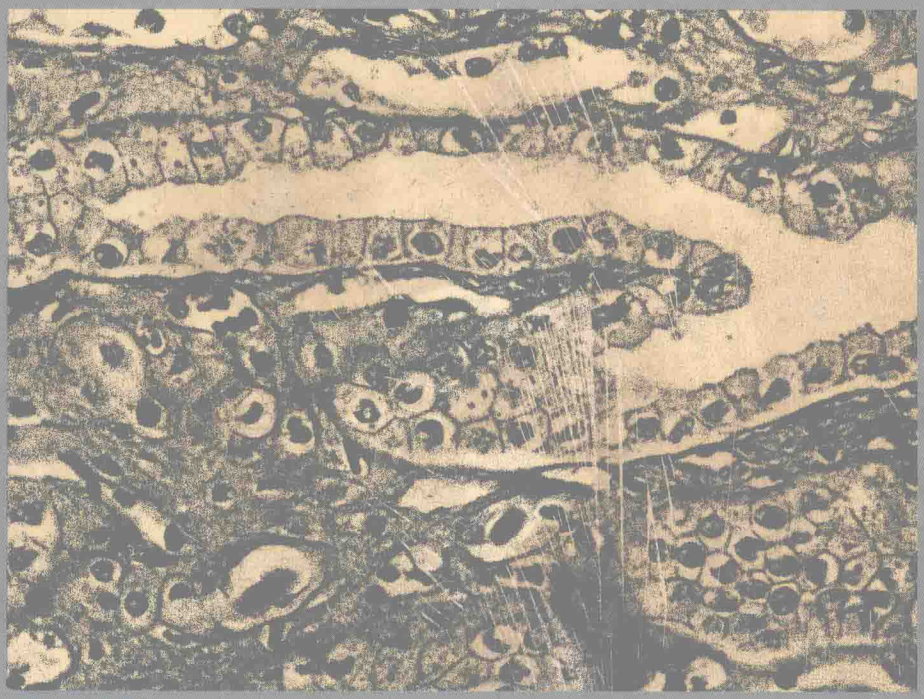
ORGAN PHYSIOLOGY

STRUCTURE AND FUNCTION OF THE KIDNEY



HAMBURGER—RICHET—GRÜNFELD

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STRUCTURE AND FUNCTION OF THE KIDNEY

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PREFACE

In our two-volume *Nephrology*, written by members of the Nephrology Department, Hôpital Necker, Paris, and so well presented by the W. B. Saunders Company, our present knowledge of renal structure and physiology was reviewed, since this is the necessary basis for any study of diseases of the kidney.

It was the idea of Mr. John L. Dusseau, Vice President and Editor of the Saunders Company, to publish these chapters separately to avail medical students of a brief and inexpensive summary of modern renal anatomy and physiology. Dr. J. P. Grünfeld agreed to write an Appendix, which includes some of the most recent developments in this field. Dr. Anthony Walsh revised this Appendix in the same careful and effective way in which he prepared the English version of our *Nephrology*.

I hope the following pages will be the beginning, for some medical students, of what we call in France a "coup de foudre," that is, a falling in love with nephrology, one of the most fascinating fields of modern biology and medicine.

JEAN HAMBURGER

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CHAPTER 1

Anatomy and Embryology. Structure of Renal Tissue

MACROSCOPIC DESCRIPTION OF THE KIDNEYS

The kidneys are retroperitoneal organs lying on the posterior abdominal wall, one at either side of the lumbar spine, the right slightly lower than the left. Bean-shaped, the convex border outward, and covered by a fine fibrous capsule, each kidney presents convex anterior and posterior surfaces, an outer convex and an inner concave border, and two poles, superior and inferior. The middle part of the inner border is occupied by the hilum.

The average kidney in the adult is 11 cm. long, 5 cm. wide, and 2.5 cm. thick; the weight is 125 to 170 gm. in a man, 115 to 155 gm. in a woman.

Longitudinal section gives a macroscopic view of the principal elements in the architecture of the kidney: (1) the *excretory channels* occupying the inner and medial part, forming, at the hilum, the renal pelvis; (2) the *renal parenchyma* completely surrounding the excretory channels and further divided into two concentric zones, an inner medulla and an outer cortex (Fig. 1).

The Excretory Channels

These form a continuous pathway from the renal parenchyma to the bladder and are, from above down, the minor calyces, major calyces, renal pelvis, and ureter. Of these, only the calyces and first part of the pelvis form part of the kidney; the remainder are extrarenal.

The *minor calyces* generally number six to ten (outside limits four to forty)[144] in each kidney and cap the renal papillae (see under The Renal Parenchyma). They run a short course and unite in groups of two or four to form the *major calyces* which may number from two to five, but most commonly three, named upper, middle, and lower. They are of variable length, and they open into and form the base of the renal pelvis.

The *pelvis* is shaped like a funnel flattened anteroposteriorly. The base measures 20 to 25 mm. long and the apex joins the ureter. The length of the pelvis varies greatly from subject to subject, and the average capacity is 4.5 ml. (2 to 12 ml.). The pelvis emerges from the kidney at the hilum.

The description just given is schematic: there are few cavities in the body that show such individual variation as the pelvicalyceal system. The main variations will be described in the discussion of urography (see Fig. 55, page 140).

The Renal Parenchyma

The *medulla* is formed of a series of tri-

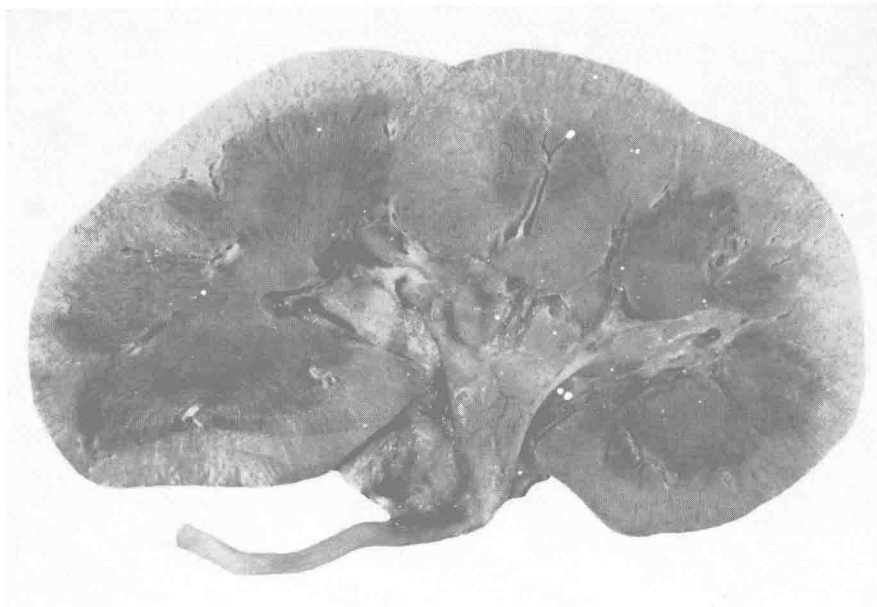

Figure 1. Normal kidney: macroscopic appearance on longitudinal section.

angular pyramids, whose apices lie centrally: they are well demarcated, dark red in color, and radially striated. These are the malpighian pyramids, which vary in number in each kidney from six to ten, corresponding to the number of minor calyces. The paler apex of the pyramid, or papilla, projects into the lumen of the corresponding minor calyx which entirely caps it. The point of junction between the medulla and the calyceal mucosa is named the fornix.

The *cortex*, which surrounds the malpighian pyramids, comprises the remainder of the renal parenchyma. Yellowish pink in color, it has two different zones. The pyramids of Ferrein occupy the space between the base of the malpighian pyramids and the kidney surface. They appear striated in the same way as do the malpighian pyramids. The remainder of the cortex has a finely granular appearance and occupies the spaces between the pyramids of Ferrein and also projects between the pyramids of Malpighi to form the columns of Bertin (Fig. 2).

The kidney may be considered as formed of several lobes, a lobe being a malpighian pyramid and the cortical substance surrounding it at the sides and externally. As will be seen, every lobe has its own vascular tree. Lobulation, normally not visible in the adult, is quite obvious in the fetus and also in some animal species.

MICROSCOPIC DESCRIPTION OF RENAL PARENCHYMA

The Nephron

The nephron is the structural and functional unit of the renal parenchyma. The number of nephrons in each kidney has been variously estimated:[1] 1 million according to Bell[9] and Smith,[152] 1.3 million according to Moritz and Hayman,[100] and 4.5 million according to Verney.[164] Each nephron consists of a glomerulus (of Malpighi) and a urinary tubule divided into several segments, the proximal convoluted tubule, the descending and ascending limbs of the loop of Henle, the distal convoluted tubule, and the collecting tubule of Bellini (Fig. 3). These various parts are placed at well defined levels in the kidney; the glomeruli, proximal and distal convoluted tubules, and part of the loops of Henle are in the cortex; the deepest part of the loops of Henle and the collecting tubules are in the medulla.

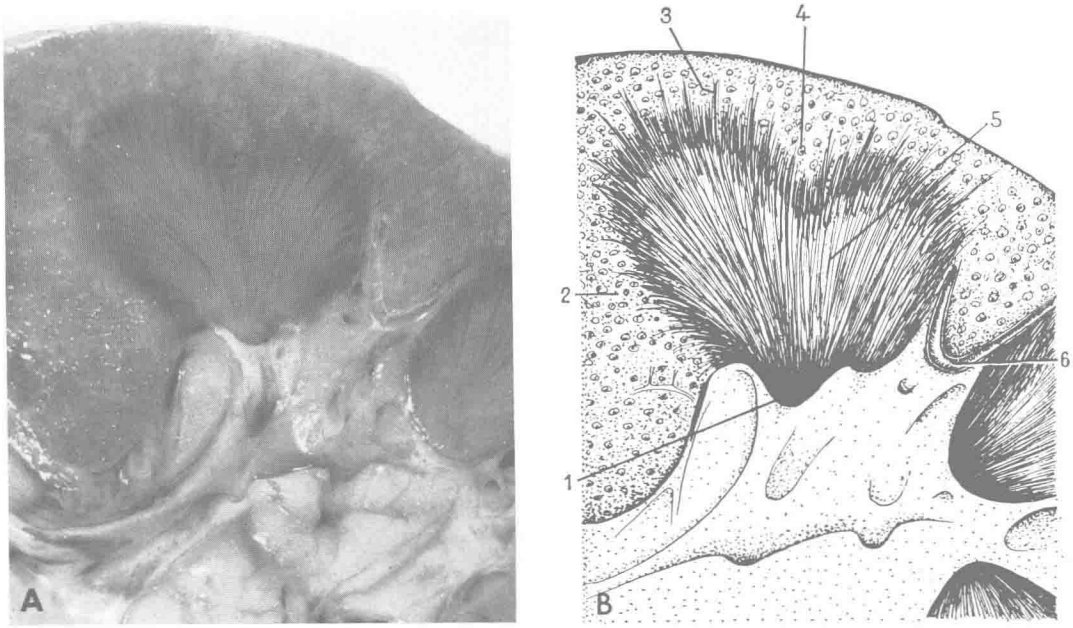

Figure 2. Detail of a renal lobe. 1, Papilla; 2, a column of Bertin; 3, a pyramid of Ferrein; 4, cortex containing glomeruli; 5, a malpighian pyramid; 6, an interlobar vessel.

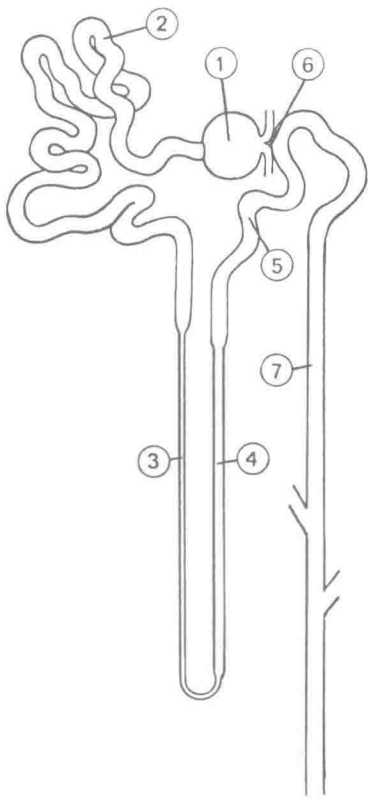

Figure 3. Diagram of a nephron. 1, Glomerulus; 2, proximal convoluted tubule; 3, descending limb of the loop of Henle; 4, ascending limb of the loop of Henle; 5, distal convoluted tubule; 6, macula densa; 7, collecting tubule.

The Glomerulus

The glomerulus was described by Malpighi in 1669 and by Bowman[24] in 1842. It is a rounded structure, some 200 or 250μ in diameter in the adult, with a volume of 0.0042 cu. mm. These measurements are derived from autopsy studies and vary considerably according to the fixation technique: they are significantly greater in renal biopsy than in postmortem material.

The glomerulus is formed by the opening out of a capillary tuft between two arterioles, afferent and efferent, which together form the vascular pole. It is surrounded by a fibrous envelope, Bowman's capsule, which is continuous with the urinary tubule. Between the capillary tuft and Bowman's capsule is the urinary space (Bowman's space) (Fig. 4).

Bowman's Capsule

Bowman's capsule is made up of a hyaline basement membrane, mucopolysaccharide in nature, lined on the outer aspect by a fibrous layer in direct contact with the interstitial tissue and on the inner aspect by a sheet of epithelial cells, or parietal epithelium. The basement membrane and the parietal epithelium are in direct continuity with the basement membrane and epithelium of the tubule. At the vascular pole, the basement membrane turns in to fuse with the basement membrane of the capillaries of the glomerular tuft at their origin, and fuses also at this point with the subendothelial layer of the afferent arteriole. The capsule is invaginated by the blood vessels and not perforated by them, as Bowman believed in 1842.[98, 102, 103]

The epithelial cells of Bowman's capsule are arranged in a single layer. They are flattened and show no evidence of functional activity. Their nuclei are large and rounded and the cytoplasm contains mitochondria, a Golgi apparatus, and a poorly developed ergastoplasm.

The Capillary Tuft

General Structure. Where it enters the glomerulus, the afferent arteriole divides into a number of branches, usually from four to six, sometimes more. Each branch in turn gives off numerous capillary branches to

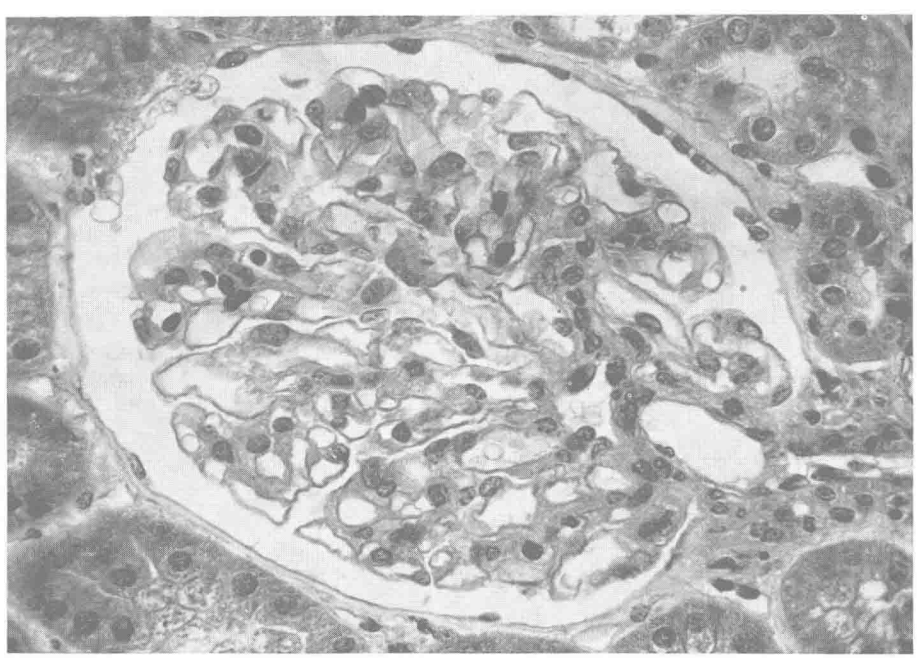

Figure 4. Normal glomerulus. The vascular pole is to the right of the picture, the urinary pole to the left. (Trichrome light green, ×600.)

form a lobule. There are as many lobules as there are primary branches of the afferent arteriole.

The capillaries of each lobule wind around a common axis in a spiral fashion. This axis is apparently the only point of fixation of the capillaries; everywhere else their walls seem to be free in the lumen of Bowman's space. On longitudinal section of the glomerulus, with light microscopy, the axis appears as a cellular stalk, issuing as an extension of a central glomerular stem which radiates from the vascular pole to the periphery. On transverse section the axes form the central part of the lobules, separating them from one another, giving something of a cloverleaf appearance (Figs. 5 and 6).[40]

Thus in the capillary tuft can be seen two different zones: (1) *the peripheral part of the capillary loops*, or the glomerular filter proper, and (2) *the centrilobular cellular axis.*

The problem of the existence of anastomoses between the capillaries of a lobule and also with capillaries of adjacent lobules has been resolved, thanks to the increasing perfection of such techniques as microdissection, vascular injection, and serial section. Johnson,[69, 70] in 1889, on the basis of serial-section studies, was the first to indicate the existence of such anastomoses. Their existence was denied by Vimtrup[165] in 1928, on the basis of microdissection, and also in 1941 by Wilmer,[168] who used celloidin injections. Hall,[57] in 1954, combining latex injections with microdissection, was able for the first time to follow the entire path of the capillaries of a single lobule from the afferent to the efferent arteriole. He produced evidence of numerous anastomoses between the capillaries of the same lobule. His work was confirmed in 1956 by Boyer,[25] who used spatial reconstruction from serial sections. Intercapillary anastomoses were further confirmed in 1958 by Bohle[20] in a serial-section study of intercapillary tissue.

Fine Structure of the Peripheral Part of the Capillary Loops. The wall of the capillary loops has three layers: a *basement membrane* lying between an *inner endothelial* and an *outer epithelial* layer (Fig. 7). The epithelial layer is peculiar to glomerular capillaries. Nearly all other capillaries, both in man and in animals, have a basement

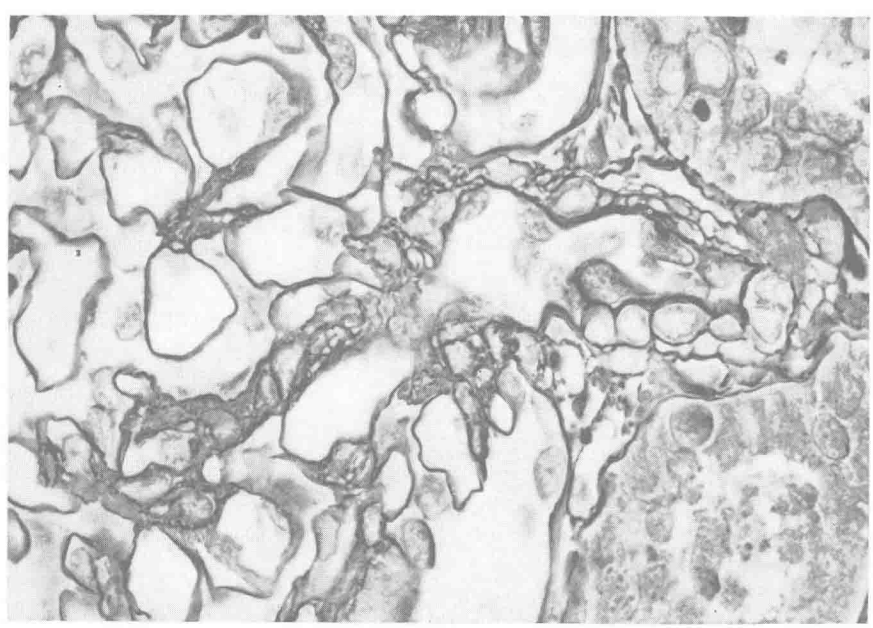

Figure 5. Normal glomerulus: note the arrangement of the intercapillary spaces and their relation to the lumen of the capillaries. To the right, the afferent arteriole; below left, an intercapillary space cut longitudinally; above left, an intercapillary space cut transversely and surrounded by four capillaries. (Silver staining by Wilder's technique, ×1000.)

membrane with endothelium on the inner aspect and a connective tissue layer on the outer aspect.

THE ENDOTHELIAL LAYER. The endothelial layer completely encompasses the capillary lumen. It consists of fairly large, flattened cells whose nuclei, usually placed in the deeper part of the loop, bulge into the lumen. The clear cytoplasm is gathered around a nucleus, thinning out progressively with increasing distance from the nucleus and forming a fine layer lining the whole of the peripheral part of capillary loop. It contains the usual intracellular structures, but not in large numbers: two centrioles, some mitochondria, a Golgi apparatus, an underdeveloped ergastoplasm, an occasional granule of free ribonucleoprotein, and many pinocytotic vesicles. The narrower part, 200 Å to 300 Å thick, is perforated by a large number of pores, varying from 500 Å to 1000 Å in diameter and separated from each other by a similar distance;[41, 42, 44] Hall[57] has named this the *lamina fenestrata*. The work of Rhodin[140] has shown that in fact there is a very thin diaphragm in each of these pores. Classically the endothelial layer was thought to be a syncytium and this hypothesis was still upheld by Mueller[102] in 1958, but it can now be finally rejected since cell boundaries have been clearly shown by electron microscopy.

THE BASEMENT MEMBRANE. The basement membrane of the glomerular capillaries forms a continuous layer that is, at least in part, mucopolysaccharide, as shown by its staining by Schiff's reagent. Its structure is amorphous (or hyaline) on light microscopy and discretely fibrillary on electron microscopy in certain conditions of impregnation by heavy metals.[78, 133] It is difficult, on light microscopy, to dissociate it from the other layers of the capillary wall, and only electron microscopy has permitted definition of its structure (Fig. 7). Rhodin[136] in 1955 described three different zones: a *central dense zone, the lamina densa*, covered on both sides by clearer zones, the *laminae rarae interna and externa*.[169, 170] Quite well defined in the young subject, these three layers tend

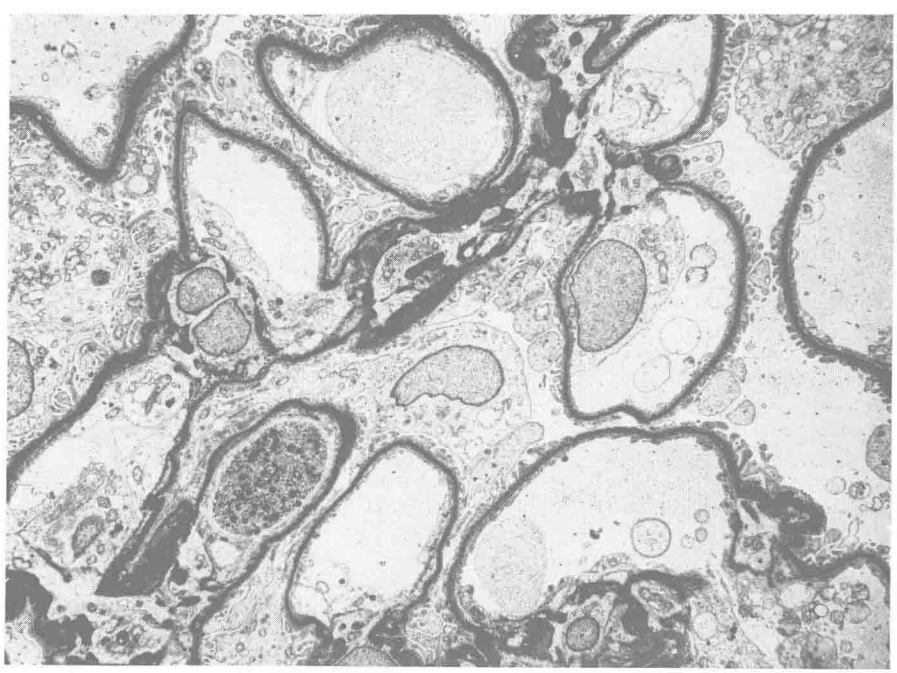

Figure 6. Electron photomicrograph (low magnification) of part of a normal glomerular tuft. In the upper part of the picture can be seen an intercapillary space and many capillary lumina around it. (Silver staining by Jones' technique, ×2300.)

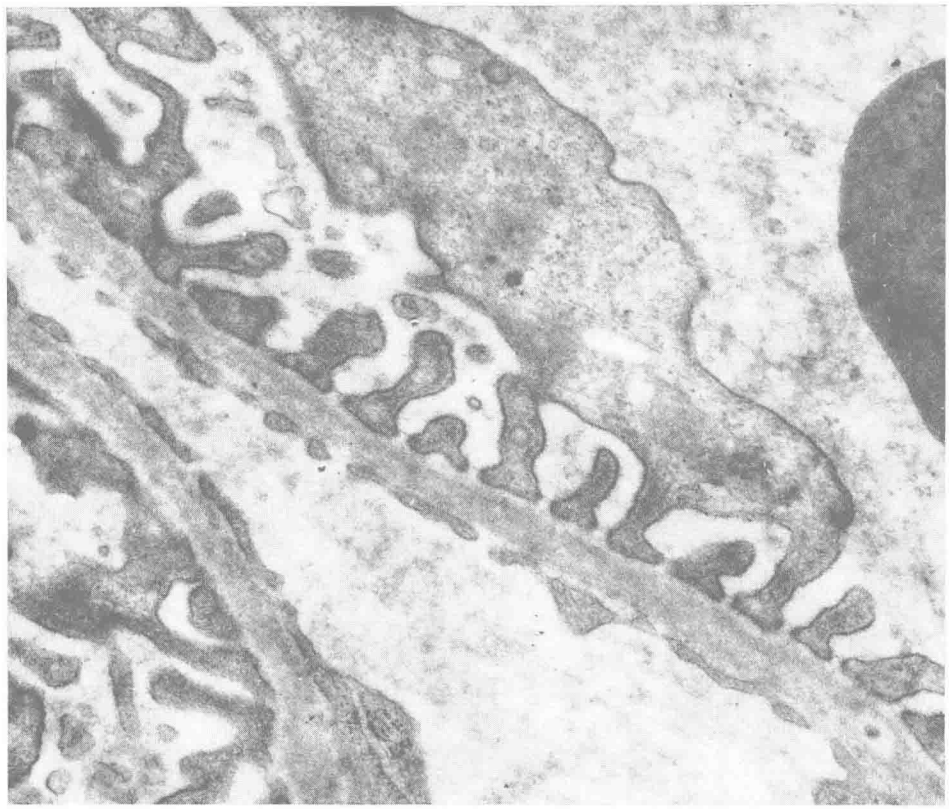

Figure 7. Electron photomicrograph of a normal glomerular capillary wall. On the side of the urinary space can be seen the epithelial pedicels, with their expanded extremities, linked together by a delicate membrane; on the side of the capillary lumen, the endothelial cytoplasm pierced by pores; between these two elements, and separated from each by a clear space, is the homogeneous basement membrane. (Uranium acetate stain, ×26,500.)

to disappear with increasing age owing to the thickening of the lamina densa.[4*]

The thickness of the basement membrane varies considerably with the age of the subject, from about 1500 Å in the young child[18] to about 3500 Å in the aged subject.

The theory advanced by the classical histologists, in particular Zimmermann and Allen,[1] which proposed that there are two conjoined basement membranes, was clearly refuted by the earliest electron microscopy studies.[124, 125, 136, 163]

THE EPITHELIAL LAYER. There has been a great deal of controversy about the nature of the cells forming the outer layer of the wall of the glomerular capillary. These cells were first described in 1848 by Gerlach as flattened cells, in continuity at the vascular pole with the cells of the inner layer of Bowman's capsule and, like the latter, epithelial in nature. But von Moellendorff,[166] in 1930, identified them as adventitious cells, the pericytes of Rouget, and proposed for them the name *Deckzellen*. Bergmann[6] in 1932 also cast doubt on their epithelial nature, which, however, was affirmed by Zimmermann.[172] On the basis of the earliest electron microscopy studies, McManus[88] considered them to be epithelial cells, and this opinion is universally held by modern morphologists.

As seen by the electron microscope, the epithelial cell, or *podocyte*, is a large cell with abundant cytoplasm and a complex

* The existence of these three zones is considered by some, Bergstrand in particular, as a fixation artifact. Most authors, however, recognize it as real, but consider that the thickness of the *lamina densa* varies with age and with the quality of fixation. Histochemical studies have shown the individuality of the *lamina densa*, which is PAS positive and stains with alcian blue, whereas the *lamina rara externa* stains with alcian blue but is PAS negative.

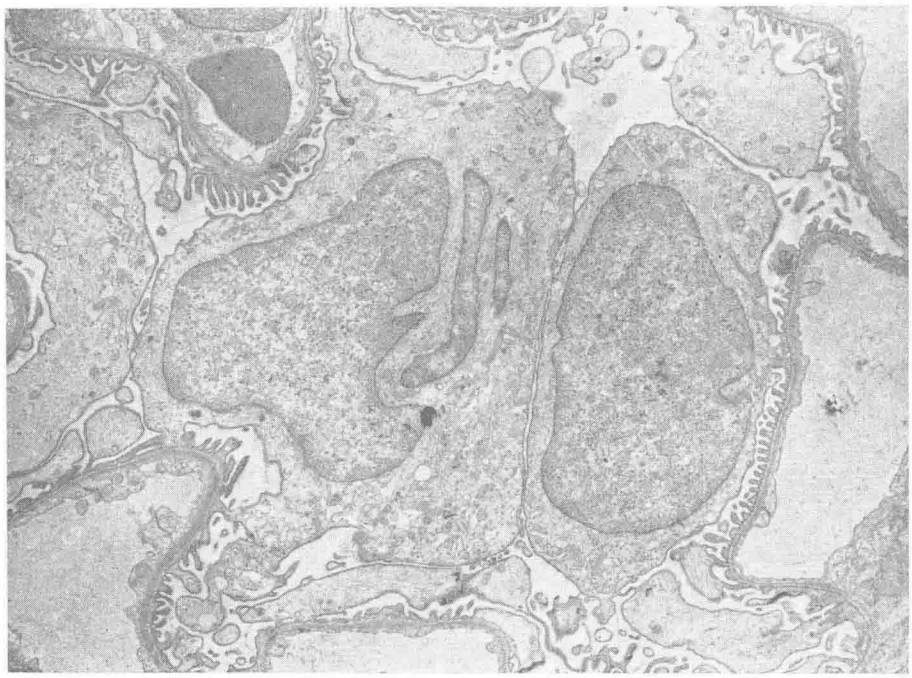

Figure 8. Two normal epithelial cells as seen on electron microscopy. They give rise to irregular trabeculae from which derive the fine processes attached to the basement membrane, the pedicels. (Uranium acetate stain, ×9250.)

structure (Fig. 8). Numerous prolongations of the cytoplasm, the trabeculae, run from the body of the cell parallel to the basement membrane to which they are attached by fine processes, the *pedicels* or *foot processes*. Each epithelial cell sends pedicels to several capillary loops, where they alternate with pedicels from neighboring cells, like pieces of a jigsaw puzzle. There is, in effect, a pericapillary network through which the primitive urine circulates: Oberling and Gauthier[108] have named this the "pericapillary lacunar apparatus."

The *foot processes* enlarge progressively from their trabecular origin to their base, which is attached to the basement membrane. Here they are separated from one another by distances of the order of less than 2500 Å.[19, 20] A fine membrane, thinner than a cell membrane, bridges the spaces between the bases of the foot processes: this is the "filtration slit membrane" of Yamada[170] and Suzuki.[158] These authors regard it as an expansion of the cell membrane but Pearse[124, 125] looks on it as part of the cement in which the foot processes are embedded, and Farquhar[44] sees an analogy with desmosomes and terminal bars.

The *nucleus* is found in the body of the epithelial cell, usually lying against the cell membrane on the side of the urinary space. The *cytoplasm* is much richer in organized structures than that of the endothelial cells. It contains a Golgi apparatus, two juxtanuclear nucleoli and many ergastoplasmic membranes as well as free granules of ribonucleoprotein, numerous smooth-walled vesicles of endoplasmic reticulum, and vacuoles of various sizes which may appear empty or may contain a flaky precipitate of low density (hyaline droplets, some of which are clearly visible on light microscopy).

The mitochondria are of the usual type; the hyaloplasm contains a network of fine fibrils of the order of 70 Å visible after staining with heavy metals.[44]

The cytoplasm of the foot processes has far fewer organized structures and these are chiefly pinocytotic vesicles.

Thus, of the three layers that make up the capillary wall, only the epithelial layer is discontinuous. The other two, the *endothelial layer* and the basement membrane, are continuous from the afferent arteriole to the efferent arteriole. Between the foot processes of the *epithelial layer* are gaps whose

diameter is much greater than that of the protein molecules, which normally do not pass through in the ultrafiltrate. Filtration must then be a function of the *basement membrane* and the *endothelial layer* whose pores, as previously described, seem to be obturated by the fine diaphragm described by Rhodin;[140] this would prevent any direct contact of the blood plasma with the basement membrane.

Structure of the Deeper Part of the Capillary Loops: the Intercapillary Cells. On transverse section of a glomerular tuft, it is easy to see with electron microscopy that the basement membrane does not surround the entire lumen of a capillary loop but is reflected onto adjacent loops—outlining the picture of a rosette (Fig. 6).

In the axis of this rosette there are cells which are separated from the capillary lumen by the deep endothelial layer (here not in contact with the basement membrane) and separated from Bowman's space by the basement membrane and its covering epithelial foot processes, both of which bridge the axis.

The spaces thus delineated have been called *mesangial, intercapillary, interluminal,* or *axial,* depending on the author (Fig. 9).

Their existence has given rise to the classic "mesangium" theory of Zimmermann:[171] a fibrous web acting as a framework for the glomerular capillaries and consisting of fibroblasts and collagen.

Electron microscopy has complicated the problem by showing that the intercapillary cells differ in structure from fibroblasts and in fact are morphologically similar to endothelial cells. For this reason certain histologists deny the individuality of these cells and regard them as endothelial cells placed deep in the axis and to be found in contact with the capillary lumen in different planes of section.[13, 39, 41, 42, 44, 56]

This latter opinion, however, is far from being accepted by all authors. Many elec-

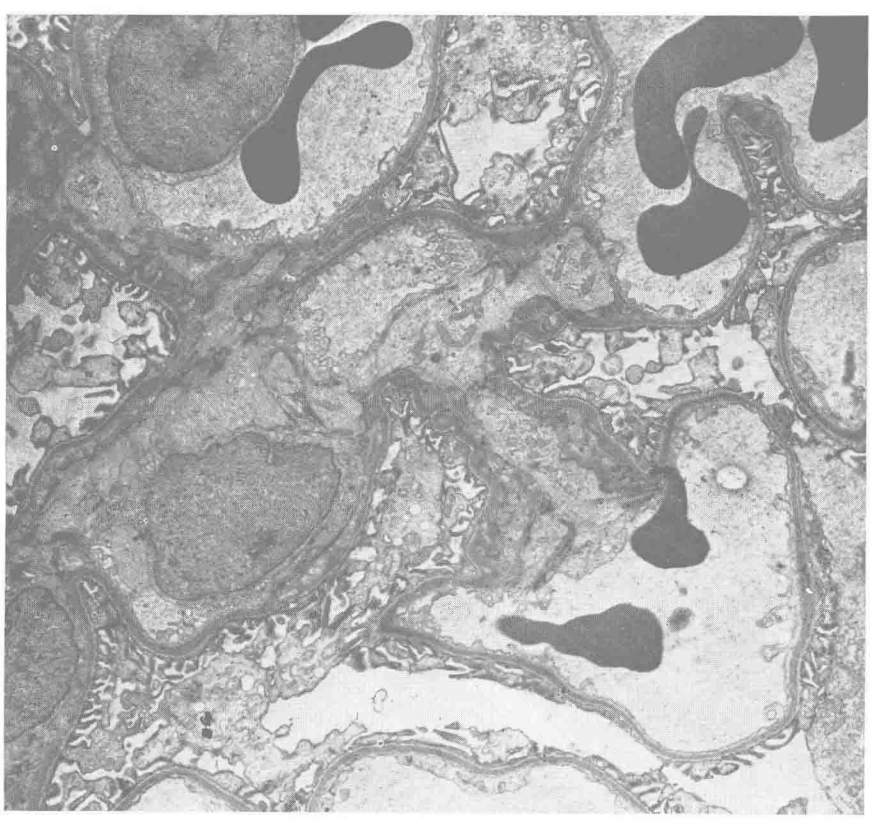

Figure 9. Electron photomicrograph of an intercapillary space. The cytoplasm of the intercapillary cell has numerous irregular prolongations separated from the endothelial cell by arches of hyaline substance; it has no direct contact with the capillary lumen. (Uranium acetate stain, ×12,900.)