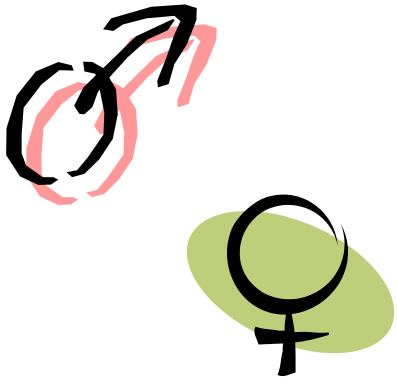
Bio& 242 A&P
Unit 4 / Lecture 2



1

Sexual Differentiation

Venus // Mars

2

For the purpose of this lecture

1. **The word, Sex, is derived for the Latin word *Sexus* – meaning gonad**
2. **A person's, Sex, is generally assigned at birth by the appearance if external genitalia**
3. **A person's, Sex, is a state of anatomic and physiologic parameters.**
4. **Physiologic sexual development progresses through distinct stages from the neonatal period through infancy, childhood, puberty and adolescence, and adulthood.**

3

For the purpose of this lecture

1. **The word, Gender, is derived from the Latin word *genus* – meaning kind, type, or sort.**
2. **Gender Identity: Personal conception of oneself as male or female, or rarely both or neither. Nearly always self-identified as a result of a combination of inherent, extrinsic, and environmental factors**
3. **Gender Role: Is manifested within society by observable factors such as behavior and appearance (dress and mannerisms)**
4. **Increasingly, the term gender is being accepted to define psychophysiologic processes involved in identity and social role**

4

Sexual and Gender Identity and of 16 Intersex Subjects

N. Engl. J. Med. 01/2004 350(4) 333-341, Discordant Sexual Identify in Some Genetic Males.....

Subject No.	Age at Initial Assessment	Sex Assigned at Birth	Sex at Initial Assessment	Sex at Last Follow-up	Age at Last Follow-up	Duration of Follow-up
	yr				yr	mo
1	11	F	F	F	19	98
2	10	F	F	F	17	86
3	12	F	F	F	17	64
4	11	F	F	F	16	64
5	6	F	F	F	9	38
6	10	F	F	Would not discuss	14	38
7[†]	9	F	Declared M	Unclear	16	84
8[†]	9	F	Declared M	Unclear	14	59
9[‡]	12	F	M	M	21	98
10[‡]	7	F	F	M	11	38
11	7	F	F	M	10	39
12	5	F	F	M	8	36
13	7	F	F	M	10	35
14	12	F	F	M	20	98
15	16	M	M	M	19	34
16	5	M	M	M	12	83

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Sequential process of sexual differentiation

1. **Establishment of genetic sex (chromosomes)**
2. **Translation of genetic sex into gonadal sex (Testes or Ovaries)**
3. **Translation of gonadal sex into phenotypic sex (External genitalia)**

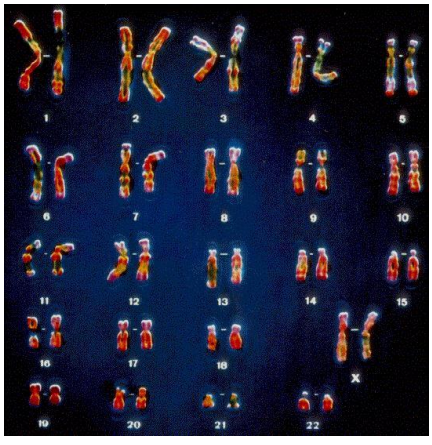
6

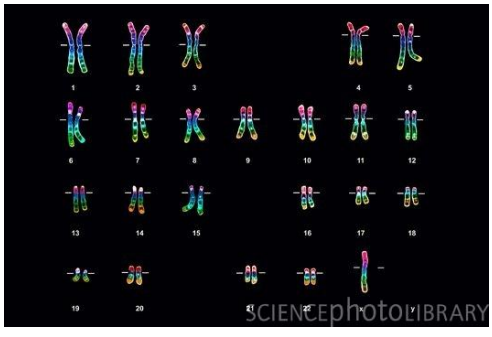
Male phenotype	Female phenotype
XY	XX
XXY	XXX (1:1,000)
XXXY	XXXX
XXYY	XXXXX
XYY(1:1,000)	XO (Turner's)
(OY)	

Conclusion: Presence of Y = MALE

7

Human Karotype

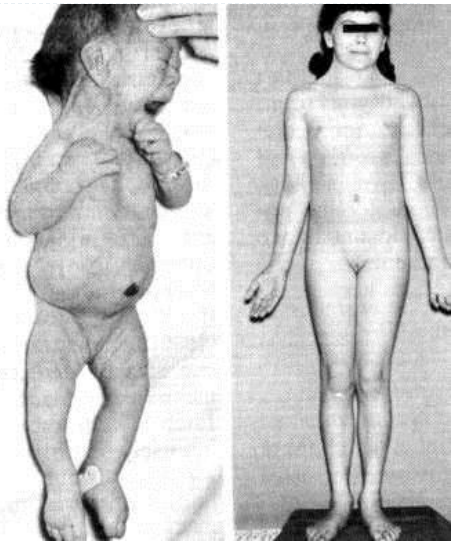




8

Turner's Syndrome (XO)

- occurs in 1/2500 live births
- caused by a partial or complete absence of the X chromosomes
- during the newborn period is puffy hands and puffy feet
- Broad chest
- short stature
- webbing of skin on the sides of the neck
- shortened 4 th metacarpal
- Adolescent girls with Turner syndrome often have failure of puberty



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XY	XX
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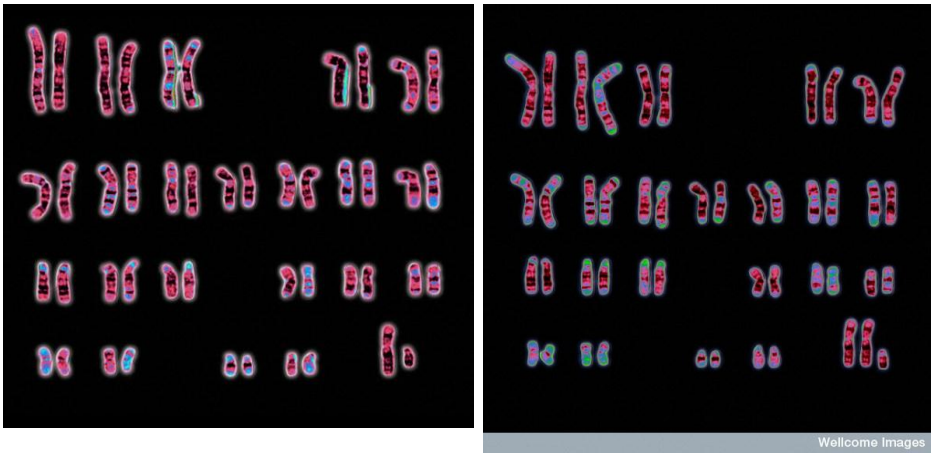

11

Klinefelter's syndrome (XXY)

- one in every 500 to 700 male births.
- testicles that haven't dropped into the scrotum
- small penis
- Learning and behavioral problems
- As adults, infertility
- Decreased sex drive
- Problems getting or keeping an erection

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Sequential process of sexual differentiation

1. **Establishment of genetic sex (chromosomes)**
2. **Translation of genetic sex into gonadal sex (Testes or Ovaries)**
3. **Translation of gonadal sex into phenotypic sex (External genitalia)**

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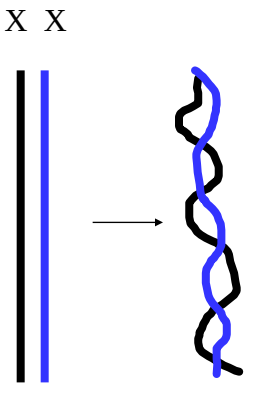

Normally, chromosomes pair, and cross-over, all along their length

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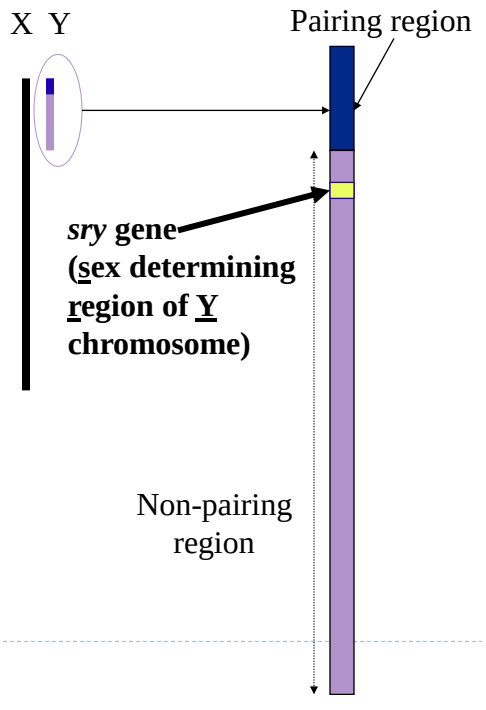

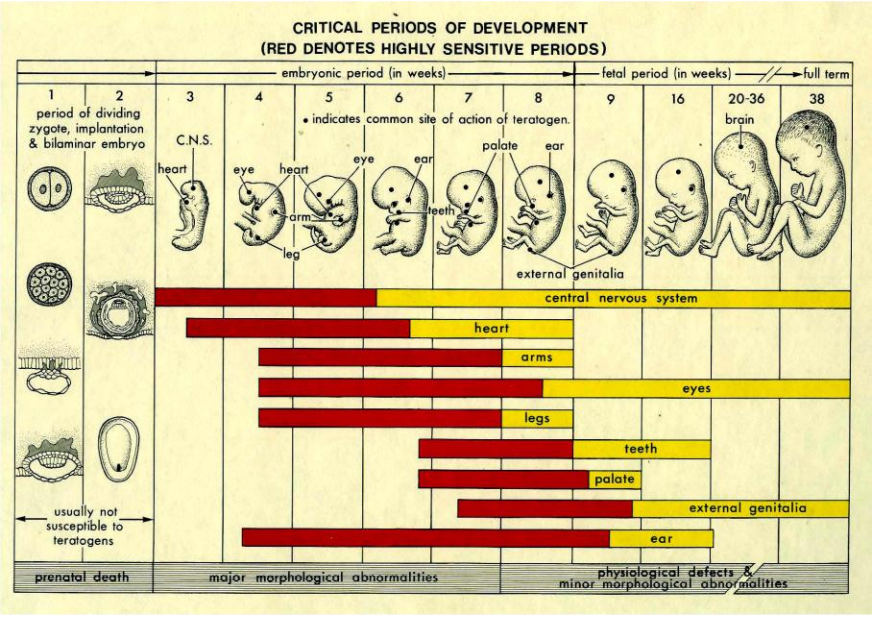

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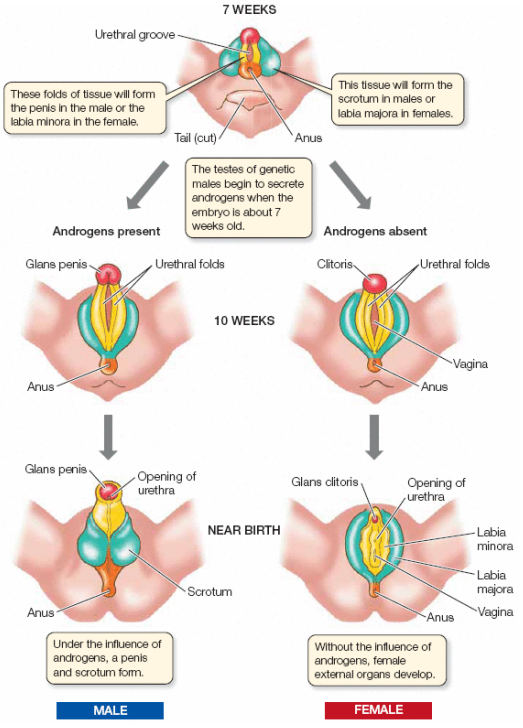
Development of Genitalia and related structures



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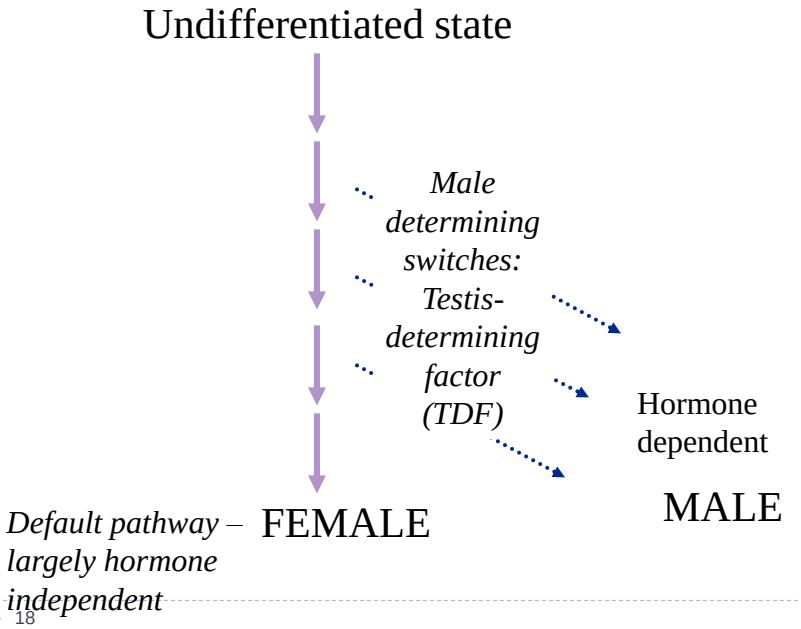
Sequential process of sexual differentiation

1. **Establishment of genetic sex (chromosomes)**
2. **Translation of genetic sex into gonadal sex (Testes or Ovaries)**
3. **Translation of gonadal sex into phenotypic sex (External genitalia)**

17



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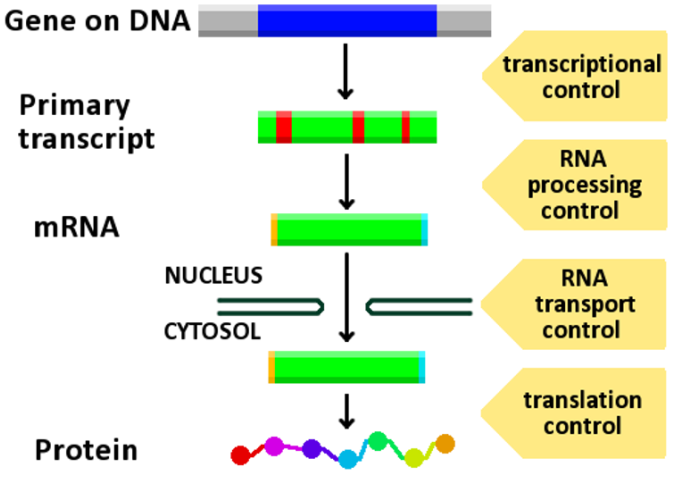
GENE EXPRESION MODEL



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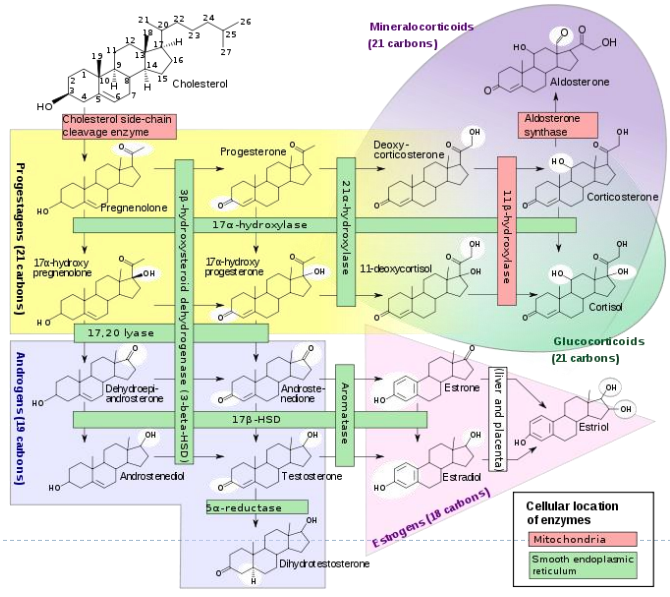
ENZYMES IN THE ESTRIOL/TESTOSTERONE PATHWAY



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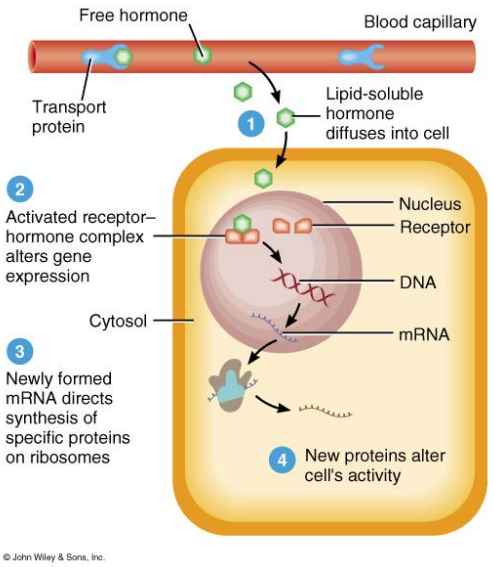
Mechanism of Action for steroid Endocrine hormones



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Classification of sexual differences

	Male	Female
Chromosomal	XY	XX
Gonadal	Testis	Ovary
Internal ducts	Wolffian (epididymis, vas deferens)	Mullerian (uterus, Fallopian tube)
External genitalia	Penis, scrotum	Clitoris, vulva
Phenotypic	“Male”	“Female”
Behavioural	“Male”	“Female”

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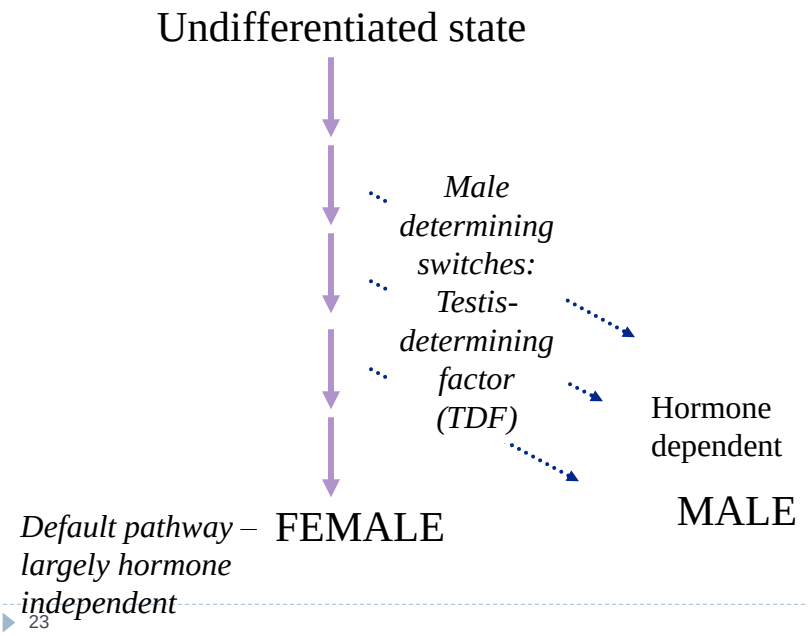
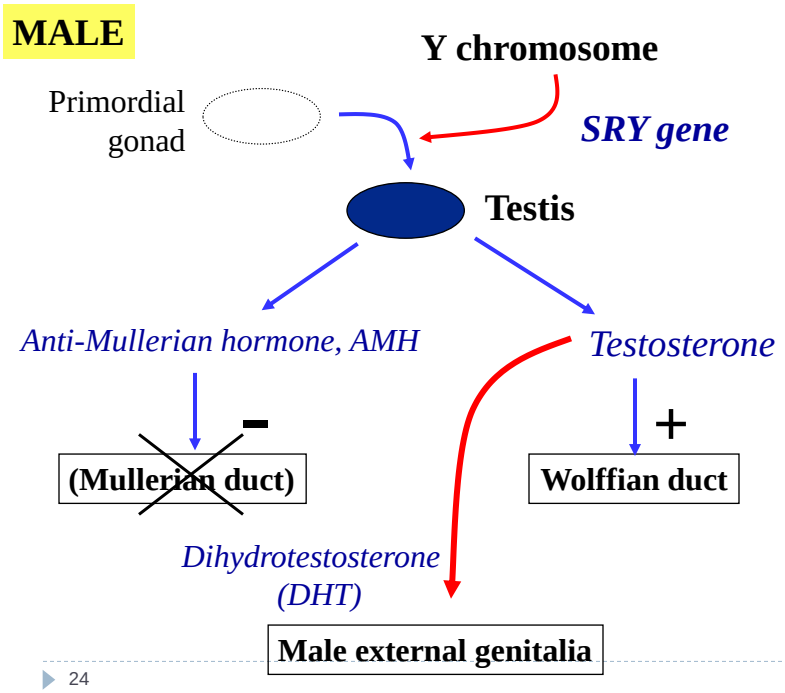

Undifferentiated state
Male determining switches: Testis-determining factor (TDF)
Hormone dependent
MALE
Default pathway – largely hormone independent
FEMALE

23


MALE
Y chromosome
Primordial gonad
SRY gene
Testis
Anti-Mullerian hormone, AMH
Testosterone
-
+
(Mullerian duct)
Wolffian duct
Dihydrotestosterone (DHT)
Male external genitalia

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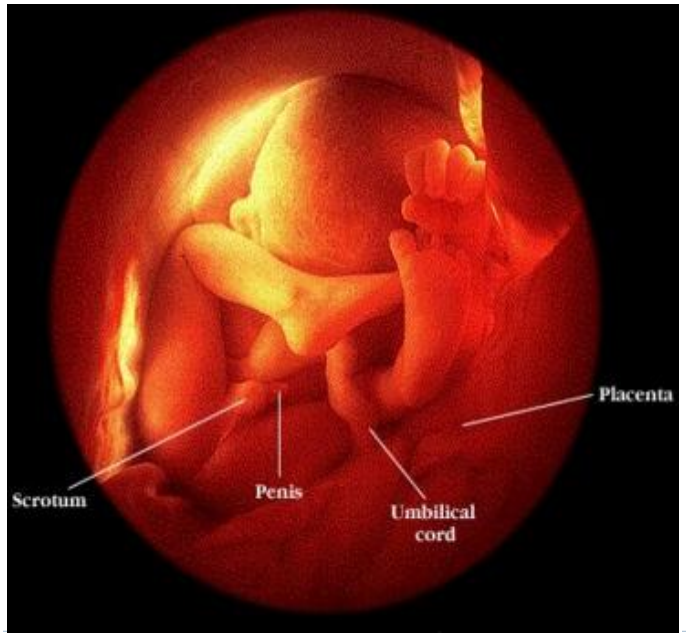
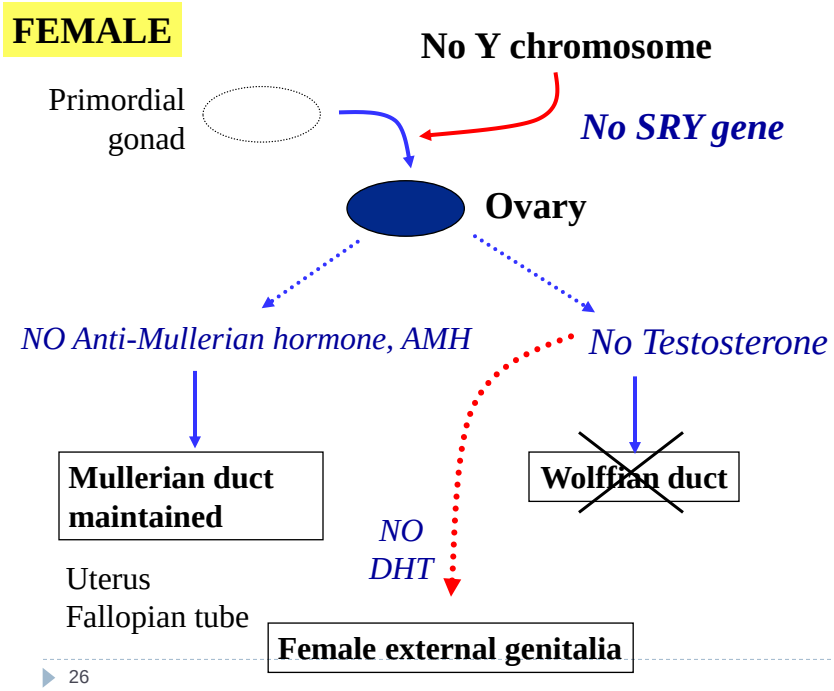

Placenta
Scrotum
Penis
Umbilical cord

25


FEMALE
No Y chromosome
Primordial gonad
No SRY gene
Ovary
NO Anti-Mullerian hormone, AMH
No Testosterone
Mullerian duct maintained
Wolffian duct
NO DHT
Uterus
Fallopian tube
Female external genitalia

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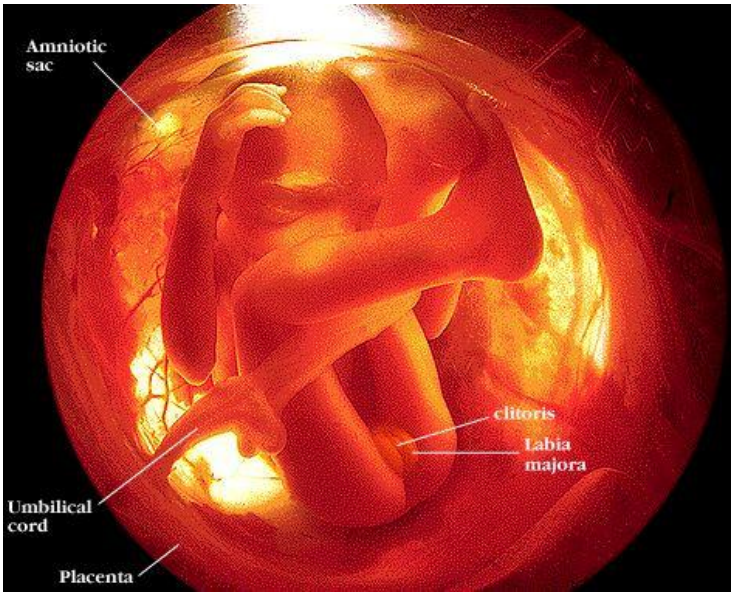
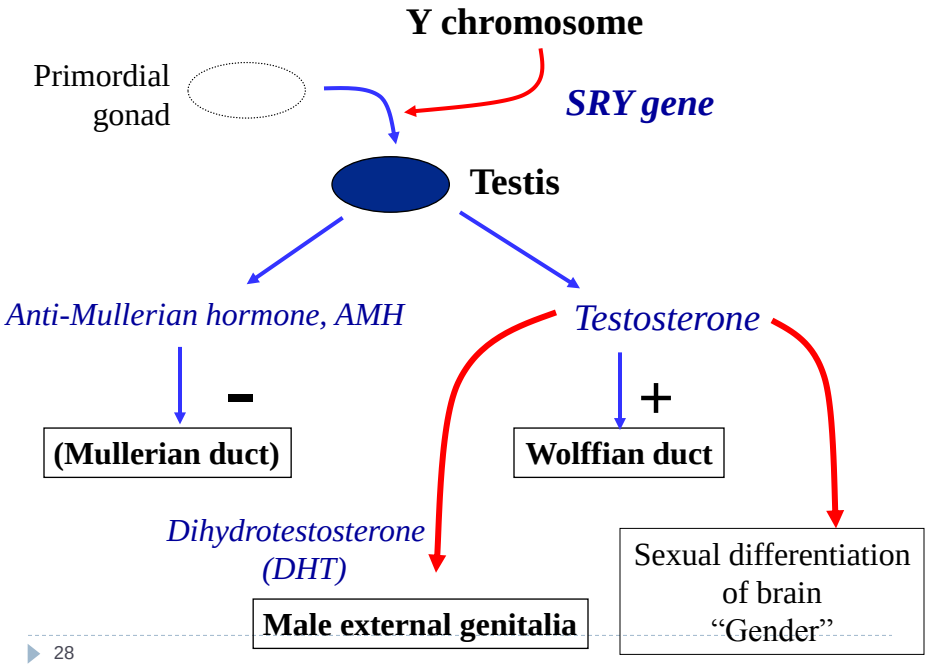

Amniotic sac
clitoris
Labia majora
Umbilical cord
Placenta

27


Y chromosome
Primordial gonad
SRY gene
Testis
Anti-Mullerian hormone, AMH
Testosterone
-
+
(Mullerian duct)
Wolffian duct
Dihydrotestosterone (DHT)
Male external genitalia
Sexual differentiation of brain "Gender"

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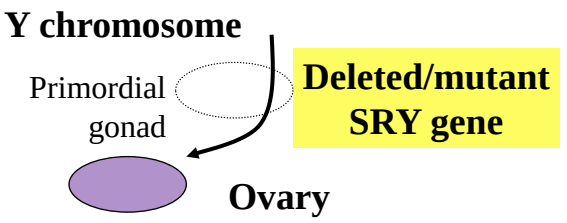

i.e. XY FEMALE!

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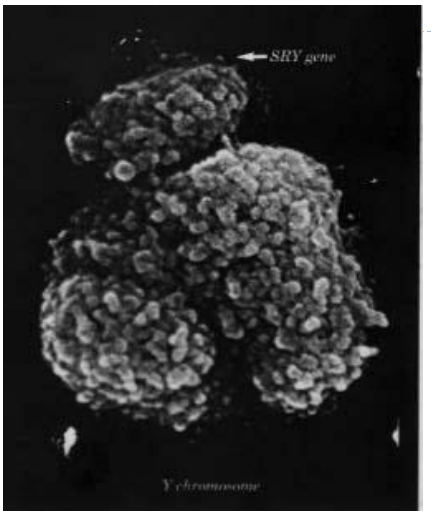

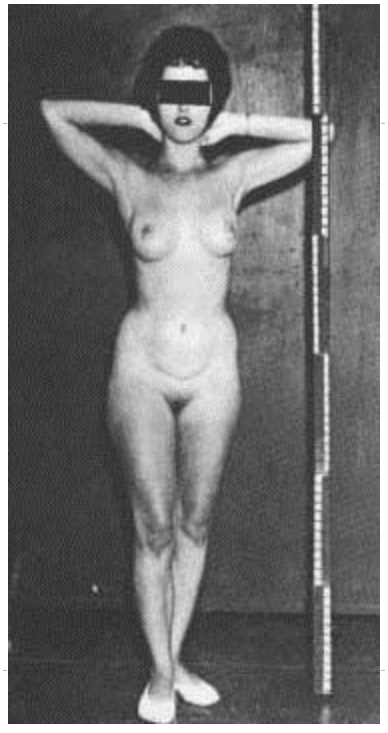

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Sexual differentiation of brain

- While chromosomal regulation of sexual differentiation of the brain is well understood, the genes involved and their actions are still under investigation.
- The SRY gene is a major player in the process.
- Gene mutations have revealed that prenatal testosterone masculinizes the brain.
- The complexity of other genes now known to play a role, discovered through the Human Genome Projects, are an area of active research.
- New genes include: DMRT-1, GATA 4, KIMI, LHX9, EMX2, M33, SFI, PODI, Vnn 9, and FGF-9

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Hermaphrodite

- An organism having both male and female reproductive organs, such as earthworms

Based upon Greek Mythology

- l**Hermaphroditus** was the child of Aphrodite and Hermes. Born a remarkably handsome boy, he was transformed.
- At the age of fifteen he traveled to the cities of Lycia and Caria. In the woods of Caria (modern Turkey)he encountered Salmacis the Naiad in her pool. She was overcome by lust for the boy, and tried to seduce him, but was rejected. When he thought her to be gone, Hermaphroditus undressed and entered the waters of the empty pool. Salmacis sprang out from behind a tree and jumped into the pool. She wrapped herself around the boy, forcibly kissing him and touching his breast. While he struggled, she called out to the gods that they should never part. Her wish was granted, and their bodies blended into one **intersex** form

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What causes ambiguous genitalia?

- **True Intersex (hermaphroditism) -** children who have:
  - both ovarian and testicular tissues.
  - both internal reproductive organs.
  - external genitalia that are partially ambiguous.
  - chromosomes that are either 46, XX, 46, XY, or a mixture (referred to as "mosaic").
- **Gonadal dysgenesis -** children who have:
  - an undeveloped gonad.
  - internal sex organs that are usually female.
  - external genitals that may vary between normal female and normal male, with the majority female.
  - chromosomes that are 45, X, 46, XY, 46, XX, or a mixture (referred to as "mosaic").

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What causes ambiguous genitalia?

- **Pure gonadal dysgenesis -** a female child who has a 46, XY karyotype, underdeveloped gonads, internal female reproductive organs and female external genitalia.
- **Pseudo-intersex (hermaphroditism) -** children who have questionable external genitalia, but have only one sex internal reproductive organs. The term male (gonads are testes) or female (gonads are ovaries) pseudohermaphrodite refers to the gonadal sex (the internal reproductive organs).

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Causes of Male Pseudohermaphroditism

- **Mutated SRY Gene -** childern who have:
  - 46, XY karyotype.
  - normal female external genitalia.
- **Androgen insensitivity syndrome -** children who have:
  - 46, XY karyotype.
  - normal female external genitalia.
- **5-alpha-reductase deficiency -** children who have:
  - 46, XY karyotype.
  - genital ambiguity.
  - Enzyme responsible for converting testosterone into dihydrotestosterone (DHT)

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Causes of Female Pseudohermaphroditism

- **Congenital adrenal hyperplasia (CAH):**
  - is caused by a defect in an enzyme (21-hydroxylase) in the steroid hormone synthesis pathway in the adrenal gland.
  - is the most common cause of ambiguous genitalia in newborns.
  - causes females to be masculinized due to a deficiency of the enzyme 21-hydroxylase.
  - is present in about one in 15,000 newborns.
  - is inherited by an autosomal recessive gene.
- **Overproduction of male hormones before birth:**
  - is often due to adrenal gland abnormality (as described in CAH above)
  - high levels of male hormones may also enter the placenta via the mother, such as when the mother receives progesterone to prevent a miscarriage or has a hormone-producing tumor.

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To determine the sex, a physicians will consider the following:

- a pelvic ultrasound (to check for the presence of female reproductive organs)
- a genitourethrogram to look at the urethra and vagina if present
- a chromosomal analysis (to help determine genetic sex: 46, XX or 46, XY)
- fertility potential of a female intersex
- size and potential for growth of a penis present in a male intersex
- ability of an internal reproductive organ to produce appropriate sex hormones for the gender "assigned" to the child
- risk of future health conditions (i.e., cancer) that may develop in the original reproductive organs later in life
- the actions of male or female hormones on the fetal brain
- your opinion or preference

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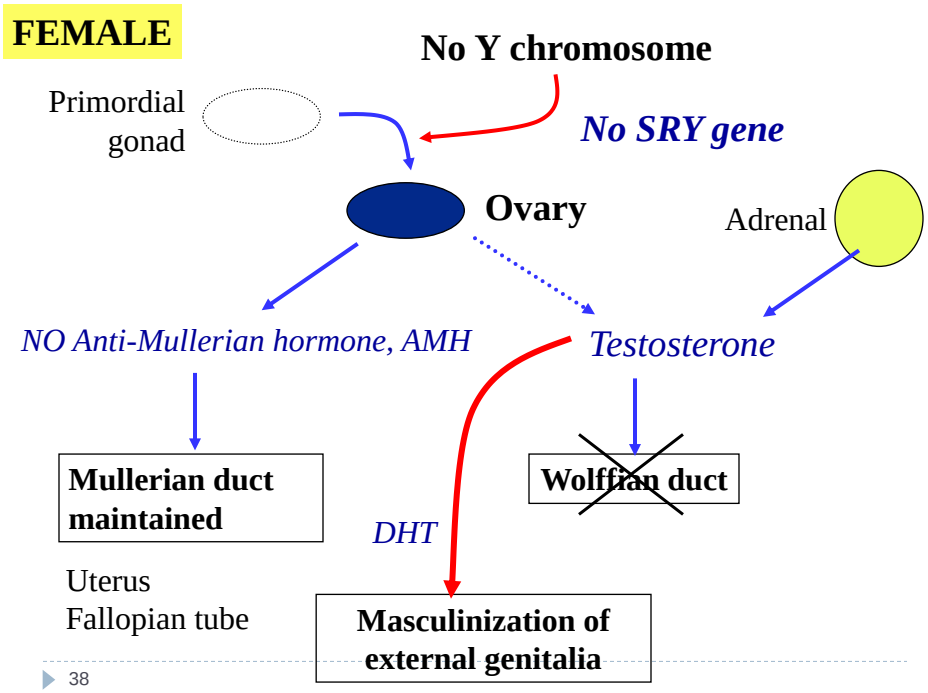

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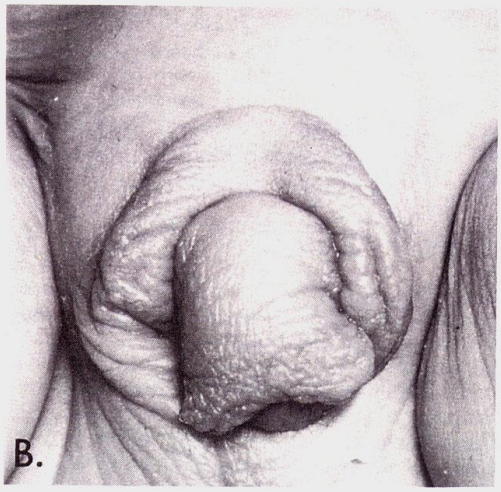
Clitoromegaly



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Clitoromegaly and Posterior Labial Fusion

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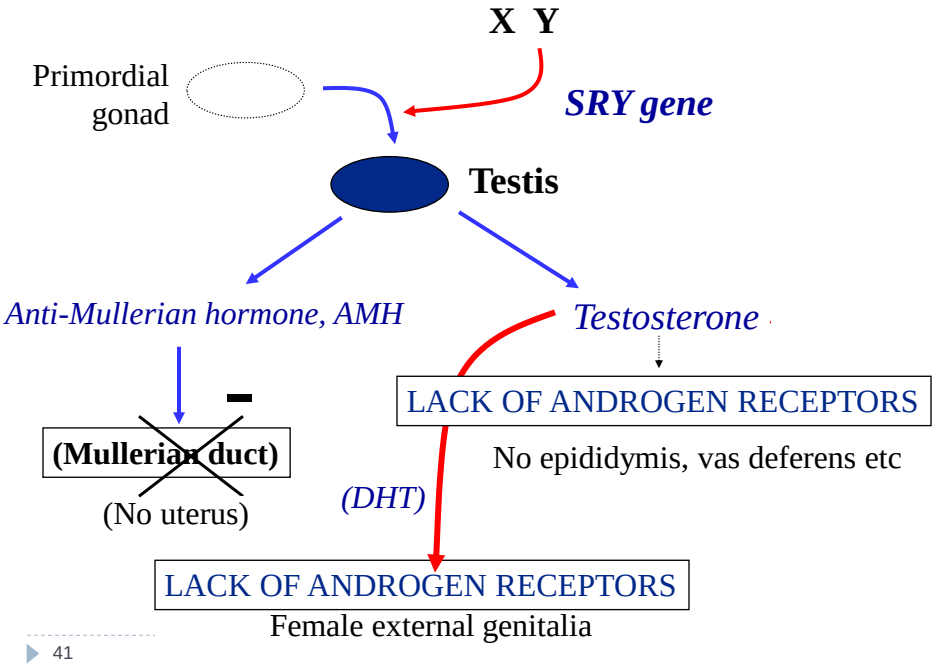

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What can go <u>wrong</u>?

1. "Testicular feminization" (androgen insensitivity syndrome)

- Phenotypic female
- Not menstruating
- Blind-ending vagina

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What can go wrong?

1. "Testicular feminization" (androgen insensitivity syndrome)

Mode of Inheritance
AIS is inherited in an **X-linked recessive** manner.

Prevalence
Standard references quote prevalence of **2-5/100,000** for complete AIS (CAIS) and are based on estimates derived from otherwise healthy **phenotypic** females found to have histologically normal inguinal or abdominal testes. A recent survey done in the Netherlands over a ten-year period based on reported cases of AIS reported a minimal incidence of 1/99,000 [Boehmer et al 2001].

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What can go wrong?

1. "Testicular feminization" (androgen insensitivity syndrome)

Natural History

Complete AIS (CAIS; testicular feminization; Tfm). Individuals with CAIS have normal female external genitalia. They typically present either before puberty with inguinal masses that are subsequently identified as testes or at puberty with primary amenorrhea and sparse to absent pubic or axillary hair. Breasts and female adiposity develop normally. Sexual identity and orientation are **unaffected**. CAIS almost always runs true in families; that is, **affected** XY relatives usually have normal female external genitalia and seldom have any sign of external genital masculinization, such as clitoromegaly or posterior labial fusion [Boehmer et al 2001].

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What can go wrong?

1. "Testicular feminization" (androgen insensitivity syndrome)

Natural History

Partial AIS (PAIS) and predominantly female external genitalia presents in a manner similar to CAIS; however, **affected** individuals have signs of external genital masculinization including clitoromegaly or posterior labial fusion.

Partial AIS with ambiguous genitalia or predominantly male genitalia (PAIS; Reifenstein syndrome). Determining the sex of rearing may be an issue for children with frank genital ambiguity. In families with PAIS, **phenotypic** disparity may warrant opposite sexes-of-rearing [Rodien et al 1996 , Evans et al 1997 , Boehmer et al 2001]. Individuals with PAIS and predominantly male genitalia are raised as males. Gynecomastia at puberty and impaired **spermatogenesis** occur in all individuals with PAIS. Pubic hair is usually moderate; facial, body, and axillary hair are often reduced.

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What can go wrong?

1. "Testicular feminization" (androgen insensitivity syndrome)

Natural History

Mild AIS (MAIS; undervirilized male syndrome). The external genitalia of these individuals are unambiguously male. They usually present with gynecomastia at puberty. They may have undermasculinization that includes sparse facial and body hair and small penis. Impotence may be a complaint. **Spermatogenesis** may or may not be impaired [Larrea et al 1978 , Grino et al 1988 , Pinsky et al 1989 , Tsukada et al 1994]. MAIS almost always runs true in families

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Clitoromegaly and Posterior Labial Fusion.

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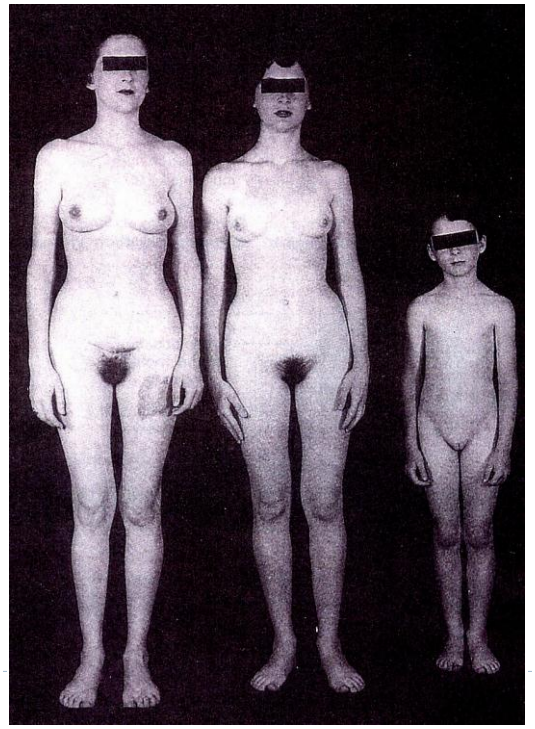

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The 46, XX male syndrome is a rare sex chromosomal disorder in man

- It mostly occurs due to unequal crossing over between X and Y chromosomes during meiosis, possibly due to translocated SRY gene.
- Eleven SRY-positive 46,XX males were compared with age-matched controls: 101 47,XXY Klinefelter patients, 78 healthy men, and 157 healthy women
- The 46,XX males were significantly smaller than Klinefelter patients or healthy men, resembling female controls in height and weight.
- The incidence of maldescended testes was significantly higher than that in Klinefelter patients and controls.
- All XX males were infertile and most were hypogonadal
- **Elena Vorona, Michael Zitzmann, Jörg Gromoll, Andreas N. Schüring and Eberhard Nieschlag** *Institute of Reproductive Medicine (E.V., M.Z., J.G., E.N.) and Department of Obstetrics and Gynecology (A.N.S.), University Clinics of Münster, D-48129 Münster, Germany*

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The 46, XX male syndrome is a rare sex chromosomal disorder in man

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Development of Genital and related structures

Urogenital Sinus

Male	Female
Prostate Gland	Urethral/paraurethral gland
Bulbourethal glands	Greater Vestibular Glands

Phallus

Glans penis	Glans Clitoris
Corpora cavernosa	Corpora cavernosa
Corpus spongiosum	Bulb of the vestibule
Ventral aspect of penis	Labia minora
Scrotum	Labia Majora

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