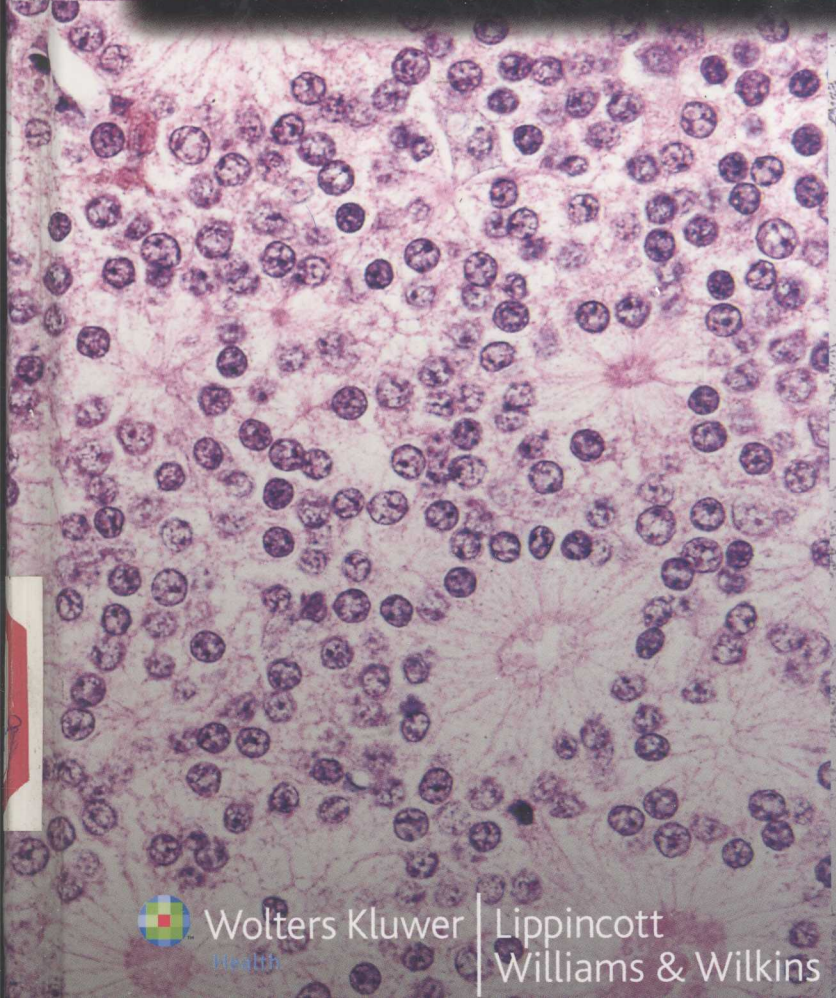
Urologic Pathology

THIRD EDITION



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THIRD EDITION

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Lippincott Williams & Wilkins
a Wolters Kluwer business
Philadelphia • Baltimore • New York • London
Buenos Aires • Hong Kong • Sydney • Tokyo

Acquisitions Editor: Jonathan Pine
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Senior Marketing Manager: Angela Panetta
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Production Services: Laserwords Private Limited, Chennai, India

530 Walnut Street
Philadelphia, PA 19106 USA
LWW.com

Printed in China

Library of Congress Cataloging-in-Publication Data

Petersen, Robert O.
Urologic pathology / Robert O. Petersen, Isabell A. Sesterhenn, Charles J. Davis.—3rd ed.
p. ; cm.
Includes bibliographical references and index.
ISBN 978-0-7817-5343-2
1. Genitourinary organs—Diseases. I. Sesterhenn, I. II. Davis, Charles J. III. Title.
[DNLM: 1. Urologic Diseases—pathology. 2. Genitalia, Male—pathology. 3. Urinary Tract—pathology. WJ 140 P485u 2008]
RC873.9.P47 2008
616.6—dc22

2008020772

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Urologic Pathology

THIRD EDITION

We wish to dedicate this book to Dr Mostofi and Colonel Davis. There are no words to express the admiration and personal affection we developed for Drs Mostofi and Davis during the three decades of our association. We were privileged to witness first hand their remarkably innovative approach to genitourinary pathology, and the lasting quality of their contributions that continues to benefit generations of pathologists, urologists, and most importantly, the patients we serve. Their kind and patient teaching, and the blessings of their friendship are part of our lives.

Robert O. Petersen
Isabell A. Sesterhenn

Preface

The preface of the first edition, published in 1986, alluded to "the advances . . . occurring in recent years have no equal in any comparable period of time." I hesitate writing the third edition with a quotation from 20 years ago; however, the statement is even more appropriate now, thereby justifying underwriting the third edition in 2008.

In contrast to the writing of the first two editions (each, the result of one author, ROP), the third edition is the collaboration of two additional authors, who joined me, Drs Isabell Sesterhenn and Charles J. Davis, from the Genitourinary Laboratory of the Armed Forces Institute of Pathology in Washington, DC. This collaboration culminated a three decade-long sharing of diagnostically interesting and challenging cases. I was the beneficiary of their gracious hospitality and friendship on the multiple occasions of my visits to Armed Forces of Institute of Pathology (AFIP), and honored by their acceptance to collaborate on this book.

The writing of this book was accompanied by two major events, the deaths of Dr F. Kash Mostofi on April 6, 2003, and more recently, Colonel Charles J. Davis on June 19, 2007. Their deaths contributed to an unshakeable sadness during the completion of this tome.

When the invitation to collaborate on this edition was extended, Dr F. Mostofi expressed much enthusiasm for the project, but his untimely demise precluded any writing contribution. His contribution was his towering stature, the result of innumerable major contributions in the historical development of genitourinary pathology. His inspiration was present throughout the writing. Dr Davis was able to contribute his vast experience and material until his death. This book is dedicated to these two giants in genitourinary pathology, with whom we had the honor to work and learn.

The expanded third edition is approximately 25% larger than the second edition, reflecting increases in text, figures (all in color), and references (approximately 13,000). The figures, approximately 800, represent a 100% increase in images including many rare entities from the archives of the AFIP. The references have been expanded reflecting the major advances in virtually all aspects of urologic pathology continuing to this date.

The text has been significantly revised and expanded in parallel with the advances in the field. The classification of renal neoplasms, urothelial neoplasms, testis and prostate neoplasms have all undergone major revisions in the past years. The contribution of molecular genetics to the formulation of these classifications, especially renal malignancies is fully discussed. Concurrent with the new classifications of neoplasms, is the recognition of the histologic variants of renal, urothelial, prostate and testicular germ cell neoplasms, all fully described and illustrated. Additionally, the histogenetic role and their histologic variability of precursor lesions in prostate malignancies (high-grade prostate intraductal neoplasia), and testicular germ cell neoplasms (intratubular germ cell neoplasia) are fully discussed and illustrated. The expanded role of genetic markers of renal and testicular neoplasms in the diagnosis and management of patients is discussed. The enormous impact of immunohistochemical staining as an ancillary diagnostic tool in tumor diagnosis is discussed and illustrated. Finally, the identification of risk factors affecting the natural history of renal, urothelial, prostate, and testicular neoplasms are outlined and discussed. This third edition is written with the intent to update and synthesize all of these recent advances at the close of the 20th century and the beginning of a new century of continuing progress.

This third edition continues the perspective of the diagnostic urologic pathologist established in the first two editions. The influence of our clinical colleagues is present throughout this book. We express our gratitude to all for the personal and professional satisfaction of a close working relationship.

Although the book reflects the perspective of urological pathologists, it is intended for use by all those interested in the pathological basis of urogenital disorders, including surgical pathologists, urologists, oncologists and all those in the training programs of these medical specialties.

The book is presented in ten chapters. Chapters 1 to 4 are devoted to organs of the urinary tract: kidney, renal pelvis and ureter, urinary bladder, and urethra. Chapters 5 to 10 are devoted to organs of the male genital tract: testis, testicular adnexa, prostate, seminal vesicles, penis, and scrotum. The diseases of each organ are organized in the traditional manner with non-neoplastic disorders (congenital, inflammatory, vascular, and proliferative diseases) followed by presentations of primary and metastatic neoplastic lesions.

The illustrated material derives from personal case studies, multiple consultation cases, and importantly, from the archives of the AFIP. The combined sources provided a wealth of diagnostic material for this edition.

Special mention is made of the photographic wizardry of Frank Avallone of the Genitourinary Laboratory of the AFIP. His patience, graciousness, and computer imaging skills made this book a visual presentation of perfection.

The authors express their gratitude also to Dr Sesterhenn's secretary, Renee Upshur-Tyree for excellent assistance with numerous tasks of transcription and electronic communication.

We express our thanks to the publishers Lippincott Williams and Wilkins for guidance and patience in the writing of this edition. A special thank you to Jean McGough; Debjani Gill and Jonathan Pine are specifically acknowledged.

Finally, the completion of this edition would not have been possible without the selfless assistance of my wife Olga. Her patience, constant encouragement, and assistance with matters dealing with computer Internet communication were critical both here in Philadelphia, and at the AFIP in Washington, DC. I will forever be in her debt. The second edition was written when our daughter Danielle was an infant. She is now a young woman, whose patience, good humor, and enviable writing skills have been a frequent benefit to a proud father.

Robert O. Petersen, MD, PhD

Preface to the Second Edition

The undertaking of the writing of the second edition of Urologic Pathology within 4 years of the publication of the first edition was a task I regarded justified only if (1) sufficient new knowledge in urologic pathology could be synthesized beyond that in the first edition and (2) the publisher expressed interest in the project. Both conditions were indeed satisfied, and thus this second edition is completed. I would be remiss not to acknowledge an additional factor, the encouragement derived from the gracious and constructive criticism offered by numerous colleagues after the publication of the first edition.

The expanded second edition is approximately 25% larger than the first edition, reflecting increases in text, figures, and references. The space limitations of the previous edition precluded discussion of many rare neoplasms of the kidney, prostate, testis, and testicular adnexa, as well as of disorders of the seminal vesicles; these are among the new sections included here. The photomicrographs were reviewed and some were replaced, with a net increase of about 100 figures. In addition, color figures of selected gross specimens and photomicrographs have been added. The references have been updated to retain historically valuable references and to include recent publications reflecting the most current advances. A net gain of some 2500 citations brings the reference total to almost 7000.

In addition to the new sections already noted, virtually all sections have been significantly revised and expanded. Where the recent advances in diagnosis of urogenital disorders have resulted from the application of immunohistochemistry, this is discussed and frequently illustrated, as are the contributions of cytogenetics, DNA flow cytometry, in situ hybridization techniques, and morphometric investigations.

The perspective reflected in the second edition mirrors that of the first-that of a surgical pathologist committed to the resolution of the diagnostic problems encountered in urologic pathology. This commitment is not an isolated pursuit but requires close collaboration with colleagues in urology. I acknowledge special gratitude to A. Richard Kendall, MD, Barry Stein, MD, Richard, Greenberg, MD, and Ronald Rosenthal, MD, whose influence is reflected throughout both editions of this book.

The contributed pathologic material graciously provided for the first edition of *Urologic Pathology* is again acknowledged. In the years intervening, additional cases were contributed by Dana D. Copeland, MD, Raleigh; W.D. Cuadra, MD, Charlestown, West Virginia; Richard M. Fedderson, MD, Albuquerque; Susan Gisser, MD, Camden, New Jersey; Stanley Irving, MD, Duluth; Yung Kim, MD, Trenton; Michael Kowalyshyn, MD, Philadelphia; David Page, MD, Memphis; Paul Putong, MD, Philadelphia; Alek Talerman, MD, Philadelphia; Stuart Wilson, MD, Farmington, New Mexico; and Sam Ward, MD, Harrisburg. I am sincerely grateful to each of these pathologists for their gracious contributions of slides used to produce the illustrations of rare disorders affecting the urogenital tract.

The final phase of the preparation of this second edition was completed while I was a faculty member in the Department of Pathology and Cell Biology at the Thomas Jefferson University Medical College. I express my gratitude to Emanuel Rubin, MD, Chairman, for developing a department supportive of the completion of this book and other books.

My wife Olga again contributed to the completion of this book, typing the entire manuscript as the did for the first edition. The journey to completion of the second edition was shared with our newborn daughter Danielle, requiring her mother's virtually complete sacrifice of everything exclusive of baby and book. My gratitude to my wife is without limits.

Finally, I am grateful to the publisher, J. B. Lippincott Company, for guidance and support in the writing of the second edition. The assistance of Richard Winters, Beth Oram, Grace Caputo, and Anne-Adele Wight is acknowledged specifically.

Robert O. Petersen, MD, PhD

Preface to the First Edition

The advances in urologic pathology occurring in recent years have no equal in any comparable period of time. Significant advances in our understanding of the etiology, pathogenesis, pathology, and natural history of many diseases of the urinary tract and male genital system have been recorded. The introduction and application of technical advances including histochemical staining, immunoperoxidase staining with tumor markers, and diagnostic electron microscopy have greatly increased the diagnostic armamentarium of the surgical pathologist interested in disorders of the urogenital system. These advances are of such a fundamental nature that the classification of urogenital disorders has undergone significant revision in recent years. The very language used in discussing many of these disorders has changed. Not only have numerous new diseases been described, but previously described disorders are identified with new terminology.

The scope of these advances has created a major challenge for both the urologist and the surgical pathologist. Although monographs dealing with the pathology of disorders of individual organs of the urinary tract and the male genital system are currently available, I am unaware of any standard textbook published since 1952 that deals with the entire field of urologic pathology.[1] The major advances noted earlier have been the product of studies during the subsequent years and in particular during the 1970s. Currently, awareness of these advances, by necessity, requires referral to available monographs, chapters in textbooks of surgical pathology, and the increasing volume of journal articles.

This book is written in an attempt to synthesize these new advances and thereby update the established body of knowledge in urologic pathology. Although it reflects the viewpoint of a surgical pathologist, this book is intended for use by all those interested in the pathologic basis of urogenital disorders, including surgical pathologists, urologists, oncologists, and all those in the training programs of these medical specialties. The practical significance of these recent advances can be realized only through a close working relationship of the surgical pathologist and his clinical colleagues. With the application of these advances, the potential contribution of the surgical pathologist to quality patient care is unprecedented.

The book is presented in 11 chapters. The first five chapters are devoted to the organs of the urinary tract including kidney, renal pelvis, ureter, urinary bladder, and urethra, Chapters 6 through 10 discuss the pathology of the male genital organs including testis, testicular adnexa, prostate, penis, and scrotum. Disorders of the adrenal gland are presented in Chapter 11. Each chapter is introduced with a review of embryologic development, normal structure, and age-related changes, with particular emphasis on their histogenetic and topographical relationship to diseases of the respective organ. The diseases of each organ are organized in the traditional manner with non-neoplastic disorders (congenital, inflammatory, vascular, and proliferative diseases) followed by presentations of primary and metastatic neoplastic lesions.

Each section devoted to a disease process (i.e., congenital, inflammatory, neoplastic) is introduced by a classification of the specific disease entities accompanied by a discussion of the histogenetic and pathologic basis for the classification. The current terminology of disease classification is emphasized.

With the exclusion of those renal disease treated by nephrologists (i.e., glomerulopathies and systemic vascular diseases with renal involvement), I have attempted to include all diseases traditionally within the spectrum of disorders treated by urologists. Within the scope of urologic pathology, I intended for the book to be comprehensive in both the total number of disease discussed and the depth of the discussion of each disorder. The epidemiology, etiology, and histogenesis of each disorder is reviewed. The gross and microscopic features of the typical lesion and variants are discussed and illustrated in more than 300 photographs. Where appropriate, I have contrasted the most important diagnostic features with those characteristics of other lesions in consideration of the differential diagnosis. When of diagnostic value, photomicrographs of special staining techniques, including histochemical and immunoperoxidase stains, as well as electron micrographs are included. Finally, discussions of the clinical–pathologic aspects of the natural history of each disease, including results and complications of therapy, unusual clinical presentations, local and distant dissemination, and where applicable, the findings reported in autopsy studies are included.

Special emphasis has been given to recent developments dealing with the embryology of the kidney, testis, and prostate, with reference to disorders of these organs ranging from cysts to neoplasms; the early morphologic

[1] Herbut PA. Urologic pathology. Philadelphia, Lea & Febiger, 1952.

changes in cryptorchidism; the etiology, pathogenesis, and natural history of urinary tract infections including xanthogranulomatous pyelonephritis and malakoplakia; the biologic significance of metaplastic and dysplastic changes of the urothelium and their relationship to urothelial neoplasia; and the current staging and grading protocols of all urogenital malignancies.

The illustrations derive primarily from cases studied in the Departments of Pathology of Temple University Hospital, Fox Chase Medical Center, and St. Christopher's Hospital for Children in Philadelphia. The text reflects a synthesis of 4,300 references from the appropriate urology and pathology literature of the last eight decades, and my studies and personal experience of the last decade. During this time I have been the beneficiary of a close and productive working relationship with the Departments of Urology and Radiology at Temple University Hospital, Jeanes Hospital, and American Oncologic Hospital in Philadelphia. The book fundamentally reflects the perspective of a surgical pathologist, but the influence of my clinical colleagues is present throughout.

The preparation of this book is the result of the cumulative contributions many, to whom I express my gratitude. The entire manuscript was typed with critical review and comments by my wife, Olga, to whom I am also indebted for countless hours of assistance in the many medical libraries in Philadelphia and with the task of translating hundreds of articles from foreign journals. We shared the journey to completion of this book.

To the four contributors of this textbook, Drs Stein, Shea, Radecki, and Friedman, I express my gratitude for their added perspective afforded this textbook. Their additional dimension will be of future benefit to all pathologists approaching diagnostic problems in urologic pathology.

I express my gratitude to Otto Lehman and Ski Scarano whose expert photographic developing assistance is demonstrated throughout the book.

Contribution of pathologic material was graciously provided by many to whom I express my gratitude and acknowledgment including: A. Bernard Ackerman, MD, New York; Arthur Aufderheide, MD, Duluth; J. Bruce Beckwith, MD, Denver; Norman Coopersmith, MD, Trenton; Ian D. Craig, MD, London, Ontario; Richard Estensen, MD, St. Paul; Dale Huff, MD, Philadelphia; Frank B. Johnson, MD, Washington, DC; Yung Kim, MD, Trenton; Anand Lattanand, MD, Philadelphia; Michael T. Mazur, MD, Birmingham; John W. Roberts, MD, Berkeley; Livia Ross, MD, Oakland; Robert E. Scully, MD, Boston; Joseph Sherrick, MD, Chicago; Harvey Slater, MD, Pittsburgh; John K. Wyatt, MD, London, Ontario; Charles Yang, FRACP, Melbourne; Nayere Zaeri, MD, Philadelphia.

To Ivan Damjanov, MD, Donald F. Gleason, MD, Wayne Johnson, MD, and Edith Potter, MD, I express my gratitude for major contributions of photographic material utilized in this book.

Finally, I wish to express my gratitude for the support and patience provided by the publishers, J. B. Lippincott Company. The greatest tribulations of publishers wrought by first time authors were graciously endured by Lisa Biello, Sanford Robinson, and Virginia Barishek. I will be forever in their debt for their guidance and patience.

Robert O. Petersen, MD, PhD

Contents

Kidney

1

NORMAL STRUCTURE

Embryologic Development

The kidney in the newborn is embryologically the final kidney in a series of three that develop during gestation. Its two predecessors sequentially regressed in the events leading to the development of the final kidney.[5,8,12]

The first excretory system is the pronephros, which develops from the dorsal specialized mesenchyme at approximately 3 weeks of gestation. The paired solid cord forms caudally, gradually develops a lumen, and enters the cloaca. The pronephric kidney consists of tubules (pronephric tubules) that develop laterally from the pronephric duct. The pronephric kidney never attains functional capacity but rather evidences regression at the cephalad end even as the most caudal pronephric tubules are forming.

The second excretory system, the mesonephric (or Wolffian) system, begins development during the fourth gestational week. Solid cords, which soon demonstrate a lumen, develop from the specialized mesenchyme (nephrostome). The mesonephric duct courses dorsolaterally and connects with the pronephric duct, the most cephalad portion of which has regressed. The pronephric duct is now called the *mesonephric* or *Wolffian duct*. Branches of the abdominal aorta grow laterally to connect with the most proximal ends of the mesonephric tubules, forming a glomerular structure. It is not resolved whether the mesonephric kidney functions, even though transiently, in the human embryo.

The subsequent function of the mesonephric duct, exclusive of its role in the urinary tract, occurs only in males. In females the duct regresses, but it can be found as vestigial rudimentary tubules in the ovarian hilum, walls of the fallopian tubes, and uterus as paroophoron, hydatids of Morgagni, and Gartner's ducts. This association with the female gonadal structures is the result of the close proximity of the mesonephric duct to the precursors of the genital organs. In males the mesonephric duct, in the proximity of the gonad (future testis), develops as the efferent ductules of the epididymis. Vestigial terminal ends of the mesonephric duct are also observed as appendices of the epididymis (see Chapter 6).

The final kidney, the metanephric kidney, takes origin at the caudal end of the mesonephric duct, just proximal to the duct's ostium in the cloaca. In the fifth gestational week the metanephric diverticulum, or ureteric bud, develops and grows in a dorsocephalad direction into a specialized mesenchyme, the metanephric mesoderm, which forms a cap on the advancing ureteric bud. Both migrate in a cephalad direction to arrive ultimately at the position of the normal kidneys (renal fossa). These events occur bilaterally to result in the paired metanephric or final kidneys.

The advancing end (the ampulla) of the ureteric bud undergoes dichotomous branching within the metanephric blastema with corresponding segmentation of the latter around the clusters of metanephric duct branches. By sequential generations of branches, the renal pelvis, major and minor calyces, and terminal collecting ducts are formed (Fig. 1.1).[5,8,12] Nephrons begin to form within the metanephric blastema; these are initially seen as oval condensations of blastemal cells in the vicinity of the terminal collecting duct ampulla. This mass of blastemal cells forms cords that develop a lumen, and these nephrons subsequently make connections with the collecting duct. Osathanondh and Potter describe four stages of growth of the collecting ducts (Figs. 1.2 to 1.4).[6,8] During stage one there is active branching of the collecting ducts. In stage two there is reduction of tubule branching and attachment of the nephrons to the collecting tubules in arcades. In stage three, branching stops but nephrons continue to form and attach to the terminal ends of the collecting ducts. The final stage, stage four, is characterized by collecting tube elongation (interstitial growth) and cessation of all branching and nephron formation. Ultimately, the nephron, derived from the metanephric blastema, gives rise to the glomerulus, proximal convoluted tubule, loop of Henle, and distal convoluted tubule. The metanephric duct gives rise to the collecting tubules (attached to the distal convoluted tubules of the nephron), the minor and major calyces, the renal pelvis, and the ureter.

Renal disorders, including congenital anomalies, renal dysplasias, and some renal cystic lesions, are significant manifestations of disordered embryogenesis. Understanding these disorders requires an understanding

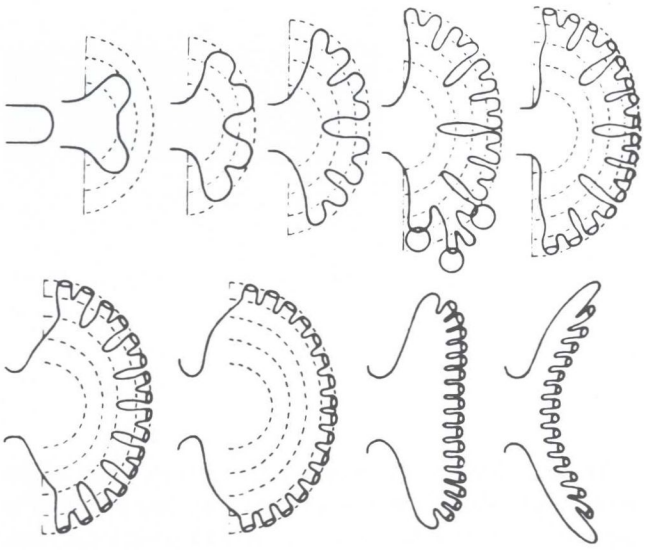

Figure 1.1 Embryologic development of minor calyx of kidney. Sequential branching and intrapyramid growth of the terminal collecting tubules result in the configuration of the minor calyx. (Potter EL. *Normal and abnormal development of the kidney*. Chicago, IL: Year Book Medical Publishers; 1972 with permission.)

of the sequential events in the normal embryologic development of the final or metanephric kidney.

Anatomy and Histology

The metanephric (or final) kidneys, located on each side of the great vessels within the abdomen, increase in length from 6 cm at birth to a maximum of 13 cm at 25 years to 30 years of age. Thereafter, a gradual decrease in size and weight continues. At birth the kidneys weigh 26 g, increasing progressively to an average of 150 g to 160 g attained in the third decade.[3,4] In the kidney's normal

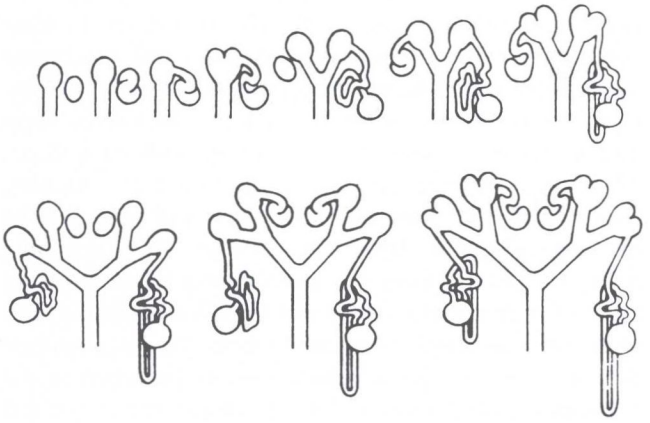

Figure 1.2 Embryologic development of nephron and terminal collecting tubules, period one. During period one there is active growth of the terminal collecting tubule and ampullary branching. Developing nephrons attach to the ampullae. (Potter EL. *Normal and abnormal development of the kidney*. Chicago, IL: Year Book Medical Publishers; 1972 with permission.)

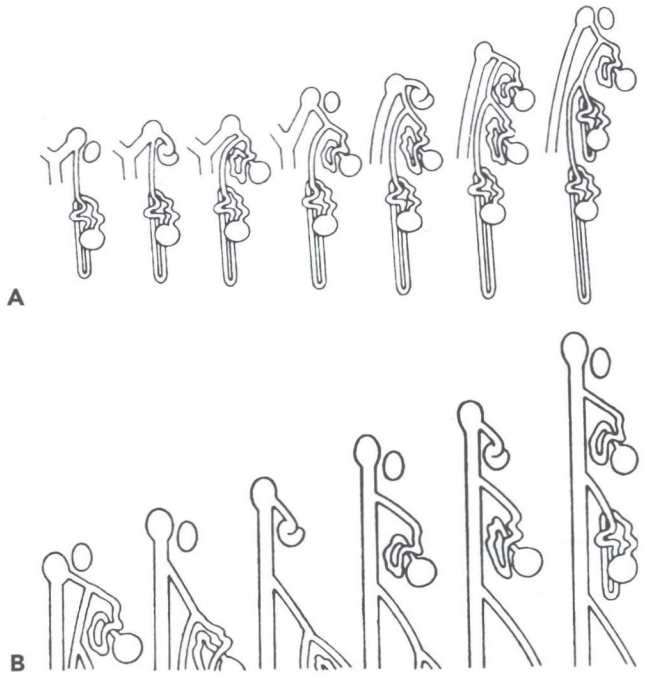

Figure 1.3 Embryologic development of nephron and terminal collecting tubules, periods two and three. *(A)* Decreased ampullary branching and development of nephron arcades characterize period two. *(B)* Cessation of ampullary branching with continued direct attachment of nephrons to advancing ampullae occurs in period three. (Potter EL. *Normal and abnormal development of the kidney*. Chicago, IL: Year Book Medical Publishers; 1972 with permission.)

position, between T12 and L3, the anterior surface of the left kidney lies adjacent to the tail of the pancreas, the ipsilateral adrenal, the fundus of the stomach, the posterior-inferior surface of the spleen, the splenic flexure of the colon, and the proximal jejunum. The anterior surface of the right kidney is adjacent to the ipsilateral adrenal, the posterior surface of the liver, and the hepatic flexure of the colon. Enveloping the kidney immediately outside the capsule is the perirenal adipose tissue within Gerota's fascia.[9]

The renal arterial supply is highly variable. The most common pattern includes a single renal artery that originates from the aorta and traverses laterally to divide into anterior and posterior arterial branches. These segments, still within the extrarenal hilum, divide as follows: the anterior branch gives rise to the apical segmental artery supplying the entire superior pole, a lower pole artery, and the upper and middle segmental arteries; the posterior branch supplies only the middle posterior segment of the kidney. All segmental arteries enter the renal parenchyma at the renal columns of Bertin, which protrude into the renal sinus of the hilar region.[2,11]

On entering the kidneys, the segmental arteries are called the *interlobar arteries*. These give rise to numerous arcuate arteries traversing the renal parenchyma near the corticomedullary junction. These arterial segments in turn

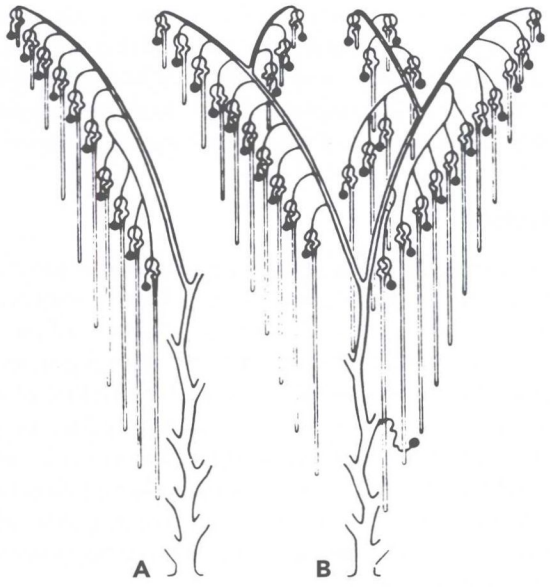

Figure 1.4 Embryologic development of nephron and terminal collecting tubules, final period. The ampullae disappear, nephron formation ceases, and further elongation of the terminal collecting tubules is the result of growth of the more distal segments. The final arborizing patterns of terminal collecting ducts and nephrons are depicted in their usual *(A)* and variant *(B)* patterns. (Potter EL. *Normal and abnormal development of the kidney*. Chicago, IL: Year Book Medical Publishers; 1972 with permission.)

give rise to the interlobular arteries, from which originate numerous afferent arterioles that course into the glomerular capillary tufts. The vascular supply to the renal medulla is through the vasa recta, which originate at the afferent arterioles and alternatively directly from the interlobular arteries.[7] The renal capsule has a dual arterial supply from anastomosing intrarenal and the extrarenal arteries. Capsular arteries, taking origin from the segmental arteries, anastomose with capsular perforating arteries arising from interlobular arteries. The venous system follows the arterial tributary pattern in reverse.

The lymphatic vessels are located in the cortex adjacent to the interlobular vessels. Lymphatic drainage exits the kidney at the hilum where the vessels join the left and right lumbar lymphatic chains, either directly into para-aortic nodes or through lymph nodes within the renal hilum.[10] Parker (1935) identified no direct connections from one kidney to the contralateral kidney.[1]

The structural unit of the kidney is the lobe, of which there are approximately 14. The individual lobes can be identified from the cortical surface in the newborn, but thereafter the surface depressions defining the adjacent lobes gradually disappear in most persons, resulting in a smooth cortical surface. The lobe is composed of a cortical zone that is draped over the medulla and tapers to form the renal pyramid, indenting a calyx. The cortex of a lobe, in three dimensions, overlies the medullary component in a configuration resembling the cap of a mushroom. The convergence of the cortical areas of adjacent lobes forms the columns of Bertin, into which the arterial supply enters the kidney, as noted earlier. The lobe comprises multiple repeating functional units called *lobules*, composed of glomeruli and their contiguous tubules coursing internally into the medulla and ultimately opening at the tip of the pyramid as converging collecting tubules. The lobule is bordered by the interlobular arteries, which radiate toward the capsule from the accurate arteries. The clustered collecting tubules running parallel to each other and subserving the nephrons of a lobule are called *medullary rays*. They are adjacent to and intermingled with the vasa recta and the parallel medullary rays, and the vasa recta can be observed in the outer medulla on close gross inspection of the kidney's cut surface. The contents of the cortex include the glomeruli, segments of the proximal and distal convoluted tubules, straight segments of the loop of Henle, and collecting tubules (Fig. 1.5). The outer medulla, immediately within the cortex at the corticomedullary junction, contains the collecting tubules and straight segments of the loops of Henle with admixed blood vessels (the vasa recta) (Fig. 1.6). The inner medulla contains the converging collecting tubules, sparse capillaries surrounding the tubules, and minimal interstitium, which for practical purposes is not apparent in the normal cortex and outer medulla because of tight packing of the nephron components. Interstitial cells, although they are sparse in numbers, can be identified most readily in the inner medulla. On electron microscopy, these cells have ultrastructural features differing from those of fibroblasts (see discussion on renomedullary interstitial cell tumors later in this chapter).

The ostium of the collecting ducts at the papillary tip is the location where the tubular epithelium makes a transition to the urothelium of the calyx and becomes continuous with the epithelium of the renal pelvis and the remainder of the lower urinary tract. The transition will, at

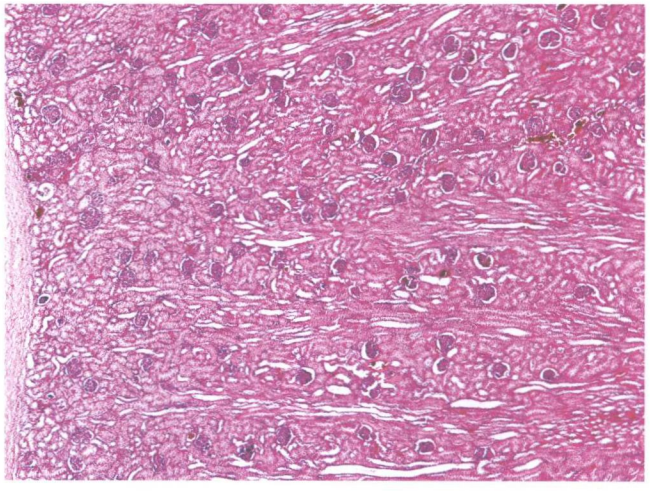

Figure 1.5 Normal kidney. Renal capsule (*upper field*). The clustered parallel collecting tubules are the medullary rays and between them are the nephrons, consisting of glomeruli and convoluted tubules.

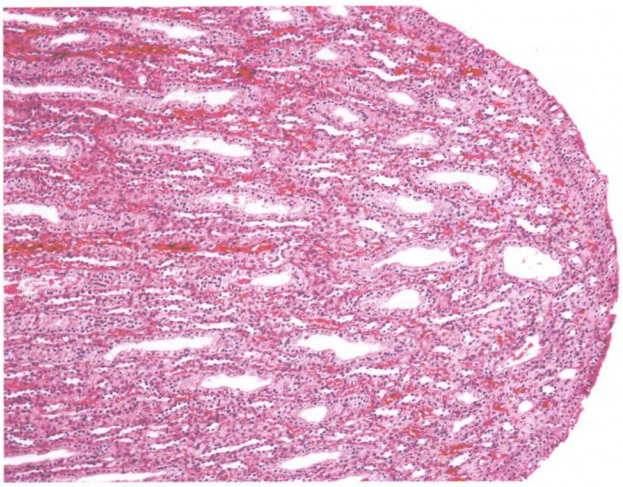

Figure 1.6 Normal kidney. The inner or lower medulla in the renal papilla consists of collecting ducts lined by cuboidal cells and numerous capillaries. The papilla is lined by urothelium.

times, be seen at some point over the surface of the renal papillae or in the distal collecting ducts.

CONGENITAL DISORDERS

Congenital disorders of the kidneys are classified into six categories as outlined in Table 1.1. Each category is represented by a spectrum of individual disorders with unique clinical and pathologic features described in the following discussion. Many of the congenital disorders of the kidney are associated with additional defects of the urinary tract, and some with disorders of nongenitourinary systems. Some of the congenital renal disorders are typically sporadic, isolated, and of variable clinical significance.

TABLE 1.1
CLASSIFICATION OF RENAL CONGENITAL DISORDERS

1	Number
	Bilateral agenesis
	Unilateral agenesis
2	Size
	Hypoplasia
	Hypoplasia with meganephronia
	Segmental hypoplasia (Ask-Upmark)
3	Location
	Ectopia
	Crossed ectopia
	Thoracic kidney
4	Rotation Anomalies
5	Configuration
	Horseshoe kidney
	Supernumerary kidney
	Adrenal-renal fusion
6	Structure
	Renal dysplasia
	Multicystic dysplasia

Agenesis

Bilateral renal agenesis (Potter's syndrome) is incompatible with life, and most afflicted newborns die within days of birth. A significant number of affected infants are stillborn. Associated oligohydramnios resulting from the absence of fetal urine production is characteristic of such pregnancies. There are also associated findings of pulmonary hypoplasia, and characteristic abnormalities of the head and face (Potter's facies), including large, low-set ears, wide-set eyes, flattening of the nose, receding chin, and a prominent skin fold below the eyes extending downward and lateral from the inner canthus.[15–17]

Bilateral renal agenesis is more frequent in male newborns. Associated anomalies include absence or abnormal development of the müllerian organs, imperforate anus, and musculoskeletal abnormalities.[17]

Unilateral renal agenesis may occur as an isolated congenital anomaly, or in association with a wide variety of urinary, genital, and nongenitourinary anomalies. It occurs with a frequency of approximately 1 in 1000 adults but, based on pediatric autopsy studies, has been reported to be more common in children. This difference in frequency can be partly attributed to the significant mortality resulting from renal disease affecting the extant kidney, or from associated congenital disorders found in unilateral renal agenesis. Early literature reviews by Campbell (1928), Collins (1932), and Doroshow and Abeshouse (1961) indicate that this congenital anomaly is more common in males (64%), and slightly more frequent on the left side (56%).[13,14,19] Unilateral renal agenesis has been found in persons ranging in age from newborn to 92 years. Unilateral renal agenesis is no longer regarded as a relatively innocuous anomaly, adequately compensated for by enlargement of the contralateral kidney. Significantly higher frequencies of renal infection and lithiasis with resulting renal failure have been reported in these patients.[20–23] Cascio and coworkers reported urinary tract abnormalities including vesicoureteral reflux, obstructive megaureter, and ureteropelvic junction (UPJ) obstruction in 28%, 11%, and 3% of patients, respectively.[24] Associated congenital anomalies, especially among female patients, are reported in approximately 20% of cases. In female patients, unicornuate uterus and absence of fallopian tubes, ovaries, or all the müllerian organs have been observed. Cryptorchidism, absence of the ipsilateral seminal vesicle, seminal vesicle cyst, and absence of epididymis or testis are the most common associated findings in male patients. The ipsilateral ureter is absent or rudimentary in most cases, and a complete and patent ureter is distinctly rare. Nongenitourinary anomalies associated with unilateral renal agenesis

include cardiovascular (septal defects, pulmonary artery stenosis, tricuspid atresia, and others with lesser frequency), gastrointestinal (imperforate anus, atresia, and duodenal atresia), and musculoskeletal defects (spinal deformities, absence of thumb, and multiple other defects).

The frequent absence of the ureter underlies one pathogenetic explanation of this anomaly. The failure of the ureteric bud to contact and stimulate the metanephric blastema to differentiate into a kidney results in the renal agenesis. Alternatively, Ashley and Mostofi (1960) believe that the metanephric blastema is capable of differentiation without the ureteral bud stimulus, an explanation based on the observations of 11 kidneys without ipsilateral ureters.[18] This interaction of ureteral bud and metanephric blastema remains unresolved.

Hypoplasia

Hypoplasia of the kidney(s) takes one of three recognized forms: (1) true or simple hypoplasia; (2) hypoplasia with oligomeganephronia; and (3) segmental hypoplasia (Ask-Upmark kidney). The pathogenesis of the Ask-Upmark kidney is controversial and currently unsettled, as will be discussed in the following text.

True or simple renal hypoplasia is a rare congenital defect of unknown cause. It is most commonly unilateral, but it may be bilateral. **True hypoplasia is characterized by a reduction in the number of renal papillae and minor calyces (fewer than six).** For unknown reasons, renal hypoplasia is more common in male patients, and more often affects the left kidney. Boissonnat described three patterns of renal hypoplasia based on the extent of involvement (partial or complete) of the kidney.[25] Renal hypoplasia, when unilateral, is commonly associated with adequate compensatory enlargement of the contralateral kidney. The diagnosis is best achieved by combining the observations of specimen radiographic examinations with contrast material in the pelvicalyceal system, with gross and microscopic observations of the size of the kidney. The affected kidney is small, with reduced numbers of renal papillae and minor calyces, with histologically normal renal parenchyma without evidence of dysplasia.[26] True hypoplasia must be differentiated from other forms of small kidneys, including renal dysplasia, "end-stage" kidney of vascular origin, and pyelonephritis. This latter distinction may be difficult or impossible in some cases.

Renal Hypoplasia with Oligomeganephronia

Renal hypoplasia with oligomeganephronia is a rare form of renal hypoplasia, first described by Royers and colleagues and Habib and colleagues in 1962.[27,28] This congenital disorder usually presents in infancy and childhood and is clinically characterized by slowly progressive renal failure occurring during the second decade.[29–34] Nausea, vomiting, episodic dehydration, polyuria, proteinuria, systemic acidosis, and growth retardation are characteristic of the clinical progression. No inheritance pattern is associated with this disorder, but congenital renal lesions have been reported in family members of some patients.[35] It is bilateral in all reported cases, with the exception of two patients who were noted to have agenesis of the contralateral kidney. Oligomeganephronia is associated with chromosomal changes with 4p deletion.[36]

Morphologically, the kidneys show marked reduction in size with a simplified calyceal system characteristic of hypoplasia. The corticomedullary junction is poorly delimited. The diagnostic histologic features vary with the stage of disease progression, but **a reduction of the number of nephrons and marked enlargement of the extant glomeruli are characteristic of all stages.** Initially, the proximal tubules are markedly dilated, a feature that gradually changes to tubular atrophy and accompanying interstitial fibrosis. Enlarged and sclerotic glomeruli, tubular atrophy, and interstitial fibrosis characterize the late stages of the disease, all nonspecific features of end-stage renal disease, with the exception of the enlarged glomeruli. There is no histologic evidence of renal dysplasia. Ultrastructurally, the glomeruli show nonspecific increase in mesangial matrix and increased pericapsular stromal collagen.

The pathogenesis of this disorder is unknown. The combined clinical and histologic features differentiate this type of renal hypoplasia from other hypoplastic and dysplastic disorders of the kidney.

Segmental Hypoplasia (Ask-Upmark Kidney)

In 1929, Ask-Upmark described a unique form of hypoplasia characterized by renal hypoplasia (unilateral and occasionally bilateral), characterized by deep capsular grooves and a decrease in the number of pyramids. The grooves represent areas in which the cortex is thin due to atrophy and the medulla is essentially absent and usually represented by only a few ducts. Where the medulla should have been, the calyx is dilated (Figs. 1.7 to 1.9).[37] This lesion is most common in adolescent girls, who frequently demonstrated

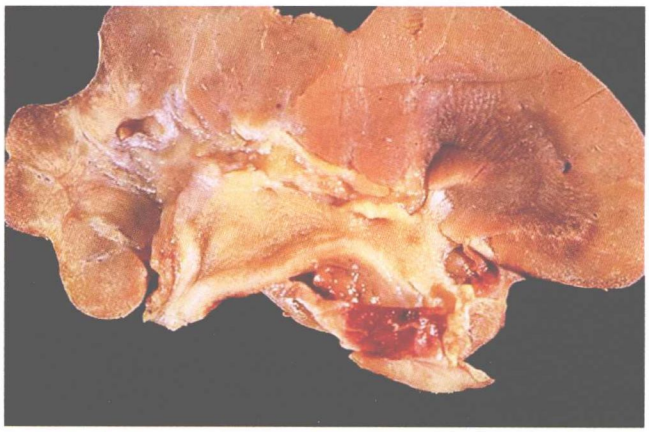

Figure 1.7 Ask-Upmark kidney. The cut surface shows three cortical grooves due to the reduction of underlying renal parenchyma.