Contents

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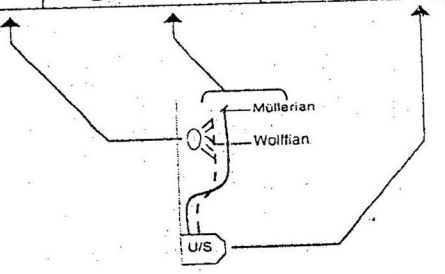
Sexual Differentiation: From Gonad to Phallus

EMBRYOLOGY

- Bipotential: gonads and external genitalia (urogenital sinus; two labioscrotal swellings; genital tubercle)
- Unipotential: wolffian or müllerian ducts

	GONADS		INT. GENITALIA		EXT. GENITALIA	
	SRY		T / AMH	Wolff / Müllerian	DHT	Phallus/urogen. sinus labioscrotal folds
XX	⊖	ovaries	⊖ / ⊖	regress / oviducts/uterus upper vagina	⊖	clitoris/labia lower vagina
XY	⊕	testes	⊕ / ⊕	epididymis/vas SVs / regress	⊕	penis/scrotum prostate



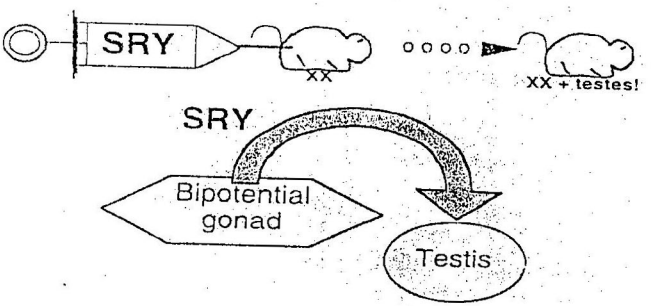
T, testosterone
AMH, anti-müllerian hormone
SVs, seminal vesicles
DHT, dihydrotestosterone
SRY, sex-determing region of the Y-chromosome
U/S, urogenital sinus

Gonads

- Formation of a testis occurs in the presence of the Y chromosome (46,XY).
- Formation of an ovary occurs in the absence of the Y chromosome and the presence of a 2nd X chromosome (46,XX).
- Gonads begin development during weeks 5–6 of gestation.

Testicular Determinants

- *Sex-determining region of Y (SRY)* is the gene involved in testis determination (short arm [p] of Y chromosome) (Sinclair 1990; Tilford 2001).



Ovarian Determinants

- Unless *SRY* and *SOX9* are expressed, ovarian development ensues (assuming XX is present).
- 2nd X chromosome required for normal ovarian development
- Autosomal genes (see diagram on page 4 regarding three facets of sexual differentiation).

Internal Genitalia

- Wolffian ducts (dependent on testosterone [T] from testes) → epididymis/vas deferens/seminal vesicles (internal genitalia)
- AMH = anti-müllerian hormone, produced by Sertoli cells
- Müllerian ducts (in absence of AMH) → fallopian tubes/uterus/upper vagina (internal genitalia)

- Müllerian and wolffian development begin simultaneously; they are local phenomena (i.e., they occur *ipsi*laterally depending on presence/absence of T/AMH).

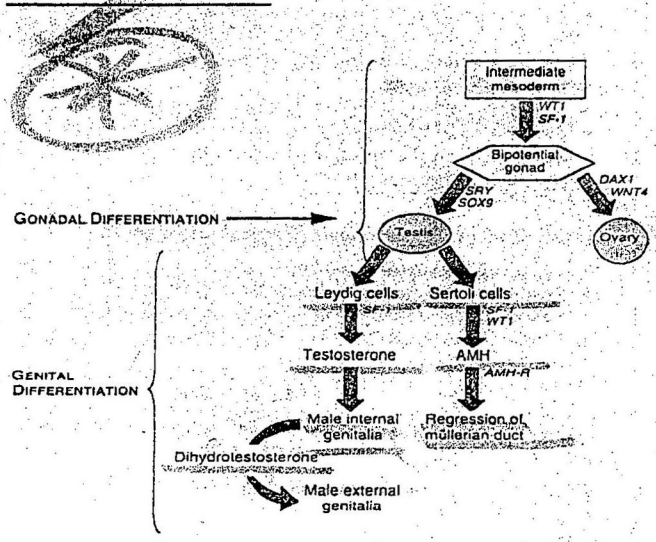
External Genitalia

- DHT is crucial in the development of external genitalia:
  - presence of DHT: male
  - absence of DHT: female
- DHT is produced in sufficient amounts from gestational weeks 7–8 until birth.
- Human chorionic gonadotropin (hCG) stimulates Leydig cells →↑ T
- Feminization of external genitalia completed by approximately 14 weeks.
- Masculinization of external genitalia completed by approximately 16 weeks.
- T, insulin-like 3 ligand, and its receptor (Lgr8) mediate descent of testes.

THREE FACETS OF SEXUAL DIFFERENTIATION

1. Gonadal differentiation
2. Genital differentiation
3. Behavioral differentiation
   - Sexual or gender identity:
     - → Sense of oneself as man or woman
     - → Established by age 2 ½ years
     - → Derived through internalization of social cues based on the external genitalia
       - Patients with 5α-reductase (5αR) deficiency or 17β-hydroxysteroid dehydrogenase (17βHSD) deficiency may change from female to male gender identity at puberty; therefore, there is a *hormonal role* in sexualization of the brain.

SEXUAL DIFFERENTIATION



Factors involved in the determination of male sex. HOX, homeobox transcription factor; AMH-R, AMH-receptor; SF-1, steroidogenic factor 1; SOX9, SR homeobox gene (on autosome); SRY, sex-determining region of the Y chromosome, in Y chromosome, "testis-determining factor"; WT1, Wilms' tumor 1. (Source: Adapted from Federman DD. Three facets of sexual differentiation. *N Engl J Med* 350[4]:323, 2004.)