Glomerular proteinuria. The underlying cause of this type of proteinuria are disturbances of glomerular filter. If they are not severe only proteins with lower molecular weight pass into the urine. The others are not filtered. Thus in this condition mainly the albumin is in urine. In clinical praxis is this type of proteinuria usually named the selective proteinuria. When the damage is more severe proteins with high molecular weight are filtered into the urine (e.g. IgG with molecular weight 150 000 daltons). Glomerular proteinuria occurs most frequently in all forms of glomerulonephritis. The filtered proteins are partly reabsorbed in the tubules, however the filtered amount exceeds the absorptive capacity of tubules, hence the protein passes into the definitive urine.

Tubular proteinuria The tubular proteinuria is a pathologic condition where the tubules are incapable to reabsorbe the small amount of proteins with low

molecular weight filtered in glomeruli. More frequently however, the underlying cause of the tubular proteinuria is a direct impairment of tubules (toxic lesions of tubular cells caused by heavy metals) or a congenital defect of enzymatic system participating in protein tubular reabsorption.

An intensive reabsorption of proteins with low molecular weight takes place in tubules, whereby the kidneys participate significantly in the metabolism of polypeptides and protein hormones (e.g. angiotensin, insulin, etc.).

Tubular proteinuria is usually not very substantial. The protein loss does not exceed 2 to 3 g/24 hours. During chronic renal insufficiency a combined form of proteinuria occurs. The postrenal proteinuria is the condition in which proteins from renal interstitium appear in the definitive urine. It occurs usually during peylonephritis when the proteins of inflammatory exudate are present in urine.

Proteinuria need not to be a permanent sign of renal impairment. In clinical praxis is rather a transient proteinuria observed being usually not associated with a persistent renal impairment. Apart from the mentioned causes, proteinuria may be due to infectious diarheic diseases with dehydratation. The underlying cause is probably the direct renal damage by microbial toxins combined with haemodynamic changes due to dehydration. Proteinuria can be observed also during viral or staphylococcal infections. The febrile proteinuria usually disappears after the primary disease is healed, or when the fever falls to normal values.

Proteinuria can be seen also following hard physical exertion and exposure to extreme cold. The occurence of proteinuria after vegetative crises is almost regular (colic, epileptic seizure, myocardial infarction). It appears also during hypertension, and pregnancy associated with various complications (pre-eclampsia, eclampsia, abruptio placentae etc.). Decreased renal blood flow and the renal hypoxia is most probably the underlying cause of proteinuria in heart failure.

If a **persistent proteinuria** is found with further pathologic renal findings, it indicates usually a severe renal lesion.

Proteinuria observed in connection with upright position is the orthostatic proteinuria. It occurs in younger subjects usually when a higher degree of lumbar lordosis is present. Suggestions, that the underlying mechanism of this type of proteinuria could be the compression of inferior vena cava by the liver against the lordotic spine, with retrograde condution of this pressure to the renal veins causing renal congestion and proteinuria; or leaking of lymph into the urine, are not longer accepted. In most cases, however, minute lesions of glomerular membrane can be observed by electron microscopy, hence the orthostatic proteinuria is thought to be rather the consequence of glomerulonephritis.

Under pathologic circumstances in proteinurias of renal origin glomerular basement membrane lesions are found by electron microscopy. The portion of proteins with low and high molecular weights in urine depends on the type of morphologic lesions. If the electrophoretic, or immunoelectrophoretic findings of protein fractions do not differ from the plasmatic protein fractions – the condition is considered to be the **nonselective proteinuria** (e.g. in membraneous glomerulonephritis). In selective proteinuria more portions of proteins with lower molecular weight are found in urine (e.g. in lipoid nephrosis in children). The above mentioned **functional proteinurias** are also of selective type.

The concomitant finding in proteinuria of any origin is usually the presence of hyaline cylinders (cylindruria). The casts (cylinders) are formed by protein praecipitations in distal tubule where the process of urine concentration occurs. The acidity of urine facilitates the change of filtered protein in tubules into its colloidal form. Thus, **the cylinders are de facto the casts of tubules**. Cylinders are the single elements in urine originating certainly in kindneys, not in urinary outflow tract.

Under physiological circumstances the proteins with low molecular weight are filtered into the glomerular ultrafiltrate. Their molecular weight is usually lower than 40 000 daltons, most frequently the microglobulins (with m.w. 11 600 daltons), lysozyme (with m.w. 14 000 daltons) or light chains of proteins (m.w. 22 000 daltons) are very easily filtered, yet they are absent in the definitive urine, or only trace-amounts of them are found, because they are very efficiently reabsorbed in tubules. Diseases affecting selectively more the tubules than the glomeruli lead to an excessive excretion of small proteins into definitive urine, without enhancing the albumin excretion.

4.5.2.2 Haematuria

The term haematuria designates the presence of blood in the definitive urine. According to blood amount it can be micro- or macrohaematuria distinguished.

Isolated haematuria. Bleeding from urinary tract is termed isolated haematuria. In isolated haematuria, appart from erythrocytes, no other cells are found in urine, proteinuria and renal casts are not present. If during the urination blood appears at the beginning, it is usually of urethral or prostatic origin.

Very frequently the underlying cause of isolated haematuria is the nephrolithiasis, neoplastic processes, trauma, tuberculosis of urinary tract and prostatitis. It occurs also in primary renal diseases. If the isolated haematuria is observed it is necessary to exclude the haemocoagulation disorders, the thrombocytopenia and the infections of urinary tract.

Haematuria in renal diseases The haematuria in urinary tract infections is accompanied usually with pyuria (finding of pus in definitive urine). The acute cystitis or urethritis in women use to be accompanied with rather massive haematuria and a moderate pyuria.

The blood can get into the urine from any part of nephrons. The erythrocytes may form cylindric shapes in tubules, being a convincing evidence that they originate in an haemorhage in nephrones. The haemorhage from nephrone combined with glomerular proteinuria is always evidence of a very severe renal disease. The renal diseases where both haematuria and proteinuria are not present or if proteinuria alone, without haematuria is found, have a better prognosis than conditions where both symptomes are present simultaneously.

It is always necessary to exclude an other causal relation of haematuria with proteinuria. There is however a possibility of both disorders combination without mutual correlation. Thus, nephrosclerosis with hypertension can be the cause of proteinuria and the present haematuria can be of extrarenal origin. It can originate in urinary outflow tract, not in kidneys. In urine examination however, occur both findings in simultaneously although the underlying mechanisms are different.

Following a severe albuminuria or dehydration the hyaline casts can appear in definitive urine. They can combine with lipoid particles forming fatty cylinders or oval fatty corpuscules. In all inflammation processes affecting the nephron leucocytes and epithelial cells can appear in definitive urine. These cells may form cylinders (casts).

4.5.3 The involution of nephrons

Renal diseases frequently lead to the **involution of nephrons manifested by decrease of glomerular filtration rate**. Despite of this fact certain balance can be preserved between the sodium intake and its excretion. This can be ensured only when some compensatory mechanisms are employed. When the glomerular fitration rate is decreased because the number of nephrons has been reduced and when the excretion of sodium amount is maintained – this can be achieved only if every "healthy" nephron filters more sodium. It means that during decreased glomerular filtration, the sodium excretion, calculated for one nephron, raises.

The involution of functional nephrons does not remain without consequences in interstitium. The hydrostatic and oncotic pressures can not act as under normal circumstances. This results in suppression of sodium and water reabsorption in tubules. The rise of hydrostatic pressure in peritubular capillary network may reduce the reabsorption in proximal segments of nephrons. This can be preceded by systemic arterial hypertension – a frequent finding in renal failure.

When the glomerular filtration is reduced by involution of nephrons the urea, creatinine and organic acids accumulation develops. These substances are excreted by glomerular filtration and tubular secretion. When the decrease of glomerular filtration is severe the rise of organic acids level is considerable. Organic acids can pass into the proximal tubules by osmosis. The increased urea concentration in ultrafiltrate may lead to the osmotic diuresis.

During the osmotic diuresis the sodium excretion is enhanced by reduction of its reabsorption. Some forms of chronic renal failure are associated with a considerable loss of salt. It occurs in nephropathy, chronic pyelonephritis, tubulointerstitial diseases. These diseases are associated with a large destruction of renal medulla and interstitium and with a minor impairment of cortex renis and of glomeruli. Nevertheless, the tubular reabsorption is considerably impaired, less sodium is reabsorbed from the filtrated amount, hence the sodium loss of organism becomes larger.