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# 1

## Nonneoplastic Diseases of the Kidney

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*"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

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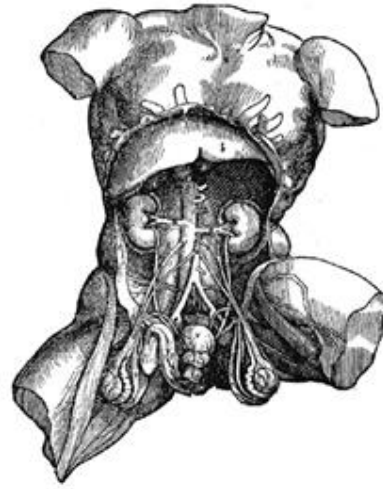
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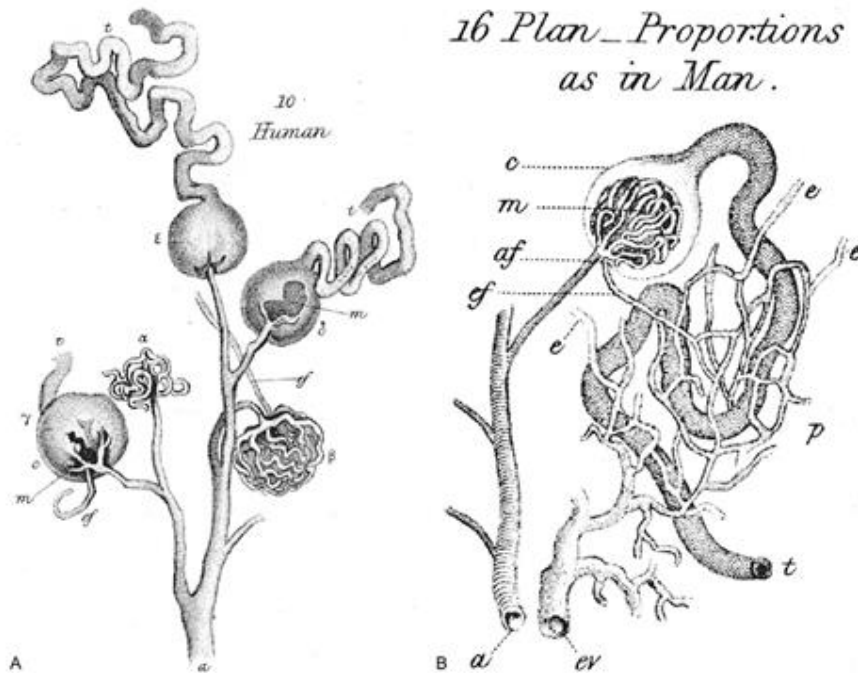
## Introduction

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.<sup>1</sup> However, unlike Malpighi, today's knowledge draws extensively on the labors, discoveries, and insights of investigators of the past centuries.

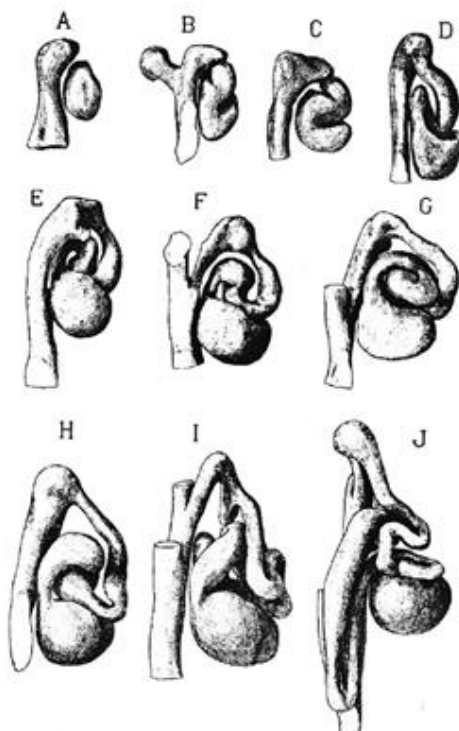
Knowledge of the normal structure and function of the kidney has been acquired over centuries of scholarly effort. We have come a long way since Aristotle taught that urine was formed by the bladder and that kidneys were present "not of actual necessity, but as matters of greater finish and perfection."<sup>1</sup> Reference to the excretory functions of the bladders and kidneys can be found in early Indian Ayurveda, Chinese, or Egyptian literature.<sup>2-4</sup> 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."<sup>5-13</sup> 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).<sup>14,15</sup> 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).<sup>16,17</sup> 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).<sup>1,18</sup> 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).<sup>19</sup> 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.<sup>20</sup> Potter and Osathanondh validated the findings in a series of microdissection studies of developing kidneys, which were published in the 1960s.<sup>21-26</sup>

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.<sup>27-34</sup>

## 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.<sup>27-34</sup>

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.<sup>26,27,33</sup> 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

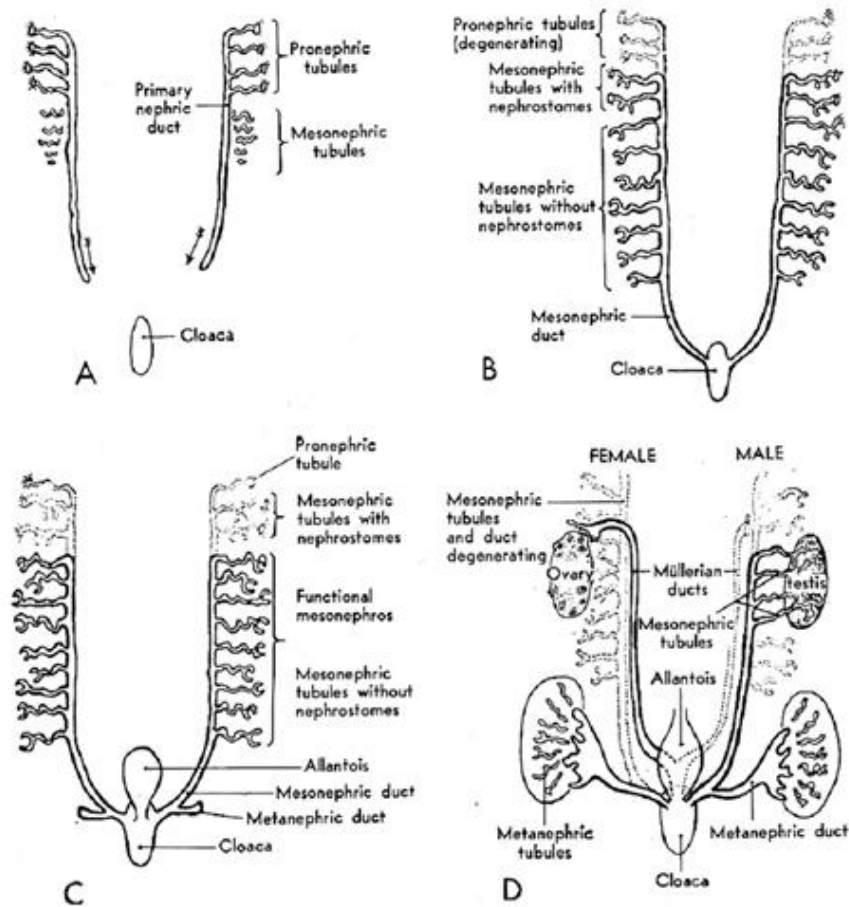
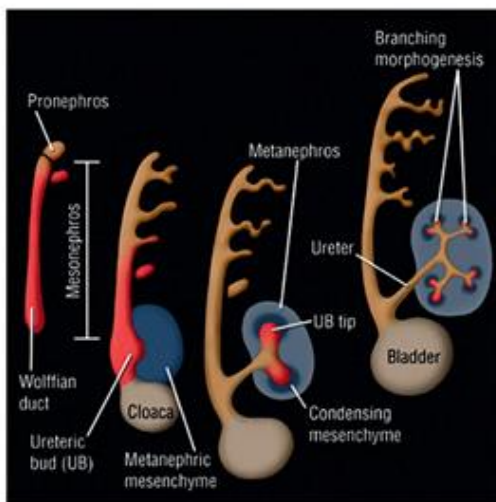


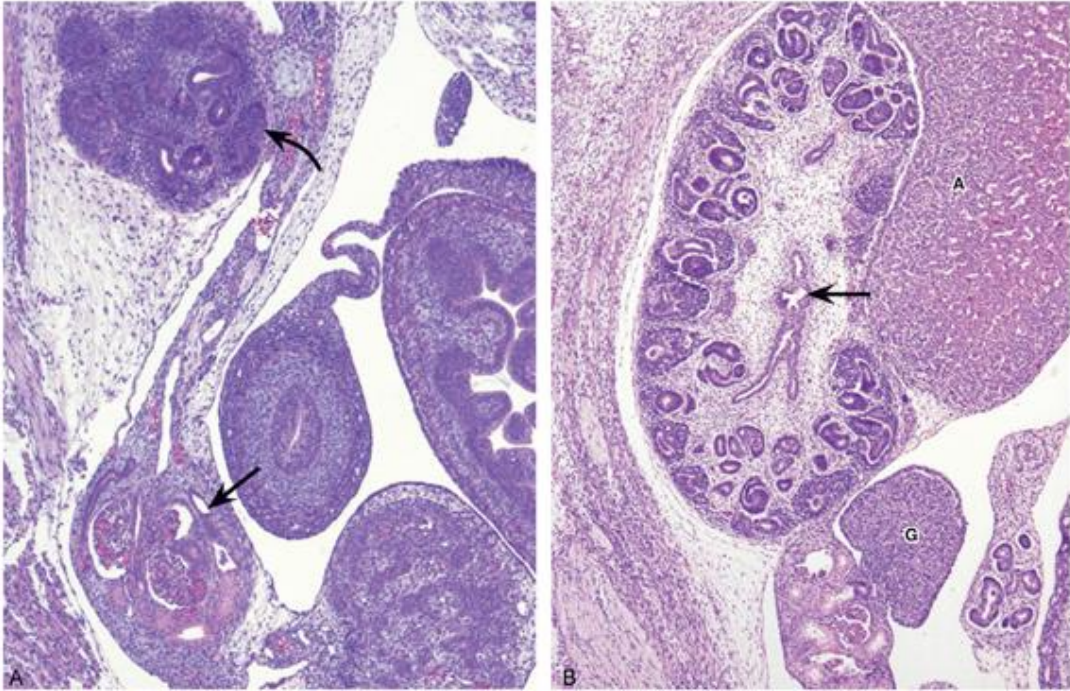
Fig. 1.4 Diagram illustrating the relationship between reproductive tract and urinary tract development. (From Patton BM. Human embryology. New York: McGraw Hill, 1968; with permission.)



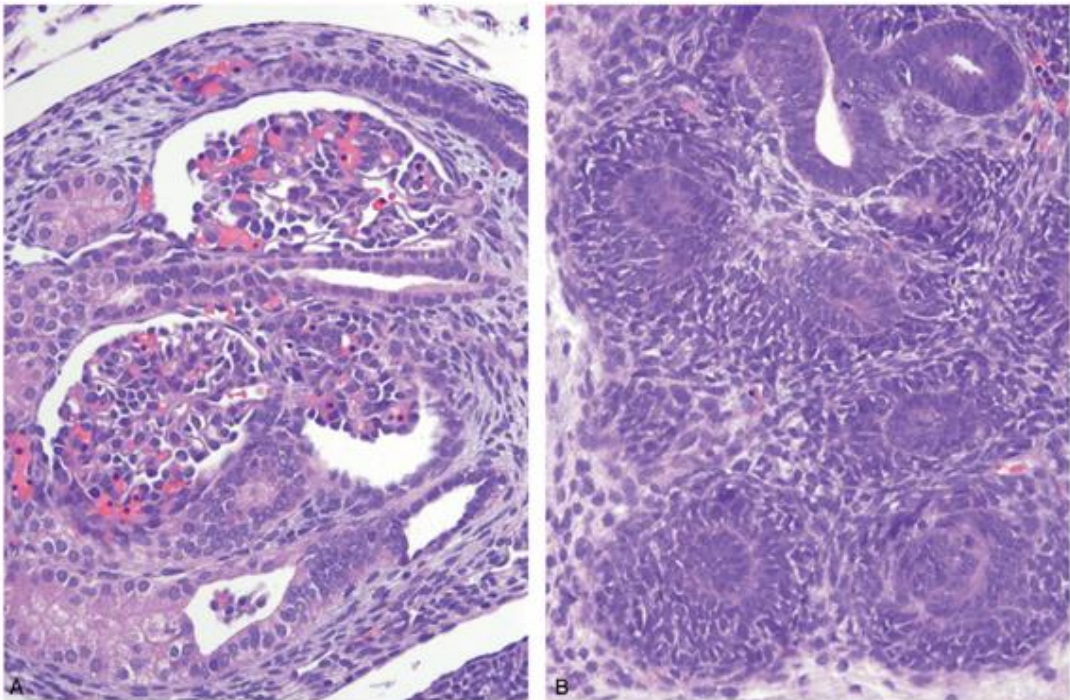
appreciated that while the collecting system and renal pyramids are forming there is simultaneous induction of thousands of nephrons, and neurovascular and lymphatic components ramify in a carefully organized architecture throughout the cortex.

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.



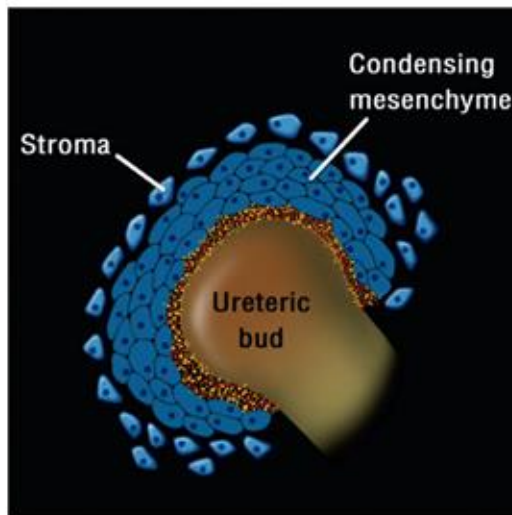
**Fig. 1.7** (A) A portion of the mesonephric kidney (from Fig. 1.6A) showing well-developed glomeruli and tubules. (B) Metanephric kidney (from Fig. 1.6A) beginning to form and showing condensations of cells destined to form a nephron.

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.

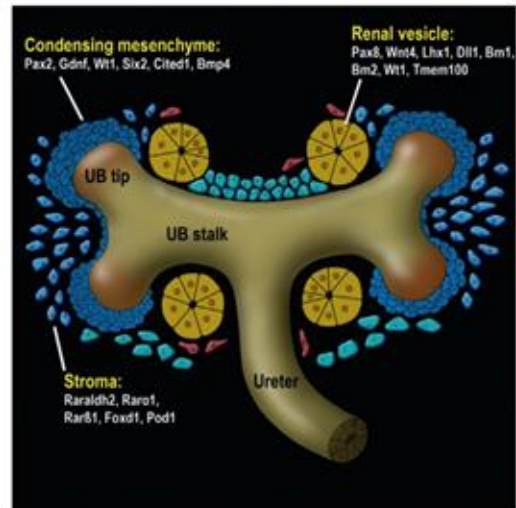
On contact with metanephric blastema the ureteric bud undergoes a rapid sequence of dichotomous branching and fusion, forming the renal collecting system by the 14th week (Figs. 1.8 and 1.9). The initial two branches form the renal pelvis, the third to sixth branches form the major and minor calyces, 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.

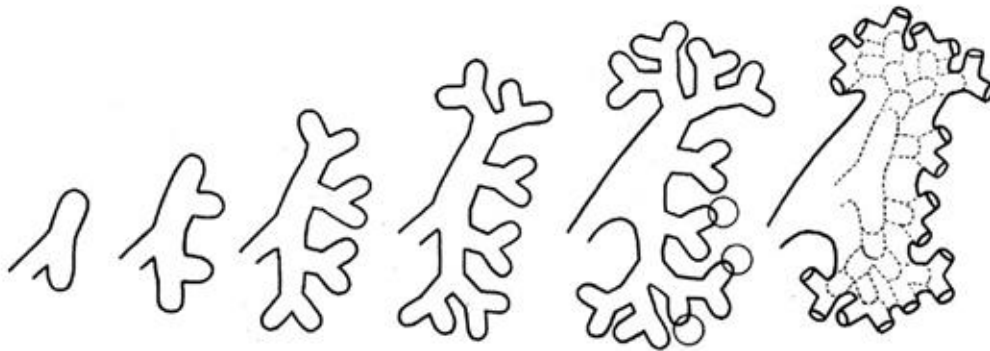
While the collecting system is forming, nephron induction has already begun (Figs. 1.6B, 1.7B, 1.8, 1.10, and 1.11). The kidneys have moved into the flanks because of a combination of migration out of the pelvis and rapid caudal growth of the embryo (Fig. 1.12). The kidney also has rotated from its original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



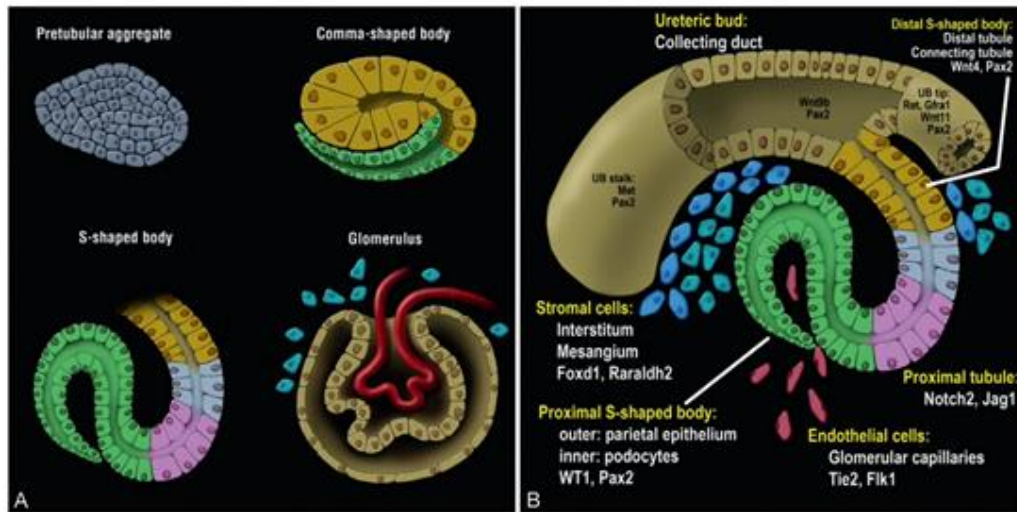
**Fig. 1.8** Invasion of the ureteric bud into the mesenchyme results in condensation of the mesenchyme around the ureteric bud tip. (From Jain S. "Normal kidney development." In "Diagnostic pathology: kidney diseases" by Colvin RB and Chang A, pages 36–45. Philadelphia: Elsevier, 2016; with permission.)



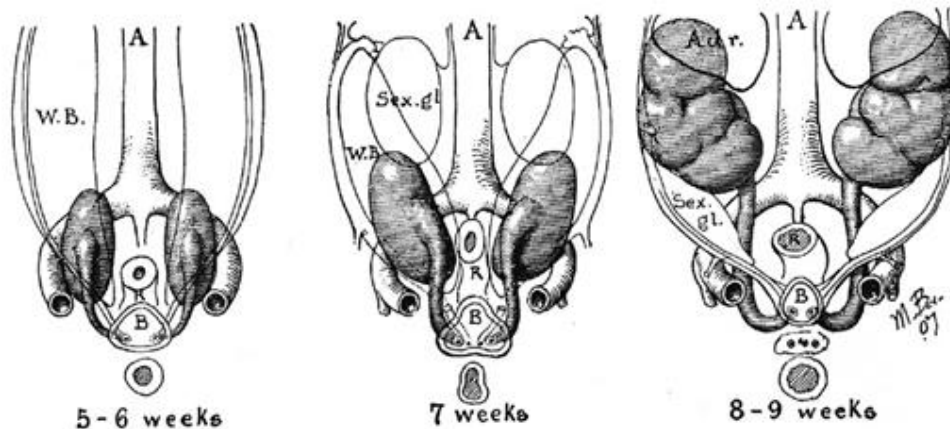
**Fig. 1.10** Reciprocal interactions between the ureteric bud, condensing mesenchyme, and stroma involve cross talk between cells with involvement of many genes and their products, some of which are highlighted in this figure. (From Jain S. "Normal kidney development." In "Diagnostic pathology: kidney 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 Osathanondh 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