EMBRYOLOGY

Urinary Tract

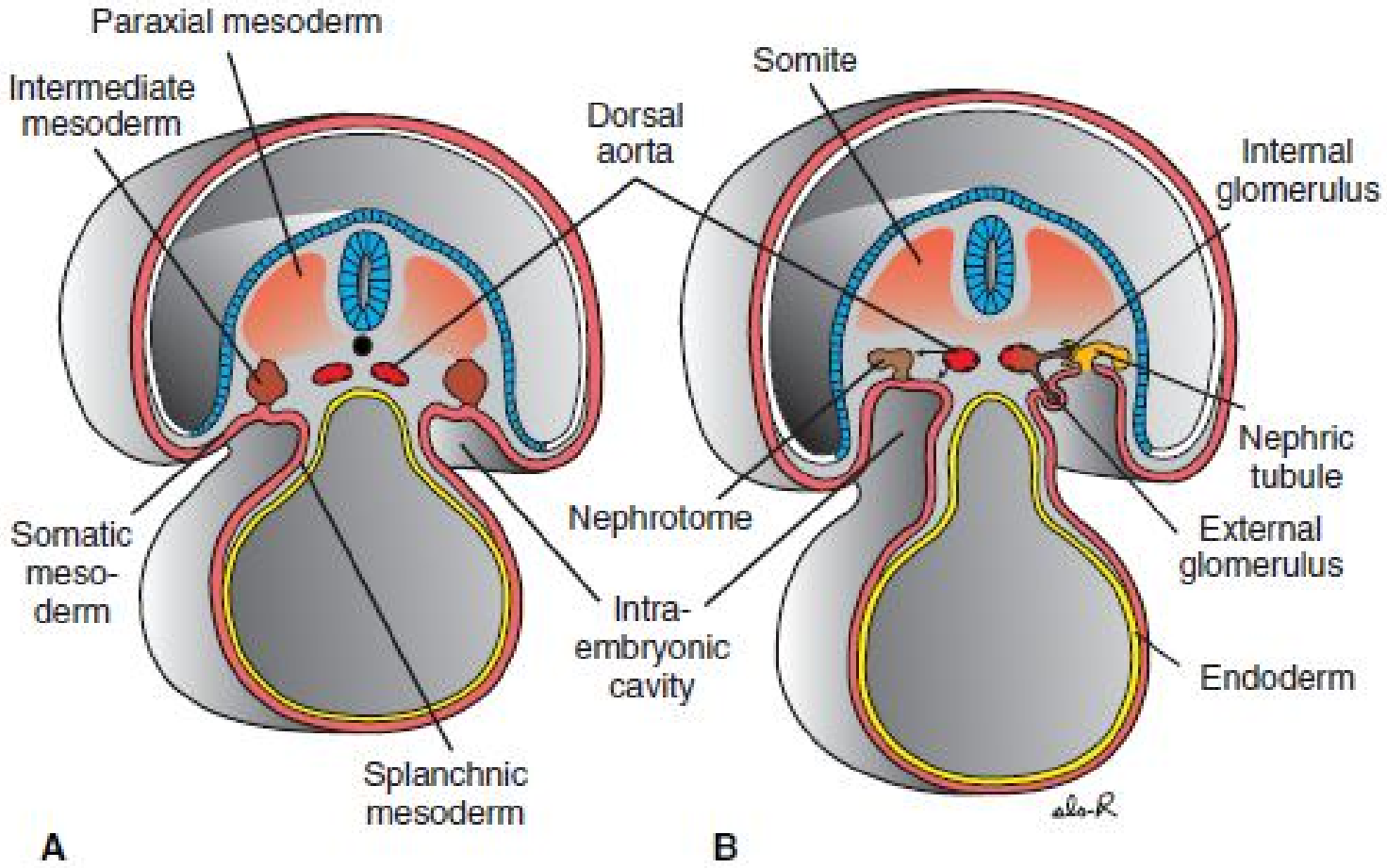


Figure 16.1 Transverse sections through embryos at various stages of development showing formation of nephric tubules. **A.** 21 days. **B.** 25 days. Note formation of external and internal glomeruli and the open connection between the intraembryonic cavity and the nephric tubule.

Kidney System

From Cephalic To Caudal :

Pronephros :

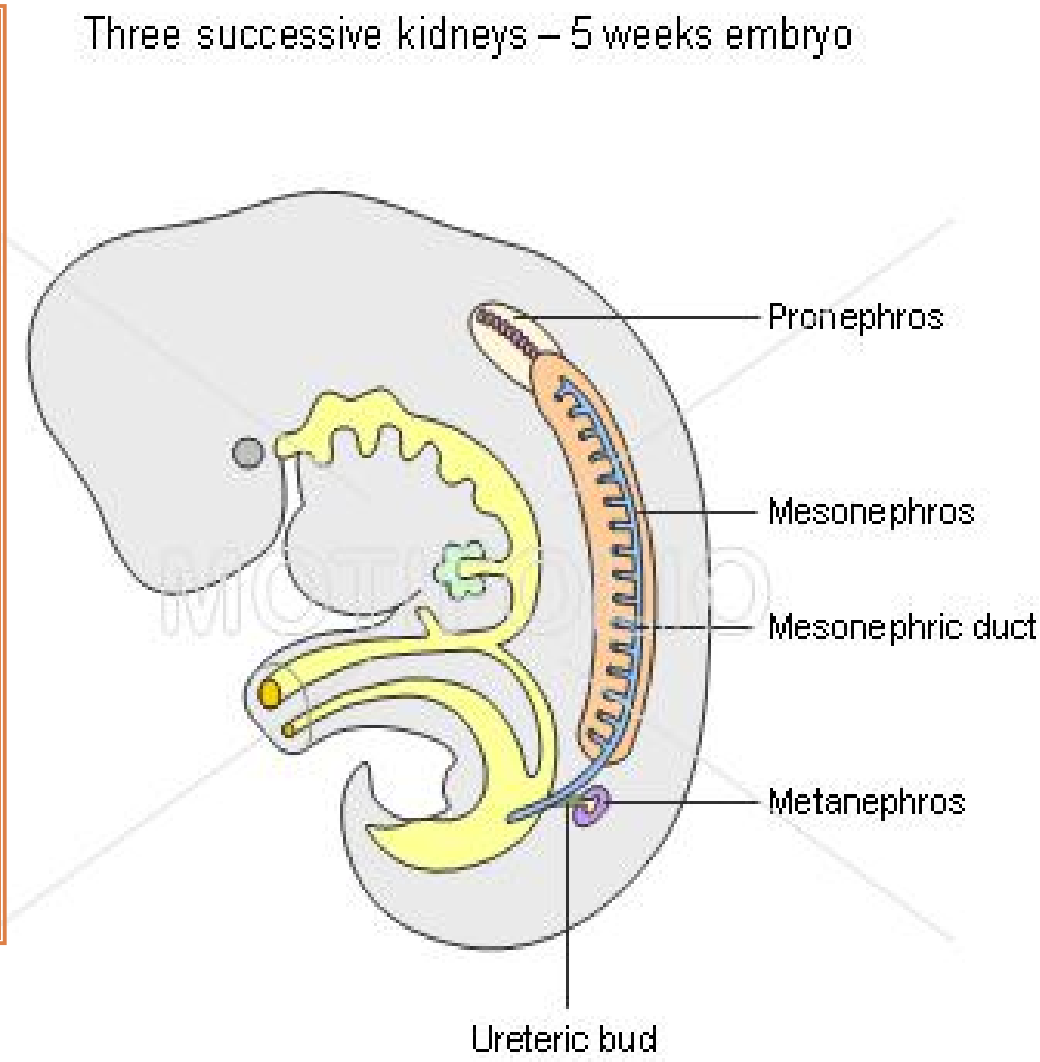
Cervical position / Without Function / 4th week

Mesonephros:

T1-L3 position / Have Function For Few Times / 4th week up 2th month

Metanephros :

Permanent Kidney / 5th week



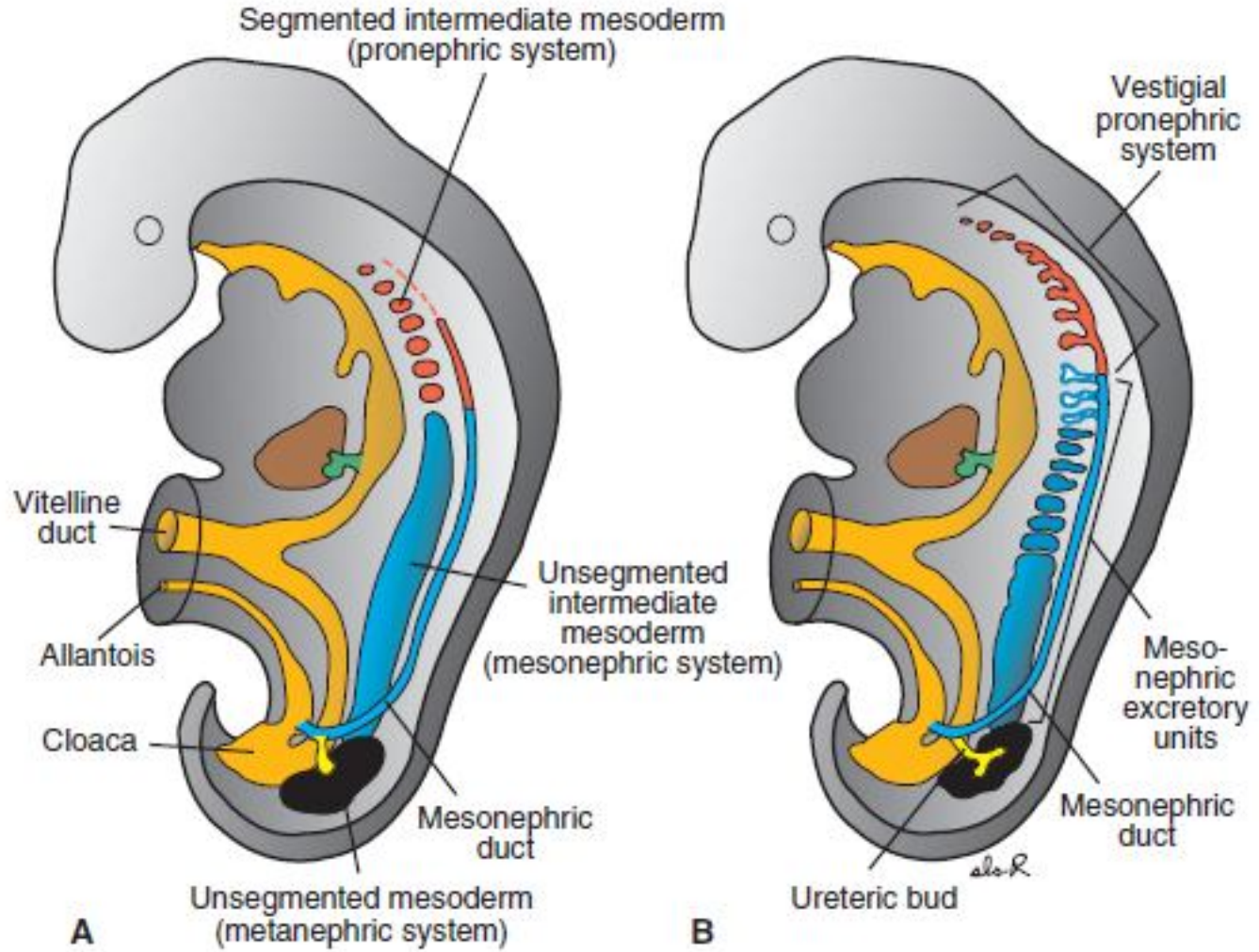


Figure 16.2 A. Relationship of the intermediate mesoderm of the pronephric, mesonephric, and metanephric systems. In cervical and upper thoracic regions, intermediate mesoderm is segmented; in lower thoracic, lumbar, and sacral regions, it forms a solid, unsegmented mass of tissue, the nephrogenic cord. Note the longitudinal collecting duct, formed initially by the pronephros but later by the mesonephros (Mesonephric duct). **B.** Excretory tubules of the pronephric and mesonephric systems in a 5-week embryo.

mesonephros

Urogenital mesentery

Lateral to mesonephros:

Masonephric duct

Medial to mesonephros:

glomerulus/ bowmans capsule /gonad

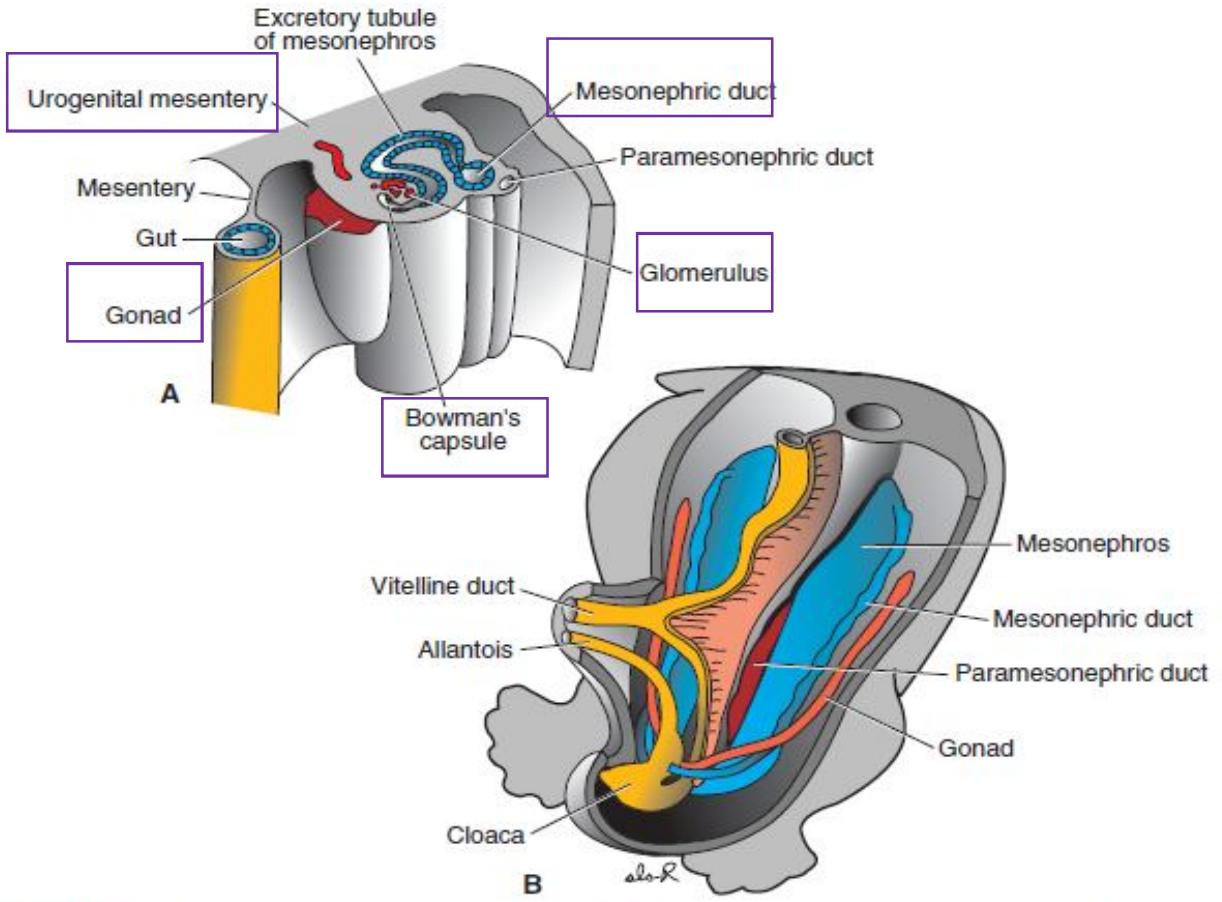
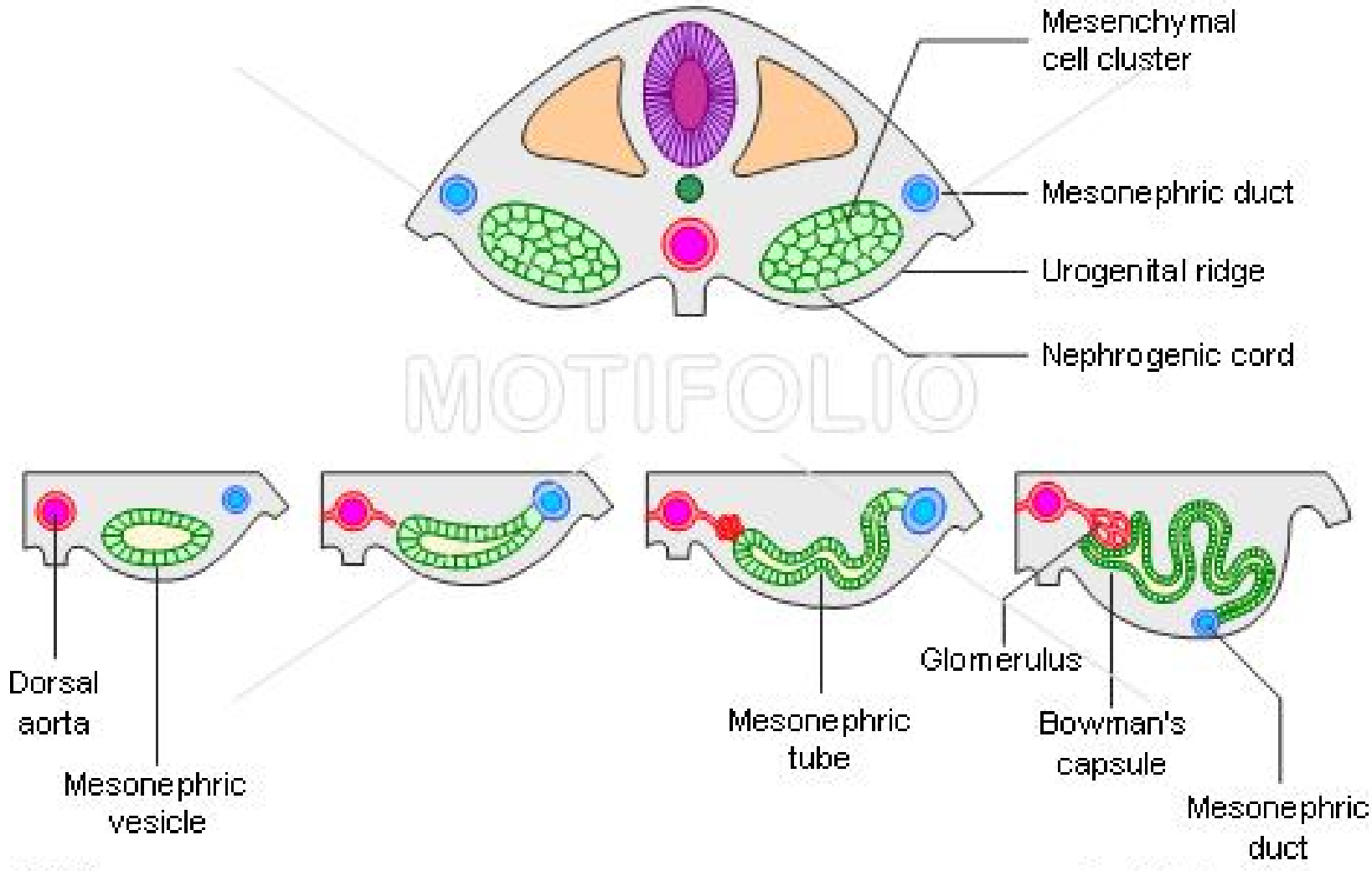


Figure 16.3 **A.** Transverse section through the urogenital ridge in the lower thoracic region of a 5-week embryo showing formation of an excretory tubule of the mesonephric system. Note the appearance of Bowman's capsule and the gonadal ridge. The mesonephros and gonad are attached to the posterior abdominal wall by a broad urogenital mesentery. **B.** Relation of the gonad and the mesonephros. Note the size of the mesonephros. The mesonephric duct (wolffian duct) runs along the lateral side of the mesonephros.

Development of mesonephric tubules – 3-5 weeks



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Metanephros

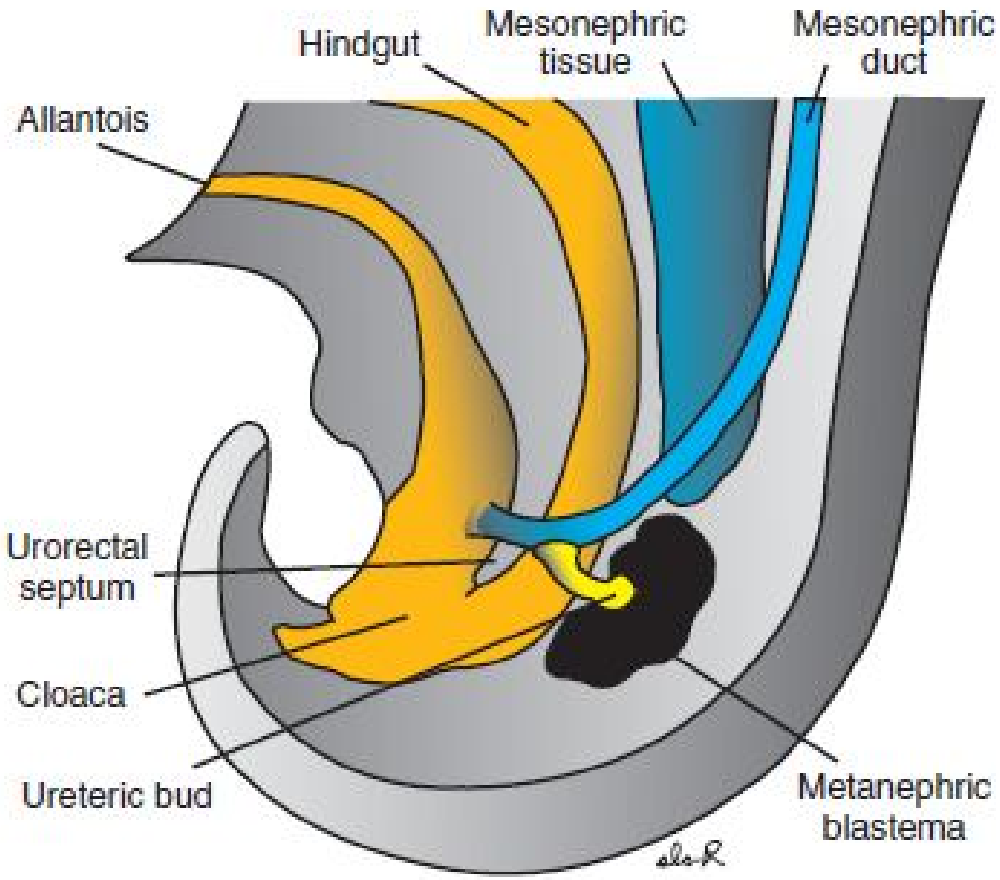


Figure 16.4 Relation of the hindgut and cloaca at the end of the fifth week. The ureteric bud penetrates the metanephric mesoderm (blastema).

Ureteric Bud – Collecting Tubules

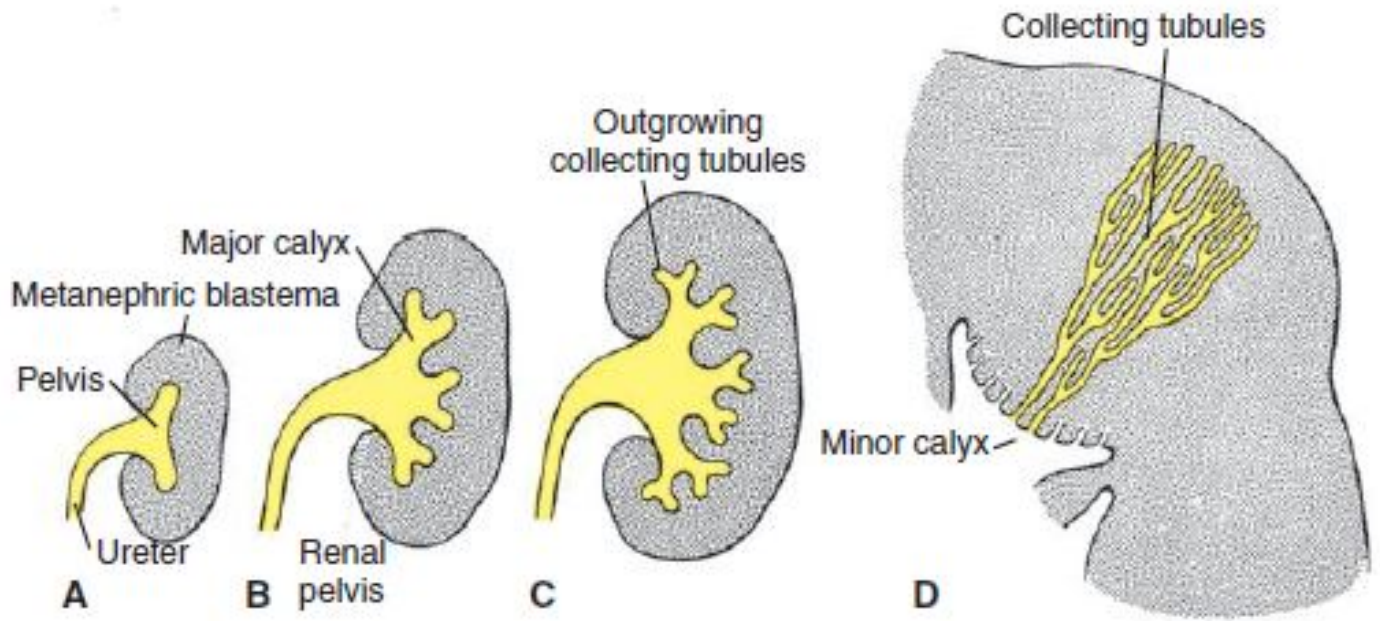
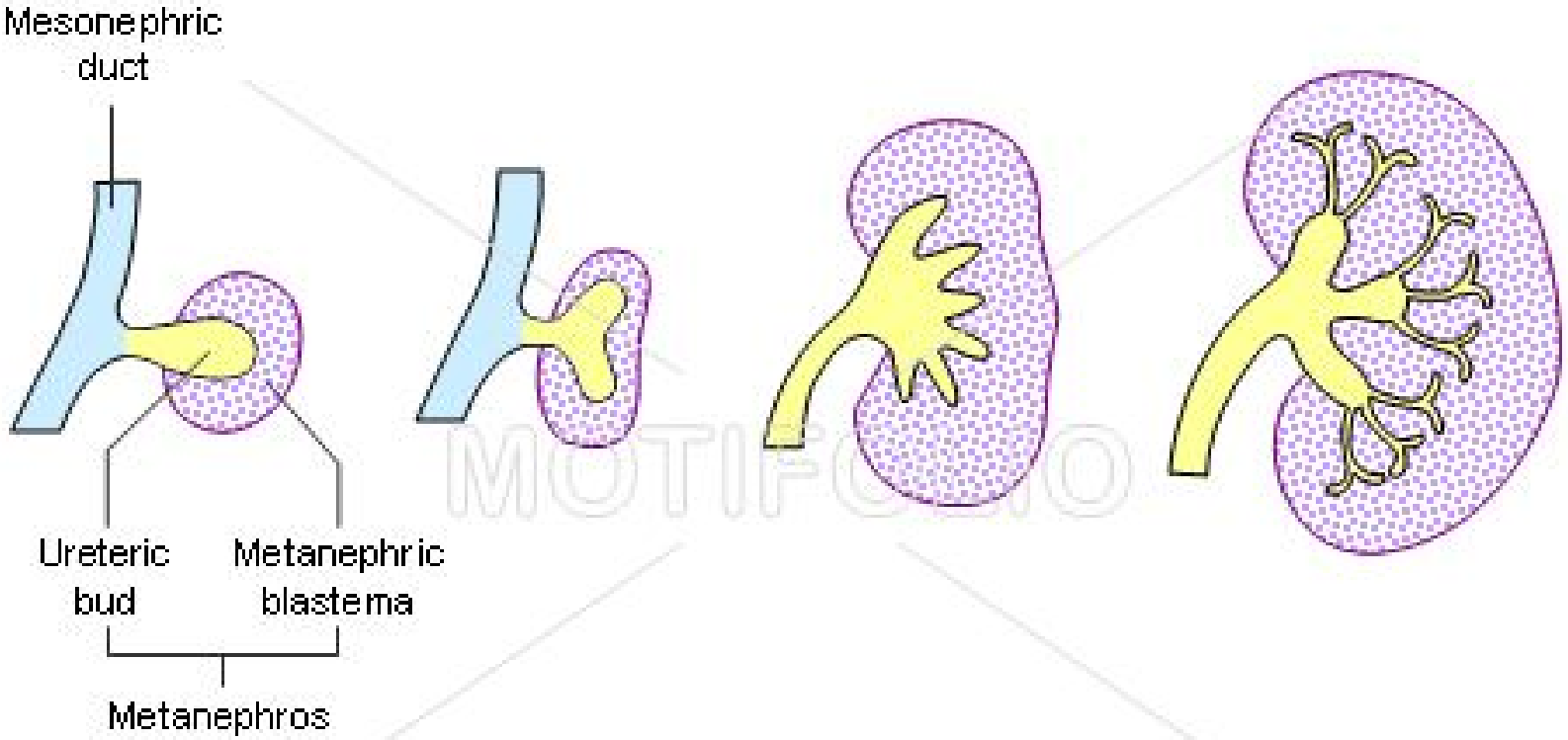


Figure 16.5 Development of the renal pelvis, calyces, and collecting tubules of the metanephros. **A.** 6 weeks. **B.** At the end of the sixth week. **C.** 7 weeks. **D.** Newborn. Note the pyramid form of the collecting tubules entering the minor calyx.

Development of the metanephros and its duct system – 5 – 8 weeks



Renal pelvis → Major calyx → Minor calyx → Collecting duct

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Metenephric Cap – excretory system

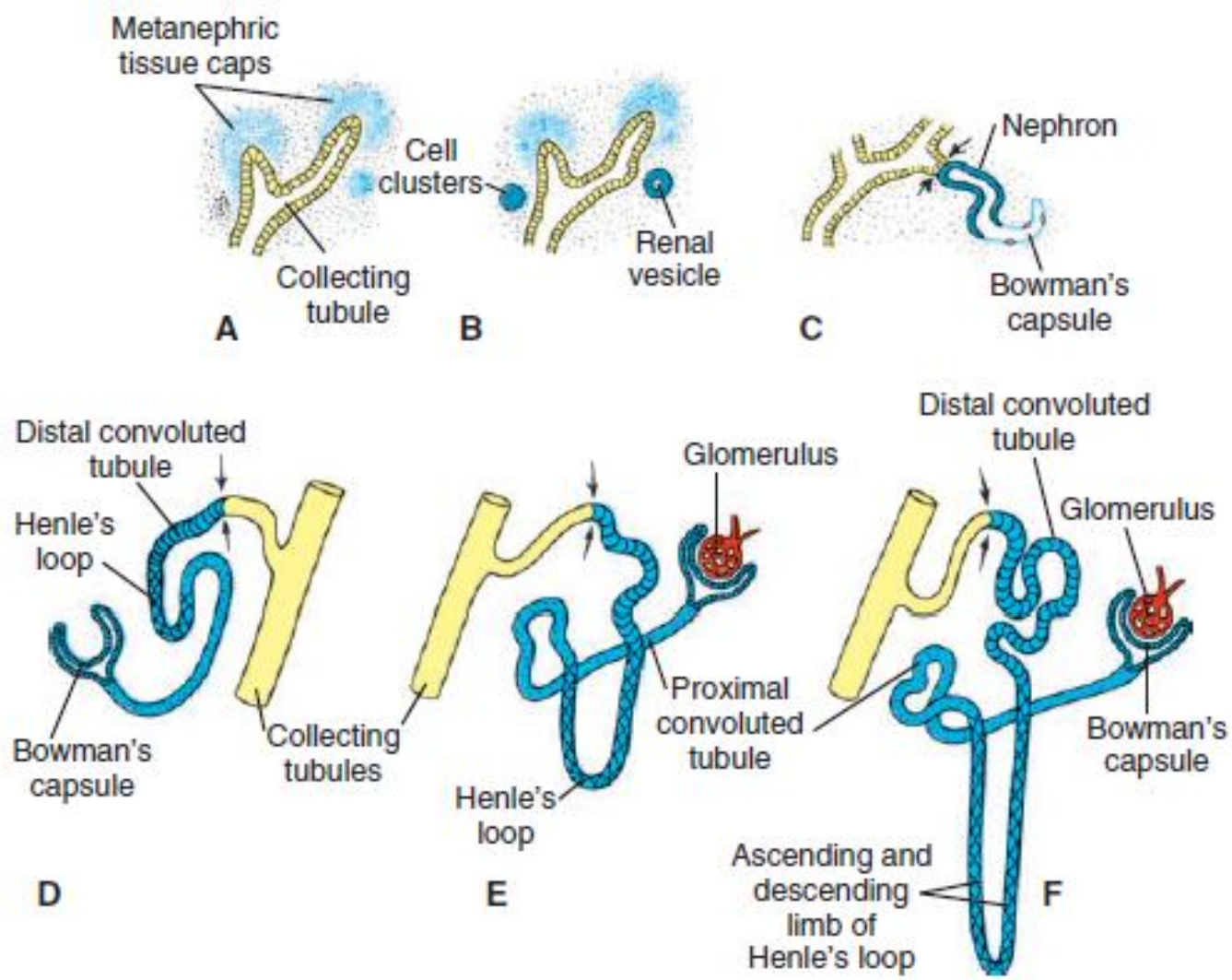
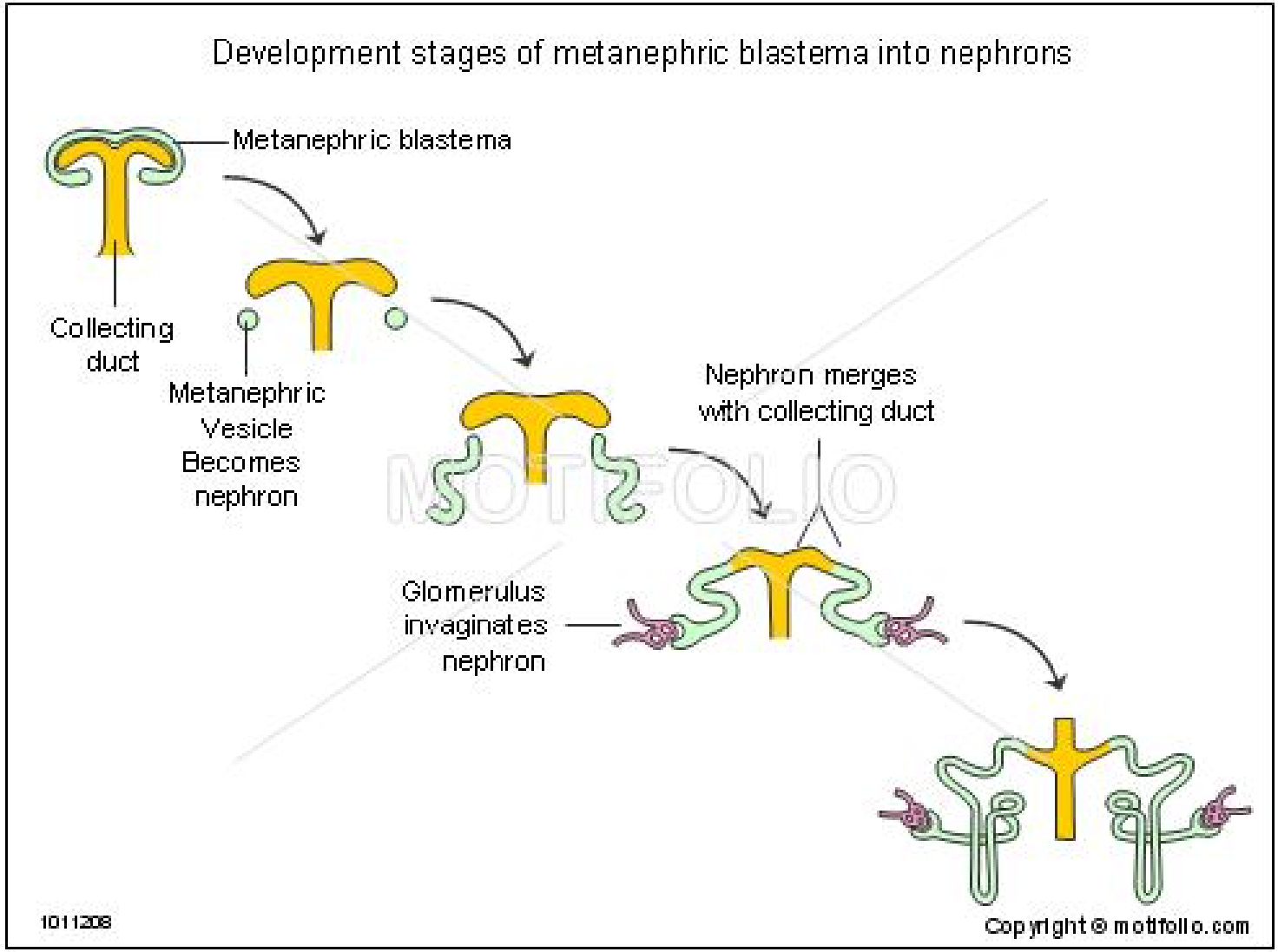


Figure 16.6 Development of a metanephric excretory unit. *Arrows*, the place where the excretory unit (*blue*) establishes an open communication with the collecting system (*yellow*), allowing flow of urine from the glomerulus into the collecting ducts.


Development stages of metanephric blastema into nephrons
Metanephric blastema
Collecting duct
Metanephric Vesicle Becomes nephron
Nephron merges with collecting duct
Glomerulus invaginates nephron
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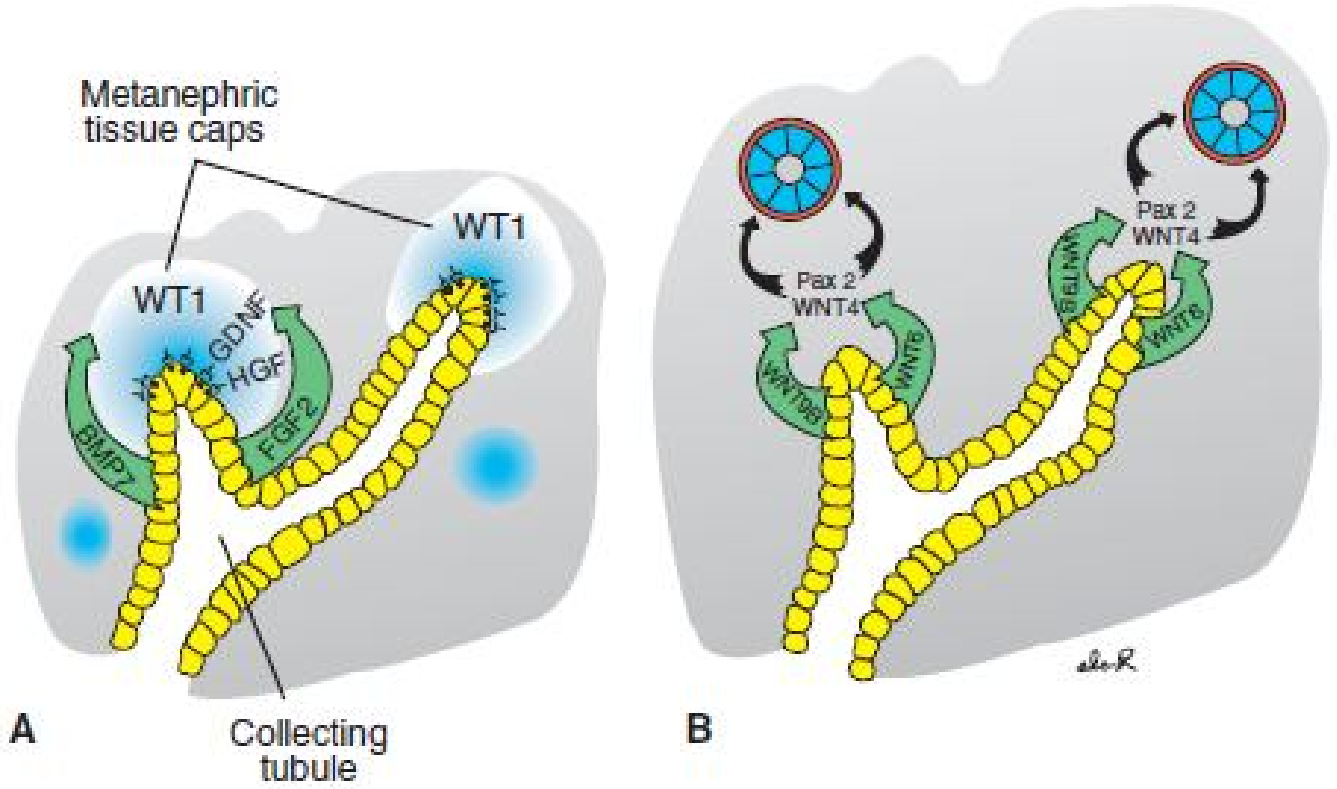

Figure 16.7 Genes involved in differentiation of the kidney. **A.** *WT1*, expressed by the mesenchyme, enables this tissue to respond to induction by the ureteric bud. GDNF and HGF, also produced by the mesenchyme, interact through their receptors, RET and MET, respectively, in the ureteric bud epithelium, to stimulate growth of the bud and maintain the interactions. The growth factors FGF2 and BMP7 stimulate proliferation of the mesenchyme and maintain *WT1* expression. **B.** WNT9B and WNT6 secreted by branches of the ureteric bud epithelium cause upregulation of *PAX2* and *WNT4* in the surrounding mesenchyme. In turn, these genes cause the mesenchyme to epithelialize (*PAX2*) and to then form tubules (*WNT4*). Changes in the extracellular matrix also occur, such that laminin and type IV collagen form a basement membrane (orange) for the epithelial cells.

Renal Tumors and Defects

Wilms' tumor is a cancer of the kidneys that usually affects children by 5 years of age but may also occur in the fetus. Wilms' tumor is due to mutations in the *WT1* gene on 11p13, and it may be associated with other abnormalities and syndromes. For example, **WAGR syndrome** is characterized by Wilms' tumor, **a**niridia, **g**onadoblastomas (tumors of the gonads), and mental **r**etardation (intellectual disability). The constellation of defects is due to a microdeletion in chromosome 11 that includes both the *PAX6* (aniridia) and *WT1* genes that are only 700 kb apart. Similarly, **Denys-Drash syndrome** consists of renal failure, ambiguous genitalia, and Wilms' tumor.

Renal dysplasias and **agenesis** are a spectrum of severe malformations that represent the primary diseases requiring dialysis and transplantation in the first years of life. **Multicystic dysplastic kidney** is one example of this group of abnormalities in which numerous ducts are surrounded by undifferentiated cells. Nephrons fail to develop, and the ureteric bud fails to branch, so that the collecting ducts never form. In some cases, these defects cause involution of the kidneys and **renal agenesis**. Renal agenesis may also arise if the interaction between the metanephric mesoderm and the ureteric bud fails

dominant disorder or may be caused by other factors. **Autosomal recessive polycystic kidney disease (ARPKD)**, which occurs in 1/5,000 births, is a progressive disorder in which cysts form from collecting ducts. The kidneys become very large, and renal failure occurs in infancy or childhood. In **autosomal dominant polycystic kidney disease (ADPKD)**, cysts form from all segments of the nephron and usually do not cause renal failure until adulthood. The autosomal dominant disease is more common (1/500 to 1/1,000 births), but less progressive than the autosomal recessive disease. Both types of disease are linked to mutations in genes that encode proteins localized in cilia and that are important for ciliary function. These abnormalities belong to a growing group of diseases called the **ciliopathies** that are due to mutations in cilia related proteins. These disorders include **Bardet-Biedal syndrome**, characterized by renal cysts, obesity, intellectual disability, and limb defects, and **Meckel Gruber syndrome**, characterized by renal cysts, hydrocephalus, miropthalmia, cleft palate, absence of the olfactory tract, and polydactyly. Since cilia are present on most cell types and in most tissues, many organ systems can be affected by abnormalities in ciliary structure and function.

Duplication of the ureter results from early splitting

to occur. Normally, during the interaction, **GDNF** produced by the metanephric mesoderm produces branching and growth of the ureteric bud. Thus, mutations in genes that regulate *GDNF* expression of signaling may result in renal agenesis. Examples include the gene *SALL1*, responsible for Townes-Brock syndrome; *PAX2* that causes renal coloboma syndrome; and *EYA1* that results in branchio-otorenal syndrome. Bilateral renal agenesis, which occurs in 1/10,000 births, results in renal failure. The baby presents with **Potter sequence**, characterized by anuria, oligohydramnios (decreased volume of amniotic fluid), and hypoplastic lungs secondary to the oligohydramnios. In 85% of cases, other severe defects, including absence or abnormalities of the vagina and uterus, vas deferens, and seminal vesicles, accompany this condition. Common associated defects in other systems include cardiac anomalies, tracheal and duodenal atresias, cleft lip and palate, and brain abnormalities. Because of the oligohydramnios, the uterine cavity is compressed resulting in a characteristic appearance of the fetus, including a flattened face (Potter facies) and club feet.

In **congenital polycystic kidney disease** (Fig. 16.8), numerous cysts form. It may be inherited as an autosomal recessive or autosomal

of the ureteric bud (Fig. 16.9). Splitting may be partial or complete, and metanephric tissue may be divided into two parts, each with its own renal pelvis and ureter. More frequently, however, the two parts have a number of lobes in common as a result of intermingling of collecting tubules. In rare cases, one ureter opens into the bladder, and the other is ectopic, entering the vagina, urethra, or vestibule (Fig. 16.9C). This abnormality results from development of two ureteric buds. One of the buds usually has a normal position, whereas the abnormal bud moves down together with the mesonephric duct. Thus, it has a low, abnormal entrance in the bladder, urethra, vagina, or epididymal region.

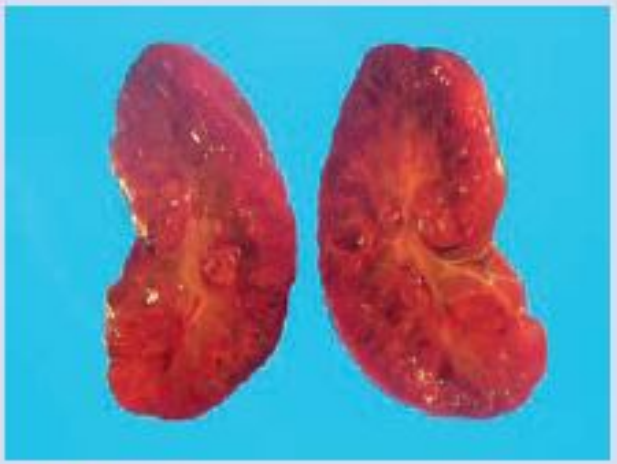

Figure 16.8 Surface view of a fetal kidney with multiple cysts characteristic of polycystic kidney disease.

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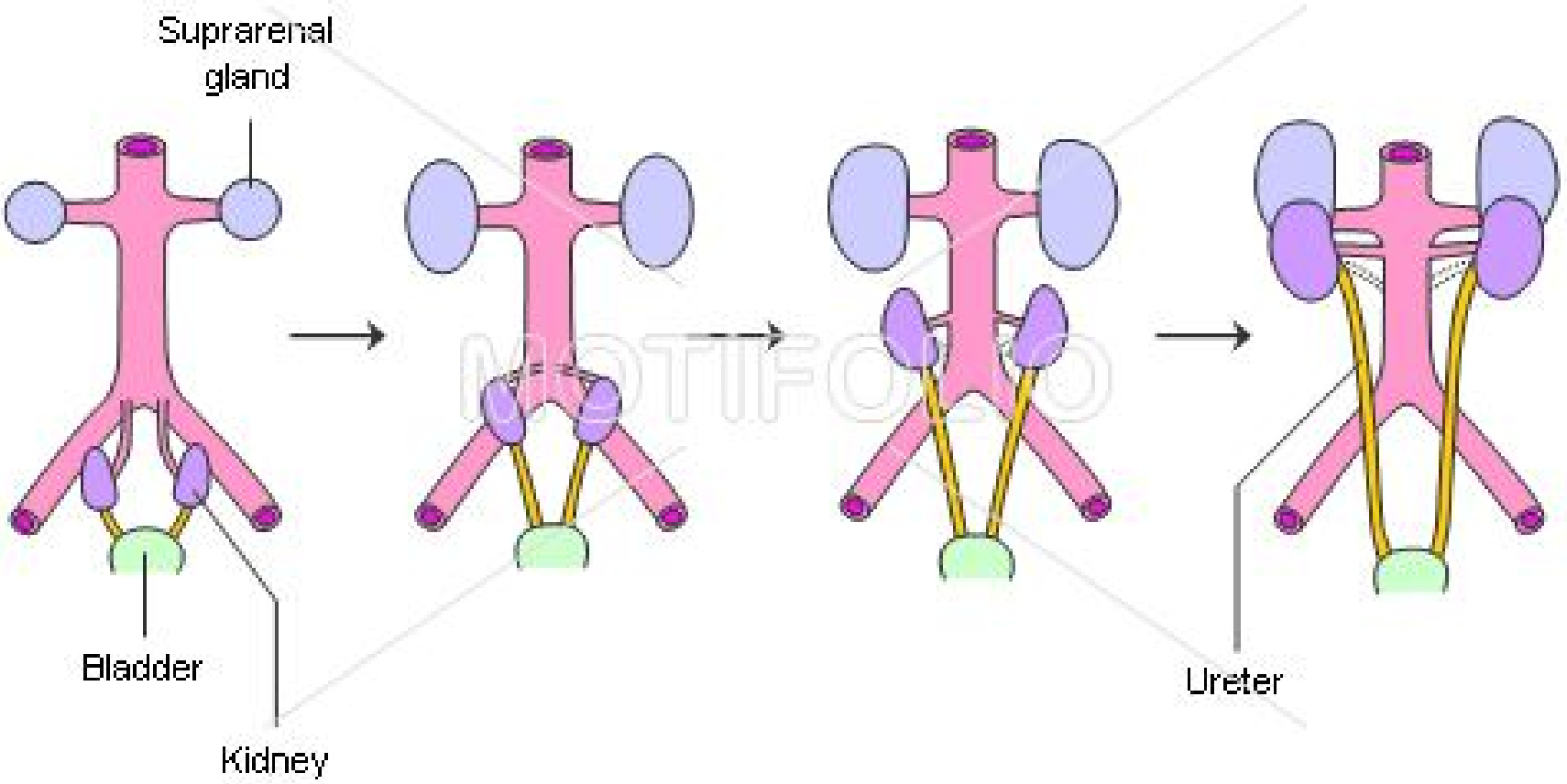
Kidney Position

The ascent of the kidneys from the sacral to the lumbar position – 6- 9 weeks



Kidney Position

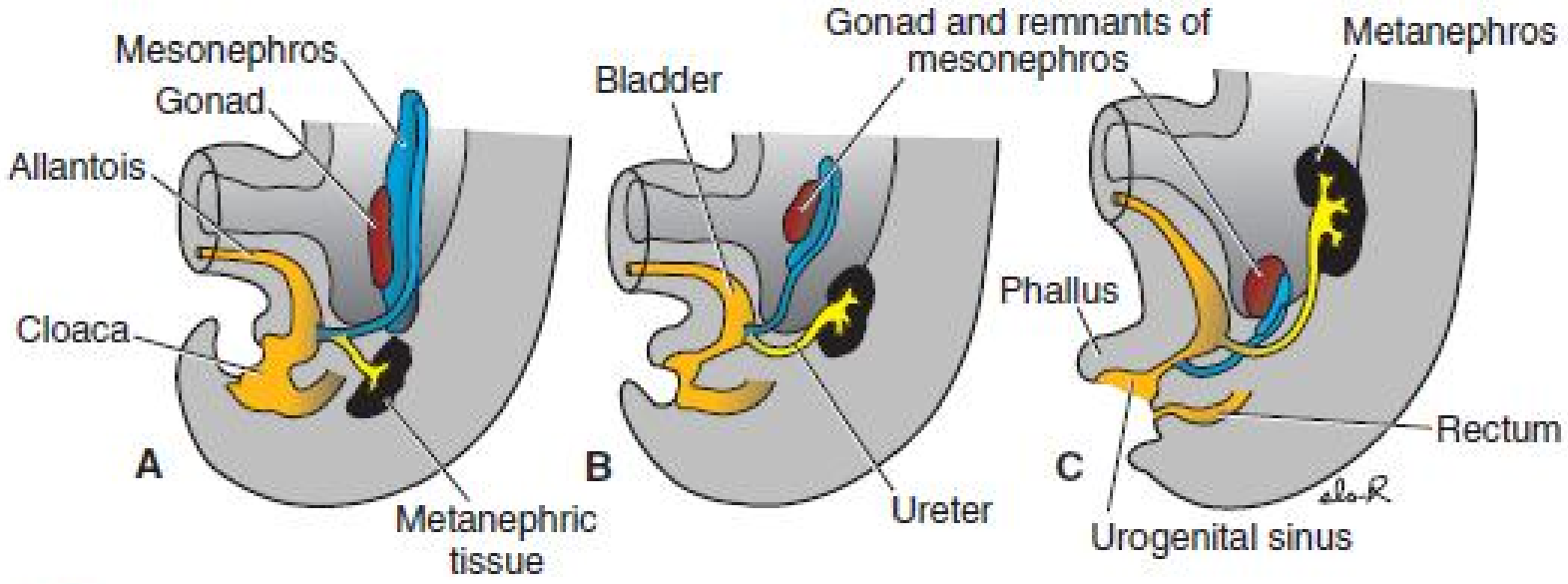
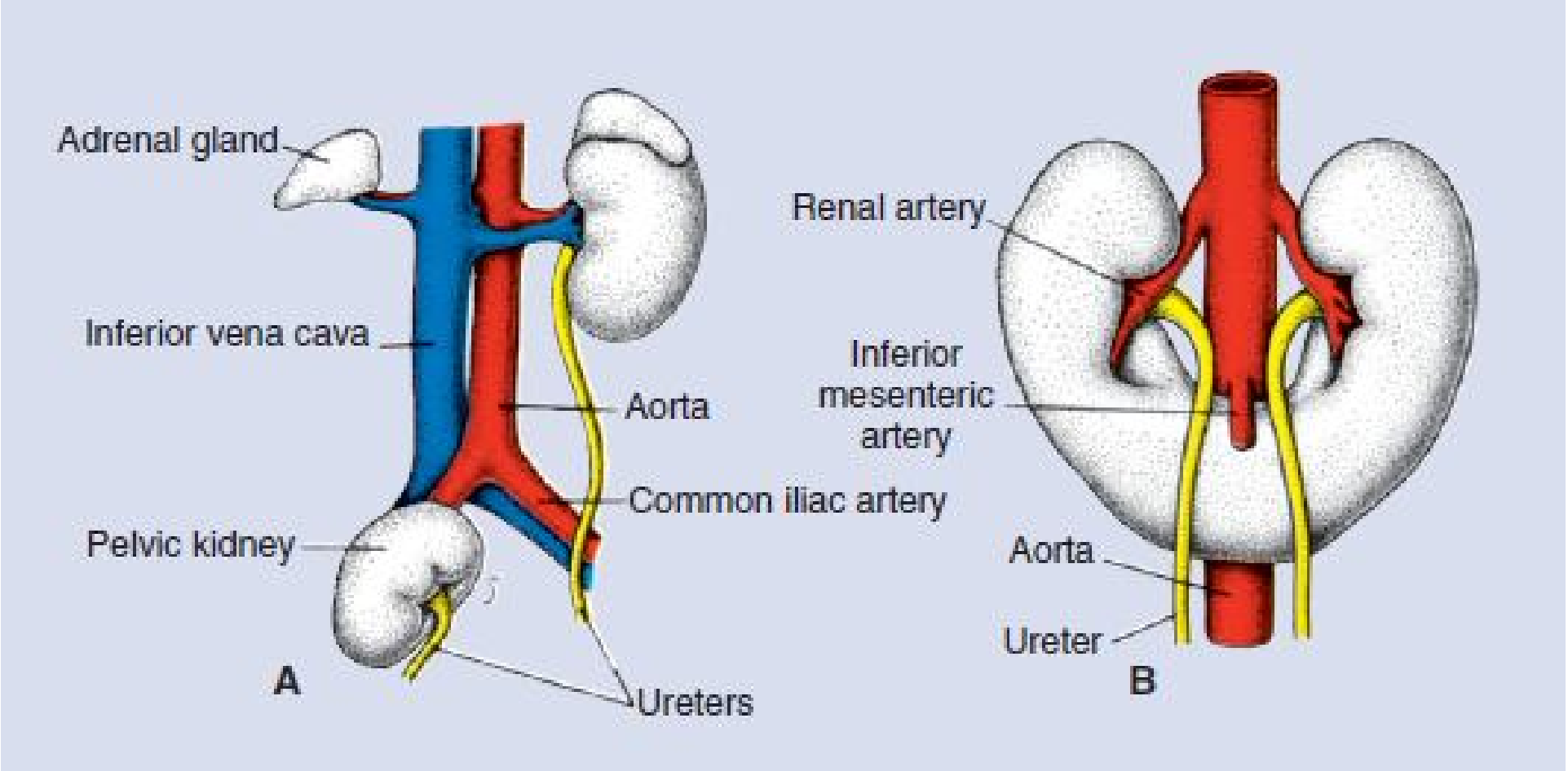


Figure 16.10 A–C. Ascent of the kidneys. Note the change in position between the mesonephric and metanephric systems. The mesonephric system degenerates almost entirely, and only a few remnants persist in close contact with the gonad. In both male and female embryos, the gonads descend from their original level to a much lower position.

Pelvic kidney / horseshoe kidney



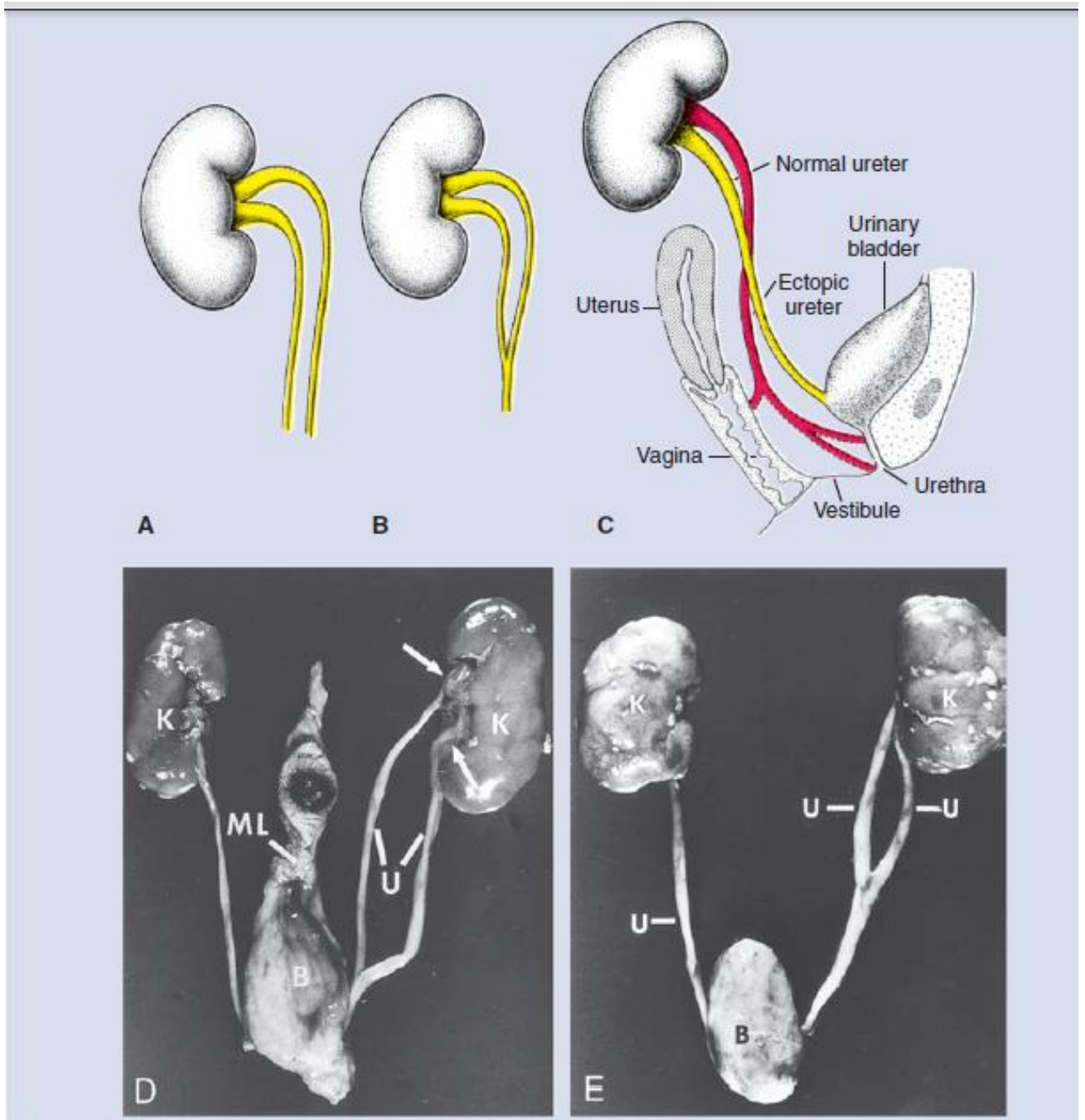


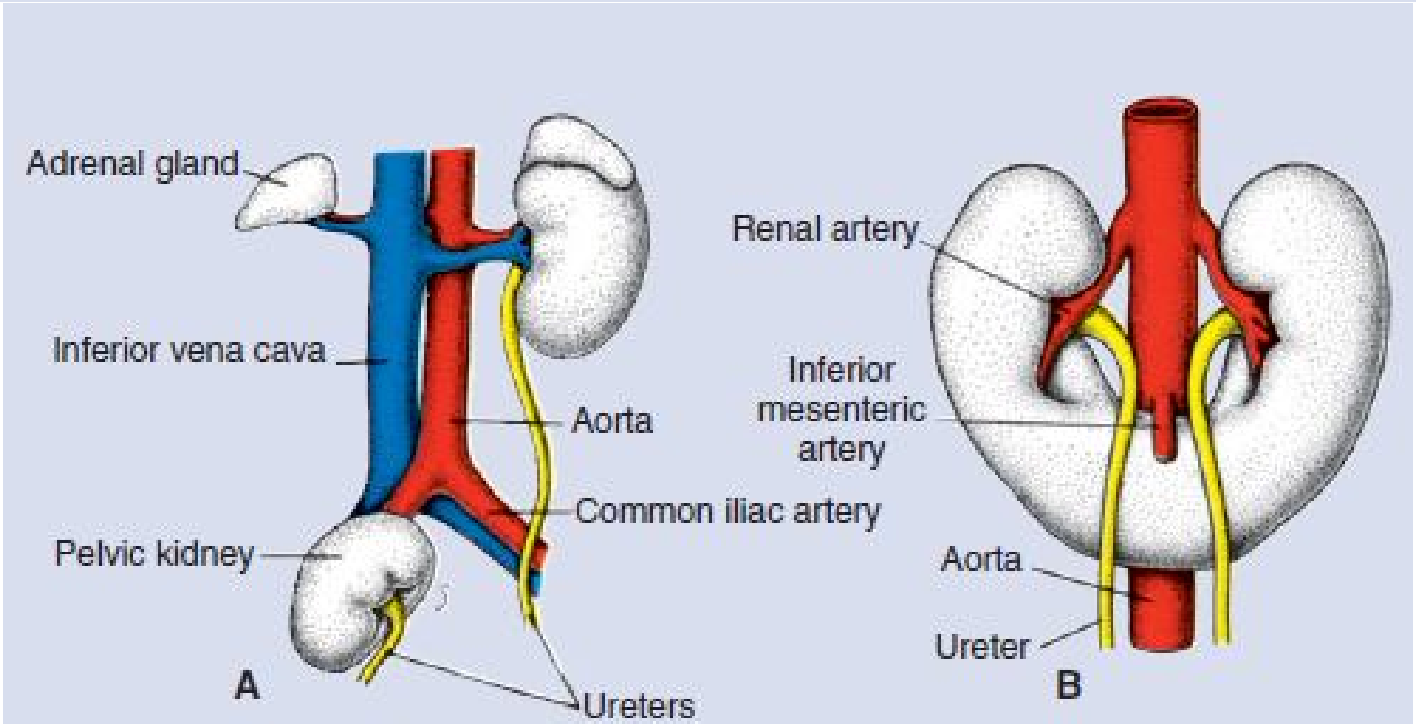
Figure 16.9 **A,B.** A complete and a partial double ureter. **C.** Possible sites of ectopic ureteral openings in the vagina, urethra, and vestibule. **D,E.** Photomicrographs of complete and partial duplications of the ureters (*U*). *Arrows*, duplicated hilum; *B*, bladder; *K*, kidneys; *ML*, median umbilical ligament.

Clinical Correlates

Abnormal Location of the Kidneys

During their ascent, the kidneys pass through the arterial fork formed by the umbilical arteries, but occasionally, one of them fails to do so. Remaining in the pelvis close to the common iliac artery, it is known as a **pelvic kidney** (Fig. 16.11*A*). Sometimes, the kidneys are pushed so close together during their passage through the arterial fork, that the lower poles fuse, forming a **horseshoe kidney** (Fig. 16.11*B,C*). The horseshoe kidney is usually at the level of the lower lumbar vertebrae, since its ascent is prevented by the root of the inferior mesenteric artery (Fig. 16.11*B*). The ureters arise from the anterior surface of the kidney and pass ventral to the isthmus in a caudal direction. Horseshoe kidney is found in 1/600 people.

Accessory renal arteries are common; they derive from the persistence of embryonic vessels that formed during ascent of the kidneys. These arteries usually arise from the aorta and enter the superior or inferior poles of the kidneys.



Cloaca Devision (4TH -7TH WEEKS)

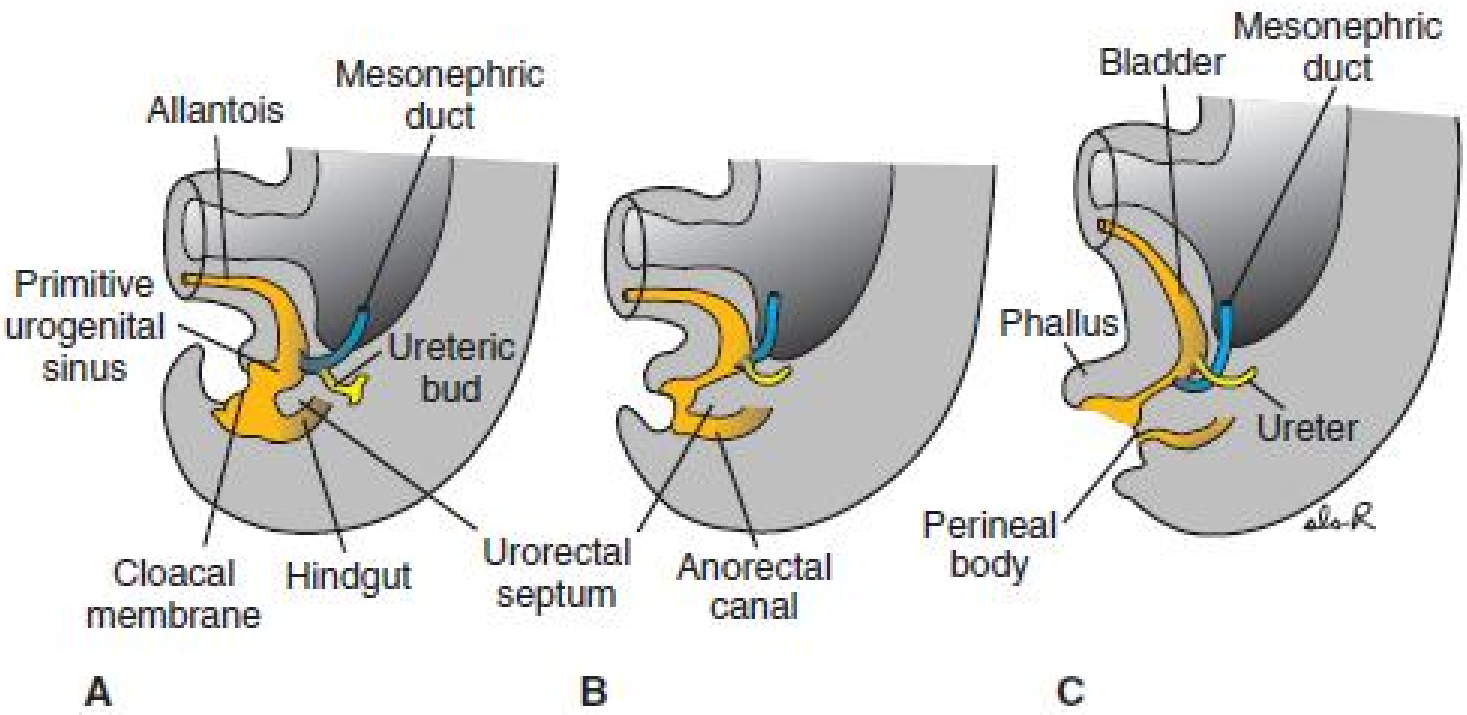


Figure 16.12 Divisions of the cloaca into the urogenital sinus and anorectal canal. The mesonephric duct is gradually absorbed into the wall of the urogenital sinus, and the ureters enter separately. **A.** At the end of the fifth week. **B.** 7 weeks. **C.** 8 weeks.

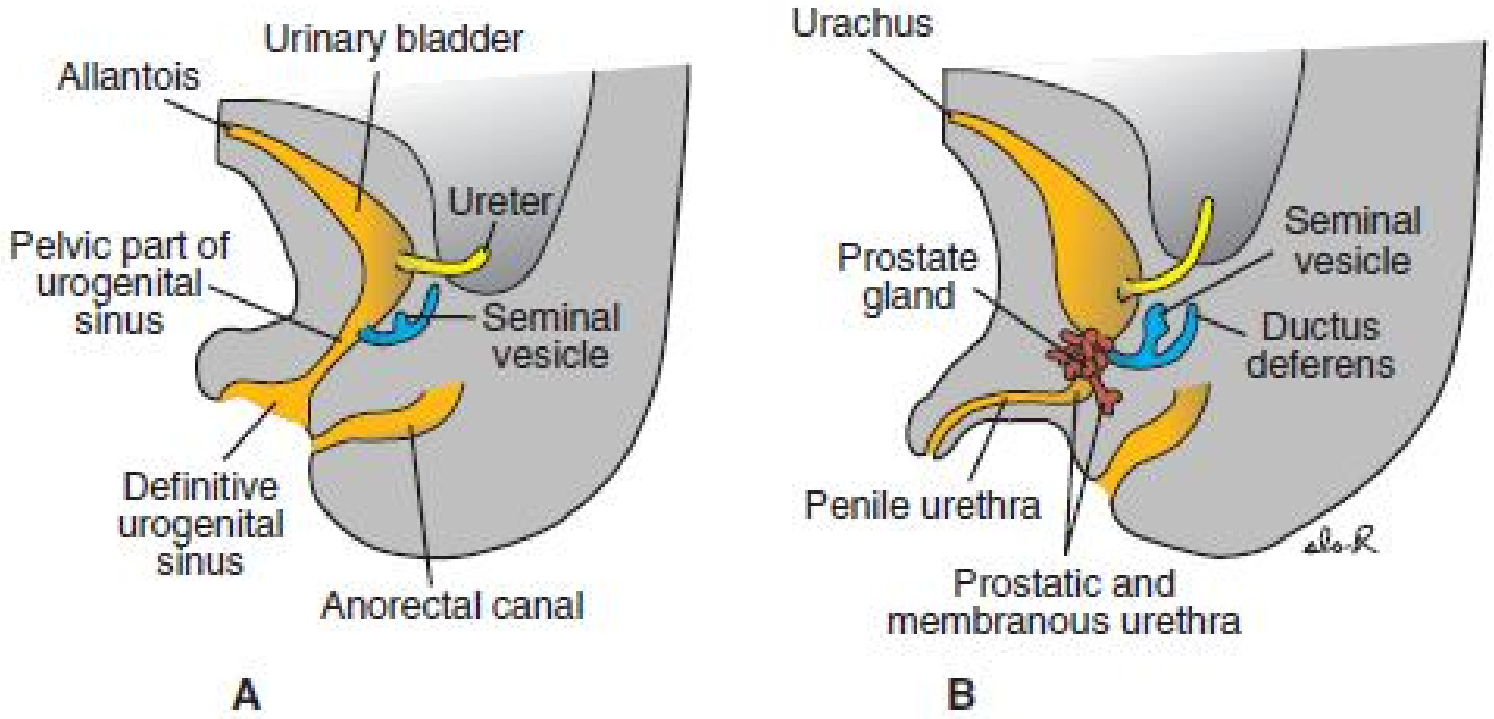


Figure 16.13 **A.** Development of the urogenital sinus into the urinary bladder and definitive urogenital sinus. **B.** In the male, the definitive urogenital sinus develops into the penile urethra. The prostate gland is formed by buds from the urethra, and seminal vesicles are formed by budding from the ductus deferens.

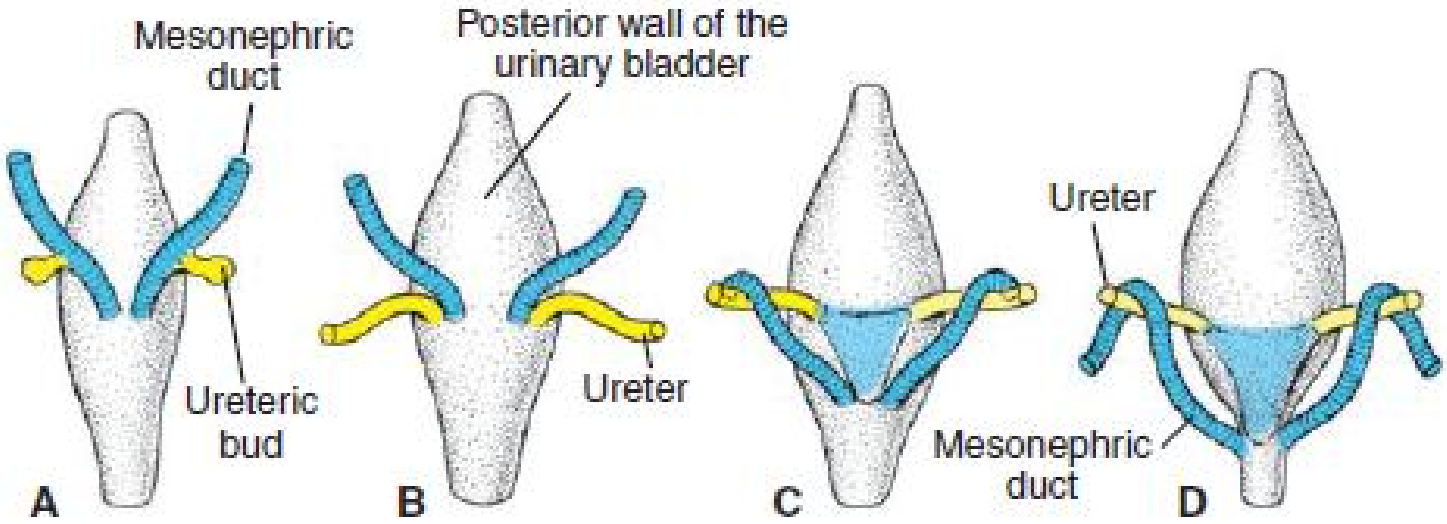


Figure 16.14 Dorsal views of the bladder showing the relation of the ureters and mesonephric ducts during development. Initially, the ureters are formed by an outgrowth of the mesonephric duct **A**, but with time, they assume a separate entrance into the urinary bladder **B–D**. Note the trigone of the bladder formed by incorporation of the mesonephric ducts **C,D**.

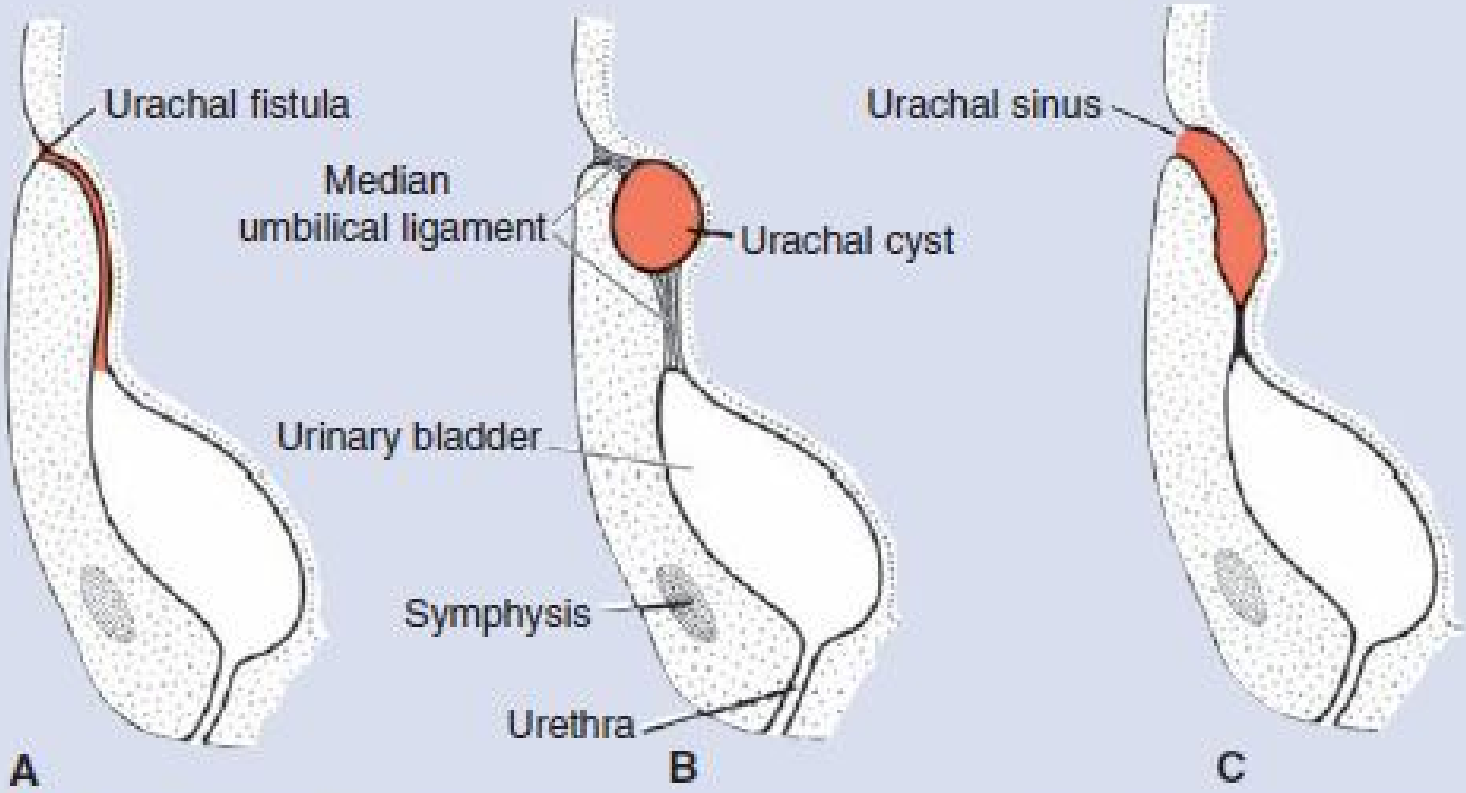


Figure 16.15 **A.** Urachal fistula. **B.** Urachal cyst. **C.** Urachal sinus. The sinus may or may not be in open communication with the urinary bladder.