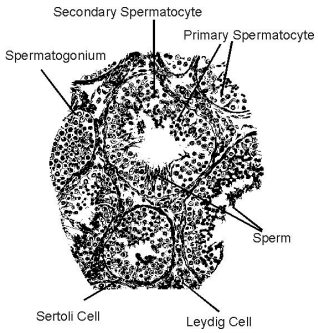
4/16/97

Male Reproduction and Sex Differentiation

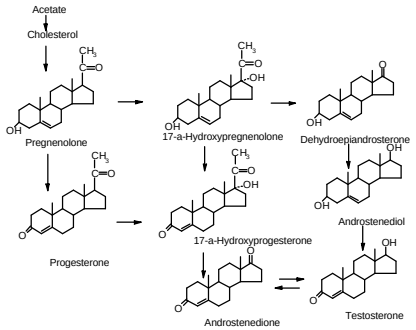
R. Martinez-Zaguilan, Ph.D.

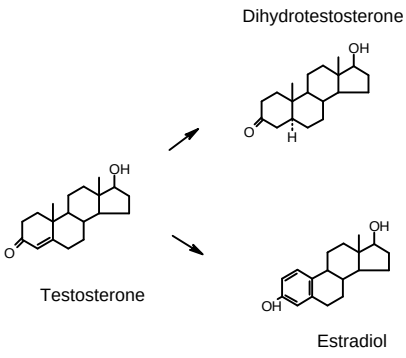
- Leydig Cells- Androgens
- Sex Differentiation



Functions of Leydig Cells

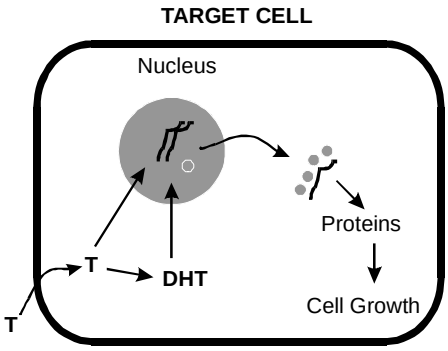
- Synthesis and secretion of the male sex steroid hormones (e.g., testosterone)
- Respond to LH, producing androgens

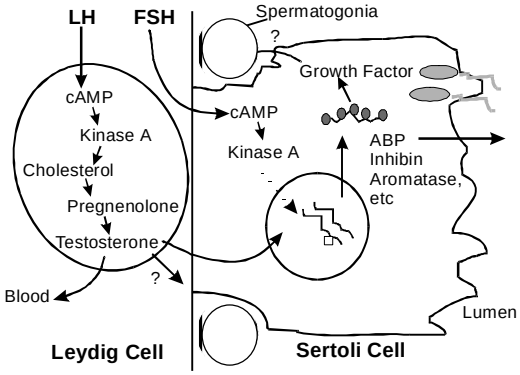


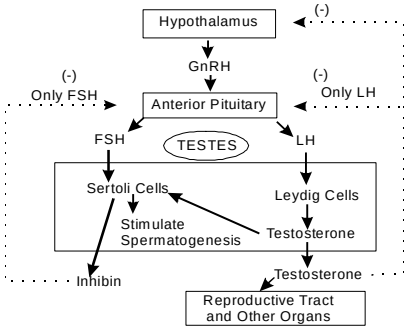


Steroids: Male vs Female

Serum Steroid Conc. (ng/dl)	**Male**	**Female**
Testosterone	700	40
Androstenedione	120	170
Dihydrotestosterone (DHT)	45	20
17β-estradiol	≤ 0.60	0.6-7.0







Effects of Testosterone in the Male

- Required for spermatogenesis (via Sertoli cells)
- Decrease GnRH secretion (via hypothalamus)
- Inhibits LH secretion (via adenohypophysis)
- Induces and maintains differentiation of male accessory reproductive organs and maintains their function

Effects of Testosterone in the Male

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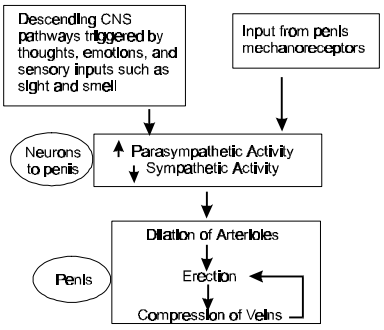
- Induces male secondary sex characteristics
- Stimulates protein anabolism, bone growth, and cessation of bone growth
- Maintains sex drive and may enhance aggressive behavior

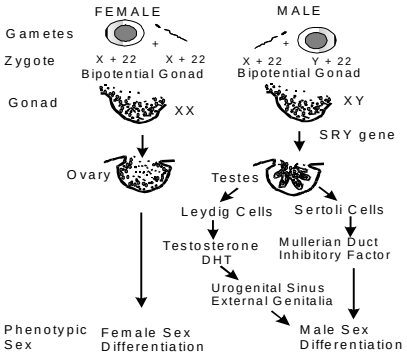


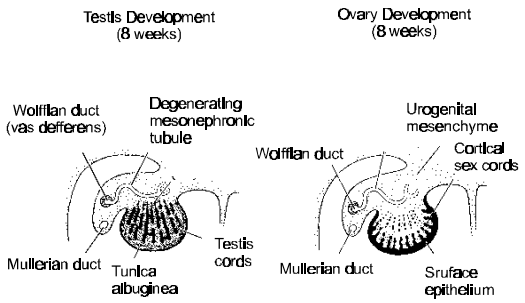
Sex Differentiation

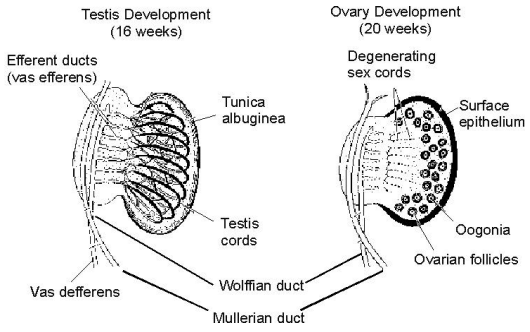
Raul Martinez-Zaguilan, Ph.D.

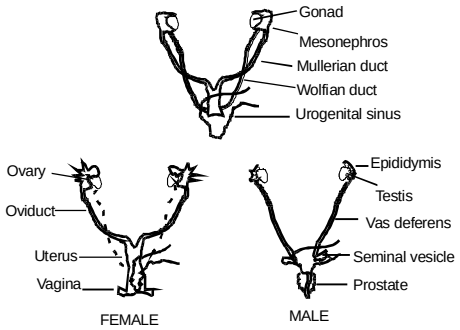
Sex Differentiation

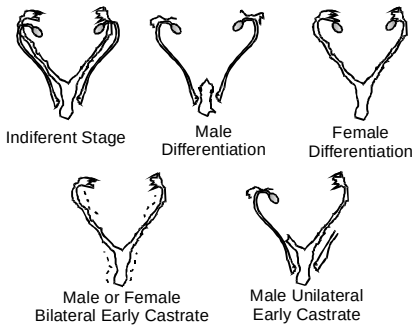
- Sex Determination
- Differentiation of the Gonads
- Differentiation of the Internal and External Genitalia
- Sexual Differentiation of the Nervous System











Sex Determination and Sex Differentiation

- Sex is determined by the two chromosomes: Males XY, Females XX
- The SRY gene on the Chromosome Y is responsible for the development of testes. In the absence of a Y chromosome ovaries do develop

Sex Determination and Sex Differentiation

- cont…
- Testes secrete testosterone and MIF allowing development of a male reproductive tract. In the absence of testes a female reproductive tract develops

Sex Determination and Sexual Differentiation.

Raul Martinez-Zaguilan, Ph.D.

Supplemental Reading

1. Sex Determination

2. Differentiation of the Gonads

3. Differentiation of the Internal and External Genitalia

4. Differentiation of the Nervous System

1. Sex Determination. The sexual genotype of an individual is determined at the moment of the conception. This is determined by two of the 46 chromosomes present in all human cells. If these two sex chromosomes are XX, the individual is genetically female; if they are XY, the individual is male. Since the haploid (23 chromosomes) germ cells of females contain only X chromosomes, the ovum must also contain an X chromosome (Fig 1). Thus, the genetic sex of the fetus is determined by the haploid (23 chromosomes) genetic material of the sperm. The presence of a Y chromosome directs development of the male gonad, its absence directs development of the female gonad. This does not imply that the X chromosome plays no role in sexual development. The X chromosome contains a number of genes essential to development of both females and males. For example, the gene encoding the

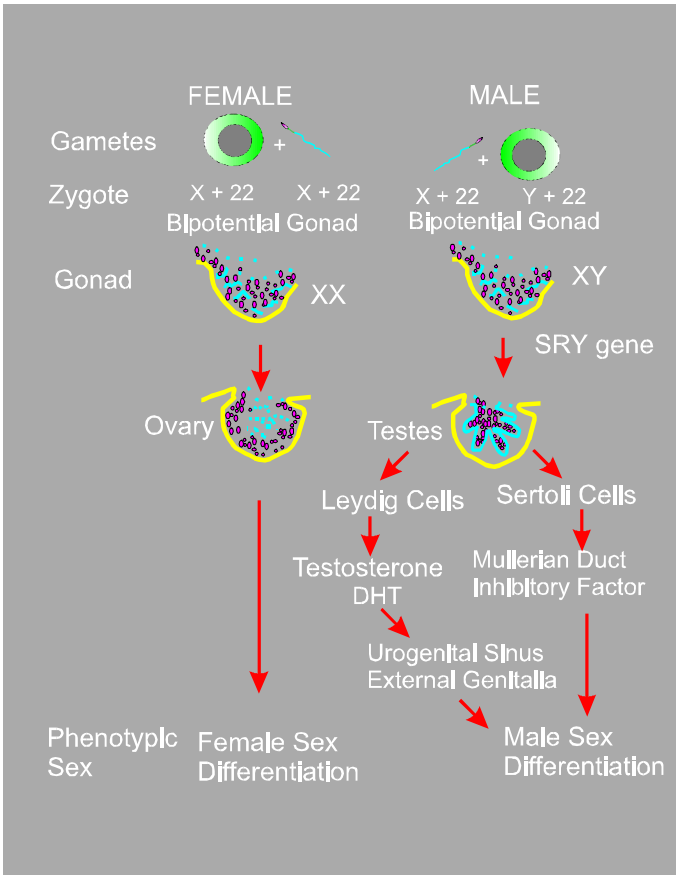


Figure 1. Sequence of events involved in sexual differentiation.

androgen receptors is located on the X chromosome.

2. Sex Differentiation.

The indifferent gonad anlage forms at ca. 5 weeks of gestation with the arrival of the primordial germ cells which migrate from their site of origin near the yolk sac. In the XY fetus, differentiation of the testes is first evident at ca. Week 6, with the appearance of seminiferous cords. The Y chromosome exerts its effect on development by controlling expression of specific genes of the *sry* (sex determining region of the Y chromosome; cf., Fig 1). The genes expressed (formerly named the H-Y antigen) are secreted by the Sertoli precursors early in gestation. This causes testicular differentiation (ca. Week 8; Fig 2). Gonadal cells in the ovary also contain receptors for the H-Y antigen, but since this protein is not produced in females, these cells never receive the signal for testicular formation, and the indifferent gonad develops into an ovary (Fig 3).

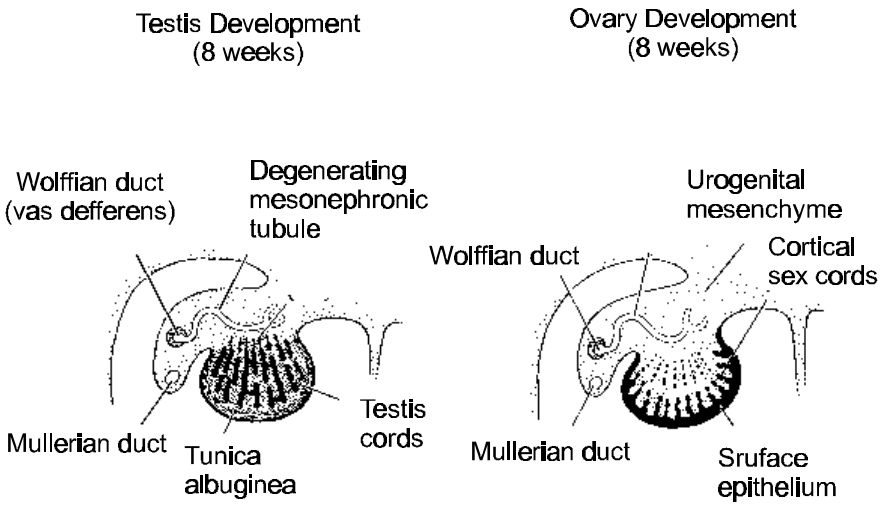


Figure 2 Differentiation of human gonads. Testis development in the 8-week. The sex cords lose contact with the cortical epithelium. The rete testis develop in with 16 (cf., Fig 3). Ovary development in an 8-week human embryo showing degeneration of primitive sex cords.

3. Differentiation of the Internal and External Genitalia

Phenotypic sex refers to the structure of the reproductive tracts and external genitalia. Male genitalia (by week 16) and female genitalia (weeks 11-20) develop from the same common anlage;

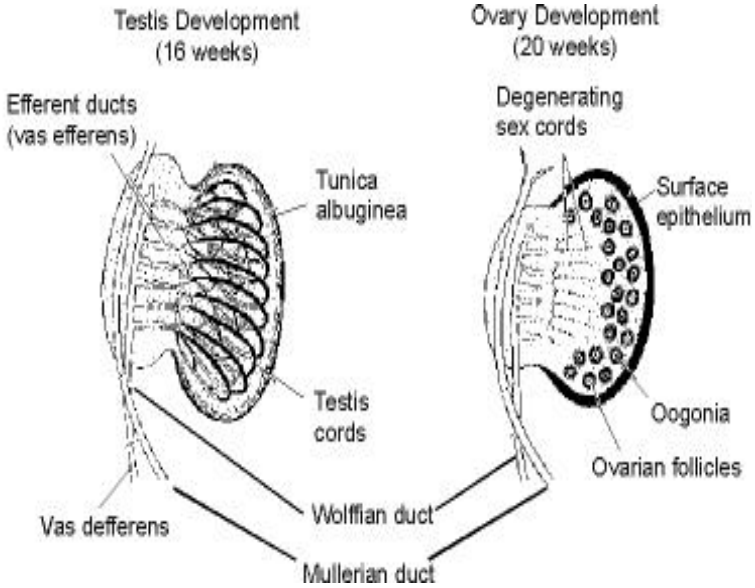


Figure 3 The rete testis develops at ca. week 16. The testis cords are continuous with the rete testis and connect with the wolffian duct. The 20-week human embryo does not connect o the Wolffian duct , and new cortical sex cords surround the germ cells that have migrated into the genital ridge.

but this is not true for the reproductive tracts. The male reproductive tract is derived from embryonic structures known as the wolffian ducts, while the female tract derives from the müllerian ducts (Fig 4). The early embryo has the potential to develop either male or female reproductive tracts because both duct systems are present before sexual differentiation occurs.

Development of phenotypic sex is determined by two hormones secreted by the fetal testis: testosterone and müllerian inhibiting factor. Testosterone released from the Leydig cells stimulate development of the wolffian ducts and differentiation of the male genitalia (weeks 8-16). Müllerian inhibiting factor is produced by Sertoli cells and causes regression of the müllerian ducts. Shortly after the fetal testis begins to form, both of these hormones are secreted. consequently the mullerian ducts regress and the wolffian ducts and genitalia develop into the male reproductive tract, penis and scrotum. Testosterone must be converted by 5 α reductase to DHT to cause virilization of the external genitalia. This conversion however, is not necessary for the effects of testosterone on the wolffian ducts. Therefore, both of these androgens are required to provide successful expression of the male phenotype. Since there is no testosterone released by the ovary in the female, the wolffian ducts regress and the external genitalia develops into the clitoris, labia minora, and labia majora (Fig 2). At the same time, in the absence of müllerian inhibiting factor, the müllerian ducts develop into the oviducts, uterus and vagina. Differentiation of the phenotypic sex in the male occurs early in development and is essentially complete by week 14-16. During most of this period, there is little or no secretion of LH by the fetal pituitary, so LH cannot be responsible for the critical increase in testosterone production from the fetal testis. Instead, human chorionic gonadotropin (hCG) from the placenta appears to be the stimulus for this early rise in testosterone secretion.

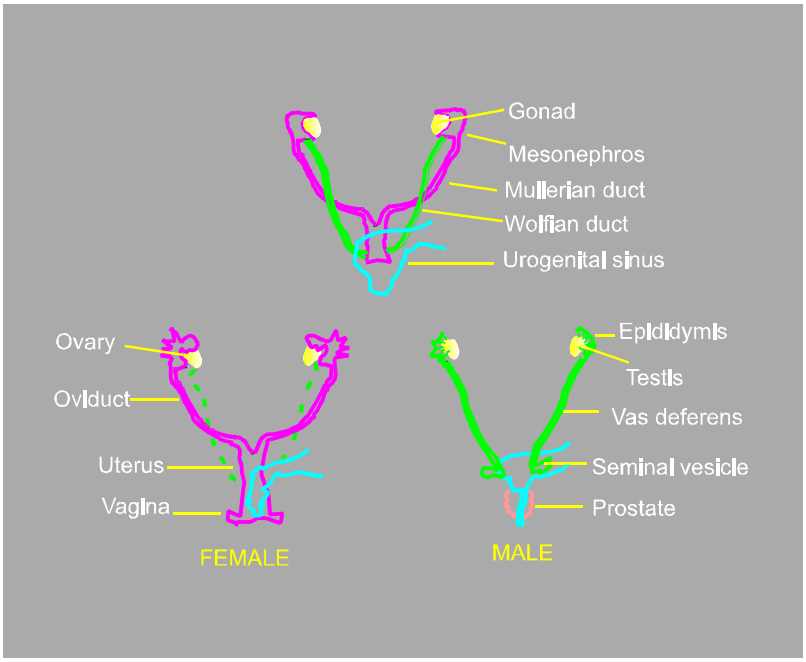


Figure 4 Differentiation of internal and external genitalia

The relevance of the testes for proper development of internal genitalia has been demonstrated by experiments in which only one testis was removed from embryonic rabbits (Fig 5). Under these conditions, the müllerian duct regresses only on the side with the remaining gonad, indicating that antimüllerian hormone mus act locally as a paracrine factor. The wolffian duct regressed on the

opposite side, suggesting that testosterone too must act locally to sustain the adjacent wolffian duct because the amount that reached the contralateral duct through the circulation were inadequate to prevent its regression (cf., Fig 5).

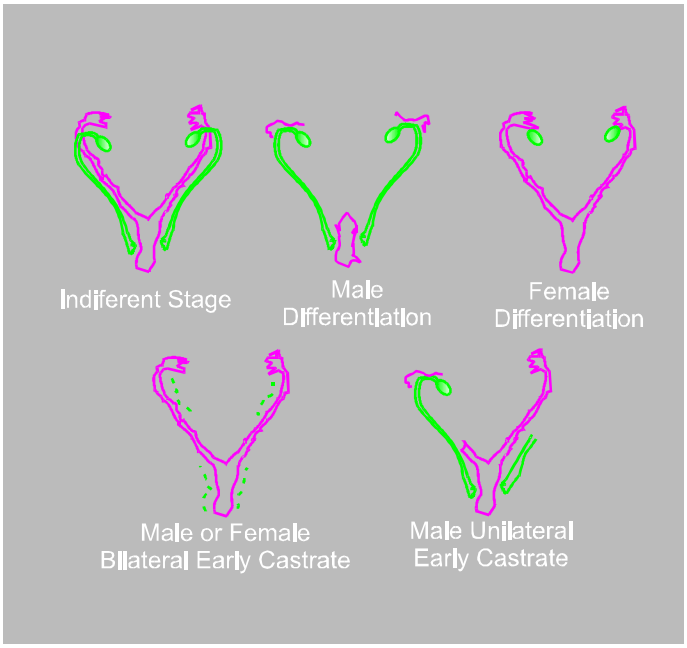


Figure 5 Normal development of the male and female reproductive tracts. Shown in green are tissues destined to be the male tract whereas those in purple are destined to be the female tract.

4. Differentiation of the Nervous System

. In humans there are no inherent male female differences in the ability of the hypothalamus to secrete GnRH in response to neuronal or hormonal stimulation. Administration of estrogen to castrated male monkeys or rats, for example, elicits release of LH similar to those surges exhibited by females.

However, important hypothalamic differences must exist that explain the different sexual behavior observed between males and females. These hypothalamic differences are established earlier during pre-natal or perinatal development, depending on the species. Specifically, genetic female monkeys given testosterone during late fetal life manifest evidence of male behaviors as adults (i.e., mounting behavior). It is therefore possible that similar brain and hypothalamic differences exist in humans of different gender.

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SUMMARY

	GONADS	
Gonadal Type	Testis	Ovary
Sex cords	Medullary (internal)	Cortical (external)
	DUCTS	
Remaining duct for germ cells	Wolffian	Müllerian
Duct differentiation	Vas deferens, epididymis, Seminal vesicle	Oviduct, uterus, cervix Upper portion of vagina