and endoplasmic reticulum and secretory granules. Some of these granules are considered to be specific secretory granules containing renin the other granules do not contain renin, but it is suggested, that renin could be deposited in these cells in a non granular form.

In the juxtaglomerular triangle cells called lacis cells occur designated also as extraglomerular mesangial, or Goormaghtig's cells. They have numerous microvilli forming a fine network.

The interstitium consists of cells and cell-free substance. Interstitial cells resemble in their structure to fibroblasts. They contain lipoid drops of prostaglandin precursors and a system of fibrils, probably identical with elastic fibrils. The thicker fibres cross the juxtaglomerular cells entering the Bowman's capsule and the podocytes.

4.2.2 The urinary outflow tract

Urine from collecting ducts is excreted into the renal pelvis, passing calyces renales minores et maiores. From the renal pelvis is the urine transported into the urinary bladder by the contractive activity of ureters. The wall of the urinary excretory system has in all its segments almost the same structure. It cosits of three coats: mucous, muscularis nad fibrous. The mucosa is lined by transitional epithelium. In the proximal parts of urinary outflow tract 2-3 cellular layers in the more distal portion 5-7 layers can be found. Lamina propria mucosae lying beneath the epithelium consists of collagenous connective tissue.

The middle coat of urinary tract excretory system consists of an inner longitudinal and an outer circular layer of smooth muscle. **Calyces renales** have two muscle layers enabling contraction waves wich aid the urine transport into the renal pelvis. The renal pelvis has the same structure, consisting of two muscle layers. The distal third of ureters consists of three muscle coats – the thirth, outer coat is formed of longitudinally oriented smooth muscle layer. The peristaltic waves of ureter occur 1-5/min. shifting the urine towards the urinary bladder. The stimulus initiating these movements is not understood till now. It could be a certain filling pressure in renal pelvis. The oblique "entrance" of ureters into the urinary bladder inhibits the urine reflux, though ureters are not provided with sfincters at their terminal portion.

Urinary bladder is the reservoir for urine. Its physiologic capacity is variable, it varies about 300 ml. The urinary bladder wall consists of three muscle coats, the lining of a superfiacial layer of flat cells, and a deep layer of cuboid cells. In the region of trigonum vesicae urinariae is an inner sfincter.

The man **urethra** is divisible into three portions: prostatic, membranous and cavernous. The female urethra is short. It's lining consists of pavement epithelium.

4.3 Peculiarities of renal blood flow

Concerning the blood flow the kidneys are exeptional organs. The peculiarity of renal haemodynamics is a consequence of the fact, that the kidneys have 100 times greater blood flow than other organs and tissues in human organism. The arteriovenous difference in blood oxygen content is low in renal blood vessels. In healthy adult man at rest the renal blood flow is about 1200 ml per minute representing 25 per cent of cardiac output. In fact, almost the whole blood flows through the glomeruli, only 5-10 per cent of it courses trhough the paraglomerular anastomoses.

It was found that the **blood pressure whitin the glomerular capillaries** is about 50-60 per cent of the blood pressure in systemic arteries – 10 kPa (80 torr). The blood pressure in peritubular capillaries is about 1,9 kPa (15 torr) and in **vena renalis** about 0,8 kPa (6 torr). The glomerular capillary network can be so considered to be a high – pressure capillary network in contrast to the low – pressure peritubular capillary network. The striking difference in pressure between the glomerular and peritubular capillaries is caused by the high resistance within the vas efferens.

The **high-pressure region of cortical glomerular network** resembles the arterial end of capillaries. In the low-pressure peritubular capillary network prevails the retrograde diffusion of fluids according to Starling's law, thus the peritubular capillary bed functions as the venous end of capillaries. Blood flowing through the peritubular capillary network is deprived of the water volume which has been filtered

in glomeruli, thus its osmotic pressure is high, and thereby it has the ability to reabsorb the water.

The rate of blood flow within the perilobular arteries is relatively high, hence the erythrocytes move mainly in the centre of this flow. Vasa afferentia are derived from the aa. interlobulares in a nearly rectangular direction, therefore more plasma than erythrocytes flow in them. Owing to this fact the cortical glomeruli are supplied with blood containing more erythrocytes than plasma.

The arrangement of two successive capillary networks is very important concerning urine production and its concentration. For understanding the disorders arising in kidneys during glomerular blood flow alterations is very important to know these facts.

The blood distribution in kidneys is uneven. Almost 80 per cent of renal blood perfuses the outer cortical regions. This is why all changes in blood flow will be reflected in alterations of this region. The blood flow in renal medulla does not depend of systemic arterial blood pressure.

Blood flow through the juxtamedullar glomeruli enables to maintain the blood flow in renal medulla to the detriment of cortical glomeruli, especially when the blood supply of kidneys is diminished, or the systemic arterial pressure falls considerably.

The high blood flow through the renal cortex responds sensitively to blood volume and pressure changes. An important fall of blood pressure or volume can elicit development of ischaemia, even of necrosis in outer cortical layers. Inflammatory alterations in the renal cortex can vice versa affect the blood flow through the medulla renalis.

Oxygen consumption in cortical region is 9 ml per minute, it is about 20 times higher than in medullar region (0,4 ml per minute). Thus, the renal blood flow supplies the organ with oxygen and nutriments for its own metabolic processes and it ensures simultaneously the processes of ultrafiltration of plasma and thereby of urine formation. Kidneys are therefore provided with several mechanisms enabling the adaptation of blood flow according the given requirements of organism.

The autoregulation of renal blood flow is accomplished by nerves and humoral factors. The most important **regulation** is accomplished **by the renin-angiotensin system.** There are two types of intrarenal receptors recording stimuli for renin release: the first type are the baroreceptors localized on the wall of vas afferens, stimulated by tension changes affecting the vessel wall. If this tension is diminished e.g. during reduction of blood flow through kidneys the renin secretion by these cells rises and vice versa. The second type of receptors (chemoreceptors) is found in the wall of distal tubules in their portion lying near to glomeruli: - the granular cells of macula densa. They respond to changes in sodium concentration of tubular fluid. The stimulation of renin secretion occurs if the NaCl concentration in the vicinity of macula densa cells decreases. On the contrary, an augmented NaCl content in this area supresses renin release. Renin is releases from cells into the intersticium and from there it gets into the capillaries. Renin is a specific endopeptidase converting angiotensinogen. A glycoprotein present in blood plasma - to angiotensin I which is converted by converting enzyme to a substance with very strong vasoconstrictive activity - the angiotensin II.

Renin-angiotensin system is one of the key systems regulating the blood pressure. Despite of extensive research projects, all facts concerning the release and regulation of this very important factor are not known in detail till now. The baroreceptor and chemoreceptor mechanism explaining the triggering off this system is in principle accepted.

The mechanism of angiotensin action is not well understood. Angiotensin II stimulates the calcium uptake and the calcium release from celullar organelles in target cells. Angiotensin II induces vasoconstriction of renal vessels, above all in vas efferens. In vas afferens is its vasoconstrictive action probably masked by vasodilatation due to prostaglandins, synthesis of which is stimulated by angiotensin. During decreased blood flow the constriction of vas efferens ensures the glomerular filtration. This vas efferens constriction causes blood pressure fall in peritubular capillary network leading further to improvement of fluid resorption in proximal tubule. The angiotensin receptors are situated also on mesangial cells within the glomeruli. These cells may influence the permeability of glomerular capillaries. Enhanced angiotensin level suppresses by feedback mechanism the renin release from juxtaglomerular apparatus. But the suppression of renin production can be induced by an other pathway – by aldosterone release, sodium reabsorption and by its increased concentration in region of macula densa.

The renin-angiotensin system is involved not only

in regulation of renal functions but it plays a very important role in control of systemic arterial blood pressure. Angiotensin II by its strong vasoconstrictive effect increases the peripheral resistance of vessels and maintains so the blood pressure on appropriate desired level. Apart from this, angiotensin II stimulates the sympathetic activity and facilitates the noradrenaline release from peripheral endings. Angiotensin II indirectly promotes the sodium and water retention in organism. By its action is aldosterone released from suprarenal glands ensuring the tubular reabsorption of sodium. It also stimulates the vasopressin release and induces the dipsogen effect in central nervous system (CNS). This complex action results in correction of disproportion between the capacity and filling of the vessel system during arterial hypotension and hypovolaemia. The correction is performed by renin-angiotensin-aldosterone system that induces vasoconstriction, increase of water intake with reduction of its elimination, and enhancement of sodium retention.

In the regulation of renal blood flow participates the nervous system. **The adrenergic fibres of sympathetic system** come from Th 10 to Th 12 segments and a part of them in Th 12 to L2 segments. These fibres enter the kidneys with renal arteries and pass along them. They innervate afferent and efferent arterioles, intrarenal veins and tubules. Parasympathetic fibres were found in the same areas. Application of alfa-adrenergic agonists (e.g. noradrenaline) elicits vasoconstriction of a. afferens and a. efferens resulting in blood flow decrease through kidneys. Only minor changes of glomerular filtration arise thereby. Also hypoxia can be the stimulus triggering the renal vasoconstriction mediated by chemoreceptors.

Activity of the sympathetic system is low under basal circumstances. Renal flow is therefore not considerably increased by adrenergic receptor blocking agents or by renal denervation, but it can be raised under the influence of vasodilating agents which can reduce the myogenic tonus of vessels. This is accepted at present, although the myogenic theory does not explain the renal blood floow changes.

Adrenergic stimuli induce in kidney the vasodilating **prostaglandin PGE_2 and PGA_2** release. They antagonize the vasoconstrictive adrenergic stimuli. Increased level of noradrenaline or angiotensin II triggers the prostaglandin release. Increased concentration of vasoconstrictive substances is the result of enhanced sympathetic activity. In this situation have the prostaglandins a protective influence upon the renal circulation.

The natriuretic hormone is very probably substance with low molecular weight, produced in brain, mainly in hypothalamus. In experiments it inhibits the sodium transport through the frog skin. The mechanism of this effect is the inhibition of the transporting enzyme Na^+–K^+–ATP–ase activity. Natriuretic hormone enhances the contractility of smooth musle cells in the vessel wall. Increased sodium excretion induced by natriuretic hormone is explained by inhibition of the sodium pump in proximal tubule and in other parts of tubular system. Elevated natriuretic hormone activity was found in patients with chronic renal failure, with essential hypertension and with low renin hypertension. Nevertheless, in patients with heart failure and in patients with oedemas of various origin a zero activity of natriuretic hormone was observed. These facts indicate that natriuretic hormone regulates the volume of extracelullar fluid under physiological circumstances and in pathologic conditions. The chemical structure of natriuretic hormone was not identified till now.

On the other hand, the **atrial natriuretic peptide (factor)** was identified in heart atrial tissue. It is a peptide with a molecular weight of 2 500 to 3 000 daltons. Applied to experimental animals it induces acceleration of renal sodium excretion without inhibition of Na^+–K^+–ATP–ase, thus it is not an inhibitor of this enzyme and it does not exhibit vasoconstrictive activity, but has vasodilating effects. Its release into the blood is initiated by expansion of circulating blood volume, by enlargement of heart atria and enhanced plasmic sodium concentration. The mechanism how the natriuretic factor increases the renal sodium excretion is not fully understood. It is known at present that it enhances the glomerular fitration and causes vasodilatation in kidneys. Glomerular filtration is increased by influencing vas efferens and vas afferens, resulting in elevation of filtration pressure and thereby of sodium and water load in tubules. Sodium is not completely absorbed in tubules, but the water reabsorption influenced by vasopressin is unchanged leading to natriuresis.

Thanks to regulating mechanisms remains the renal blood flow relatively constant even during mean arterial pressure fluctuations in extent of 10 to 24 kPa

(80 to 180 torr). The **ability of autoregulation** is persisting even following denervation (renal transplantation), indicating that neural mechanism does not play an important role in renal blood flow regulation. Mechanisms of autoregulation fail only in conditions where the blood pressure is extremely low occuring in massive bleeding when the renal blood flow is considerabily restricted. Global blood flow falls also in anatomic restriction of vessel bed, e.g. in chronical renal disease and in all renal diseases connected with shrinkage of renal parenchyma.

4.4 The urine formation

Urine formation is a very complex process including glomerular ultrafiltration, tubular resorption and excretion (see figure 4.5, page 267).

4.4.1 Glomerular filtration

180 l of plasma is daily filtered through glomerular capillaries and 120 ml of ultrafiltrate is produced each minute. The **glomerular filter** is permeable for substances in a manner as if it would be provided by pores with diameter measuring 10 nm. Substances with molecular weight under 70 000 daltons appear in glomerular filtrate depending on the molecular configuration. The plasmic globulines with molecular weight of about 90 000 daltons are not at all filtered, but few amounts of albumines (m. w. 69 000 daltons) is filtered and reabsorbed in proximal tubules. **Glomerular filtration** does not differ substantially from filtration process occuring at arterial end of capillaries anywhere in the body. The driving force of ultrafiltration is the hydrostatic pressure of blood ensured by heart action. Ultrafiltration of blood plasma does not require local energy supply. In comparison with capillaries in striated muscles is the permeability of glomerular capillaries 400 times greater and the pressure considerably higher. The resulting effective filtering pressure is given by the difference between hydrostatic blood pressure, the oncotic pressure of plasmic proteins and the pressure inside the Bowmans capsule. The effective filtrations pressure is about 3,3 kPa (25 torr). The ultrafiltrate (primary urine) contains few proteins (maximally 150 mg/l), non-electrolyte substances with low molecular weight (glucose, aminoacids, urea etc.), monovalent ions (sodium, potassium, chlorides etc.) approximately in the same concentration as in plasma. As the proteins of plasma are not diffusible, the rules of Gibbs-Donnans distribution governs the process of monovalent diffusible ions distribution. Small differences in concentration are due to Gibbs-Donnans effect, owing to which is the cation concentration in ultrafiltrate lower by about 5 per cent and the concentration of anions by about 5 per cent higher than in plasma. In severe paraproteinaemia and hyperlipidaemia is the concentration of these lowmolecular substances higher in ultrafiltrate than in plasma. The divalent ions concentration (calcium, magnesium) and the concentration of organic acids and bases, concerning their binding to the plasmic proteins, is substantionally lower in ultrafiltrate than in plasma.

Should a substance pass from blood into the primordial urine it has to cross **three barriers**:

1. the endothelial layer with pores-fenestrations on the inner surface of glomerular capillaries

2. the basement membrane composed of three layers. The central layer is the proper filtering membrane. It consits of thin collagenous fibres arranged in a three-dimensional network inserted in a homogenous matrix provided by pores of 30 to 60 nm in diameter

3. the layer of epithelial cells (podocytes) with numerous foot processes spanning the outer wall of glomerular capillaries. At the surface of podocytes is a layer of acid mucopolysaccharides (glycocalyx) filling the gaps between the podocytes. The permeability of capillaries is affected also by electric charge and the configuration of particles permeating into the ultrafiltrate.

Concerning the electrolyte and fluid metabolism is the glomerular filtration extremely important. It follows from the fact that kidney filter daily a fourfold volume of the entire body fluid, the fifteenfold volume of extracelullar fluid, and sixtyfold volume of blood plasma.

Glomerular filtration is affected by following factors: