RENAL PATHOLOGY

with

Clinical and Functional Correlations

Volume II

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RENAL PATHOLOGY

Volume II

To
Audrae Tisher and Jane Brenner

Preface

The discipline of renal pathology has enjoyed dramatic growth in the past 3 decades, in parallel with remarkable progress in clinical nephrology. Both areas of medical knowledge have benefited from expansion of our understanding of normal renal structure and function and of the selective influences on structure and function imposed by disturbances due to definable immunologic, infectious, vascular, and metabolic causes. Furthermore, the enormous benefits attributable to glucocorticoids, immunosuppressive drugs, and other therapies intensify the need to define and categorize renal structural injury at its earliest stages in order to salvage renal parenchyma and minimize permanent nephron destruction. This necessity for precise and thorough analysis of kidney biopsy specimens has fostered a crucial collaboration between the renal pathologist and the clinical nephrologist, and the resulting marriage of interests and effort has fueled splendid conceptual, methodologic, and interpretational advances.

As the title implies, *Renal Pathology with Clinical and Functional Correlations* embodies this evolving union in two volumes that synthesize renal structure, function, and clinical course into a dynamic resource designed to be helpful to all serious students of kidney disease. The chapters are authored jointly by leading specialists in renal pathology and medicine, thus ensuring that the material is both authoritative and accurate. By enlisting the efforts of a large number of contributors, it has been possible to acquire a significant body of information in a relatively brief span of time, further ensuring that the stated concepts, mechanisms, clinical and morphologic descriptions, and interpretations are as contemporary as possible.

Renal Pathology is organized into seven major sections which reflect, at least in part, an attempt to provide a practical working classification of kidney disease. We recognize, however, that no classification system yet devised is perfect, and our organizational scheme is no exception.

Part One: General Considerations provides a review of the clinical indications for kidney biopsy and a thorough step-by-step description of the proper manner in which to evaluate the kidney biopsy specimen. This section also includes an overview of structural and functional information pertaining to the nonimmunologic progression of kidney disease to end-stage. The final chapter in Part One presents a detailed description of the gross anatomy, the embryology, and the architectural organization of the human kidney.

Part Two: Glomerular Diseases begins with a detailed discussion of the structure and function of the normal glomerulus. This is followed by a consideration of the immunopathogenetic mechanisms that lead to glomerular injury. The remainder of Part Two comprises 13 chapters that discuss specific disease entities that are generally classified as glomerular in type. These include the proliferative, membranous, membranoproliferative, and anti-GBM forms of glomerulonephritis; minimal change nephrotic syndrome and the focal sclerosis complex; the nephropathies of drug addiction and acquired immunodeficiency; preeclampsia–eclampsia; and IgA nephropathy. Certain systemic diseases that lead primarily to glomerular disease are also considered in this section and include systemic lupus erythematosus, Schönlein-Henoch purpura, and mixed connective tissue disease. Other chapters provide descriptions of renal involvement in parasitic diseases and those forms of glomerulonephritis associated with systemic bacterial and viral infections.

Part Three: Tubular and Interstitial Diseases begins with a discussion of the structure and function of the normal renal tubule and interstitium, followed by a detailed review of the immunopathogenetic mechanisms of tubulointerstitial injury. The subsequent nine chapters include pathologic and clinical descriptions of such diverse entities as acute tubular necrosis and toxic nephropathy, cortical necrosis, infarction and atheroembolic disease, interstitial nephritis, pyelonephritis and reflux nephropathy, obstructive uropathy, analgesic nephropathy and papillary necrosis, Balkan nephropathy, and radiation nephropathy.

Part Three also includes a chapter devoted to the anatomy and the pathology of the juxtaglomerular apparatus, with particular emphasis on Bartter's syndrome.

Part Four: Vascular Diseases is introduced with a beautifully illustrated chapter that describes the structure and function of the renal vasculature. This is followed by a comprehensive review of mechanisms of vascular injury. The remainder of Part Four comprises five chapters that provide thorough pathologic and clinical descriptions of specific disease entities including scleroderma (progressive systemic sclerosis), polyarteritis nodosa, Wegener's granulomatosis, allergic granulomatous angiitis, and lymphomatoid granulomatosis. Other chapters describe the hemolytic-uremic syndrome, thrombotic thrombocytopenic purpura, postpartum renal failure, renal vein thrombosis, benign and malignant nephrosclerosis, and fibromuscular dysplasia.

Part Five: Renal Involvement in Heredofamilial, Metabolic, and Hematologic Diseases begins with a chapter dealing with hereditary nephritis and benign recurrent hematuria. Other heredofamilial diseases with renal involvement presented in this section include the nail-patella syndrome, lipodystrophy, Fabry's disease, lecithin-cholesterol acyltransferase deficiency, and the nephrotic syndrome of infancy. This section also includes chapters on cystic diseases and congenital malformations of the kidney. Metabolic disorders including diabetic nephropathy, uric acid and urate nephropathy, cystinosis, and oxalosis are discussed in detail. A chapter devoted to paraproteinemias and dysproteinemias includes descriptions of multiple myeloma, light chain deposition disease, amyloidosis, monoclonal gammopathy, Waldenström's macroglobulinemia, heavy chain disease, and POEMS syndrome. Part Five concludes with a description of the nephropathies of certain benign hematologic disorders including sickle cell anemia, sickle cell trait, other anemias, and polycythemic states.

Part Six: Renal Neoplasms is composed of two comprehensive chapters that address the entire spectrum of renal tumors in pediatric and adult populations.

The final section of the book, *Part Seven: The Renal Allograft,* addresses the rapidly expanding body of knowledge in this field. The initial chapter reviews the immunopathogenetic mechanisms of allograft rejection. The subsequent chapter is devoted to the pathology of the renal allograft and includes descriptions of the several forms of rejection, as well as of pyelonephritis, drug-induced interstitial nephritis and *de novo* and recurrent glomerulonephritis. The final chapter is devoted to a detailed discussion of cyclosporine nephrotoxicity.

An *Appendix* provides the reader with a practical guide to the proper handling and processing of kidney biopsy and nephrectomy specimens.

This work has been made possible by the dedication of a large number of outstanding scholars who have described in exquisite detail the breadth and depth of their knowledge and personal experience with the specific disease entities represented in this book. We express our gratitude to each contributor for the countless hours they have devoted to the writing of their respective chapters, and for their willingness to accept the suggestions of the Editors.

To the many outstanding professionals at the J.B. Lippincott Company, we extend our thanks for their patience, wise counsel, and assistance in the preparation and publication of this book. We especially wish to acknowledge the outstanding efforts of Ms. Rosanne Hallowell, Mr. Richard Winters, and Mr. Dean Manke, without whose cooperation and dedication to excellence this project would not have succeeded.

C. Craig Tisher, M.D.
Barry M. Brenner, M.D.

RENAL PATHOLOGY

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Structure and Function of the Renal Vasculature

Kevin V. Lemley
Wilhelm Kriz

INTRODUCTION

The renal vasculature comprises a number of unique structural and functional features, such as postcapillary arterioles and countercurrent arterial and venous blood flows in the medulla. These features, in turn, underlie some of the kidney's manifold capabilities. In addition to its usual nutritive role, blood flow to the kidneys directly serves the process of glomerular filtration, the sensation of the circulating red cell mass, and the regulation of systemic blood pressure, and also plays an important role in the process of urine concentration. Because it is involved in several different renal functions, the rate and intrarenal distribution of blood flow to the kidney are subject simultaneously to a number of distinct regulatory influences. The need to integrate these regulatory systems may, in part, explain the large number of neural, hormonal, and intrinsic factors that affect renal blood flow.

The importance of the structural organization of the vasculature to renal function is underscored by the striking structural regularities that are apparent from the macroscopic to the ultrastructural level. Pronounced regional differences in structural organization and blood flow patterns have been appreciated for decades, but are still poorly understood. This is due, in large part, to the complexity of tubular-vascular structural relations and the lack of an adequate quantitative method for determining regional blood flow.

In this chapter, the structure and function of the renal vasculature, with the exception of the glomerular capillaries, are discussed in an attempt to provide a framework from which both the normal structure and function of the renal vessels and their derangement in disease can be understood. Additional information is available in several recent reviews.[1–6]

STRUCTURE OF THE RENAL VESSELS

In general, the pattern of the large arteries and veins in the human kidney differs from that in other species. The microvasculature, however, is very similarly organized in humans and in other mammalian species. Therefore, the macroscopic blood vessels are described specifically as they occur in the human kidney, whereas the subsequent presentation of the structure of the intrarenal vessels is based on findings from many mammalian species.

Major Arteries and Veins of the Human Kidney

The two renal arteries branch off the aorta nearly at right angles. Just before reaching the hilum of the kidney, the renal arteries divide into several branches. Two patterns may be distinguished.[4,7] Most often, only an anterior and a posterior division occur, although an additional inferior division may be found occasionally. The anterior division gives rise to four *segmental arteries* supplying the apical, upper anterior, middle anterior, and lower segments of the kidney. The posterior division (lying deep to the renal pelvis) gives rise to the posterior segmental artery. When an inferior primary division is present, it supplies the lower segment of the kidney, replacing the lower segmental artery of the anterior division. No attempt will be made to describe other, more rare branching patterns or the various types of accessory arteries that may occur.[4,8,9] The segmental arteries have virtually no anastomoses with their neighbors and, thus, are end-arteries, as are their branches down to the afferent arterioles.

Within the hilar tunnel and the renal sinus, the segmental arteries divide several times, finally forming *interlobar arteries,* which enter the kidney substance roughly

between adjacent renal lobes[4] (Figure 31-1). They extend toward the cortex on either side of a renal pyramid, running in the space between the caliceal wall and the adjacent cortical tissue as long as a renal calix is present. At the junction between cortex and medulla, the interlobar arteries divide dichotomously into *arcuate arteries,* which follow a curved course between the cortex and medulla (see Fig. 31-1 and 31-2). Particularly in the human kidney, the arcuate arteries gradually ascend within the juxtamedullary cortex. The arcuate arteries undergo several further divisions. From each of these branches a series of *interlobular arteries* arise, which, possibly after additional branchings, finally ascend radially through the cortex (Fig 31-3). Given their course and the fact that renal lobules cannot be delineated clearly, these arteries probably should be called *cortical radial arteries. No arteries penetrate the renal medulla.*

Most of the interlobular arteries terminate within the cortex. Only a small number (about five in each kidney in humans[10]) reach the surface of the kidney (the so-called perforating arteries), where they may anastomose with capsular branches derived from the inferior suprarenal, renal, and gonadal arteries.

The intrarenal veins accompany the arteries. Central to the venous drainage of the kidney are the *arcuate veins* which, in contrast to the arcuate arteries, do form anastomosing arches at the corticomedullary border[11] (see Fig. 31-1). They accept veins from the cortex as well as from vessels draining the medulla. In humans, there are two types of *interlobular veins* draining the cortex. One type originates at the surface of the kidney as *stellate veins.* These drain the most superficial parts of the renal cortex and are so named because of their surface appearance. Stellate veins continue as typical interlobular veins and traverse the entire cortex to empty into the arcuate veins. Most interlobular veins, however, are of the second type, which originate in the cortex as a result of the joining of venules from the peritubular plexus; they also accompany interlobular arteries and drain into arcuate veins (Fig. 31-4).

The arcuate veins join to form *interlobar veins* which, together with their corresponding arteries, are located in

FIGURE 31-1. Schematic illustration depicting the course of the major arteries *(black)* and veins *(white)* of a compound, multipapillary kidney similar to the human kidney. Calices, pelvis, and ureter are stippled. Note that the arcuate arteries, running at the corticomedullary border, do not form true arches, but rather are end-arteries. In the human kidney, there are two types of interlobular veins; one group, starting as stellate veins (★), drains the most superficial cortex, whereas a second, more numerous group starts at deeper levels in the cortex. Both drain into arcuate veins. In contrast to the arteries, the veins do form anastomoses at the level of the arcuate and interlobar veins.

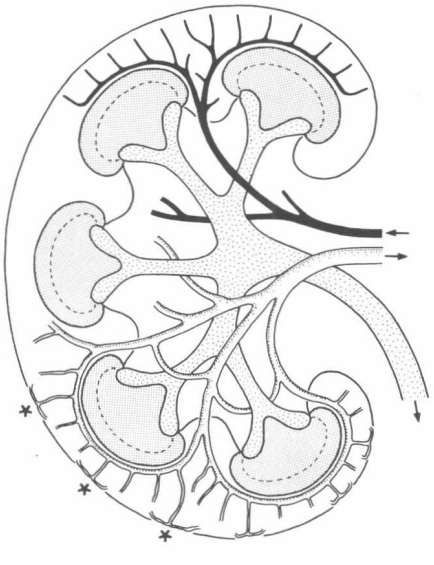
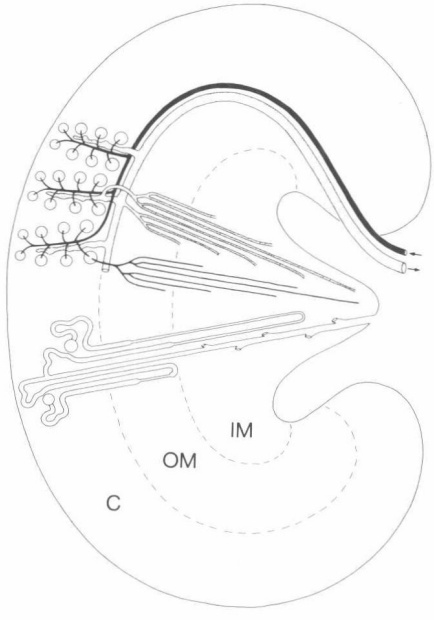


FIGURE 31-2. Schematic illustration of a unipapillary kidney (or an individiual lobe of a multipapillary kidney). Arterial vessels are drawn in black, whereas venous vessels are stippled. Note that the interlobular arteries split off into afferent arterioles that supply the glomeruli. No arteries enter the medulla. The medulla is supplied by the efferent arterioles of juxtamedullary glomeruli (a single example of which is shown), which break up into the descending vasa recta. Ascending (venous) vasa recta drain the medulla, emptying into arcuate or interlobular veins. A short-looped and a long-looped nephron also are depicted, together with their collecting duct. *C,* cortex; *OM,* outer medulla; IM, inner medulla.



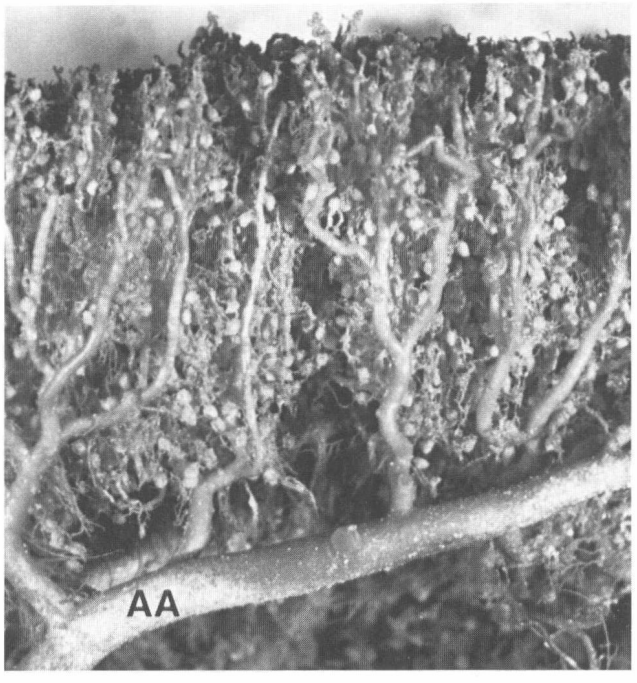


FIGURE 31-3. Human kidney: silicone rubber (Technovit) filling of arterial vessels. An arcuate artery *(AA)* running along the corticomedullary border gives rise to interlobular arteries that extend radially within the renal cortex toward the surface. (Magnification ×~9)

the spaces between the caliceal walls and the cortical tissue of the renal columns. At the level of the papillary tips, anastomoses are established among the interlobar veins by side branches that run in a circular fashion around the calices[11] (see Fig. 31-1). Finally, the interlobar veins join together in a variable pattern to form several (two to six) trunks, most of which lie anterior to the renal pelvis. These exit at the renal hilum, joining together into a single *renal vein.*

Microvasculature of the Kidney

The microvascular pattern of the kidney appears to be very similar among various mammalian species. Details regarding this pattern have been derived from research in laboratory animals, including studies of the mouse,[12] rat,[13,14] rabbit,[15] and dog.[16–18] The data available from studies of human kidneys show no fundamental differences. Therefore, it is possible to describe a basic mammalian pattern for the intrarenal microvasculature[4–6,15,19–21] (Fig. 31-5 and 31-6). Relevant variations in this pattern are mentioned wherever appropriate.

Most *afferent arterioles* arise from interlobular arteries. Additional afferent arterioles arise from interlobar and arcuate arteries. Afferent arterioles that originate from interlobular arteries tend to leave the parent vessel at characteristic angles (see Fig. 31-5 and 31-7). The afferent arterioles to superficial glomeruli continue essentially in the direction of their parent vessel, and the afferent arterioles to midcortical glomeruli run more or less transversely,

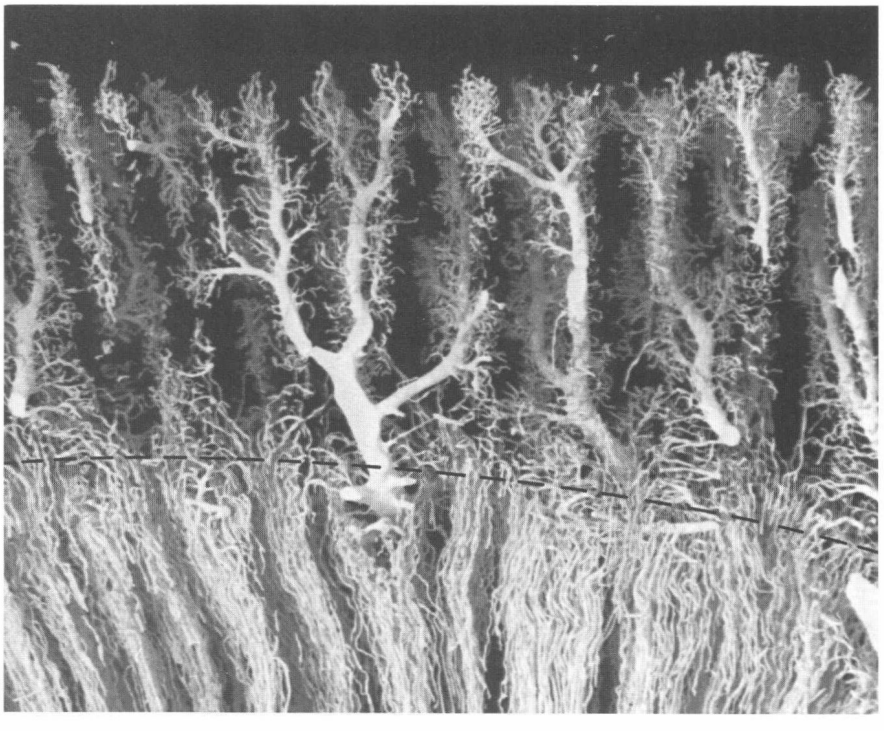


FIGURE 31-4. Rabbit kidney: silicone rubber (Microfil) filling of venous vessels. The dashed line indicates the border between the cortex and the outer stripe of the medulla. Interlobular veins are regularly distributed throughout the cortex. Note the dense pattern of ascending vasa recta which drain into arcuate veins or basal parts of interlobular veins. (Magnification ×~20)

whereas those to juxtamedullary glomeruli tend to arise at a recurrent angle (see Fig. 31-7). Thus, as stated by Fourman and Moffat,[22] the angle of origin of afferent arterioles gradually opens up as the "interlobular artery approaches the periphery, until the final branches are more or less a continuation of the line of the main vessel."

Afferent arterioles arising from arcuate or interlobar arteries supply juxtamedullary glomeruli located along the course of these vessels. Arterioles from interlobar arteries frequently supply ectopic glomeruli that are often situated near the pelvic wall.[4]

Apart from small branches of interlobar and arcuate vessels that supply the plexus of the pelvic mucosa, all branches of interlobar, arcuate, and interlobular arteries terminate in capillary tufts of glomeruli. Aglomerular vessels are rarely found within the cortex. They occur more frequently in the juxtamedullary region, where they supply the renal medulla. It is now generally agreed that aglomerular vessels supplying either the cortical plexus or the medulla result from degeneration of the associated glomeruli[4,23] and, therefore, are found most frequently in older individuals. The blood supply to the peritubular capillaries of the cortex and the medulla is, however, overwhelmingly postglomerular.

The glomerular tufts of renal corpuscles are drained by *efferent arterioles* (see Fig. 31-5 and 31-7). By definition, the efferent arteriole extends from its origin as a coalescence of the tuft capillaries until it first branches. Two basic types of efferent arterioles may be distinguished: *cortical* efferent arterioles, which supply the cortical capillary plexus, and *juxtamedullary* efferent arterioles, which supply the medulla. The latter will be described together with the medullary vessels.

Among cortical efferent arterioles, two further types (with some variations[16]) may be distinguished.[5,14] To appreciate this distinction, it must be remembered that glomeruli generally lie within the cortical labyrinth, completely surrounded by convoluted tubules. The first type of cortical efferent arteriole traverses this labyrinthic layer of convoluted tubules before splitting up into capillaries. These arterioles include the superficial efferent arterioles, which generally run to the surface of the kidney before branching, and a portion of the midcortical efferent arterioles, which extend toward a medullary ray before splitting up into capillaries. Juxtamedullary efferent arterioles are also of this type. The second, larger class of cortical efferent arterioles is characterized by short arteriolar trunks that divide into capillaries not far from the glomerulus. This type of arteriole is found most frequently in the midcortex, but may also occur in the superficial and juxtamedullary regions.

As already mentioned, all peritubular capillaries originate from efferent arterioles. Both the proximal and distal convoluted tubules of the cortical labyrinth and the straight tubules of the medullary rays receive direct branches of efferent arterioles, and thus are perfused in a parallel fashion with each other—that is, there is no fundamental separation between the peritubular blood supply of the corti-

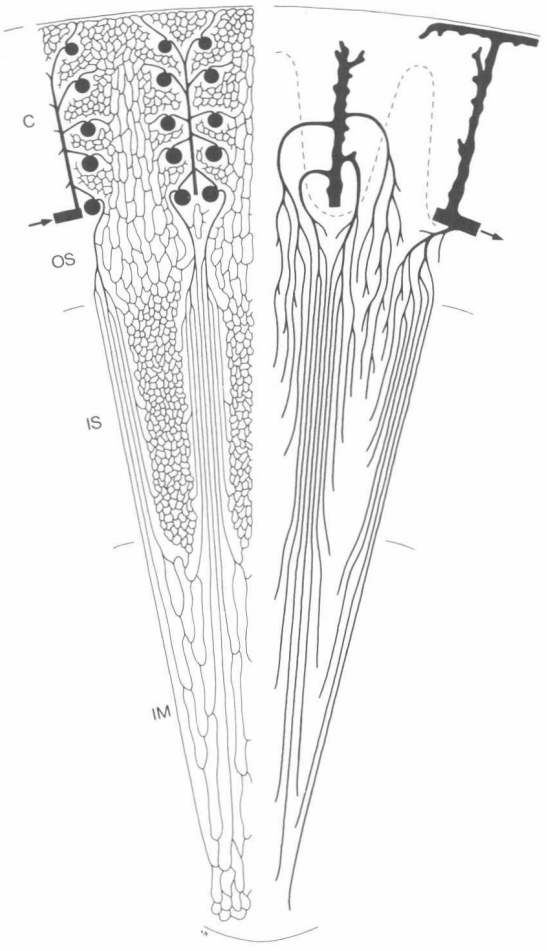


FIGURE 31-5. Organization of the intrarenal vasculature (basic pattern). The left half of the drawing shows only the arterial vessels and capillaries. The right half shows the venous vessels. The dashed line within the cortex *(right)* indicates the medullary rays. *C,* cortex; *OS,* outer stripe; *IS,* inner stripe; *IM,* inner medulla. At the corticomedullary border, a short segment of an arcuate artery is shown giving rise to an interlobular artery. This, in turn, gives off afferent arterioles to superficial, midcortical, and juxtamedullary glomeruli. The efferent arterioles of superficial and midcortical glomeruli supply the dense capillary plexus of the cortical labyrinth and the looser, long-meshed plexus of the medullary rays. The efferent arterioles of juxtamedullary glomeruli descend into the outer stripe and divide into descending vasa recta. At intervals, descending vasa recta leave the vascular bundles to supply the adjacent capillary plexus. Note the different appearance of the capillary plexus in the outer stripe, inner stripe, and inner medulla. The cortex is drained by interlobular veins, some of which begin as stellate veins at the renal surface. The medulla is drained by ascending vasa recta. (Modified from Rollhäuser H, Kriz W, Heinke W: Das Gefäßystem der Rattenniere. Z Zellforsch 64:381–403, 1964)