5. DISORDERS OF KIDNEY FUNCTIONS

Excretion of certain water-soluble waste-products and contribution both to the salt- and water-balance and to the pH regulation are the most fundamental functions of the kidney. Renal function is deemed insufficient if and when the maintenance of these roles cannot be fully secured or can only be partially fulfilled. However, since the kidneys also perform non-excretory functions, various disorders of these may also be observed during examination of renal failure.

EXCRETORY FUNCTIONS

Excretion is not exclusively associated to kidney function, as *non-renal excretory* functions commonly related to bile, sweat, or the enteral system are also regarded almost equally important. From another perspective, renal failure may affect *non-excretory renal* functions as well. However, the abnormal excretory functions are regarded of utmost importance throughout renal pathophysiology (the non-excretory dysfunctions are important primarily in chronic renal failure).

Urinary excretion of waste-products relies on two basic steps (Fig. 5.1.): 1) glomerular filtration and 2) tubular processing of the filtrate (reabsorption and secretion). Disorders may occur in both steps.

5.1. GLOMERULAR FILTRATION AND ITS DISORDERS

Autoregulation (discussed later; Fig. 5.3.) of renal blood flow (RBF) secures an extraordinarily large perfusion, reaching 20-25% of resting cardiac output (Fig. 2.7.). This serves the needs of glomerular filtration rather than the need of renal oxygen supply. Although renal oxygen consumption per 100g tissue is considerably high, it is much smaller when compared with the RBF, and therefore, the oxygen utilization is also considerably low, measured at or about 1.7-2.1% (Fig. 5.2.).

Renal arteries exhibit a special double capillarization. The first is in the glomeruli, serving the filtration, in which, the oxygen extraction is minimal. Efferent vessels collect the still arterial blood from the glomeruli and provide a second capillarization around the tubules (and the peritubular parenchyma), in which tubules secretion and absorption take place with the aid of an oxygen-dependent active transport. Oxygen demand of the tubules is dependent partially upon the amount of filtrate to be processed: diminished levels in filtration bring about a de-escalation in tubular oxygen need. Tubular hypoxia/ischemia develops only in cases of extreme hypoperfusion (≤25% of normal RBF), or if the oxygen content of the arterial blood is considerably low and to a certain extent seen also in cases of lasting severe renal, venous congestion (congestive hypoxia, ch. 3.4.2.).

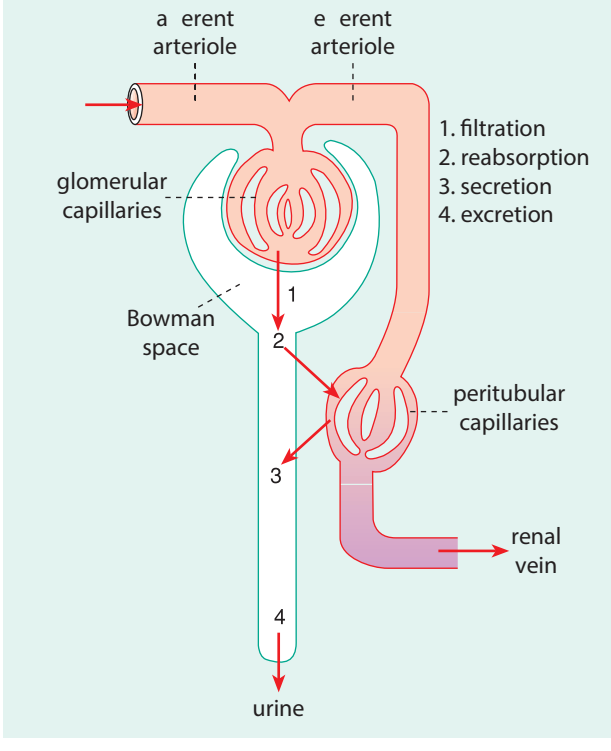

Fig. 5.1.: Scheme of the nephron and its perfusion, and functional characteristics of various segments. The tubules consist of proximal and distal parts: the latter ones (beyond the loop of Henle) convolute and give a loop to the corresponding glomerulus, the cells of their thick wall forms the macula densa, which influences the JGA.

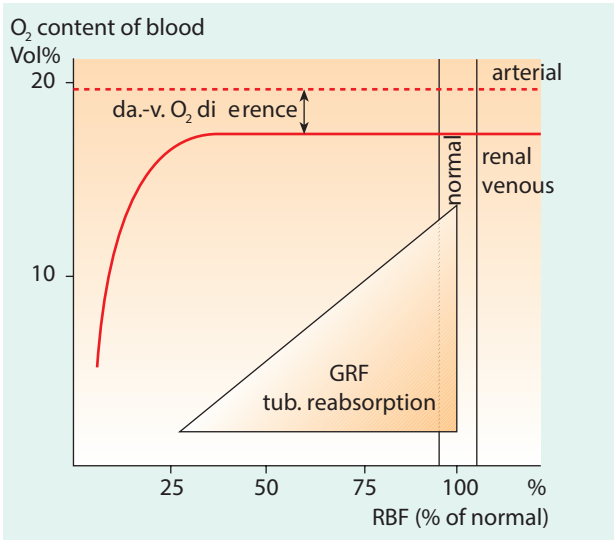

Fig. 5.2.: Effect of decreasing RBF on glomerular filtration and on oxygen utilization (a-v difference of oxygen content). The resting oxygen-utilization is small and does not increase when the perfusion, filtration and tubular transports decrease. Only a severe decrease of perfusion and GFR leads to enhancement of oxygen utilization (to save tubular functions) and finally to tissue (tubular) hypoxia.

5.1.1. THE RATE OF GLOMERULAR FILTRATION

The glomerular filtration rate (= GFR) is dependent upon the following aspects:

- blood perfusion of the glomeruli
- effective filtration pressure
- size of filtration surface
- filtration coefficient

Specifically, it is the perfusion what can change most easily, both physiologically and (rather frequently) pathologically. The altered RBF may be partly compensated due to changes of effective filtration pressure consequent to vasomotor changes of afferent and efferent arterioles (afferent dilatation or efferent constriction induces an increase in the filtration pressure, while the opposite changes can decrease filtration pressure). Additionally, the compensation involves humoral mechanisms, which also participate in the tubulo-glomerular feedback (discussed later; Fig. 5.4.). Humoral factors may also serve to modify the filtration coefficient, without altering the filtration pressure (they may alter hydraulic permeability and slightly modify the size of filter surface): e.g. angiotensin II, vasopressin, PGE_1, bradykinin, or PTH may decrease, while cortisol or atriopeptin may increase the filtration coefficient. The alteration of the filtration surface is important primarily in pathological processes.

Filtration is ”free” for electrolytes, small molecules and water (but not for larger molecules), i.e. the filtrate composition in the Bowman space generally corresponds to the protein/macromolecule-free plasma, and its osmotic pressure is also identical with that in the plasma: 280-300 mOsm/kg. The remaining (non-filtered) water + small molecules are carried further from the glomerular capillaries into the efferent arterioles (i.e., if e.g. 5 mmol/l is the se-glucose level in the afferent arteriole, the same is seen in the filtrate and also in the efferent vessel). Changes of pore structure and negative electrical charge of the filtration surface modify permeability (e.g. decrease of electrical charge enhances the filtration of macromolecules) and alter the filtrate composition, with a relatively normal amount of filtrate. Macromolecules can pass through the filter according to their size, shape and electric charge, particularly in cases in which the structure and charge of pores are abnormal.

The GFR can be determined by the endogenous creatinine clearance*. Its normal value is 120-130 ml/min, or about 180 liters/day. The clearance and purging of other endogenous or exogenous substances represent other kidney functions.

In the regulation of GFR the **autoregulation** of renal blood flow plays a prominent role (Fig. 5.3.). This relies on the activity of local smooth muscle and neural elements (muscle relaxants and local anesthetics given to the renal artery and can suspend autoregulation). Autoregulation can secure a standard RBF and GFR in the zone of 60-160 mmHg mean arterial pressure. The autoregulation can be demonstrated in vitro (and in transplanted, or denervated) kidneys, too. In normal

*Creatinine gets into the urine exclusively by filtration, since the tubules do not secrete it. From a different perspective, all filtered creatinine eventually enters the urine, since the tubules do not reabsorb it either. The amount of creatinine appearing in the urine over a period of time corresponds to the amount filtered creatinine during the same period. If the creatinine concentration of the filtrate is known (it is the same as in the plasma), the volume of filtrate containing the amount of urinary creatinine can be calculated, and the volume should be expressed with regards to time (minutes). This is GFR, or the volume of plasma which was virtually cleared of creatinine within a minute. In regards to substances reabsorbed or secreted in the tubules, the **clearance** value is lower or higher, respectively, and as a result, such clearances may represent tubular functions.

kidneys, sympathetic activation may induce a strong constriction of the renal artery and may serve in decreasing the renal perfusion (e.g. redistribution of cardiac output during physical exertion or hypovolemia). While autoregulation aims to ensure an ideally superb flow of blood intended for filtration, a redistribution of cardiac output may overwrite this tendency repeatedly (but hardly so in transplanted kidneys). Deviation from the normal typically results in a decrease in the levels of RBF and GFR, however, inevitably both possess the potential to rise, as seen in hyperfiltration during pregnancy. Regarding brief episodes, as much as a 50% reduction of RBF and GFR is not likely to cause ischemia, severe excretory abnormality or complete renal failure. Hypofiltration of this extent, even if it persists for a lengthy period of time, leads only to the retention of certain, mainly N-containing waste-products (azotemia), yet, not to ischemia. Only severe hypoperfusion (<25% of normal, Fig. 5.2.) results in ischemia, which, in turn, damages preferentially the oxygen-dependent and hypoxia-sensitive tubular system, and only in extremely severe chronic cases affects also the glomeruli.

In addition to autoregulation, **tubulo-glomerular feedback** (TGF) also contributes to the stability of GFR (Fig. 5.4.). Accordingly, signals of tubular origin influence glomerular filtration. If, for some reason, an increase in GFR is produced, more Na reaches the distal tubules, what is detected by the macula densa, which alters the functional system of the juxtaglomerular complex. Consequently, constriction of the afferent and dilation (due to suppression of angiotensin II production) of the efferent vessel follows, therefore the filtration pressure decreases, causing normalization of GFR. Similarly, the originally normal filtration decreases, if an insufficient tubular Na-reabsorption is the cause of high Na concentration in the distal tubules. The opposite process is seen in which GFR primarily decreases or the Na reabsorption is elevated, resulting in an increase in the filtration per nephron.

Humoral factors also modify the glomerular perfusion and effective filtration pressure. Noradrenaline, originating from circulation, and endothelin as a result of damaged vascular wall serve in creating preglomerular (afferent) vasoconstriction. In contrast, the small amounts of nitric oxide (NO) produced by the intact endothelium exhibit a vasodilator effect. Constriction of the afferent vessel is inhibited by prostaglandins and kinins produced locally (primarily in the cortex), while physiological concentrations of angiotensin II induce constriction of the efferent vessels and thereby influence glomerular perfusion, filtration pressure and filtration coefficient.

On the basis of TGF, glomerular hyperfiltration is understandable in cases when the Na reabsorption in

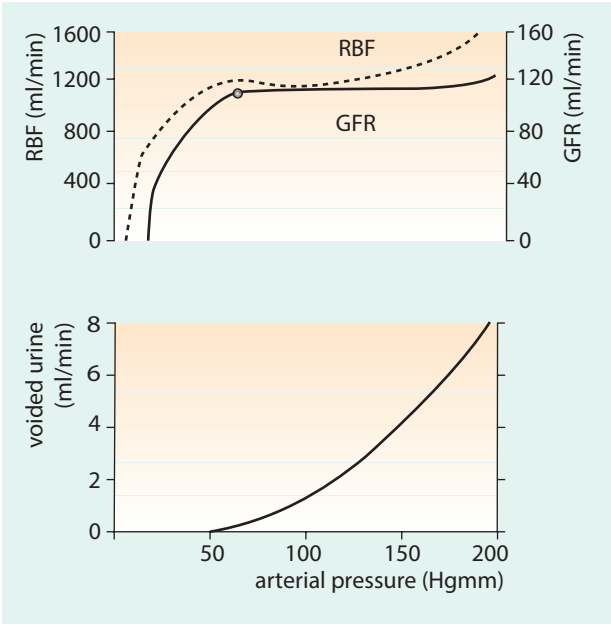

Fig. 5.3.: Autoregulation of RBF and GFR. The pressure-diuresis (lower panel) is independent of the phenomenon of autoregulation.

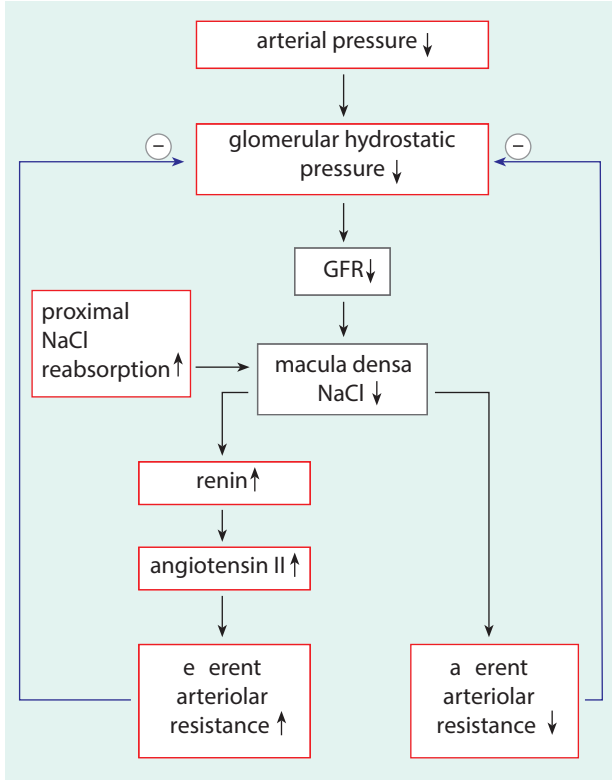

Fig. 5.4.: Mechanism of the tubulo-glomerular feedback (TGF).

the proximal tubules, for any reason, is enhanced (e.g. enhanced absorption of amino acids together with Na, following large protein intake). Hyperfiltration can also be expected if the Na concentration decreases in the distal tubules, for any other reason. For example, as seen in diabetic hyperglycemia, more glucose is filtered, and as a result more is reabsorbed in proximal tubules combined with Na symport, however, an abundance of glucose still remains within the tubules, and it binds with water thereby leading to a decrease in Na-concentration. Consequently, as seen. Consequently, as seen in the distal tubules, the macula densa function changes and it leads to a higher single nephron glomerular filtration rate (SNGFR) – as long as the glomerular number and morphology are intact, this also means a higher total GFR. In the same manner, tubular damage is accompanied by decreased salt reabsorption, and the increased Na concentration within the distal tubules due to decreased SNGFR and hypofiltration: this is particularly important in acute tubular nephropathies (ch. 5.5.3.).

Autoregulation of RBF and stability of GFR do not mean that the salt/water excretions are independent of blood pressure. Any increase in mean arterial pressure leads to slightly increased filtration pressure and pressure in peritubular vessels. A smaller fraction of the filtered salt/water is reabsorbed, resulting in an increase in salt/water excretion through the urine. This phenomenon of **pressure-diuresis** (Fig. 5.3.) is of great importance in the regulation of extracellular volume and blood pressure.

In cases of long lasting high salt intake, a decrease of angiotensin level and dilation of efferent vessels may ensure a higher rate in the transmission of arterial pressure to postglomerular/peritubular vessels with a consequent elevation in salt/water excretion, thereby, the salt/water balance is secured (adaptation to high salt intake). The defective suppression of angiotensin results in salt retention and volume hypertension (this is an explanation why ACE-inhibitors can be used in treatment of hypertension). Later, an increase in peripheral resistance will be added.

5.1.2. ABNORMALITIES OF THE FILTER SURFACE

In addition to its size, the structure of the filter surface may also undergo to changes (Fig. 5.5.), influencing not only the quantity of filtrate, but also its composition. All processes involving generalized inflammation (primarily immune processes) or severe generalized ischemia will likely injure the glomerular structures.

Endothelial cells can present antigens to T-helper cells, the surface antigens can bind circulating antibodies and the produced immune-complexes may initiate local inflammatory processes. In generalized inflammation, the circulating cytokines may activate endothelial cells and this activation results in the expression of adhesion molecules and aggregation of various leukocytes (phagocytes, macrophages, etc.). This can also be provoked by severe ischemia. The local release of free radicals, proteolytic enzymes and phospholipase products follows, subsequently result-

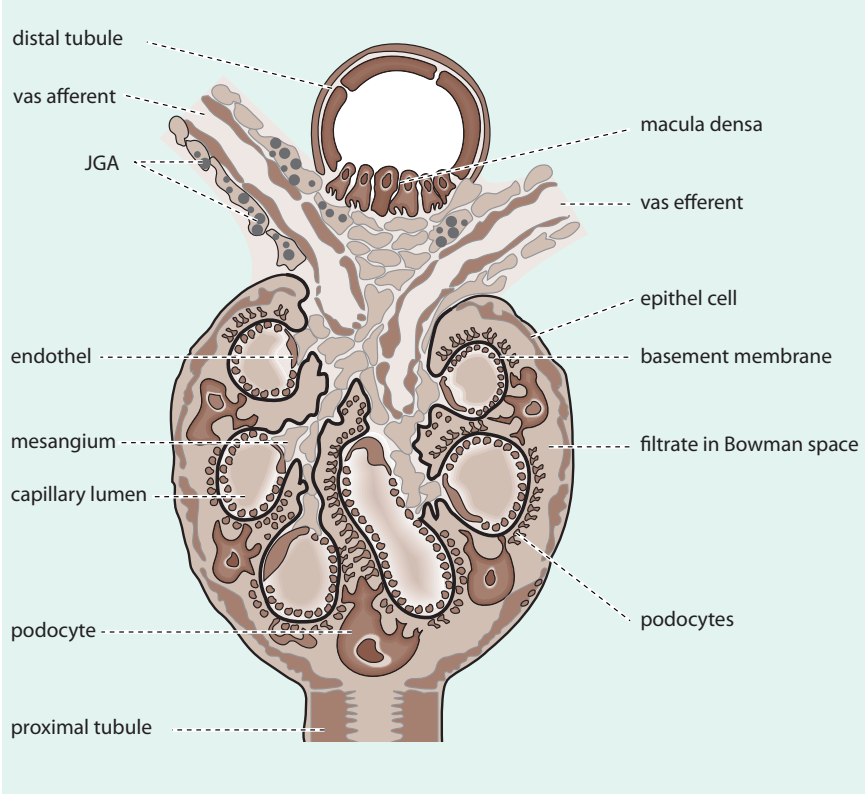

Fig. 5.5.: The structure of glomerular filter, juxtaglomerular apparatus with renin-granula and also the macula densa.

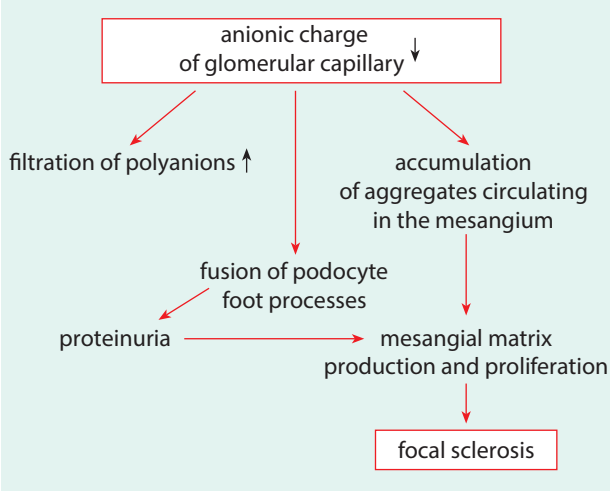

Fig. 5.6.: Development of focal sclerosis, an important factor in glomerular damage.

ing in additional damage to the endothelial cells. Endothelial injury enhances the production of endothelin and PDGF (platelet derived growth factor), however, leads to decreased production of NO and PGI_2. Consequently, the capillary perfusion falls, the production of anticoagulant substances (heparan-S, thrombomodulin, etc.) and the plasminogen-plasmin transformation decreases, while coagulability increases within the capillaries. A growing number of capillaries inevitably become occluded and circulating immune-complexes are deposited subendothelially. Fenestration between the endothelial cells is simultaneously enlarged.

In reference to **podocytes,** in situ immune-complex formation is possible, as well as complement activation by attachment of circulating immune-complexes which likely will injure the podocyte membrane. Direct toxic injury (e.g. puromycin) is also possible. Proteinuria similarly destroys podocytes, presumably due to an altered negative charge. The damage induces local accumulation of cytokines, lipid mediators and free radicals. In its combined form, this leads to a disarrangement of podocyte structure with changes in the layout of foot processes and in the negative charge of the luminal surface (due to the decrease of surface sialic glycoproteins and membrane heparan-S). Immune-complex deposits may be detected beneath the podocytes (e.g. in post-streptococcal glomerulonephritis). The focal detachment of podocytes is combined with an increase of various gaps between foot processes (other gaps become narrower), the anionic charge of the surface decreases, resulting in the enhancement of glomerular permeability, allowing filtration of macromolecules (Fig. 5.6.).

The **mesangial cells** are located in the centrilobular region of the glomerulus. They originate from connective tissue and/or bone marrow and are special phagocytes of immune functions. Their roles include the followings: 1) due to their contractility, they influence the hemodynamics of glomerular perfusion, 2) they produce an extracellular mesangial matrix (collagen, glycoproteins, proteoglycans, glycosaminoglycan, etc.) that modify the receptor expression upon the surface of mesangial cells (these receptors bind factors influencing contractility, phagocyte functions and growth), 3) they remove macromolecules and immune-complexes, thereby becoming activated. Activation of mesangial cells elicits further production of growth factors, causes progressive cell/matrix proliferation, and, finally compresses the capillaries from the ”outside” and leads to focal sclerosis (Fig. 5.7.), and later glomerulosclerosis. Activation may be initiated by abnormal filtrate (e.g. an immense quantity of protein), immune processes, phagocyte accumulation, and by various growth factors. Immune-complex deposits may appear in the matrix.

Antibodies may also bind to the glomerular **basement membrane** (e.g., Goodpasture syndrome), and they can be characteristically demonstrated through immunofluorescence. Despite thickening, the permeability of the basement membrane becomes enhanced, since the permeability is dependent upon the structure (rather than thickness) of the filter, and the end result is that larger particles can pass through the membrane, as seen in acute diffuse glomerulonephritis (ch. 5.5.3.4.).

Abnormalities of the glomerular filter first lead to alterations in the composition of the filtrate (e.g. proteinuria). The amount of the filtrate may be normal (e.g. puromycin-induced injury), or even higher (e.g. early diabetes), but also, lower (e.g. acute diffuse glomerulonephritis). These are usually *progressive changes* and lead to chronic nephritis with *gradually decreasing GFR: the hemodynamics of the glomerular capillar-*

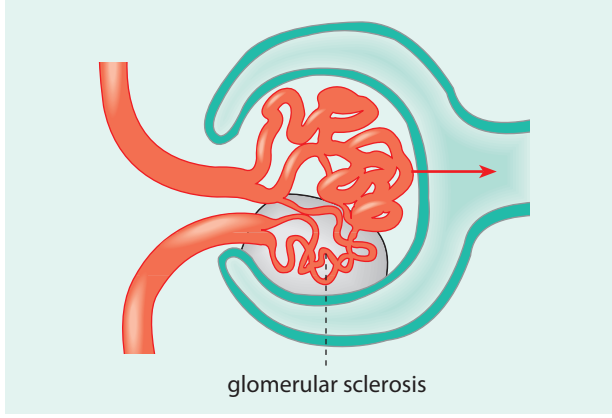

Fig. 5.7.: Glomerular sclerosis damages the structure of glomerulus.

ies and the coagulability/fluidity of the capillary blood changes, the pores are altered, the filter surface decreases and the permeability increases, finally fibrin deposits appear, mesangial matrix proliferation and progressive sclerosis develops.

5.1.3. DISORDERS OF FILTRATION

- Despite the normal GFR amount, the *filtrate* ***composition*** may be abnormal, either due to prerenal causes (e.g. plasma composition is abnormal: hyperglycemia, immunoglobulin chains, Hb and/or direct bilirubin) or due to abnormal filtration mechanisms (e.g. podocyte damage, enhanced permeability and protein filtration).
- The total ***amount of GFR*** may be abnormally small or large. ***Decreased*** *GFR* (hypofiltration) is characteristic for *decreased renal perfusion* (this develops even physiologically during physical activity, pathologically in heart failure, shock, hepatorenal syndrome, severe anemia, renal hypertension), or it may adjoin a *decrease in filter surface, decrease of effective filtration pressure* or *filtration coefficient* (e.g. in acute diffuse glomerulonephritis). Hypofiltration occurs most frequently as a result of decrease in the number of functioning glomeruli or capillary loops, of which, may be related simply to *aging*, but often develops in *chronic renal failure, or glomerulosclerosis*. ***Enhanced*** GRF (hyperfiltration) develops in the opposite way, e.g. due to enhanced perfusion as seen in *pregnancy* (ch. A13), due to TGF in *diabetes or in protein-rich diet*, or due to complex mechanisms in hyperthyroidism, in acute febrile states, in pyelonephritis. Fig. 5.8. illustrates how GFR changes with age and pregnancy.
- Normal or a lower amount of GFR may be accompanied by increased amount of ***single-nephron-GFR*** (SNGFR),

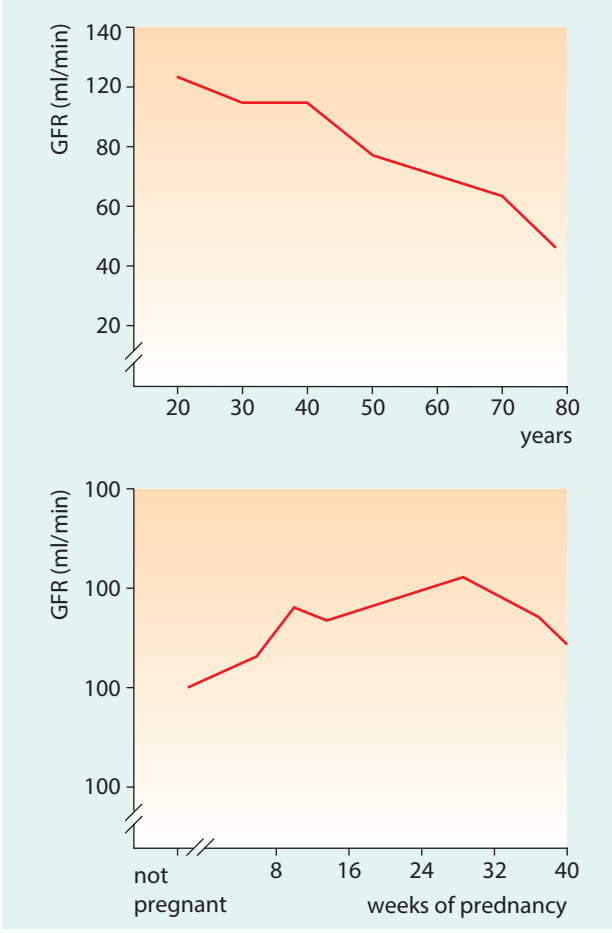

Fig. 5.8.: GFR changes regarded as physiological: it decreases with age, increases in pregnancy.

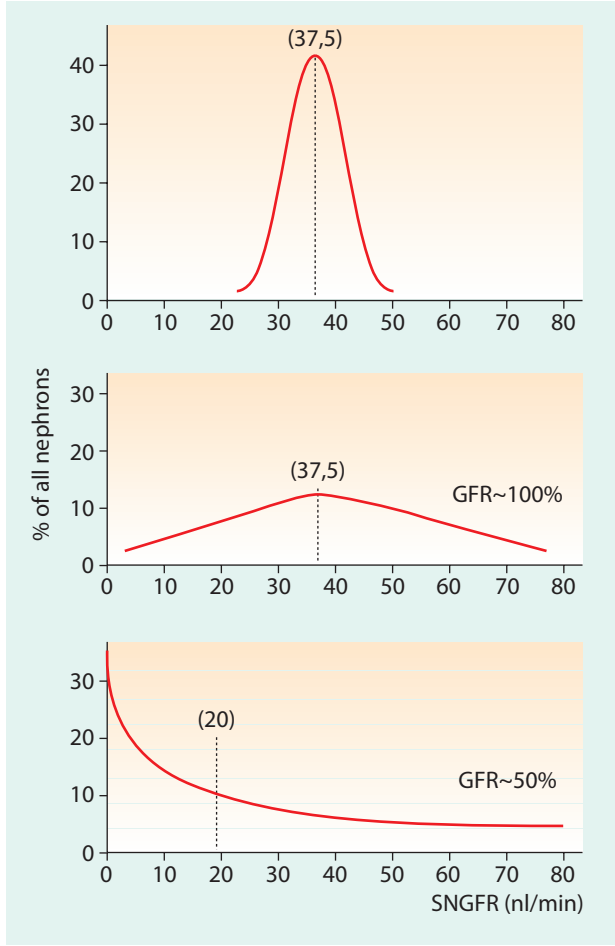

Fig. 5.9.: The SNGFR values in healthy young person (upper curve) are very similar (small scatter), with chronic renal damage the ratio of hyperfiltrating and hypofiltrating nephrons, although the total GFR is still normal (middle curve), finally the hyperfiltrating nephrons disappear and the total GFR decreases (lower curve).

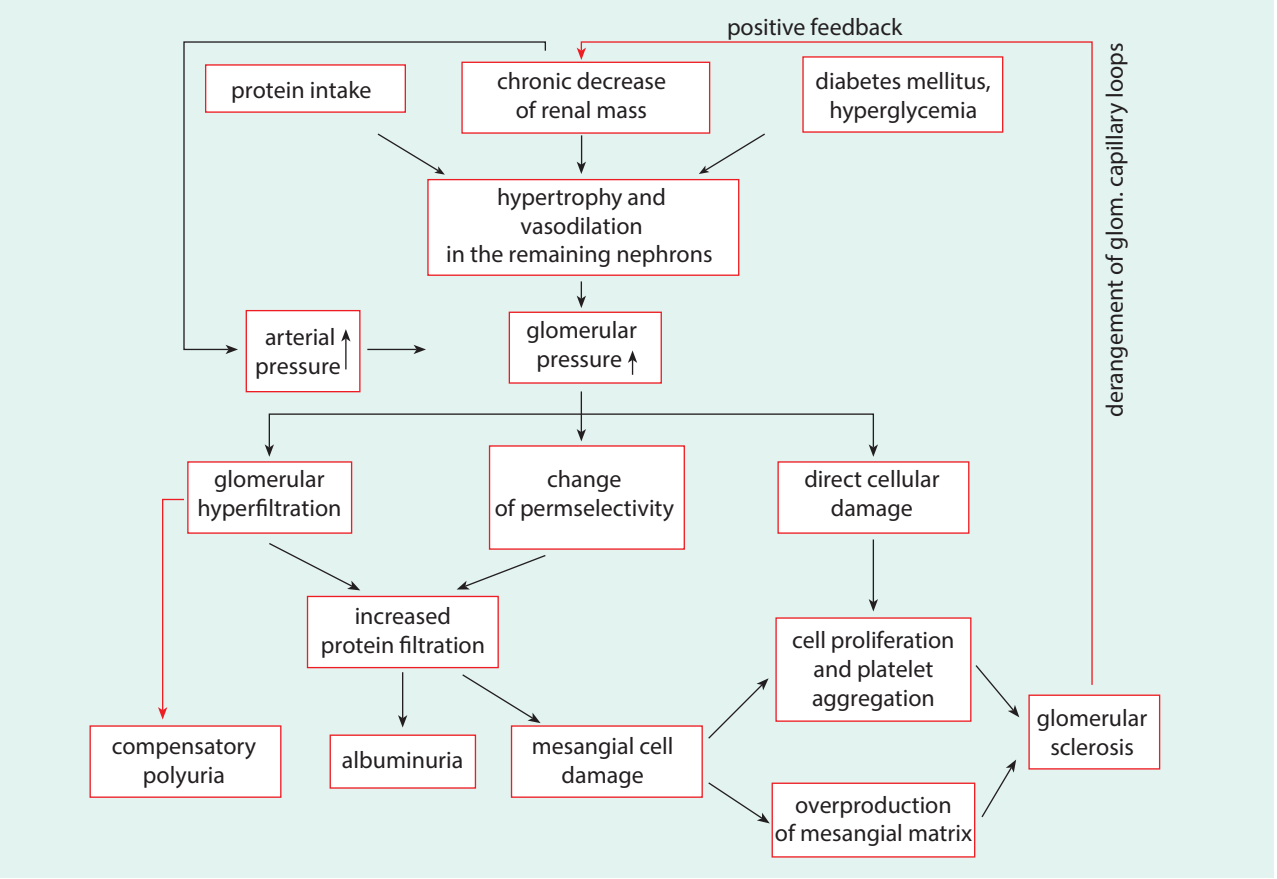

Fig. 5.10.: Development and consequences of hyperfiltration. In its development the rise of glomerular pressure is always a basic moment, it damages the glomeruli on the long run.

particularly in chronic renal failure. This may be regarded as a form of compensation: when the number of functioning nephrons decreases, a large SNGFR promotes excretion of N-containing waste-products. Hypertrophy of the still functioning nephrons and TGF may offer an explanation for the phenomenon. A high SNGFR in the presence of normal nephron population results in hyperfiltration (the total GFR is high, e.g. in early diabetes) and also in polyuria.

While it is easy to accept that hypofiltration decreases the excretory capacity, the interpretation of hyperfiltration (large SNGFR) is more difficult (Fig. 5.9.). In case of chronic kidney damage, glomerular hyperfiltration is regarded as a positive and "compensatory" step in the sense that, despite a decrease in the number of nephrons it secures to make an acceptable level of total GFR, therefore clearing out the N-containing waste-products (which are emptied by filtration only) may also be sufficient. However, hyperfiltration secondarily activates mesangial cells, thereby causing glomerular loop injury and makes kidney damage progressive. In lasting hyperfiltration of primarily normal kidneys (e.g. in diabetes but not in pregnancy), the negative consequences prevail (Fig. 5.10.).

5.2. TUBULAR FUNCTIONS AND THEIR DISORDERS

In contrast to the 180 liters/day of ultrafiltrate, the urine output is only 1-1.5 l/day, the composition, pH, and specific gravity of which differ from those of the ultrafiltrate. The differences are results of tubular functions (transports, hormone productions, and the tubular actions of hormones). Tubular dysfunctions are expected to alter both urine output and these parameters of the urine.

5.2.1. PRIMARY TUBULAR DYSFUNCTIONS

Some of these are **congenital** abnormalities: in addition to normal GFR, one or the other tubular function (transport function, hormone production, hormone

action, etc.) is defective in an isolated or combined form, but always in a hereditary way. The most important ways include the followings:

- *Renal glucosuria*: Normally, the filtered glucose (if its amount is not excessive) is completely reabsorbed in the proximal tubules. The glucose-reabsorbing capacities of the tubular cells are not identical: in some of them, this capacity is exhausted earlier as compared with others. This may explain the relative and absolute thresholds of the glucose reabsorption maximum, as seen between the two distinct thresholds, glucose may appear in the urine but its urinary concentration becomes parallel (not identical) with the further rise of plasma glucose concentration only beyond the absolute maximum. Isolated abnormality of the relative maximum causes glucosuria at moderate hyperglycemia, however, the absolute threshold is normal. In other cases, glucose reabsorption is nearly impossible, resulting in continuous glucosuria even without hyperglycemia. Such glucosuria is not simply a diagnostic problem, since it causes polyuria and the threat of exsiccosis, including the loss of calories, a tendency for hypoglycemia and for fasting-induced ketosis. In regards to galactose reabsorption, sometimes simultaneously, similar disorders have been demonstrated.
- *Renal phosphaturia*: Since the renal clearance is smaller in reference to phosphate when compared to that of creatinine, there is an overall phosphate reabsorption. Renal phosphate handling is dependent upon vitamin D and PTH. Renal phosphaturia may develop due to vitamin D resistant (1-25-DHCC-resistant) or 1-25-DHCC deficient types of tubular transport abnormalities, including PTH overproduction or enhanced PTH-sensitivity of the tubular cells. The PTH-dependent forms cannot be effectively normalized by 1-25-DHCC. Hypophosphatemia develops in all forms, along with the inhibition of bone formation and renal rickets. Renal phosphaturia may be evident in the development of Fanconi syndrome.
- *Renal aminoaciduria*: The enzymes of energy-supply at the brush-border of tubular cells are required for amino acid reabsorption towards the basolateral membrane. Deficiency or exhaustion of these enzymes prevents amino acid reabsorption. Cystinuria is the disturbance of tubular reabsorption of cystine (and typically, lysine, ornithine, arginine): it causes the formation of cystine-containing stones. Defective tryptophan reabsorption may contribute to Hartnup disease (ch. 9.1.2.2.) and to pellagra (niacin deficiency).
- *Renal tubular acidoses (RTA) (ch. 6.2.2.1.)*: Metabolic acidosis is common to all forms of these particular tubular defects. Notably, several forms are known. **RTA-I**: H^+ excretion of distal tubules is defective and acidification of the urine cannot take place (urine pH > 5,5); the hyperchloremic acidosis (low H^+ excretion also is defined as the defective absorption of regenerated bicarbonate; ch. 6.2.1.3.) may be accompanied by hypokalemia (instead of Na^+/H^+, there is a Na^+/K^+ exchange in the distal tubules). Na^+-loss and hyposthenuria (ch. 5.3.2.) may accompany the picture. **RTA-II**: Metabolic acidosis develops due to defective bicarbonate reabsorption in proximal tubules, however, in severe acidosis the urinary pH max may be lower than 5.5 thus proving that the distal tubules are indeed, active. Fructose intolerance, multiple myeloma and intestinal malabsorption may directly or indirectly provoke its development. **RTA-III**: This form has not yet been clarified. **RTA-IV**: It occurs in hyporeninemic hypoaldosteronism (relatively frequent: e.g. diabetes mellitus, interstitial nephritis, effect of NSAID-s, ACE-inhibitors or loop diuretics), or in aldosterone resistance (e.g. tubular obstruction and/or sickle-cell anemia). It is accompanied by hyperchloremic acidosis, however, the urine can be acidified.
- *Fanconi syndrome*: This is a complex anomaly of reabsorption, originating from the derangement of proximal tubules or the entire nephron. It is characterized by glucosuria, aminoaciduria (various amino acids), phosphaturia, bicarbonate loss, RTA-II, Na-loss, K-loss, (in proximal forms), Ca-loss, polyuria and/or acidosis. It also occurs in acquired forms (6-mercaptopurine, tetracyclines, heavy-metal toxins, multiple myeloma, amyloidosis, vitamin-D deficiency and/or a transplanted kidney).
- *Renal rickets*: It is caused by a deficiency of 1-hydroxylase enzyme (needed for 1-25-DHCC formation), and it causes vitamin D resistant rickets and bone deformities.
- *Renal diabetes insipidus*: Despite the presence of endogenous or exogenous ADH, the urine cannot be concentrated: the urine is always diluted, irrespective of the plasma osmotic pressure. Inexplicably, even exogenous ADH cannot exert its action (in real diabetes insipidus ADH can induce

concentration). Exsiccosis, anorexia, cachexia and later, chronic renal failure may develop.

Other abnormalities are **acquired**, as seen in the various forms of hypoxia or tubulointerstitial nephropathy. The nephron lesions affect primarily the tubules. Often a congenital disorder of non-renal enzymes leads to the tubulopathy (discussed later: oxalate).

- ***Hypoxemic**/anemic/stagnation type hypoxia:* Renal hypoxia or an early phase of transplant rejection is accompanied by the non-specific damage of the tubular functions with hyposthenuric polyuria (discussed later), Na-loss, and, eventually with glucosuria, aminoaciduria, proteinuria and/or bicarbonate loss. Later, at the completion of the rejection process, the decrease in GFR is pronounced and oliguria develops.

  The decrease of renal perfusion causes hypoxia (and acute tubular nephropathy) only if the decrease corresponds to shock, however, the decrease in arterial oxygen content (anemia, hypoxemia, etc.) may similarly injure the functional system of the tubules.
- *Substances causing **acute tubulointerstitial** nephritis and tubular damage include* antifreeze fluid (ethylene glycol), mushroom toxins, the effects of drugs including various side-effects (sulfonamides, penicillin, thiazides, phenylbutazone, etc.), infections and/or non-specific hypersensitivity reactions.

– ***Chronic drug effects*** may also cause tubulointerstitial nephritis, notably, phenacetine(!), NSAID-painkillers are known to result in analgetic nephropathy.

- Metabolic disorders:
  a) Urate-nephropathy: Acute and chronic forms are known. It is most frequently seen in gout, however, it may occur in myelo- and lympho-proliferative diseases, epilepsy, heat stroke and/or tissue necrosis. The tubular functions change as seen in hypoxia. In addition to tubular obstruction, interstitial fibrosis, urolithiasis, chronic parenchymal damage and renal failure may also develop.
  b) Oxalate/glyoxylate: The transformations of glycolic acid, such as glyoxylic acid and oxalic acid, are performed by various enzymes (glycine oxidase, glycolate oxidase, etc.). This specific category of acids participates in the metabolism of a number of amino acids, ascorbic acid, ethylene glycol, etc. In the absence of these enzymes or in case of their deficiency, any load (dietary or other) by these acids causes (in an "acquired" form) an enhanced excretion of oxalate or glyoxylate. Due to their poor solubility, these may precipitate (particularly at low pH) in the tubules and may induce tubular damage, urolithiasis, and later, consequently, nephrocalcinosis and chronic renal failure. The most frequent ways of occurrence: *1)* ethylene glycol (antifreeze) intoxication, *2)* GI disorders (e.g. bypass, intestinal resection, chronic pancreatitis and/or cirrhosis), such as seen in poor fat absorption, allowing absorption of more oxalate (Fig. 7.18.), *3)* vitamin C overdose (even if considered moderate, particularly, if the enzyme is missing), *4)* deficiency of vitamin B_6 (this is a coenzyme in support of glyoxylate-glycine transformation).
  c) Hypokalemia: It causes vacuolization and dysfunction in the proximal tubules. Later, multivesicular lesion of the papilla may follow.
  d) Hypercalcemia: Myeloma multiplex, PTH-overproduction, vitamin D intoxication, bone metastases and sarcoidosis all lead to high se-Ca, and threaten the mitochondria of the tubular cells, and leads to Ca-deposits upon lesioned membranes and debris. The calcification of tubules, vessels, glomeruli and frequently the stone formation, all lead to chronic renal failure.

– ***Immunological abnormalities:*** The deposition of circulating immune-complexes mediate various forms of tubulointerstitial nephritis: systemic lupus erythematodes, cryoglobulinemia and Sjögren's syndrome. Antibodies may be formed in situ against the tubular basement membrane.

– ***Disorders associated to neoplastic processes:*** Direct tumor invasion to renal tissue, elevated se-Ca and se-urate, amyloid and abnormal proteins may be emptied, however, chemotherapy and irradiation may also contribute to renal injury. In multiple myeloma, massive proteinuria often develops in association with acute or chronic renal failure.

– ***Fibrosis, compression and tubular occlusion:*** (e.g. hemoglobin-cylinders in hemolysis, myoglobin cylinders in rhabdomyolysis) the consequent tubular injury is also an acquired disorder.

All these characteristics induce isolated or complex (always primary) tubular dysfunctions, while orig-

inally, the filtration is normal. These changes are secondary in the sense that they may be ascribed to known causes, but primary in the sense that there is no previous renal damage lurking in the background.

5.2.2. SECONDARY (ADAPTIVE) CHANGES IN TUBULAR FUNCTIONS

Primary changes of glomerular filtration must be followed by functional changes in the corresponding tubules, as an adaptation to the novel need of processing the altered filtrate. The decreased amount of filtrate (physiologically, at smaller plasma volume and decreased renal perfusion) leads to a slower flow rate in the tubules, allowing a relatively enhanced tubular reabsorption (and fall in urine volume), as a compensation to re-elevate the plasma volume.

In contrast, if the SNGFR is elevated, not all of the excess filtrate is to be emptied (in order to avoid salt- and water-loss), i.e., tubular reabsorption increases. However, not all of the excess is reabsorbed, either (full reabsorption of substances filtered in excess would not allow for any compensation). Some, but not all of the excess filtrate must be reabsorbed. Due to this adaptive process, the excretion per nephron increases, allowing for a near normal total excretion rate, despite smaller number of nephrons. However, hyposthenuria is common. Such tubular adaptation is important in the compensatory mechanisms of the injured kidneys (ch. 5.5.2.).

These adaptive changes are not identical for all substances. The tubular adaptation is very suitable regarding Na reabsorption (lessening the reabsorption of the excess filtrate, i.e., increasing the Na excretion per nephron) and also for the secretion of K, therefore, the plasma levels of Na and K remain normal even if the GFR is very low (5-20 ml/min). In reference to phosphate and H^+, the adaptation is not nearly as ideal: their plasma levels increase upon moderate decrease of GFR. There is no tubular adaptation for the excretion of N-containing waste-products (Fig. 5.11.), but until GFR decreases to about 40-50% of normal in chronic renal failure, hyperfiltration and polyuria prevent the development of pronounced azotemia.

The tubular adaptation is a precisely regulated process, with a host of supportive, specific regulatory factors in the background. In the case of Na-excretion, endogenous natriuretic substances are responsible for the regulation, and in consideration of K-excretion, a rise in the aldosterone is the regulating factor (this should decrease excretion of Na, however, a lack of proportionate decrease aids K-excretion), for phosphate excretion, the elevation in PTH level (Fig. 5.12.) explains the adaptation, etc. With respect to the entire kidney, such adaptation leads to changes in urine volume and in concentrating/diluting ability of the kidney, to retention of substances of poor adaptation, and to deficiency of renal contribution to pH regulation. Naturally, all adaptations possess various limits: the adaptation provides no defense against supernormal loads, even in the cases of Na and/or K.

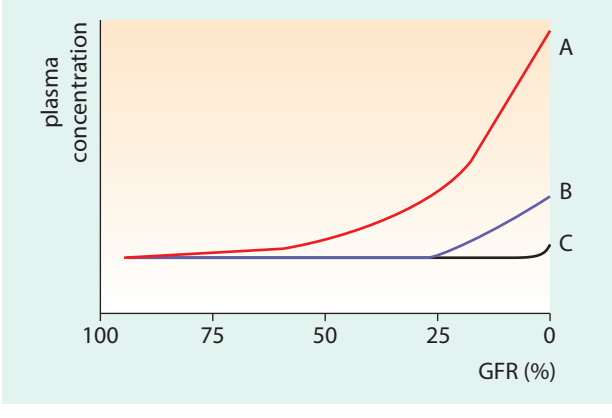

Fig. 5.11.: Types of tubular adaptation: For substances of group "C" (Na, K) the adaptation is excellent: their plasma-concentrations are maintained even at minimal GFR. The tubular adaptation is less good for group "B" (H-ion, phosphate) and there is practically no tubular adaptation for substances of group "A" (urea, creatinine).

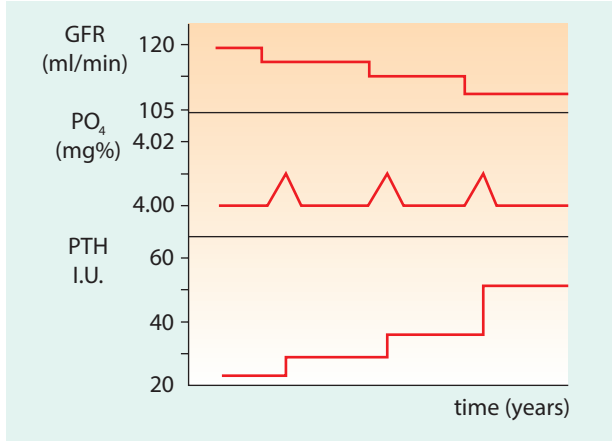

Fig. 5.12.: A stepwise decrease of GFR causes repeated elevation of se-phosphate, but a compensatory stepwise rise of PTH level again and again normalizes the se-phosphate levels.

5.3. MIXED (GLOMERULAR AND TUBULAR) DISORDERS

5.3.1. ABNORMALITIES OF URINARY VOLUME

Oliguria: It is defined as the daily urine output which is less than 400-500 ml. Normally, the amount of waste-products produced each day can be excreted in this volume, provided the urine is maximally concentrated (ca. 1200-1300 mOsm/kg). Quantities below this volume infer the waste-products are retained, even if the kidney itself is normal. A larger volume is required, if the concentrating capacity is smaller. Anuria refers to urine output which is less than 50 ml/day (sometimes zero). Both low GFR and enhanced tubular reabsorption (or their combination) may contribute to the development of oliguria.

Polyuria: It implies that the daily urine output exceeds 2 liters. In theory, this may be up to 30 l/day (although practically never reaches this amount) – after obligatory reabsorption of the filtrate, this amount reaches the collecting ducts. From the collecting duct, depending on concentrating ability (ch. 5.3.2.) water is reabsorbed by the help of ADH, thereby determining the final urine output, which is normally ca. 1.5 liters. If, for any reason (increased GFR, decreased concentrating capacity, lack or small efficacy of ADH) this is limited, polyuria develops. In primary polyuria abnormal thirst induces polydipsia, followed by polyuria, despite normal renal structure and function – after decreasing water intake the polyuria stops. In secondary forms of polyuria some renal function is altered (diabetes mellitus, diabetes insipidus, compensatory polyuria in early phase of chronic renal failure, acquired tubulopathies with defective salt/water retention, diuretic treatment, etc.).

MECHANISMS OF ACTION OF DIURETICS (= SALURETICS)

All diuretics induce some form of change through tubular functions. In theory, enhanced filtration could also increase diuresis (increased levels of GFR, result in an increase in fluid which is likely to remain in the tubules and this may serve as in osmotic diuresis). Currently, there are no prescription medication and/or prescribed methods available to increase GFR. Regardless, the peril of high GFR would be the development of glomerular damage due to hyperfiltration.

Osmotic diuretics (e.g. mannitol): These are not, or only minimally reabsorbed in the tubules. They bind water and a large volume (with smaller Na-concentration) reaches the end of the proximal tubule. The transit through the loop of Henle is faster, and the salt-reabsorption is also smaller in the ascending loop. Less water leaves passively the descending loop. More salt/water reaches the distal tubule, in which somewhat more NaCl and bicarbonate may be reabsorbed, and the K^+ and H^+ loss increases. Hypokalemia and alkalosis follow.

Loop-diuretics (e.g. furosemide): They inhibit salt reabsorption from the ascending part of the loop of Henle. As a consequence, the corticomedullary osmotic gradient decreases, less water leaves the descending portion and more reaches the distal tubule, and the resulting effect is similar as that of the osmotic diuretics. The urine volume (minute-diuresis) may show a 20-25-fold increase within a few minutes.

Carboanhydrase inhibitors (e.g. acetazolamide): They inhibit carbonic acid production (and thus, bicarbonate reabsorption) at the luminal surface of proximal tubules. The retained bicarbonate serves as an osmotic diuretic. Due to bicarbonate loss, acidosis develops and the slightly enhanced activity of distal tubules leads to K-loss.

Thiazides: These drugs inhibit salt (and water) reabsorption in the distal tubule (NaCl is emptied, rather than bicarbonate): 3-5% of GFR can be excreted, however, large amount of K is also lost.

Epithelial Na-channel inhibitors (e.g. amiloride): In the last portion of distal tubules, the Na-uptake is blocked upon the luminal surface of epithelial cells, and the result is that H^+ and K^+ will be retained in the body. The effect is rather moderate.

Spironolactone derivatives: Due to aldosterone antagonism the salt reabsorption decreases in the distal tubules, and the salt remaining in these tubules acts as an osmotic diuretic. The K-excretion decreases, leading to the risk of hyperkalemia. These are specified as potassium-spearing diuretics.

It is a common feature of all diuretics that their action is **not** directed to water or volume, rather, they act as saluretic substances and enhance tubular salt loss (the water only follows NaCl). Their action is usually coupled with decreased concentrating and diluting ability, hence, they cause hyposthenuria. The emptied salt/water is non-reabsorbed filtrate, i.e., it originates from the vascular space. Thus, diuretics decrease the vascular volume, its refilling from the extracellular space (interstitium or other parts of the body) is only secondary; however, this is how a generalized edema can be decreased. It is more difficult to decrease the amount of intracellular fluid

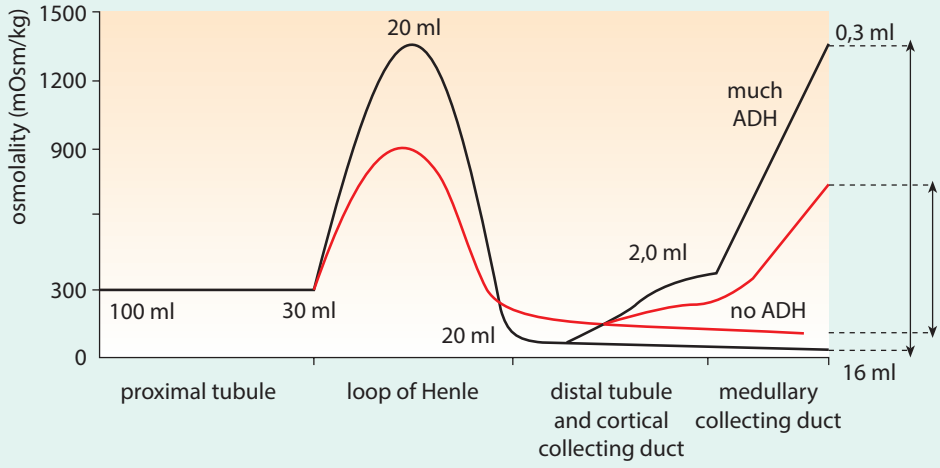

Fig. 5.13.: Changes of osmotic pressure and fluid volume along the nephron. Without ADH, large volume (16% of GFR) of diluted urine, in case of high ADH levels small volume (0.3% of GFR) of concentrated urine is formed. The possible limits of dilution and concentration are determined in the loop of Henle: at its tip the fluid is more concentrated at the end of its ascending part it is more diluted than the filtrate (in case of lasting concentration urea accumulates in the medulla, its passive rediffusion may further increase the osmotic pressure at the tip). Little happens in the distal tubule to influence final concentration/dilution of the urine, real changes happen in the collecting ducts, the main point of action of ADH. In case of hyposthenuria (red line), the concentration-changes are moderate in the loop, and the renal concentration gradient decreases. Values shown in the Fig refer to normal kidneys.

(e.g. brain edema) through the use of these substances. In heart failure associated with edema, diuretics may decrease the edema, however, the concomitant decrease in venous return may result in more pronounced forward failure symptoms. Diuretic overdose may lead to lasting hypovolemia, consequently increasing ADH production, and often causing severe hyponatremia and hypotonicity. Some decrease of plasma volume may, however, be useful in volume-hypertension.

5.3.2. DISTURBANCES OF CONCENTRATING AND DILUTING ABILITY

Osmotic pressure of the filtrate is identical to the plasma ca. 280-300 mOsm/kg, corresponding to 1.010-1.012, specific gravity. During concentration, the specific gravity is much higher, ca. 1.030-35 (1200-1300 mOsm/kg), while at levels of dilution, the corresponding values are 1.001 (60-80 mOsm/kg). The special countercurrent mechanism which is in the background can be associated with the functional system of the loop of Henle. Normally, the amount of ADH (acting mainly in the collecting ducts) can determine the *strength* by which concentration or dilution occurs between the limits of 1.035-1.001, however, these *potential limits* are independent of ADH, and rather, they are dependent upon tubular functions, first of all on the reabsorption of salt (without water) in the ascending part of the loop of Henle.

At the end of the proximal tubule, the composition of fluid differs from that of the filtrate, yet the osmotic pressures are similar. Only 30% of GFR reaches this point. This decreases to 20% at the tip of the loop of Henle, since water exits the descending portion of the loop, concomitantly the osmotic pressure increases. This water moves passively, largely due to salt reabsorption (without water) from the ascending portion and to the consequent rise of osmotic pressure in the interstitium. In the ascending portion only salt is reabsorbed (actively) therefore the volume does not change, however, the osmotic pressure decreases and the specific gravity reaches 1.001 (maximally diluted level) at the beginning of the distal tubule (and remains the same further on). Osmotic pressure does not change exclusively in the loop, but also in the interstitium, among the routes of the vessels, and a cortico-medullary gradient is established for the entire kidney, notably, with the greatest osmotic pressure in the medullary, and the lowest one in the cortical region. Although there is some aldosterone-dependent salt- and water-reabsorption in the distal tubules (accounting for 4% of GFR), however, together with water, and the osmotic pressure remains low throughout the distal tubule. Nearly 16% of GFR (30 l) reaches the end of this tubule, which fluid is diluted and may or may not be reabsorbed from the collecting ducts. In consideration of practically impermeable collecting ducts, the immensity of this fluid will be emptied or purged, in the form of urine (specific gravity 1.001, ad 30 l/day, i.e. the maximal water excret-

ing capacity) – in reality this practically never happens. If ADH (via aquaporin channels) increases the permeability, the water exits towards the interstitium the osmotic pressure of which gradually increases in the direction of the medulla, therefore, a small amount (0.3% of GFR) of highly concentrated urine is produced (Fig. 5.13. and 5.14.).

Apparently, the renal mechanisms of concentration and dilution are interconnected, a single mechanism establishes the cortico-medullary gradient, and this gradient determines the potential limits for both concentration and dilution abilities. Obviously, the process is uniform, irrespective of the volume and concentration of the final phase of the urine production. The final step will be determined exclusively by the action of ADH between the limits given by the gradient.

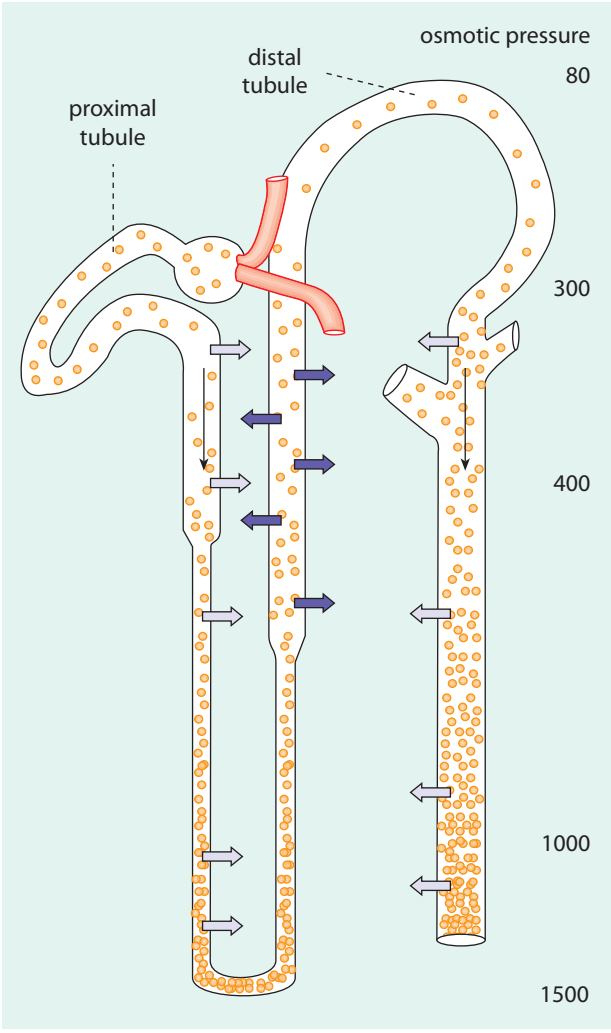

Fig. 5.14.: Concentration and dilution as referred to individual parts of the nephron. Dark arrows indicate the active Na^+-reabsorption, the light ones the passive water reabsorption.

Without ADH, even normal kidneys cannot effectively concentrate, and the specific gravity will be continuously low (diabetes insipidus). The contrasting results are expected in the case of ADH overproduction, and as such, the diluting ability will be lost. However, these changes do not influence primarily, the cortico-medullary osmotic gradient of the kidney.

In contrast, if the osmotic gradient decreases, normal concentration is impossible, even in the presence of maximal ADH activity, and normal dilution is also impossible, even in the complete absence of ADH action: the normal 1.001-1.035 range of specific gravity becomes narrower (e.g. 1.004-1.020, a difference of 16 units) and gradually approaches the specific gravity of the filtrate. This is clinically known as hyposthenuria. Asthenuria (or isosthenuria) is the state of complete loss of concentrating and diluting abilities, and the specific gravity (but not the composition) of the urine is isotonic with that of the filtrate (Fig. 5.15.). If the specific gravity of the GFR is abnormally high (as seen in hyperglycemia), e.g., 1.030, then this serves as the reference point: in the case of hyposthenuria, the range will be shifted to e.g. 1.024-1.040 (i.e. the difference is, again 16 units instead of the normal 34). Accordingly, hyposthenuria (and concomitant water loss) is possible, such as in cases of urine characteristically featuring an extremely high (1.040) specific gravity, as seen in diabetes mellitus.

Although the decrease in concentrating ability is typically noticed earlier, since normally, the specific gravity of spontaneously voided urine is moderately concentrated and it is rarely in the narrower diluting side, the functional abnormality is always bidirectional and affects the diluting ability as well. A disturbance of

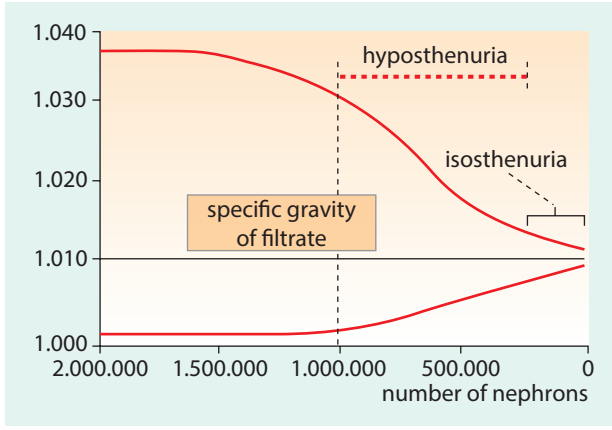

Fig. 5.15.: Development of hyposthenuria, isosthenuria: as compared with the filtrate the specific gravity of the urine exhibits gradually decreasing difference from filtrate during both dilution and filtration.

concentrating ability may be regarded as a defect of water-retention, while a limitation of diluting ability may be regarded as a defect of water-excretion. Limited capacity of either process can cause severe clinical consequences (hypovolemia/hypernatremia/exsiccosis, or by contrast, hypervolemia/hypotonicity, intra/extra-cellular edema, etc.).

Hyposthenuria can be induced by any decrease of the cortico-medullary osmotic gradient:

- Inhibition of Na-reabsorption (diuretics, natriuretic factors and hypoxia),
- Hyperglycemia, although in the proximal tubule, the glucose (and due to symport, also Na) reabsorption increases and the residual glucose retains water: A large volume and low-Na-/high-glucose-concentration + high osmotic pressure fluid circulates through the loop of Henle and the distal tubules (**osmotic diuresis**), and the general result implies a loss of increased levels of glucose, water and Na (exsiccosis tendency),
- "Washout" of the medullary hyperosmolarity by relatively high medullary perfusion (pyelonephritis and shock),
- The gradient decreases if the SNGFR increases (fast tubular flow),
- Pronounced decrease in the total GFR (the total Na-reabsorption and the gradient are smaller)
- Severe decrease in nephron number/density.

Distinctly, any form of hyposthenuria tends to cause salt/water loss (defect of retention). As long as the filtered volume is relatively sufficient, the urine quantity is relatively large – this predisposes to a decrease in extracellular volume, hypovolemia, exsiccosis and their consequences (the intracellular space is not influenced directly). Obviously, the salt/water excretion capability is also disturbed, therefore, the patient is now unprotected against water-loads (risk of hypotonicity) or against salt loads and (particularly in severe cases, the se-Na and plasma volume may easily increase, and/or salt/water may accumulate in the interstitium) these may cause hypertensive crisis and/or generalized edema.

Hyposthenuria is often associated with alterations in volume of the urine: Urine output per nephron is always larger, however, depending on the number of functioning nephrons and total GFR, the total urine output may be either larger or smaller than normal, i.e., either polyuria or oliguria may occur. Due to increasing SNGFR, the total GFR may remain normal for a period, but later it also decreases far below the normal level. In the functioning nephrons, the excess filtrate cannot be processed, the urine output per nephron is so large that the total urine amount increases, despite a low total GFR, and the result is the development of hyposthenuric polyuria. With a further decrease in the functioning nephrons, the hyposthenuria becomes more severe, the polyuria gradually develops into oliguria.

The hyposthenuric polyuria, based on increased SNGFR, although coupled with salt/water loss, may be regarded a compensation of decreased excretory functions (in clinical practice, this phase is defined as "compensatory polyuria", in the course of gradual loss of nephrons). At this stage the total GFR is near-normal, creatinine and other waste-products can be more or less eliminated, only in larger urine volume. Hyposthenuric polyuria without a high level of SNGFR, but due to primary tubular dysfunction (e.g. anemic hypoxia, aging-related tubular dysfunctions) cannot be regarded as a compensatory phenomenon, rather as a kidney now losing salt/water ("salt-losing kidney"). Both the extracellular volume (ECV) and plasma volume decreases in all forms (this may be regarded "beneficial" in the concurrently developing hypertension).

When, due to high levels of SNGFR additional nephrons are destroyed, the polyuria cannot be maintained and gradually oliguria develops, however, the hyposthenuria persists or progresses. Oliguric hyposthenuria is defined as a severe complex failure of excretory functions. It results in a rise of extracellular volume with a tendency for edema formation, hence, the extracellular volume cannot be controlled and it is dependent entirely on salt/water intake.

5.3.3. DISORDERS OF URINE COMPOSITION

5.3.3.1 PROTEINURIA

Plasma proteins are macromolecules featuring a negatively charged surface and their glomerular filtration is limited, due to the pore size and the similarly negative charge of both the podocytes and the filter surfaces. Most of the remaining filtered yet small amount of various proteins is absorbed by the tubular cells, in which they are metabolized (effectively, these are also lost for the body). The tubular reabsorption of proteins is a normal process, however, lasting excessive reabsorption may disturb the metabolic processes of these cells

and may induce cellular damage, such as seen in the nephrotic syndrome. Normally less than 100-150 mg protein is excreted into the urine, what is not enough to demonstrate through simple laboratory methods. Proteinuria exceeding this amount features a diagnostic importance, as in most cases, it is a symptom of renal damage, and the resultant hypoproteinemia in itself may lead to pathological consequences.

FORMS OF PROTEINURIA

1. *Prerenal:* If small-size proteins appear and accumulate in the plasma, they can be filtered, however, the tubular uptake cannot keep pace (e.g. hemoglobin, albumin, or Bence-Jones protein in multiple myeloma). Secondary glomerular injury may follow, due to the activation of mesangial cells. Hemoglobin may damage the tubular cells, too.
2. *Glomerular:* A disorder of the glomerular filter or the filtration process. It is an early symptom commonly seen in diabetes and presents itself in the form of a "warning sign", one which affects the kidneys. The disarrangement of the filter pore allows filtration of larger sized proteins, particularly if the filter selectivity is altered (selectivity depends not on thickness but on the structure of the filter). The amount of lost protein easily exceeds 2 g/day and characteristically increases with progression. In the **nephrosis** syndrome, up to 50 g/day may be lost. Consequently, hypoproteinemia will increase the activity of the liver: it induces hyperlipoproteinemia (ch. 9.3.2.) and enhanced coagulability (including in glomerular capillaries), therefore later further glomerular damage (capillary microthrombi and mesangial cell damage due to the lipoproteins) and progressive deterioration of excretory functions may develop. [Historical interest: The nephrosis originally was regarded as a primary *degenerative* (-"osis") tubular damage: the early techniques did not show the glomerular injury, this became obvious only at later stages. Today, we know that nephrosis begins with enhanced glomerular filtration and the overburdened tubules degenerate.]
3. *Tubular:* The disorder of tubular active transport processes (e.g. hypoxia) inhibits tubular uptake of proteins. Usually moderate (<2 g/day) proteinuria develops, and primarily, a small number of proteins are lost. The minimal amount of proteins secreted by the tubules (e.g. Tamm-Horsfall protein) may also extend into the urine.

Selective and nonselective proteinuria: Selectivity refers to the size and type of protein. Microproteinuria indicates a relatively minor glomerular injury, in which not all of the small-size proteins that are filtered in excess can be taken up by the tubules. Microproteinuria typically means *microalbuminuria,* (= 30-300 mg/day relatively small-size albumin that is often difficult to demonstrate by routine laboratory methods). Occurrence is important in hypertension, diabetes (early stage), heart failure (late stage), etc. It was assumed to be a signal of mild glomerular injury, in which the excess protein cannot be taken up by tubules. Recently, a premise suggests that generalized endothelial damage may be lurking in the background, and microalbuminuria may be just one manifestation. However, it may be an early sign of dangerous complications regarding cardiovascular functions (hypertension, heart failure, vascular damages, AMI and/or rhythm abnormalities) (cf. cardiorenal syndrome, ch. 2.1.3.), or the acceleration of late stage diabetic complications (ch. 9.2.2.4.2.). Later on, primarily due to the large quantities of filtered protein (Figs. 5.10 and 5.16.), the glomerular injury becomes more severe (Fig. 5.7.) and this proteinuria can be easily detected. At this stage of non-selective *(macro) proteinuria,* an immense quantity of protein, featuring

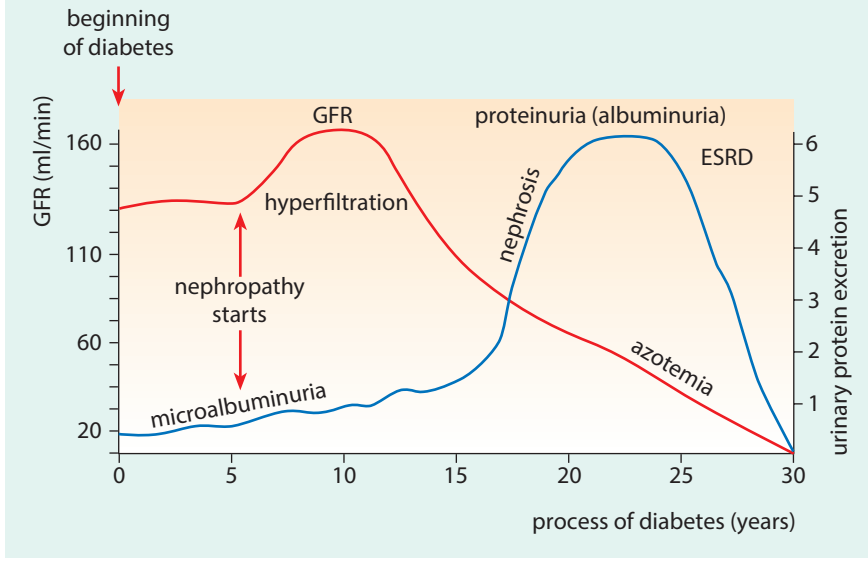

Fig. 5.16.: Course of GFR and proteinuria in a diabetic patient.

a variety in sizes, is purged – this is a sign of massive injury of the glomerular filtrating surface.

The often referred orthostatic proteinuria (<1g/day) is typically not regarded as being pathological. It is present during physical activity (in the very least, walking) and ceases upon bed-rest. It is commonly explained by a greater lordosis and congestion of the renal vein (and decreased tubular reabsorption, due to congestion/hypoxia). However, in some cases renal biopsy revealed histological abnormalities. Since structural kidney damage may be assumed in all other forms of proteinuria (even if, in itself, it gives no direct clinical signs), and this cannot be ruled out, in the eyes of specialists *all forms of proteinuria must be regarded as signs of potentially progressive renal damage and must be regularly controlled, lessened, although cannot be cured* (in contrast to some cases of pyuria or hematuria, which characteristically appear frightening, yet, they may be treated or cured relatively easily).

CONSEQUENCES OF PROTEINURIA

Clinically significant hypoproteinemia may develop more or less proportionately with the lost protein. The consequences may include hypoproteinemic edema and secondary hyperaldosteronism, lack of specific proteins, transportproteins, immunoproteins, etc., and anemia, endocrine disorders and/or cachexia. Macroproteinuria affects liver functions and lipoprotein metabolism: the liver attempts to increase albumin production (although, not sufficiently), together with apoprotein A-I and apo-B100, causing secondary hyperlipoproteinemia with elevated LDL/VLDL levels (ch. 9.3.2). Renal loss of apo-A-I, low HDL and high LDL level, including the inhibition of lipoprotein lipase in chronic renal failure with hypoproteinemia are strongly atherogenic. Hypoproteinemia also promotes steatosis of the liver, and consequently, liver function disorders (cf. kwashiorkor syndrome, ch. 9.1.1.1.).

5.3.3.2. HEMATURIA

Generally, nearly all hematuria is associated with postrenal origin and traced from the urogenital tract (e.g. nephrolithiasis and hemorrhagic cystitis). Mechanical renal injury may also cause hematuria, particularly in patients suffering from coagulopathy. In these cases, fresh blood is mixed with the urine and the shape of each red blood cell is normal. Once the initial problem is solved, the hematuria ceases.

Real renal hematuria may develop in the case of an injury of the glomeruli, such as seen in Henoch-Schönlein purpura (ch. 4.4.1.) and acute glomerulonephritis (ch. 5.5.3.4.). In these cases, the red blood cells are reduced in size and deformed due to the high osmotic pressure of the urine. Treatment of renal hematuria is far more difficult and the disorder often progresses to chronic renal failure.

Hematuria is not to be mixed with hemoglobinuria, when intravascular hemolysis happens.

5.3.3.3. CYLINDRURIA

Cylinders are cylindrical particles in the renal tubules, made of clashed cellular elements, debris, proteins, pigments (Hb, myoglobin, etc.) and occasionally, crystals (oxalate, urate, cystine, etc.). This combined sediment is produced in the urine, and is characteristically often seen in cases involving acute tubular nephropathy (ch. 5.5.3.3.) or other forms of tubular injury, however, may easily occur in acute glomerulonephritis and chronic nephritis. The hemoglobinuria is accompanied with Hb-cylindruria and rhabdomyolysis joined with myoglobin cylinders, and these pigments are tubulotoxins.

5.3.3.4. NEPHROLITHIASIS

Human urine consistenly contains substances of small solubility (Ca-salts, urate, oxalate, etc.), and all easily precipitate. Other substances (citrate, Mg, pyrophosphate, etc.) inhibit stone formation. The basis of nephrolithiasis represents an imbalance among these functions and often occurs in the case of a diet including high protein-, purine-, calcium-, vitamin C, salt-content, as seen in vitamin B_6 deficiencies. Similarly, dehydration, in which heat is lost by heavy sweating, continuously produces concentrated urine which promotes the development of nephrolithiasis, e.g. it is generally associated with the Southern portion of the USA, often referred to as the ”Stone Belt”, with a notoriously hot climate, in which kidney stones are reportedly far more common.

Ca-phosphate stones are formed in alkaline urine, often in association with an infection of the renal pelvis, or with high Ca-excretion (not necessarily hypercalcemia, rather hyperparathyroidism, or RTA lurks in the background), and also, in the case of a low citrate-excretion (protein/salt-rich diet and/or thiazide diuretic). The *Ca-oxalate* stone is more frequent and it characteristi-

cally precipitates at acidic pH, and is eventually layered among urate crystals, mainly in the case of hyperoxaluria and includes the following aspects: a dietary oxalate, a transformed oxalate, such as a form of vitamin C-metabolite, and fat malabsorptions (ch. 7.4.1.), and, lastly, metabolic acidosis promotes its development.

Urate stones are commonly associated in gout (ch. 9.1.3.) and in acidic levels of pH. Regarding infections, the bacterial urease enzyme leads to ammonia production and alkaline pH, which serves as the basis in reference to *struvite* (Mg-ammonium-phosphate) stone formation. Characteristically, these stones can attain rather large sizes, even fill the entire renal pelvis. The *cystine* stones are formed due to autosomal recessive disorder of tubular functions, and these directly injure the tubules, similarly to urate and oxalate crystals (cf. ATN, ch. 5.5.3.3.).

Stones reaching the ureter may cause extreme pain often accompanied with fainting, vomiting by reflex, and reflex constriction of the bilateral renal artery. In addition to the potential injury of the ureter and distal urinary tract, the stone causes obstruction and congestion of the renal pelvis, the pressure generated is forced back to the tubules and the renal parenchyma (postrenal failure).

Interestingly, relatively small stones create immensely far more lasting occlusions of the ureter, and this may result in the development of a sacciform kidney, chronic failure and complete destruction of the kidney. Large stones within the renal pelvis may entirely fill the area, and characteristically, this is referred to as "coral stone", and typically is accompanied with less severe acute complaints, however, the potential damage is generally associated with chronic levels of congestion and infection, and often leading to pyelonephritis, a frequent cause of chronic renal disease leading to end-stage renal failure (ESRF).

5.3.3.5. DISORDERS OF THE pH-REGULATORY ROLE OF THE KIDNEY

These are analyzed in details throughout chapters 6.2.1.3. The fundamental problem is a defect of the Na^+/H^+ tubular exchange, which may limit either the reabsorption of bicarbonate or the acidification of the urine. The ammonia-producing capacity may also be decreased. Anions of strong acids (e.g. sulfate, phosphate) may accumulate in the plasma, and additionally, due to defective acidification of the urine metabolic acidosis develops.

5.4. NON-EXCRETORY KIDNEY FUNCTIONS

5.4.1. ROLE IN BLOOD PRESSURE REGULATION

There are two methods in which the kidneys influence blood pressure regulation (Fig. 2.29.):

1. *Pressor effects* conveyed by the activation of the renin-angiotensin-aldosterone (RAAS) system in the juxtaglomerular apparatus (JGA): Essentially, constriction of the renal artery and the decrease in intrarenal pressure enhances renin secretion, and this cleaves angiotensinogen (produced in the liver) to angiotensin I, which then is cleaved by angiotensin converting enzyme (ACE) to angiotensin II, and lastly, activates aldosterone production. Angiotensin II has a direct vasoconstrictor effect and enhances salt/water intake, while aldosterone increases the tubular salt- and water-reabsorption and the circulating plasma volume. Accordingly, the activation of the RAAS features double action to elevate blood pressure. The hyperfunction of this system is responsible for the renovascular type of hypertension.

2. *Depressor effects*: The renal parenchyma produces substances of the prostaglandin group, kinins and renomedullary lipids/lipoxides. These substances can cause systemic vasodilation, and in the kidney they inhibit tubular Na-reabsorption (the natriuretic effect decreases plasma volume). These are two mechanisms implemented towards decreasing blood pressure. A deficiency in either mechanism explains reno-parenchymal/renoprive type of hypertension often observed in chronic renal failure, in which the depressor system is, over time, exhausted in all forms of hypertension.

5.4.2. EFFECTS ON ERYTHROPOIESIS

Hypoxia of the renal tissue enhances erythropoietin production in cells of the juxta-tubular interstitium. Erythropoietin, a growth factor, is an important stimulant of red blood cell formation in bone marrow. A moderate change of renal blood flow does not prove largely influential regarding the tissue oxygen tension or erythropoietin production, while in hypoxemic hypoxia, anemic hypoxia and stagnation hypoxia (extreme, lasting congestion of the renal veins), the low oxygen tension of renal tissue is fundamental in the enhanced erythropoietin formation and also (with the

exception of anemia) in the development of polyglobulia. Elevated erythropoietin production may also occur due to steroids and androgen hormones. Low levels of erythropoietin contribute to the extreme anemia of chronic renal failure, in which erythropoietin therapy nearly normalizes the red blood cell number in uremia.

5.4.3. VITAMIN-D AND Ca-HOMEOSTASIS

The last step in the formation of 1,25-dihydroxy-cholecalciferol, the final form of vitamin D, takes place in the kidney, and it is a hydroxylation at the C_1 position. Parathormone (PTH) is needed for the production and activation of 1α-hydroxylase enzyme. Apparently, in addition to a rapid effect on Ca-homeostasis (Ca-mobilization from the bone), PTH activates a slow method of regulation via vitamin D. Vitamin D enhances Ca absorption from the gut and its reabsorption from the tubules, and it also mobilizes some Ca from the bone. Distinctively, it acts as a D *hormone*, of which, in its role as a steroid hormone, binds to nuclear receptors within the intestinal mucosa cells enhancing the production of a Ca-binding protein which is important for absorption of Ca (ch. A6.2.3.2.). In chronic renal diseases, both Ca-loss and PO_4 retention enhances PTH production (Fig. 5.8.) and the secondary hyperparathyroidism leads to severe bone deformities, while in extreme concentrations (common in renal disease) the PTH acts as uremic toxin. Simultaneously, the defective 1α-hydroxylase production in the failing kidney leads to symptoms of vitamin D deficiency. The administration of calcitriol (D_3) and Ca serves to alleviate the symptoms.

Hydroxylation in the kidney may happen on $C_{24,}$ including (this is likely independent of PTH) the production of 24-25-dihydroxycholecalciferol, which thereby supports the incorporation of Ca into the bone.

5.4.4. METABOLIC FUNCTIONS

By the production of ammonia (from glutamine), the kidneys contribute to the maintenance of the pH balance. Some of renal glycogen may be converted to glucose and occasionally (malnutrition and/or the reversal of hypoglycemia) the kidneys support the liver in maintenance of normal blood glucose. The kidneys are also important in the breakdown and excretion of insulin and several other hormones. Through tubular reabsorption, amino acids contribute to protein metabolism, and the importance of this process is similar to the reabsorption of filtered glucose. In lipid metabolism, the kidneys have only an indirect role under pathological conditions, as seen in kidney diseases, in which hyperlipoproteinemia may develop due to abnormalities of protein metabolism.

5.5. RENAL FAILURES

5.5.1. UREMIA

Definition

Acute failure or *chronic* disease of excretory functions result in the elevation of those substances within the blood, which should be excreted by the urine (uremia refers to ”urine in the blood”). Plasma concentration of other substances (e.g. bicarbonate, Ca and Fe) may, as a secondary reaction, decrease, since renal reabsorption does not replace their depletion by other ways (e.g. poor intestinal absorption). Hormones which should be metabolized or excreted by the kidney (e.g. insulin, glucagon, gastrin, prolactin) accumulate. The shift in the level of different substances is variable and dependent on the availability of adaptive mechanisms. First, the urea level (BUN) increases in cases of moderate severity, and this is regarded only as *azotemia*, not yet a complete uremia, rather, as a sign of accumulation of weak toxins. In real *uremia,* the stronger toxin, phosphate and H^+ concentrations increase (while the Ca^{++} and Fe^{++} concentrations decrease). Inevitably, at later phase hyperkalemia develops and se-Na becomes entirely dependent upon salt intake. An immense number of stronger uremic toxins is present and the laboratory changes of uremic metabolic derangement can be demonstrated. The clinical picture of uremia is much more complex, and the function of several systems (circulation, nervous system, endocrine systems, etc.) is altered, which is particularly striking in the chronic form of renal failure, however, the acute form of renal failure (e,g, crush syndrome) may also lead to uremic coma and/or uremic death (ch. 2.2.2.5. and 5.5.3.3.). The non-excretory renal functions are also compromised, particularly in the chronic form, in which the production of renal hormones, prostaglandins, vitamin D, etc., decreases, hormone actions in the kidney (e.g. ADH) become defective, however, the erythropoietin production decrease is pronounced even in acute renal failure.

Metabolic abnormalities in uremia

The glucose tolerance test is abnormal (”diabetoid”) and glucose utilization decreases, even in the presence of high insulin levels, suggesting insulin antagonism.

The lipoprotein lipase activity is suppressed and the level of some lipoproteins (LDL, VLDL) is elevated (ch. 9.3.2.), the lipid content of the liver is high. Protein catabolism is enhanced, meaning that more N-containing waste-products are produced, and (together with proteinuria) the result is markedly pronounced hypoproteinemia. The tissue/cellular metabolic rate decreases, as seen in histotoxic hypoxia, in which hyperosmolarity, acidosis and toxins all lead to non-specific inhibition of intracellular enzymes, which in turn, decreases the cellular metabolism and creates an energy deficit. In regards to the cells, K^+ is lost, while Na^+, water and Ca^{++} all enter and together result in cellular swelling ("sick cell"). Both the membrane potential and the active transport decreases, while the permeability of various membranes (cell membrane, serous membranes, etc.) increases. Despite cellular swelling, the relative amount of interstitial fluid still increases since the cell number decreases. Some of these changes (e.g. disorder of glucose metabolism, but not protein metabolism) can be alleviated by dialysis, suggesting that dialyzable toxin may have contributed to the abnormality.

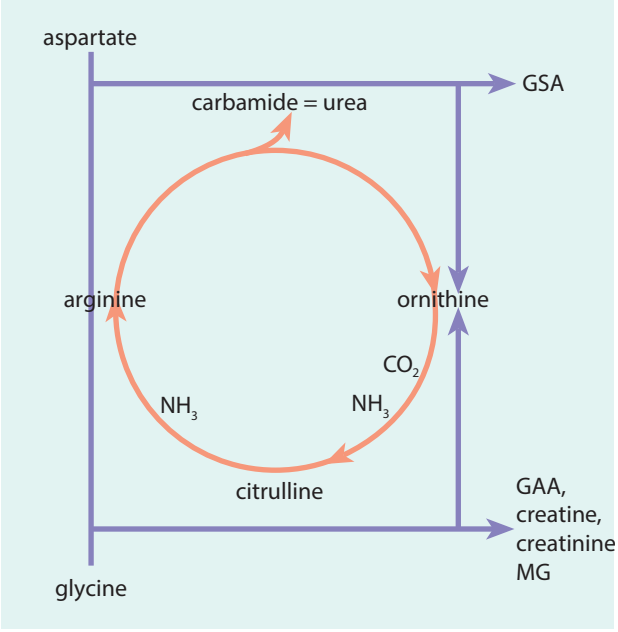

Fig. 5.17.: Urea cycle and its changes in uremia. The accumulated urea, as an end-product, blocks further urea production and for arginine-ornithine transformation other pathways are used (with aspartate or glycine). Byproducts of these pathways are the guanidine-succinic acid (GSA, or arginine-succinic acid), guanidine-acetic acid (GAA or arginine-acetic acid), and these derivatives (methyl-guanidine = MG, creatinine, etc.). These pathways do exist physiologically, but function on a low level (e.g. creatinine is produced normally), in uremia their function is enhanced and the concentration of toxic byproducts increases.

Uremic toxins

Previously, one specific toxin, particularly urea, was assumed to act. However, in early human studies with administration of huge urea amounts to healthy young volunteers, urea caused only minor discomfort, but not the clinical symptoms of uremic toxemia. Today, many substances are known to play a role as uremic toxins, urea is one of them, acting not specifically but at least by its osmotic activity. All of these toxins are produced normally in the body, it is only their large concentrations which result in their toxicity. Non-excreted waste-products (including urea), secondary byproducts (e.g. 'guanidino-' derivatives, creatinine, Fig. 5.17., all which are primarily stronger toxins, ch. 7.6.1.3.) and other, even physiologically important substances (e.g. PTH) may produce toxic effects in large concentrations. Although the exact way of action differs among various substances, they typically inhibit cell metabolism by non-specific enzyme inhibition, enhance membrane permeability and strongly impair the function of the nervous, hemopoietic, immune and cardiovascular systems. Through altering the surface glycoproteins of the platelets, the toxins impair adhesion, aggregation and coagulation. Degeneration of axon-cylinders and demyelinization are also induced. Uremic toxins inhibit ADH secretion.

The most important uremic toxins: N-containing catabolites, such as, urea, cyanate (faraway catabolite of urea), creatinine, methylguanidine, guanidino-succinic-acid (GSA), guanidino-acetic-acid (GAA); parathormone, myoinositol, "middle-size molecules", ammonia, phenols, indole, uric acid, oxalate, glycation products (advanced glycation endproducts = AGE, ch. 9.2.2.4.2.), etc. Urea at high concentrations is also excreted in the oral cavity and is evident in the characteristic odor of breath.

Uremic coma

The gradually progressing unconsciousness can be explained by impaired function of the central nervous system. Factors of its development include the following:

- Intracellular enzyme-inhibitions (toxins, hyperosmolarity and/or acidosis)
- Histotoxic and anemic hypoxia and hypocapnia-induced brain hypoperfusion
- Metabolic acidosis (+CO_2-loss due to Kussmaul breathing) and/or IC buffering
- Hyperkalemia and/or hypocalcemia (se-total-Ca /for long, not the ionized/ decreases, however,

with increased levels of Ca within the brain cells at mitochondria)
- High (>350 mOsm/kg) plasma osmotic pressure and also, within the cells (urea can enter the cells)
- Action of various toxins upon neural cells
- Disorders of amino acid transport may cause cerebral transmitter abnormalities, such as in the case in which the cerebral glutamine-content is high rather than that of the excitatory glutamate (glutamate + NH_3 → glutamine).

5.5.2. CHRONIC RENAL FAILURE (CRF)

Uremia often develops in a process lasting for many years. The prolonged process allows the development of pathological changes in several organs, organ systems (e.g. cardiomyopathy, hypertension and its consequences, anemia, bone abnormalities and/or endocrinopathies). Apart from anemia, these are not characteristic in acute renal failure, however, the fundamental laboratory and clinical consequences and signs are similarly independent of the speed and velocity in the development of uremia.

Causes and forms

Primary chronic renal damage (ca. 20% of all CRF):
Chronic glomerulonephritis forms
Interstitial nephritis forms
Pyelonephritis
Cysts and nephrolithiasis
Urogenital infections
Drug (medication) side-effects

Systemic diseases related morphological/functional kidney damage:
Hypertension (ca. 25-30% of all CRF)
Diabetes mellitus (ca. 30-40% of all CRF)
Autoimmune diseases
Heart failure
Cirrhosis
Gout and hypercalcemia
Systemic lupus erythematodes (SLE)

Highlighted pathophysiological mechanisms regarding the process

***Intact nephron principle*:** Only those nephrons function which are entirely intact throughout their length. Those nephrons in which either the glomerulus or some tubular section is damaged are completely lost for the excretory functions, only the morphologically intact nephrons can be considered in the excretory functions. However, the function of morphologically intact nephrons is not necessarily normal, and hyperfiltration, magnification, etc. may develop in such intact nephrons.

***Hyperfiltration*:** In the glomeruli of the remaining "intact" nephrons, the filtration is enhanced. This may be regarded as *glomerular adaptation* with respect to those substances which are emptied exclusively through filtration: the high SNGFR (hypertrophy of the glomerular capillary loops plus the tubulo-glomerular feedback) attenuates the fall of total GFR and promotes excretion of N-containing waste-products. Unfortunately, in the long run, hyperfiltration leads to glomerular impairment (by activation of mesangial cells) and due to this, the progression of CRF accelerates.

***Magnification phenomenon*:** This is the most important aspect of *tubular adaptation* to changes in filtration. Normally 0.5-1% of the filtrate is emptied in the form of urine and much higher % if the SNGFR is increased (although not all of the filtered excess). Thus, the salt excretion (or "non-reabsorption") per nephron increases up to 20-25 fold, what is defined as magnification. Since, however, due to the number of functioning nephrons which indeed, is smaller, the total amount of excreted or reabsorbed salt may be normal. Endogenous natriuretic factors (atriopeptin, PGE_2, PGI_2, bradykinin and/or renomedullary lipids) are thought to be responsible for this phenomenon. Undoubtedly, through magnification, it is apparent that the normal salt intake regarding the Na-excretion and se-Na remain in the normal range, despite a decrease in both the nephron number and total GFR. Assuredly, there is a substantially fine tubular adaptation regarding K. This is partly due to the level of aldosterone, what is relatively high, i.e., it does not decrease proportionately with the required Na-excretion, and aldosterone elevates K-excretion in the kidney and intestine, in part, since the activity of microsomal Na^+/K^+ ATP-ase enhances fractional K-excretion within the tubules. Regarding other substances (H^+, phosphate), the tubular adaptation is nearly not as suitable, since phosphate magnification relies entirely upon high PTH levels. For other substances, such as N-containing waste-products, there is no tubular adaptation at all, only the demonstrated glomerular adaptation through hyperfiltration.

***Trade-off mechanisms*:** The retained substances induce secondary changes, e.g. urea accumulation leads to overproduction of guanidino products which feature toxic effects, similarly, the phosphate-retention induced

extreme PTH levels imply the potential among a host of formerly unlikely consequences specifically, in reference to bones, brain, etc. These biochemical pathways normally also function, yet on a minimal level, and now the levels are massively, although not proportionally, increased.

Possibility of glomerular/tubular compensation

To compensate the effort of lost nephrons, the SNGFR increases and tubular adaptation is initiated. Both scenarios have their price, as such an increase in filtration leads to progressive glomerular damage, and the factors of tubular adaptation lead to severe secondary functional abnormalities, such as bone deformities due to PTH.

Compensation may allow temporary maintenance of plasma levels of some substances in the normal range, however, the capacity of renal adaptation to further challenges unavoidably decreases. Protein breakdown quickly results in rise of se-urea and se-creatinine. Tubular adaptation provides the opportunity to maintain a normal se-K level, however, a minimal increase in K-intake or bigger tissue/cell necrosis causes hyperkalemia, thus, despite that the glomerular/tubular adaptation secures a normal resting level, there is a decrease in the reserve capacity. Similarly, a moderately high Na-load soon results in a rise of se-Na, while the salt/water retention and the consequent hypervolemia evoke an uncompensated soaring rise in blood pressure and also a potential for edema to develop.

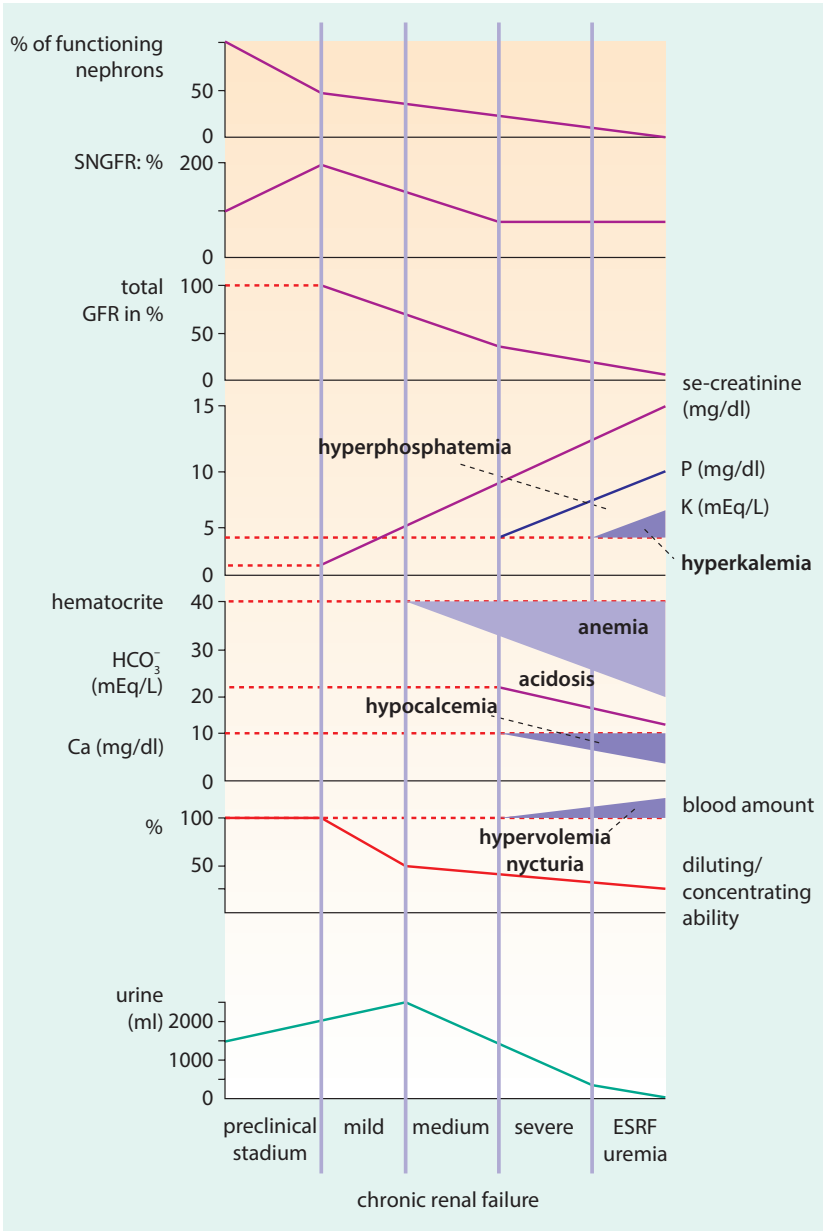

Fig. 5.18.: Characteristics of the stadia of chronic renal failure.

Phases of the development of CRF

Null-phase: As long as the nephron population exceeds 50% of the normal number of two million, no excretory abnormalities are to be expected, although both the normal aging process of the kidney and the loss of additional nephrons is simultaneously accelerated. The same characteristic refers to individuals born with small kidneys, and also in those individuals who have a single kidney, or a resected kidney.

Phase I: Between 50 → 25% nephron-population and decreasing GFR azotemia can be expected and hyposthenuric polyuria is initiated, despite the low GFR. In the clinical practice this is regarded as "compensatory polyuria".

Phase II: At or nearly 25% (20-30%) nephron totals, the reserve capacity decreases and the adaptation

methods towards exogenous/endogenous loads prove insufficient. Hyposthenuria is maintained and the polyuria is less pronounced.

Phase III: At the nephron population in the vicinity of 5-20%, the polyuria abates and even oliguria may develop. The hyposthenuria is more severe and the reserve capacity is minimalized.

Phase IV: (end-stage renal failure = ESRF): At ≤5%, GFR oliguria and isosthenuria are present, severe uremic symptoms are characteristically heightened, even without a special load, consequently dialysis or transplantation is direly needed.

Recently, the phases are provided in accordance to the GFR value, thus >90, 60-89, 30-59, 15-29, and <15 ml/min stadia are described.

Factors promoting the progression of CRF

Systemic and intraglomerular hypertension: There is constriction of the vas efferent, primarily due to angiotensin II or the dilation of vas afferent, due to PG-s and NO, in which all promote progression. Blood pressure exceeding the zone of autoregulation increases renal perfusion, glomerular hydrostatic pressure, and additionally, it causes hyperfiltration associated with progression-enhancing consequences. Accordingly, ACE inhibitors and temporarily NSAID-s may slow down the progression.

Intraglomerular coagulation: Injured endothelial cells and platelet activating factor (PAF) result in microthrombi and occlusions within glomerular capillaries. The prothrombotic uremic toxins act strongly within the glomeruli. Heparin and NSAID attenuate the damage.

Renal Ca-deposition: There is fibrin and sclerosis in the occluded capillary loops. High phosphate and PTH levels promote Ca-phosphate deposition. Restriction of phosphate intake may help.

Hyperlipidemia: The cholesterol /LDL/ binds to glucosaminoglycanes, and this decreases the negative charge of the basement membrane, enhances its permeability and accelerates mesangial proliferation. The thromboxane production increases. The secondary hyperlipoproteinemia should be decreased.

Dietary Protein: Excessive protein intake increases the intraglomerular pressure, filtration, coagulation tendency, activates mesangial cells (certain cytokines including TGF, PDGF, etc.) which possess fibrogenetic activity, in addition to inhibiting collagenase, metalloproteinase and plasminogen activator functions, the turnover of mesenchymal matrix decreases; the filtered protein elevates the activity of proinflammatory cytokines (e.g. IL-1, IL-6, TNF-α, which increases the production of mesangial matrix). All these lead to glomerulosclerosis. The high protein filtration is followed by high protein and Na reabsorption in the proximal tubules, thus, decreased levels of Na reaches the macula densa and the tubulo-glomerular feedback leads to hyperfiltration. Proteins in excess also injure the tubules and in doing so, help the release of lysosomal enzymes, the inflammatory and vasoactive proteins, in which aids is the production of chemoattractant protein-1 (MCP-I); osteopontin and endothelin appear in the tubules, of which may induce parenchymal fibrosis. Smaller sized proteins upon the surface of tubules may also induce inflammation through complement activation, while the Fe released form transferrin acts via free radicals. Accordingly, limiting protein intake may be useful and not only by decreasing the N-containing waste-products. Although in CRF hypoproteinemia is characteristic, the protein intake must still remain limited.

Preventive steps to slow progression

Avoidance or attenuation of factors of progression generally proves beneficial.

Control of blood pressure: In diabetes, followed with >1 g/day proteinuria 125/75, otherwise 130/80 mmHg is the advised maximum. Mainly ACE inhibitors, or angiotensin-receptor antagonists (ARB) are used, occasionally combined with Ca-channel blockers, β-adrenergic blockers, diuretics.

Lessening proteinuria: Low protein diet, ACE-inhibitors and/or ARB.

Reducing hyperlipidemia: Inhibition of cholesterol-synthesis (statins), [earlier: inhibiting VLDL-production (fibrates – potential risk of rhabdomyolysis)] and diet.

Glycemic control (maintain HbA1c levels below 7%, cf. 9.2.2.): to decrease the vascular changes resembling those seen in hyperlipidemia.

Cease smoking, as it influences glomerular circulation.

Potential progression-slowing treatments in the experimental stage:

- Endothelin receptor antagonists in diabetes, or without it (in endothelin transgenic mice kidney lesions develop spontaneously)

- Endopeptidase and vasopeptidase inhibitors (inhibit the breakdown of natriuretic factors and the ACE activity)
- Leptin antagonism (leptin stimulates the endothelial cells, enhances the expression of fibrogenic TGF-β and their receptors and the collagen-I production of mesangial cells; lasting leptin infusion induced experimental proteinuria and enhanced the collagen-IV production)
- Glycosaminoglycan supplementation reduced the albuminuria in diabetes.

Non-excretory functions in CRF

In CRF, over time, hypertension occurs more and more frequently and in increasingly severe forms. This is due to the deficiency of depressor mechanisms and to an enlarged plasma volume (Fig. 5.19.). The blood pressure is labile: salt load induces sudden increase, while in rare cases of severe exsiccosis, even relatively low blood pressure may be seen. The hypertension enhances the additional progression of the renal injury and accelerates the development of other, primarily cardiovascular complications, such as myocardium hypertrophy, ischemic heart disease and atherosclerosis. These changes may be included in the cardiorenal syndrome (ch. 2.1.3.), and generally, such disorders of the circulation accelerate the deterioration of renal functions.

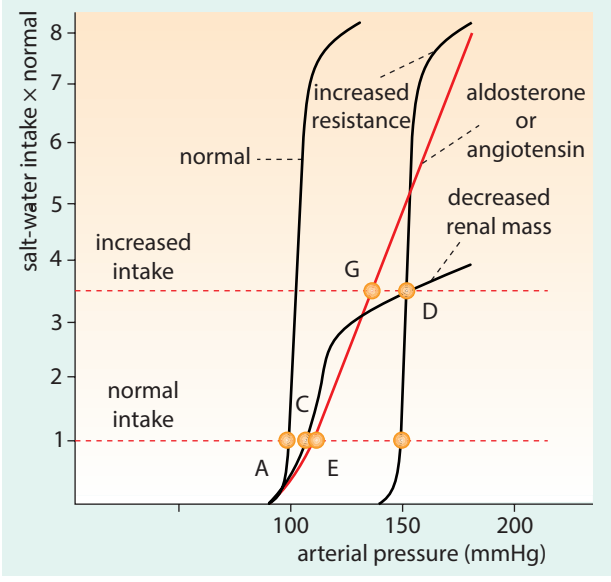

Fig. 5.19.: With decreasing renal mass the salt-excreting capacity decreases and salt can be excreted only at elevated levels of blood pressure (cf. Figs 2.28. and 5.3.).

The extremely frequent and severe anemia may be explained partially by a decrease in production of red blood cells, including the following causes: a deficiency of protein and iron, a lack of erythropoietin, the toxic dysfunction of bone marrow, partially due to an increase in the destruction and loss of these cells. Thered blood cells of a small resistance in a toxic environment are easily destroyed, and a tendency towards bleeding causes further loss. Leukocyte functions also decrease and the immunological defense is thus compromised. The decreased platelet number and function cause diffuse petechial bleedings, primarily in the serous membranes. The hematological changes, particularly the anemia, may also appear in acute renal failure.

A wide scale of bone deformities is commonly seen in CRF, including osteodystrophy, osteomalacia and osteoporosis. These are caused by decreased se-Ca, high phosphate and PTH levels plus by the deficiency of the active form of vitamin D.

The complex picture of uremia (*end-stage renal failure – ESRF*)

Both excretory and non-excretory dysfunctions develop, although not in entire parallelism. They interact and augment one another's effects. Acidosis, hyperosmolarity, electrolyte- and water-imbalances are combined with anemia, circulatory abnormalities, gastrointestinal, endocrine and neurological disorders (Fig. 5.20.).

Due to hyposthenuria, the limits of maximal/minimal amounts of urine are altered in CRF. The maximal water-excreting capacity decreases together with the water retaining capacity. In the clinical practice, initially, the latter proves striking, as the primary polyuria is characteristic. Later on, as the number of functioning nephrons and GFR decreases, the polyuria abates or develops into oliguria, hence, the water-excreting capacity simultaneously worsens, however, the hyposthenuria progresses. In the polyuric phase, the excretion of waste-products is near-normal and the polyuria is regarded as a form of "compensation" regarding the decrease in renal functional mechanisms. In contrast, the combination of oliguria and hyposthenuria, occurring in later phases, indicates the most severe disorder of excretory functions and the quickened progression of uremia.

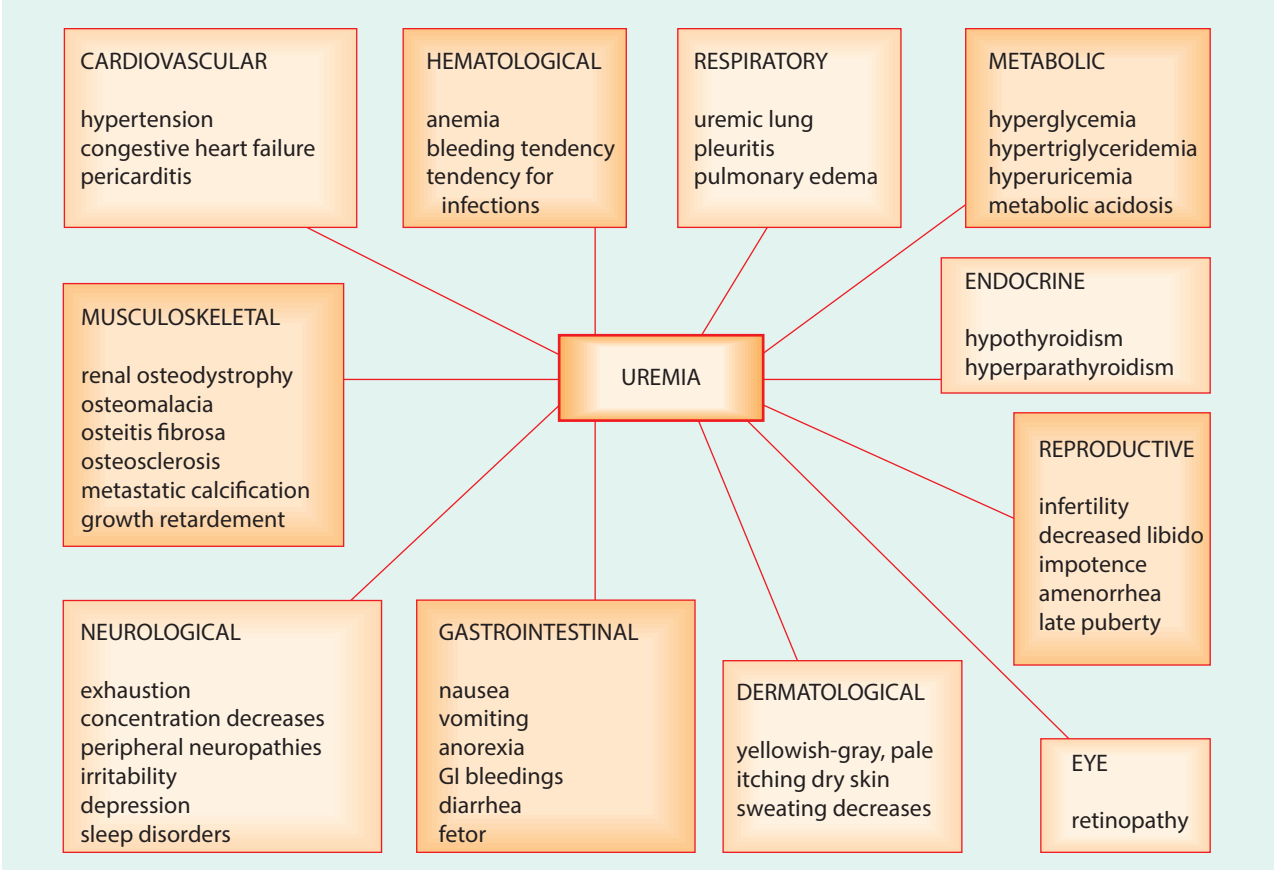

Fig. 5.20.: The complex picture of uremia in ESRF.

Polyuria means a tendency for exsiccosis, associated with high osmotic pressure due to the urea, creatinine, BUN, therefore, generalized edema is NOT characteristic, only sites of lose connective tissue exhibit moderate edema. Such is the periorbital edema, primarily due to the enhanced permeability. In contrast, in the oliguric ESRF phase, excretion of both salt and water becomes difficult, and patients cannot withstand even minimal loads. Water deficiency quickly results in exsiccosis, while salt/water load is followed by an increase in water spaces, including plasma, interstitium, and intracellular spaces. Following salt/water loads, rapid development of edema is characteristic, not only in the periphery, but the permeability allows edema formation throughout both the lung and the brain, while the elevation in plasma volume causes sudden and a marked increase of the subsequently high blood pressure. The osmotic pressure is typically high, however, in the oliguric phase, a water load may still easily evoke hyponatremia. In the late phase, hyperkalemia develops and hypocalcemia manifests (although acidosis can prevent over a long period of time, the decrease in ionized se-Ca levels and symptoms of Ca-deficiency). Originating from the waste-products and toxic substances, urochromes are produced which give a yellowish/grey color to the edematous, dry skin.

The uremic disorders of circulation include hypertension, high cardiac output to compensate anemia, and myocardial impairment due to toxicosis, anemia, coronary sclerosis, hypertrophy, acidosis and hyperkalemia. Both congestive or ischemic/toxic heart failure with secondary dilative cardiomyopathy may develop including rhythm abnormalities. Congestion, enhanced capillary permeability and thrombasthenia all contribute to the bleedings and edema formation in serous membranes and the lung. Gastrointestinal disorders are rather frequent in ESRF, and characteristically exhibit various forms of dysfunctions as inflammation, bleedings, ulceration, malabsorption and vomiting. Severe endocrine disorders and hypometabolism are observed. Bone deformities are common, as well as the muscle atrophy due to protein deficiency. The neuromuscular excitability is enhanced by the decreased ionized se-Ca level (acidosis can no longer increase Ca-ionization). Even dialysis cannot completely prevent the uremic encephalopathy and peripheral neuropathy.

5.5.3. ACUTE RENAL FAILURE (ARF)

Definition

Exogenous/endogenous injuries may induce acute disorder/failure of excretory functions, even in originally intact kidneys. In various forms of acute renal failure, the severe, often life-threatening disorders of excretion are present, however, not necessarily accompanied by proportionate changes in all non-excretory functions, functions. Anemia may develop rapidly and may appear in ARF, while the development of bone deformities requires a longer period of time and these are not seen in ARF. Whereas CRF is always progressive, it can be slowed but not entirely halted or reversed, ARF can often be cured without lasting consequences, as seen in the following treatment of the acute phase, all renal functions may be normalized, except for some severe cases of acute diffuse glomerulonephritis and acute tubular nephropathy. Although some forms of ARF (e.g. acute diffuse glomerulonephritis) involve direct renal injury, excretory failure develops in most cases with originally intact morphology of the kidney, and these are often classified as "extrarenal uremia". One form or the other of ARF is observed in ca. 5% of all hospital admissions and ca. 30% of emergency cases. Depending on its form, the mortality rate is still high (16-60%) and in about 5-50% of ARF cases cortical necrosis or CRF develops.

There are basically three forms of ARF. In the first category, the glomerular function is failing, while the tubular functions are more or less saved, and its prototype is prerenal azotemia. In the second group, the tubular functions are defective with basically normal glomerular filtration, and the prototype is postrenal ARF. The combination of the two aspects define the third version, and is typically is seen in various forms of acute renal failure (e.g. shock kidney), in which both the glomerular and tubular functions are affected. The renal parenchyma including severe acute damage (of immune origin, inflammation) is also seen in acute glomerulonephritis or in the nephrotic syndrome.

5.5.3.1. PRERENAL ACUTE RENAL FAILURE – AZOTEMIA

(Represents nearly 55% of all acute renal failures)

The pathophysiological basis: There is a significant decrease of renal blood flow and GFR, however, the efferent vessels still propel enough blood to peritubular capillaries to effectively supply oxygen for the tubules. Otherwise, the tubular oxygen requirement is rather low, since less filtrate has to be processed, therefore the tubular need is satisfied (Fig. 5.2.) and the tubular functions are normal. Since these normal tubules reabsorb

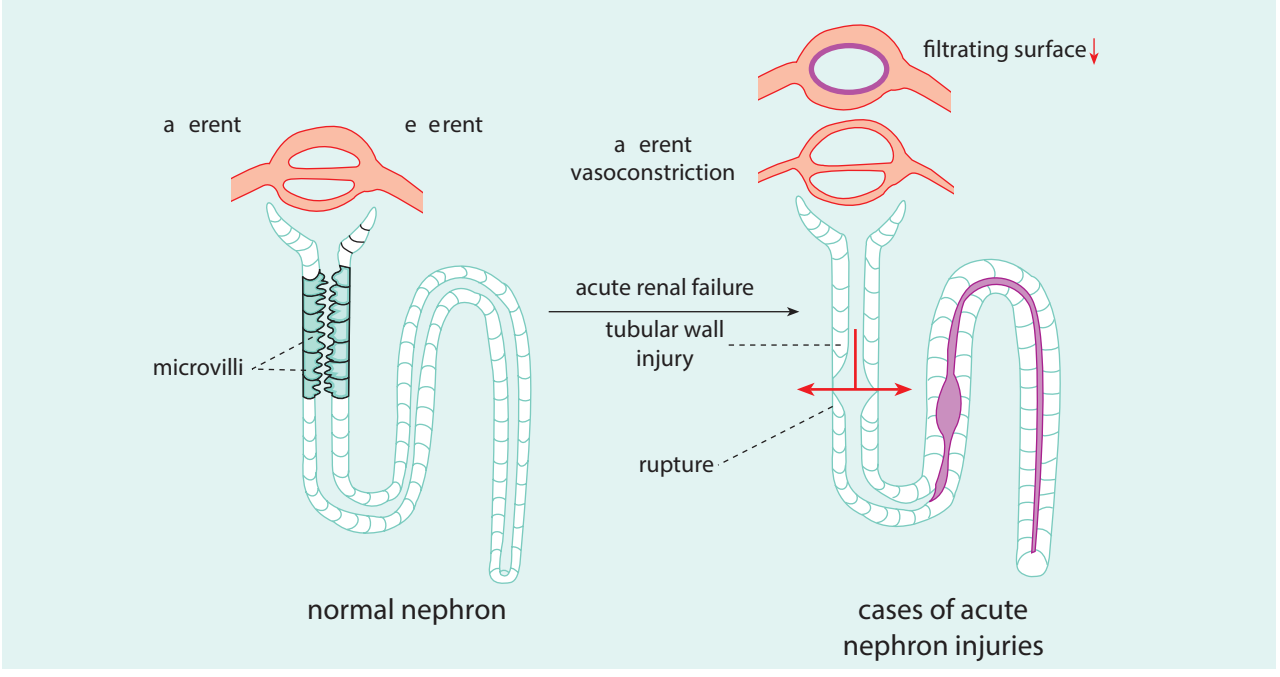

Fig. 5.21.: Possible nephron injuries (glomerular, tubular) in various acute renal failures. In the injured tubule cylinder (cast) may occlude the flow (see dilated section).

relatively more of the small amount of filtrate, oliguria develops. The tubular transports (including Na-reabsorption and K-excretion) are normal, and the Na-concentration is low, while the K-concentration is high in the urine. The tubules can maintain a more or less normal concentrating/diluting capacity, and as such, there is no significant hyposthenuria. This state is most often caused by hypovolemia, therefore, the urine is usually concentrated (its osmotic pressure is high due to other osmotically active substances and not specifically to Na). Due to the oliguria, the excretory function is still insufficient. In the plasma, those substances accumulate, which are normally excreted exclusively through filtration, primarily the N-containing waste-products, therefore azotemia develops (the se-urea exceeds the normal 1.7-8.3 mmol/l and the se-creatinine is above the normal 60-120 μmol/l, while their levels may increase by 10-12 mmol/l/day (up to 100-times normal) and 150-200 μmol/l per day, respectively. The rise of creatinine level increases up to 20-times faster than urea, partly due to the slow tubular flow, which allows greater rediffusion of urea, and, partly due to the urea, as an end-product, inhibits further urea production in the urea cycle of the liver, while the creatinine synthesis is strongly enhanced. However, the complex disorder of uremia does not develop except if, in the case of sustained damage, the parenchyma is also injured. In these cases, the concentration of urea, creatinine and other uremic toxins show a ong-term elevation, the prolonged circulatory disorder corresponds to chronic systemic inflammatory state and cardiorenal syndrome (ch. 2.1.3.) leads to the accumulation of uremic toxins, and inevitably, to renal failure. Hyperkalemia (a daily rise of 0.5 mmol/l) is a frequent complication and the quickly developing acidosis aggravates this hyperkalemia.

Within the clinical practice, various severity of prerenal azotemia is the most frequently seen ARF since the renal blood flow is often compromised and redirected from the kidney to the systemic circulation: by overwriting the autoregulation of renal blood flow only a smaller fraction of cardiac output reaches the kidneys. For example, to compensate a decrease in blood pressure, the sympathetic system, catecholamines and RAAS are activated, the vasopressin production increases and the renal perfusion decreases. The renal defense response is a dilation of the afferent arteriole (NO and PG effect), and the constriction of the efferent arteriole (angiotensin II effect), however, these are not always enough to maintain GFR, in which case, the renal excretory function acutely decreases. The most frequent causes of prerenal azotemia include the following:

Bilateral vascular disorder: (e.g. renal artery stenosis, embolism), inhibition of autoregulation (ACE- or COX-inhibitors, NSAID), renal artery constriction (catecholamines, hypercalcemia, amphotericin-B), or compression. These may cause even more severe renal failure, however, they are not distinctively frequent cases.

Any form of exsiccosis, dehydration and *hypovolemia* (NOT reaching in severity the clinical state of shock): These are the most frequent yet typically transient cases.

A decrease of effective arterial volume: Congestive heart failure, portal congestion, cirrhosis and hepatorenal syndrome, all notably, very frequent and severe in form. In the late stage of chronic heart failure, the pronounced hypoperfusion of the kidney is continuous, and it is followed not simply by prerenal azotemia, but the entire renal parenchyma is damaged and various renal functions become insufficient (cardiorenal syndrome, ch. 2.1.3.).

Fluid accumulation and abnormal distribution of blood: Ileus and the early stages of septic states, extensive vasodilatation and/or a large peripheral edema, in which, azotemia may develop acutely.

Hyperviscosity syndromes: Myeloma multiplex, polycythemia and polyglobulia.

In the case of prerenal azotemia, the normalization of systemic circulation and renal blood flow quickly normalizes the process of filtration. Shortly thereafter, cessation of oliguria occurs and the azotemia and hyperkalemia subside.

5.5.3.2. POSTRENAL RENAL FAILURE

(about 5% of all acute renal failures)

Pathophysiological basis: Obstruction of urinary tract (obstruction of the ureter, urethra, bladder-neck by stone, ruptured papilla, prostatic hypertrophy/hyperplasia, tumors, compression, etc.) causes increased pressure in the renal pelvis and the tubules. This evokes only the functional disorder at the onset, later morphological tubular injuries follow. Since the high pressure (20-30 mmHg) is transmitted to the Bowman space, the filtration pressure decreases, and even the cortical blood flow may decrease by reflexes and due to local release of vasoconstrictor thromboxanes, thus, despite the normal glomerular structure, the filtration decreas-

es (yet never ceases completely). All filtrate must return from the tubules, although not by active transport, rather by passive rediffusion (back-leak), since the tubular epithelial cells are dilapidated by the high pressure. Naturally, there is no excretion as long as the obstruction persists. Upon release of the obstruction, the pressure, the renal perfusion and GFR are practically immediately normalized. The dilapidated tubules may require more time for regaining their functions. During this period, the tubular processing of the filtrate is not yet sufficient, and the Na-reabsorption is less than normal. This leads to hyposthenuric polyuria, including a high urinary Na-concentration and low K-concentration, since no tubular active transport is as yet perfectly normal. Additionally, the ADH-receptors do not function normally. Urea-induced osmotic diuresis may contribute to the development of hyposthenuric polyuria. The duration (hours, days) of these abnormalities is dependent upon the duration of the obstruction and damage of the tubular epithelium.

Repeated obstructions may cause permanent injury and lead to the tendency for infections, in which nearly every case, CRF gradually develops.

A combined disorder of tubular dysfunctions is also possible in other forms of tubulopathies without the typical postrenal causes: anemia, hypoxia, interstitial nephritis, etc., in which these tubular disorders may be early signs of the onset of CRF.

5.5.3.3. ACUTE PARENCHYMAL RENAL FAILURE

(Nearly 40% of all acute renal failures)

Acute tubular nephropathy (acute tubular necrosis or, ATN) accounts for nearly 80% of all acute parenchymal renal failures. Although it is generally defined as a severe acute uremic state with at least 5-10% mortality rate, but with additional cases of permanent damage, strikingly, within a significant part of ATN cases, complete normalization of renal functions is possible.

The kidneys are morphologically and functionally intact prior to the acute disease. Regardless of the evoking factor, at the onset the excretory function becomes abnormal corresponding to “extrarenal uremia” (i.e. uremia of extrarenal origin), but later the kidney structure is also severely damaged. Characteristically, the morphological changes affect the tubules, causing isolated injury of the tubular epithelium or a more complex injury of tubulorrhexis, which also involves the basement membrane (acute tubular necrosis), while the glomeruli exhibit at most, moderate or only functional disorders.

The most important evoking factors of ATN are ischemia and various nephrotoxins and pigments (Fig. 5.22.).

- ***Ischemic ATN*:** This can be evoked essentially by the same factors as those of prerenal azotemia, except here, the decrease in renal perfusion is much more pronounced than when compared to that of the prerenal form, and severe local or systemic circulatory failure (shock) may be present. In the course of World War II, during the air strikes and subsequent bombing of London, a great number of traumatized patients, primarily due to muscle crush, were lost due to uremia 2-3 weeks following the trauma. The observation was named, ”crush syndrome”, and defined the kidney with cortical necrosis as crush kidney. Today, it is clear that in this state traumatic type of circulatory shock was lurking in the background.

  In shock the renal blood flow decreases, particularly in the cortex (a change in the intrarenal distribution). Through the constriction of the afferent and dilation of the efferent vessels, the blood is shunted from the capillary loops, and the resultant filtration pressure decreases. Simultaneously, glomerular swelling decreases the permeability. All these result in an even greater decrease in GFR than the decrease of perfusion. However, the perfusion also decreases at the second (postglomerular) capillarization, and decreases to such an extent, that it leads to a diffuse ischemia affecting both the proximal and the distal tubules. As a result, the active tubular transport becomes insufficient, while the passive tubular rediffusion of the fluid from the tubular lumen (between the injured, necrotizing tubular epithelial cells) to the interstitium is enhanced. The debris of the necrotic cells (casts) may obstruct the tubules, further enhancing the back-leak at more proximal parts of the tubule. The urine will be not only oliguric, but also hyposthenuric, with high Na and low K concentrations, and with quantities of mixed debris and cylinders. The relatively high flow rate of the medulla (congestion) contributes to the development of hyposthenuria. Uremia develops very quickly. If, following an episode of shock, the cir-

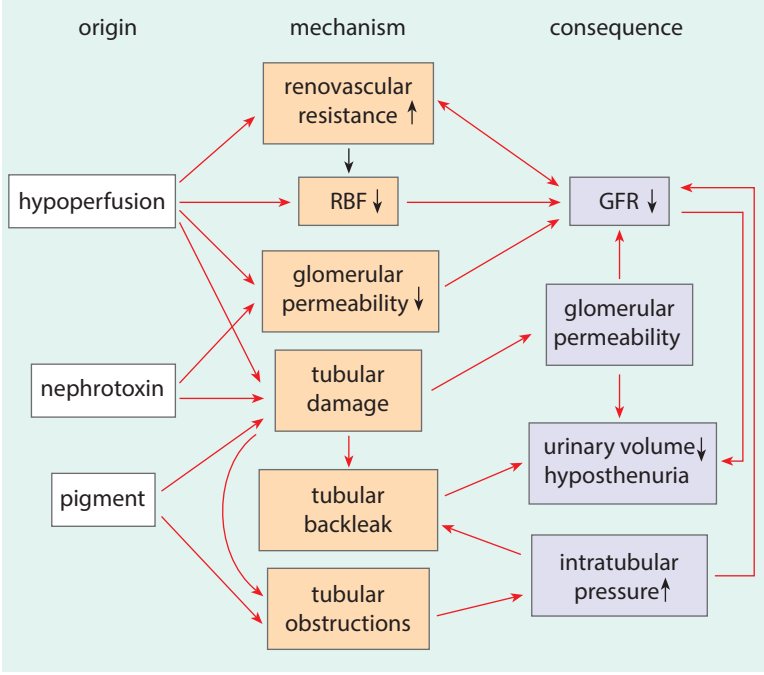

Fig. 5.22.: Forms, mechanisms and consequences of acute tubular nephropathy.

culation is normalized, the renal blood flow and glomerular filtration, yet not the tubular functions, are also relatively quickly normalized. The tubules with injured basement membrane cannot regenerate (tubulorrhexis). Those in which strictly the epithelial cells are damaged can, if only gradually: the basement membrane serves as a template in this process (Fig. 5.23.). The initial oliguria plus hyposthenuria are therefore, followed by a period of polyuria instead of oliguria, with no change of hyposthenuria-isosthenuria (this corresponds to the picture of postrenal failure, in which the filtration is returning to a normal state, the regenerated tubular lumens are open, but the tubular cells are not yet functional). Later, as the tubular cells slowly regenerate and begin functioning, both the hyposthenuria and the polyuria gradually cease. Since this process may require months, during this period, dialysis must be applied. The clinical picture is similar in the case of the rejection of a transplanted kidney, in which the rejection-induced hypoxia has a stronger effect upon the tubules as compared to that of the glomeruli, and the result is the function of transplanted kidney changes and hyposthenuric polyuria begins following a period of elevation in se-creatinine and urinary Na (and increased se-K).

– ***Toxic ATN*:** Endogenous toxins/pigments (hemoglobin following hemolysis, myoglobin following rhabdomyolysis, trauma, exhaustion, heat stroke and/or cramps), also alcohol-abuse, direct bilirubin, urate, oxalate, hypokalemia, Ig-chain, etc., or exogenous toxins, such as radiocontrast materials, antibiotics (aminoglycosides, sulfonamides), chemotherapeutic agents (methotrexat, cisplatin), acetaminophen, heavy metals (Hg, Pb), ethylene glycol (antifreeze), mushroom toxins are the most frequent evoking factors. These toxins are excreted renally and injure the tubules, which is not a diffuse injury, however, specifically affects the tubular segment which confronts the specific toxin (in contrast to the ischemic injury which affects several sections of the tubule). The injury may affect only the epithelial cells or, additionally, the basement membrane. The primary tubular damage is followed by a swelling of the entire kidney and the decrease of perfusion and filtration. The secondary decrease of GFR can be explained by the tubulo-glomerular feedback, in which, due to the defective tubular Na-reabsorption: more Na reaches the macula densa and this leads to the suppression of GFR. Later, the process is nearly the same as the ischemic ATN, since the filtration and tubular functions are simultaneously and severely compromised.

Whatever may be the original cause of ATN, throughout its maintenance and its later transversal course, the same factors are important.

Clinical/laboratory appearance of ATN:

ATN is characterized by hyposthenuric oliguria. The resultant salt/water retention (with the exception of hypovolemic shock) leads to generalized edema, wet lung, jugular congestion, and in severe cases, to pulmonary edema. Paradoxically, the thirst is greatly enhanced and this may cause a tendency for hypoosmolar hypervolemia. The consequent hyponatremia/hypotonicity leads to elevated intracranial pressure, headache, nausea, vomiting, eventually diarrhea, spasms and inevitably, death. The rapid increase in the levels of urea, creatinine and se-K, particularly, if due to muscle injury,

trauma, and/or hemolysis is present, aggravates the clinical symptoms. Hyperkalemia, per se, may be life threatening. In less severe forms, the oliguria is not pronounced, or there may even be polyuria corresponding to the phase of restitution, however, the hyposthenuria remains a salient feature.

The renal excretion of the daily 50-100 nM acid produced by metabolism is nearly impossible, resulting in high anion-gap metabolic acidosis. Although this may temporarily attenuate the entry of Ca into the tubular cells (the IC Ca could damage the mitochondria in the cells), it enhances the K loss from the cells and aggravates hyperkalemia.

Moderate hyperphosphatemia and hypocalcemia may develop (vitamin D deficiency and/or PTH-resistance); and, in anuric cases, the total level of se-Ca rather increases and its high ionization due to acidosis leads to severe symptoms of hypercalcemia.

The uremic plasma milieu may cause thrombasthenic type bleedings and enhanced hemolysis. Anemia develops quickly. Bleeding stress-ulcer is not a rarity and it occurs in 10-30% of the cases. The bone marrow function is suppressed, and the production of not only RBC but all cell forms decreases. Occasional leukocytosis indicates frequently occurring, often fatal infection.

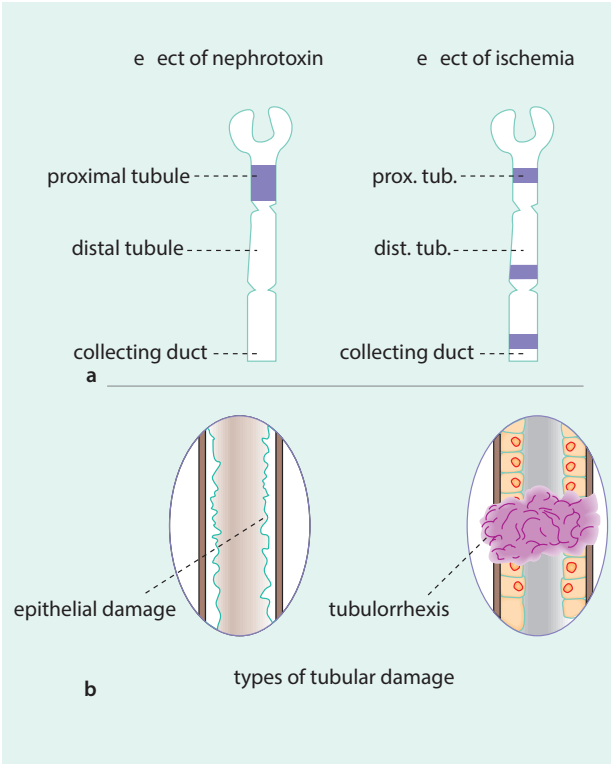

Fig. 5.23.: Forms of tubular injury: according to the damaging factor (a), or to the type/severity of the damage (b).

Out of the adjoining cardiovascular disorders arrhythmias, acute myocardial infarction, and pulmonary edema of immobilization origin are the most frequent.

Phases of ATN:

1. *Initial phase* (hours and/or days): The hypoperfusion is the most pronounced in the zone of inner cortex and outer medulla, and the hypoxia is most severe in the area of the proximal tubules and the loop of Henle. The filtration is minimal. The tubular epithelial cells become progressively hypoxic/ischemic.

2. *Phase of maintenance* (days and/or weeks): The GFR remains 5-10 ml/min, even if the systemic and renal perfusion are normalized (in contrast with the postrenal forms). The explanation of persisting intrarenal vasoconstriction includes the followings:
   a) the low NO and high endothelin production within the endothelial cells of capillaries,
   b) medullary congestion,
   c) tubulo-glomerular feedback (poor tubular Na reabsorption, as more Na reaches the macula densa) and afferent vessel constriction with efferent vessel constriction (shunt formation),
   d) reperfusion damage within the epithelial cells, accumulation of free radicals and lysosomal enzymes from leukocytes, Ca influx into tubular cells, and an intrarenal effect of vasoactive substances upon the circulation (prostanoids, leukotrienes, endothelin, adenosine)

   As a result of all these characteristics, the structure and function of "sick" tubular epithelial cells changes, and they lose their polarity, and the Na^+/K^+ ATPase exits the cytoskeleton. Vesicles are formed at the apical part of the brush-border. Following apoptosis, the desquamating cells and debris form cylinders (casts) in the tubular lumen, these cause obstruction and back-leak at the more proximal segments. Among the most severe cases, the basement membrane beneath the epithelial cells is also disrupted, and it is deemed irreversible. Oligo-anuria and hyposthenuria are characteristic, and, without dialysis, uremia rapidly develops.

3. *Restitution* (weeks and/or months, with dialysis): The GFR improves by a daily increment of 5 ml/min. Reparation of tubular cells is much slower, and this explains the persistence of hyposthenuria and azotemia, even if the filtration is near normal. As soon

as the tubular lumens are cleared from debris, the onset of sudden polyuria can be expected, coupled with hyposthenuria. At this point, without salt- and water-replacement, hypovolemia and prerenal azotemia may persist. This will be sustained, until the tubular functions become normal. Complete normalization is possible, unless there was an abundance of tubulorrhexis.

In less severe cases, these accompanying phases may be modified, such as, in the case of the early oliguric phase, which is less pronounced, or even polyuria is possible, corresponding to the restitution phase, yet the hyposthenuria is always pronounced.

5.5.3.4. ACUTE GLOMERULONEPHRITIS

Acute glomerulonephritis (about 10% of all acute parenchymal renal failure): in addition to severe damage of the glomeruli, the entire kidney is swollen, under tension and therefore, causes an increase in the intrarenal pressure. The tubules are less severely disordered. In most cases, immunological process lurks in the background of acute diffuse glomerulonephritis (post-streptococcal states, autoimmune disease, precipitation of circulating antigen-antibody complexes, etc.), of which, the process is followed by complementing activation and local inflammation (Fig. 5.24.).

The circulating immune-complexes bind to the walls of glomerular capillaries, and this induces binding the complement, including the appearance of an immense number of neutrophils and monocytes. A similar process is initiated once circulating antibodies bind in situ on the antigens of the glomerular capillaries. The released lysosomal enzymes and free radicals damage the wall and basement membrane of the capillaries and, thereby decrease the filtering surface. Within the injured capillaries, the endothelin production of endothelial cells increases, their NO production decreases and the capillary perfusion is poor. The platelets aggregate, the coagulability increases, and there is a tendency for coagulation within the capillary loops. Vasoactive substances released from the aggregated platelets can cause additional worsening of the glomerular perfusion. In the impairment of perfusion, the mesangial cell contraction is also important, as this is induced by inflammatory mediators. The decreased anionic charge of the capillary wall and the increased pore size can lead to proteinuria, despite the progressive hypofiltration. In the Bowman space, fibrin deposits and ”half-moon”-like proliferation of macrophages, mesangial cells and cells of epithelial origin can

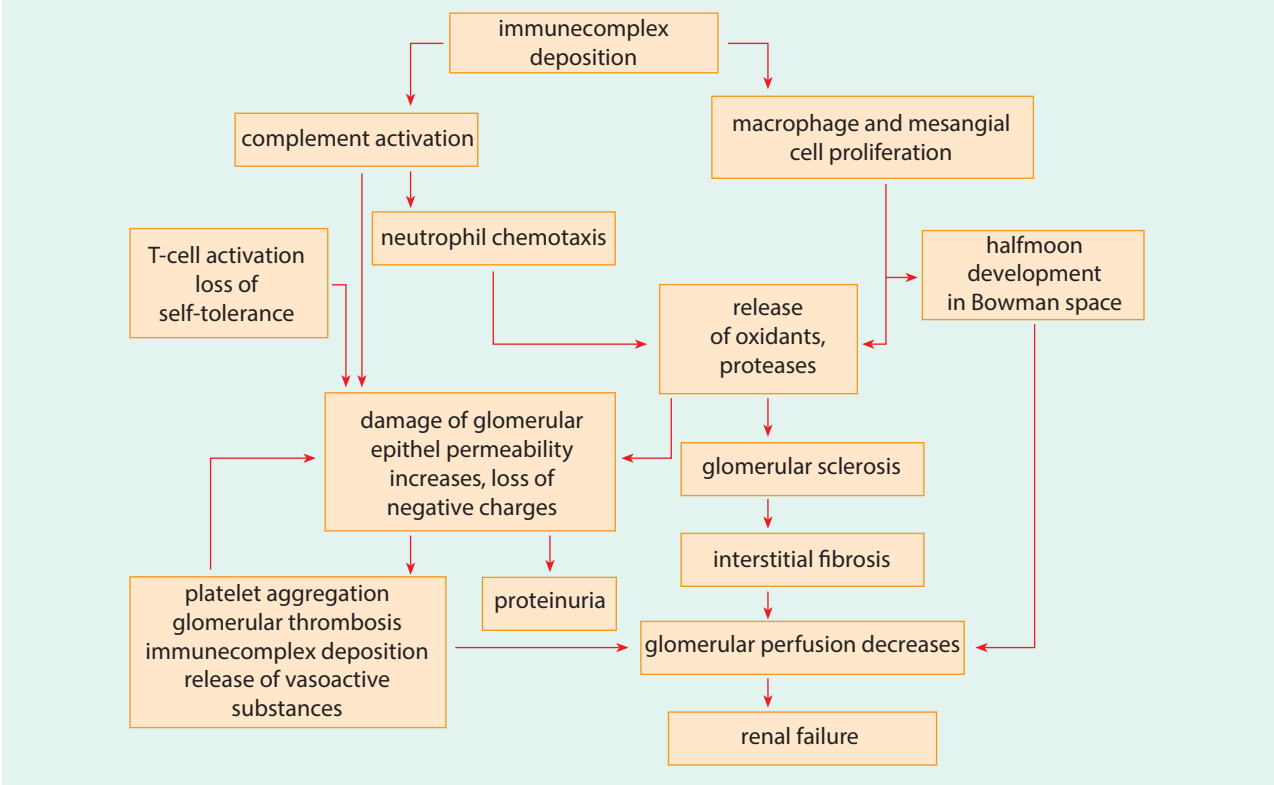

Fig. 5.24.: Factors of pathomechanism of immune-complex glomerulonephritis.

be seen by the use of histology. This is followed by sclerosis of the capillary loops and by interstitial fibrosis. As compared with the extreme decrease in GFR, the tubular functions are relatively salvaged, therefore oliguria with relatively low Na (and high K) concentration can be observed, the hyposthenuria is moderate, and, characteristically, the urine is nearly concentrated. Within the urine various elements of debris, blood and a large quantity of protein is evident. First, the salt- and water-retention expedites the development of the periorbital, followed by the generalized edema and the rapid rise in blood pressure. The hypertension is partly explained by the inflammation adjacent to the juxtaglomerular apparatus and activation of the RAAS. The hypervolemia may also contribute to the hypertension. In regards to acute glomerulonephritis, the patient may recover spontaneously, however, due to the morphological injury of the glomeruli, the acute abnormality is often converted into CRF, in which the speed and velocity of transition is dependent upon the type of the original evoking factor.

Within clinical practice, various forms and courses are known, depending on the actual etiology, such as the different bacterial or viral infections, Goodpasture syndrome, Henoch-Schönlein purpuras, IgA-nephropathy (e.g. deposition of circulating IgA in inflammatory enteropathies), and the various forms of rapidly progressing glomerulonephritis, etc.).

5.5.3.5. NEPHROSIS (NEPHROTIC) SYNDROME

It appears most often in an idiopathic acute form, or in response to various pharmaceuticals (penicillamine, NSAID, captopril, etc.), infections (e.g. bacterial endocarditis, hepatitis-B) acutely, however, it may also develop in polysystemic diseases (e.g. amyloidosis, SLE), tumors (e.g. Hodgkin disease, malignant myeloma), and also adjoining diabetes mellitus (mostly, much more slowly).

In the acute idiopathic form, the most characteristic feature is the massive (>3,5 g/day) proteinuria (ch. 5.3.3.1.), which is followed by similarly massive hypalbuminemia (<30 g/l) and consequently, generalized hypalbuminemic edema and hyperlipoproteinemia. Symptoms of protein malnutrition (ch. 9.1.1.1.) involve defective albumin binding, therefore they are often combined with an increased drug-toxicity, and on occasion, vitamin-D deficiency. It is important that there is no obvious disorder of GFR, no azotemia and, except for proteinuria (eventually protein cylinders), there is no abnormality within the urine and the blood pressure is normal. The edema may be enormous, particularly among small children, in whom it may reach the level of >10-30% of body weight. Due to this characteristic form of edema, the vascular volume decreases and hemoconcentration develops. A frequent complication is the thrombosis of the renal vein and generally, a host of thromboembolic complications. Originally, it had been described histologically as the various degeneration of tubular epithelial cells (vacuolar-hydropic, turbid, hyalinic, lipid-droplets), associated with normal-looking glomeruli. Later, it was clarified that all these are secondary, and the tubular alterations are consequences of continuous, maximal protein reabsorption, due to the strongly enhanced protein filtration within the glomeruli. The basis of the disorder is the increased permeability of glomerular capillaries, what was demonstrated by specially developed techniques. The disorders of vascular wall may also induce increased coagulability, of which, is compensated by the increased protein (and coagulation factor) production by the liver and this, combined together with hemoconcentration, likely explains the tendency for thrombus formation.

The idiopathic nephrosis (nephrotic syndrome) occurring in childhood is typically a treatable disease with good prognosis. Among adults and various forms adjoining polysystemic diseases or diabetes, it can be expected that the process will eventually develop into CRF.

Within clinical practice, several kidney diseases are known (e.g. membranous glomerulonephritis and focal glomerulosclerosis), of which, at the onset, demonstrate symptoms of nephrosis, however, this is soon followed by the decrease in GFR, hematuria and hypertension, and the patient's status is positioned near the end stage of renal failure and varies regarding the speed of the failure.

5.5.3.6. OTHER FORMS OF ACUTE RENAL FAILURE

Interstitial nephritis, intrarenal obstructions and vascular disorders may also cause ARF, in which the glomerular and tubular dysfunctions are mixed. Similarly, as in acute diffuse glomerulonephritis, many of the abnormalities often appear repeatedly, or can be sustained in the form of CRF. The possibility of destruction due to a variety of side-effects, due to pharmaceuticals, as in the case of NSAID, must be emphasized.

Disorders of the glomerulus or the microvessels: acute glomerulonephritis or vasculitis, Goodpasture syndrome (5-10%); hemolytic uremic syndrome (HUS),

DIC, toxemic pregnancy, thrombotic thrombocytopenic purpura, radiation nephritis, malignant hypertension and SLE

Bilateral renovascular obstruction: arterial (atherosclerosis, thrombosis, embolia, vasculitis, dissecant aneurysm) and venous (thrombosis, compression)

Interstital nephritis:

- Allergic: antibiotics (sulfonamide, β-lactam, trimethoprim, rifampicin), NSAID and captopril
- Nephrotoxins: oxalate, urate, hypercalcemia, etc.
- Infections: leptospira, cytomegalovirus, candida, hantavirus, etc.
- Infiltrations: sarcoidosis, leukemia and lymphoma
- Idiopathic

Rejection of renal allograft: in addition to the decreasing GFR (rising se-creatinine), hypoxic damage of the tubules (hyposthenuric polyuria–oliguria and high urine-Na-concentration) are all characteristic.

5.6. AGING AND KIDNEY FUNCTIONS

With regards to the aging process, the renal blood flow exhibits a continuous and gradually more pronounced decrease, not necessarily in a parallel manner with the number of functioning nephrons and the thickening of basement membrane. The causes can be found partly in cardiovascular physiology, such as in the case of the redistribution of cardiac output and decreasing renal blood flow, what becomes more frequent with aging, partly in the fact that the renal tissue becomes atrophic. The decreased blood flow may influence both the glomerular and tubular functions.

During the aging process, the GFR decreases. It may be often disputed whether or not this is physiological, however, statistics verify this fact. During youth, the GFR decrease is routinely followed by an elevation of se-creatinine, however, this is not the case among seniors, in whom the destruction of decreased muscle mass results in lesser amounts of creatinine. Thus, it is entirely understandable that to effectively examine renal functions, in particular those among the elderly, the determination of GFR may be necessary even if there was no azotemia present. However, it should be also emphasized that even small changes in the salt/water balance will soon be realized by the presence of azotemia. In the course of aging, the SNGFR changes: at the onset, despite unchanged mean values and normal total GFR, the SNGFR values show a greater variability. However, later on in the life of a human, the scattering intensifies and the distribution among glomeruli differs: increasing number of glomeruli are associated to hypofiltration rather than to the hyperfiltration category, and the mean total GFR also decreases (Fig. 5.9.). This can be explained by the gradual obstruction and destruction of the glomerular capillary loops. The change in the glomerular structure allows an otherwise healthy (non-diabetic, non-hypertensive) patient a potential increase in proteinuria corresponding to the aging process. A way to avoid this, is in the avoidance of excessive protein intake, since the consequential proteinuria may progressively damage the glomeruli. Nonetheless, the importance of sufficient protein intake should not be forgotten or overlooked, although some seniors become some sort of vegetarian to avoid proteinuria-induced renal damage.

The tubular functions also change. Lower transfer-maxima allow smaller Na-reabsorption capacity, which cannot effectively secure the maintenance of a normal cortico-medullary osmotic gradient. Accordingly, there is a tendency for hyposthenuria, in which the ability to retain water decreases including alterations in the water excreting ability. Consequently, seniors are far more likely to lose (salt and) water (salt-losing kidney), in them exsiccosis potentially develops far more easily, however, the excretion of excess (salt and) water is similarly reduced, therefore these more easily accumulate and cause hypervolemia with hypertensive attacks or lead to edema. The efficacy of ADH is smaller (Fig. A14.8.), and the same ADH dose results in a smaller urinary concentration than in younger individuals, and this results in a tendency for hypertonicity. From another perspective, the ADH-level is high and the suppression of it is insufficient, therefore, hypotonicity (hyponatremia) may also develop far more easily – this is of particular importance in patients treated with diuretics (= saluretics). The efficacy of aldosterone is also decreased. The excretion of K proves to be far more difficult, hyperkalemia may develop. However, the secondary hyperaldosteronism, which is rather frequent among seniors (primarily due to cardiovascular issues) implies a tendency rather for hypokalemia, despite the decreased efficacy of aldosterone.

Primarily, those nephrons are lost, which formerly featured a diminished glucose-reabsorbing capacity. The tubular cells of the remaining nephrons possess a higher capacity for glucose reabsorption and, even at high plasma glucose concentrations, these nephrons

keep reabsorbing the filtered glucose, therefore, the glucosuria is even less parallel with blood glucose than in younger individuals, and this may be a relevant issue among diabetic patients.

The age-related changes also affect the excretion of toxins, drugs and drug-metabolites, generally, due to the decreased excretory functions in which the plasma level and effect of those drugs excreted by the kidney (digitalis, penicillin, tetracyclines, etc.) far exceeds those seen in younger individuals, and, if using similar doses, even toxic levels may develop. Regarding prescription medication, this should always be a consideration, although it is too often sadly disregarded.

In consideration of the non-excretory functions, it is very important to mention the decreased level of erythropoietin production, what is often responsible, at least in part, for the anemia of seniors. Lurking in the background, the decrease of gonadal hormones may be assumed, however, an atrophy of renal parenchyma, low se-Fe (and/or vitamin B_{12}) levels may also contribute to the anemia. Another very important non-excretory dysfunction is the decreased production of active vitamin D, since this contributes to the development of senile osteoporosis. Sclerosis of the renal artery and degenerative changes of the renal parenchyma have also a role towards modifying the regulation of blood pressure – these all or contribute to the age-related rise in prevalence of hypertension.

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