This overview follows the various sections of the vascular tree, starting with the extra renal arteries and going as far as the peritubular capillaries. The main focus is on non-inflammatory changes of the vascular system, which are worthy of closer attention in view of increasing life expectancy. Thrombi and emboli, especially ateroembolisms, are only briefly mentioned.

**Extra-renal artery**
The most important changes are artherosclerosis of the Arteria renalis, fibromuscular dysplasia and aneurysms.

The *artherosclerosis* of the arteria renalis is typically limited to the proximal third of the artery. The morphological characteristics, complications (thrombosis, emboli, aneurysm) as well as the etiology and pathogenesis are the same as in artherosclerosis of the aorta. The frequency is age dependent and it is more common in males. Stenosing artherosclerosis was seen in 5% of cases in unselected autopsies over 65 years of age. In cases with critical stenosis (over 80%) of the arteria renalis, 90% had arteriosclerosis.

The changes in the ipsilateral kidney vary with age. Especially in younger patients, a pure ischemic injury will be seen. The presence of a contracted kidney with smooth surface is typical. The contraction of the kidney affects the cortex in particular; normally the weight ratio cortex to medulla is 3:2, with an ischemic contracted kidney this may reach 1:10. Histologically, closely spaced glomeruli and atrophic tubuli of the “endocrine type” (thin or barely visible basement membranes) are seen. In unselected autopsy cases an “ischemic contracted kidney” is seen in about 1%, and in patients with a history of hypertension in 5%.

The second most important change of the extra renal arteries is *fibromuscular dysplasia*. In contrast to artherosclerosis, these changes dominate in earlier age groups (under 40 in men and women). Depending on the extent of involvement of the vessel wall, an intimal, medial or adventitial form can be differentiated. The medial dysplasia is the most frequent. It is typically bilateral and other vascular regions (carotid and cerebral arteries) may be affected as well. The pathogenesis is still unclear, it may be inherited as well as acquired. Morphologically, the most frequent form, medial dysplasia, reveals ridges of collagen in longitudinal sections, followed by areas with atrophic media and loss of the Lamina elastica. As a result the typical angiographic picture with stenoses and aneurysms is seen.

The third important pathology of the extra renal artery is the *aneurysm*. The frequency is estimated to be about 0.1% in unselected autopsy cases. Most
aneurysms can be ascribed to atherosclerosis, whereby sack-like aneurysms are more frequent than fusiform types. In general they are small (<2cms in diameter). As with all aneurysms, they can calcify. Dissecting aneurysms, resulting from idiopathic medial necrosis of the aorta, atherosclerosis or from a trauma are rare.

**Intra-renal artery**

The most important changes seen in the intra-renal artery are intima fibrosis with elastosis (fibro-elastosis = arteriosclerosis), intima fibrosis without elastosis and vasculitis.

Practically all adult renal arteries, from the Arteria arcuata and less frequently the interlobular arteries, exhibit variable degrees of **fibro-elastosis**. Morphologically, matrix, collagen and sparse myofibroblasts are seen between concentric layers of elastic lamellae in the widened, cell poor intima. The media can be normal, but often is atrophic. Hypertrophy is rarely present. The width of the intima increases with age. Excessive intimal fibrosis is seen in patients with risk factors for atherosclerosis and in contracted kidneys. Of interest in such cases is the lack of typical artheromas with foam cells, cholesterol crystals, areas of necrosis and calcification in the widened intima. The elastic lamellae stain as elastin, but are said to consist of abnormal collagen (pseudo-elastin). However, the only stain suitable for revealing elastosis is an elastin stain, e.g. the Verhoeff van Gieson elastin stain. The pathogenesis is still unclear. The endothelium appears normal, as far as this can be judged by light microscopy. Fibrin deposition is not seen. However, the close correlation between fibro-elastosis and the degree of general atherosclerosis on the one hand, and arteriolar hyalinosis on the other, strongly suggest that a similar, if less pronounced, endothelial lesion is the cause of the intimal fibrosis. This restructuring of the vessels leads to hardening of the arteries. The constriction of the vessel lumen due to intimal fibrosis is not trivial, but rather an important cause of ischemic cortical scarring. Fibro-elastosis probably is the most neglected diagnosis in both tumor nephrectomies and in renal biopsies.

The **intimal fibrosis without elastosis** is quite different to fibro-elastosis. As known from general pathology, elastin formation is not seen in organisation or granulation tissue, nor in inflammation. This means that an elastin stain is necessary for differentiation between the two forms of intimal fibrosis. This phenomena - lack of elastin formation in scarred tissue – is not specific for the kidney and occurs in skin scars as well.

These areas of intimal fibrosis are frequently focal and eccentric. The structure varies with the age of the lesion. They usually consist of collagen without sclerosis and contain only a few myofibroblasts and even fewer inflammatory cells. Intimal fibrosis without elastin is seen in the course of vasculitis (in transplantation in cases of endarteritis) and in the organisation of emboli and thrombi. However, when contracted kidneys are investigated, for example as a result of vascular rejection or malignant hypertension after long term dialysis, a fibro-
elastosis is found in practically all arteries. This indicates that, following a variable time lapse, elastin formation is seen in areas of intimal fibrosis that primarily do not contain elastin.

**Arteriole**

The next stopping point on our trip through the vascular tree is the arteriole. This is just as frequently the site of pathology as the arteries. The main lesions in the arterioles are arteriolosclerosis and lesions in connection with a thrombotic microangiography. Vasculitis may affect the arterioles, either in isolation or together with other arteries.

The arteriolosclerosis (arteriolar hyalinosis) is seen predominantly in the afferent arteriole, it may however also affect the efferent arteriole. Arteriolosclerosis of the efferent arteriole may only be diagnosed when both the afferent and efferent arterioles of a single glomerulus can be seen in the same section. Arteriolar hyalinosis owes its name to the deposition of hyaline (glassy) material. It begins with an excentric accumulation of PAS positive material beneath the endothelium. Later on, these deposits can expand circumferentially. As the degree of severity increases, an increase in basement membrane-like material in the neighbourhood of the hyaline deposits and between the smooth muscle cells is seen. As long as the changes are excentric, the media remains unaffected. In case of circumferential deposits, the media atrophies and then the smooth muscle cells form only a thin band around the outer side of the vessels. Finally, the whole arterial wall seems to be replaced by hyaline material (at least as seen by light microscopy). This replacement process is often accompanied by dilatation of the vessels and is very common in diabetic nephropathy.

The hyaline deposits can stretch proximally into the interlobular arteries. With severe hypertension, the glomeruli may be affected too (focal segmental glomerulosclerosis, decompensated hypertension). Even though rarely seen in biopsies, the arteriosclerosis may regress completely. Immunohistology shows that the PAS positive glassy material contains IgM and complement components (C5-9, C3, C1q, C4). Lipids (lipoproteins) may also be present in large quantities as well. Arteriolosclerosis occurs in scarred tissue, in advanced age and diabetes mellitus. It is however best correlated with hypertension in contrast with arteriolosclerosis in other organs (spleen, mesentery).

Experimental studies have shown that these hyaline deposits do not occur at random along the arterioles, but primarily at dilated segments of the vessels following contraction rings. In post stenotic sections endothelial damage may result from turbulent blood flow, which promotes insudation of plasma components into the vessel walls. Arteriosclerosis of the efferent arterioles is typically found in diabetes mellitus, but is not proof of diabetes.

In the case of arteriolonecrosis (today we usually speak of malignant nephrosclerosis or TMA with malignant hypertension) it is less the arteriole but
rather the interlobular artery that is mainly involved. Proximal vessel involvement can reach as far as the lobar arteries and distal involvement may reach the glomeruli.

The typical lesions are thrombi, fibrinoid necroses, mucoid expansion of the intima and onion skin-like changes of the vessel walls. Initially severe endothelial and myocyte injury is present. Vessels that are particularly severely affected may, in part, lack an endothelial lining. This, on the one hand, promotes thrombi formation and, on the other hand, favours the insudation of plasma components and fibrin into the vessel wall producing medial necrosis (fibrinoid necrosis), which may extend into the perivascular connective tissue. The arteries often reveal a mucoid widening of the intima, superimposed on an underlying intimal fibrosis. Within the mucoid intima, a few proliferated myofibroblasts are seen, which may later arrange themselves in a circular pattern and produce collagen and elastin (pseudoelastin). This then results in an onion skin-like structure of the arteries. The changes in the arteries do not differ from those seen in TMA of any other etiology. Depending on the severity of disease, infarction may occur. The cause of the lesion is malignant hypertension, which is usually a complication of an underlying but inadequately or untreated hypertension.

Hyaline deposits of PAS positive material are not solely seen in arteriolosclerosis, but also occur in thrombotic microangiography and in particular are especially typical for calcineurine-inhibitor arteriolopathy. Here, in contrast to arteriolosclerosis, the hyaline material is not primarily found subendothelially but rather in the region of the media or even on the outside of the arteriole. This arises since individual endothelial and muscle cells die (become necrotic) and knot-like protein deposits are formed by plasma insudation in the empty basement membrane “bags”. Finally the arteriolar wall is transformed into a ring of pearls form, consisting of hyaline material. Even though the lesions resemble one another in advanced stages, knot-like deposits should not be classified as hyalinosis. They should be interpreted as arteriolopathy accompanying a late stage of TMA or calcineurine-inhibitor arteriolopathy, which must be considered as a special, abortive form of TMA. In the case of calcineurine-inhibitor arteriolopathy, following dose reduction, regression of hyaline deposits and reconstruction of the vessels is seen.

**Capillary**

The last stopping point in the vessel landscape is the capillary. In the past pathologists have concentrated mainly on the glomerular capillaries. In connection with the capillaritis of humoral rejection, the peritubular capillaries have attracted renewed attention.

In this connection we can learn something from a disease that was never common in the USA, but in Switzerland was responsible for more than 30% of end stage renal disease till 1980: the Phenacetin-Kidney (incorrectly termed analgesic nephropathy).
This latter disease is essentially due to injury of the peritubular capillaries in the kidney and the mucosal capillaries of the descending urinary tract (capillary sclerosis). By light microscopy the capillaries exhibit massive thickening of the vessel walls. The capillaries are lined by endothelium; in advanced stages this endothelial lining is lost. The electron microscope reveals that the capillary wall consists of concentric basement membrane layers separated by deposits of cell debris. These changes are induced by toxic intermediary products of phenacetin. The multi-layered structure of the basement membrane is due to repeated episodes of epithelial necrosis and regeneration, whereby the regenerating epithelial cells form a new layer of basement membrane.

From this finding we can generalise that capillary endothelial injury can best be judged on the basis of changes in the basement membrane. Mild injury results only in subendothelial edema, whereas severe, widespread injury as a rule leads to endothelial regeneration and synthesis of new basement membrane. Similar phenomena are seen not only in peritubular capillaries, but equally well in the glomerular capillaries, and are recognised as TMA and/or transplant glomerulopathy.

Multi-layering of the peritubular capillaries seen in humoral transplant rejection is thus a result of repetitive endothelial injury, probably with necrosis. Here, the endothelial lesions are not of a toxic nature, but result from an antigen-antibody reaction with subsequent complement activation.

**In summary**, it is true to say that virtually all blood vessel pathology of acquired diseases has a common final pathway of injury: Following primary endothelial damage and, depending on the severity, reparation with matrix formation, vessel wall thickening and possibly renal injury occurs. The type of morphological lesion varies, depending on the vessel caliber and the cells present i.e. endothelium, myofibroblasts, and inflammatory cells.