Biology of Sexual Development

Objectives:

1. Sex vs. Gender defined.
2. Biological sex based on inheritance of sex chromosomes from gametes.
3. Biological sex during embryonic development driven by testosterone & estrogen exposure.
4. Intersex: exception when biological sex is NOT binary.
5. Biological causes of intersex condition.

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Reading Assignments:

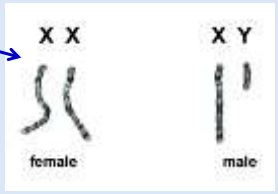
1. Rediscovering Biology: Sex & Gender (Pgs 5 – 9)
2. Should We "Fix" Intersex Children?
3. Gender-Bender Chemicals Are Harming Unborn Boys

2

Human Biological Sex vs Gender - Defined

Sex = biological binary system.

> Can be either male or female ONLY in lifetime (Gonochoristic).
> Based on chromosomes, genes, and body's response to hormones
> not defined by social construct.



Gender = not biological or binary system

> includes a fluid spectrum
> defined by social construct of gender "norms"
> might not match with biological sex
> perception of gender in brain

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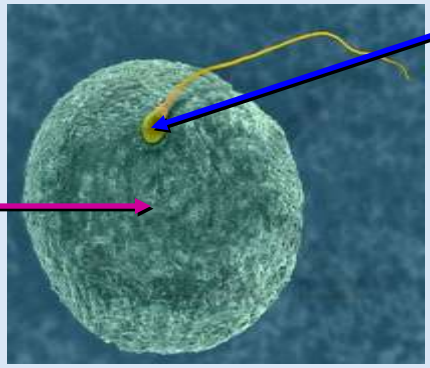
1. Gametes, chromosomes, and sexual reproduction.

Gametes = eggs or sperm, formed by meiosis in ovaries or testes.

> They are haploid = cells with 23 individual chromosomes.

> Includes 22 autosomes and 1 sex chromosome.

Review



22 autosomes

1 sex chromosome (either X or Y)

22 autosomes
1 sex chromosome (X)

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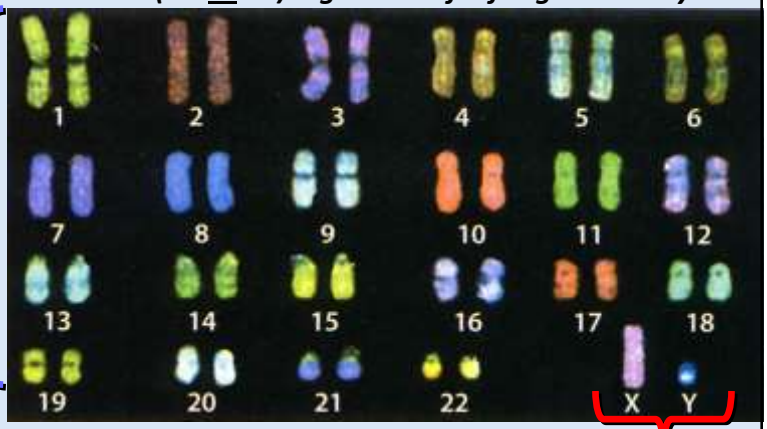
Somatic cells - ***have 23 chromosome pairs***

> 22 autosome pairs

> 1 pair sex chromosomes (XX or XY) - genetic info. for gender only

Autosomes (1 – 22)



Review

Sex Chromosomes:

X – has thousands of genes. Code for most of our traits.

Y – has few dozen genes. Most code for "maleness".

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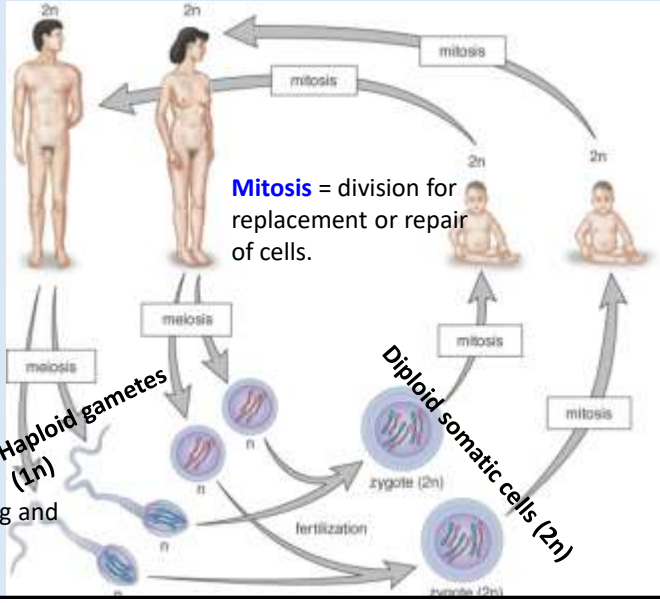
Sexual Reproduction (review of basic Biology)

Review



Mitosis = division for replacement or repair of cells.

Meiosis = division for production of haploid gametes (eggs or sperm) only.

Zygote = union of one egg and sperm. Zygote is now "diploid"

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Sex determination:

Upon fertilization: creates diploid (2n) **zygote**

Review

Mother (XX)

Punnet Square

50 % chance female

50 % chance male

Father (XY)

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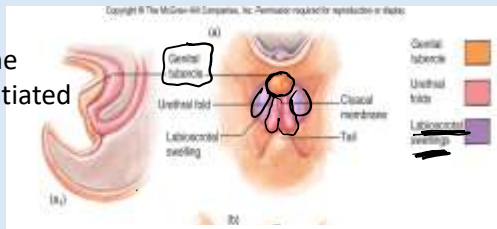
Sex determination:

We start out, by default, with the same non-specific gender having undifferentiated Structures:

Genital tubercle

Urethral Folds

Labial Folds



If have Y chromosome have the following genes, which turn on at 8 weeks of development:

- SRY gene = sex determining region of Y.
- TDF = testis-determining factor.

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Sex determination:

SRY & TDF genes:

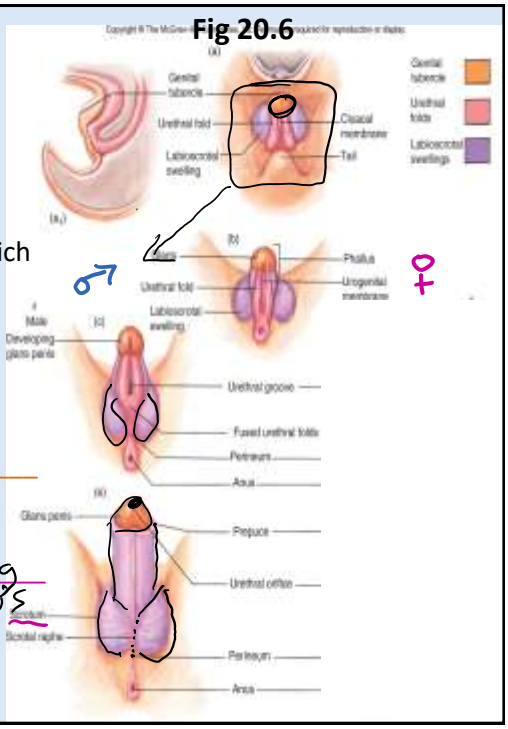
> Both genes start **testes** formation.
>Testes produce **testosterone (T)**, which turns:

- **Wolffian duct** into vas deferens, epididymis, & male glands

Genital tubercle → penis head

Urethral fold - urethral opening at head of penis

Labial folds → scrotal sac



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Sex determination:

2. Absence of Y-genes = female genitalia

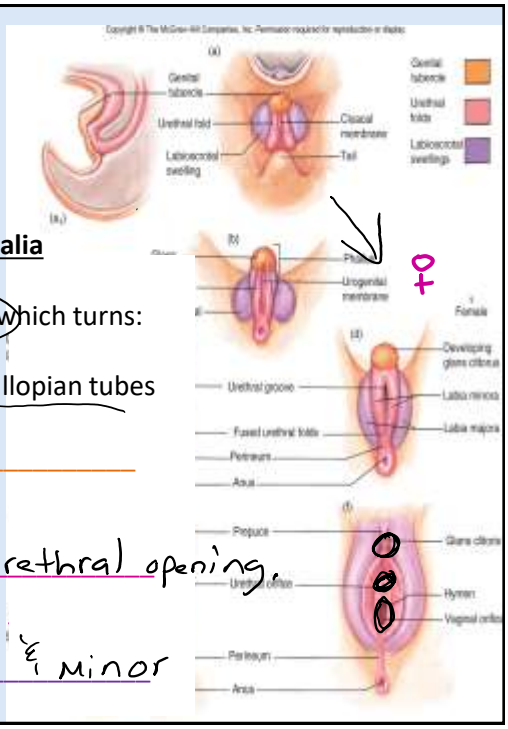
> **Ovaries** develop
> No testosterone, but **Estrogen (E),** which turns:

- **Mullerian duct** becomes uterus & fallopian tubes

Genital tubercle → Clitoris

Urethral fold → vaginal & urethral opening.

Labial folds → Labia major & minor



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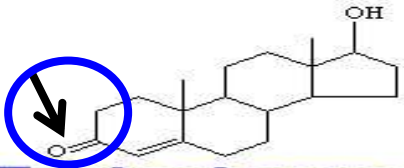
Estrogen



Testosterone

Ovaries Develop → Produce:
estrogen
mullerian ducts
- uterus, cervix
- fallopian tubes
- vagina
- clitoris
- vulva

Exposure to T or E affects all subsequent sexual development!

The difference between male and female comes down to 1 double bond, found in T!!!

Testes Develop → Produce:
- testosterone, DHT
- sertoli cells produce
- anti-mullerian hormone
- wolfian ducts
- accessory glands
- all male repro. struct

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Rediscovering Biology: Sex & Gender Pgs 1, 5 – 9
(topics we are covering are in yellow)

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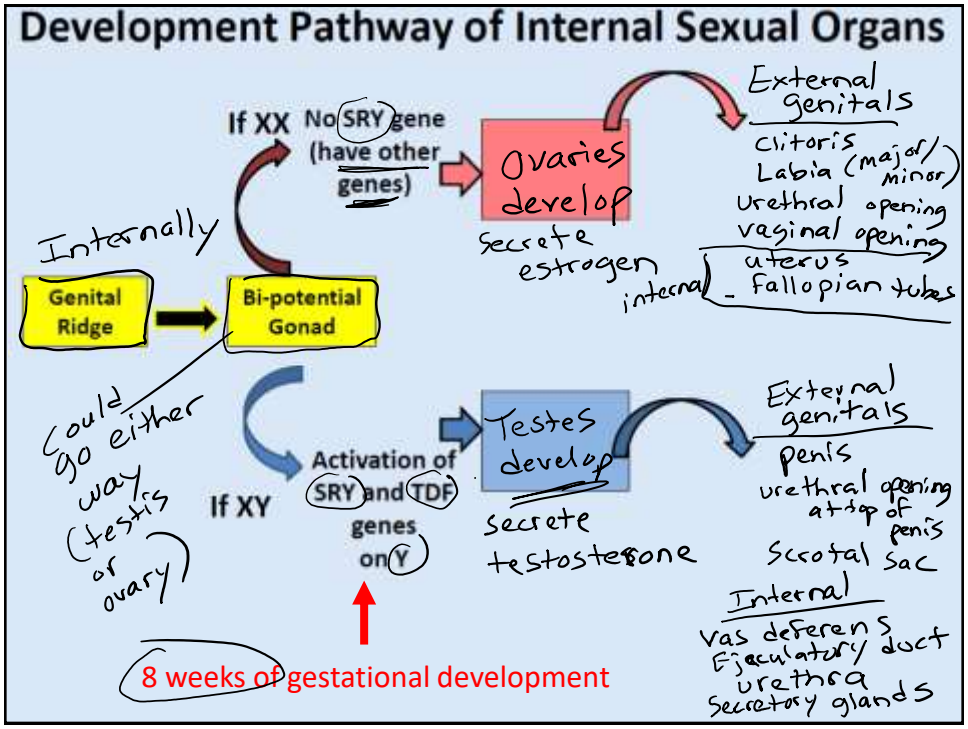

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Review:

- **Gametes (sex cells) versus somatic cells**
- **haploid versus diploid**
- **role of mitosis & meiosis**

- **Sexual reproduction**

- **Sexual differentiation at 8 weeks:**
  - > development from undifferentiated gonad (genital tubercle, labial folds, urethral folds, wolffian and mullerian ducts)
  - >role of SRY & TDF genes
  - > influence of testosterone
  - >influence of estrogen

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2. When Sexual Development Goes … Differently

Inter Sex **(or disorders of sexual development, "DSD") =** chromosomal sex is inconsistent with phenotypic sex, or in which the phenotype is not classifiable as either male or female. There is a discrepancy between the external genitals and the internal structures. Occurs in 0.018% of the population

Criteria for being intersex quite diverse, but includes:

> Having both ovary and testis (internally)
> External genitals don't match clear male / female
> Sex chromosomes don't match clear XX or XY.

Source: Intersex Society of North America – www.isna.org/faq

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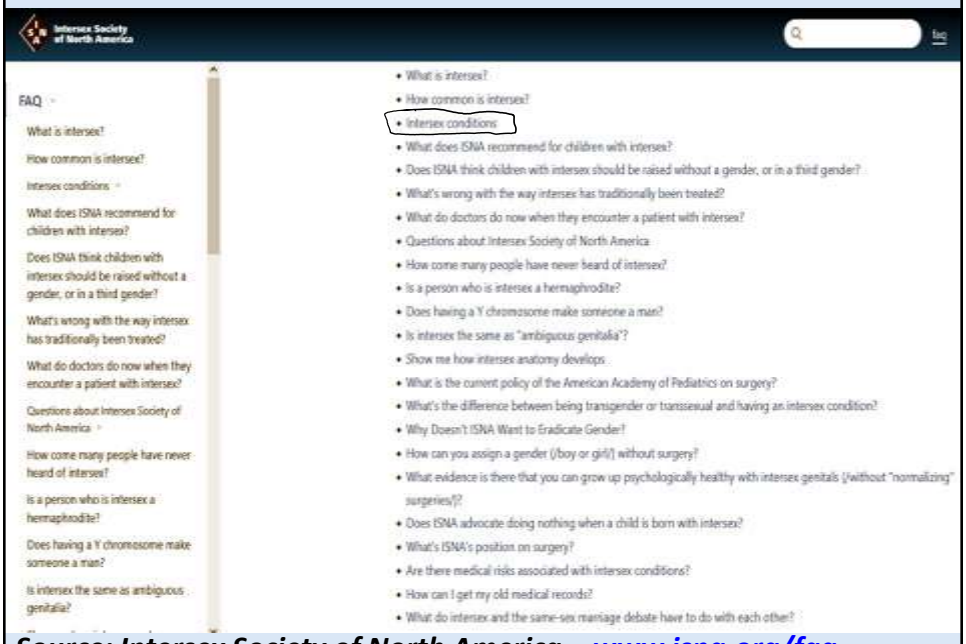

Source: Intersex Society of North America – www.isna.org/faq

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2. When Sexual Development Goes … Differently

The following is a list of disorders of sex development that sometimes involve intersex anatomy.

- How do I know if I have an intersex condition?
- 5-alpha reductase deficiency
- Androgen Insensitivity Syndrome (AIS)
- Aphallia
- Clitoromegaly (large clitoris)
- Congenital Adrenal Hyperplasia (CAH)
- gonadal dysgenesis (partial & complete)
- hypospadias
- I have a line along the underside of my penis
- Klinefelter Syndrome
- micropenis
- mosaicism involving "sex" chromosomes
- MRKH (Mullerian agenesis; vaginal agenesis; congenital absence of vagina)
- ovo-testes (formerly called "true hermaphroditism")
- Partial Androgen Insensitivity Syndrome (PAIS)
- Progestin Induced Virilization
- Swyer Syndrome
- Turner Syndrome

Source: Intersex Society of North America – www.isna.org/faq

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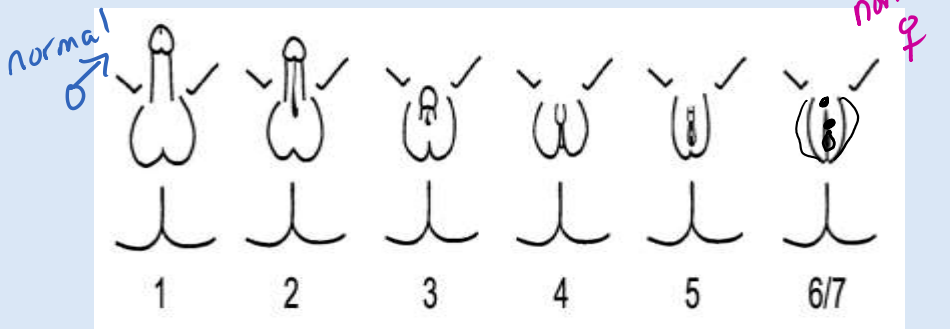
Intersex: exception when biological sex is NOT binary.

> Approx.0.5 - 1% of humans born intersex.
Sources: Wikipedia, Planned Parenthood



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Intersex: exception when biological sex is NOT binary.

Micropenis **Hypospadia** **Clitoromegaly, hypospadia**

Micropenis = smaller than normal penis
(1.5 / 10,000 male births)

Cliteromegaly = larger than normal clitoris
(rare, usually due to hormones (exposure to testosterone) in girls, such as those with congenital adrenal hyperplasia or polycystic ovarian syndrome)

Hypospadia = urethral opening somewhere other than head of penis
(fairly common, 1 / 250 male births)

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Possible Causes of Intersex Condition:

1. **Nondisjunction of sex chromosomes** (during meiosis) – Meiosis problem.
2. **Kallman syndrome (hypogonadism)** – Brain problem.
3. **Androgen-insensitivity syndrome (AIS)** – Tissue problem.
4. **Congenital adrenal hyperplasia (CAH)** – Adrenal gland problem.
5. **5-alpha reductase deficiency** – Enzyme problem.
6. **Endocrine-Disrupting Chemicals** – Environmental problem

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1. Nondisjunction in the sex chromosomes

= Failure of homologous (pair) chromosomes to seperate during meiosis.

> Egg or sperm has extra, or too few, sex chromosomes.

> May affect as many as 18 % of all ova and 4% of all sperm!

Source: Science Direct

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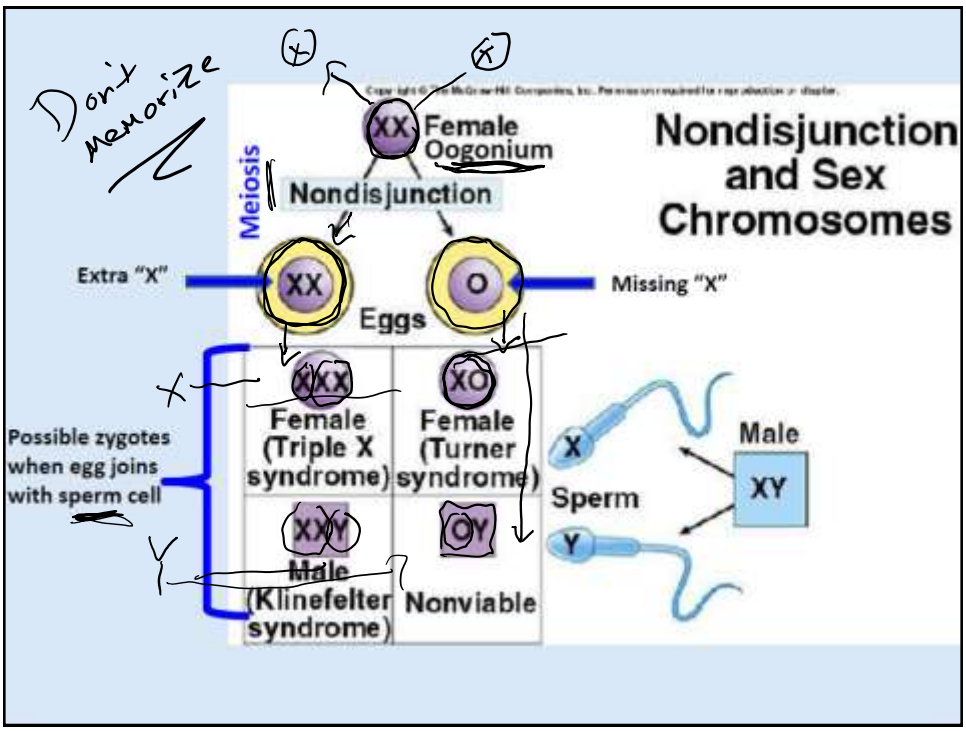

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1. Nondisjunction in the sex chromosomes

Example:

A) Klinefelter Syndrome = XXY male (extra X chromosome)

> Affects about 1 / 650 newborn boys.

> It is among the most common sex chromosome disorders.

> Have smaller testes, & low testosterone.

> Some degree of feminized features after puberty if not diagnosed & treated with supplemental testosterone.

May or may not also have:

- **> Gynocomastia** = breast development in men.
- **> Cryptorchidism =** testes retained in abdomen
- **> Hypospadia =** urethral opening not on head of penis
- **> Micropenis** = smaller than normal penis
- **>** Hip development - due to estrogen changing fat deposition.z
- > Infertility
- > Taller than average
- **>** Poor muscle development

Source: https://medlineplus.gov/genetics/condition/klinefelter-syndrome/

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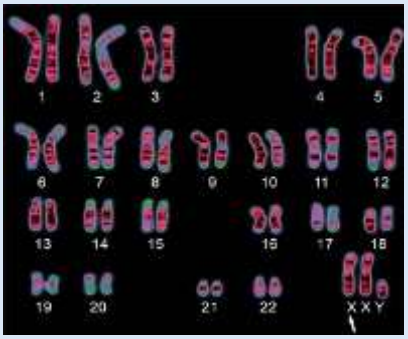
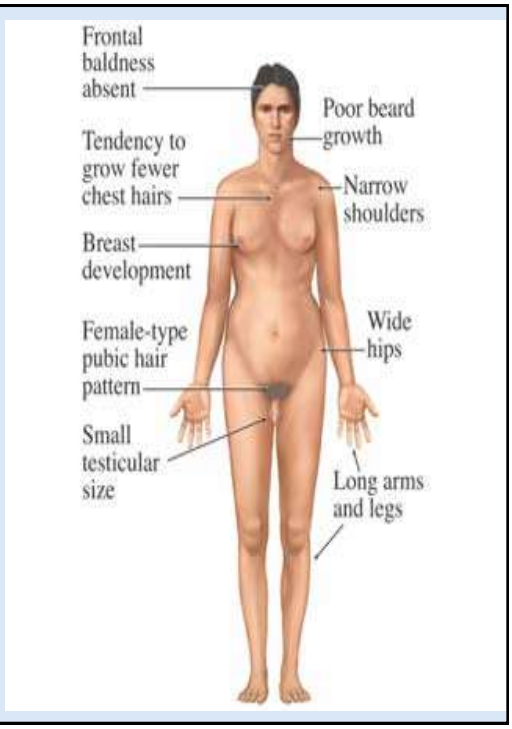
Klinefelter Syndrome





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1. Nondisjunction in the sex chromosomes -

B) Turner Syndrome = XO female (missing second X chromosome)

> Female appearance

> 1 / 2,500 female births (often goes undiagnosed until older)

May or may not also have:
> Short, wide neck
> Wide chest
> Widely spaced nipples
> Might have fertility problems

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TRB1

2) Kallman Syndrome (Hypogonadism)

= **Brain problem – hypothalamus doesn't stimulate gonads.**

> Rare - 1 out of 50,000 births

Genetic male XY

Problem

Normal pathway

Hypothalamus

GnRH → gonad

Pituitary Gland

LH, FSH

Ovaries make - E & ovulate, mature eggs

Testes make - mature sperm, make T

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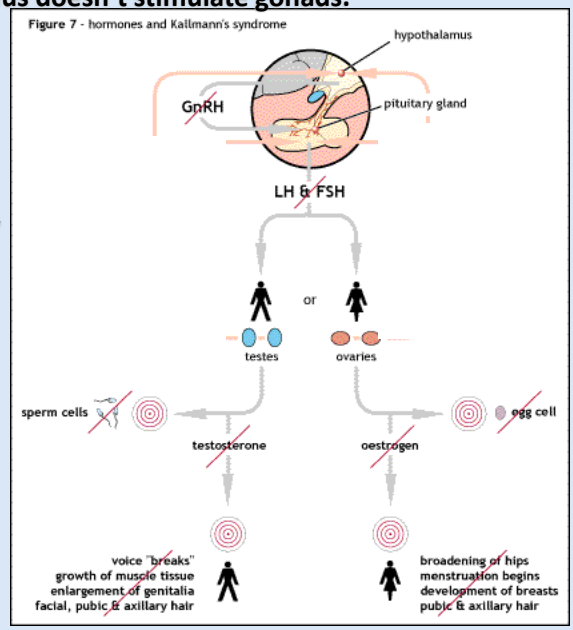
= **Brain problem – hypothalamus doesn't stimulate gonads.**

> Rare - 1 out of 50,000 births

Treatment:

Hormone replacement therapy



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3. Androgen Insensitivity Syndrome (AIS)

= genetic male (XY) with normal genes, testes development, normal vas deferens, normal testosterone production BUT tissues fail to respond to testosterone. (androgen-insensitivity)

> 1 / 13,000 male births

Born with varying degree of intersex
> micropenis
> incomplete fusion of labial folds into scrotal sac
> hypospadias
> poor or no sperm production (sterile)
> extra testosterone converted into estrogen & get female hip development & gynecomastia.

Partial AIS – partial fusion of scrotal skin, micropenis or enlarged clitoris

Complete AIS

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4. Congenital Adrenal Hyperplasia
born with it · adrenal gland · high growth

= fetus with overgrown adrenal cortex. Produces high testosterone. In genetic female (XX) – testosterone masculinizes fetus. Born intersex with ambiguous genitals.

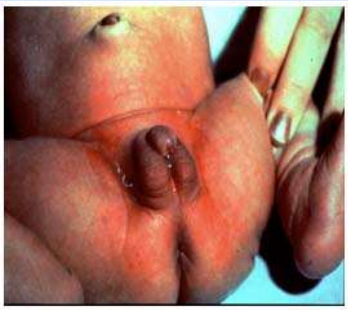
XX

> 1 / 13,000 girl births

> **Megaloclitoris** (enlarged "phalli

> Full or partial fusion of labia into

> Studies have shown CAH girls have masculinized brain.



Increased androgen production results in ambiguous genitalia in newborn girls.

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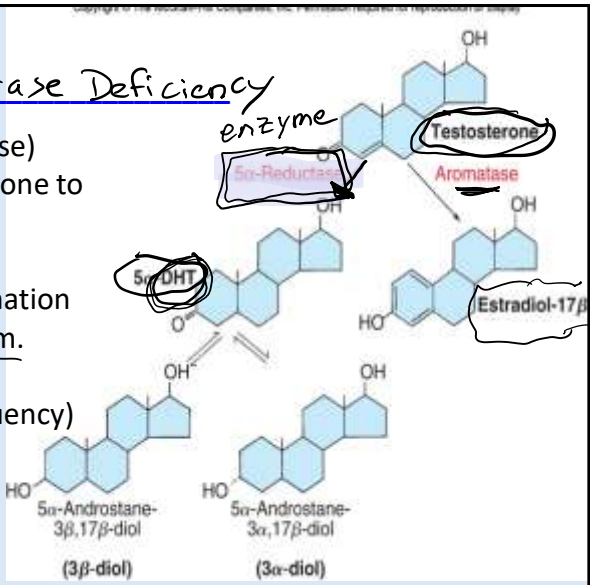
5. 5-Alpha Reductase Deficiency

= Lack enzyme (5-α reductase) needed to convert testosterone to dihydrotestosterone (DHT).

> Need DHT for proper formation of penis, prostate, & scrotum.

> Rare (no estimate of frequency)



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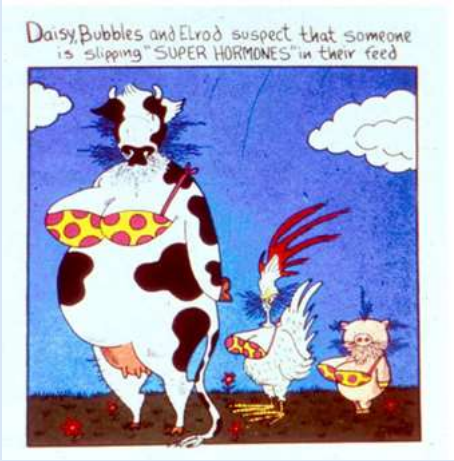
6. Endocrine-Disrupting Chemicals (EDCs)

= Man-made chemicals released into environment that mimic or disrupt natural hormones that influence sex development and functions.



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6. Endocrine-Disrupting Chemicals (EDCs)

Ex. **Bisphenol** = estrogen-mimic found in plastics. Can feminize males at 30 ug/kg/day. At 20 ug/kg/day can damage eggs & chromosomes. At ~2 ug/kg/day can cause early puberty in girls, increase growth prostate and breast cells.

Dose (µg/kg/day)	Effects (measured in studies of laboratory animals)	Study Year [20]
0.025	Permanent changes to genital tract	2005
0.025	Changes in breast tissue that predispose cells to hormones and carcinogens	2005
1.6	**Low levels of human exposure from diet**	**2003**
2	30% increase in prostate weight	1997
2.4	Signs of early puberty	2002
2.4	Decline in testicular testosterone	2004
2.5	Breast cells predisposed to cancer	2006
10	Prostate cells more sensitive to hormones and cancer	2006
10	Insulin resistance	2006
10	Decreased maternal behavior	2002
13	**High levels of human exposure from diet**	**2003**
20	Damage to eggs and chromosomes	2003
25	Health Canada provisional human exposure limit	1999
30	Hyperactivity	2004
30	Reversal of normal sex difference in brain structure	2001
50	U.S. human exposure limit	1998

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Review

5 ways sexual development can go wrong

1. **Problem in meiosis - Non-disjunction of sex chromosomes in eggs or sperm**
   - **Klinefelter & Turner Syndromes**
2. **Brain problem – Kallmann Syndrome**
3. **Problem with tissues – AIS**
4. **Problem with adrenal glands – CAH**
5. **Enzyme problem - 5-α reductase deficiency**
6. **Endocrine-Disrupting Chemicals**

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