Human Reproduction

Physiology and Pathophysiology

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HUMAN REPRODUCTION:
PHYSIOLOGY AND PATHOPHYSIOLOGY

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preface

For the last ten years a basic course in Human Reproductive Physiology and Pathophysiology has been taught to sophomore medical students at the University of Texas Medical School at San Antonio. This book contains material presented in the course. Techniques which have proven successful in classroom teaching have been retained. The reader will notice the presence of objectives at the beginning of each chapter. Although there are no references listed in the text, several general references are provided at the end of each chapter. A series of questions with answers at the end of each chapter assures the reader that salient points have not been overlooked.

No attempt has been made to write an all-encompassing textbook of Obstetrics and Gynecology. Operative techniques, histopathology and modalities of treatment have been omitted except where absolutely necessary. Despite these omissions, the material in this book has been useful daily to junior medical students during their clinical clerkship. Houseofficers in Obstetrics and Gynecology have found the book helpful for a quick review of basic material, and it is thought that the book will be of value to practicing physicians preparing for examinations.

The editors wish to thank members of the department who wrote chapters for the book and Dr. C. E. Gibbs who contributed greatly even though he is not an author. Jo Wiglesworth and Mary Gonzales typed most of the original drafts, Pat Schriver did the art work, and a special thanks goes to Gretta Small for her excellent final draft of the manuscript. Our thanks also go to Ruth Wreschner of John Wiley and Sons for her patience in guiding the book to completion.

Robert W. Huff
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HUMAN REPRODUCTION:
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part one
reproductive biology

chapter one
developmental and anatomic correlates of reproduction

OBJECTIVES

1. To review the stages of embryogenesis during which the pattern common to the male and female urogenital systems is developed.
2. Describe control mechanisms in differentiation of the gonads, internal genital organs, and external genital organs.
3. List four important facts concerning differentiation of the gonads.
4. Describe the processes by which the paramesonephric cords become the fully developed internal genital organs in the female.
5. Describe the body changes at puberty in boys and girls.
6. Identify disorders associated with confusion of sex assignment at birth.
7. Describe the steps in differential diagnosis of a newborn with sexual ambiguity.
8. Know basic principles of management of neonates with ambiguous genitalia.

NORMAL DEVELOPMENT

The genotype exerts the strongest influence on gonadal differentiation. The precise mechanisms by which genetic factors control sex differentiation remain unresolved. However, the consensus holds that the gonads, internal ducts, and external genitalia develop along female lines unless induced toward male differentiation by a Y-linked determinant, which may exert its influence directly or by modifying the activity of other genes.

Although the sex genotype is determined at fertilization, sex differentiation of the gonads and internal and external genitalia does not become evident until the seventh week and is not completed until 12 weeks in the female and 14 weeks in the male. During the intervening weeks, the primordia of the male and female gonads are established. Just as the genotype determines the direction in which the gonads will differentiate, so the gonads determine the differentiation of the internal ducts and the external genitalia.

Gonad—Undifferentiated Stage

Both ovaries and testes develop from an undifferentiated gonadal primordium. At about the fifth week of embryonic life, the genital ridge may be distinguished as a thickening of the epithelium covering the medial aspect of the mesonephros. In this region, the epithelium is not separated from the underlying mesenchyme by a basement membrane. The gonadal blastema elevates the medioventral surface of the urogenital ridge, forming a lateral mesonephric ridge and a medial genital ridge (Fig. 1–1). During subsequent differentiation, primordial germ cells and mesoblastic cells form the epithelial structures of the definitive gonad, whereas the mesenchymal cells contribute to the interstitial tissues of the gonads.

The germ cells arise in the yolk sac or gut endoderm, migrate to the root of the mesentery of the primitive gut, and become incorporated into the urogenital ridge. The indifferent gonad has two major components, the cortex and medulla. The medullary element is capable only of becoming a testis. The cortical element is capable only of development as an ovary. Initially, the gonadal ridge is contiguous with the intermediate three-fifths of the mesonephros. As the mesonephros regresses, the gonads are suspended by a "urogenital" mesentery plus the ligaments of the degenerated mesonephros. The cranial ligament disappears, and the caudal suspensory ligament anchors the gonad to the genital swelling and persists as the gonadoinguinal ligament (gubernaculum).

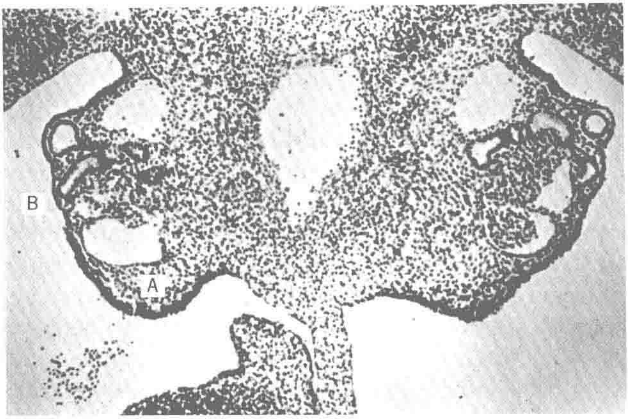

Figure 1–1. Section through an embryo at about the fifth week of embryonic life. The epithelium is thickened over the mesenchyme in the region of the developing gonad. (*A*). Laterally, mesonephric structures are seen in the region of the mesonephric ridge (*B*).

Gonad—Ovarian Differentiation

If so destined, the gonad differentiates into an ovary during the seventh week of embryonic life. One can then distinguish connective tissue and epithelial tissue, in the form of medullary cords. These cords contain primordial germ cells (oogonia) as well as primitive granulosa cells.

At this point, it is necessary to address a subject that causes confusion to all students of reproductive embryology: the nomenclature of the female gamete. The cells that migrate from the hindgut are called primordial germ cells. After reaching the genital ridge, they are designated oogonia. Early generations of oogonia enter into the formation of the medullary cords and degenerate. Later generations of oogonia remain in the cortical region. They then enter meiotic prophase and differentiate into oocytes. Meiosis is arrested in the diplotene phase of the first division and is only resumed in the mature ovary just prior to ovulation. The second meiotic division occurs after fertilization.

Late in embryonic life, the fetal ovary contains many primary follicles, each characterized by an oocyte surrounded by a single layer of flattened granulosa cells. Each of these follicles is surrounded by connective tissue. These changes allow ready recognition of the gonad as an ovary.

Gonad—Testicular Differentiation

The embryonal testis becomes distinguishable during the seventh week of embryonic life. The indifferent gonad is divided into cords by septae, formed of reticular fibers and fibroblasts. These cords are then segregated from the surface epithelium by a sheet of connective tissue, which will become the tunica albuginea. The primordial germ cells become incorporated into the testicular cords. The cords are lined by several layers of Sertoli cells. The incorporated germ cells are now called spermatogonia. At about 60 days, Leydig cells are seen in the interstitial tissues near the tunica albuginea. These cells reach their maximum number during the third and fourth months and begin to decrease during the fourth month. The fetal testes actively produce androgens, which influence the development of the internal ducts and the external genitalia.

Internal Ducts—Indifferent Stage

During the indifferent stage, the embryo possesses both mesonephric (Wolffian) and paramesonephric (Müllerian) ducts. The progenitor of the mesonephric duct, the pronephric duct, is completed by the seventh week, at which time it is called the mesonephric duct. The pronephric tubules arise from the lateral portion of the urogenital ridge to connect the pronephric duct by the fourth week of embryonic life. By the sixth week, the Müllerian cleft appears between the pronephric and gonadal components of the urogenital ridge. The cleft is the cranial end of the future Müllerian duct.

Just caudad to the cleft, the solid tip of the Müllerian cord grows downward, intimately associated with the Wolffian duct ventrally and reaches the urogenital sinus. Here the tips of the right and left cords elevate the dorsal wall of the urogenital sinus to form Müller's tubercle, which eventually opens into the urogenital sinus (Fig. 1–2). At the conclusion of the indifferent stage, each Müllerian cord has become a hollow tube, meeting in the midline. The Wolffian ducts are also present at this stage. They have also grown downward, as solid cords, to reach the region of the mesonephric blastema. They canalize and enter the caudal portion of the hindgut, which then becomes the cloaca. Mesonephric tubules differentiate next to the mesonephric duct, to degenerate after formation of the metanephros. Some of the mesonephric tubules will persist as vestigial structures.

The urogenital sinus initially appears during the fifth to sixth week.

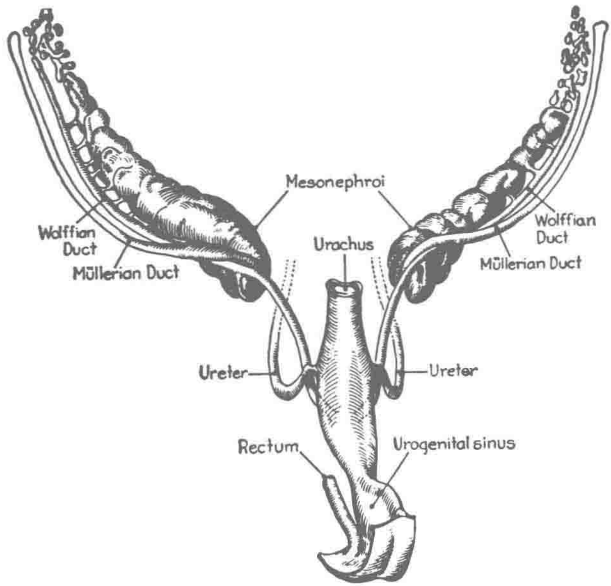

Figure 1–2. Reconstruction of the urogenital system during the indifferent stage. Note the relationships of the Wolffian and Müllerian ducts to each other and to the mesonephros. (From Hunter RH: Observations on the human female genital tract. *Contrib Embryol* 22:91–108, 1930. Courtesy of the Carnegie Institute of Washington, D.C.)

The transverse septum (urorectal septum) divides the cloaca into the rectum and a ventral segment that is the vesicourethral canal and the urogenital sinus. These regions give rise to structures of both the genital and urinary system. The most cranial portion gives rise to the urinary bladder. The midportion and caudal portion form the posterior urethra and membranous urethra. Subsequent urethral evaginations develop into the prostate.

Internal Ducts—Female Differentiation

If embryos are castrated at the indifferent stage, the mesonephric ducts regress, and the paramesonephric ducts develop. Local implantation of a testosterone crystal in a female fetus prevents mesonephric regression but does not induce paramesonephric regression. In contrast, local implantation of a testis both supports the mesonephric ducts and induces paramesonephric regression. The embryonic testis has two organizing functions, only one of which can be replaced by testosterone. In the absence of testes, the internal ducts always develop along female lines, whether or not ovaries are present.

By the end of the third month, the mesonephric ducts in the female have largely disappeared. The medial walls of the right and left Müllerian ducts fuse. Fusion usually starts at Müller's tubercle and progresses cranially, ending at the junction of each duct with the round ligament. This process results in a single tube with two lumens (Fig. 1–3). The medial septum then disappears, completing the creation of the uterus simplex. Canalization is complete by the 16th week. The

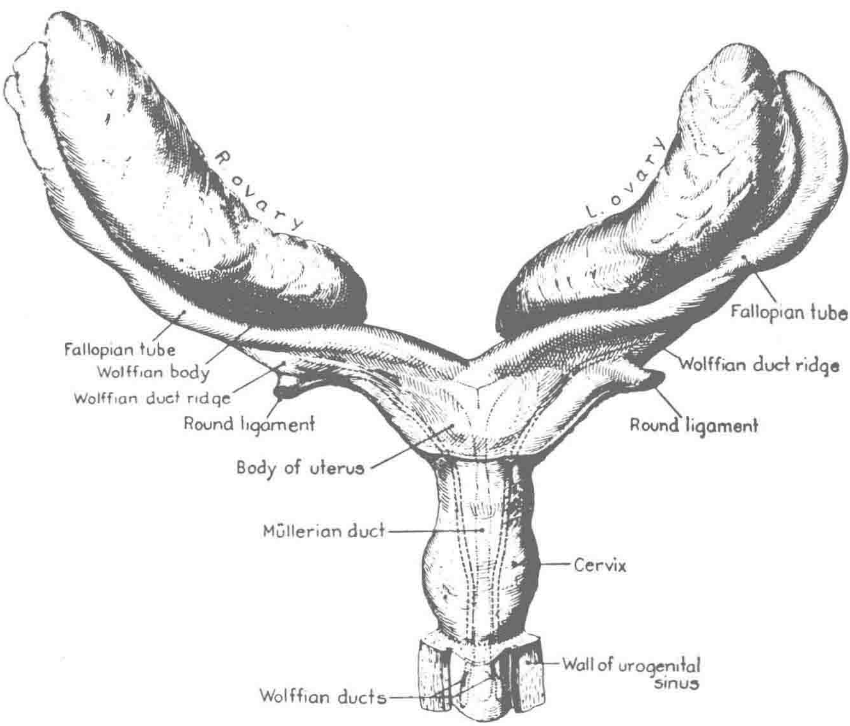

Figure 1–3. Internal ducts in embryo that has undergone female differentiation. The Wolffian ducts have regressed, and the Müllerian ducts have come together in the midline. (From Hunter RH: Observations on the human female genital tract. *Contrib Embryol* 22:91–108, 1930. Courtesy of the Carnegie Institute of Washington, D.C.)