Fourth Edition

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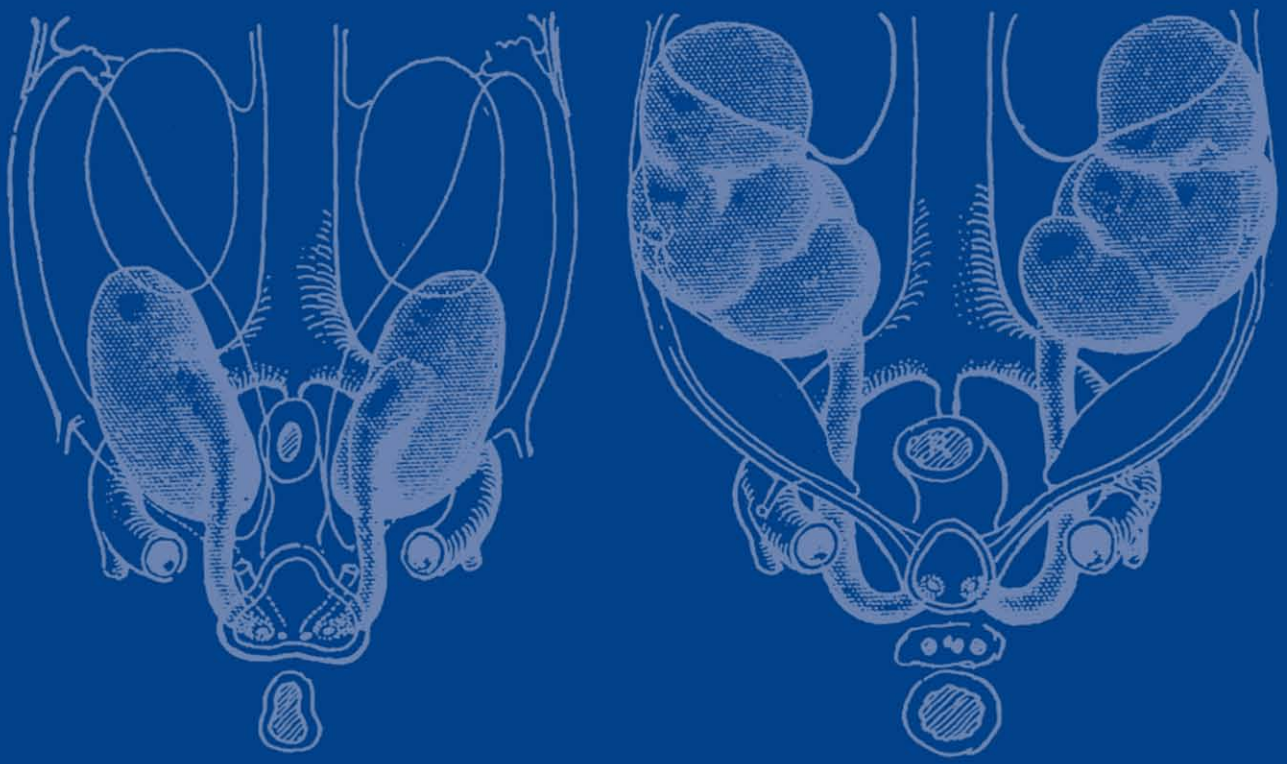
UROLOGIC SURGICAL PATHOLOGY



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FOURTH EDITION

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Preface to the Fourth Edition

It is our great privilege to present the fourth edition of *Urologic Surgical Pathology*. As our understanding of urologic diseases continues to rapidly evolve and advance, this newest edition has been substantially revised and incorporates the most current knowledge, understanding, and terminology in the field of genitourinary pathology. As with previous editions, the fourth edition is authored by leading contemporary international experts and serves as an evidence- and criterion-based reference that encompasses the present scope of our specialty. The emphasis remains on the practical aspects of diagnostic pathology with detailed discussions of the clinical and histopathologic components across the continuum of urologic disease processes. Additionally, there is added focus on novel diagnostic biomarkers, newly characterized histologic variants, and recent advances within the understanding of cancer genomics. The text's framework also incorporates the most recently published TNM staging classifications (2017 revision) by the American Joint Committee on Cancer (AJCC) and the 2016 World Health Organization (WHO) Classification of Tumours of the Urinary System and Male Genital Organs.

This work is designed to provide contemporary, comprehensive, and evidence-based information not only for pathologists, but also for urologists, medical oncologists, and other healthcare professionals involved in patient care. In today's era of precision medicine, effective patient care is a collaborative effort requiring medical professionals of various specialties to synthesize new pathologic discoveries toward translational clinicopathologic correlations at the patient's bedside. With this in mind, the fourth edition of *Urologic Surgical Pathology* highlights the burgeoning role that molecular pathology has secured within modern health care, particularly in the management of urologic malignancy. The reader will subsequently appreciate the increased emphasis placed on discussions of new molecular genetic discoveries and their applications within tumor diagnosis, classification, and practical utility in personalized patient care.

We are grateful to our contributing authors for sharing their knowledge and experience with our readers. We extend utmost thanks to both Fredrik H. Skarstedt from the Multimedia Education Division of the Department of Pathology at Indiana University, who edited the digital images for this book, and Tracey Bender, who provided outstanding editorial assistance. We also thank the dedicated and talented staff at Elsevier, especially Angie Breckon and Michael Houston, who have given invaluable support throughout the development and production of this book. Finally, we are incredibly grateful to our colleagues and readers for their continued support in our efforts to produce the most comprehensive and up-to-date reference for the study and understanding of urologic disease. We hope that the fourth edition of *Urologic Surgical Pathology* becomes a valuable resource for all of our readers.

Liang Cheng
Gregory T. MacLennan
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January 2019

1

Nonneoplastic Diseases of the Kidney

MD. SHAHRIER AMIN AND STEPHEN M. BONSIB

"Study with me, then, a few things in the spirit of truth alone so we may establish the manner of Nature's operation. For this essay which I plan, will shed light upon the structure of the kidney. Do not stop to question whether these ideas are new or old, but ask, more properly, whether they harmonize with Nature. I never reached my idea of the structure of the kidney by the aid of books, but by the long and varied use of the microscope. I have gotten the rest by the deductions of reason, slowly, and with an open mind, as is my custom."

—Marcello Malpighi, 1666

CHAPTER OUTLINE

Introduction

In keeping with the spirit of Marcello Malpighi, this chapter also aspires to reveal "the manner of Nature's operation" as it affects the kidney.[1] However, unlike Malpighi, today's knowledge draws extensively on the labors, discoveries, and insights of investigators of the past centuries.

Knowledge of the normal structure and function of the kidney has been acquired over centuries of scholarly effort. We have come a long way since Aristotle taught that urine was formed by the bladder and that kidneys were present "not of actual necessity, but as matters of greater finish and perfection."[1] Reference to the excretory functions of the bladders and kidneys can be found in early Indian Ayurveda, Chinese, or Egyptian literature.[2-4] Some of the earliest scientifically valid experimental methods are described in *The Canon of Medicine* by the famous Persian Muslim physician Abu Ali Sina, also known as "Avicenna."[5-13] He meticulously described the layers of the bladder and its two-stage function, the intramural ureter and antireflux mechanisms, and scientifically classified urethral and bladder diseases, notably calculi. The foundation of modern urology was established in the sixteenth century by Leonardo da Vinci and Vesalius, who provided the first accurate and detailed drawings of the female and male genitourinary tracts (Fig. 1.1).[14,15] More than 300 years passed before William Bowman, in 1842, coupled intravascular dye injection with microscopic examination to demonstrate the structural organization of the nephron and its vascular supply (Fig. 1.2).[16,17] Bowman's

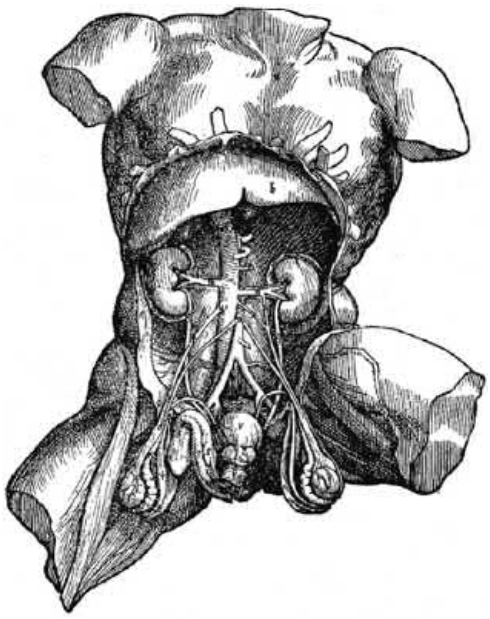


Fig. 1.1 Vesalius's anatomic illustration of the male genitourinary tract published in 1543. Note that the left kidney is incorrectly placed lower than the right. (From Murphy LJT, ed. The history of urology. Springfield, Ill: Charles C Thomas, 1972; with permission.)

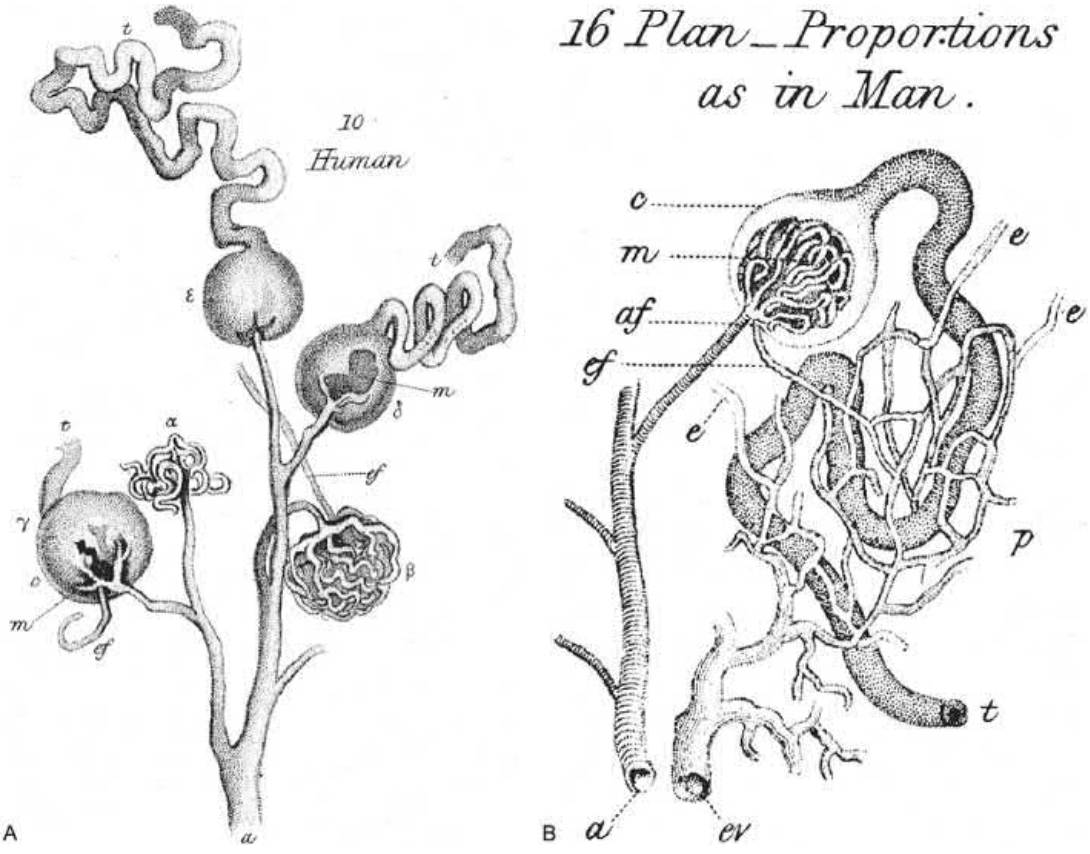


Fig. 1.2 William Bowman's illustration of the vascular supply to glomeruli and the relationship of the efferent arteriole to the convoluted tubules (A and B). (From Bowman W. On the structure and use of the malpighian bodies of the kidney, with observations on the circulation through that gland. Philos Trans R Soc Lond Biol 1842;132:57; with permission.)

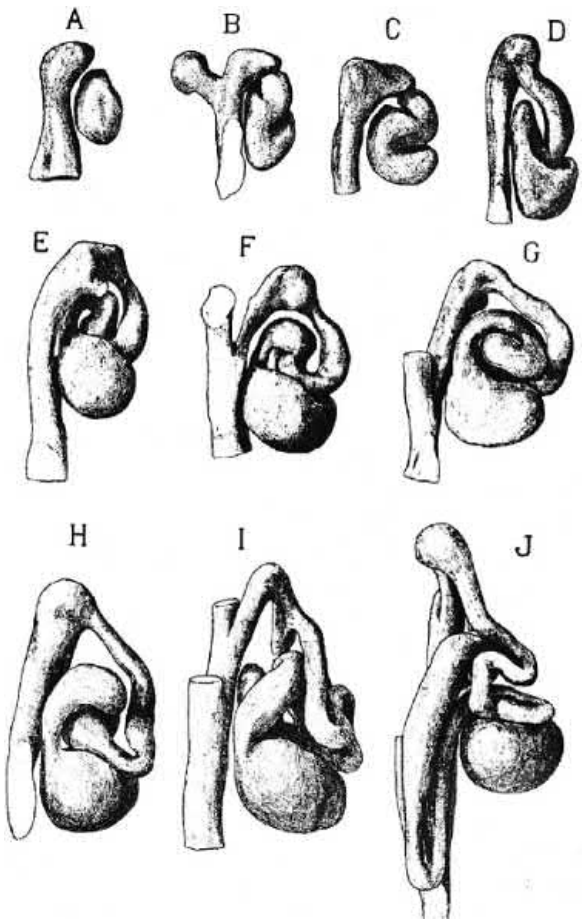


Fig. 1.3 Wax model serial reconstruction of nephron differentiation by Huber. (From Huber GC. On the development and shape of uriniferous tubules of certain of the higher mammals. Am J Anat 1905;4:29; with permission.)

observations provided morphologic support for Malpighi's seventeenth-century speculation of a filtration function for the malpighian body (the glomerulus).[1,18] Sixty years later the embryologic development of the nephron was demonstrated by Huber in a thin-section serial reconstruction study of embryos (Fig. 1.3).[19] Huber's observations were refined and elegantly illustrated by Brödel in Kelly and Burnam's *Diseases of the kidneys, ureters and bladder* published in 1914.[20] Potter and Osathanondh validated the findings in a series of microdissection studies of developing kidneys, which were published in the 1960s.[21-26]

The ultrastructural features and immunohistochemical profiles of the normal kidney and of many diseases were elucidated in the 1970s and 1980s after refinement of the percutaneous biopsy technique and advances in morphologic analyses. Since 1990 there has been an explosion of new information about the genetic basis of normal and abnormal renal development, and about numerous disease processes.[27-34]

Embryologic Development and Normal Structure

This chapter begins with a brief review of the embryology and normal gross and microscopic structure of the kidney. For more in-depth coverage of these topics, several excellent resources are available.[27-34]

The development of the urinary and genital tracts is closely related (Fig. 1.4). These tracts both develop from paired longitudinal cords of tissue lateral to the aorta that are known as the intermediate mesoderm.[26,27,33] From the portion caudal to the seventh somite, known as the nephrogenic mesoderm (or nephrogenic cord), three nephronic structures develop in quick succession: the pronephros, the mesonephros, and the metanephros. Although the pronephros and the mesonephros are transient organs, they are crucial for the proper development of both the urinary and the reproductive tracts.

Pronephros

The first embryologic derivative of the nephrogenic cord is the pronephros, a structure functional only in the lowest forms of fish. It arises from the most cranial portion of the nephrogenic cord during the third week of gestation (1.7 mm stage; 7th to 14th somite stage). Approximately seven pairs of tubules form, only to regress 2 weeks later (Figs. 1.4 and 1.5). The pronephros is important because the pronephric tubules grow caudally and fuse with the next pronephric unit, which gives rise to the pronephric duct. The pronephric duct is the only remnant of the pronephros, and henceforth is called the mesonephric duct.

Mesonephros

The mesonephros develops from the dorsolumbar segments of the nephrogenic cord from day 24 of gestation. Cells of the mesonephric duct proliferate caudally (Fig. 1.4) and begin to form the mesonephric kidney during the fourth week of gestation (4 mm; 26th to 28th somite stage). The mesonephros is a highly differentiated structure and is the functional kidney of higher fishes and amphibians.

The mesonephric kidney consists of approximately 40 pairs of nephrons. The cranial nephrons sequentially regress while caudal nephrons form, with 7 to 15 nephrons functional at all times (Figs. 1.4 and Fig. 1.5). The nephrons are induced in a fashion analogous to their metanephric counterparts.

A fully developed mesonephric nephron consists of a glomerulus connected to the mesonephric duct by a convoluted proximal and distal tubule (Figs. 1.6A and 1.7A). The glomerulus is vascularized by capillaries that branch from small arterioles originating from the aorta, and its efferent arteriole empties into the posterior cardinal vein. The glomerulus appears to filter plasma. Its proximal tubule possesses a brush border; the proximal and distal tubules appear capable of nutrient resorption, as well as concentration and dilution of urine. The tubules connect with the mesonephric duct, which extends distally to connect to the cloaca at about 4 weeks postconception. The mesonephric kidney remains functional until the end of the fourth month of gestation.

Portions of the mesonephric kidney can be easily identified in small embryos (1 to 3 cm), which are occasionally encountered in surgical specimens such as those from ectopic pregnancies. In the male, some of the caudal mesonephric tubules develop into the efferent ducts of the epididymis, while the mesonephric duct becomes the epididymis, the seminal vesicle, and ejaculatory duct. In the female, the entire mesonephros degenerates during the end of the first trimester; however, vestigial structures such as the epoophoron, paroophoron, and Gartner duct, as well as mesonephric remnants, can occasionally be seen in surgical specimens from the ovary and fallopian tubes.

Metanephros

The metanephric kidney is the product of a complex orchestration of embryologic processes. Although discussed separately, it must be

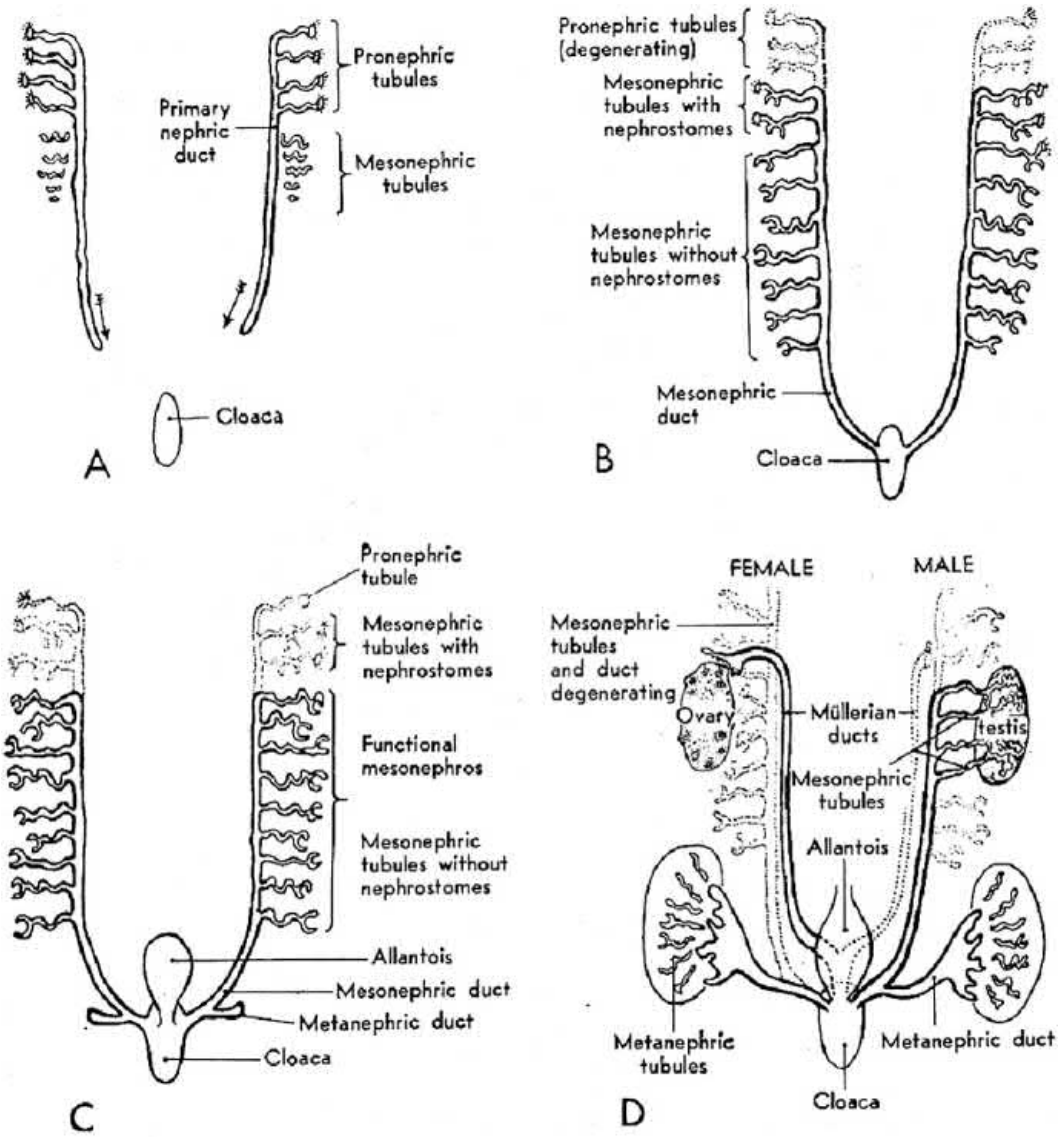
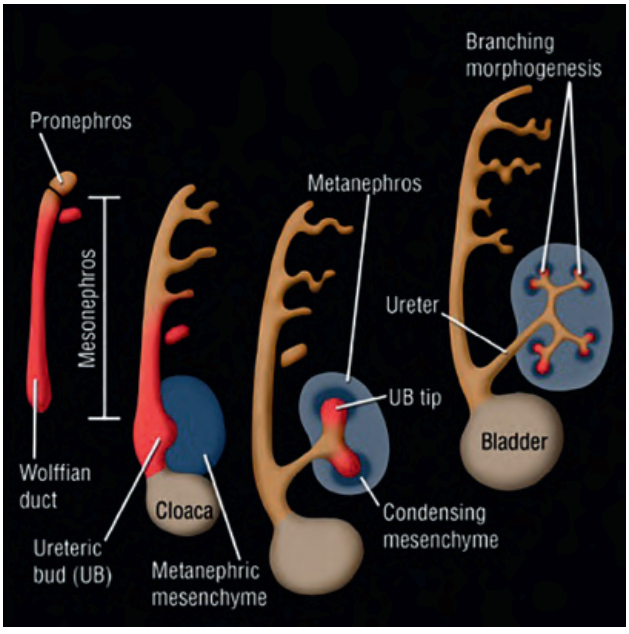


Fig. 1.4 Diagram illustrating the relationship between reproductive tract and urinary tract development. (From Patton BM. Human embryology. New York: McGraw Hill, 1968; with permission.)



appreciated that while the collecting system and renal pyramids are forming there is simultaneous induction of thousands of nephrons, and neurovascular and lymphatic components ramify in a carefully organized architecture throughout the cortex.

The formation of the adult metanephric kidney begins during the fourth to sixth weeks of gestation (4 to 5 mm), after the mesonephric duct has established communication with the urogenital sinus (Fig. 1.5). A diverticulum, known as the ureteric (or ampullary) bud, forms on its posterior medial aspect (Figs. 1.4 and Fig. 1.5) and then establishes contact with the sacral portion of the nephrogenic mesoderm, the nephrogenic blastema. A complex

Fig. 1.5 Early morphogenesis of the kidney. The pronephros and mesonephros begin to develop at 3 and 3.5 weeks, respectively, but gradually regress. The metanephros forms in the metanephric mesenchyme at the distal end of the mesonephros, after the mesonephric duct has established connection with the urogenital sinus, usually after 4 weeks of gestation. It is then invaded by the ureteric bud, which undergoes branching to form the collecting system while the overlying condensing mesenchyme forms the nephrons.

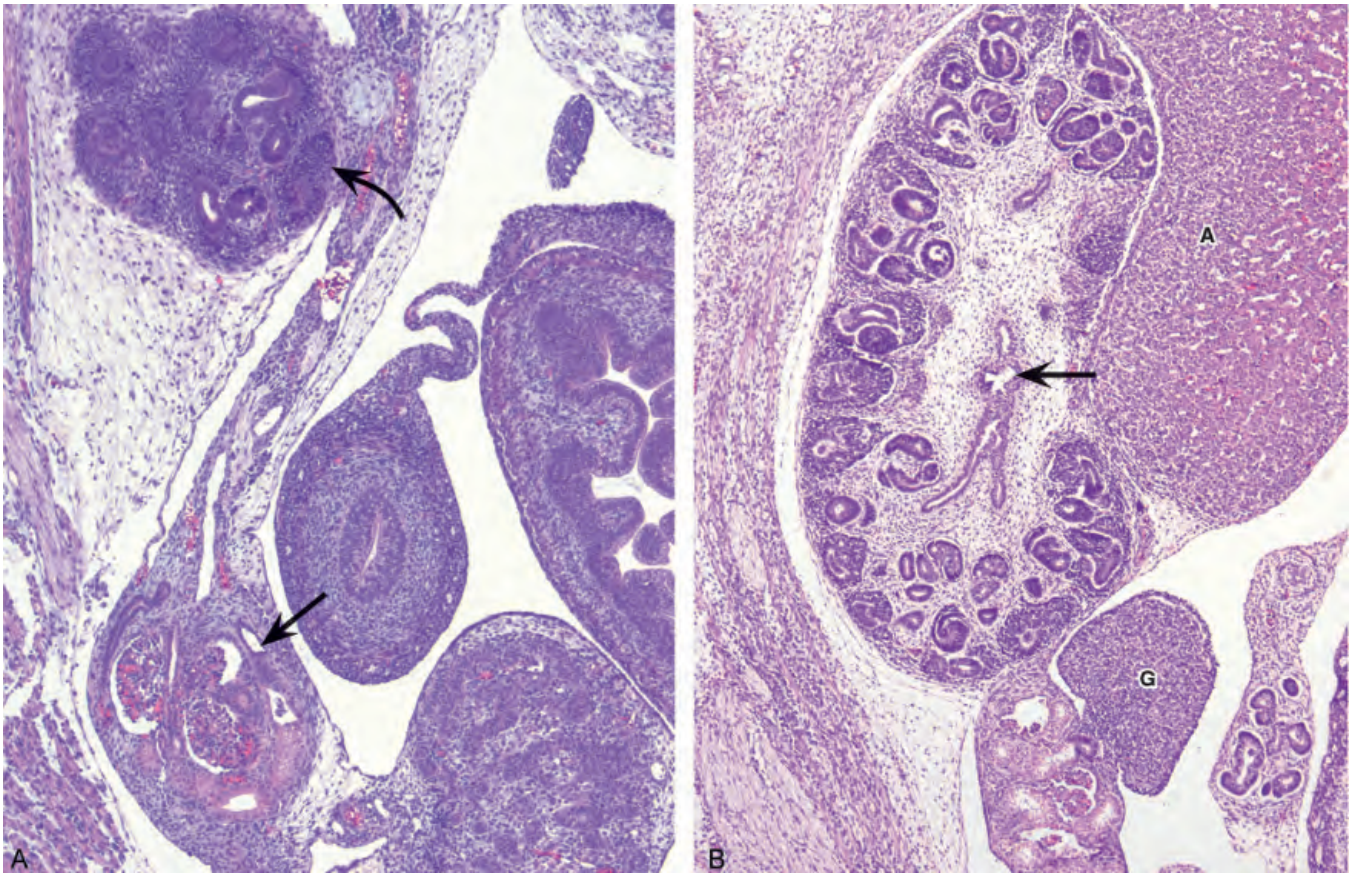


Fig. 1.6 (A) An embryo of 7 weeks of gestation showing initial induction of the metanephric kidney (*curved arrow*) and glomeruli of the mesonephric kidney (*arrow*). (B) Embryo 12 weeks of gestation showing a metanephric kidney with a rudimentary collecting system (*arrow*) and active nephrogenesis. The adrenal gland (*A*), gonad (*G*), and mesonephric kidney are also visible.

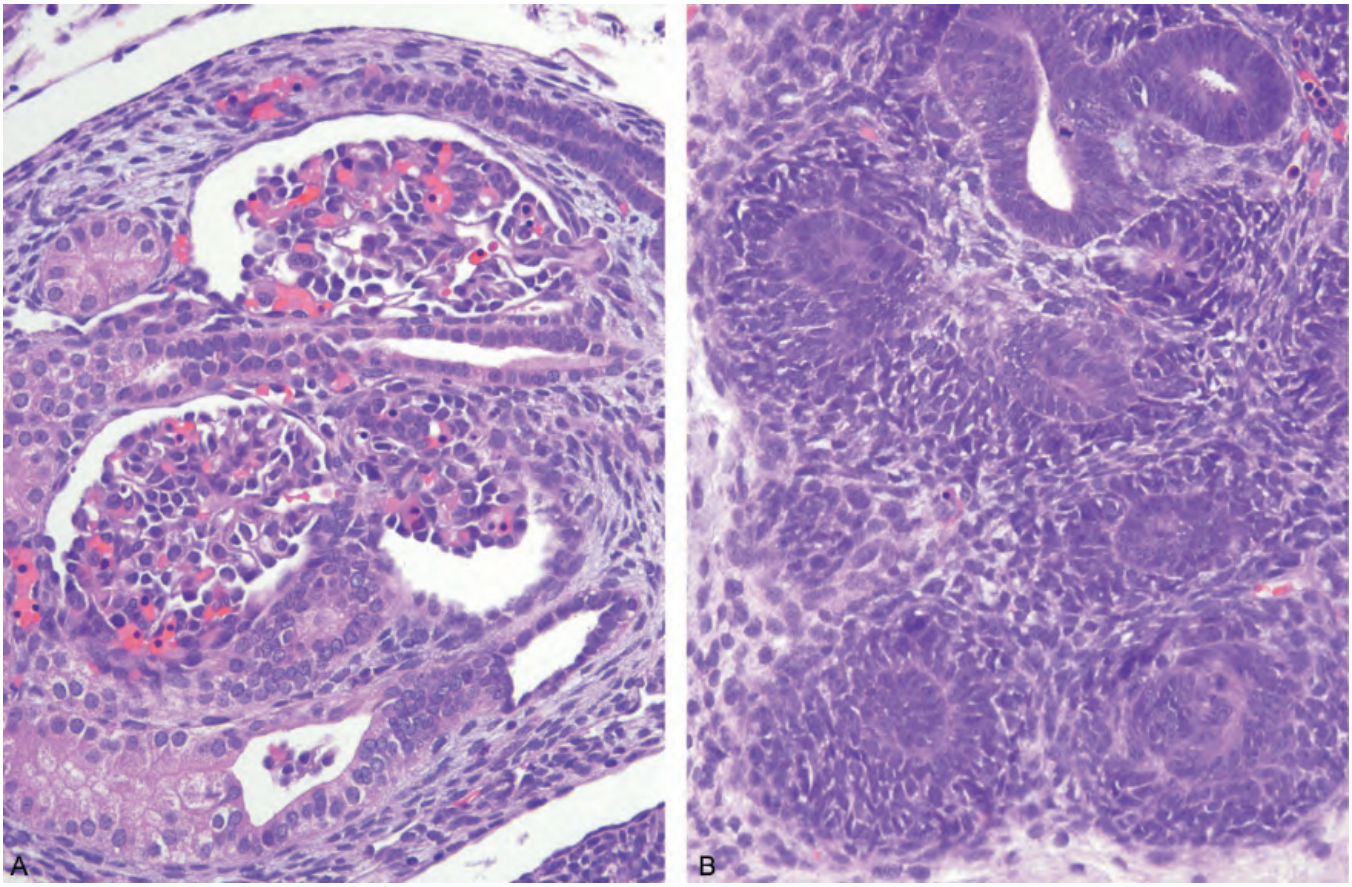


Fig. 1.7 (A) A portion of the mesonephric kidney (from Fig. 1.6A) showing well-developed glomeruli and tubules. (B) Metanephric kidney (from Fig. 1.6A) beginning to form and showing condensations of cells destined to form a nephron.

reciprocal inductive process results in dichotomous ureteric bud branching and nephron induction that eventually culminate in the adult metanephric kidney. The metanephros is therefore a product of two embryonic derivatives; the nephrons are of blastemal origin, whereas the ureter, pelvis, calyces, and cortical and medullary collecting ducts are derived from the ureteric bud.

On contact with metanephric blastema the ureteric bud undergoes a rapid sequence of dichotomous branching and fusion, forming the renal collecting system by the 14th week (Figs. 1.8 and 1.9). The initial two branches form the renal pelvis, the third to sixth branches form the major and minor calyces, and the sixth to eleventh branches form the papillary ducts (Fig. 1.9). Because ureteric bud branching is more rapid in the upper and lower poles, the calyces and papillae in those regions are more numerous.

While the collecting system is forming, nephron induction has already begun (Figs. 1.6B, 1.7B, 1.8, 1.10, and 1.11). The kidneys have moved into the flanks because of a combination of migration out of the pelvis and rapid caudal growth of the embryo (Fig. 1.12). The kidney also has rotated from its original position with the pelvis anterior, to its final position with the pelvis medial.[20] By week 13 or 14, the minor calyces and renal pyramids are well formed and

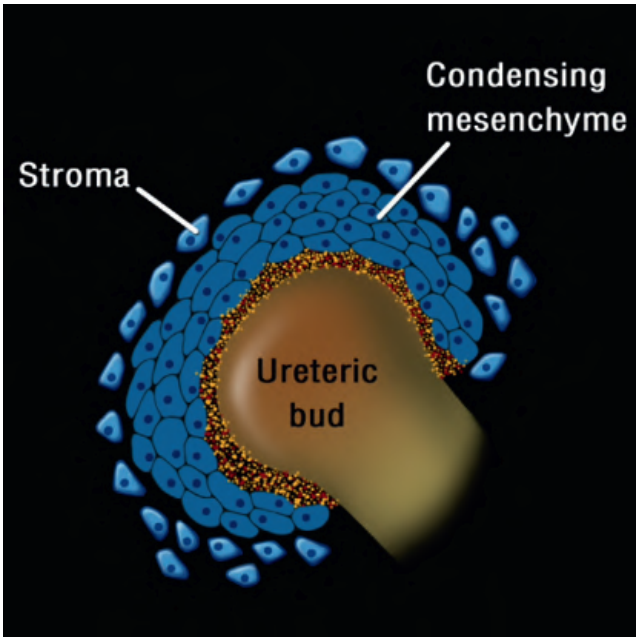


Fig. 1.8 Invasion of the ureteric bud into the mesenchyme results in condensation of the mesenchyme around the ureteric bud tip. (From Jain S. "Normal kidney development." In "Diagnostic pathology: kidney diseases" by Colvin RB and Chang A, pages 36–45. Philadelphia: Elsevier, 2016; with permission.)

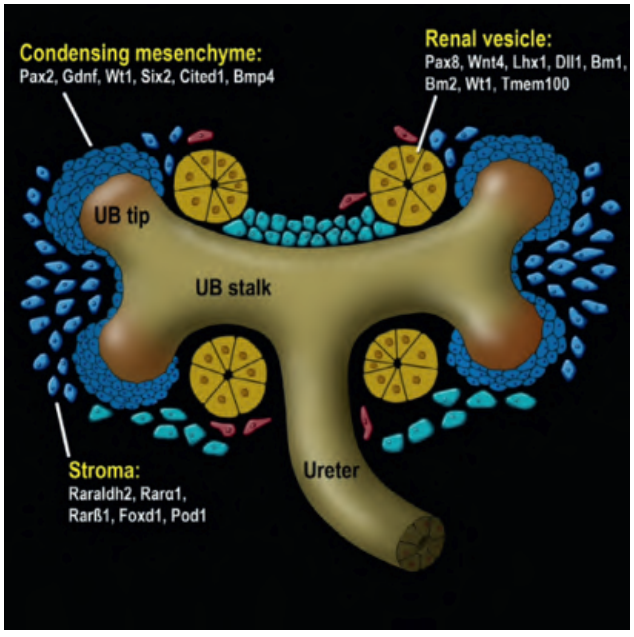


Fig. 1.10 Reciprocal interactions between the ureteric bud, condensing mesenchyme, and stroma involve cross talk between cells with involvement of many genes and their products, some of which are highlighted in this figure. (From Jain S. "Normal kidney development." In "Diagnostic pathology: kidney diseases" by Colvin RB and Chang A, pages 36–45. Philadelphia: Elsevier, 2016; with permission.)

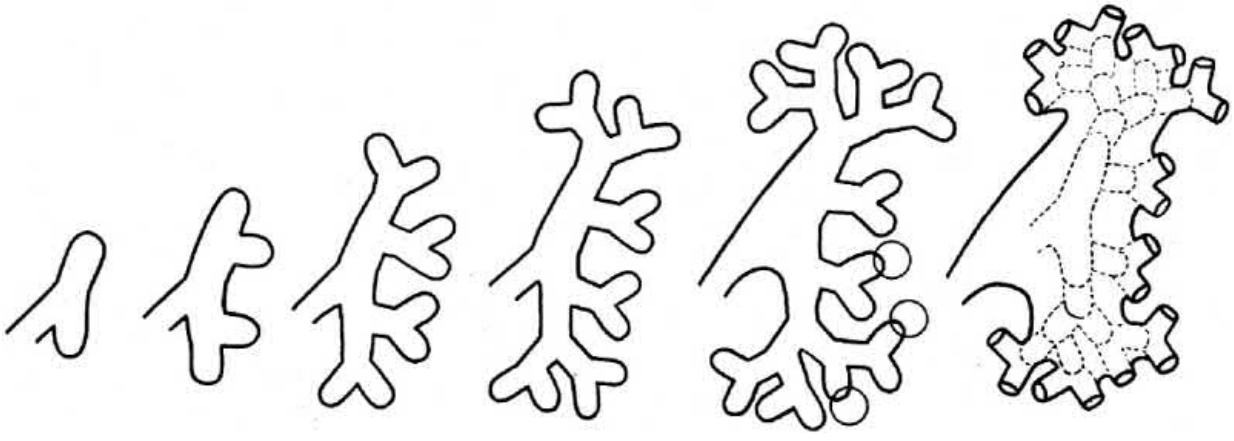


Fig. 1.9 Development of the renal pelvis. Diagram showing branches of the ureteral bud. *Circles* indicate possible locations of minor calyces at level of third-, fourth-, or fifth-generation branches. The figure at the right indicates ureteral bud branches that may dilate to form the renal pelvis. (From Osathanondth V, Potter EL. Development of the human kidney as shown by microdissection III. Formation and interrelationship of collecting tubules and nephrons. Arch Pathol 1963;76:61. Copyright © 1963. American Medical Association. All rights reserved.)

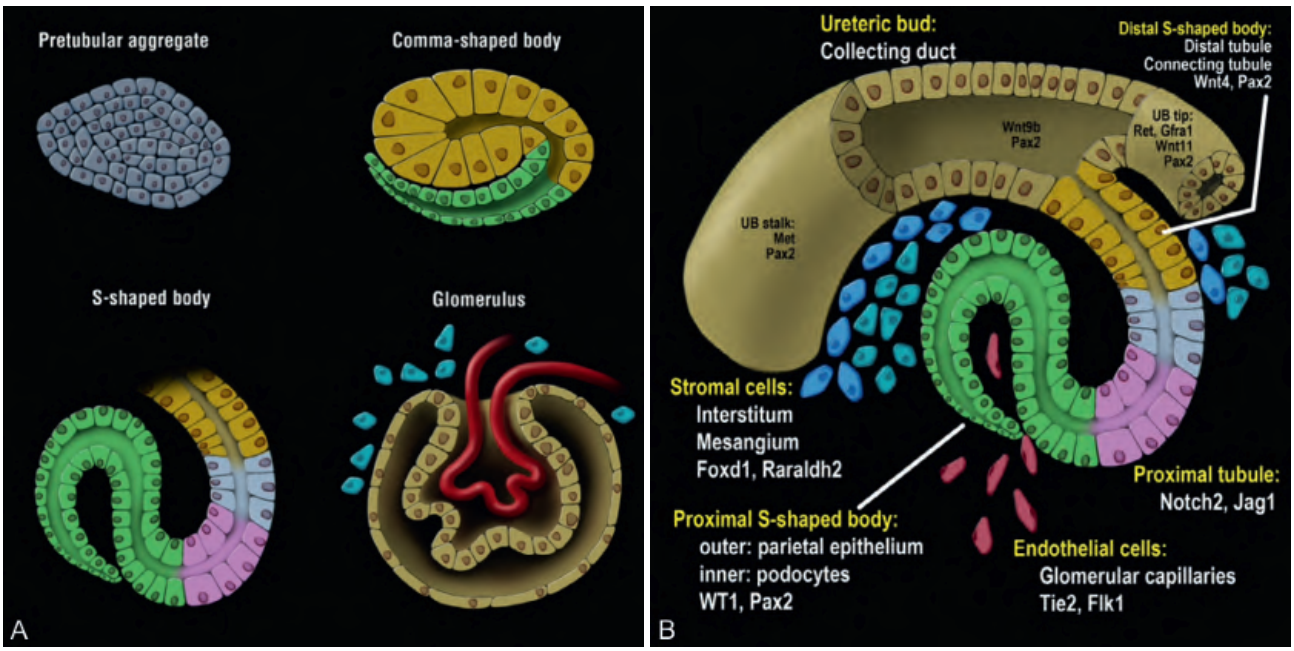


Fig. 1.11 (A) Schematic showing how the pretubular aggregate differentiates to form successively the comma shaped body and S-shaped body. The proximal portion becomes the tubules, and the distal portion forms the glomerular epithelial cells. (B) Endothelial cells invade the cleft of the S-shaped body and form the glomerular tuft. Some of the involved genes are also shown. (From Jain S. "Normal kidney development." In "Diagnostic pathology: kidney diseases" by Colvin RB and Chang A, pages 36–45. Philadelphia: Elsevier, 2016; with permission.)

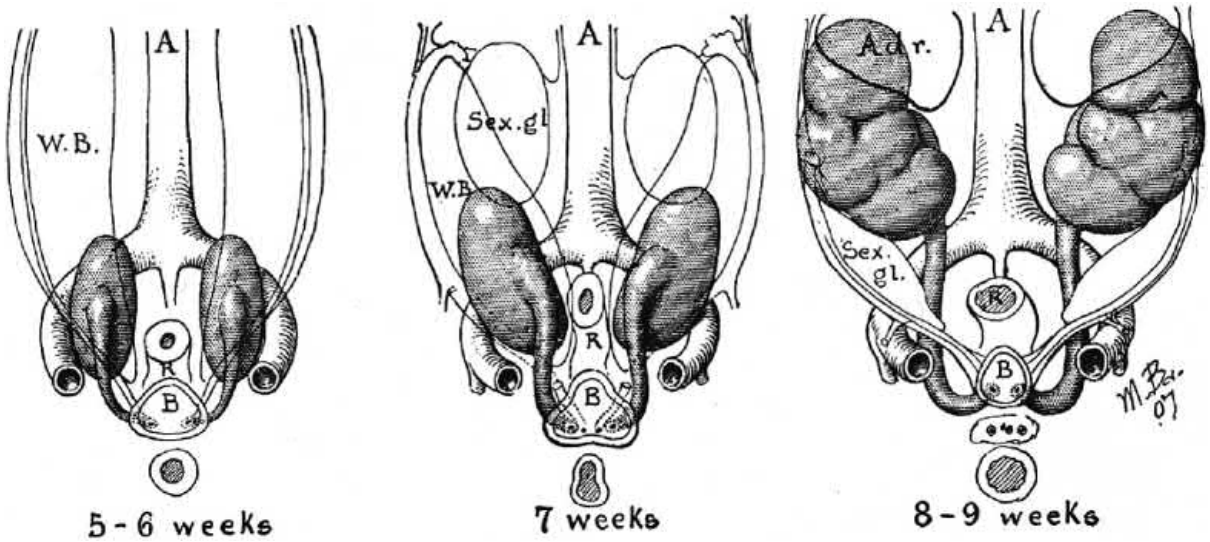


Fig. 1.12 A 1907 diagram by Max Brödel showing the ascent and medial rotation of the kidney. (From Kelly HA, Burnam CF. Diseases of kidneys, ureters and bladder. New York: Appleton, Century Crofts, 1914; with permission.)

the lobar architecture can be appreciated grossly (Figs. 1.13 through 1.15). At this time, the cortex contains several generations of nephrons, and the lateral portions of adjacent lobes begin to merge to form the columns of Bertin.

By weeks 20 to 22 the renal lobes are well formed, and the kidney is a miniature of the adult kidney (Fig. 1.15). The ureteric bud has ceased branching, but the branches continue to lengthen. As they lengthen they induce arcades of four to seven nephrons, which are connected to the collecting duct by a connecting tubule (Fig. 1.16). Additional groups of three to seven nephrons then form, each attached directly to a collecting duct without a connecting tubule. Therefore each cortical collecting duct will have 10 to 14 generations of nephrons attached, with the most recently formed and least mature nephrons located beneath the renal capsule.

Nephron Differentiation

The formation of individual nephrons begins as early as 7 weeks of gestation and results in a limited degree of "renal function" by

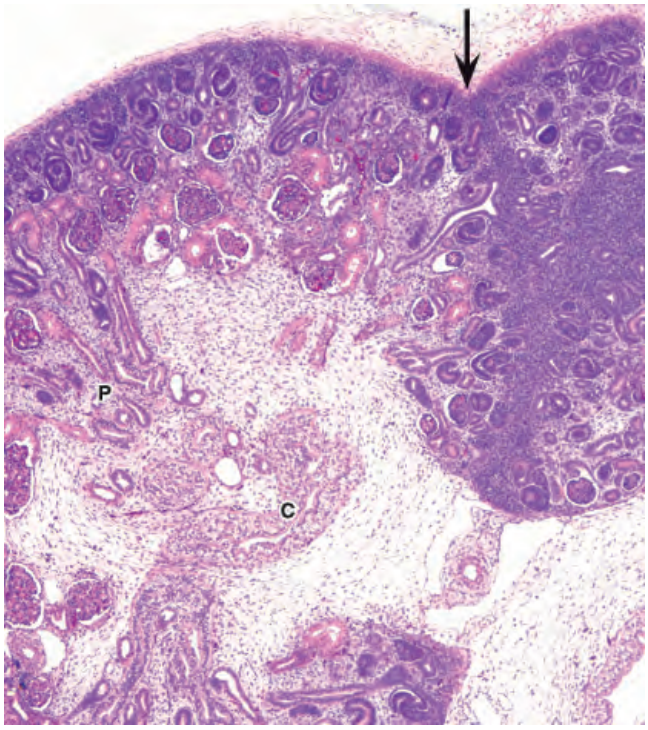


Fig. 1.13 Kidney from a 13-week fetus (compare with Fig. 1.14) showing a renal lobe with a pyramid (*P*) and the collecting system (*C*). Fusion of adjacent lobes forms columns of Bertin (*arrow*).

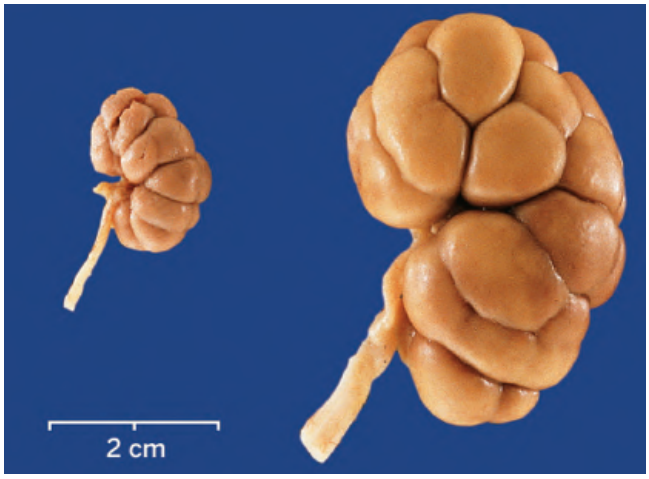


Fig. 1.15 A 22-week fetal kidney (*left*) and a 40-week term kidney (*right*) showing distinct fetal lobes.

9 weeks. In the subcapsular nephrogenic zone of any immature kidney (Fig. 1.17) the sequence of nephron induction can be observed in its various stages of completion. The historic wax models and illustrations made by Huber (Fig. 1.18), the drawing by Brödel (Figs. 1.3 and 1.14), and the illustrations by Dressler and Jain (Figs. 1.5, 1.8, 1.10, and 1.11) provide a three-dimensional perspective useful in understanding the cellular events during renal development as demonstrated in Fig. 1.17.[26,28]

An individual nephron begins to form when the metanephric blastema aggregates adjacent to the ureteric bud to form a hollow vesicle (Fig. 1.10). The molecular basis for this event is complex and involves the coordinated induction of numerous genes that encode for growth factors, adhesion molecules, matrix components, and other regulatory proteins (Table 1.1 and Figs. 1.10 and 1.11). The cells within the vesicle grow differentially, first forming a comma-shaped aggregate of cells that then elongate and eventually develop two indentations creating an S-shaped structure (Fig. 1.11). The distal portions of the S-shaped body (segments attached to the ureteric bud) are destined to become the proximal and distal tubules (Fig. 1.11). They form tubular structures and establish communication with the collecting duct. The proximal part of the S-shaped body (segment away from the

Fig. 1.14 Microdissected 13-week kidney showing the collecting system, renal pyramids, and several generations of glomeruli. Most of the tubules have been removed. (From Osathanondth V, Potter EL. Development of the human kidney as shown by microdissection III. Formation and interrelationship of collecting tubules and nephrons. Arch Pathol 1963;76:61. Copyright © 1963. American Medical Association. All rights reserved.)

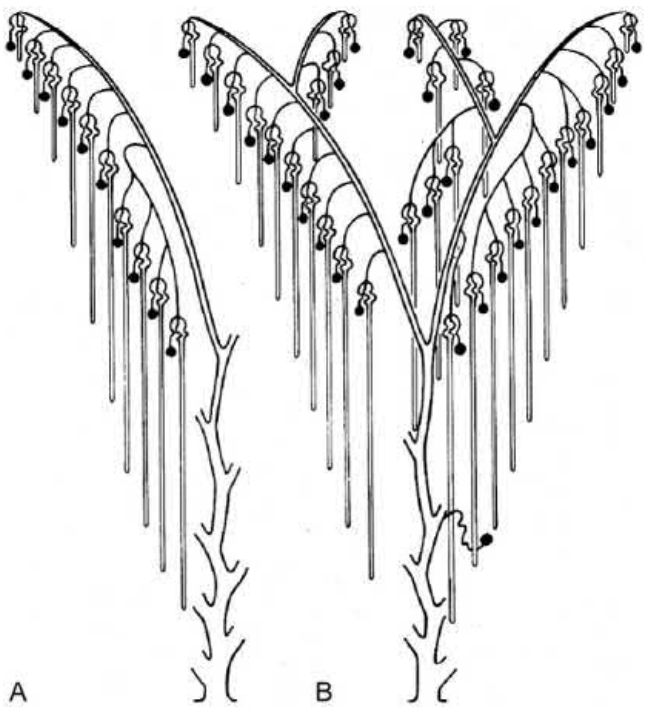


Fig. 1.16 Kidney showing arrangement of nephrons at birth. (A) Usual pattern. (B) Possible variations. (From Osathanondth V, Potter EL. Development of the human kidney as shown by microdissection III. Formation and interrelationship of collecting tubules and nephrons. Arch Pathol 1963; 76:61. Copyright © 1963. American Medical Association. All rights reserved.)

ureteric bud) gradually broadens and separates into two cell layers: the outer layer becomes the parietal epithelium of the Bowman capsule, whereas the inner layer becomes the visceral epithelium (podocytes). Endothelial cells migrate into the indentation in the proximal part and eventually form a podocyte-invested and vascularized glomerular tuft within Bowman capsule.

Cells of the upper layer continue to proliferate to form a connecting duct and the distal convoluted tubule, whereas cells of the middle limb produce the proximal convoluted tubule and the limb of Henle. Finally, the limb of Henle grows down along the collecting duct to form the medullary rays. Nephrogenesis is usually complete by 32 to 36 weeks of gestation. Maturation occurs beyond this period and continues until adulthood, with resulting renal enlargement that reflects tubular elongation and cellular enlargement of the tubular portions of the nephron. There appears to be some correlation (Table 1.2) between fetal gestational age and layers/rows of mature glomeruli, which can be useful in forensic assessment or to correlate with development in other organs.

Gross Anatomy

The kidneys are paired retroperitoneal organs that normally extend from the 12th thoracic vertebra to the 3rd lumbar vertebra. The upper poles are tilted slightly toward the midline, and the right kidney is slightly lower and shorter than the left kidney. The average adult kidney is 11 to 12 cm long, 5 to 7 cm wide, and 2.5 to 3 cm thick, and it weighs 125 to 170 g in men and 115 to 155 g in women.[20,27,31,33,34] The combined mass of the kidneys correlates with body surface area, whereas age, sex, and race have relatively less influence.[35] Its volume can increase or decrease by 15% to 40% with major fluctuations in blood pressure (BP), hydration, or interstitial expansion by edema.

The posterior surfaces are flatter than the anterior, and the medial surface is concave with a 3-cm slitlike space called the *hilum*. The hilum is the vestibule through which the collecting system, nerves, arteries, veins, and lymphatics pass. In the adult, these structures are invested by fat within the renal sinus and are usually arranged from anterior to posterior as artery and vein and ureter.

The subcapsular surface of the renal cortex may be smooth and featureless, or may show grooves corresponding to the individual renal lobes (Fig. 1.19). The persistence of distinct fetal lobes is common and is a normal anatomic variant. In some kidneys, three zones are created by two shallow superficial grooves that radiate from the hilum to the lateral border (Fig. 1.20). The three regions define the upper pole, middle zone, and lower pole, and usually reflect regions drained by the three lobar veins.

The normal adult kidney has a minimum of 10 to 14 lobes, each composed of a central conical medullary pyramid surrounded by a

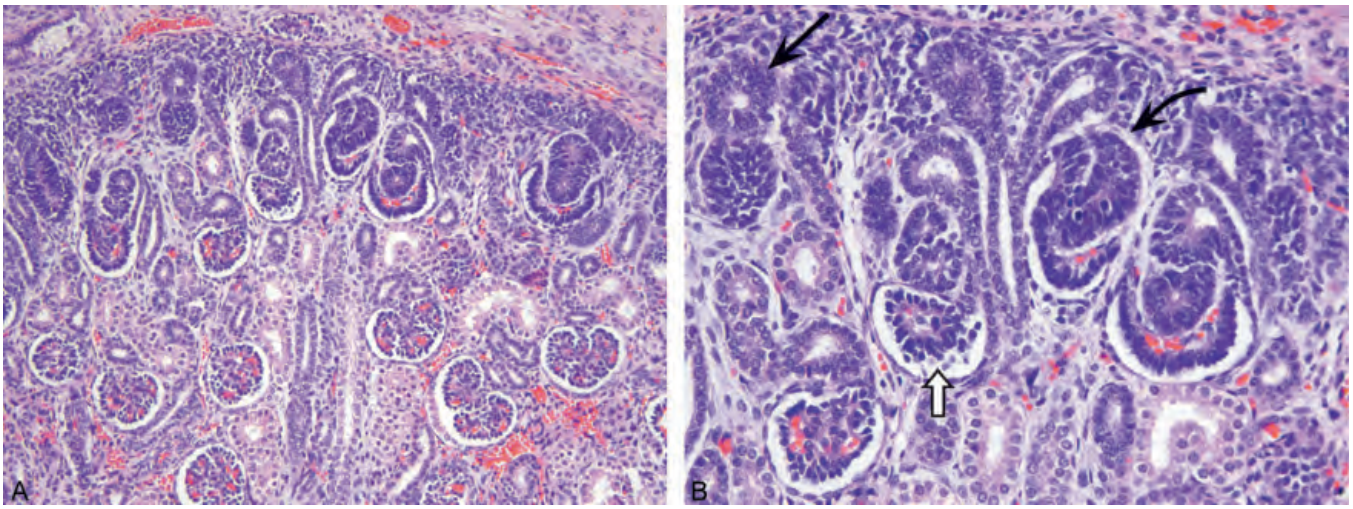


Fig. 1.17 (A) Nephrogenic zone of a 14-week kidney. (B) Notice the ampullary bud and hollow vesicles (*arrow*), early S-phase (*curved arrow*), primitive glomerular tuft (*open arrow*), and increasingly mature glomeruli.

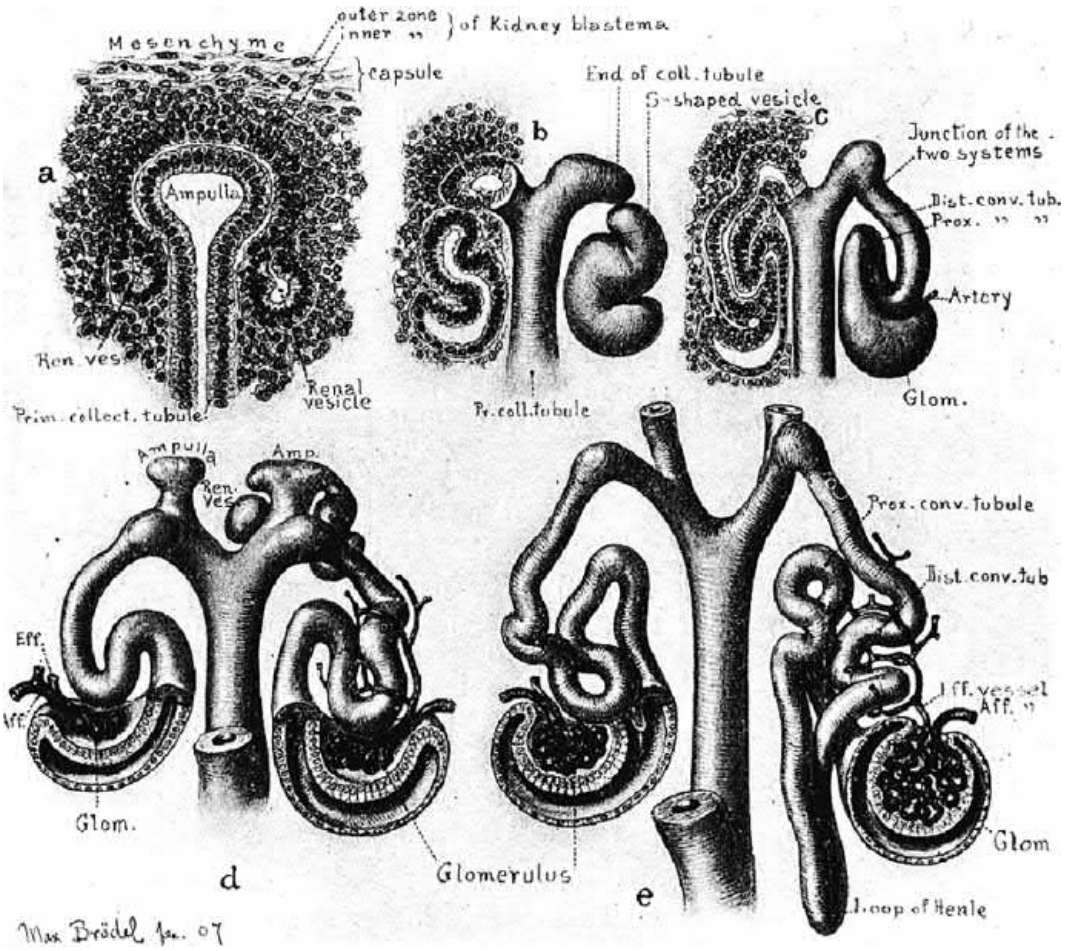


Fig. 1.18 1907 illustration by Max Brödel that shows the sequence of nephron induction. (From Kelly HA, Burnam CF. Diseases of kidneys, ureters and bladder. New York: Appleton, Century Crofts, 1914; with permission.)

TABLE 1.1 Expression of Selected Genes and Proteins Involved in the Development of the Kidneys

Name	Role in Development	Effect of Mutations	Expression in Normal Kidney	Comment
PAX2 (paired box 2)	Acts as a survival signal in ureteric bud/collecting duct lineage	Renal agenesis in null mutant; large gene deletions implicated in 3% of cases of renal-coloboma syndrome[582]	Intermediate mesoderm, nephric duct, mesonephros, ureteric bud, induced metanephric mesenchyme	Nuclear stain; can be used to confirm renal, Müllerian, or Wolffian duct origin of cells
N-myc (avian myelocytomatosis viral oncogene homologue)	Differentiation and organogenesis	Hypoplastic mesonephros, decreased ureteric bud tips and nephrons, renal hypoplasia	Induced metanephric mesenchyme	Amplification (>10 copies) associated with poor prognosis in neuroblastoma
HNF1B (hepatocyte nuclear factor 1β)	Maintains differentiated state of renal epithelia	Null mutants do not survive; renal cysts, single kidneys, renal hypoplasia, electrolyte abnormalities	All tubular epithelia and collecting ducts	Renal tubules become cystic if HNF1B is mutated
WT1 (Wilms tumor 1)	Transcription factor	Renal agenesis in null mutant; proteinuria in heterozygous mice; disturbed podocyte differentiation, glomerulosclerosis	Intermediate mesoderm, mesonephros, uninduced and induced metanephric mesenchyme, comma- and S-shaped bodies; restricted to podocytes in adult kidney	Marker in tumors

Name	Role in Development	Effect of Mutations	Expression in Normal Kidney	Comment
FOXD1 (forkhead box D1)	Expressed in interstitial progenitor cells in the cortex and medulla	Fused kidneys	FOXD1 + progenitors form stroma that becomes vascular smooth muscle, juxtaglomerular cells, mesangial cells, pericytes, and resident fibroblasts	Marker of interstitial progenitor cells that form renal stroma
RARα/RARβ2 (retinoic acid receptor)	Ureteric bud branching, stroma signaling	Kidney and ureter malformations	RARα: ureteric bud, metanephric mesenchyme, stroma RARβ: stroma only	Marker in tumors
GDNF (glial cell line–derived neurotrophic factor)	Growth factor	Ureteric bud fails to form or has abnormal branching; renal hypoplasia or agenesis	Intermediate mesoderm, mesonephros, induced metanephric mesenchyme, pretubular aggregate	
Angiotensinogen	Renin substrate	Hypoplastic papillae, hydronephrosis, thickened blood vessels, hypotension	Ureteric bud, stroma, glomeruli, proximal tubules	
Angiotensin receptor types 1a and 1b	Angiotensin receptor	Hypoplastic papillae, hydronephrosis, thickened blood vessels, hypotension	Ureteric bud, stroma, proximal tubules	
Angiotensin receptor type 2	Angiotensin receptor	Duplicated collecting system, hydronephrotic upper pole	Stroma adjacent to ureteric bud stalk	
Fibroblast growth factor	Growth factor	Increased apoptosis, truncated nephrons, renal hypoplasia	Pretubular aggregates, vesicles, tubule progenitors	
Platelet-derived growth factor (PDGF) receptor b	Growth factor (PDGF) receptor	Dilated glomerular capillaries with no mesangial cells	Glomerular mesangial cells	
Vascular endothelial growth factor	Growth factor	Small glomeruli, lack capillary loops, few endothelial cells	S-shaped body, podocytes, collecting ducts	
Laminin α_5	Basement membrane protein	Abnormal glomeruli with displaced endothelial and mesangial cells, and clustered podocytes	Basement membrane of ureteric bud, developing tubules, and glomeruli	
Laminin β_2	Basement membrane protein	Absence of podocyte foot processes, proteinuria	Glomerular basement membrane	Nephrotic syndrome
Laminin $\alpha_3\beta_2$	Transmembrane adhesion receptor	Dilated and fewer capillary loops; loss of podocyte foot processes, dual GBMs	Ureteric bud, collecting ducts, podocytes	
Nephrin	Transmembrane protein	Foot process effacement, absence of filtration slit diaphragm, proteinuria	Podocyte filtration slit diaphragm	Congenital nephrotic syndrome of the Finnish type
PKD1 and PKD2 (polycystin 1 and 2)	Transmembrane proteins	Metanephric cysts in null mutants; postnatal PKD in heterozygous mice	Developing nephron segments and collecting ducts	Mutated in autosomal dominant PKD
UP II and III (Uroplakin)	Transmembrane proteins	Hydronephrosis; vesicoureteric reflux (UPII); ureteric obstruction (UPIII)	Superficial umbrella cells of urothelium	

GBM, Glomerular basement membrane; *PKD*, polycystic kidney disease.

cap of cortex (Fig. 1.21). Often there are six lobes in the upper pole and four lobes each in the middle zone and lower pole. However, substantial variability occurs both in the number of lobes in the adult kidney and in their visibility when the renal capsule is removed.

The renal parenchyma consists of the cortex and the medulla, which are grossly quite distinct (Fig. 1.21). The renal cortex is the nephron-containing parenchyma. It forms a 1.0-cm layer between the renal capsule and medulla (also known as the renal pyramids) and extends down between the renal pyramids forming the columns of Bertin. The midplane of a column of Bertin is the line of fusion of two renal lobes. The renal medulla is divided into an outer medulla and the inner medulla or papilla (Fig. 1.21). The outer medulla is further divided into an outer stripe and an inner stripe. Each segment of the renal medulla is defined by its unique tubular components, as discussed later. The outer medulla receives input from nephrons in the overlying cortex and nephrons in the adjacent half of a column of Bertin. The papilla protrudes into a minor calyx. Its tip has 20 to 70 openings of the papillary collecting ducts (Bellini ducts).

The arterial supply to the kidney follows a general overall blueprint, and knowledge of its details is useful when evaluating lesions in a kidney affected by vascular abnormalities.[36-38] In 1901, Brödel first appreciated the distinctive renovascular segmentation of the kidney.[38] The nomenclature used here was established by Graves in 1954.[37]

The main renal artery arises from the aorta and divides into an anterior and a posterior division, and five segmental arteries are usually derived from these two divisions (Figs. 1.20 and 1.22). The anterior division supplies most of the kidney and often divides into four segmental arteries: the apical, upper, middle, and lower segmental branches. The apical and lower segmental arteries supply

TABLE 1.2 Correlation of Fetal Gestational Age and Glomerular Development

Gestational Age (weeks)	Rows of Glomeruli in Cortex From Medulla to Capsule	Number of Mature Glomerular Layers
16-23	3	–
24	3-5	4.3 ± 0.8
25	4-6	4.6 ± 0.7
26	5-7	–
27	6-8	6.1 ± 1.1
28	7-9	6.0 ± 1.2
29	8-10	6.3 ± 1.3
30	9-11	–
31	10-12	7.1 ± 0.9
32	11-13	–
33	12-13	7.7 ± 0.8
34	12-14	–
35-42	12-14	7.6 ± 0.4 to 8.6 ± 1.3
Newborn to adult	12-14	–
	Cortex between columns of Bertin	Radial counts; excludes columns of Bertin

From Jain S. Normal kidney development. In: Diagnostic pathology: kidney diseases. Philadelphia: Elsevier, 2016 (with permission).

Fig. 1.19 Two adult kidneys with capsules removed showing subtle fetal lobation (*left*) and prominent fetal lobation (*right*).

the anterior and posterior aspects of the upper and lower poles, respectively (Fig. 1.22). In 20% to 30% of kidneys, one or both arteries will arise separately from the aorta to form supernumerary arteries (also known as aberrant, accessory, or polar arteries). The posterior division becomes the posterior segmental artery. It passes behind the pelvis and supplies the middle two-thirds of the posterior surface. The five segmental arteries and all their branches are end arteries with no collateral blood flow. Thus occlusion of a segmental artery or any of its subsequent branches results in infarction of the zone of parenchyma it supplies.[36]

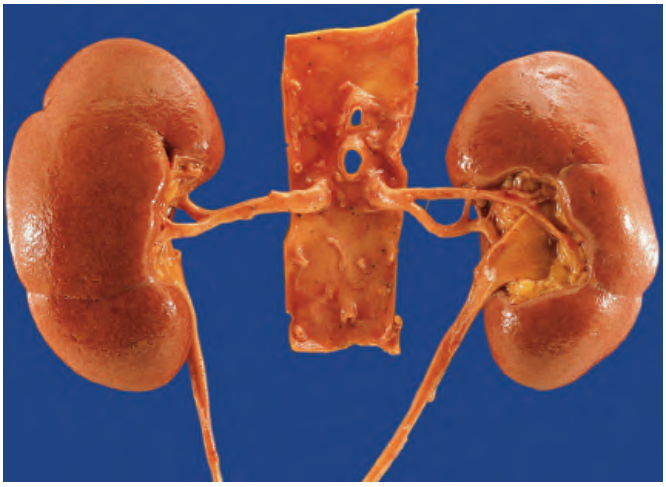


Fig. 1.20 Kidneys showing two grooves defining the renal poles. In each kidney an anterior and posterior division of the renal artery is visible. The left kidney (*right side*) is incompletely rotated.

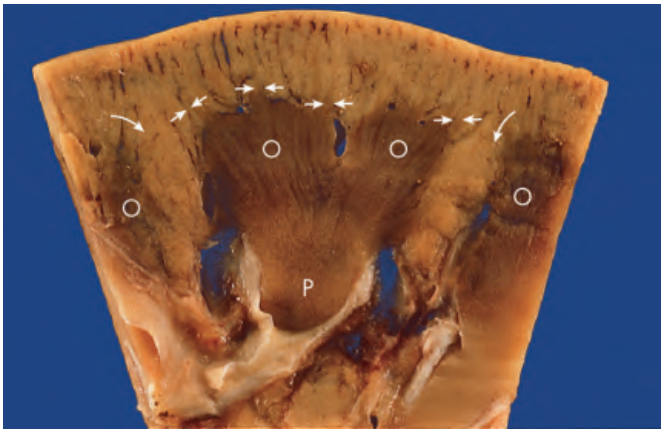


Fig. 1.21 This renal lobe shows the cortical medullary rays. The columns of Bertin invest the outer medulla (*O*), whereas the papilla (*P*) or inner medulla is nestled within a minor calyx.

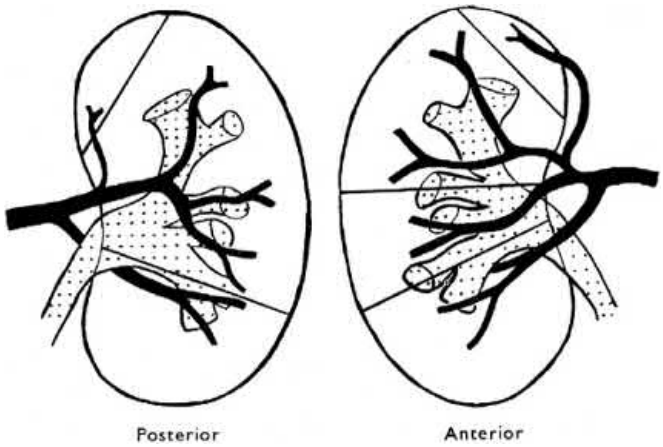


Fig. 1.22 A diagram of the most common arterial pattern of the kidney showing the main renal artery, anterior and posterior divisions, and the segmental, interlobar, and arcuate arteries. (From Graves FT. The anatomy of the intrarenal arteries and its application to segmental resection of the kidney. Br J Surg 1954;42:133; with permission.)

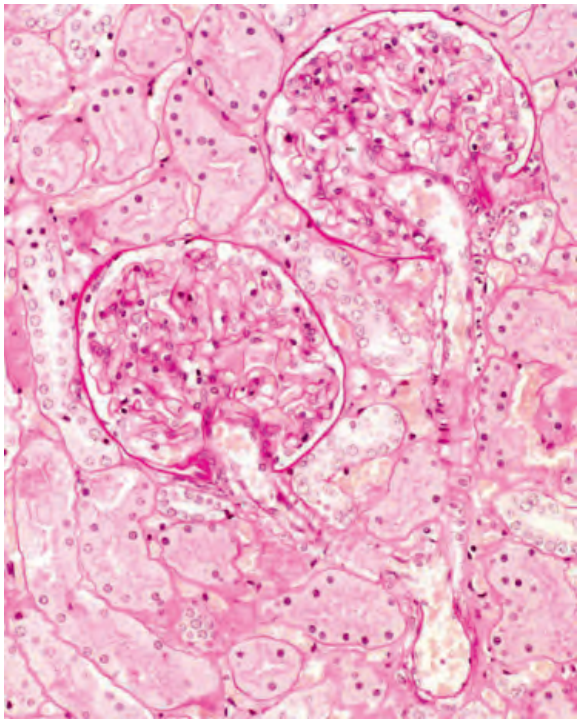


Fig. 1.23 The interlobular artery supplies arterioles to glomeruli (periodic acid–Schiff stain).

From segmental arteries, the interlobar arteries, arcuate arteries, interlobular arteries, and arterioles are sequentially derived. A segmental artery branches within the renal sinus and creates several interlobar arteries. An interlobar artery enters the parenchyma in a column of Bertin between two renal pyramids (i.e., at the junction of two lobes) and forms a splay of six to eight arcuate arteries. The arcuate arteries course along the corticomedullary junction and terminate at the midpoint of a renal lobe. At perpendicular or slightly oblique angles, the interlobular arteries arise from an arcuate artery and may branch as they pass through the cortex toward the renal capsule. The interlobular arteries course between medullary rays and are encircled by tiers of five to six glomeruli, which they supply with afferent arterioles (Fig. 1.23). The glomerular efferent arteriole forms a portal system of capillaries, which supply the adjacent tubules that arise from more than one glomerulus (Fig. 1.2B).

The renal medulla has a dual blood supply.[39,40] Its principal blood supply arises from the efferent arterioles of the juxtamedullary glomeruli, which course directly into the medulla to form the vasa recta (Fig. 1.24). In addition, as an interlobar artery courses along a minor calyx it gives rise to several spiral arteries, which supply capillaries to the papillary tip. These capillaries anastomose freely with capillaries from the opposite side and form a plexus around the ducts of Bellini.

The interlobular, arcuate, and interlobar veins parallel the arteries. Unlike the arcuate arteries, the arcuate veins have abundant anastomoses. They combine to form three large segmental veins that drain the three poles of the kidney.[31,40,41] The veins lie anterior to the pelvis and unite to form the main renal vein.

The lymphatic drainage is a dual system.[31,41] The major lymphatic drainage follows the blood vessels from parenchyma to the renal sinus, to the hilum, and terminates in lateral aortocaval lymph nodes. In addition, minor capsular lymphatic drainage from the superficial cortex courses into the capsule and then around to the hilum to join the major lymphatic flow.

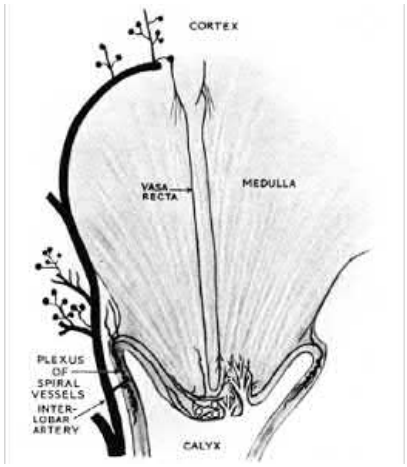


Fig. 1.24 Diagram of the dual blood supply to the papillae. (From Baker SB. The blood supply to the renal papillae. Br J Urol 1959;31:57; with permission.)

Microscopic Anatomy

The cortex is organized into two regions: the cortical labyrinth and the medullary rays (Fig. 1.25). The labyrinth contains glomeruli, proximal and distal convoluted tubules, connecting tubules, and the initial portion of the collecting ducts, as well as interlobular vessels, arterioles, capillaries, and lymphatics. The principal components of the labyrinth are the proximal tubules. In the normal cortex, the tubules are closely packed with closely apposed basement membranes (Figs. 1.23 and 1.25). The interstitial space is scant. It contains the peritubular capillary plexus and inconspicuous numbers of interstitial fibroblasts and reticulum cells. A medullary ray consists of collecting ducts and the proximal and distal straight tubules that course down into and back up from the medulla. The nephrons that empty into the collecting ducts of a single medullary ray comprise a renal lobule, the functional unit of the kidney.

The medulla is divided into an outer medulla, composed of an outer stripe and an inner stripe, and the inner medulla or papilla. Each zone contains specific tubular segments arranged in an

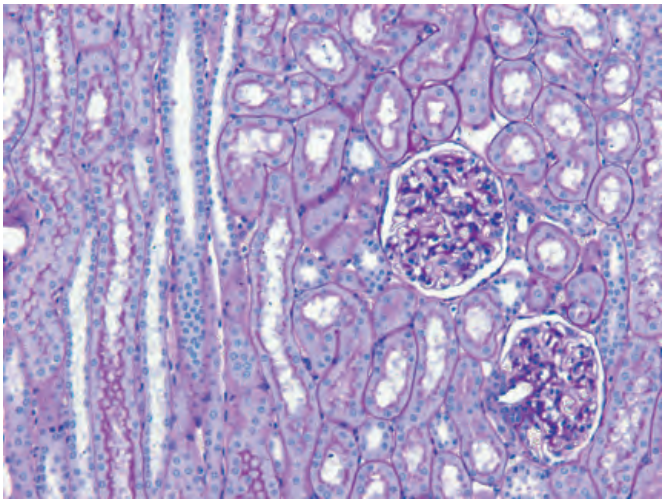


Fig. 1.25 Renal cortex sectioned perpendicular to the renal capsule that shows a medullary ray (*left side*) and the cortical labyrinth with two glomeruli (*right side*) (periodic acid–Schiff stain).

elaborate architecture to create the countercurrent concentration system. The outer stripe contains the straight portions of the proximal tubule, thick ascending limb of loop of Henle and collecting ducts. The inner stripe contains the thin descending and thick ascending limbs of loops of Henle and collecting ducts. The inner medulla contains the thin descending and ascending limbs of loops of Henle and collecting ducts of Bellini. For further details of the microscopic anatomy of the medulla, or for the ultrastructural features of all nephron components, several excellent resources are available.[27,31,41]

Parenchymal Maldevelopment and Cystic Kidney Diseases

"The more complicated an organ in its development, the more subject it is to maldevelopment, and in this respect the kidney outranks most other organs."[33]

—Edith Potter

Developmental anomalies and cystic kidney diseases occur in approximately 10% of the population.[27,42-45] They encompass a vast number of complex entities that may be limited to the kidney or part of a multiorgan malformation syndrome. These diseases may be sporadic, hereditary and syndromic, or acquired, and they include several that are associated with a neoplastic diathesis. Enormous progress has been made in unraveling the pathogenesis of many entities with delineation of their genetic and molecular basis. This knowledge has minimized the validity of the simplistic anatomic contribution of urinary tract obstruction popular for so many years by placing it within a larger paradigm of sequential genetic and molecular misadventures that culminate in the malformed kidney and urinary tract.[27,46-56]

These diseases can be separated into two large categories based on pathogenesis. A heterogeneous group of diseases results from mutation of one or more key master genes crucial for proper development of the kidneys and lower urinary tract. Collectively, these are referred to as congenital anomalies of the kidneys and urinary tract (CAKUT). These lesions may be sporadic or hereditary and syndromic. They are common and very important because they account for up to 50% of cases of renal failure in children (Table 1.3).

A second category encompasses a "family" of cystic kidney diseases, the ciliopathies, which result from mutation of genes that

TABLE 1.3 Classification of Cystic Kidney Diseases and Congenital Anomalies of the Kidney and Urinary Tract

I. Polycystic kidney diseases

A. Autosomal recessive polycystic kidney disease
  Classic in neonates and infants
  Childhood with hepatic fibrosis
B. Autosomal dominant polycystic kidney disease
  Classic adult form
  Early-onset childhood form
C. Glomerulocystic kidney
  Primary GCKD
    Sporadic GCKD
    Familial GCKD
    Hereditary GCKD associated with *UROM* or *HNF1B* mutations
  Secondary glomerular diseases in which glomerular may be present
    Associated with ADPKD/ARPKD/TSC
     Syndromic nonhereditary glomerulocystic kidney
     Ischemic glomerular atrophy
     Renal dysplasia
D. Acquired cystic kidney disease

II. Congenital anomalies of the kidney and urinary tract (CAKUT)

A. Renal agenesis and dysplasia
  Agenesis
    Sporadic: unilateral or bilateral
    Syndromic
    Nonsyndromic multiple malformation syndromes
  Renal dysplasias
    Sporadic: unilateral or bilateral
    Syndromic
    Nonsyndromic multiple malformation syndromes
  Hereditary adysplasia
B. Renal hypoplasias
  Simple hypoplasia: unilateral or bilateral
  Oligomeganephronic hypoplasia
  Cortical hypoplasia (reduced nephron generations)
  Reduced nephron numbers (premature and low birth weight risk for hypertension)
C. Abnormalities in form, position, and number
  Rotation anomaly
  Renal ectopias
  Renal fusions
  Supernumerary kidney
  In combination with A, B, or D
D. Ureteral and urethral abnormalities
  Ureteropelvic junction obstruction
  Ureteral duplication/bifid ureter
  Vesicoureteral reflux
  Primary megaureter
  Ureteral ectopia
  Posterior urethral valves
  In combination with A, B, or C

III. Tubulointerstitial syndromes that may be cystic

A. Nephronophthisis
B. Autosomal dominant tubulointerstitial disease
  UROM kidney disease
  REN kidney disease
  HNF1B kidney disease
  MUC1 kidney disease
C. Renal tubular dysgenesis
D. Bardet-Biedel syndromes

IV. Cystic neoplasms and neoplastic cysts

A. Mixed epithelial and stromal tumor family (includes cystic nephroma)
B. Cystic partially differentiated nephroblastoma
C. Multilocular cystic renal cell carcinoma of low malignant potential
D. Tubulocystic renal cell carcinoma
E. von Hippel–Lindau disease
F. Lymphangioma/lymphangiectasia

V. Miscellaneous cysts

A. Simple cortical cysts
B. Medullary sponge kidney
C. Localized cystic kidney disease

ACE, Angiotensin-converting enzyme; *ADPKD*, autosomal dominant polycystic kidney disease; *ARPKD*, autosomal recessive polycystic kidney disease; *GCKD*, glomerulocystic kidney disease; *HNF1B*, hepatocyte nuclear factor 1β; *MUC1*, mucin-1; *REN*, renin; *TSC*, tuberous sclerosis complex; *UROM*, uromodulin.

TABLE 1.4 The Ciliopathies

Autosomal dominant

Autosomal dominant polycystic kidney disease
Von Hippel–Lindau disease
Uromodulin-associated kidney diseases (medullary cystic kidney disease type II, familial juvenile hyperuremic nephropathy, glomerulocystic kidney disease)

Autosomal recessive

Autosomal recessive polycystic kidney disease
Nephronophthisis (with or without renal-retinal dysplasia, Joubert syndrome, or Senior-Loken syndrome)
Bardet-Biedl syndrome
Meckel-Gruber syndrome
Orofacial-digital syndrome
Jeune syndrome

encode for certain proteins crucial to the formation and function of the primary cilium of renal tubular cells. Most renal tubular cells have a single primary cilium, a slender organelle that originates from the basal body and extends from the apical surface of tubular cells. It is a structure long regarded as vestigial, but it is now apparent that the primary cilium has critical sensory and cell signaling functions that affect cell proliferation, polarity, and differentiation. The ciliopathies are hereditary diseases. Several have associated liver diseases that include bile duct cysts and bile duct plate malformations that may lead to congenital hepatic fibrosis.[55] The ciliopathies include one of the most common genetic diseases, autosomal dominant polycystic kidney disease (ADPKD), as well as numerous other uncommon syndromic disorders. The members of this family of diseases are listed in Table 1.4. However, this list is likely not complete because new entities are regularly added.

Finally, there are miscellaneous other cystic kidney diseases of uncertain pathogenesis. These include the common simple cortical cyst, the uncommon isolated polycystic kidney disease that resembles ADPKD, and acquired cystic kidney disease, which is of great importance because of its neoplastic diathesis.

Construction of a classification system designed to logically organize this vast compendium of developmental and cystic diseases is challenging. Many schemas have been proposed.[57,58] The ideal scheme would account for morphologic features, their clinical importance, and their pathogenesis. Although knowledge of the embryologic development of the kidney provides a tempting basis for explaining departures from the normal renal development, it must be accepted that little experimental evidence exists to defend such conjectures.

Classification of developmental anomalies and cystic kidney diseases based on their underlying genetic defects will likely gradually replace current schemes. However, even with a more thorough understanding of the genetic basis of these diseases, organizing these entities will remain difficult. For instance, CAKUT lesions may affect a single kidney–lower urinary tract unit with a completely normal contralateral kidney. Conversely, CAKUT lesions may show distinctly different types of anomalies that affect each kidney–lower urinary tract unit. Finally, the spectrum of CAKUT diseases may arise in both syndromic and nonsyndromic contexts. Similarly, although the diseases associated with mutation of ciliary proteins are all hereditary, the inheritance can be dominant or recessive. In addition, the renal diseases encountered in the ciliopathies range from cystic diseases that arise in normally formed kidneys, to cystic kidney disease resulting from metanephric maldevelopment identical to several CAKUT abnormalities, to chronic progressive tubulointerstitial diseases that may or may not form cysts. Another complicating factor is the polygenetic nature of many disorders, in which the variable presence of, or accumulation of, multiple minor genetic defects affects susceptibility and influences the nature of the malformation expressed. This conundrum of developmental misadventures prompted Edith Potter to offer the comment quoted earlier. The classification scheme offered in this chapter is more of a tabulation of entities based on a selected major anatomic feature that is the avenue through which pathologists encounter these entities (Table 1.5).

Abnormalities in Form and Position

It is useful to group abnormalities of form and position because they often occur in combination. For instance, fused kidneys are always ectopic, and most ectopic or fused kidneys also are

TABLE 1.5 Parenchymal Maldevelopment and Cystic Kidney Disease

Abnormalities in form and position

Rotation anomaly
Ectopia
Fusion

Abnormalities of mass and number

Supernumerary kidney
Renal hypoplasia
  Simple hypoplasia
  Oligomeganephronia
  Cortical hypoplasia
  Segmental hypoplasia (Ask-Upmark kidney)
Renal agenesis
  Unilateral renal agenesis
  Bilateral renal agenesis (Potter syndrome)
  Syndromic and hereditary renal agenesis

Renal dysplasia

Multicystic and aplastic dysplasia
Segmented dysplasia
Dysplasia associated with lower tract obstruction
Dysplasia associated with hereditary syndromes
Hereditary renal dysplasia and urogenital dysplasia

Polycystic kidney disease

Autosomal recessive polycystic kidney disease
Autosomal dominant polycystic kidney disease

Cysts (without dysplasia) in hereditary syndromes

Nephronophthisis
Medullary cystic disease
Von Hippel–Lindau disease
Tuberous sclerosis
Glomerulocystic kidney

Miscellaneous

Renal tubular dysgenesis
Acquired cystic kidney disease
Localized cystic kidney disease
Medullary sponge kidney
Simple cortical cyst
Pyelocaliceal ectasia and diverticula

abnormally rotated. Each anomaly may occur in isolation or may represent one component of a more serious complex of malformations affecting other urologic sites or other organ systems. Each may be completely innocent and asymptomatic; however, if urinary tract symptoms develop, they invariably result from impaired urinary drainage, which may cause hydronephrosis or pain, and may be complicated by infection or nephrolithiasis.

Rotation Anomaly

During ascent of the kidney to a lumbar location, the renal pelvis rotates 90 degrees from an anterior to a medial position (Fig. 1.12). Failure of the pelvis to assume a medial orientation, reverse rotation, and overrotation to a posterior or even lateral location comprises a spectrum of orientation abnormalities known as rotation anomalies.[59] Some degree of malrotation occurs in 1:400 to 1:1000 individuals. The most common rotation anomaly is nonrotation or incomplete medial rotation resulting in an anterior location of the pelvis and ureter (Figs. 1.20 and 1.26). This may occur as an isolated abnormality in an otherwise normal kidney. It always accompanies renal ectopia or renal fusion. Ureteropelvic obstruction may on occasion result from a crossing vessel (Fig. 1.26). Excess rotation and reverse rotation with the pelvis posterior or lateral are rare.

Renal Ectopia

Failure of the kidney to assume its proper location in the renal fossa is known as renal ectopia.[60-63] The several varieties are named according to location (Table 1.6). Renal ectopia should be distinguished from renal ptosis in which a normally situated kidney shifts to a lower position. The origin of the renal artery from a normal aortic location identifies a lower-situated kidney as ptotic rather than ectopic. The incidence of ectopia at autopsy ranges from 1:660 to 1:1200. Renal ectopia is bilateral in 10% of cases.

TABLE 1.6 Types of Renal Ectopia

- Pelvic: opposite sacrum
- Iliac: opposite sacral prominence
- Abdominal: above iliac crest
- Cephaloid: subdiaphragmatic
- Thoracic: supradiaphragmatic
- Crossed: contralateral
  - With fusion (90%)
  - Without fusion (10%)
  - Solitary crossed (rare)
  - Bilateral crossed (rarest)

The three most common forms of renal ectopia are pelvic, iliac, and abdominal, all of which are inferiorly located. The kidney may be nonreniform in shape, its pelvis and ureter are anterior (nonrotated), and the ureter is short and usually placed in the bladder, but it may have a high insertion on the pelvis that leads to obstruction. The vascular supply is influenced by the final location of the kidney, arising from the aorta or from the common iliac, internal or external iliac, or inferior mesenteric arteries (Fig. 1.27). The contralateral kidney may be normal or occasionally may be absent or even dysplastic. Other anomalies of urologic organs and cardiovascular, skeletal, and gastrointestinal systems are frequent in both sexes.

Cephaloid ectopia is usually associated with an omphalocele. The kidney appears to continue its ascent when the abdominal organs herniate into the omphalocele sac. The ureter and pelvis are typically normal. Thoracic ectopia is rare and usually involves the left kidney. The kidney resides in an extrapleural location in the

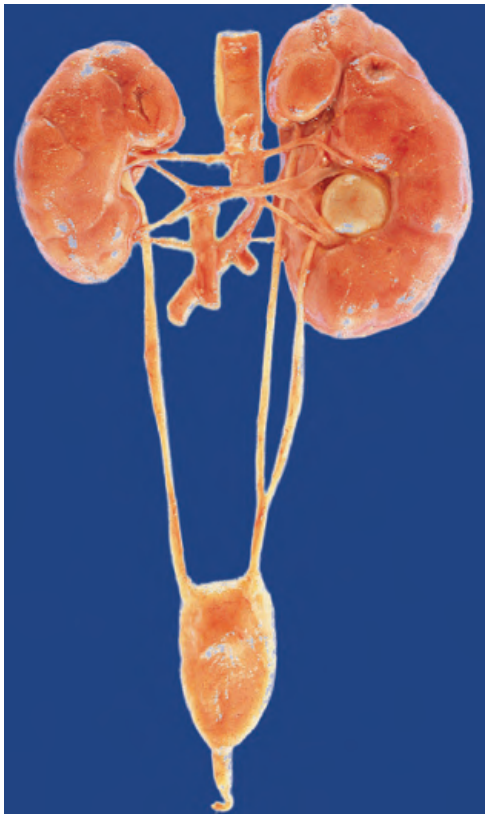


Fig. 1.26 A duplex left kidney with a bifid ureter and a nonrotated (anterior) lower pelvis. An inferior supernumerary artery and a normal vein cross the ureter, with resulting ureteropelvic junction obstruction.

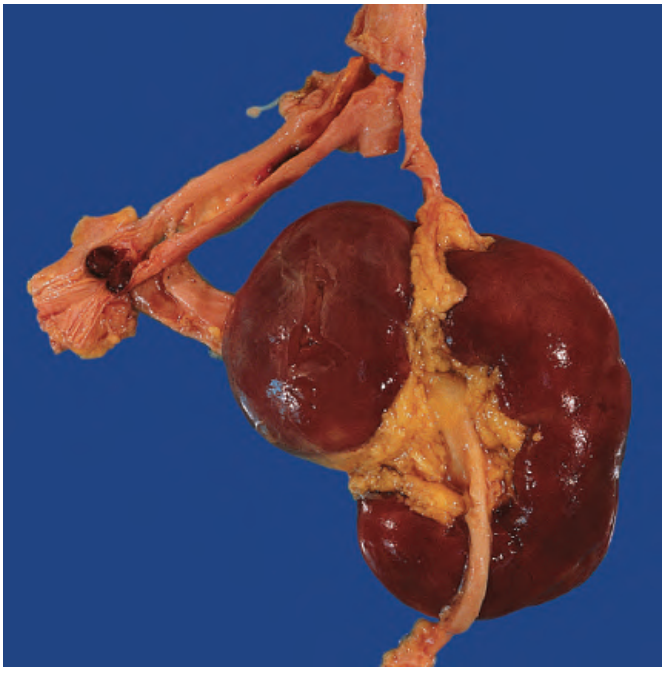


Fig. 1.27 A hypertrophic ectopic pelvic kidney from an asymptomatic patient with unilateral agenesis. Notice the anterior ureter and the vascular supply derived from the iliac vessels.

posterior mediastinum. The diaphragm must be intact to distinguish this anomaly from herniation of the kidney and possibly other abdominal organs into the thorax secondary to diaphragmatic hernia. The lower lobe of the lung may be hypoplastic, but other anomalies are not present. Thoracic ectopia is usually asymptomatic, with a normal ureter and pelvis.

In crossed ectopia the kidney is situated opposite the side of insertion of its ureter in the trigone. Four combinations are possible (Table 1.6). In 90% of cases there is also fusion to the other kidney. In crossed fused ectopia the kidneys may assume a variety of shapes and positions giving rise to six "types": inferior, superior, lump, sigmoid, disk, and L-shaped. The kidneys function normally and their ureters are normally located within the bladder, but their pelves are nonrotated. Extrarenal anomalies (genital, skeletal, and anorectal) occur in 20% to 25% of patients.

Renal Fusion

Horseshoe kidney is the most common form of renal fusion.[64-66] It is the midline fusion of two distinct renal masses, each with its own ureter and pelvis (Figs. 1.28 and 1.29). Horseshoe kidney is relatively common (1:400 to 1:2000) with a 2:1 male predominance. Horseshoe kidney is commonly seen as part of other anomalies such as trisomy 18 (25%), caudal dysplasia syndrome, and Zellweger syndrome.[67] The fusion is typically at the lower poles but can vary greatly in the quantity of fused parenchyma. A horseshoe kidney is ectopic and usually situated anterior to the aorta and vena cava. Occasionally the fusion is posterior to the vena cava or posterior to both the aorta and vena cava. The ureters and pelves are always anterior. This placement, coupled with commonly encountered high insertion of the ureter on the pelvis, can result in obstruction (Fig. 1.28). Approximately 30% of patients also have other anomalies of the urinary tract, central nervous system, heart, gastrointestinal tract, or skeletal system.

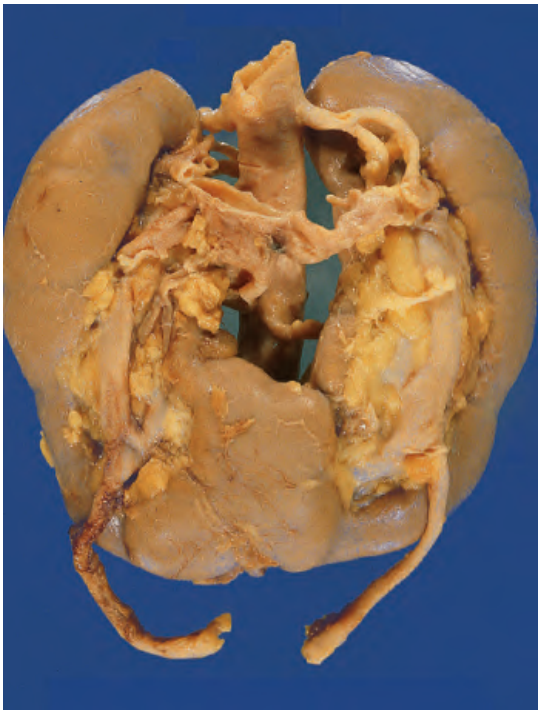


Fig. 1.29 Horseshoe kidney as an incidental autopsy finding in an adult.

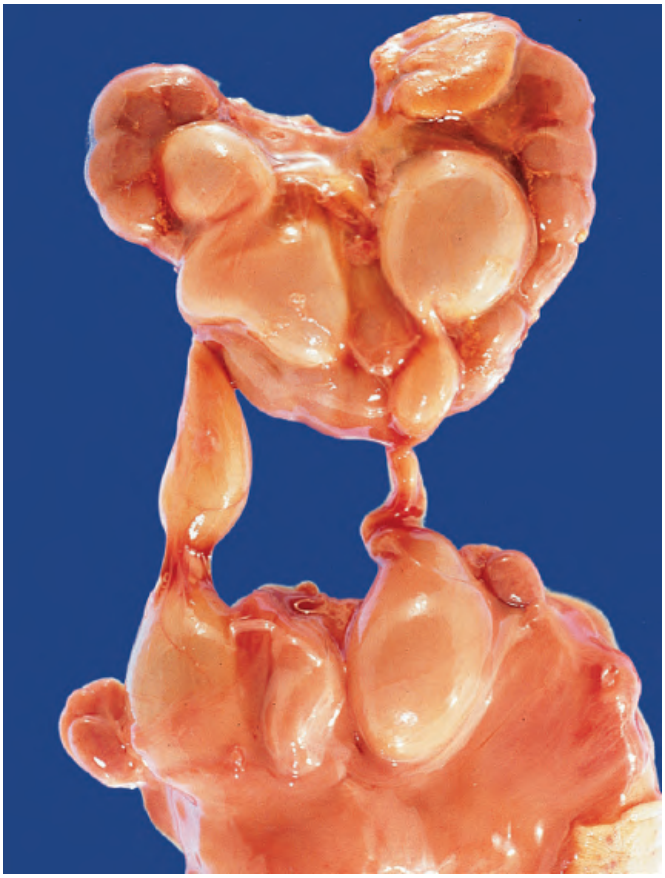


Fig. 1.28 Horseshoe kidney showing hydroureteronephrosis from a neonate with trisomy 18 and multiple congenital anomalies.

Abnormalities in Mass and Number

The following group of anomalies is much less common than those described in the preceding section. Hypoplasia is usually bilateral, whereas supernumerary kidney is usually unilateral, and neither is hereditary. The renal parenchyma in each is normally formed. In contrast, renal agenesis can be either unilateral or bilateral, and may be hereditary.

Supernumerary Kidney

A supernumerary or duplicated kidney is one of the rarest disorders.[68,69] It has been defined as "a free accessory organ that is a distinct, encapsulated, large or small parenchymatous mass topographically related to the usual kidney by a loose, cellular attachment at most and often by no attachment whatsoever."[68] It may be located below (most common), above, or adjacent to the kidney and is rarely bilateral. It is connected to the lower urinary tract by either a bifid ureter or its own separate ureter (Fig. 1.30). In half of the reported cases, complications have developed related to obstruction and infection.

Hypoplasia

Hypoplasia refers to a small (<50% of normal) but otherwise normally developed kidney.[70] By definition, nephron formation is normal, albeit deficient, in quantity, and dysplastic elements (metanephric dysgenesis) are absent. There are four types of hypoplasia (Table 1.7).

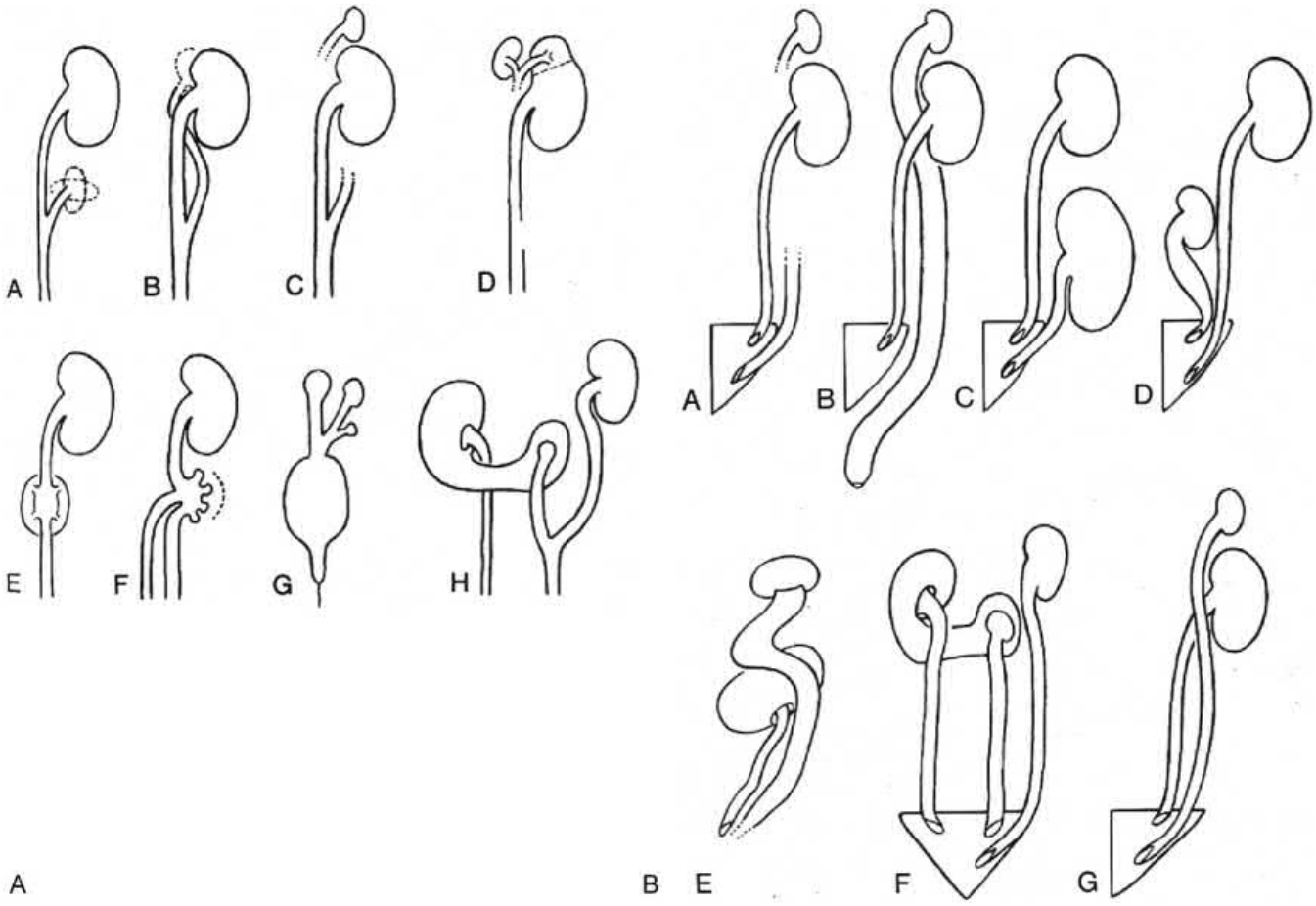


Fig. 1.30 Morphologic variants of supernumerary kidneys with bifid ureters (A) and separate ureters (B). (From N'Guessan G, Stephens FD. Supernumerary kidney. J Urol 1983;130:651; with permission.)

TABLE 1.7 Types of Renal Hypoplasia

Simple hypoplasia
Oligomeganephronia
Cortical hypoplasia
Segmental hypoplasia/Ask-Upmark kidney

Simple Hypoplasia

Simple hypoplasia is a rare, usually bilateral, and often nonhereditary disease in which the small size of the kidney usually reflects a marked reduction in the number of renal lobes.[70] Frequently only one to five lobes are present (Fig. 1.31). Dysplastic elements, by definition, are absent. When the condition is unilateral, the contralateral kidney may be hypertrophied. When it is bilateral, the small kidneys may eventually fail to provide renal function with body growth, and renal failure and nephron sclerosis may develop, the onset of which is determined by the degree of hypoplasia.

Oligomeganephronia

Oligomeganephronia may be the most common form of renal hypoplasia. It is a bilateral, nonhereditary disorder.[71-76] Most cases are sporadic; however, few associations have been described with mutations in transcription factors involved in renal development including PAX2, HNF1B, and SIX.[77-79] The kidneys are small because of a reduction in the number of renal lobes and the number of nephrons within each lobe. Microscopically, the nephrons present are tremendously enlarged (Fig. 1.32). Glomerular and tubular volumes have been measured to be 12 times and 17 times normal, respectively.

Children with oligomeganephronia present with a concentration defect causing polyuria, polydipsia, and salt wasting, resembling patients with nephronophthisis. Renal insufficiency and proteinuria gradually develop with body growth as progressive glomerular and tubulointerstitial scarring occur. The absence of a family history of renal disease, the presence of proteinuria, and imaging studies revealing symmetrically small noncystic kidneys usually permit separation from nephronophthisis.

Cortical Hypoplasia

Cortical hypoplasia is a type of hypoplasia not generally recognized; it does not appear in standard texts of urologic pathology. Examples of cortical hypoplasia, however, are amply demonstrated in the *Atlas of Medical Renal Pathology* by Bonsib.[70] *Cortical hypoplasia* refers to a reduction in the number of nephron generations that results in cortical thinning, reduction in overall renal size, and, if severe, a clinically significant reduction in nephron endowment, a major risk factor for hypertension and renal insufficiency.[80-82] The "normal" number of generations ranges from 10 to 14, although rarely are more than 9 to 10 generations evident even in a well-oriented section. Determination of nephron generations is best performed with a nephrectomy specimen with sections

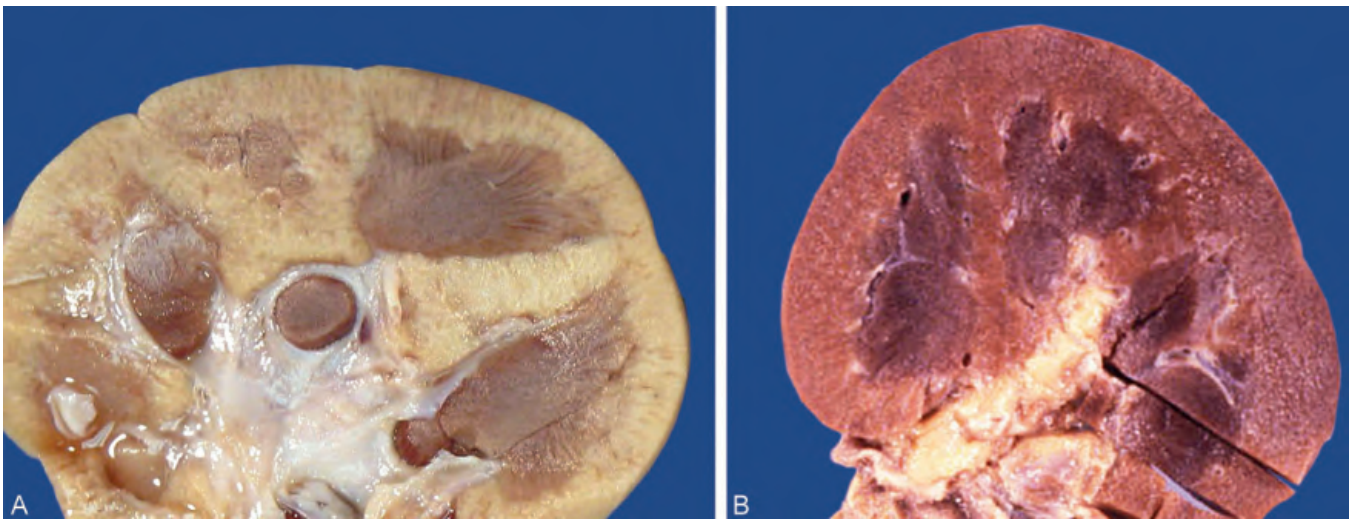


Fig. 1.31 (A) This 3-cm hypoplastic kidney was from a 2-year-old child with a contralateral duplex kidney. It appears to have only five lobes. (B) This 5.5-cm hypoplastic kidney was from an adult with a 13.5-cm hypertrophic contralateral kidney.

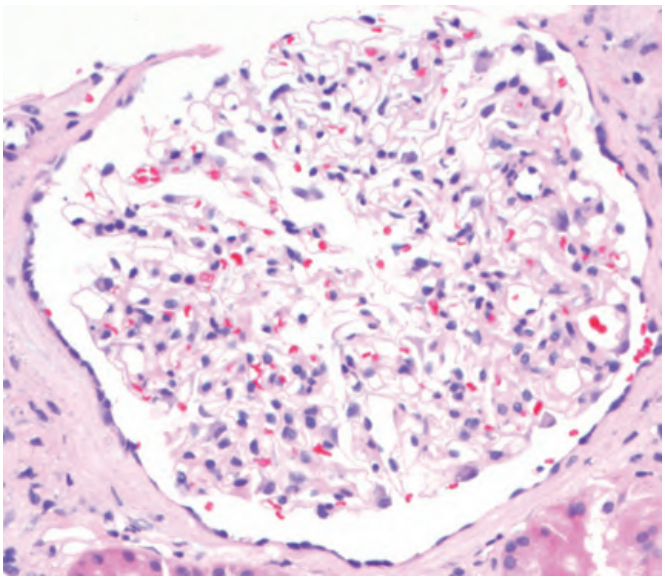


Fig. 1.32 Oligomeganephronia in a 22-month-old child. This markedly enlarged glomerulus is twice the normal diameter. Notice the numerous capillary loops, far more than in a normal glomerulus.

oriented along medullary rays. Nephron generation counting is admittedly imprecise. However, if there is a 50% reduction in nephron generations, that is, four to five generations in a properly oriented section, then the reliability of this assessment is reasonable (Fig. 1.33). This form of hypoplasia may coexist with other forms of hypoplasia, especially Ask-Upmark segmental hypoplasia.

Segmental Hypoplasia (Ask-Upmark Kidney)

Segmental hypoplasia may manifest in neonates or adults and is often associated with hypertension.[83-87] There is widespread agreement that vesicoureteral reflux is the fundamental injury. Some investigators regard it as an acquired lesion because its evolution over time has been radiographically documented in a few cases. Others agree with reflux-related injury but believe that most cases are developmental in origin secondary to in utero reflux that damages the developing renal lobe. That this condition often manifests in neonates and children supports a developmental basis. Furthermore, it is associated with renal vascular anomalies in 40% of cases and may be coexistent with lobes that show cortical hypoplasia. Segmental hypoplasia is defined as a small kidney with a deep cortical groove and dilatation of adjacent calyx (Fig. 1.34A). Microscopic features include sharply delineated cortical lesions (Fig. 1.34B). The cortex contains few tubules, with no or only rare glomeruli. There is little or no inflammation, nor is glomerulosclerosis or tubular atrophy present to indicate a regressive lesion. Finally, the kidney should have no evidence of metanephric dysgenesis. The medulla is characteristically absent. If present it may be rudimentary or flattened, with no loops of Henle, and may contain a distinctive cellular interstitial mesenchymal tissue not present in the normal renal pyramid.

Renal Agenesis

Absence of the kidney and its corresponding ureter is known as renal agenesis (Table 1.8).[88-94] The corresponding bladder hemitrigone is also absent because it represents the distal continuation of the ureteral smooth muscle (Fig. 1.35).[90] Failure to identify a kidney in a child or an adult does not prove congenital absence of the kidney because cystic dysplastic kidneys identified in newborns have been shown radiographically to regress further over time and may become undetectable.[95]

Unilateral Renal Agenesis

In unilateral renal agenesis the contralateral kidney may be hypertrophic up to twice the normal size. The overall renal function may be normal, and the condition may be entirely asymptomatic (Fig. 1.27). Several genetic and environmental factors have been associated with an increased risk, such as African American race, maternal diabetes mellitus, and maternal age younger than 18 years.[93] In up to 70% of patients, renal agenesis is associated with additional anomalies, most often affecting the genital tract.[90,91,93-97] This presumably reflects a common abnormality affecting development of both the mesonephric duct– and Müllerian duct–derived structures. Female genital anomalies include absence of the ipsilateral fallopian tube, uterine horn, and proximal vagina or uterine didelphia or vaginal septum. Male

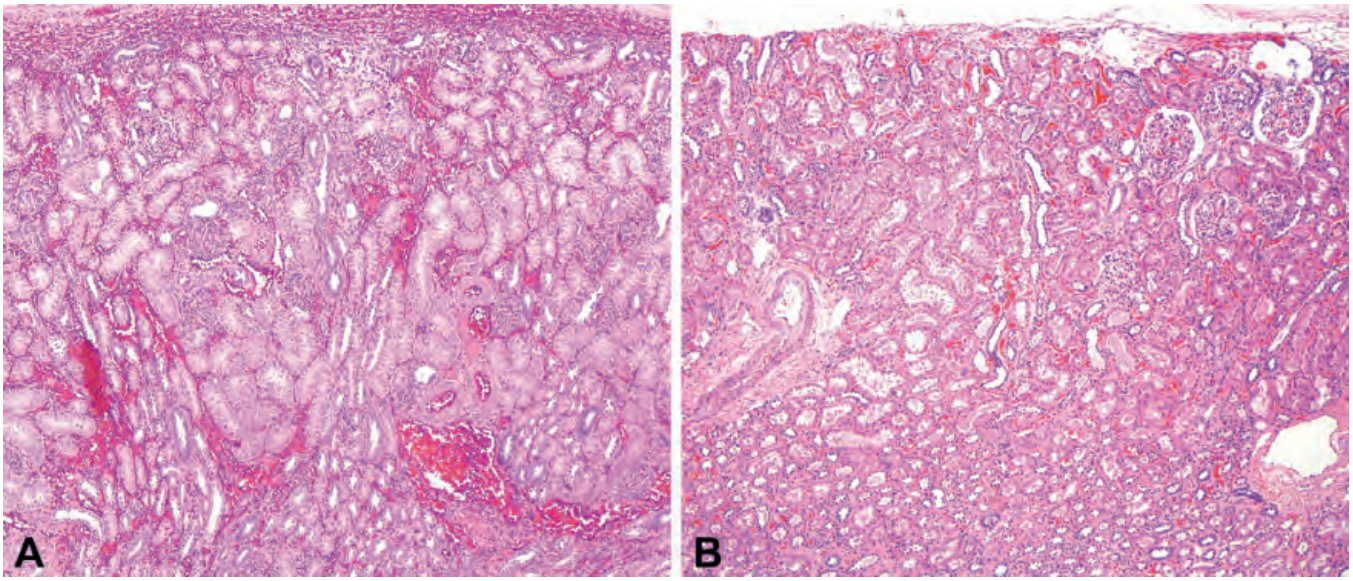


Fig. 1.33 (A) Cortical hypoplasia in a newborn kidney. Two medullary rays are visible. The renal medulla is at the bottom, and the renal capsule is at the top. Only three or four nephron generations are present. (B) This is an adult kidney with cortical hypoplasia. The medulla is at the bottom, and the renal capsule is at the top. Only two or three nephron generations are present.

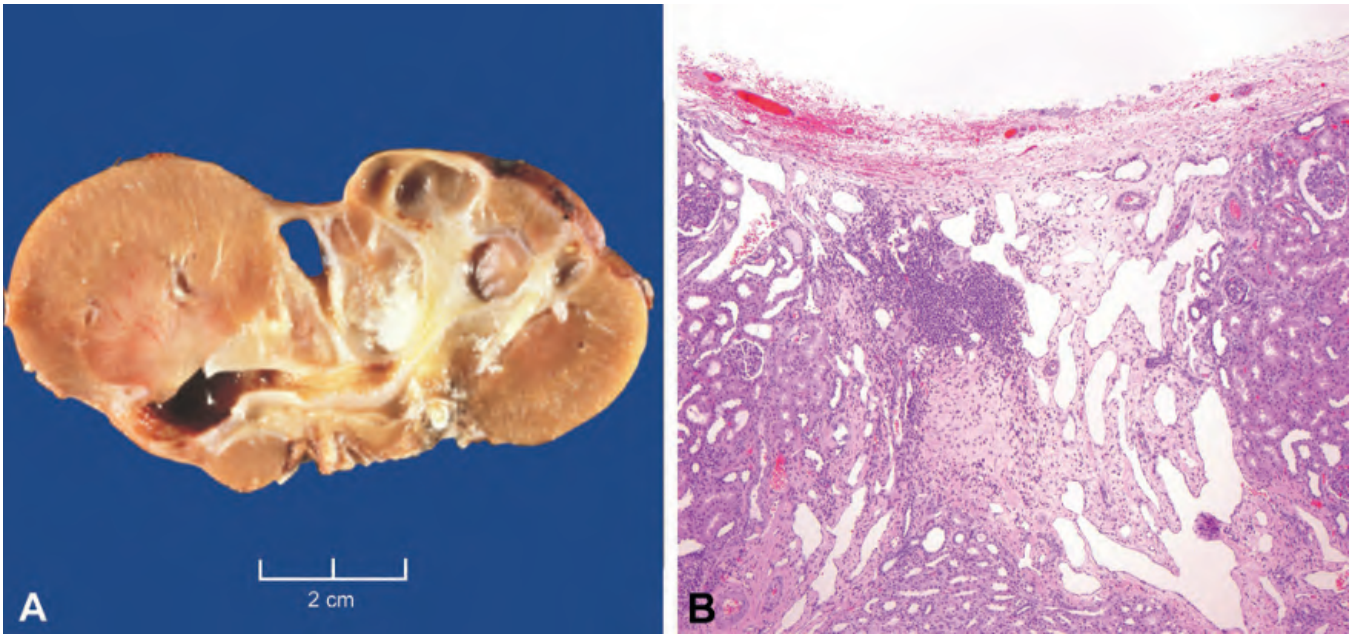


Fig. 1.34 (A) This is a bivalved Ask-Upmark segmental hypoplasia kidney showing the deep linear groove with approximation of the renal capsule and a dilated calyx. (B) The cortical groove in the Ask-Upmark kidney shows an abruptly delineated lesion with dilated veins and complete absence of normal nephrons and atrophic nephrons. (A, Courtesy of The Jay Bernstein, M.D. Consultative Collection, Nephropath, Little Rock, AR.)

genital anomalies may include absence of the ipsilateral epididymis, vas deferens, or seminal vesicle, or a seminal vesicle cyst may be encountered. Identification of a patient with a unilateral genital anomaly or renal agenesis should therefore prompt evaluation of the other organ system.

Bilateral Renal Agenesis (Potter Syndrome)

Bilateral renal agenesis is a uniformly fatal disorder known as Potter syndrome (Fig. 1.36). Both ureters are also absent, so the bladder has no ureteral orifices.[89] Approximately 40% of affected fetuses are stillbirths, and those born alive die of pulmonary failure within 48 hours. Mothers present with severe oligohydramnios because fetal urine normally accounts for most of the amniotic fluid in the second half of gestation. Oligohydramnios impairs pulmonary development that results in pulmonary hypoplasia and produces a variety of distinctive gross features known as the Potter phenotype or oligohydramnios phenotype (Table 1.9).[98-100] Figs. 1.37 and 1.38 demonstrate some of the characteristic facial and placental

TABLE 1.8 Renal Agenesis

Sporadic forms of renal agenesis

Unilateral renal agenesis
Bilateral renal agenesis (Potter syndrome)

Syndromic and hereditary renal agenesis

Chromosomal anomalies (trisomy 13 and 18)
VATER association
Müllerian aplasia syndrome (MURCS syndrome)
Sirenomelia (caudal regression syndrome)
Cloacal exstrophy
Fraser syndrome
Williams syndrome
Multiple malformation syndromes, not otherwise specified
Hereditary renal adysplasia

MURCS, Müllerian duct aplasia or hypoplasia, unilateral renal agenesis, and cervicothoracic somite dysplasia; *VATER*, vertebral defects, imperforate anus, tracheoesophageal fistula, radial and renal dysplasia.

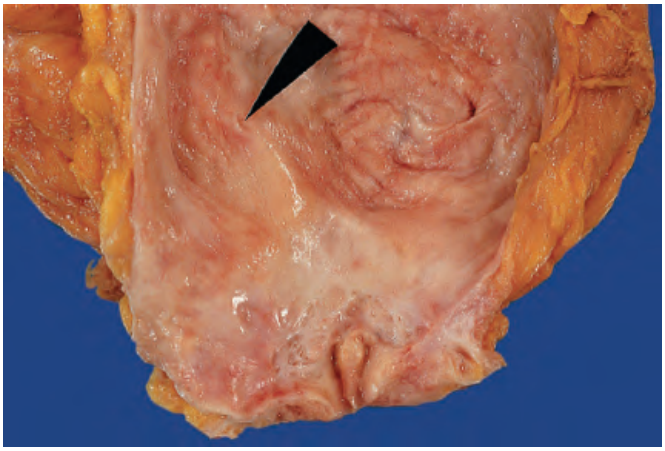


Fig. 1.35 This bladder has an absent left hemitrigone in an adult with a sporadic form of unilateral renal agenesis. The right hemitrigone with its ureteral orifice is indicated by an *arrowhead.*

findings. Some urologists refer to any fetus born with the oligohydramnios phenotype as having Potter syndrome, rather than reserving the term for the entity of bilateral renal-ureteral agenesis as initially described. This can be confusing because oligohydramnios has other causes (Table 1.10).[98]

Syndromic Renal Agenesis

Many syndromes are characterized by absence of one kidney or, rarely, both kidneys as a component of a constellation of congenital anomalies.[101-105] The list includes chromosomal anomalies, several malformation syndromes, and multiple malformation events affecting the gastrointestinal, cardiac, central nervous system, or skeletal system that do not conform to a specific syndrome. Finally, renal agenesis may also occur in a familial disorder with renal dysplasia (see Hereditary Renal Adysplasia section later in this chapter).[106-109] In each disorder, identification of extrarenal components and a detailed family history are essential for proper classification and appropriate genetic counseling. The extrarenal anomalies are responsible for many complications and for the lethal nature of many of the syndromes.

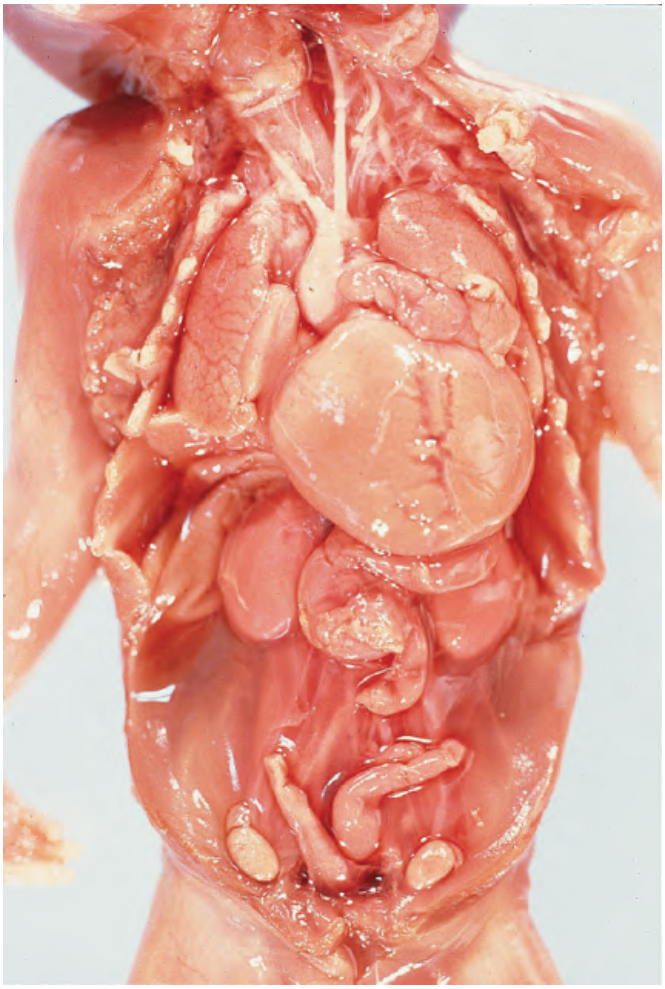


Fig. 1.36 This is the third consecutive fetus affected with bilateral renal-ureteral agenesis in a family with familial renal adysplasia. The small and large bowels have been removed to reveal the adrenal glands. Both kidneys are absent.

TABLE 1.9 Oligohydramnios Phenotype

Potter facies
Increased interocular distance
Broad, flattened nose
Prominent inner canthic folds (sweeping downward and laterally)
Receding chin
Large, low-set ears with little cartilage
Positional deformities (flexion of hips and knees, clubbed feet)
Dry skin
Hypoplastic lungs
Small bladder with absent trigone
Placenta: amnion nodosum

Renal Dysplasia

A dysplastic kidney is a metanephric structure with aberrant nephronic differentiation.[27,42-45,110-116] The term *dysplasia* is used in a developmental sense and does not connote any relationship with neoplasia. Dysplastic kidneys should not be confused with hypoplastic kidneys, which are small but have normal nephron

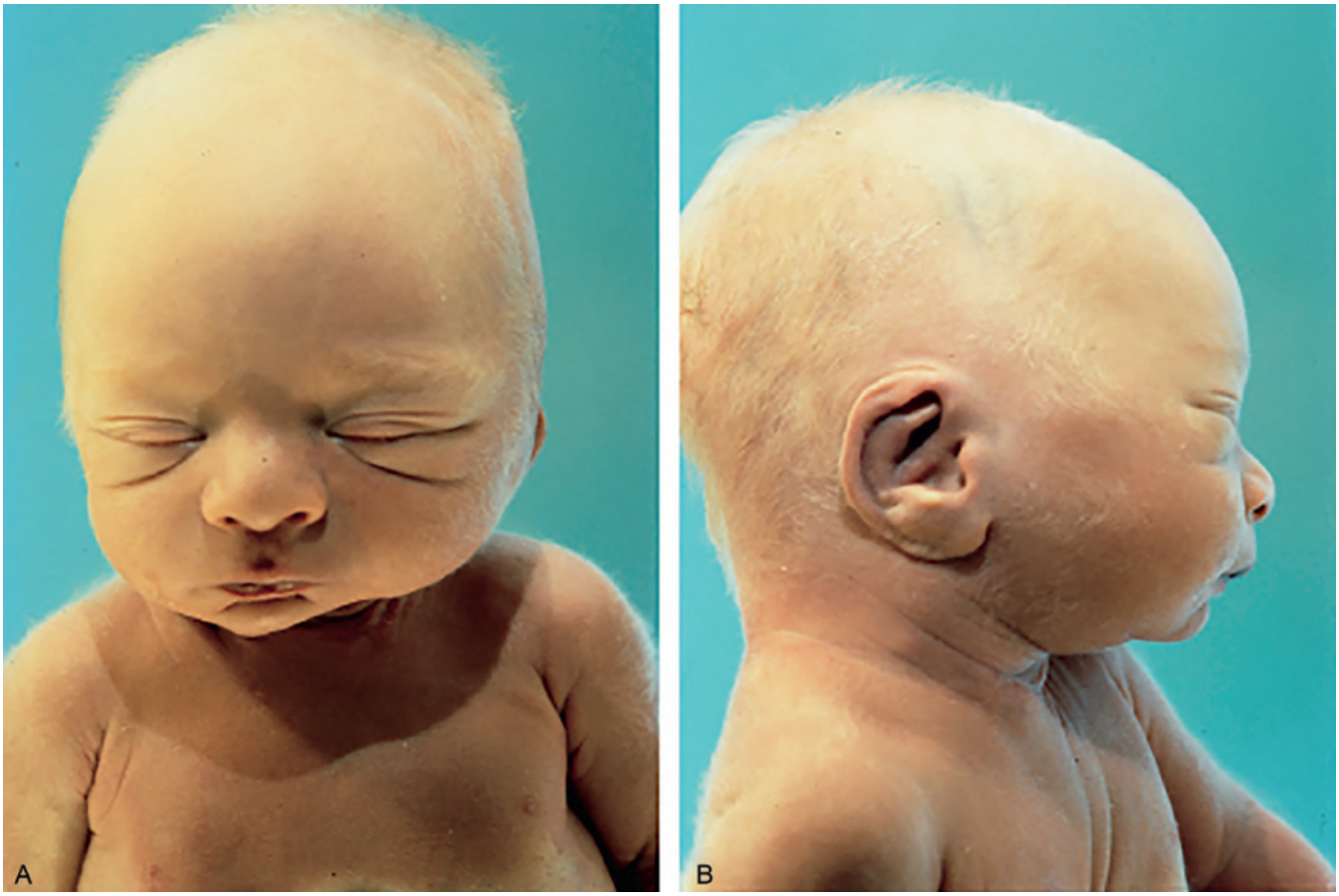


Fig. 1.37 An infant born with oligohydramnios and the characteristic Potter facies in anterior (A) and lateral (B) views.

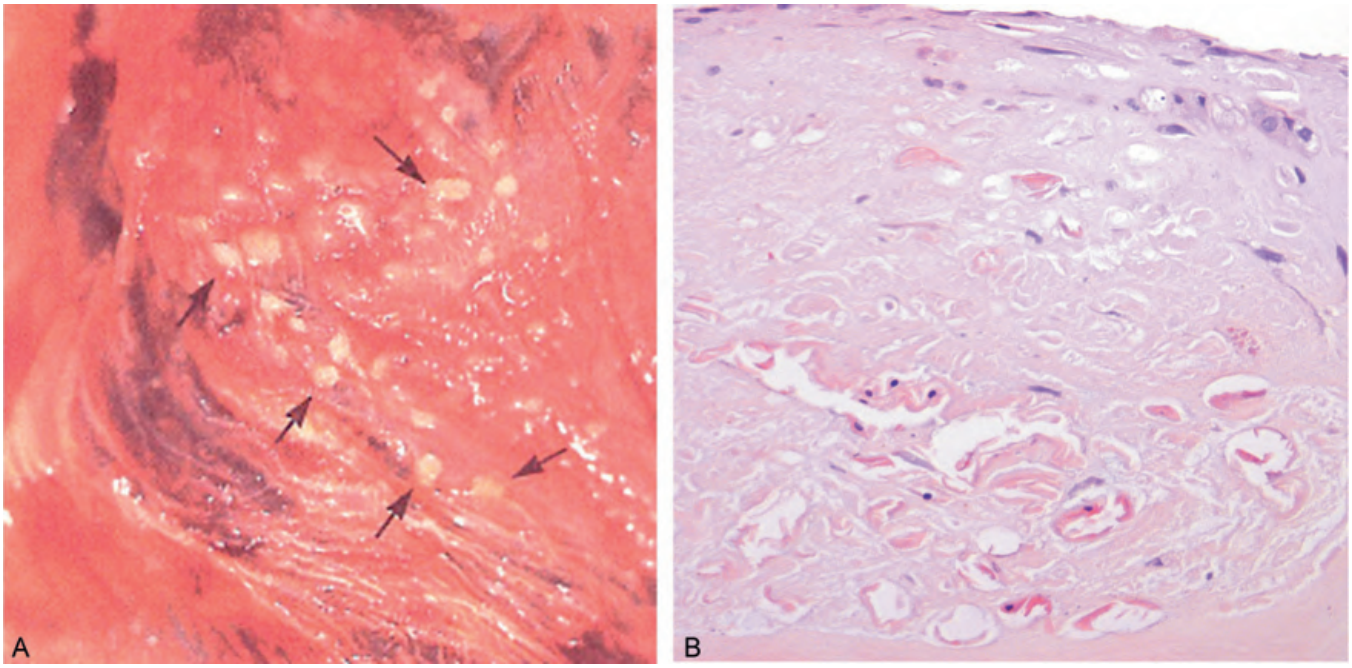


Fig. 1.38 (A) Placenta with plaques of amnion nodosum (*arrows*). (B) Plaques of amnion nodosum contain clumps of fetal squames embedded in dense collagen.

TABLE 1.10 Causes of Oligohydramnios

Major causes

Potter syndrome (bilateral renal agenesis)
Bilateral renal dysplasia
Distal (complete) urinary tract obstruction

Rare causes

Autosomal recessive polycystic kidney disease
Glomerulocystic kidney disease
Renal tubular dysgenesis
Chronic amniotic fluid leak
In utero acute renal failure
Idiopathic conditions

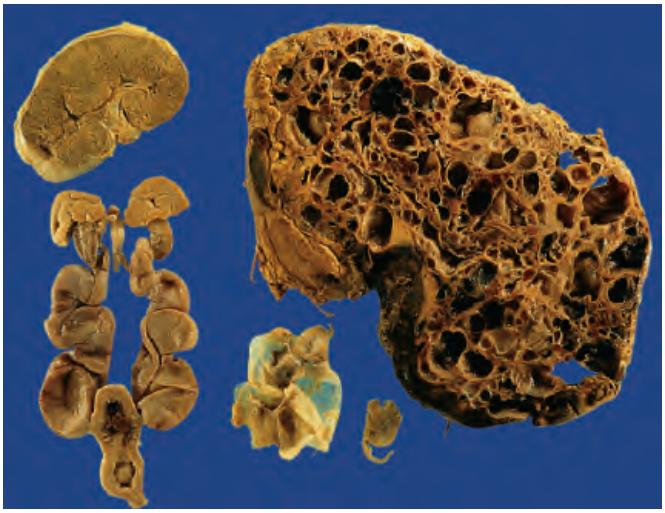


Fig. 1.39 Autosomal recessive polycystic kidney (*upper left*), autosomal dominant polycystic kidney (upper right), and three forms of renal dysplasia: aplastic dysplasia from a 35-year-old patient, multicystic dysplasia from a neonate, and bilateral dysplasia associated with lower tract obstruction (*lower left*).

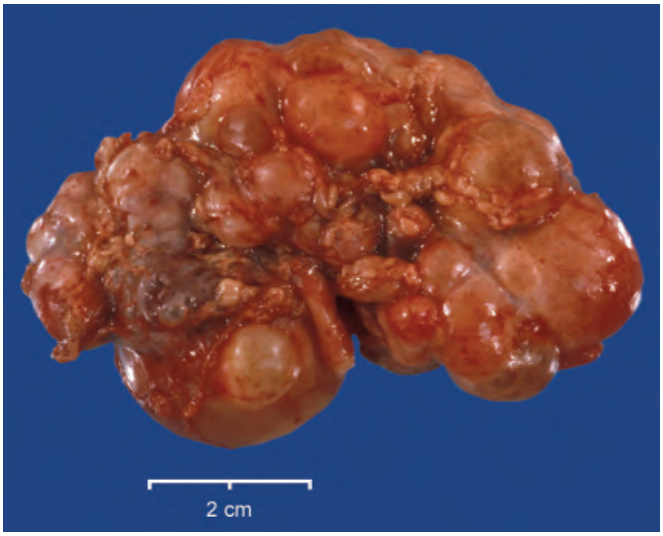


Fig. 1.40 This is the external appearance of a typical multicystic dysplastic kidney. It is markedly enlarged and diffusely cystic with cysts of variable size.

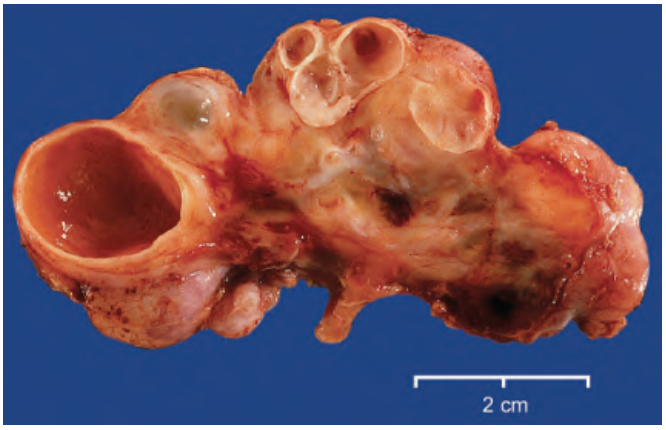


Fig. 1.41 Transverse section of a typical multicystic dysplastic kidney. There is no discernible normal architecture, and no corticomedullary junction or collecting system is seen. The parenchyma is composed solely of cysts and nondescript connective tissue.

TABLE 1.11 Renal Dysplasias: Gross Variations and Clinical Associations

Multicystic and aplastic dysplasia
Segmental dysplasia
Dysplasia associated with lower urinary tract obstruction
Dysplasia associated with malformation syndromes
Hereditary adysplasia and urogenital adysplasia

development, or with polycystic kidney diseases, which although cystic do not contain dysplastic elements. Dysplastic kidneys are, by definition, maldeveloped (Figs. 1.39 to 1.41). They are usually not reniform, can vary greatly in size and appearance, and occur in several patterns: unilateral, bilateral, or confined to the upper pole of a duplex kidney (Table 1.11). Approximately 90% of cases have a ureteral abnormality or are associated with distal obstruction resulting in ureteral stenosis or dilation and megacystis or bladder hypertrophy. Renal dysplasia most commonly is sporadic, but it may be familial, part of a multiple malformation complex, or a component of a hereditary malformation syndrome (Table 1.12). Table 1.13 and Fig. 1.39 compare the major anatomic and clinical features of renal dysplasias with the autosomal recessive polycystic kidney disease (ARPKD) and ADPKD discussed in the following sections.

Dysplastic kidneys vary tremendously in gross appearance, ranging from the large multicystic kidney to the small aplastic kidney (Fig. 1.39).[70] The typical multicystic kidney is composed entirely of variably sized cysts and is the most common cause of a unilateral renal mass in a child (Fig. 1.40). The cysts contain serous fluid. Typically, there is no corticomedullary differentiation, and a collecting system is often absent (Fig. 1.41). The typical aplastic dysplasia is tiny and contains no cysts or only microscopic cysts (Fig. 1.39). Corticomedullary differentiation and a collecting system are again absent. The multicystic and aplastic dysplasias represent extremes of a morphologic continuum differing only in the extent of cyst formation. Intermediate forms commonly occur. Most often renal dysplasia is a unilateral process, and the

TABLE 1.12 Multiple Malformation Syndromes in Which Renal Dysplasia May Occur

Common occurrence

VATER (VACTERL) association
MURC syndrome
Prune-belly syndrome
Caudal regression syndrome
Cloacal exstrophy
Urogenital sinus syndrome
Urorectal septum syndrome sequence
Meckel-Gruber syndrome[a]
Dandy-Walker syndrome[a]
Short rib–polydactyly syndrome[a]
Elejalde syndrome

Occasional occurrence

Trisomy C
Trisomy 13
Trisomy 18
Persisting mesonephric duct syndrome
Zellweger syndrome[a]
Jeune syndrome[a]
Smith-Lemli-Opitz syndrome[a]
Beckwith-Wiedemann syndrome[a]
Laurence-Moon-Bardet-Biedl syndrome[a]

MURC, Müllerian duct aplasia or hypoplasia, unilateral renal agenesis, and cervicothoracic somite dysplasia; *VACTERL*, vertebral, anal, cardiac, tracheal, esophageal, renal, limb; *VATER*, vertebral defects, imperforate anus, tracheoesophageal fistula, radial and renal dysplasia.
[a]*Autosomal recessive inheritance.*

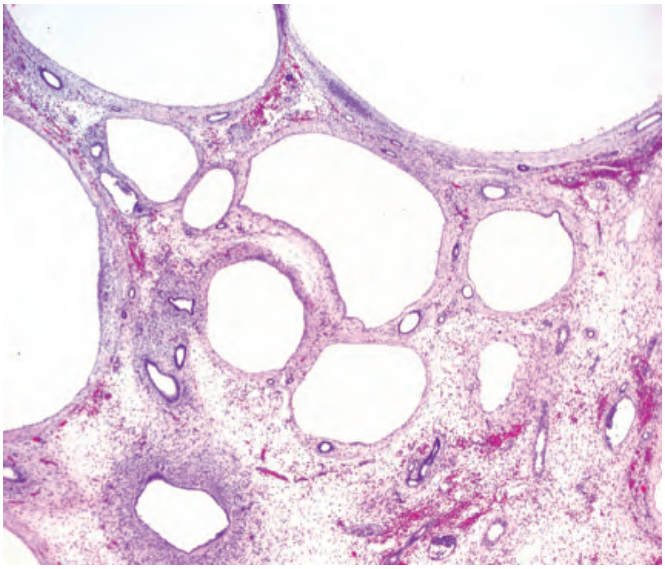


Fig. 1.42 Dysplastic kidney composed of cysts, dysplastic ducts, and a few primitive tubules.

contralateral kidney is normal or larger than normal. When multicystic dysplasia or aplastic dysplasia is bilateral, the neonate presents with a Potter phenotype and dies of pulmonary hypoplasia.

The histologic appearance of a dysplastic kidney can also be quite varied.[106-109,111,113-115] The kidney may be composed entirely of large cysts with little or no metanephric tissue represented (Fig. 1.42). The cysts are of variable size and usually lined by flat-

TABLE 1.13 Comparison of Renal Agenesis, Hypoplasia, and Dysplasia

	Agenesis/Aplasia	Hypoplasia	Dysplasia
Definition	Agenesis: no kidneys Aplasia: rudimentary kidneys	Small, architecturally normal kidneys, weight <50% expected; decreased number of nephrons (<2 SD normal)	Architecturally abnormal kidney with immature nephrons
Incidence	Unilateral: 1:1000 Bilateral: 1:10,000	Unilateral: 1:1000 Bilateral: 1:4000	Unilateral: 1:7500 Bilateral: 1:7500
Etiology	Defect in formation of Wolffian duct and/or ureteric bud	Slow induction or incorrect position of ureteric bud, decreased branching	Defective branching
Clinical presentation	Unilateral: M = F; may be asymptomatic, risk of FSGS Bilateral: M > F; perinatal death	May be asymptomatic (if unilateral) or symptomatic: • Failure to thrive • Hypertension • Salt wasting • Excessive thirst	May be asymptomatic (if unilateral) or symptomatic: • Failure to thrive • Hypertension • Salt wasting • Excessive thirst
Radiologic features	Absent kidney	Small kidney	Small kidney with noncommunicating hypoechogenic cysts
Gross appearance	No kidneys Earlobe-shaped, elongated adrenals	Small kidneys Decreased number of pyramids	Nonreniform, multicystic mass Small, normal, or large size
Microscopic features	Normal or compensatory hypertrophy in unilateral agenesis	• Normal organization • Large nephrons in oligomeganephronia	• Disorganized parenchyma • Immature glomeruli and tubules • Smooth muscle collarettes • Metaplastic cartilage (30%)

F, Female; *FSGS*, focal segmental glomerulosclerosis; *M*, male; *SD*, standard deviation.

tened cells. Immature or dysplastic ducts are commonly present. They are lined with columnar epithelium and surrounded by collars of spindle cells that express estrogen receptor and/or progesterone receptor (Fig. 1.43). Immature-appearing cartilage may be also present but is far less frequent than dysplastic ducts (Figs. 1.43B and 1.44A). The dysplastic ducts are thought to originate from the ampullary bud, whereas the immature cartilage is regarded as blastemal derived.[107] Immature tubules and aberrantly formed glomeruli may be present, or relatively normal-appearing tubules and well-formed glomeruli may be present but not sufficiently organized to contribute appreciably to renal function (Fig. 1.44).

Occasionally an infant presents with renal insufficiency and small reniform kidneys with normal ureters and pelves. Simple hypoplasia may be suspected, but biopsy reveals an admixture of normal nephrons and aberrantly formed nephrons with microcysts and cartilage or dysplastic ducts. The renal prognosis is bleak, and the infant usually develops progressive renal failure with further growth.[110]

Segmental forms of dysplasia occur in kidneys with duplication of the collecting system (duplex kidney).[93,101] Usually the duplication is complete with two separate ureters. The upper pole moiety is affected, and histologic examination shows the same range of aberrant nephrogenesis encountered in aplastic and multicystic dysplasia (Fig. 1.45). The upper pole ureter is usually ectopic, in a more cranial or caudal location relative to the normally situated lower pole ureter. The incidence and severity of dysplasia increase with the severity of the ectopia.[106,109]

Bilateral renal dysplasia can be associated with distal obstruction resulting from urethral stenosis, posterior urethral valves, or

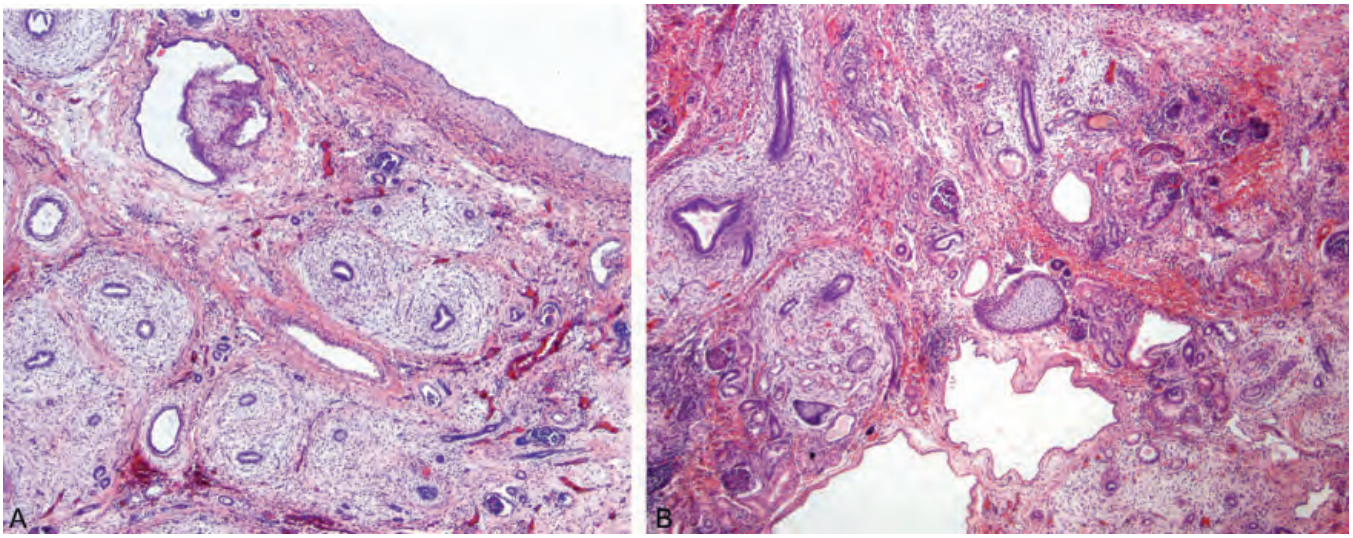


Fig. 1.43 (A) This dysplastic kidney contains large cysts and numerous dysplastic tubules with collarettes of spindle cells. (B) This dysplastic kidney contains numerous dysplastic tubules with collarettes of spindle cells and an island of immature cartilage in the center.

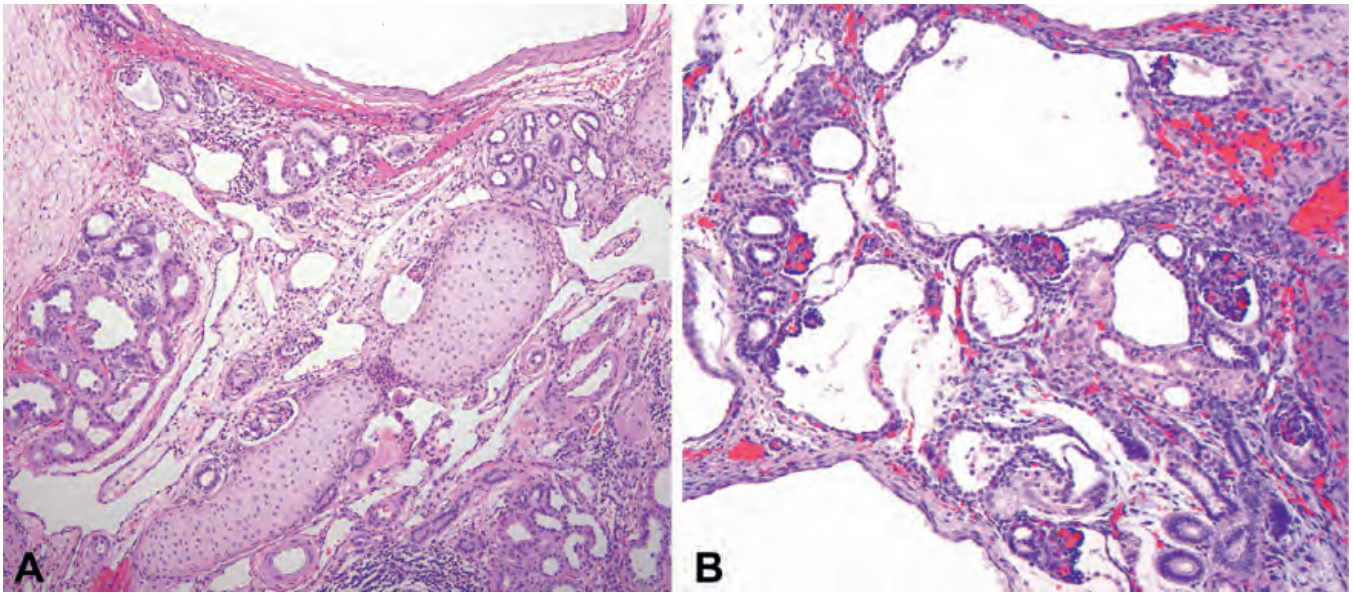


Fig. 1.44 (A) Renal dysplasia showing a portion of a cyst with several islands of immature cartilage, scattered tubules, and abnormally formed glomeruli. (B) This dysplastic kidney has microcysts (at least one is a glomerular cyst), small tubules, and atubular glomeruli.

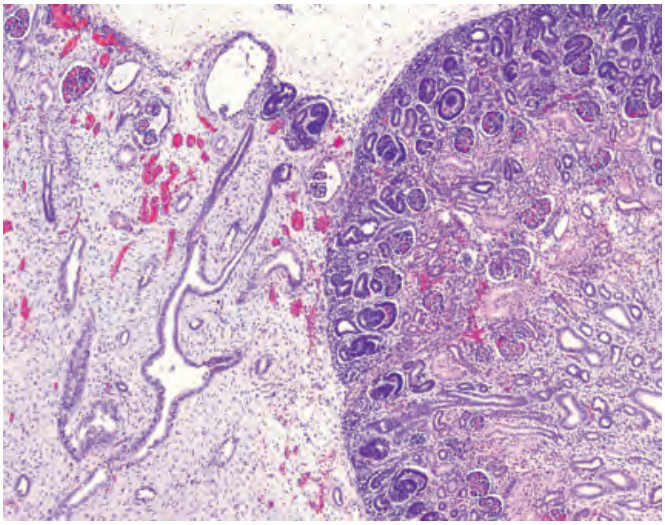


Fig. 1.45 Segmental form of renal dysplasia in a fetal duplex kidney. To the left is the dysplastic upper pole. To the right is the normally developing lower pole.

bladder neck obstruction. This form of dysplasia may have a distinctive gross appearance. The kidneys are typically reniform, and they may be large or small, but they often show corticomedullary differentiation. The bladder is either hypertrophic or greatly dilated, and the ureters are dilated and tortuous (Figs. 1.39 and 1.46A). There may be a severe degree of dysplasia with scant nephronic elements (Fig. 1.46B) or only a peripheral zone of dysplastic elements with normal deeper nephrons.

Renal dysplasia may develop in many multiple malformation syndromes, chromosomal anomalies, and hereditary malformation syndromes (Table 1.12).[70] When multiple malformations are encountered in a pediatric autopsy, it is important to obtain tissue for karyotype or genetic analysis, and to meticulously document all anomalies. Consultation with specialists in pediatrics and genetics is advisable to provide the proper classification of the disease so that appropriate family counseling can be provided.

The major features of renal aplasia, hypoplasia, and dysplasia are compared in Table 1.13. Multicystic dysplasia, aplastic dysplasia, and renal agenesis are the most severe forms of metanephric

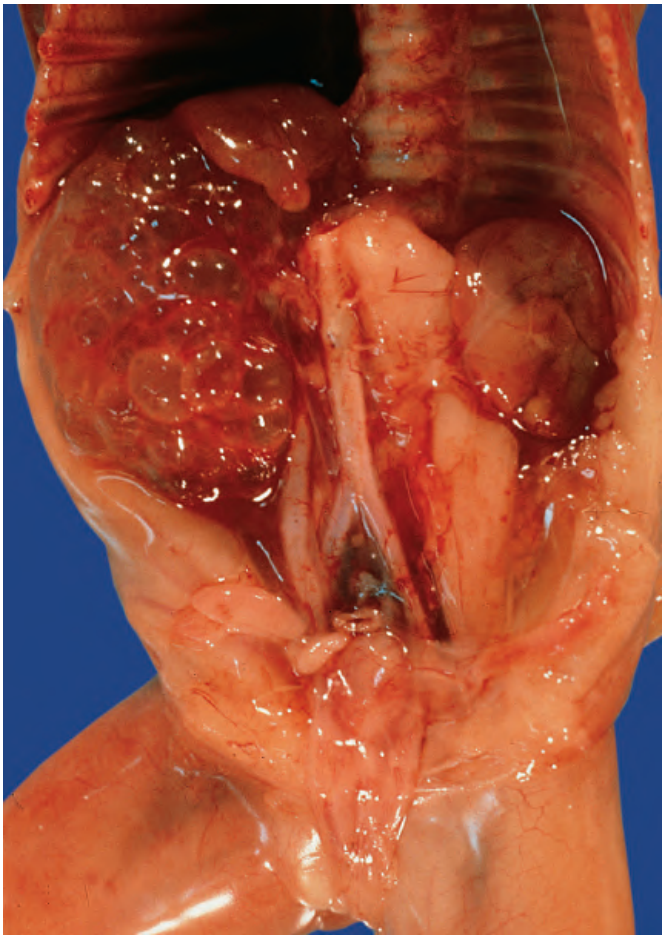


Fig. 1.47 Hereditary renal adysplasia with unilateral multicystic dysplasia and contralateral renal agenesis shown in situ.

maldevelopment. When they are not associated with extrarenal anomalies of a multiple malformation syndrome, they usually are sporadic events with low risk of a subsequently affected sibling. Rarely, however, renal agenesis or renal dysplasia, either unilateral or bilateral (Figs. 1.39 and 1.47), or combined agenesis and dysplasia may be familial (usually autosomal dominant). This is

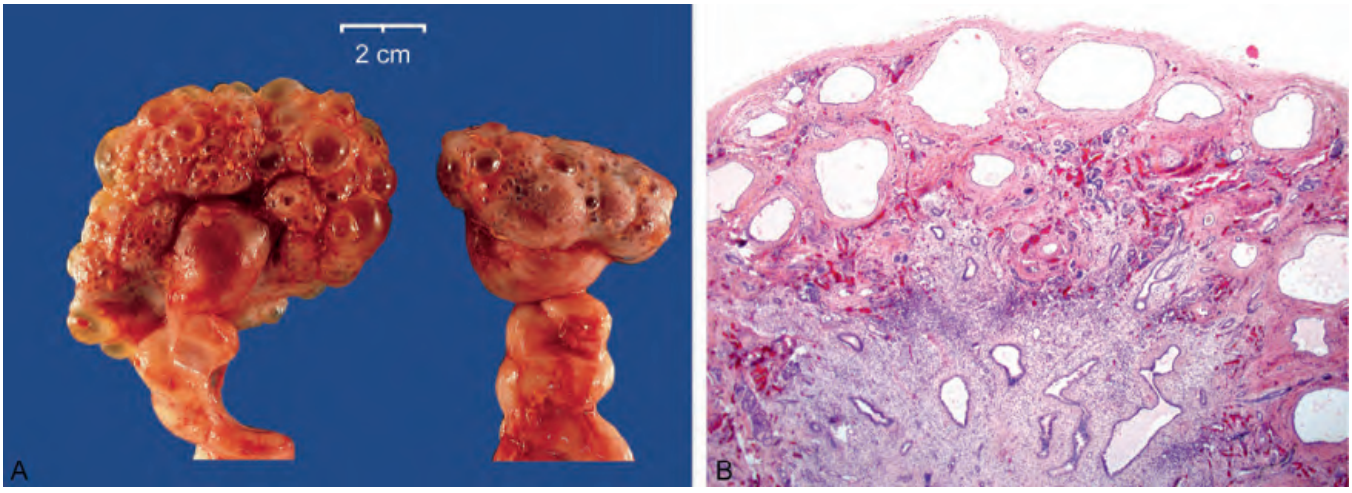


Fig. 1.46 (A) Renal dysplasia associated with urinary tract obstruction. These small kidneys have numerous small cysts and markedly dilated ureters. (B) Cortical medullary development is present, but few differentiated nephron elements.

known as hereditary renal adysplasia.[101-105] There also may be concomitant malformation of Müllerian structures, a condition referred to as hereditary urogenital adysplasia.[87] Unfortunately, neither syndrome can be anticipated until a second family member is identified with either agenesis or dysplasia.

Polycystic Kidney Disease

Autosomal Recessive Polycystic Kidney Disease

Autosomal recessive polycystic kidney is a rare disorder that occurs in 1 in 20,000 to 50,000 births (Table 1.14). In ARPKD, parents lack the disease and 25% of siblings are affected.[117-124] It is associated with mutations of the polycystic kidney and hepatic disease 1 (*PKHD1*) gene, on chromosome 6p12.[117-126] The product of this gene, fibrocystin/polyductin, localizes to the primary cilium and centrosome of renal tubule epithelial cells. Organogenesis in ARPKD appears normal based on microdissection studies of severe neonatal forms.[33] The primary lesion is fusiform ectasia of cortical and medullary collecting ducts, eventually leading to renal failure in severely affected cases. The renal lesion is accompanied by a bile duct plate malformation that develops into congenital hepatic fibrosis in surviving older patients.

Recessive polycystic kidney disease was originally believed to be an invariably lethal neonatal disorder. Observation of some patients who survived into childhood prompted Blyth and Ockenden to propose a classification of patients into perinatal, neonatal, infantile, and juvenile forms.[119] These forms vary in the degree of cyst formation. Although conceptually useful, it is often difficult to place a patient into a given category. More than 100 mutations of the *PKHD1* gene have been identified that account for the clinical spectrum.[118,120,123] The most severe neonatal cases manifest with pulmonary hypoplasia secondary to the massive renal enlargement that compromises pulmonary development. It appears that as the extent of cyst formation decreases, the child has better pulmonary development and a greater likelihood of survival. Unfortunately, with increasing duration of survival there is worsening of the liver disease that may culminate in congenital hepatic fibrosis.[55,127] If one examines the kidneys of children with congenital hepatic fibrosis, two-thirds have a concentrating defect and have some degree of medullary cyst formation, findings indicating that ARPKD and congenital hepatic fibrosis are different manifestations of a single entity.

Most cases of ARPKD result in stillbirth, early neonatal death, or end-stage kidney disease by age 20 years. Affected neonates have massively enlarged and diffusely cystic kidneys that produce abdominal distention and compress thoracic organs (Fig. 1.48A). The lungs cannot develop normally, and death results from pulmonary hypoplasia. Despite the impressive cyst formation, the kidneys may be functional. If they are nonfunctional, oligohydramnios and a Potter phenotype may develop.

In severe cases, the cysts extend throughout the cortex and medulla in a distinctive radiating pattern imparting a spongy quality (Fig. 1.48B). Histologically, the cysts consist of dilated collecting ducts lined with uniform cuboidal cells (Figs. 1.49 and 1.50). The nephrons between the collecting ducts appear normal.

The liver in patients dying in the neonatal period shows portal bile duct proliferation that assumes a distinctive dilated and irregular branched pattern of anastomosing channels at the periphery of portal triads (Fig. 1.51). There is an increase in the size of portal areas with increased fibrous tissue. In older patients, congenital hepatic fibrosis develops, resulting in portal hypertension and hepatosplenomegaly.

In less severely affected kidneys of older children the appearance is variable, and the diagnosis may be less obvious. The kidneys are smaller, and the cysts are fewer. Medullary cysts are always present and tend to be elongated. Cortical cysts if present are often rounded and variably distributed (Fig. 1.52). The parenchyma adjacent to the cysts eventually develops atrophic changes with tubulointerstitial scarring and glomerulosclerosis. These features may create a resemblance to ADPKD. The presence of the liver lesion of congenital hepatic fibrosis therefore is a useful diagnostic feature. However, many diseases may be associated with renal cysts and liver disease, and awareness of additional anomalies is required for proper classification (Table 1.15).[55,114]

Autosomal Dominant Polycystic Kidney Disease

ADPKD is the most common cystic kidney disease and the most common genetically transmitted renal disease.[128-136] It occurs with an estimated frequency of between 1:500 and 1:1000 (Table 1.14). It is the fourth leading cause of end-stage renal disease, and affected patients comprise 5% to 10% of patients treated with dialysis. Although patients vary greatly in the age of onset of symptoms, most present in their third to fifth decade of life. Penetrance is nearly 100% if the individual survives to 80 years. Approximately 25% of affected patients lack a family history and presumably represent a new mutation. The disease results from mutations of *PKD1* and *PKD2* that localize to chromosome 16 in 90% of patients and to chromosome 4 in 10%, respectively. The gene product of *PKD1* is polycystin-1, a transmembrane glycoprotein involved in cell signaling. *PKD2* encodes for polycystin-2, a member of the transient receptor potential channel superfamily of nonselective cation channels.

Patients with ADPKD present with a variety of symptoms, most referable to the urinary tract. Chronic flank pain is the most common and correlates with renal weight and cyst size greater than 3 cm. Acute flank pain often reflects hemorrhage into a cyst. Hematuria is the second most common symptom. This may be gross, resulting in clot formation and urinary tract obstruction. Hypertension often develops early in the disease, and activation of the renin-angiotensin system secondary to intrarenal vascular occlusion by expanding cysts has been implicated. Urinary tract infection develops in 50% to 75% of patients and affects women more often than men. The infection may be confined to the collecting system or a cyst, or it may involve the parenchyma. Perinephric extension with abscess is a serious complication with a 60% mortality rate. Urate or calcium oxalate nephrolithiasis develops in 10% of patients. Extrarenal complications related to

TABLE 1.14 Comparison of Major Cystic Kidney Diseases

	Dysplasia	ARPKD	ADPKD
Incidence	1:1000-2000	1:50,000	1:500-1000
Bilateral	+/−	+	+
Segmental	+/−	−	−
Ureter abnormal	+	−	−
Reniform shape	+/−	+	+
Uniform cysts	−	+	−
Liver abnormal	+/−	+	+
Other malformations	+/−	−	−

ADPKD, Autosomal dominant polycystic kidney disease; *ARPKD*, autosomal recessive polycystic kidney disease.

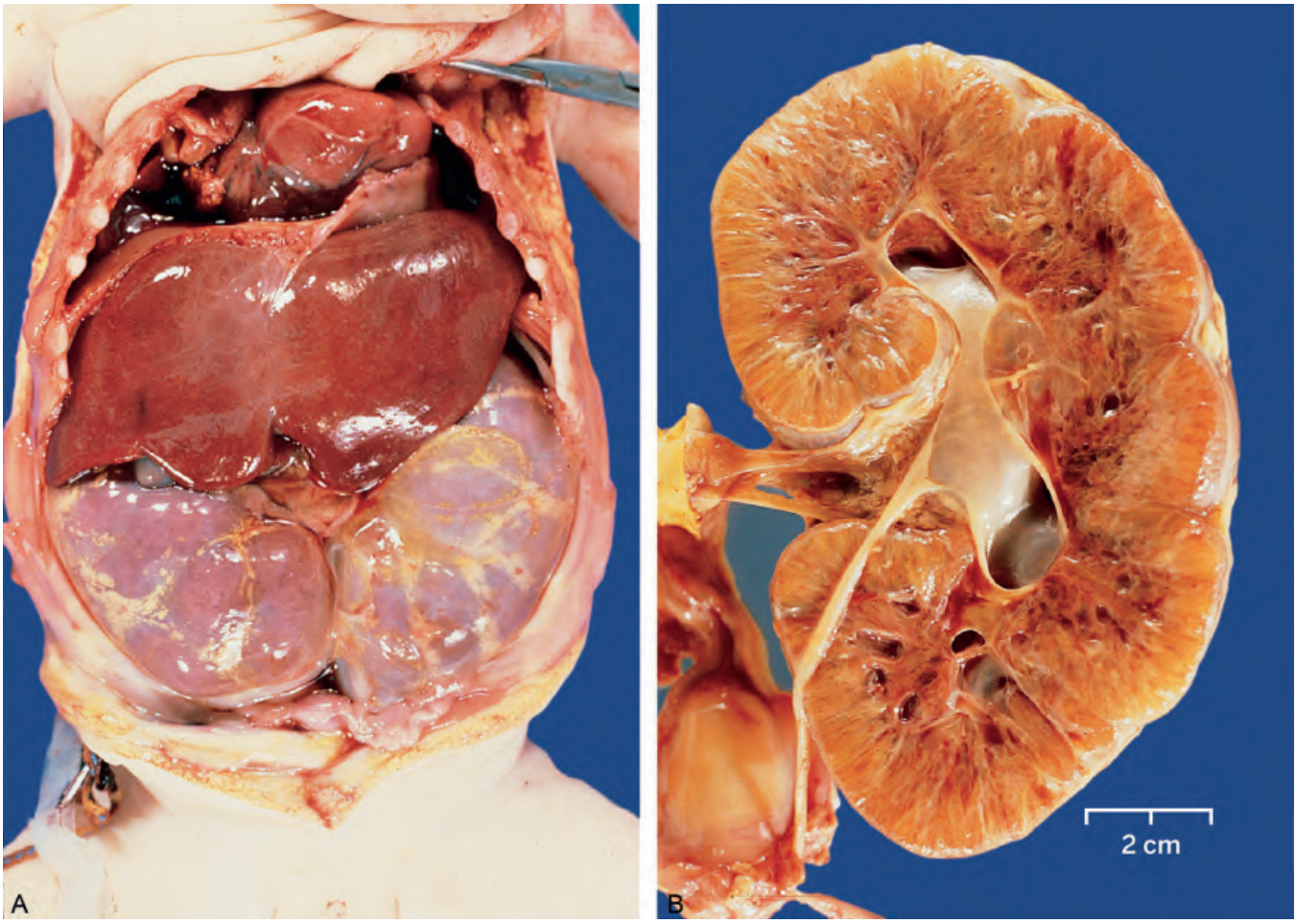


Fig. 1.48 (A) Autosomal recessive polycystic kidney disease showing massive kidneys that distend the abdomen, elevate the diaphragm, and compromise the thoracic cavity. (B) The bivalved kidney has a reniform shape and a normal collecting system. The cortex and medulla contain diffuse, relatively uniform cysts.

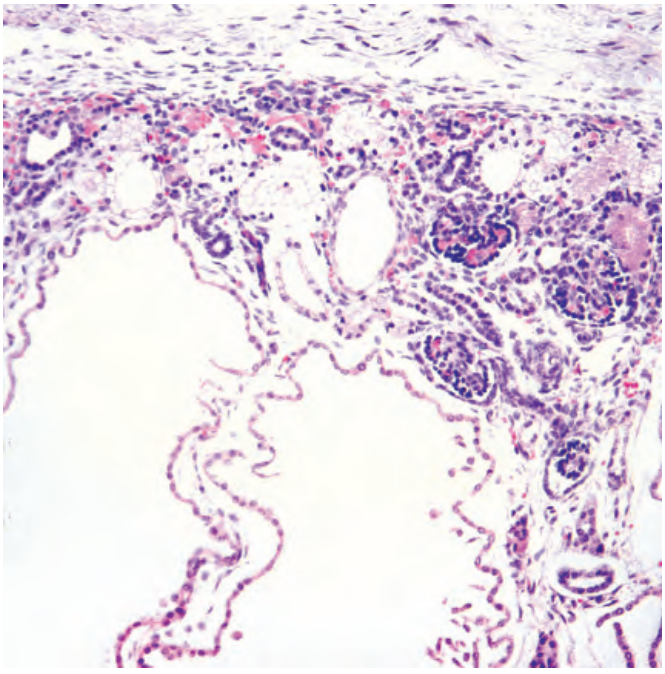


Fig. 1.49 The cortical cysts in autosomal recessive polycystic kidney disease are elongated and lined by cuboidal epithelium. Normally formed nephron elements are between the cysts.

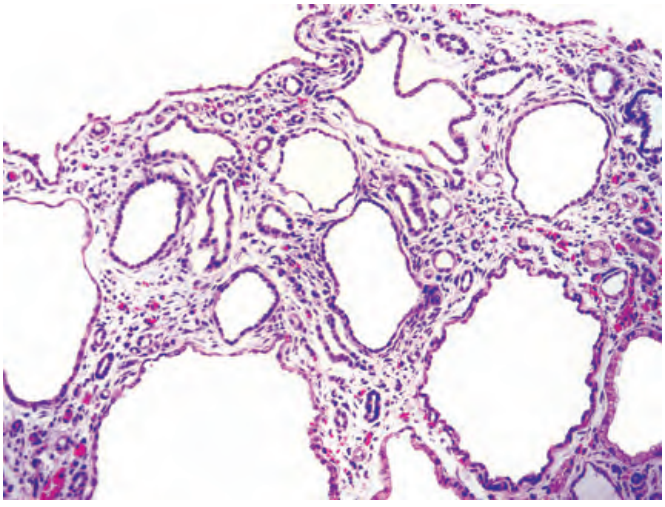


Fig. 1.50 The medullary cysts in autosomal recessive polycystic kidney disease are also lined with uniform cuboidal epithelium.

hypertension and berry aneurysms develop in 5% to 15%. Infection and cardiovascular disease represent the most common causes of death.[135,137]

Early in the disease (Fig. 1.53), the kidney may appear nearly normal with only scattered cysts in the cortex and medulla, and

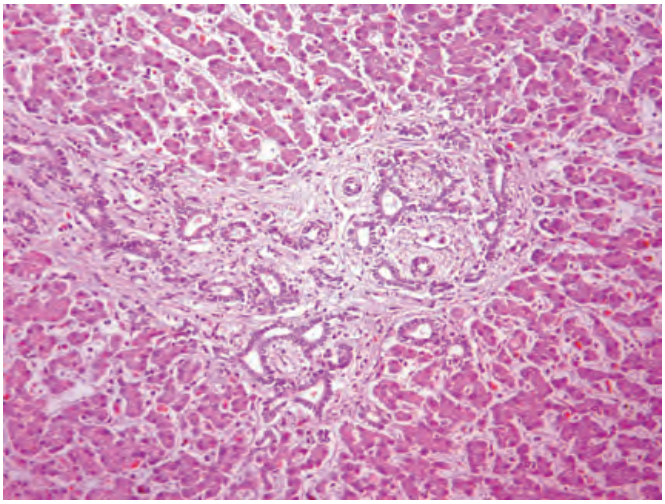


Fig. 1.51 The liver in perinatal autosomal recessive polycystic kidney disease showing the irregular branched architecture of the portal bile ducts and portal fibrosis.

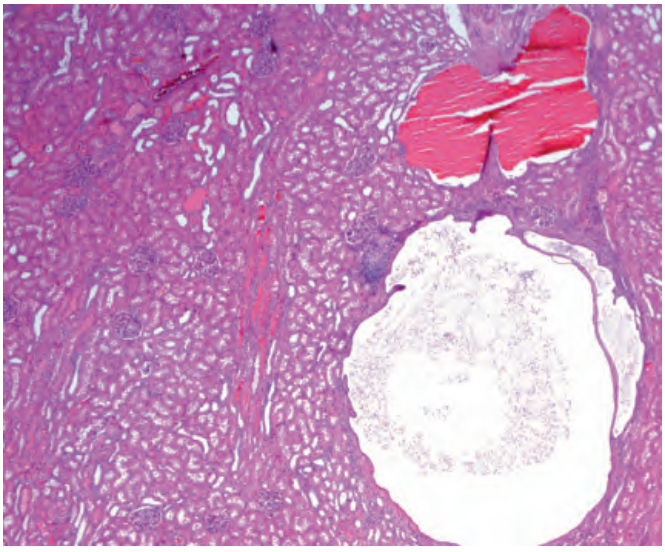


Fig. 1.53 Infantile onset of autosomal dominant polycystic kidney disease at age 7 years with a largely intact cortex and several cysts.

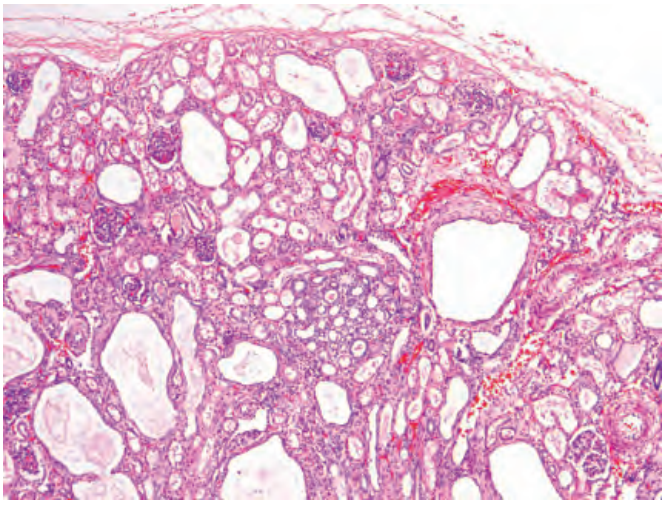


Fig. 1.52 This is an example of the infantile form of autosomal recessive polycystic kidney disease in a 4-year-old child. Collecting duct ectasia is less prominent. Interstitial fibrosis is developing.

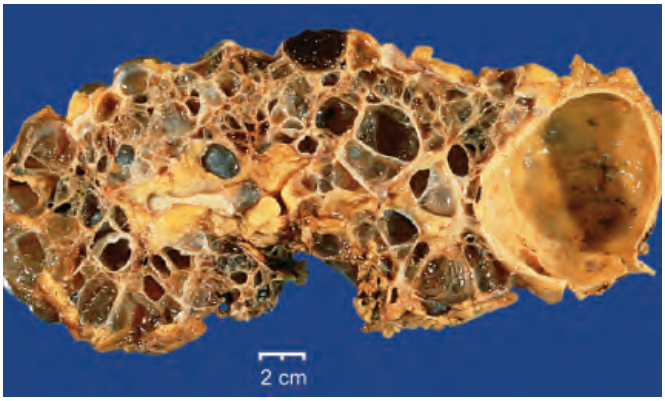


Fig. 1.54 Transverse section of an advanced-stage autosomal dominant polycystic kidney disease kidney. Both the cortex and the medulla are replaced by cysts.

TABLE 1.15 Cystic Renal Disease Associated with Congenital Hepatic Fibrosis or Biliary Cysts

Autosomal recessive polycystic kidney disease
Autosomal dominant polycystic kidney disease
Nephronophthisis
Joubert syndrome
Bardet-Biedl syndrome
Meckel-Gruber syndrome[a]
Oral-facial digital syndrome
Glomerulocystic kidney disease
Zellweger syndrome[a]
Ivemark syndrome[a]
Chondrodysplastic syndromes[a]
Trisomy C[a]
Trisomy D[a]

[a]*Additional* malformations are present.

normal intervening parenchyma. The cysts initially are small and develop in only about 1% of nephrons. Microdissection studies have shown that the cysts develop in all segments of the nephron.[132] Scanning electron microscopy and immunohistochemistry of cyst lining cells have confirmed these observations.[138]

As the disease progresses, the cysts grow in size and number, with resulting massive renal enlargement (Fig. 1.54). The cysts range in size from a few millimeters to several centimeters, and cyst contents vary from transparent to opaque to hemorrhagic fluid. Most cysts are lined with a single layer of flattened to cuboidal epithelium (Fig. 1.55). Hyperplastic foci or polyp formation are detectable in some cysts (Fig. 1.56).[139,140] The cyst contents may be proteinaceous or include red cells or calcific deposits. The intervening parenchyma shows interstitial fibrosis with a lymphoid infiltrate, tubular atrophy, and glomerular and vascular sclerosis. Despite the cystic transformation, the kidneys retain a reniform shape and preserve their collecting systems.

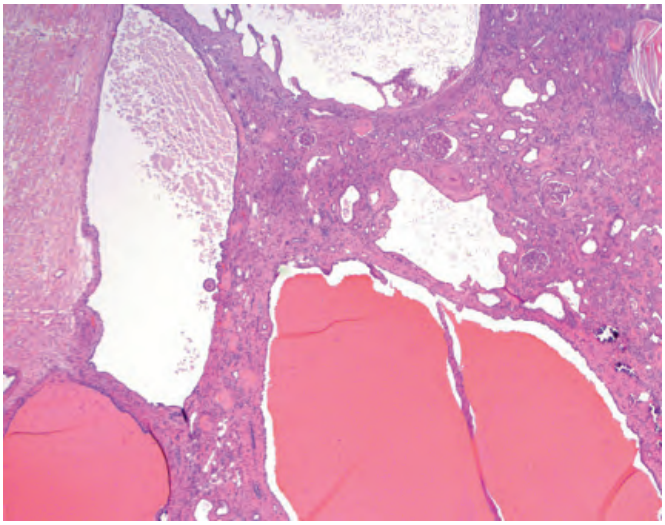


Fig. 1.55 Advanced autosomal dominant polycystic kidney disease from an adult with chronic renal failure shows severe interstitial scarring with calcifications and cysts that contain proteinaceous fluid.

Cystic Diseases (Without Dysplasia) in Hereditary Syndromes

Nephronophthisis

Nephronophthisis is an autosomal recessive tubulointerstitial nephropathy in which cysts often develop. It inevitably leads to end-stage kidney disease.[53,141-146] The first description of nephronophthisis was by Smith and Graham in 1945, who used the term *medullary cystic disease* to highlight the grossly visible medullary cysts.[141] Fanconi, in 1951, coined the term *juvenile familial nephronophthisis* in reference to its histologic outcome; *nephronophthisis* is Greek for "disintegration of nephrons." Most reports of nephronophthisis that appeared before the 1990s combined the two entities into the *medullary cystic disease/juvenile nephronophthisis complex* because of their morphologic similarities, a practice no longer appropriate considering differences in genetics and pathogenesis. Nephronophthisis is autosomal recessive and a ciliopathy, whereas medullary cystic kidney disease, now referred to as autosomal dominant tubulointerstitial disease (ADTID), is autosomal dominant and is not a ciliopathy as discussed later.[141,143-157]

There are three clinical phenotypes of nephronophthisis that are distinguished by age of onset: infantile, juvenile, and adolescent forms. Affected individuals present with polyuria and polydipsia resulting from salt wasting, a concentration defect, anemia disproportionately severe for the level of renal insufficiency, and growth retardation. Although fundamentally a tubulointerstitial disease, 15% of patients have extrarenal components: retinal dystrophy (Senior-Loken syndrome), oculomotor apraxia (Cogan syndrome), situs inversus (infantile nephronophthisis), and rarely, congenital hepatic fibrosis.[53,141-146,149]

Twenty mutated genes have been identified in nephronophthisis that encode for proteins expressed in the primary cilium, centrosome, and cell junctions of renal epithelial cells. These mutations, however, account for only 30% of nephronophthisis cases. Most mutations are responsible for some of the juvenile and adolescent forms, whereas *NPHP2* and occasionally *NPHP3* mutations are responsible for the infantile form. The juvenile and adolescent forms cannot be histologically distinguished. However, the infantile form has several distinctive features.

The kidneys in nephronophthisis are normally developed at birth. Cyst formation occurs in approximately 70% of patients but is usually delayed until advanced or end-stage disease develops. Sequential imaging shows that most patients lack cysts at presentation but many subsequently develop cysts, and that cyst frequency and size increase over time. Therefore early in the disease no cysts may be detectable to assist in the diagnosis.

Kidney size in the juvenile and adolescent forms is usually normal or smaller than normal. When cysts develop, they congregate at the corticomedullary junction and may range from 1 to several

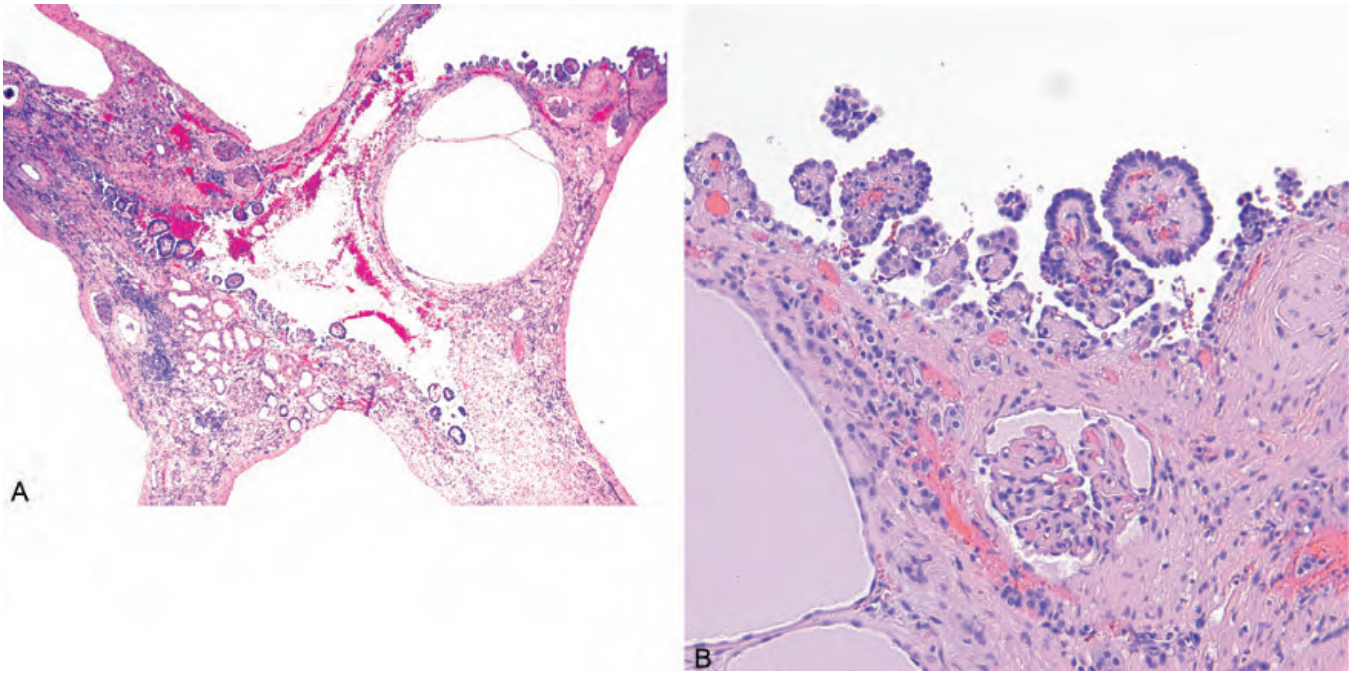


Fig. 1.56 Papillary tufts lining a cyst in autosomal dominant polycystic kidney disease (A and B).

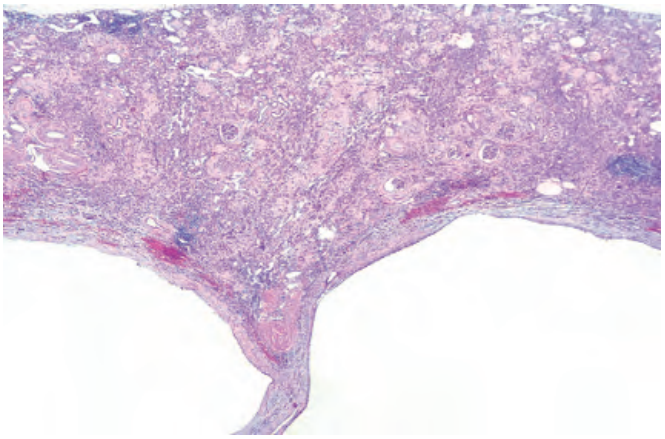


Fig. 1.57 Whole-mount kidney in nephronophthisis showing outer medullary cysts. The cortex has advanced scarring and scattered small cysts in the deep cortex. *(Courtesy of The Jay Bernstein, M.D. Consultative Collection.)*

centimeters in diameter (Fig. 1.57). In the infantile form the kidneys may be larger than normal because cyst formation occurs earlier in the disease, before contraction from tubulointerstitial scarring. If cysts develop they may involve the medulla but generally are cortical in location.

The primary histologic findings in nephronophthisis are nonspecific, so complete laboratory and clinical data are necessary. The juvenile and adolescent forms show a radial distribution of cortical injury with atrophic zones that alternate with zones of normal or hypertrophied tubules largely localized to medullary rays (Fig. 1.58A). Before end-stage renal disease the tubulointerstitial injury exceeds the extent of glomerulosclerosis, thus implicating a primary tubulointerstitial process (Fig. 1.58A). The tubules have an irregular profile sometimes described as figure-eight or T-shaped because of the tubule diverticula, particularly numerous in the limbs of Henle. Many small "cysts" are not true cysts but are localized segments of tubular dilatation with patent afferent and efferent tubule connections.[155]

The irregularly shaped atrophic tubules show prominent multilayering of their tubular basement membranes, or the tubule basement membranes may range from thick and irregular, to thin and attenuated, to segmental absence of basement membrane (Fig. 1.58B). Dense interstitial fibrosis is present often with a prominent lymphoid cell infiltrate. Periglomerular fibrosis is a common finding, as it is in other chronic inflammatory interstitial diseases. As the tubulointerstitial disease progresses, glomeruli undergo sclerosis. Advanced cases show marked fibrointimal thickening of arteries and medial hypertrophy.

Medullary cysts, when present, arise from the loops of Henle and collecting ducts. The cyst cell lining is variable. A cuboidal cell lining is present in small cysts, but large cysts may have a flattened, nondescript cell lining surrounded by a rim of dense fibrous tissue. Medullary inflammation is not usually present.

In the infantile form of nephronophthisis the cysts affect tubules, predominantly distal tubules and collecting ducts, in the form of tubular dilation or ectasia (Fig. 1.59). Macrocystic dilation of tubules occurs and may be visible grossly. The ectatic and grossly cystic tubules are lined by cuboidal to columnar epithelium typical of distal tubules and collecting ducts. The tubules between the cysts may be normal or atrophic. Atrophic tubules are small and lined by inconspicuous cuboidal epithelium with thin tubular basement membranes that lack the irregular basement membrane multilayering of the juvenile and adolescence forms. Glomeruli may develop microcysts in which the Bowman capsule is enlarged two to three times normal. Although mild interstitial inflammation occurs, it is usually less than in the juvenile and adolescent forms.

Autosomal Dominant Tubulointerstitial Disease

ADTID, previously referred to as medullary cystic kidney disease (MCKD), is like nephronophthisis, a chronic progressive tubulointerstitial disease in which cysts may develop. It is a rare disease primarily of adults, but the age of onset overlaps with older patients with nephronophthisis.[151,158-169] There are four known causes of ADTID due to mutation of uromodulin (UROM; Tamm-Horsfall glycoprotein), mucin 1 (MUC1; epithelial membrane antigen), renin (REN), and hepatocyte nuclear factor 1β (HNF1B;

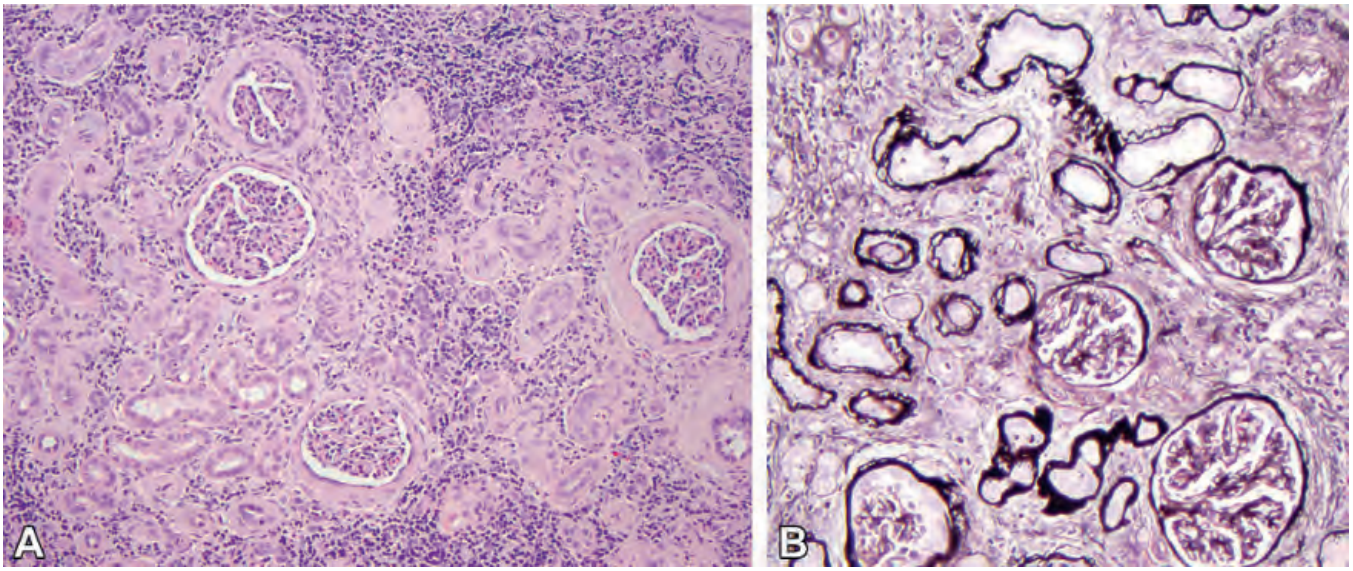


Fig. 1.58 (A) Nephronophthisis showing a chronic interstitial nephritis. Although there is periglomerular fibrosis the glomeruli otherwise are intact, associated with severe chronic tubulointerstitial injury. (B) The atrophic tubules typically show basement membrane multilayering (Jones methenamine silver stain). *(A and B, Courtesy of The Jay Bernstein, M.D. Consultative Collection.)*

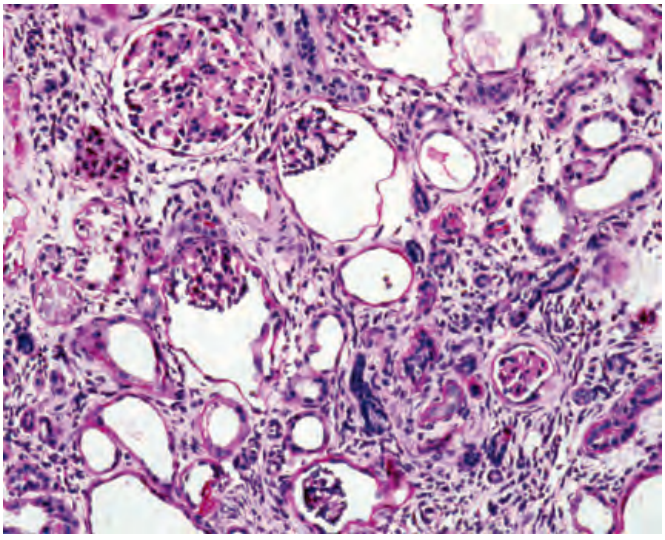


Fig. 1.59 This infantile form of nephronophthisis also shows chronic interstitial nephritis. Glomerular microcysts are visible, and the atrophic tubules lack basement membrane multilayering (periodic acid–Schiff stain.) *(Courtesy of The Jay Bernstein, M.D. Consultative Collection.)*

Table 1.16). One or more additional mutations remain to be identified. The recommended terminology for these diseases is UROM kidney disease, MUC1 kidney disease, REN kidney disease, and HNF1B kidney disease.

Most patients present in the third to fourth decade of life with polyuria and polydipsia as a result of salt wasting and a concentration defect (Table 1.16). They progress to end-stage disease, usually by the fourth to seventh decade, although the rate of progression varies within and between affected families. Hyperuricemia and gout are common, especially in UROM and REN kidney disease. REN kidney disease patients have anemia refractory to treatment, hyperkalemia, and often low BP.

The kidneys in ADTID may be enlarged if cysts are prominent. Although medullary cysts are common, they are usually present in small numbers and develop late in the disease. Within a family not all affected individuals have cysts. The cysts congregate at the corticomedullary junction and can be several centimeters (Fig. 1.60A). Microscopically, all four ADTIDs show a nonspecific chronic interstitial nephritis with tubular atrophy, interstitial fibrosis, and periglomerular fibrosis similar to nephronophthisis. If cysts are present, they are lined with a flattened to cuboidal epithelium. UROM kidney disease contains uromodulin intracellular aggregates in thick ascending limb of Henle cells (Fig. 1.60B). REN kidney disease shows reduced to absent renin staining in cells of the juxtaglomerular apparatus. MUC1 and HNF1B kidney disease have no defining histologic findings. However, patients with HNF1B kidney disease often have congenital anomalies of the kidney and/or lower urinary tract.[78,170]

Von Hippel–Lindau disease

Von Hippel–Lindau disease is an uncommon autosomal dominant disorder due to germline mutation of the *VHL* gene in which renal and extrarenal cysts and neoplasms develop.[171] The extrarenal manifestations include retinal, cerebellar, and spinal hemangioblastomas, pheochromocytoma, epididymal and pancreatic cysts, and cystadenomas. The renal manifestations consist of multiple and bilateral cysts that develop in 75% of patients, and renal cell carcinomas, often bilateral and multicentric, that develop in approximately 50% of patients (Fig. 1.61).[172-176] The mutant *VHL* gene has been localized to chromosome 3p25, adjacent to the gene implicated in development of sporadic clear cell renal cell carcinoma.[172,174,175]

The renal cysts are lined with glycogen-rich cells like those of grade 1 to 2 clear cell renal cell carcinoma (Fig. 1.62).[173,176-178] These range from a benign-appearing lining of one to two cell layers of clear cells to multiple layers of cells. The broad spectrum of neoplastic proliferative lesions ranges from cysts with papillary tufts of mildly atypical cells, to cysts with solid mural nodules of clear cell renal cell carcinoma, to markedly cystic clear cell renal cell carcinoma. This morphologic spectrum represents a challenge in the classification of lesions in biopsy and nephrectomy material. Despite awareness of the high frequency of renal cell carcinoma in this syndrome, metastatic renal cell carcinoma remains the leading cause of death.

Tuberous Sclerosis

Tuberous sclerosis complex (TSC) is an autosomal dominant disorder characterized by mental retardation, epilepsy, angiofibromas, cardiac rhabdomyomas, renal angiomyolipomas, renal cell carcinomas and renal cysts.[179-184] Two genes have been identified that cause TSC, *TSC1* and *TSC2,* mapped to chromosomes 9 and 13 that encode for hamartin and tuberin, respectively. The latter locus is within a few nucleotides of the *PKD1* locus. Although renal cysts are uncommon and usually not extensive, some individuals, usually children, have dual mutations involving *TSC2* and *PKD1.* They develop a diffuse cystic kidney disease with numerous large cortical and medullary cysts that resemble autosomal dominant polycystic disease; this disorder is known as the *TSC2/PKD1* contiguous gene syndrome.

TABLE 1.16 Autosomal Dominant Tubulointerstitial Diseases: Comparison of Major Clinical and Pathologic Features

Mutation	Onset/ESRD (years)	Laboratory/Clinical Results	Extrarenal Disease	Biopsy	Renal Cysts	Other Pathology
UROM	20-70/avg. 54	Gout, conc. defect	None	CTIN	40%	UROM inclusions
MUC1	20-70/avg. 40	Gout, conc. defect	None	CTIN	12%-17%	None
REN	Childhood/30-40	Gout, conc. defect, ↓ BP, anemia, ↑ K	None	CTIN	None	↓ Renin in JGA
HNF1B	24/Adulthood	Gout, conc. defect, DM, ↓ Mg	Pancreas hypoplasia/agenesis	CTIN	60%-80%	CAKUT

avg., Average; BP, blood pressure; *CAKUT*, congenital anomalies of the kidney and urinary tract; *Conc*, concentrating; *CTIN*, chronic tubulointerstitial nephritis; *DM*, diabetes mellitus; *ESRD*, end-stage renal disease; *HNF1B*, hepatocyte nuclear factor 1β; *JGA*, juxtaglomerular apparatus; *K*, potassium; *Mg*, magnesium; *MUC1*, mucin-1; *REN*, renin; *UROM*, uromodulin.

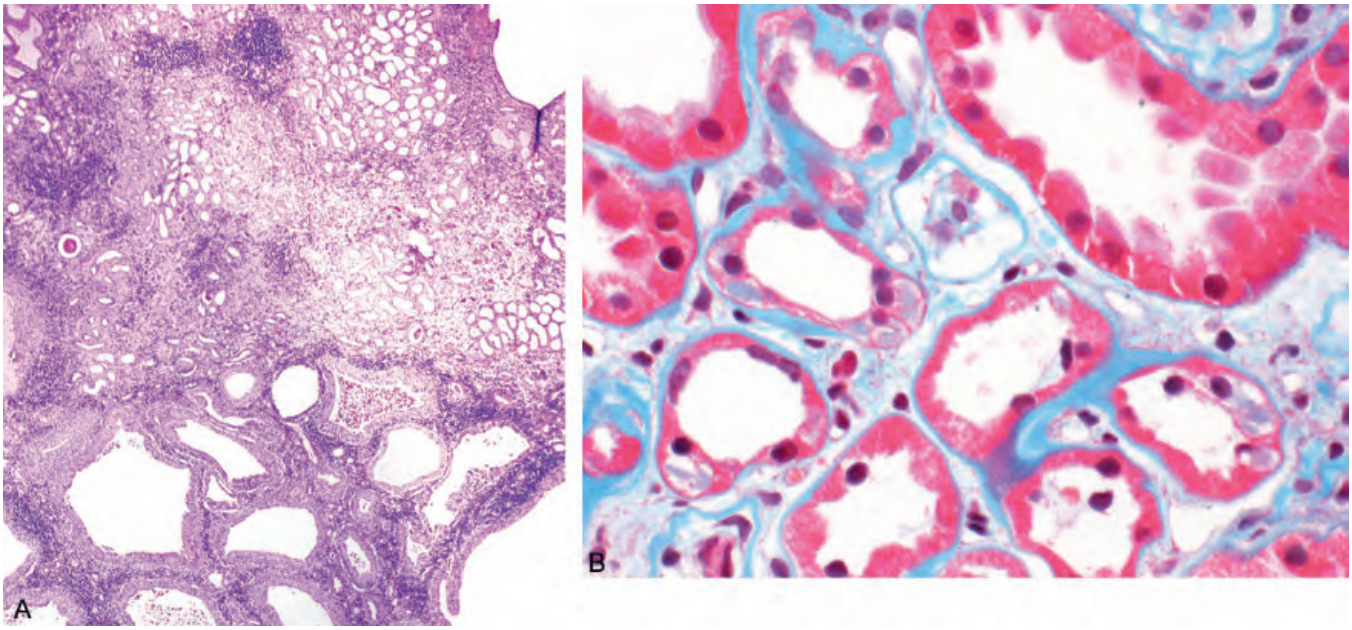


Fig. 1.60 (A) Medullary cystic disease showing cysts along the outer medulla and advanced cortical scarring. *(Courtesy of The Jay Bernstein, M.D. Consultative Collection.)* (B) This is UROM (uromodulin) kidney disease. Trichrome stain nicely demonstrated the intracellular aggregates of retained uromodulin (Tamm-Horsfall protein).

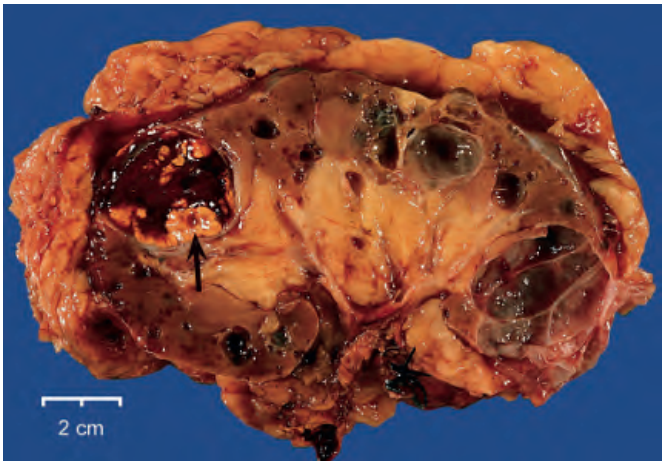


Fig. 1.61 Nephrectomy in von Hippel–Lindau disease that shows multiple cysts. One cyst contains a mural nodule (*arrow*) of renal cell carcinoma.

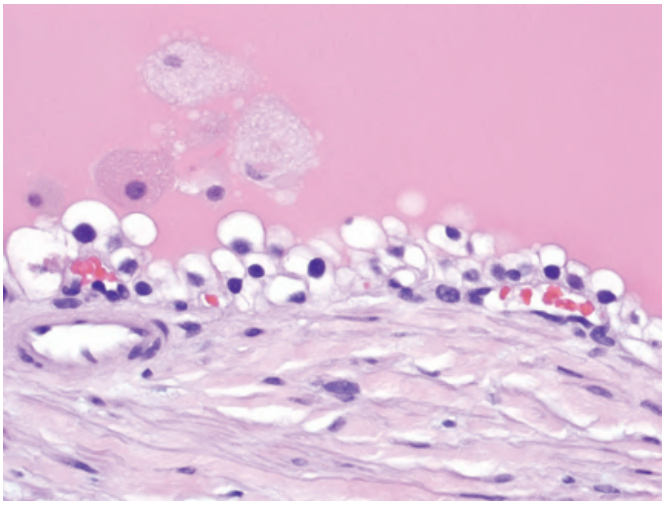


Fig. 1.62 Cyst in von Hippel–Lindau disease is lined with low nuclear grade clear cells.

Many tubules and cysts in tuberous sclerosis are distinctive and provide diagnostic specificity in the recognition of this disorder.[143,153] The cysts are lined with large eosinophilic cells with large hyperchromatic nuclei (Fig. 1.63). The cyst lining cells may form papillary or polyploid masses, and may show occasional mitotic activity. Renal cell carcinomas of several types also develop in TSC but are far less frequent than in von Hippel–Lindau disease.[185]

Glomerulocystic Kidneys

A glomerulocystic kidney (GCK) is defined as the presence of glomerular cysts in more than 5% of glomeruli in the absence of another cystic kidney disease. A GCK may be primary or secondary. *Glomerulocystic kidney disease* is used in reference to the primary forms that include a sporadic form, a familial form, and forms caused by mutations of UROM and HNF1B (Table 1.3). Secondary forms of glomerular cysts occur in many unrelated disorders such as ADPKD, ARPKD, TSC, a variety of syndromes, ischemic glomeruli, and renal dysplasias.[186-191] In these diseases, glomerular cysts may be present, but glomerular cysts are not definitional of the entity.

A glomerular cyst is defined as cystic dilation of Bowman capsule to two to three times normal. The glomerular tuft itself may be normal or abnormally formed. In most cases of GCK the glomerular cysts are widespread and affect far more than 5% of glomeruli (Fig. 1.64). The Bowman capsule dilation in some cases of GCK may be massive, sufficient to result in a grossly cystic kidney. In other cases the kidneys may be small and hypoplastic.

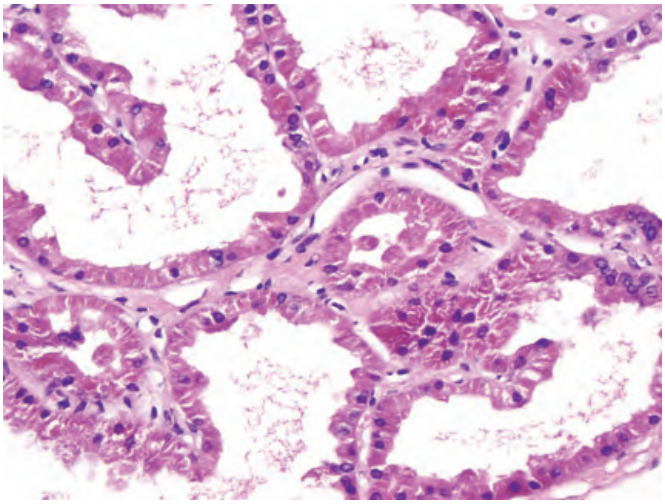


Fig. 1.63 The cysts, as well as scattered individual tubules in noncystic kidneys, in tuberous sclerosis are often lined by large cells with densely eosinophilic cytoplasm and prominent nuclei. *(Courtesy of The Jay Bernstein, M.D. Consultative Collection.)*

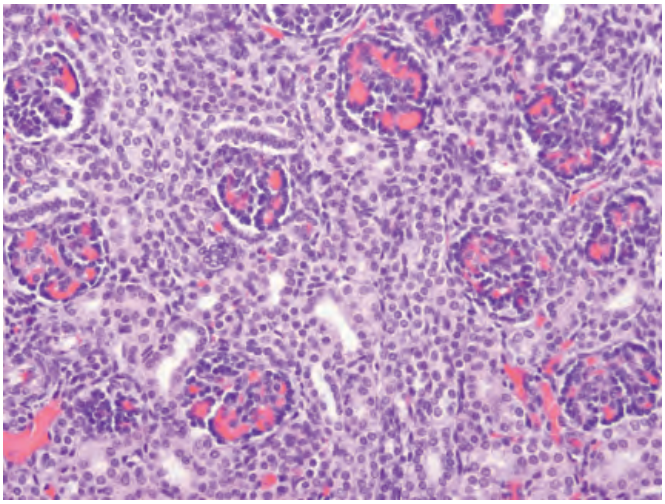


Fig. 1.65 Congenital renal tubular dysgenesis manifesting with oliguric acute renal failure. No normal proximal tubules are present. All cortical tubules resemble distal tubules and are lined by small cuboidal cells without interstitial expansion.

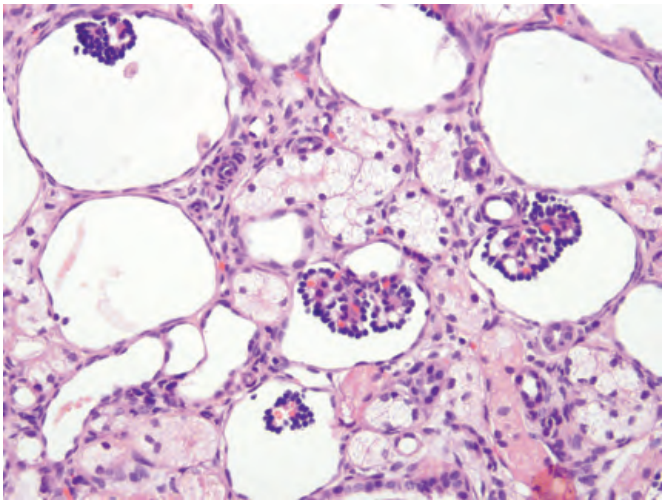


Fig. 1.64 Glomerulocystic kidney disease showing microcysts principally involving Bowman capsules.

Miscellaneous Diseases

Renal Tubular Dysgenesis

Failure of proximal tubule differentiation is known as renal tubular dysgenesis.[192-201] It results in neonatal renal failure with the oligohydramnios sequence, a Potter syndrome phenotype, and death from pulmonary hypoplasia. Renal tubular dysgenesis may be primary or secondary. Primary renal tubular dysgenesis is an autosomal recessive disorder due to mutation of one of the renin-angiotensin system genes. Secondary causes include monochorionic twins with twin–twin transfusions in which only the donor twin is affected, congenital renal artery stenosis, major cardiac malformations, and as a complication of maternal use of angiotensin-converting enzyme inhibitors (can be associated with hypocalvaria).[172]

The kidneys are usually grossly normal, although they may be decreased in weight. The glomeruli are close together because of the lack of the normally voluminous proximal tubule cells. The intervening tubules resemble distal tubules. The cells and tubular profiles are small (Fig. 1.65). The tubule cells demonstrate distal tubule and collecting duct phenotype by immunohistochemistry and lectin staining. Ultrastructural studies show an undifferentiated phenotype. The cells lack a microvillous brush border and contain scant organelles.

Acquired Cystic Kidney Disease

Acquired cystic kidney disease refers to the development of multiple and bilateral renal cysts in patients whose chronic renal failure cannot be attributed to a hereditary cystic disease. Although identified as long ago as 1847 by Simon, in 1977 Dunnill revived interest in this phenomenon when in an autopsy study of hemodialysis patients he not only observed a high prevalence of renal cysts, but also found renal tumors in 20% of the patients.[202,203] One patient had died of metastatic renal cell carcinoma. The development of both cysts and tumors appears to be related to the uremic state because it is independent of the type of dialysis and the cause of the original renal disease.[204-215]

Acquired cystic kidney disease is bilateral and asymptomatic in its early stages. Cysts are present in 8% of patients at the time dialysis is initiated and increase in incidence, number, and size proportional to the duration of dialysis. After 3 to 5 years of dialysis, cysts have developed in approximately 50% of patients, whereas by 10 years, almost 90% of patients have cysts.[216] The complications of acquired cystic kidney disease include intrarenal and retroperitoneal hemorrhage, cyst infection, and renal cell carcinoma, which may account for 3% to 4% of all deaths.[211-215] All of the major types of renal cell carcinoma can develop in the setting of acquired cystic kidney disease. However, one tumor, acquired cystic kidney disease–associated renal cell carcinoma, appears to be the most common cancer. This tumor has a distinctive morphology and a feature unique among renal cell carcinomas: the frequent presence of calcium oxalate crystals. Although improvement in the cystic disease occurs in many patients after successful renal transplantation, the influence of transplantation on neoplastic complications remains unclear. As the number of patients receiving dialysis increases and their survival rates improve, the occurrence of cystic disease and neoplastic complications can also be expected to increase.

The cysts initially form in the proximal tubules of kidneys with end-stage disease. Most cysts are less than 0.5 cm in diameter, but 2- to 3-cm cysts can develop. Initially the cysts are cortical, but in advanced cases medullary cysts form and the entire kidney may be replaced by cysts and resemble a smaller version of ADPKD (Fig. 1.66). The cysts are lined with flattened, cuboidal, or columnar epithelium and may contain a proteinaceous to hemorrhagic fluid. Foci of epithelial hyperplasia are common in the cysts and tubules. Papillary adenomas are also commonly present.

Localized Cystic Kidney Disease

Localized cystic kidney disease is an uncommon cystic kidney disease that histologically resembles ADPKD. It is not a genetic disease and lacks the progressive renal failure and extrarenal complications of ADPKD.[58,217-220] The affected kidney is usually partially involved but may be diffusely cystic (Fig. 1.67). The contralateral kidney should be noncystic. When the kidney is partially involved, it has a tight collection of variably sized cysts with thin cyst septa. The lesion is surrounded by normal kidney. The cystic lesion invariably involves the medulla but may extend into the cortex. The cysts contain serous fluid and are lined by a low cuboidal to flattened epithelium. Excision and follow-up may be required to establish the diagnosis and exclude a cystic neoplasm.

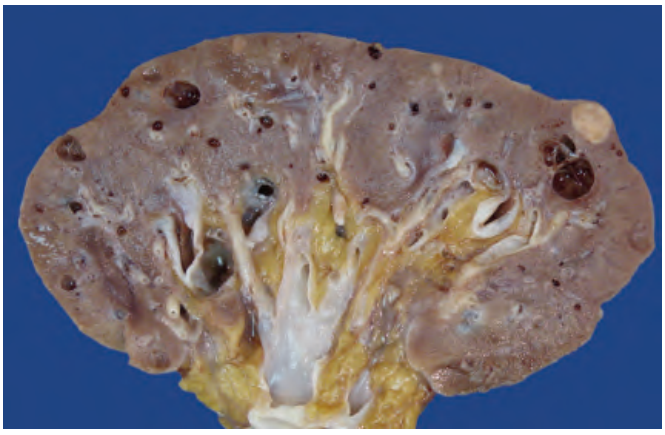


Fig. 1.66 Acquired cystic disease of the kidney. There are multiple cysts in both cortex and medulla. Although this is a mild or early example with abundant noncystic parenchyma, notice the small neoplasm to the upper right. Several smaller tumors are also present elsewhere.

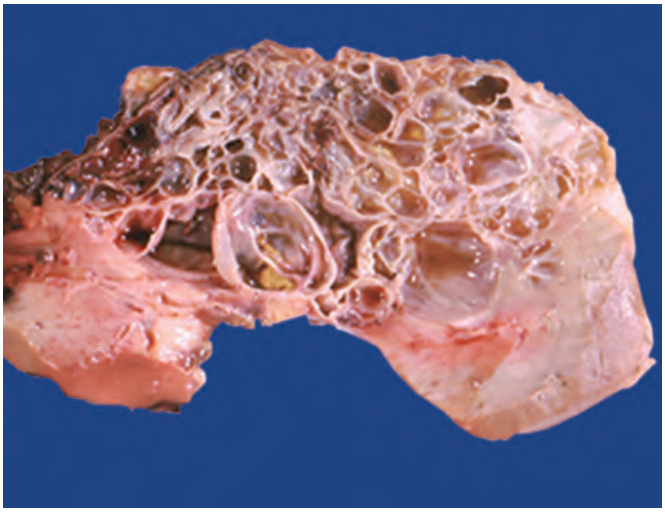


Fig. 1.67 This is an example of isolated/localized cystic kidney disease. The central portion of the kidney is replaced by a diffusely cystic lesion that on imaging studies would likely be regarded as a cystic neoplasm such as a cystic nephroma. (Courtesy of The Jay Bernstein, M.D. Consultative Collection.)

Medullary Sponge Kidney

Medullary sponge kidney is a cystic renal malformation in which there is ectasia of the papillary collecting ducts of one or more renal pyramids associated with nephrocalcinosis and nephrolithiasis (Fig. 1.68).[221,222] Medullary sponge kidney is usually bilateral and is more common in male patients. It is usually detected radiographically in adults evaluated for nephrolithiasis. The kidneys are not enlarged, and renal function is normal, although a concentrating defect may be present in more severely affected patients.

Microscopically, the collecting ducts are dilated and lined with cuboidal or flattened epithelium. Intratubular calcifications (microliths) are common. If stones have obstructed the ducts, overlying cortical scarring may be present. Medullary sponge kidney can be most readily distinguished from other diseases with medullary cysts such as ADTID, nephronophthisis (NPHP), and juvenile presentation of ARPKD by the presence of nephrolithiasis and nephrocalcinosis on imaging studies.

Simple Cortical Cyst

Simple cortical cysts are the most common cystic renal lesions.[223,224] They are rare before the age of 40 years. Therefore any cyst in a child or young adult, especially if bilateral, can be an important clue to the presence of a cystic kidney disease. Simple cysts increase in frequency with advancing age. In older patients the cysts may be multiple and large, and typically are exophytic (Fig. 1.69). The cysts are lined with a flattened layer of cells or lack

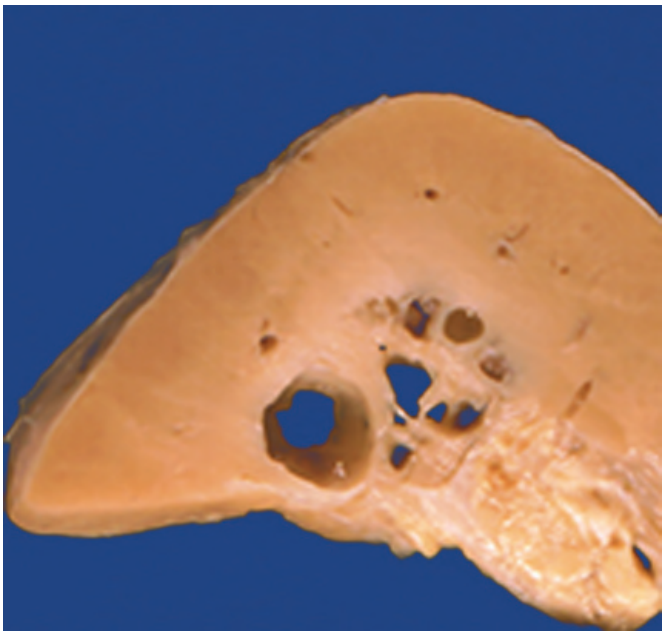


Fig. 1.68 Medullary sponge kidney showing a collection of large cysts that replace the distal renal medulla. These represent prominent ectasia of the distal collecting ducts. *(Courtesy of The Jay Bernstein, M.D. Consultative Collection.)*

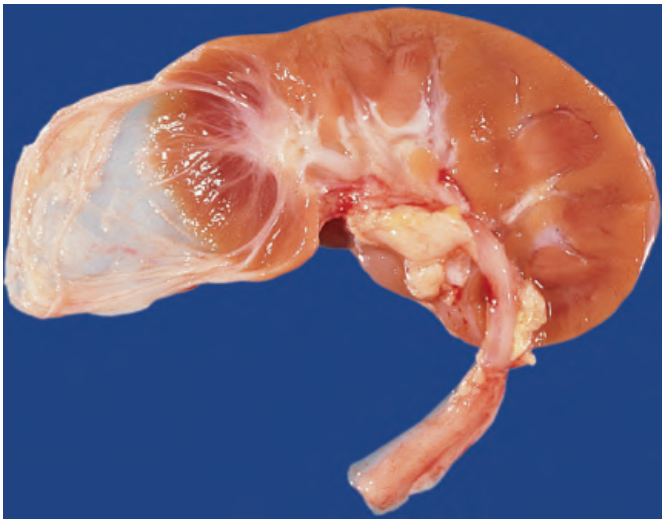


Fig. 1.69 A large, simple cortical cyst found incidentally at autopsy. Notice its thin translucent wall.

TABLE 1.17 Vascular Diseases of the Kidney

Hypertension-associated renal disease
Benign nephrosclerosis
Malignant nephrosclerosis
Thrombotic microangiopathy
Renal artery stenosis
Atherosclerosis
Fibromuscular dysplasia
Renal artery dissection
Renal artery aneurysm
Arteriovenous malformation and fistula
Renal emboli and infarcts
Renal cortical necrosis
Renal papillary necrosis
Renal cholesterol microembolism syndrome
Renal artery thrombosis
Renal vein and renal venous thrombosis
Bartter syndrome
Vasculitis

an epithelial lining. The cyst wall may occasionally calcify, a radiographic finding mimicking infection or malignancy.

Hydrocalyx, Megacalycosis, and Calyceal Diverticulum

Several lesions—hydrocalyx, megacalycosis, and calyceal diverticulum—have in common a cavity lined with urothelium that communicates with the collecting system and are associated with recurrent infections and nephrolithiasis.[225-227] In hydrocalyx there is caliectasis secondary to infundibular stenosis. The stenosis may be congenital or the sequela of inflammation. By contrast, in megacalycosis obstruction is not evident. In both lesions the renal pyramid is flattened or concave, and in cases complicated by infection, parenchymal inflammation and scarring may be present. In calyceal diverticulum the cavity communicates with a minor calyx via a narrow isthmus, and no obstruction is present. The upper pole calyx is involved in 54% of cases. Parenchymal inflammation and scarring usually are absent unless the case is complicated by infection.

Vascular Diseases

Hypertension-Associated Renal Disease

Vascular disease in its various forms is the most common cause of renal injury encountered at autopsy because of the high incidence of atherosclerosis and hypertension (Table 1.17 and Fig. 1.70).[228-230] A connection between hypertension and renal and cardiovascular diseases has been recognized for more than 100 years.[228-236] Hypertension-associated renal disease was first separated from other forms of renal disease in 1914 by Volhard and Fahr, who first recognized the existence of two forms.[237] The most common form, which they called *benign nephrosclerosis*, occurred in older individuals who had mild hypertension and little renal impairment. The second form, which Volhard and Fahr called *malignant nephrosclerosis*, occurred in younger patients with severe hypertension and renal failure.[237] Although most patients (90% to 95%) with hypertension have idiopathic disease, numerous secondary causes can produce either benign or malignant nephrosclerosis (Table 1.18).

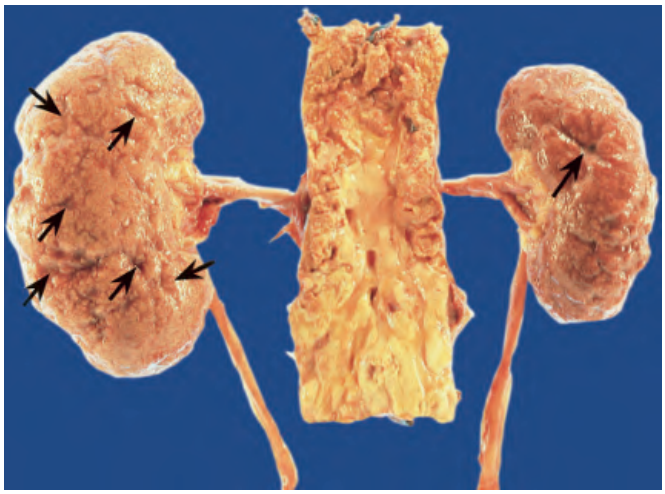


Fig. 1.70 Complicated atherosclerotic vascular disease showing arterial nephrosclerosis, small atheroembolic infarcts (*arrows*), and an atrophic right kidney from renal artery stenosis.

Benign Nephrosclerosis

Benign (or essential) hypertension is an asymptomatic disorder that affects approximately 50 million people in the United States.[228-230] The pathogenesis of essential hypertension is presumed to be multifactorial, involving genetic, epigenetic, environmental, and immune mechanisms. Heritability of BP is estimated to be 31% to 68%, but genome-wide association and linkage studies to date were able to identify only factors with small effects on BP or those that impart increased predisposition to hypertension in certain ethnic groups. Interestingly most monogenic forms of hypertension are related to defects in renal sodium handling (Table 1.19). Unfortunately, in most patients the cause of hypertension remains enigmatic. Hypertension is often first diagnosed around age 45 to 54 years, but there has been an increasing incidence of early-onset hypertension.[238-241] If unchecked, hypertension places the patient at risk not only for complications related to atherosclerotic vascular

TABLE 1.18 Types and Causes of Hypertension

Primary

Benign (essential) hypertension
Malignant hypertension

Secondary

Renal artery stenosis
Acute glomerulonephritis
Chronic renal diseases
Neoplasms
- Renin-producing tumors
- Adrenal cortical tumors
- Pheochromocytoma

Endocrine abnormalities
- Thyrotoxicosis
- Adrenal cortical hyperplasia
- Hyperparathyroidism
- Oral contraceptives

Neurogenic
Miscellaneous vascular
- Preeclampsia
- Thrombotic microangiopathy
- Vasculitis
- Coarctation of aorta

TABLE 1.19 Examples of Monogenic Forms of Hypertension

	Causative Gene/Mutation
Liddle syndrome	Epithelial sodium channel
Gordon syndrome (pseudohypoaldosteronism type II)	Thiazide-sensitive sodium chloride cotransporter
Geller syndrome	Mineralocorticoid receptor
Glucocorticoid remediable hyperaldosteronism	11-α-hydroxylase, aldosterone synthase
Syndrome of apparent mineral corticoid excess	11-α-hydroxysteroid dehydrogenase
Congenital adrenal hyperplasia	11-α-hydroxylase or 17-β-hydroxylase

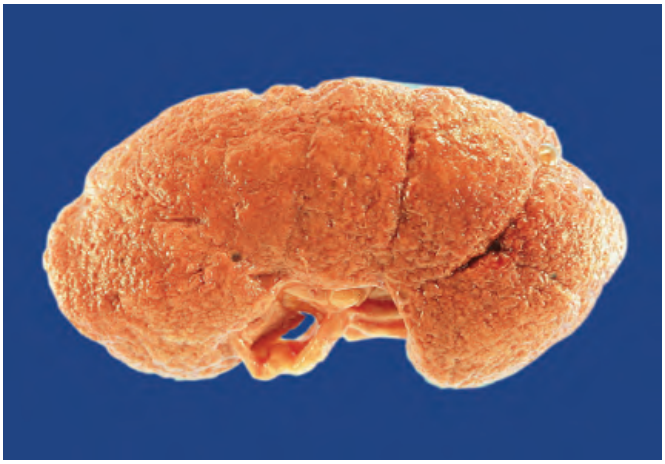


Fig. 1.71 Granular subcapsular surface of benign hypertension-associated arterial nephrosclerosis.

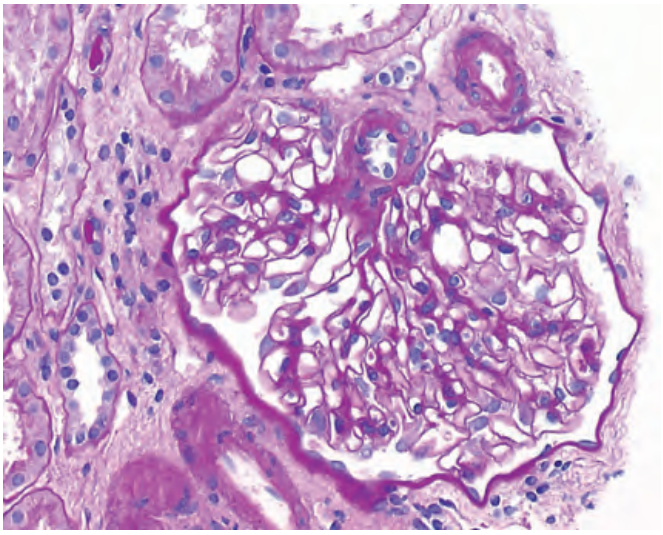


Fig. 1.72 Arteriolar hyalinosis in hypertension. In contrast with diabetes, hyalinosis in hypertension is often limited to the afferent arteriole (periodic acid–Schiff stain).

disease such as renal insufficiency, congestive heart failure, coronary artery disease, and stroke, but also other diseases such as diabetes mellitus.[242,243] Although benign hypertension will not cause renal failure in most patients, it is sufficiently prevalent to account for approximately 15% to 30% of patients with end-stage renal disease.

In benign nephrosclerosis the kidneys are symmetrically reduced in size and weigh between 60 and 100 g. They have granular subcapsular surfaces and cortical thinning, the extent of which is influenced by the severity and duration of the hypertension (Fig. 1.71).[231-233] Microscopically, arteries of interlobar size or greater show fibrous intimal thickening with reduplication or fragmentation of the elastic lamina and smooth muscle hyperplasia. In contrast with atherosclerotic disease, lipid and calcification are not usually present. The afferent arteriolar media shows thickening by hyaline material (Fig. 1.72). Hyaline deposition also occurs in diabetes mellitus but tends to affect both afferent and efferent arterioles, and develops to a mild degree in the absence of hypertension in individuals who are older than 60 years. Hyaline arteriolar thickening may be encountered in young adults, in whom it is associated with early-onset coronary artery disease. The grossly visible subcapsular granularity corresponds to shallow subcapsular scars that contain sclerotic glomeruli, atrophic tubules, and thick-walled hyalinized or hyperplastic arterioles (Fig. 1.73).

Malignant Nephrosclerosis

Malignant nephrosclerosis develops as a consequence of malignant hypertension.[244,245] Malignant hypertension usually arises in a patient with preexisting benign hypertension, but it may develop as a de novo disorder. Patients present with headache, dizziness, and impaired vision. Their diastolic BP exceeds 120 to 140 mm Hg. Retinal hemorrhages, exudates, and papilledema are present. Hematuria, proteinuria, and microangiopathic hemolytic anemia develop. Without treatment, the patient will experience renal failure and may die suddenly of heart failure, myocardial infarction, or cerebral hemorrhage.

The kidney in malignant nephrosclerosis often has petechial subcapsular hemorrhages or a mottled red and yellow cortex if