Chapter 1

Anatomy and embryology of the male reproductive tract and gonadal development

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Introduction

The understanding of embryology provides a foundation for the mastery of anatomy. In the treatment of men with infertility, it is only appropriate that one return to the basics of fetal development of the male reproductive tract. This chapter will review the germ layers from which all tissues organize themselves and develop. It will also review the ductal system and its critical role in reproduction. The cloacal development, with its eventual division of the urogenital sinus, will be reviewed, including the various roles the urogenital sinus plays in male reproductive tract anatomy. Testis growth and descent will be discussed. And finally the events involved in the development of external male genitalia will be reviewed.

The germ layers

After fertilization of the ovum by sperm, prenatal development happens quite rapidly. By day two, the first cell division creates a zygote. On day three, with ongoing rapid cell division known as cleavage, the morula (from the Latin word for mulberry) forms and travels down the fallopian tube into the uterus. On day four, the morula develops a fluid-filled cavity, the yolk sac. With the development of tightly packed cells along the periphery, it becomes a blastocyst. **At day six, implantation into the uterus has begun**.

During the second week of development, the inner cell mass also develops a fluid-filled space called the amniotic cavity, and once again the most central or anterior cells organize themselves into a bilaminar disc. The blastocyst becomes completely implanted in the wall of the uterus and the placenta begins to form (Fig. 1.1). **By the third week, the blastocyst develops a primitive streak, a notochord, and turns the bilaminar disc into three germ layers – ectoderm, mesoderm, and endoderm** (Fig. 1.2).

After the fourth week of development, the primitive streak stops producing mesoderm and the widely dispersed mesenchyme, and the streak essentially disappears. The intraembryonic mesoderm in the trilaminar disc further differentiates into paraxial mesoderm on either side of the notochord, followed laterally by the intermediate mesoderm and most laterally by the lateral mesoderm. **Both the urinary and genital systems develop from this intermediate mesoderm** (Fig. 1.3) [1,2].

Normal development of the urinary ductal system

The urogenital system consists of two distinct systems (urinary and genital/reproductive) which are developmentally very interrelated. In the adult male they remain interrelated, but in the adult female these systems are separate, although still very close neighbors. **Before expression of gonadal genotype, all embryos undergo the same development of three urinary excretory systems, the second of which will be significant for the male reproductive system**.

First, the pronephroi (singular – pronephros) appear and disappear in developing embryos during the fourth week. In humans, the pronephros itself has no function but the longitudinal ducts, known as pronephric or nephric ducts, empty into the cloaca. This lays the groundwork for the development of the more permanent structures.

Second, the mesonephroi (singular – mesonephros) are paired organs that appear as the pronephroi are disintegrating. They have glomeruli as well as tubules that empty into the mesonephric ducts, which were originally the paranephric ducts. Hence, sometime during the fifth week of development the mesonephroi function as a primitive filtering system and empty waste into the cloaca (Fig. 1.4).

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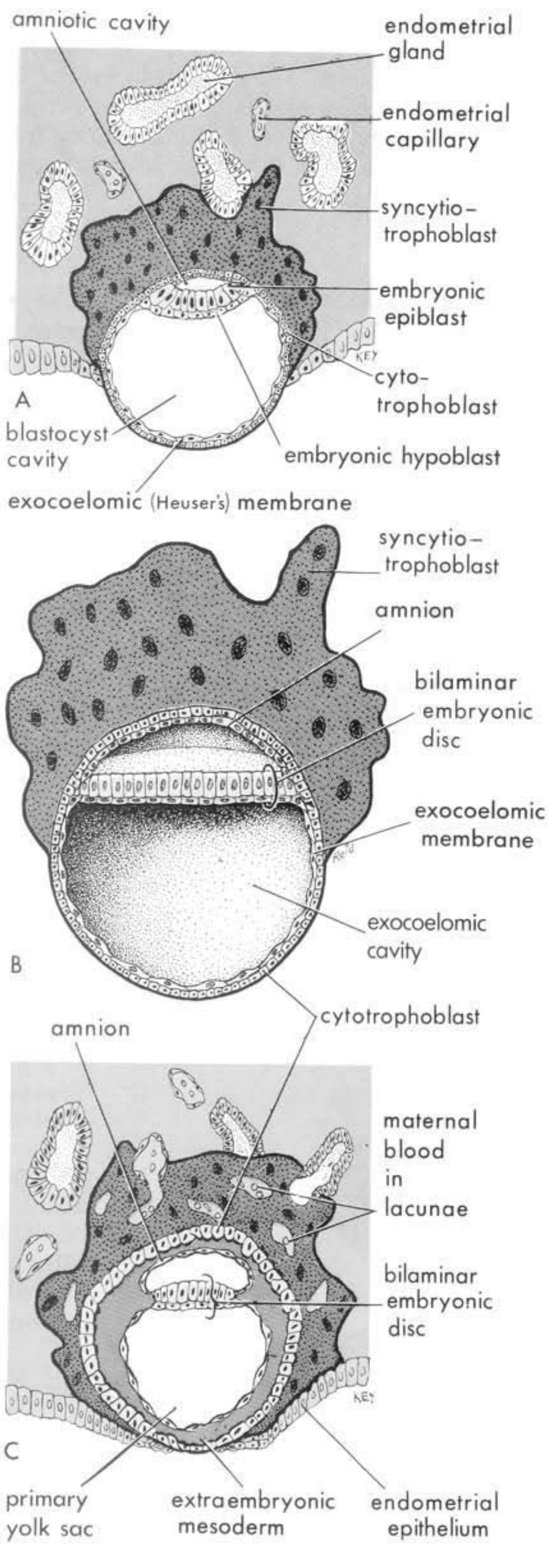

Fig. 1.1. Blastocyst in the endometrium, showing the bilaminar disc formation. (A) Partially implanted in the endometrium at around 8 days. (B) Enlarged, three-dimensional representation of blastocyst. (C) A blastocyst that has completely embedded in the endometrium; the lacunae seen in the syncytiotrophoblast will eventually communicate with the endometrial vessels, establishing the primitive ureteroplacental circulation. (Reproduced with permission from Moore KL, Persaud TVN. *The Developing Human: Clinically Oriented Embryology*, 5th edn. Philadelphia, PA: Saunders, 1993.)

Third, the metanephroi (singular – metanephros), or the permanent kidneys, develop in the fifth week and begin to function in the ninth week, corresponding to when the mesonephroi degenerate. **There are two distinct parts that contribute to the creation of the metanephroi: the ureteric bud and the metanephric blastema**. A diverticulum from the (meso) nephric duct, known as the ureteric bud, grows out into some neighboring metanephric mesoderm, which is the blastema for the future kidney. The contact of the ureteric bud induces the metanephric mesoderm to grow and differentiate. Nephrons grow through a process of branching and ongoing cell induction. The developing tubules are eventually invaginated by glomeruli from the developing aorta [3].

Finally, during the seventh to eighth week postfertilization, the effects of the gonads start to play a role. If testes are present and testosterone is being secreted, and the body's cells are receptive to it, the (meso)nephric ducts will become what are known as the Wolffian ducts and will shift their function from the urinary system to the reproductive system. They are paired, run longitudinally on either side of the midline, and empty into the cloaca. The proximal, most cranial, portion of them will become the epididymis and the remainder will form the ductus (vas) deferens and the ejaculatory duct. If testosterone is not present or is not being sensed, these ducts will disappear and leave only a few vestigial remnants. Another duct that is unique to the genital system instead of coopted from the urinary system will develop parallel to the mesonephric ducts. These are the paramesonephric ducts, to be discussed in more detail later.

The cloaca

During the rapid cell growth in the third week of the trilaminar embryo, the head and tail fold ventrally. During this folding, a part of the yolk sac is incorporated into the embryo as the hindgut, and the distal portion of this dilates into a region known as the cloaca, from the Latin word for sewer. Within this piece of incorporated yolk sac exists a diverticulum called the allantois, from

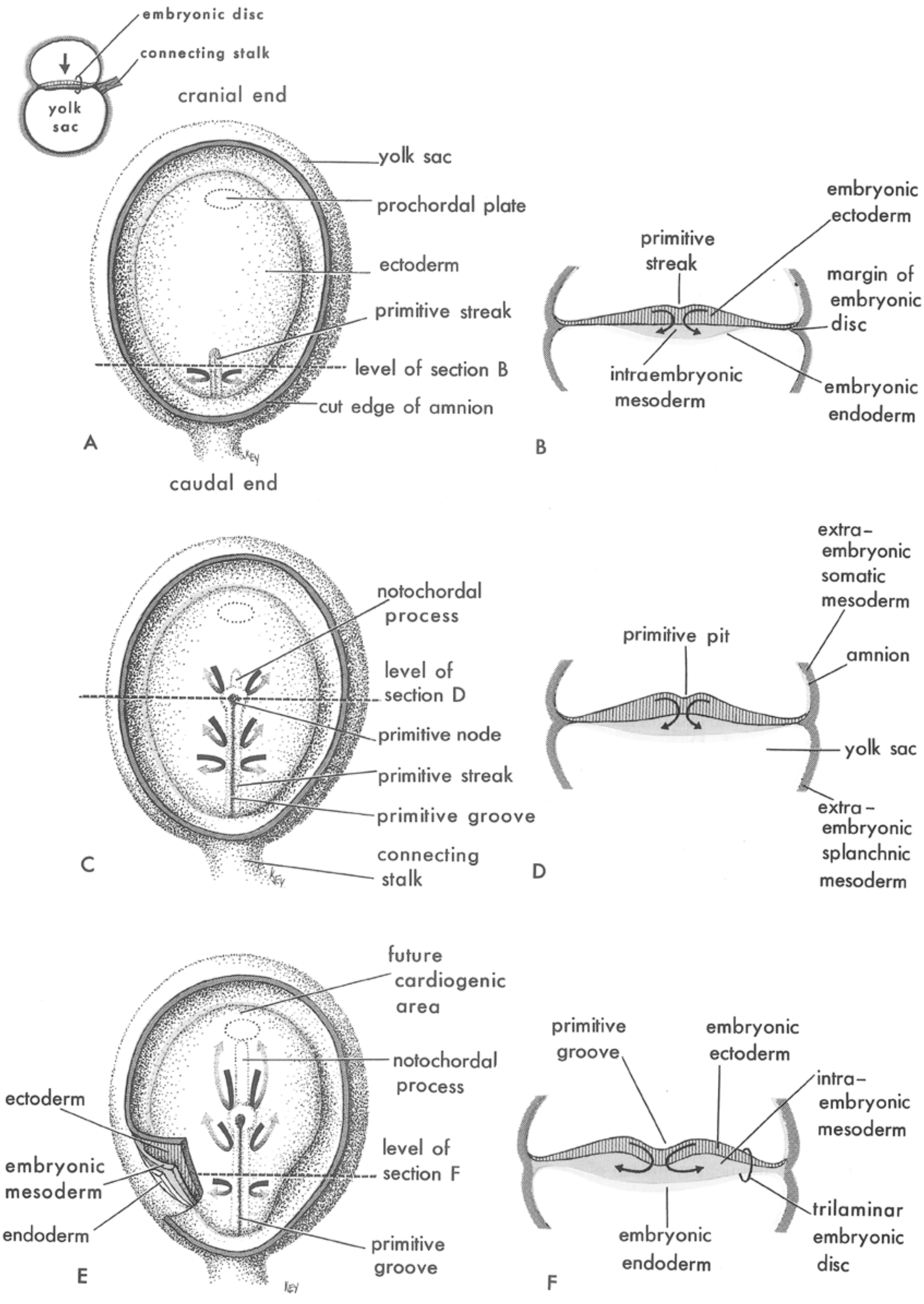

Fig. 1.2. Trilaminar embryonic disc (days 15 to 16). The arrows indicate invagination and migration of mesenchymal cells between the ectoderm and endoderm. (A, C & E) Dorsal views, with the amnion removed; (B, D, & F) corresponding cross-section views. (Reproduced with permission from Moore KL, Persaud TVN. *The Developing Human: Clinically Oriented Embryology*, 5th edn. Philadelphia, PA: Saunders, 1993.)

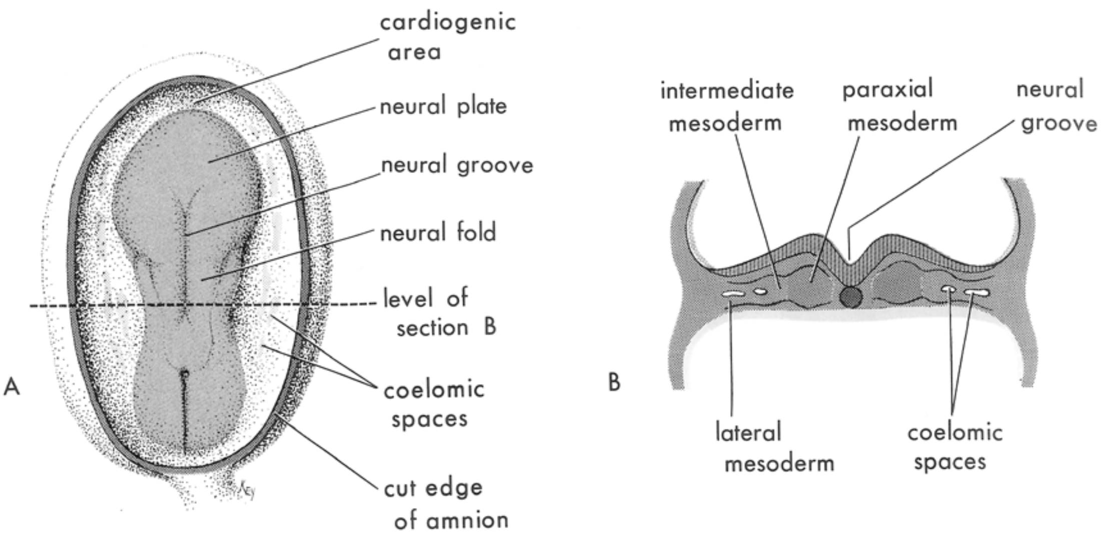

Fig. 1.3. Embryo at 18 days, showing differentiation of mesoderm: (A) dorsal view, with the amnion removed; (B) cross section indicated in image A. (Reproduced with permission from Moore KL, Persaud TVN. *The Developing Human: Clinically Oriented Embryology*, 5th edn. Philadelphia, PA: Saunders, 1993.)

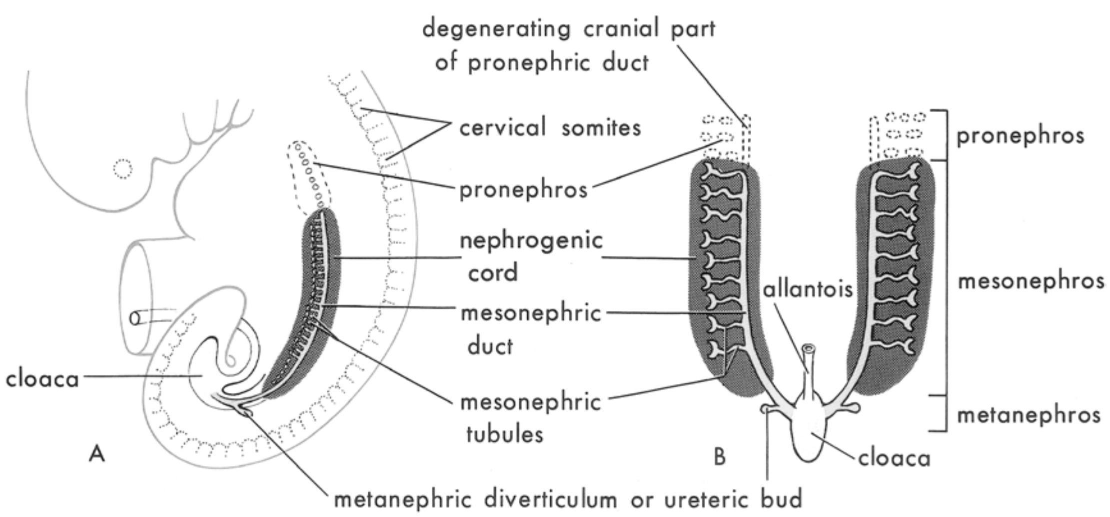

Fig. 1.4. Junction of excretory organs in fifth week. (A) lateral view; (B) ventral view with the mesonephric tubules rotated laterally for ease of viewing. (From Moore KL, Persaud TVN. *The Developing Human: Clinically Oriented Embryology*, 5th edn. Philadelphia, PA: Saunders, 1993.)

the Greek word *allas* meaning sausage. It extends up into the connecting stalk of the embryo and, although much more important in other animals' developing respiratory function, in humans it is associated with the developing bladder, and its blood vessels become the umbilical arteries and vein. The vestigial remnants are the urachus and the median umbilical ligament.

The cloaca, as incorporated yolk sac, is an endoderm-lined cavity, anchored at the caudal end by the cloacal membrane. **Currently, there are two leading theories as to the separation of the cloacal membrane**. The classic view was that mesenchyme continues to grow rapidly, extending caudally and dorsally, between the more ventral allantois and the relatively dorsal hindgut. This mesenchyme is known as the urorectal septum. As it grows caudally, it eventually fuses with the cloacal membrane, and this point of fusion in adults is known as the perineal body. The migration and fusion

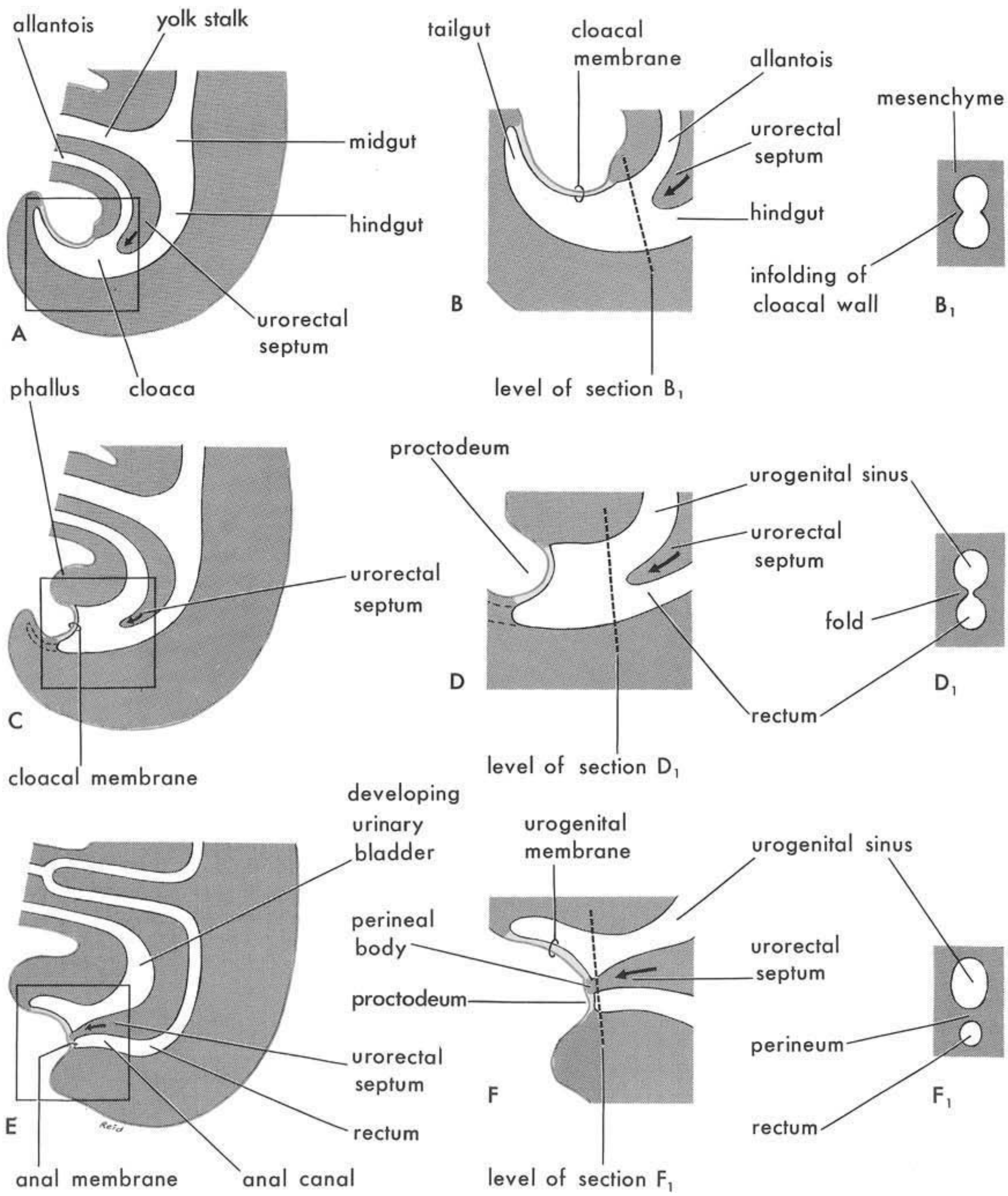

Fig. 1.5. Cloaca and urogenital sinus division: (A & B) at 4 weeks; (C & D) at 6 weeks; (E & F) at 7 weeks. (Reproduced with permission from Moore KL, Persaud TVN. *The Developing Human: Clinically* Oriented *Embryology*, 5th edn. Philadelphia, PA: Saunders, 1993.)

of the urorectal septum effectively divides the cloaca into a ventral urogenital sinus (which is contiguous with the allantois cranially) and a dorsal area including the rectum and anal canal during the seventh week of development. The cloacal membrane associated with the ventral urogenital sinus is now referred to as the urogenital membrane, and the dorsal portion is the anal membrane. By the end of the eighth week, the anal membrane usually ruptures and the urogenital membrane is degenerating (Fig. 1.5) [4].

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This theory was challenged by more recent studies utilizing three-dimensional magnetic resonance imaging. These observations led to the theory that the descending urorectal septum never fuses with the cloacal membrane [5]. Rather, the cloaca undergoes preprogrammed cell death during the eighth week of development, and the urorectal septum, which is immediately posterior to the cloacal membrane, still defines the boundary between the urogenital sinus on the ventral side, and the rectum/anal canal on the dorsal side. The tip of the urorectal septum then becomes the perineal body.

The trigone and excretory ducts

During the fifth week of development, as the final kidney is beginning to form as described above, the portion of the urogenital sinus that will become bladder is beginning to take shape. As discussed above, the mesonephric ducts, which are mesodermal structures, are connected to the urogenital sinus (ventral portion of the cloaca, and therefore endodermally lined) bilaterally. **The portions of the mesonephric ducts distal to where the ureteric buds have sprouted become known as the common excretory ducts**. The common excretory ducts then fuse in the midline and become known as the primitive trigone. With ongoing growth of the urogenital sinus, the trigone migrates more and more caudal, which causes the ureteric buds eventually to become individually invaginated into the developing trigone as well (Fig. 1.6). It is assumed that the rapid growth of the bladder, along with the relative ascent of the kidneys, exerts a force on the ureteric orifices to move superolaterally after incorporation into the bladder.

The common excretory ducts eventually move into the prostatic part of the urethra and become known as the verumontanum. Anomalies in development can occur depending on the distance between the orifice of the mesonephric duct within the urogenital sinus and the ureteric bud. If it is too short, the resultant ureteral orifice may develop distally in the bladder neck or urethra; if it is too long, it may never become incorporated into the bladder. Also, the migration of the excretory ducts, as well as the appearance of the paramesonephric ducts, all occur before testosterone and anti-Müllerian hormone (AMH), also known as Müllerian-inhibiting substance (MIS), are present [3].

The urogenital sinus: male

The urogenital sinus has three distinct regions, all lined with the same endodermal cells. The most cranial is the vesical part, which is contiguous with the allantois, which will become the bladder. There is a middle pelvic part, which in males will become the prostate and bulbourethral glands. And finally there is a caudal, phallic part, which is in contact with the urogenital membrane. This is the region that will become the spongy urethra. The distal part of the urethra originates from ectodermal cells along the glandular plate at the tip of the glans penis. This plate is evident at eleven weeks of development. By the twelfth week, the plate becomes canalized and starts growing down to meet the spongy urethra coming from the urogenital sinus by the fourteenth week. Connective tissue and smooth muscle of the urethra derive from neighboring splanchnic mesenchyme (Fig. 1.7) [6].

The growing circulation of androgens from the developing testes promotes the start of prostate development. As the urethra is growing distally from the most caudal part of the urogenital sinus, the prostate develops from the middle pelvic part of the urogenital sinus during the tenth week of gestation. This starts with various outpouchings of endoderm into the neighboring mesenchyme, which will then differentiate into stroma and smooth muscle. The endodermal or epithelial cords eventually canalize, and the lining develops into two distinct cell types, luminal and basal.

The bulbourethral glands develop as paired outgrowths from the spongy part of the urethra, just distal to the prostate [6]. As with the prostate, the epithelial portion of these glands comes from the endoderm of the urogenital sinus. The outpouchings of endoderm then induce the local mesenchyme to form the smooth-muscle fibers and stroma of the glands. These glands will produce secretions that contribute to semen (Fig. 1.8).

The urogenital sinus: female

The urogenital sinus, in its undifferentiated state, is composed of three sections: a cranial (vesical) part, a middle (pelvic) part, and a caudal (phallic) part. The fate of the vesical part is the same for females and males – it becomes the bladder. This is the area into which the distal mesonephric ducts invaginate, fuse, migrate caudally, then receive the invagination of the ureteric buds, all forming the trigone. The middle (pelvic) and the caudal (phallic) portions have slightly different fates in the developing female. **As there is no testosterone or anti-Müllerian hormone (AMH) present in the eighth week, the phallus does not grow but the urethra undergoes the same transformation,**

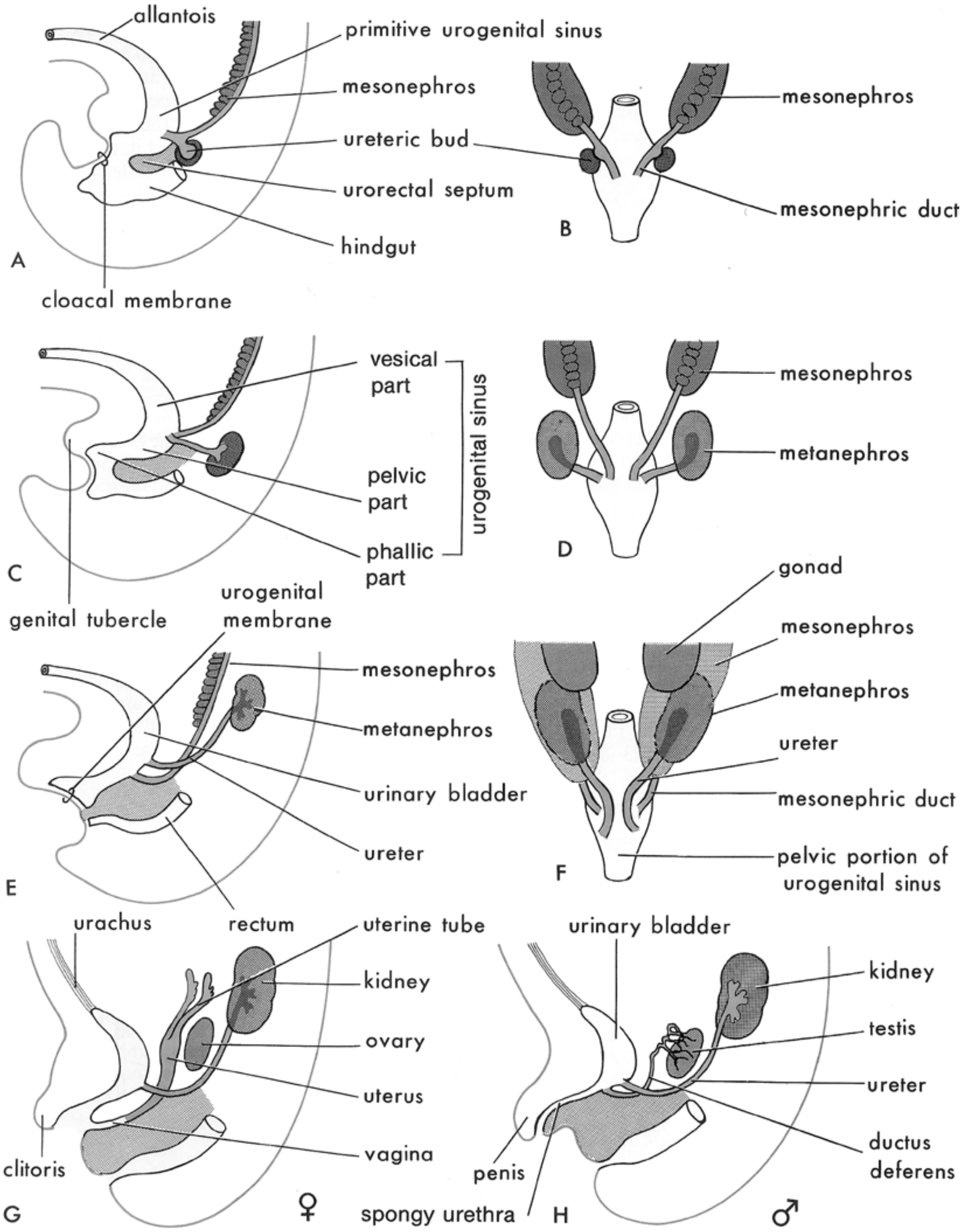

Fig. 1.6. Formation of urogenital sinus and rectum; movement of the mesonephric ducts and ureters; formation of bladder, urethra, and urachus. Shown in stages from 5 weeks to 12 weeks. (Reproduced with permission from Moore KL, Persaud TVN. *The Developing Human: Clinically Oriented Embryology*, 5th edn. Philadelphia, PA: Saunders, 1993.)

albeit much shorter, from the caudal portion of the urogenital sinus (Fig. 1.6).

In the hormonal female, the mesonephric (Wolffian) ducts degenerate, but the paramesonephric ducts persist. The ends of these ducts fuse together and then fuse into the posterior wall of the middle (pelvic) urogenital sinus – that point of fusion becomes known as the sinusal tubercle. The ducts continue to fuse with

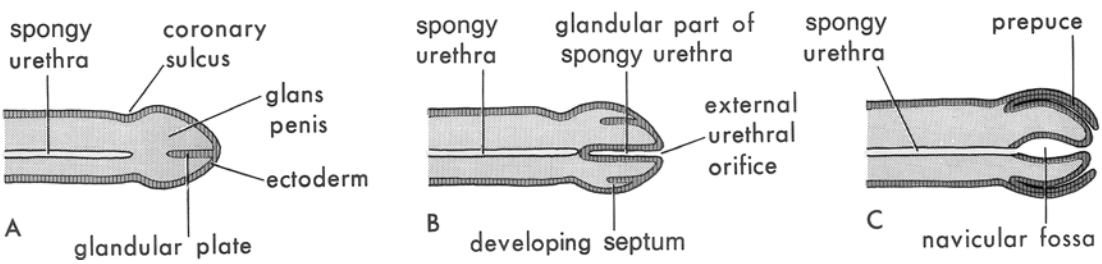

Fig. 1.7. Developing penis from 11 to 14 weeks. (Reproduced with permission from Moore KL, Persaud TVN. *The Developing Human: Clinically Oriented Embryology*, 5th edn. Philadelphia, PA: Saunders, 1993.)

the urogenital sinus and open up into a common, single-lumen chamber, known as the ureterovaginal canal. This becomes the uterus as well as the proximal portion of the vagina.

The sinusal tubercle eventually contributes to the vaginal plate, which elongates and becomes canalized. The final barrier to the outside world is a thin endodermal layer of urogenital sinus, which normally dissolves by the fifth month, but a remnant will be left as the vaginal hymen. The epithelial layer of the entire vagina and cervix may extend in from this endodermal urogenital sinus connection (Fig. 1.8) [3].

The genital ducts

To review, there are a series of ducts that develop in the genitourinary systems. Some are primarily for the rudimentary urinary system (pronephric), some start in the urinary system but are coopted by the genital system (mesonephric), and some are proprietary of the genital system (paramesonephric). **While the fate of the pronephric duct is the same for both males and females, the development of the other two ducts is dependent on gonadal differentiation**.

Regardless of chromosomal gender, during the fifth week of development, gonadal development begins. It is undifferentiated for the first two weeks. Both gonads, the testis and the ovary, arise from a mix of mesothelium (mesodermal epithelium) from the posterior abdominal wall, mesenchyme, and primordial germ cells. The process starts with the appearance of a thickened area of epithelium, the gonadal ridge. The primordial germ cells are first identified in the developing embryo during the fourth week. They eventually migrate towards the gonadal ridge. Additional epithelial tissue of the gonadal ridge thickens, becoming known as the primary sex cords. The sex cords incorporate the primordial germ cells which are now present. **At this point, the gonadal ridge is identified as having two distinct regions: the epithelial layer (cortex) and the mesenchymal area (medulla)** (Fig. 1.9) [4].

Still in an undifferentiated gonadal state, the paramesonephric ducts appear. The cranial ends of these ducts are funnel-shaped and open into the future peritoneal cavity. These ducts become known as the Müllerian ducts.

By the sixth week of development, if the embryo is chromosomally XY, cells in the sex cords in the medulla will grow and become Sertoli cells, under the influence of SRY (sex-determining region of the Y sex chromosome), and the cortex will disappear. The Sertoli cells will start to produce AMH, which will halt the development of the paramesonephric ducts and eventually cause rapid regression during the eighth to tenth week of development [7]. Remnants in the males include a small piece of tissue on the superior pole of the testis called the appendix testis. Also, extra tissue along the posterior urethra can remain, becoming known as the prostatic utricle. Rarely, a genetic male due to an AMH malfunction will have persistence of the Müllerian ducts (and thus a uterus and fallopian tubes will develop), a condition called hernia uteri inguinale. The Sertoli cells, along with the primordial germ cells, will become seminiferous tubules at puberty.

The seminiferous or testis cords are separated by mesenchyme that is stimulated to become Leydig cells by the SRY protein. This occurs from the eighth to the tenth week of development, at which point these cells start producing testosterone. Initially, the production is regulated by placental chorionic gonadotropin, but eventually the developing embryo's own hypothalamus–pituitary axis takes over control with the pituitary secretion of human chorionic gonadotropin (hCG).

Testosterone stimulates numerous changes in the existing ductal system. Specifically, the mesonephric duct definitively becomes the Wolffian duct. The most

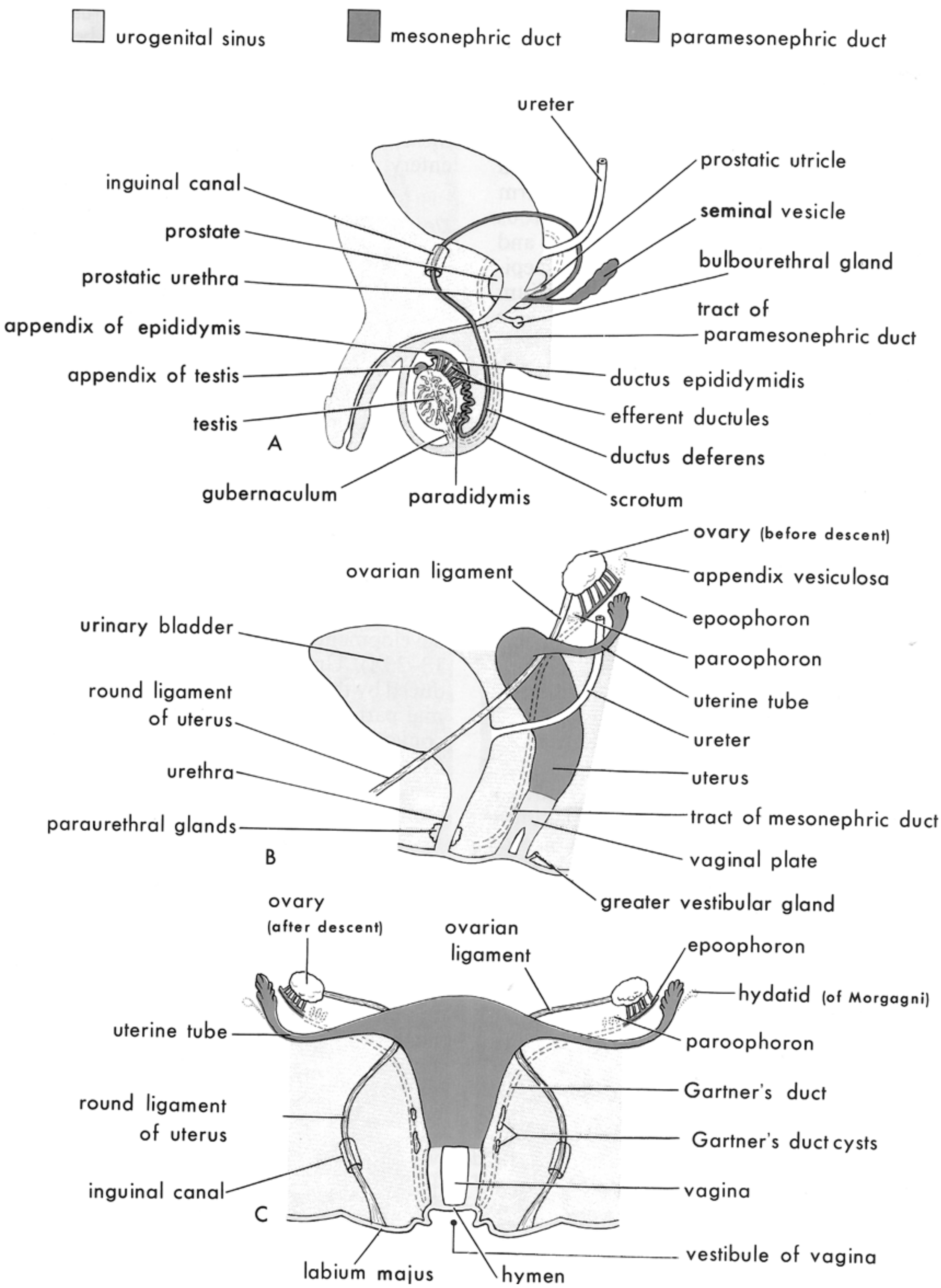

Fig. 1.8. Urogenital sinus and genital duct integration: (A) newborn male; (B) 12-week female fetus; (C) newborn female. (Reproduced with permission from Moore KL, Persaud TVN. *The Developing Human: Clinically Oriented Embryology*, 5th edn. Philadelphia, PA: Saunders, 1993.)

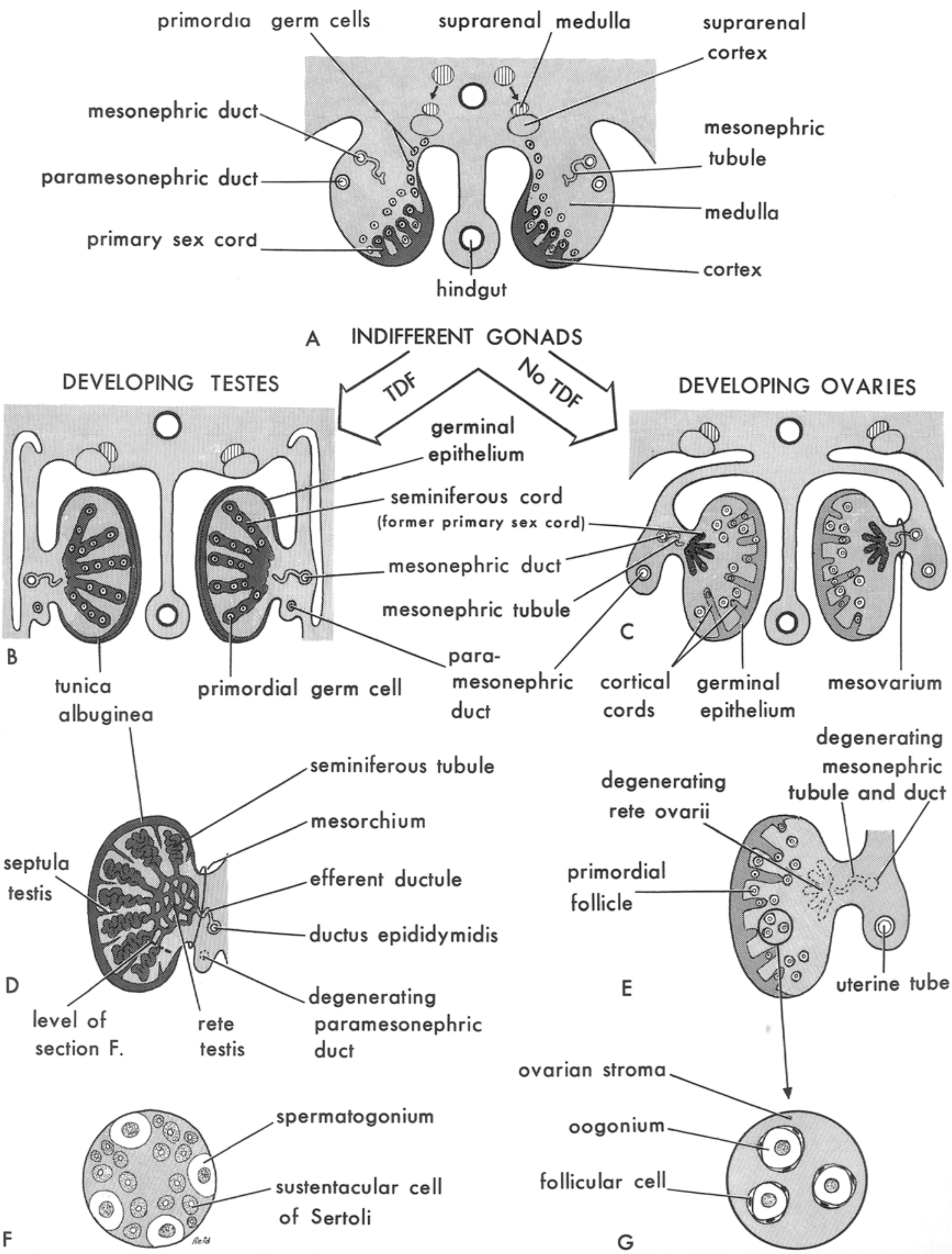

Fig. 1.9. Differentiation of the gonads: (A) 6 weeks; (B) 7 weeks; (C) 12 weeks; (D) testis at 20 weeks; (E) ovary at 20 weeks; (F & G) sections of testis and ovary at 20 weeks. TDF, testis-determining factor. (Reproduced with permission from Moore KL, Persaud TVN. *The Developing Human: Clinically Oriented Embryology*, 5th edn. Philadelphia, PA: Saunders, 1993.)