UG CBCS Semester-IV (MJC-7: Endocrinology)

Mammalian Gonads

Primary sexual characters include the vagina, uterus, and oviducts of the female and the penis, vasa deferentia, seminal vesicles, and prostate gland of the male. Secondary sexual characters are often dependent on gonadal hormones and usually enhance mating success but are not necessarily required for physically mating and producing offspring.

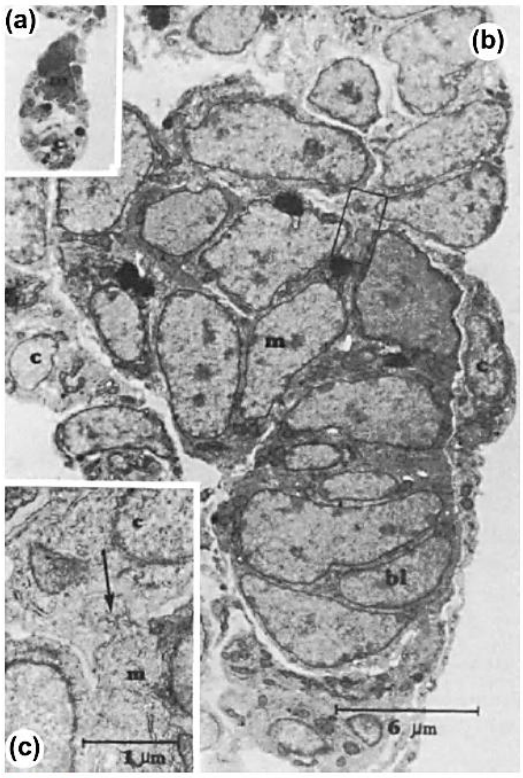

FIGURE 10-1 **Undifferentiated gonad.** Section of gonad from 25-mm tadpole of *Rana pipiens* showing cortical (c) and medullary (m) cells separated by a basal lamina (bl = basement membrane). (a) total gonad (upper left); (b) enlargement; (c) further enlargement showing contact between cortical and medullary cells (arrow). *(Reprinted with permission from Merchant-Larios, M., in "The Vertebrate Ovary" (R.E. Jones, Ed.), Plenum, New York, 1978, pp. 47–81.)*

The Gonads

The paired gonadal primordia arise from the intermediate mesoderm of the mammalian embryo as a genital ridge on either side of the midline in close association with the transitory mesonephric kidney of the embryo. Numerous derivatives of the mesonephric kidney and its duct system are retained as functional portions of the adult reproductive system, although the bulk of the mesonephric kidney degenerates. A gonadal primordium consists of an outer cortex derived from peritoneum and an inner medulla (Figures 10-1 and 10-2). Germ cells do not arise within the gonadal primordium itself but migrate from their site of origin in the yolk sac endoderm to either cortex (female) or medulla (male) depending upon the genetic sex (Figure 10-2). The basic pattern of germ cell migration is evolutionarily conserved from fruit flies to humans and requires a complex interplay between (1) guidance signals and extracellular matrix attachment proteins that ensure directed migration of the germs cells to the genital ridge mesoderm, and (2) a host of chemical signals involved in alignment of the germ cells within the gonad and coalescence of the developing gonad.

Initially, the medullary component in males and females differentiates into primary sex cords. Differentiation of the primary sex cords into seminiferous cords and regression of the cortex result in a testis. Each testis consists of seminiferous tubules derived from the primary sex cords. The germ cells migrate into the seminiferous tubules, give rise to spermatogonia, and eventually produce sperm. The Sertoli or sustentacular cells support sperm development. Steroidogenic interstitial cells or Leydig cells are located between the seminiferous tubules. These interstitial cells arise from medullary tissue surrounding the primary sex cords and become sources of androgens. In females, the primary sex cords degenerate, and secondary sex cords differentiate from the cortical region. These secondary sex cords become the definitive ovary. In the ovary, the germ cells give rise to oogonia, which soon enter meiosis to form primary oocytes. The ovaries contain follicles that consist of one or more layers of follicular cells surrounding a primary oocyte.

Accessory Ducts

In males, the central portion of each differentiating testis forms a network of tubules, known as the rete testis, that do not contain seminiferous elements. The rete testis forms a connection between the seminiferous tubules and a surviving portion of the primitive mesonephric kidney duct called the wolffian duct, which, under the influence of testosterone, differentiates into the vas deferens and conducts sperm from the testis to the urethra. Most of the mesonephric kidney in mammals degenerates, with the exception of some of the anterior mesonephric kidney tubules. In the presence of testosterone, this tissue together with a portion of the wolffian duct forms two glandular structures, the epididymis and the seminal vesicle (Figures 10-2 and 10-3). A second pair of longitudinal ducts develops in the embryo from the mesial wall of each wolffian duct and lie parallel to them. These structures are known as the ducts. In genetic females, the mu¨llerian ducts develop into the oviducts, uterus and the upper part of the vagina (Figure 10-3), usually fusing together to form a common vagina and, in some species, a single uterus as well. The wolffian ducts degenerate in female mammals. In males, it is the mullerian ducts that are suppressed in favor of wolffian duct development. Mullerian-inhibiting substance (MIS) was first proposed by Alfred Jost in the 1940s to explain the inhibitory effect of the testes on development of mullerian ducts in rabbit embryos. It also has been called the anti-Mullerian hormone, or AMH. AMH is a dimeric glycoprotein encoded by the amh gene that acts via a membrane serine/threonine kinase type-II receptor located in the gonads and in connective tissue near the mullerian ducts.

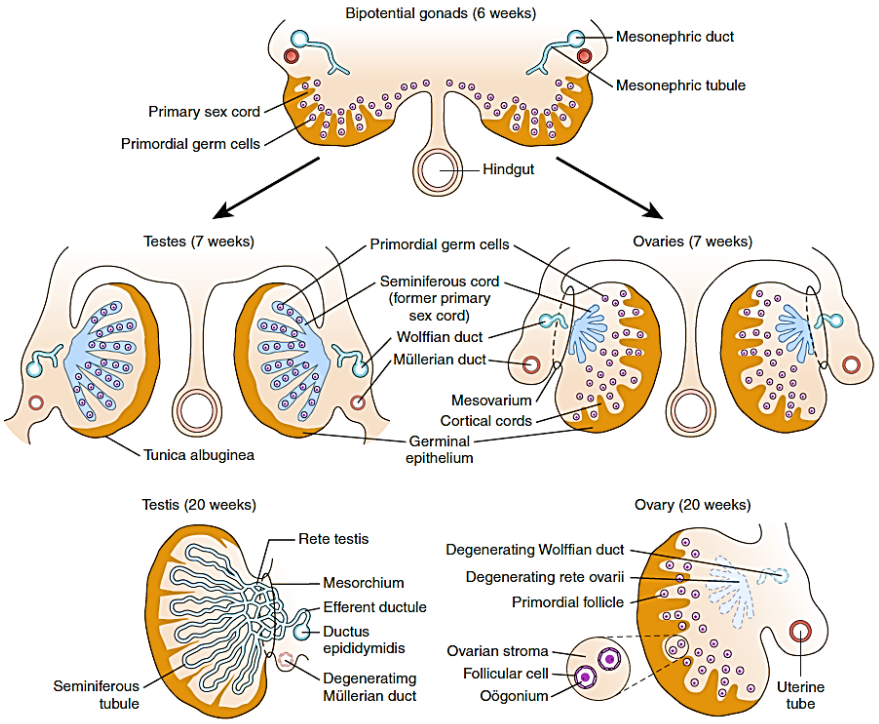

FIGURE 10-2 **Development of testis and ovary in humans.** Primordial germ cells migrate from the hindgut into the mesoderm of the bipotential gonad. In the male, the cortical tissue (orange) degenerates and the medullary tissue develops into the testis cords, which give rise to the seminiferous tubules including the Sertoli cells. Mesonephric tubules give rise to the intratesticular ducts such as the rete testis and the efferent ducts and vas deferens. In the female, the medullary cords degenerate, and the cortical cords (orange) give rise to an ovary. Some mesonephric elements remain in the female as well. The vasa deferentia are retained in amphibians but eventually they degenerate in reptiles, birds, and mammals in which the ureters develop to drain the metanephric kidneys (not found in anamniotes). *(Adapted with permission from Paxton, M., "Endocrinology Biological and Medical Perspectives," William C. Brown, Dubuque, IA, 1986.)*

Implantation of a testis into a female embryo results in sufficient AMH secretion to prevent development of the mullerian ducts. AMH not only blocks mullerian duct development but also is capable of inhibiting growth of tumors from ovaries and mullerian duct derivatives. It appears that AMH acts cooperatively with testosterone in producing these effects on the mullerian ducts. The ovary also makes AMH, but the mullerian ducts are protected by local estradiol secreted by the ovary.

Maleness in eutherian mammals is dependent upon secretion of androgens from the testis. In the absence of androgens or androgen receptors the male animal (genotype XY) will develop a female phenotype. Similarly, exposure of developing males to estrogens will result in female

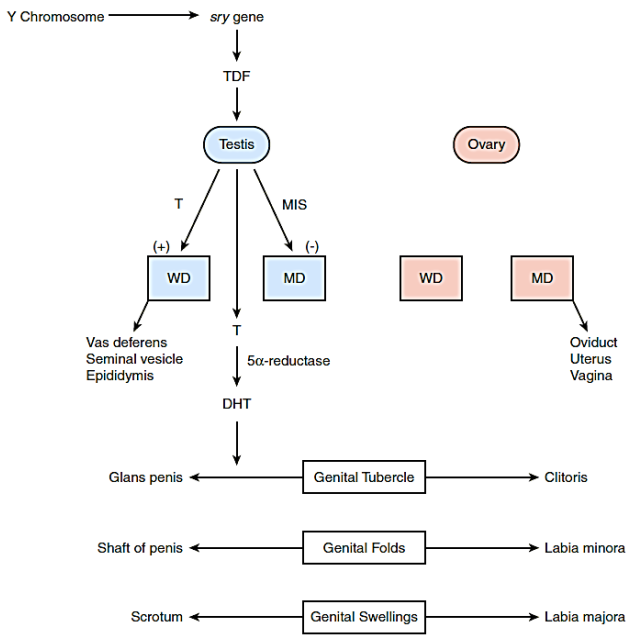

FIGURE 10-3 Patterns of development for ducts and genitalia. In males, the testis secretes testosterone (T), which stimulates differentiation of wolffian ducts, and müllerian-inhibitory substance (MIS), which causes regression of müllerian ducts. Dihydrotestosterone (DHT) is either produced by the testes or converted from T in the genital tubercle, genital folds, or genital swellings, causing them to differentiate in the male direction. Estradiol from the ovary prevents MIS (also secreted by ovary) from causing müllerian duct regression, and the absence of sufficient androgens determines the fate of the other structures. Abbreviations: *sry*, sex-determining region of the Y chromosome; TDF, testis determining factor.

phenotype development to a degree proportional to the amount of estrogen and the timing of the exposure. Conversely, treatment of newborn females with androgens destroys the cyclical secretory pattern of the HPG axis and replaces it with a noncyclical or tonic pattern like that of males. Becoming a male mammal, then, involves overcoming the basic tendency for mammalian embryos to develop as females. A gene seemingly responsible for male sex determination called sry (sex-determining region of Y chromosome) has been localized on the short arm of the Y chromosome that is characteristic of genetic males. In mice, the sry gene is activated in gonads of genetic males before they begin to differentiate into testes. Insertion of the sry gene into XX mice followed by its activation leads to formation of malespecific structures and regression of female ducts. The activated gonad secretes AMH, which causes regression of the mullerian ducts. The sry gene produces a factor called testis determining factor (TDF) (Figure 10-3) that activates the amh gene. Androgens secreted by the transformed gonad cause male-like differentiation of the external genitalia and the wolffian ducts as well as changes in the hypothalamus to suppress development of the surge center. This establishes the tonic secretory pattern for GnRH and GTHs that characterizes males. Studies with estrogen receptor knockout (ERKO) mice verify that defeminization of the male brain requires conversion of androgens to estradiol. Genetically male ERKO mice will exhibit female behavior, whereas wild-type males do not.

Although the female has been called the default sex in mammals, becoming a female is not just the absence of androgens. For example, studies have shown specific genes are required to be expressed in order for the ovary to form and that estrogens are necessary for development of the female difference in the corpus callosum of the brain. Androgens and estrogens may alter basic traits through what are termed organizational effects. Stimulation of the development of male genitalia by androgens is an example of an organizational effect. Organizational effects are permanent and cannot be reversed later by exposure to other gonadal steroids. In contrast, activational effects can be induced by gonadal steroids for example, by inducing a specific behavior in adults. The type of behavior induced depends on the steroid applied, not on the genetic sex of the individual.

References

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