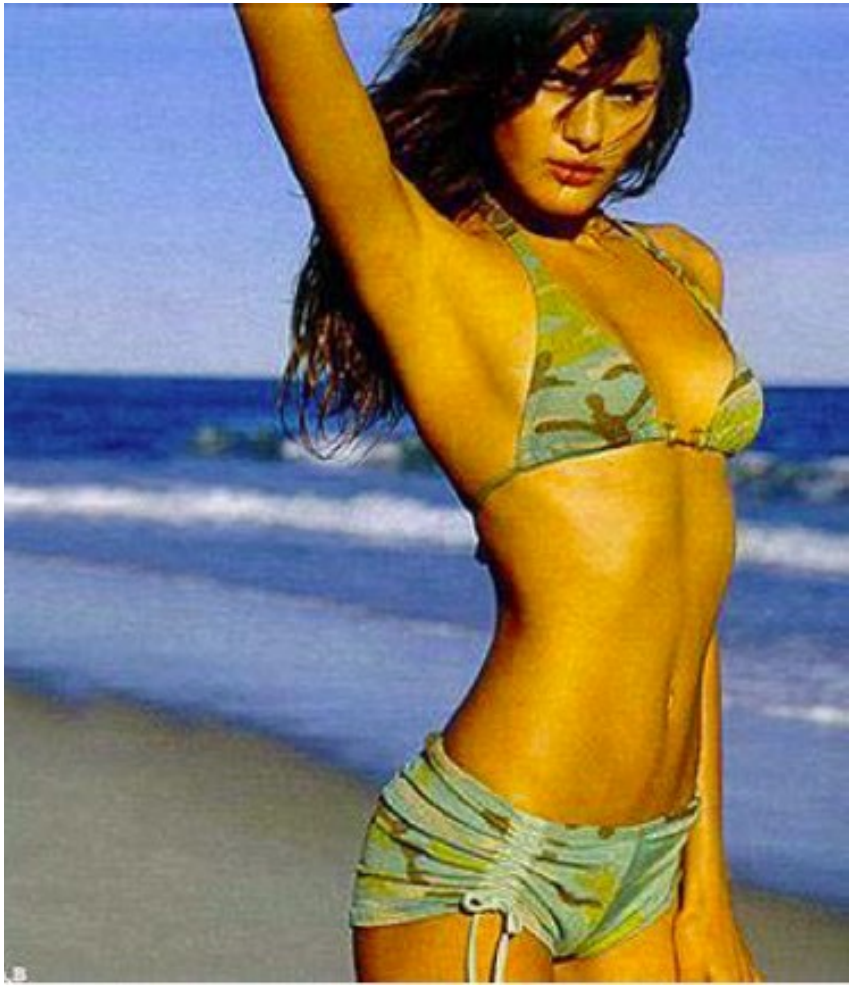
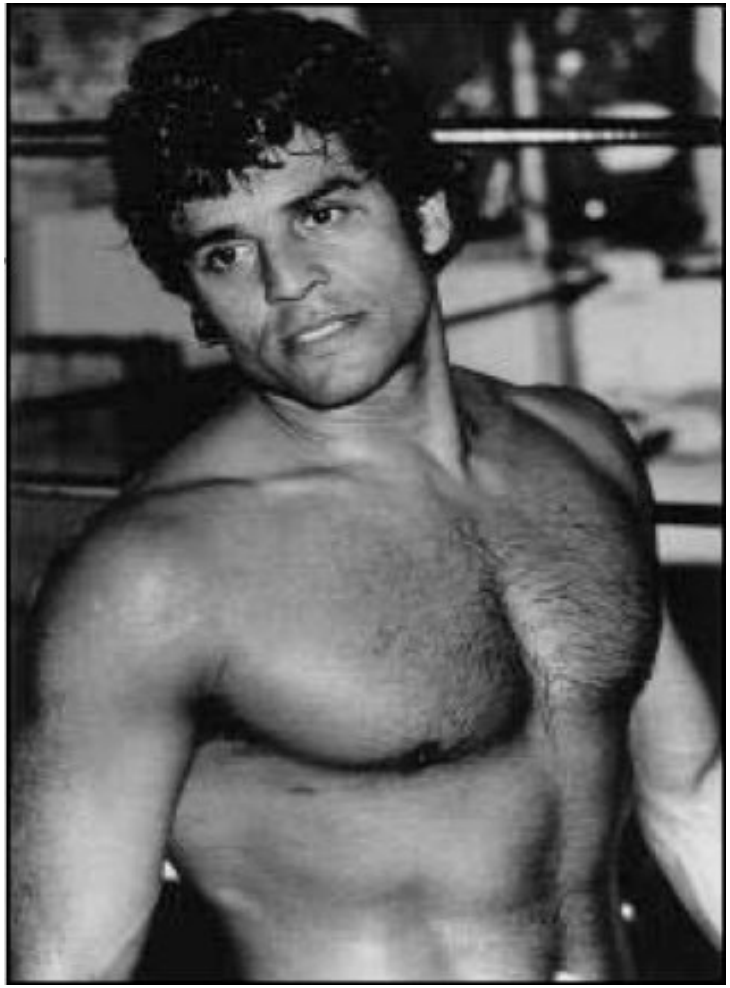
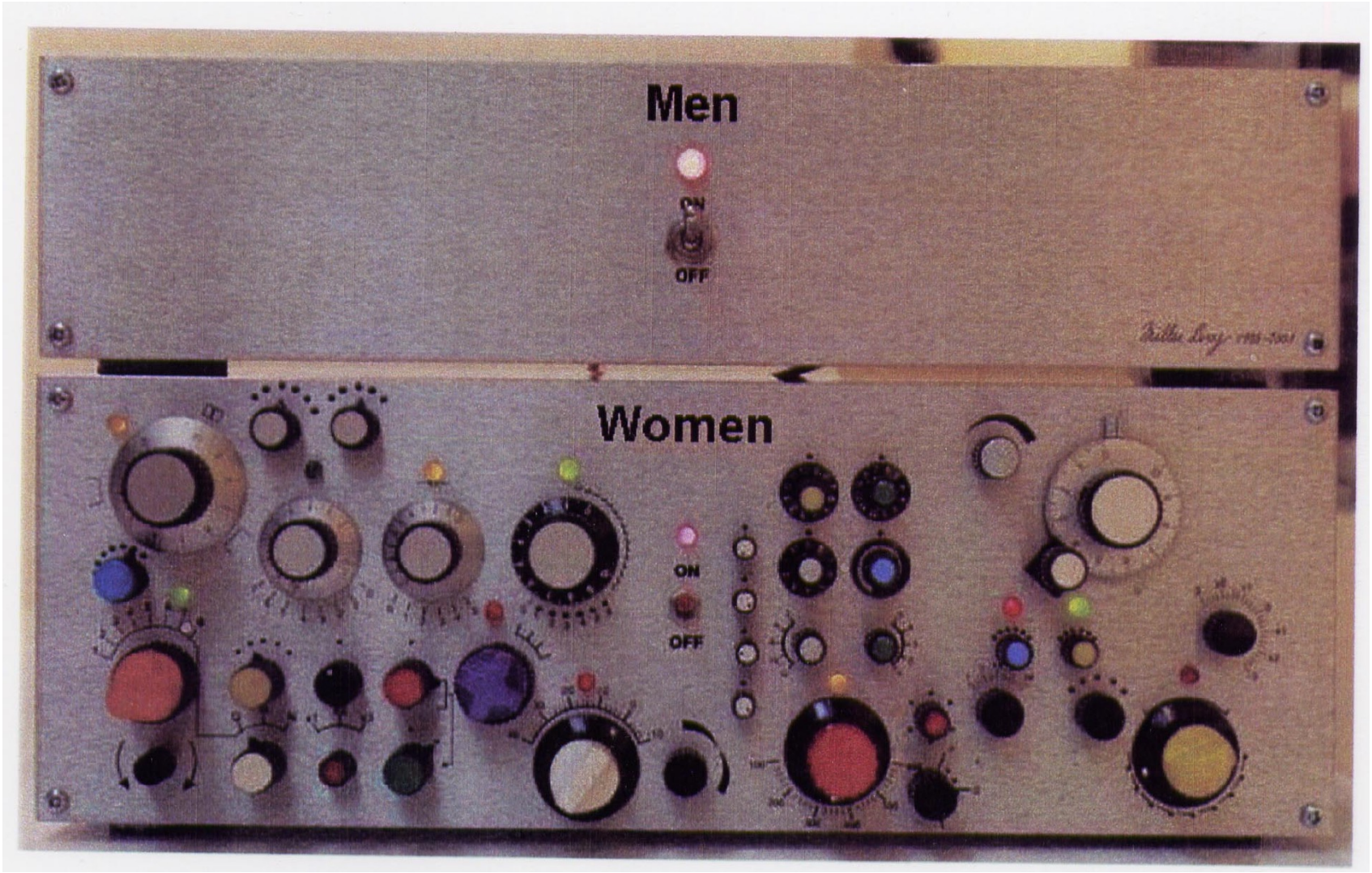
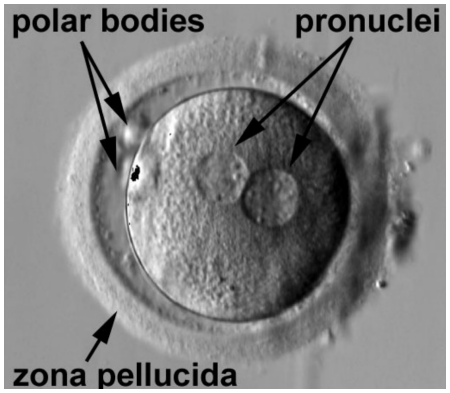
Sexual Differentiation: how males and females develop different bodies, brains, and behaviors.



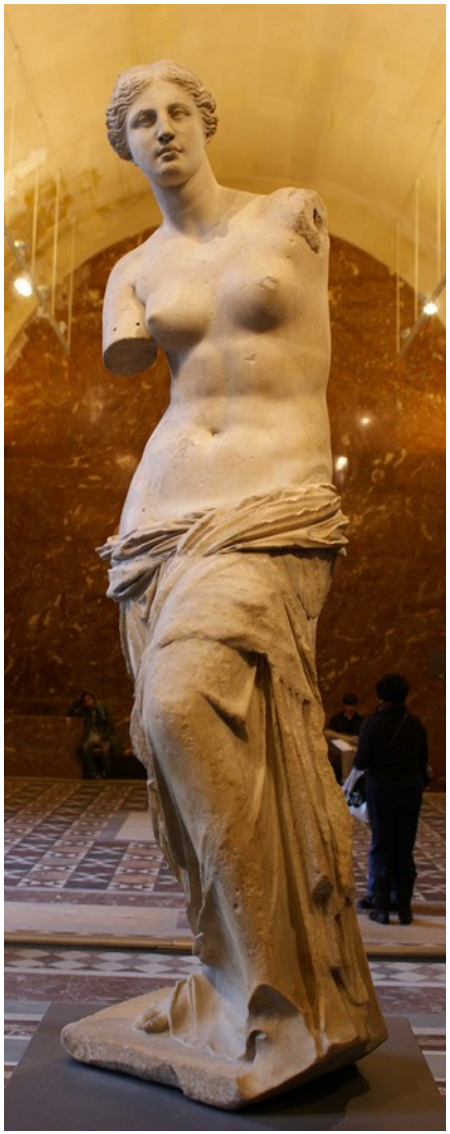



Men
ON
OFF
Women
ON
OFF

Sex determination



How the individual's sex is determined is one of the central questions of embryology since ancient times.



Endocrine Functions

- Maintain internal homeostasis
- Support cell growth
- Coordinate development
- Coordinate reproduction

Reproductive System

environmental factors:

chemical, visual,
thermal, tactile

HP thyroid axis

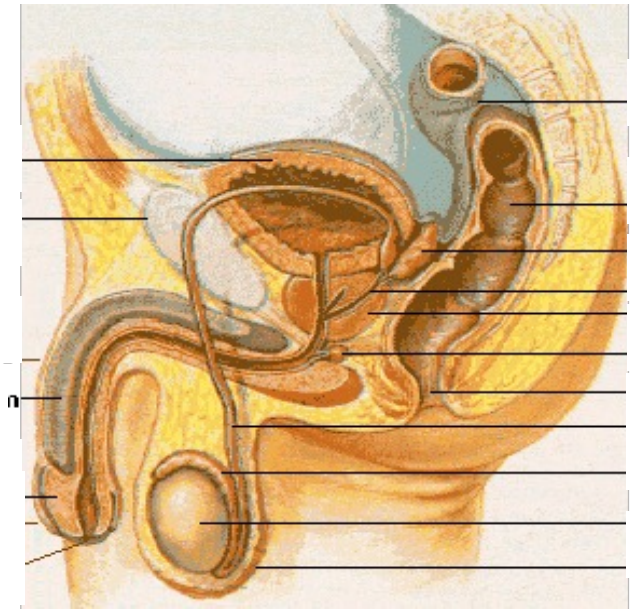
HP adrenal axis

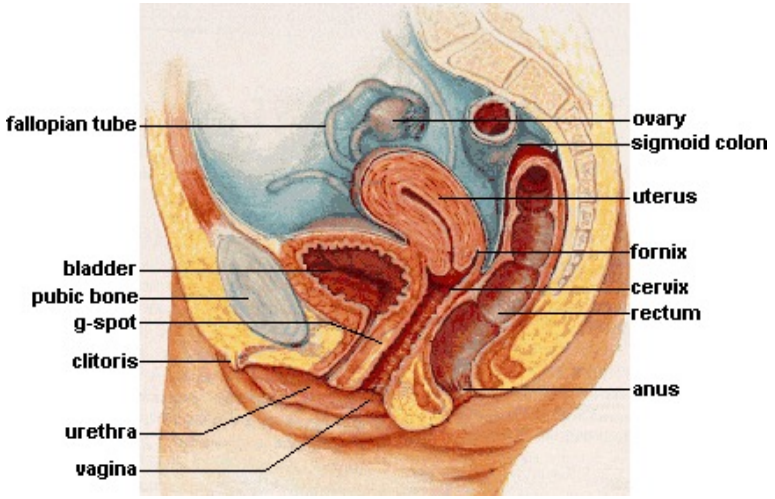
hypothalamus-pituitary-gonad (HPG) axis

+

Target cells of steroid hormones secreted by the gonads

Gonads: testes, ovary





produce gametes sperm, ovum

secrete hormones testosterone, estrogen, progesterone

The Development of the Reproductive System

- The reproductive system in both the male and female can be divided into:

  - gonads
  - internal duct system
  - external genitalia

- The gonads contain:

  Somatic cells:
  -Supporting cells
  -Steroidogenic cells
  -Stromal cells

  Germ cells

PROFESSOR

BROWN SEQUARD'S

METHOD.

EXTRACTS OF ANIMAL ORGANS.

Testicle Extract,
Grey Matter Extract,
Thyroid Gland Extract, &c., &c.

Concentrated Solutions at 30%.

These preparations, completely aseptic, are mailed to any distance on receipt of a money order. Directions sent with the fluids.

Price for 25 Injections, $2.50.
Syringe Specially Gauged, (3 cubic c.,) $2.50.

Used in the Hospitals of Paris, New York, Boston, etc.

Circular Sent on Application.

New York Biological and Vaccinal Institute,

Laboratory of Bovine Vaccine and of Biological Products.

GEO. G. RAMBAUD, Chemist and Bacteriologist, Superintendent.

..Locomotor Ataxia, Neurasthenia..

AND OTHER NERVOUS DISEASES.

EXTRACTS OF ANIMAL ORGANS.

GRAY MATTER, TESTICLE EXTRACT,

Prepared at the **New York Biological and Vaccinal Institute,** according to the method of PROFESSOR BROWN-SEQUARD.

If the treatment of Locomotor Ataxia, Neurasthenia, and other nervous diseases with **"Extracts of Animal Organs,"** has not obtained in America the great favor that it enjoys in Europe, it is chiefly owing to the numerous unreliable preparations of so-called **"Extracts"** which have been placed on the market.

Physicians desirous to try the injections of fresh and reliable extracts, may obtain them from the New York **Biological and Vaccinal Institute,** at the following prices:

TESTICLE EXTRACT, 1 vial, 25 c. c.	**$2.50.**
GRAY MATTER,	**2.50.**
SPECIAL SYRINGE, 3 c. c.,	**2.50.**

Literature sent on application.

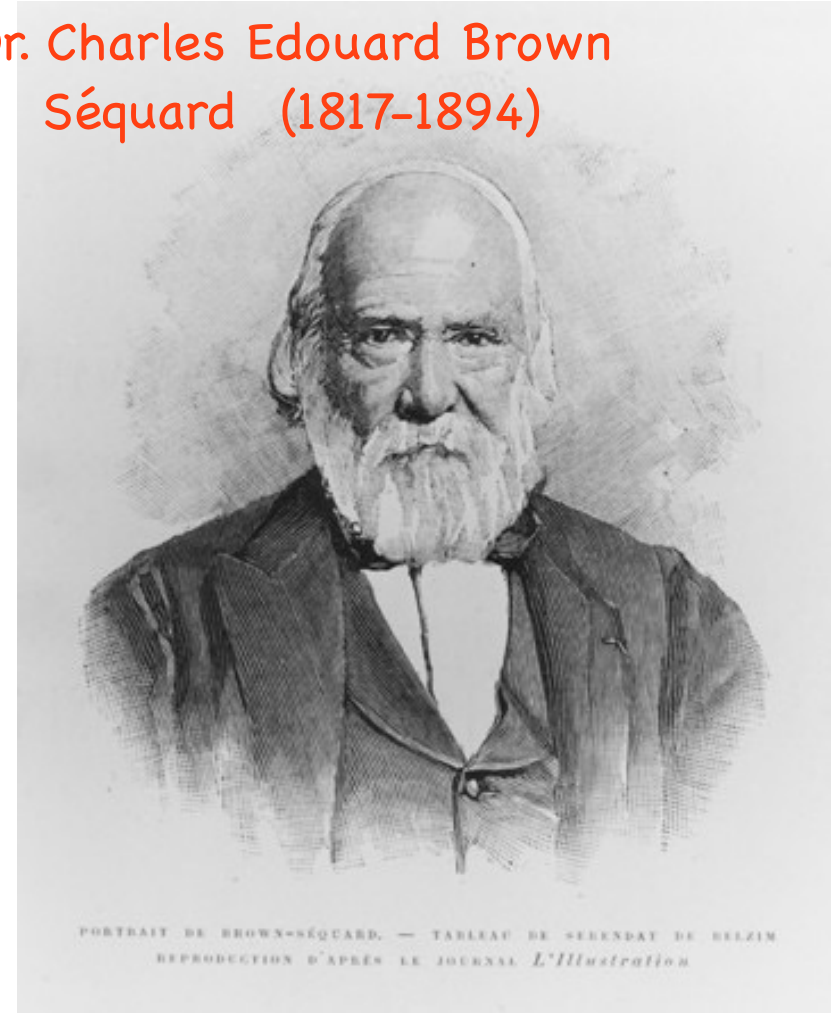
NEW YORK BIOLOGICAL AND VACCINAL INSTITUTE,

Pasteur Institute Building. 1, 3, 5 and 7 West 97th Street, New York, N. Y.

Figure 3. Ad for organ extracts, *Bulletin of the Pasteur Institute*, 1897.

i

Dr. Charles Edouard Brown Séquard (1817-1894)



PORTRAIT DE BROWN-SÉQUARD. — TABLEAU DE SERENDAT DE BELZIM
REPRODUCTION D'APRÈS LE JOURNAL *L'Illustration*

First hormonotherapist

"Pud" Galvin, a Pittsburgh pitcher

-first baseball player in North America known to have used "Brown-Séquard Elixir" in a game against Boston in 1889.

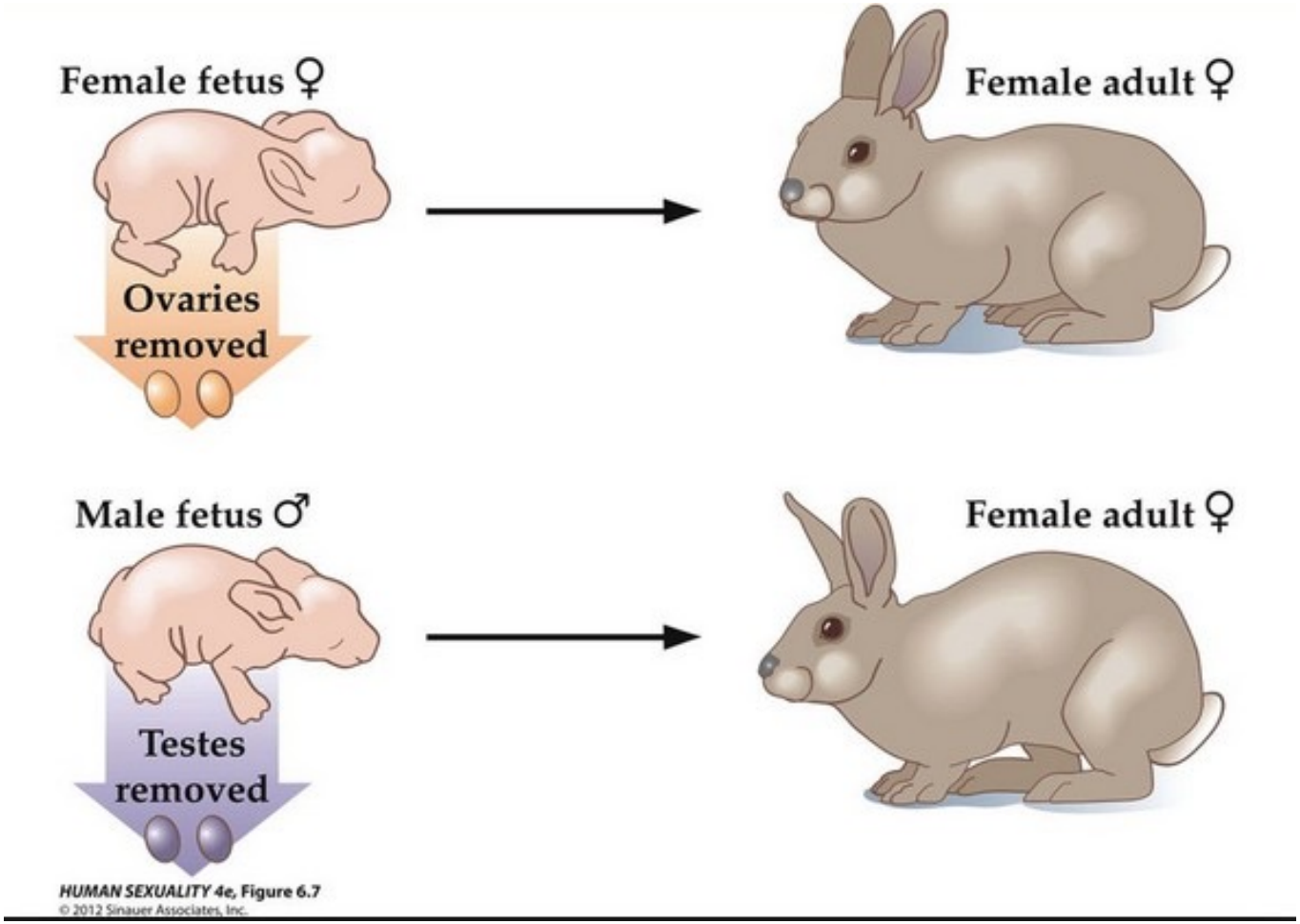
Such performance-enhancing drugs were not condemned in the 19th century.

From: CHARLES-ÉDOUARD BROWN-SÉQUARD:
AN ECCENTRIC GENIUS
Neurosurgery. 2008;62(4):954-964. doi:10.1227/01.neu.0000318182.87664

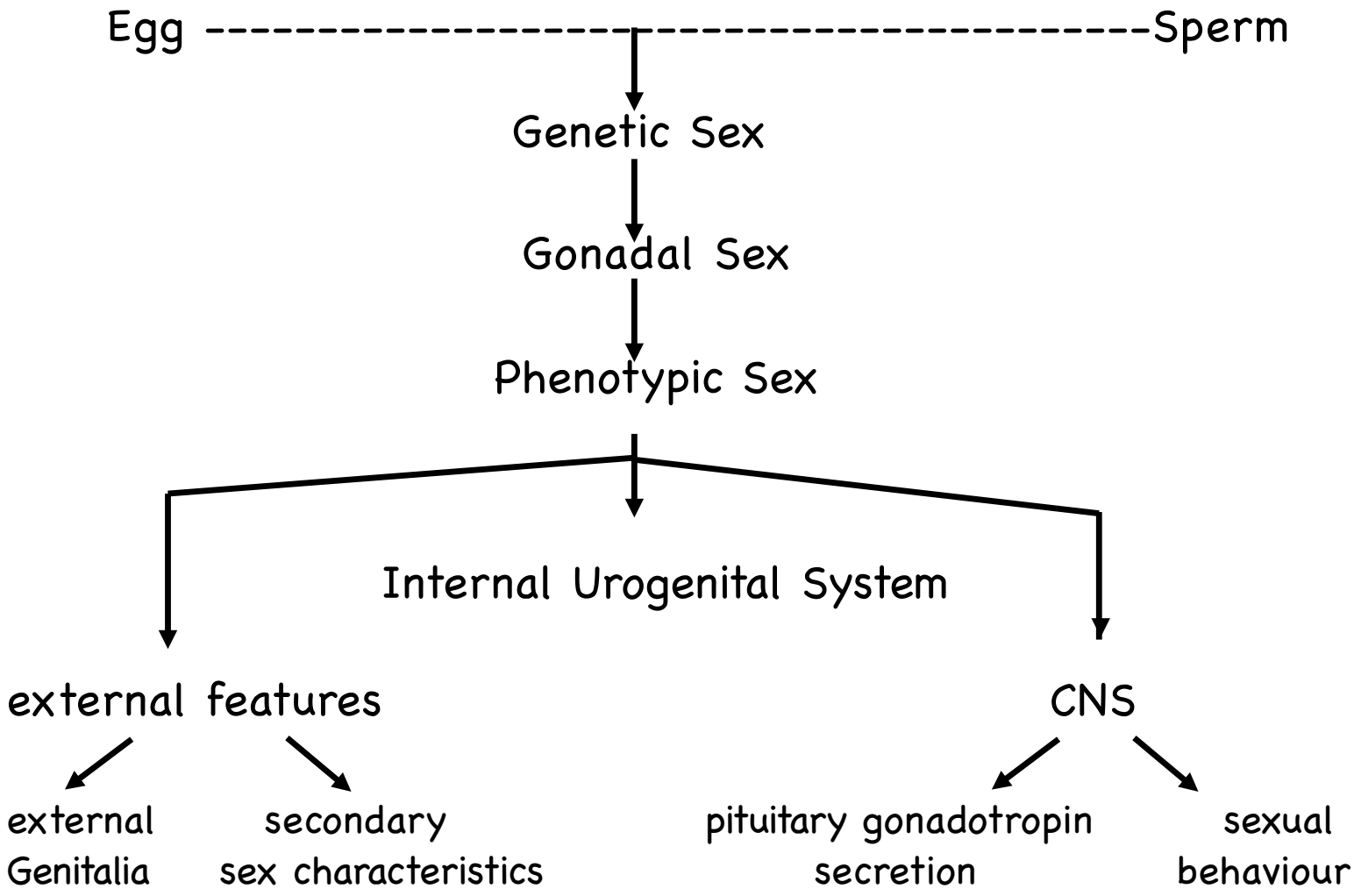
1947: Alfred Jost

Strasbourg 1916-1991

- XX and XY rabbit fetuses are castrated in utero before sexual differentiation
- Discovered anti-Müllerian hormone
- Female by default

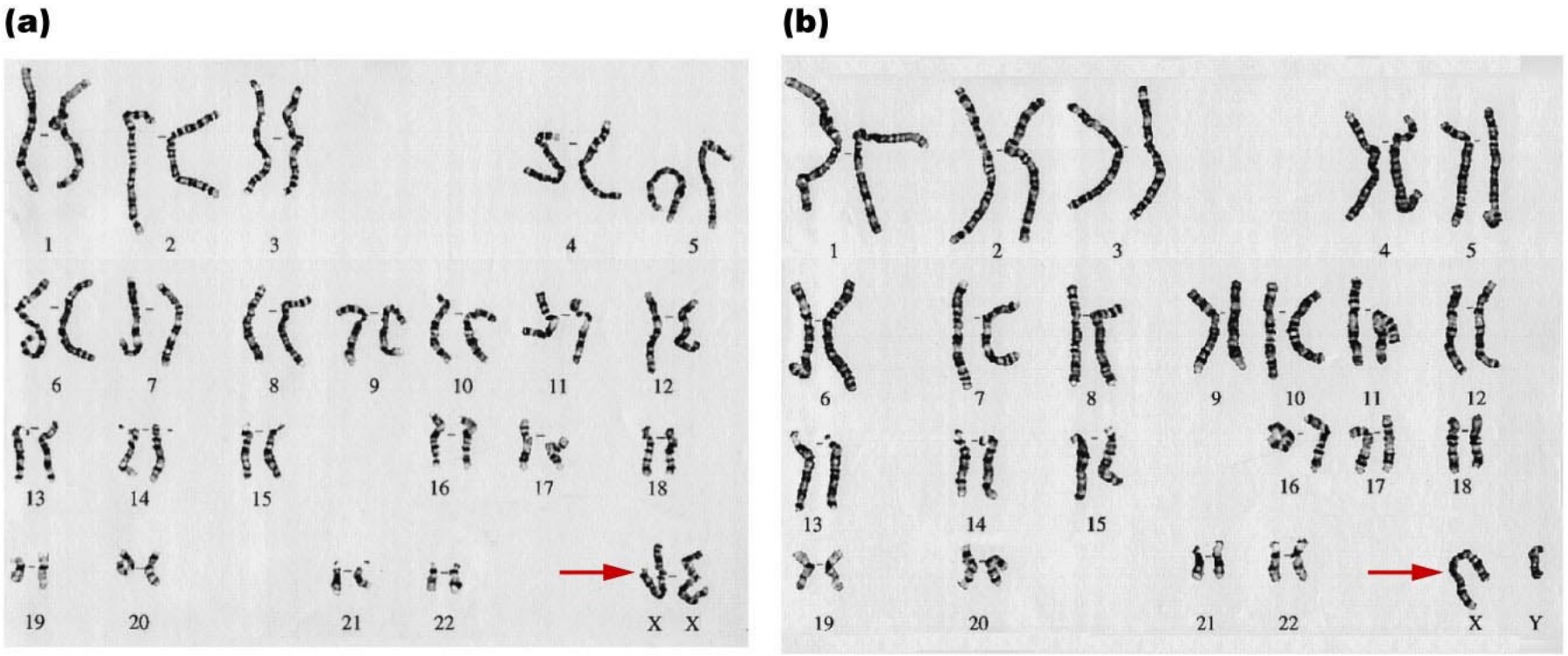


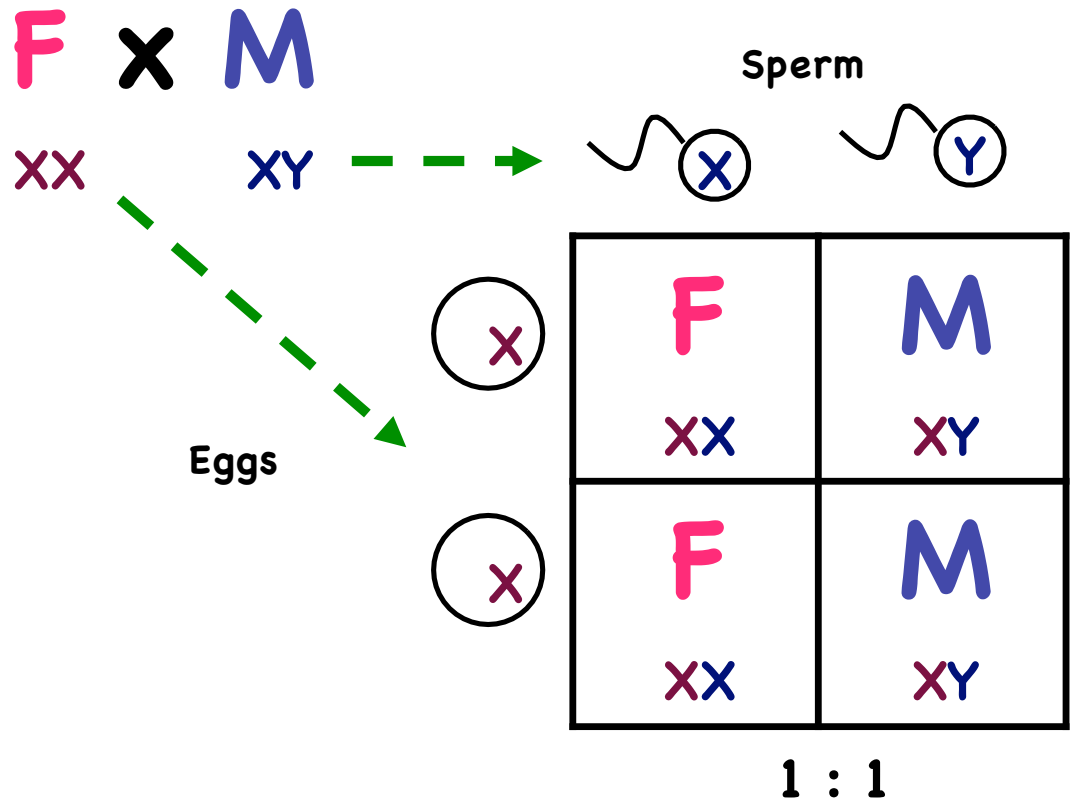
=> development of femaleness represents the default state and is independent of gonadal hormones


Egg
Sperm
Genetic Sex
Gonadal Sex
Phenotypic Sex
Internal Urogenital System
external features
CNS
external Genitalia
secondary sex characteristics
pituitary gonadotropin secretion
sexual behaviour

Genetic sex

normal human karyotype



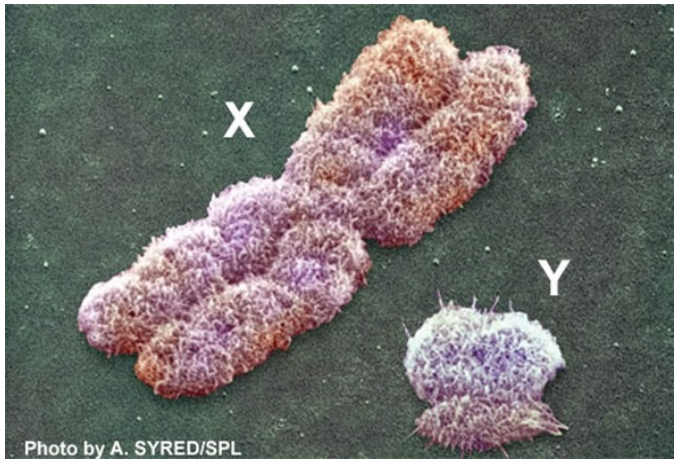


- The male-to-female ratio is one-to-one (average)

A male gets his X chromosome from his mother and transmits it only to his daughters.

The X and Y Chromosomes

- Non-identical but share a small number of genes
- Nevertheless, pair and segregate at meiosis I
- X = 160 million base pairs (Mb), Y = 70 Mb
- Y-specific genes are involved in male sexual differentiation.
- Most X-specific genes encode functions essential to both males and females.
- Females have two X chromosomes (XX genotype)
- Males = have XY genotype.
- Y chromosome: key genes that initiate the male developmental program
- No Y --> female



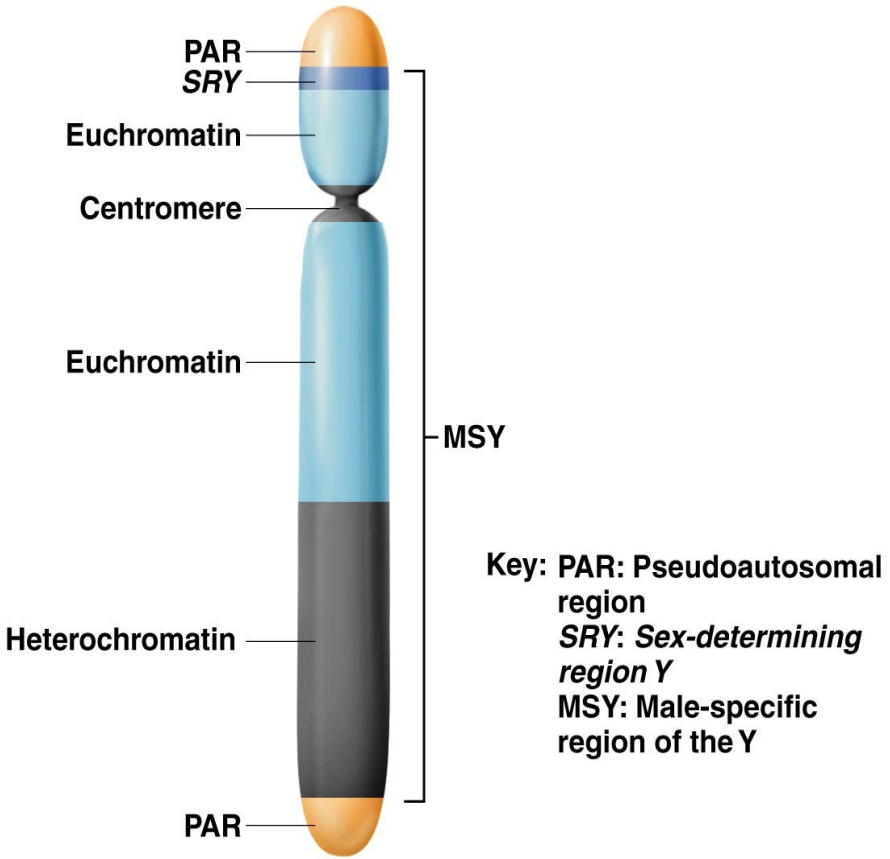
Sex determination

- is genetically controlled
- at the beginning of the 20th century it was thought that age and constitution influenced sex determination
- 1959: Testis-determining factor (TDF) on the y chromosome
- 1966: TDF is on the short arm of the Y chromosome
- 1990: the sex-determining region Y (SRY) gene is TDF

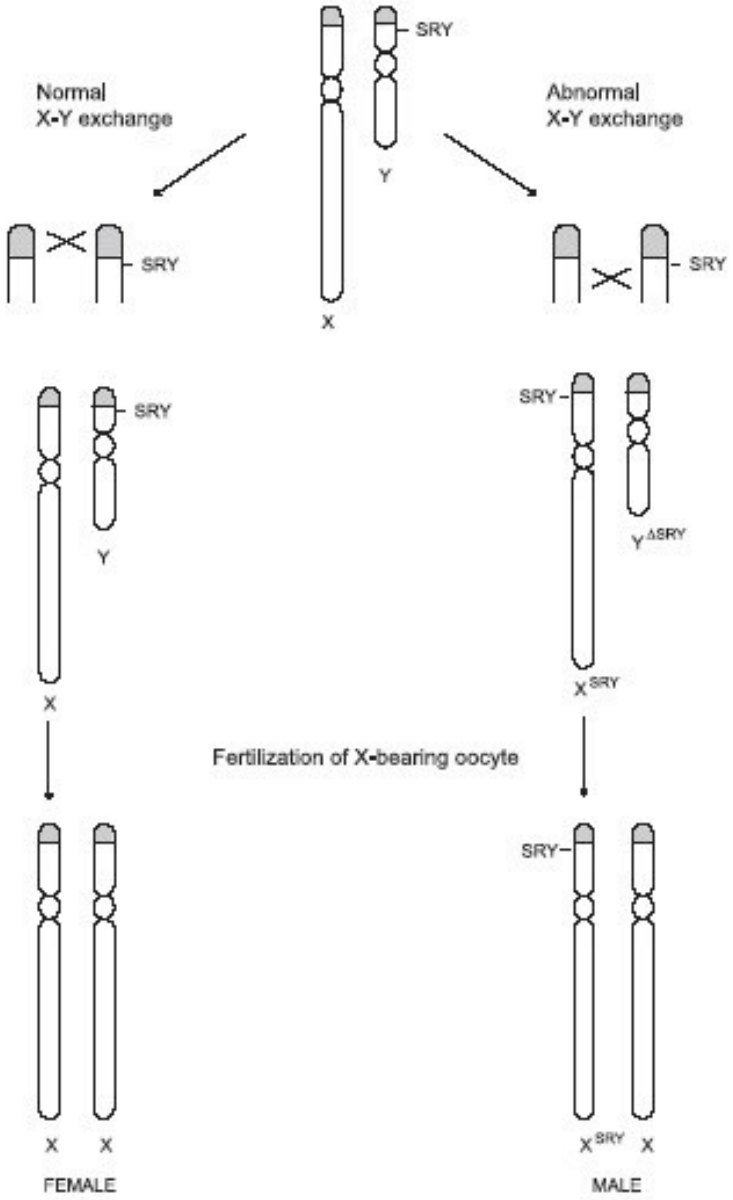
Y-chromosome

contains:

- the male-specific region of the Y (MSY)
- a sex-determining region of the Y (SRY)



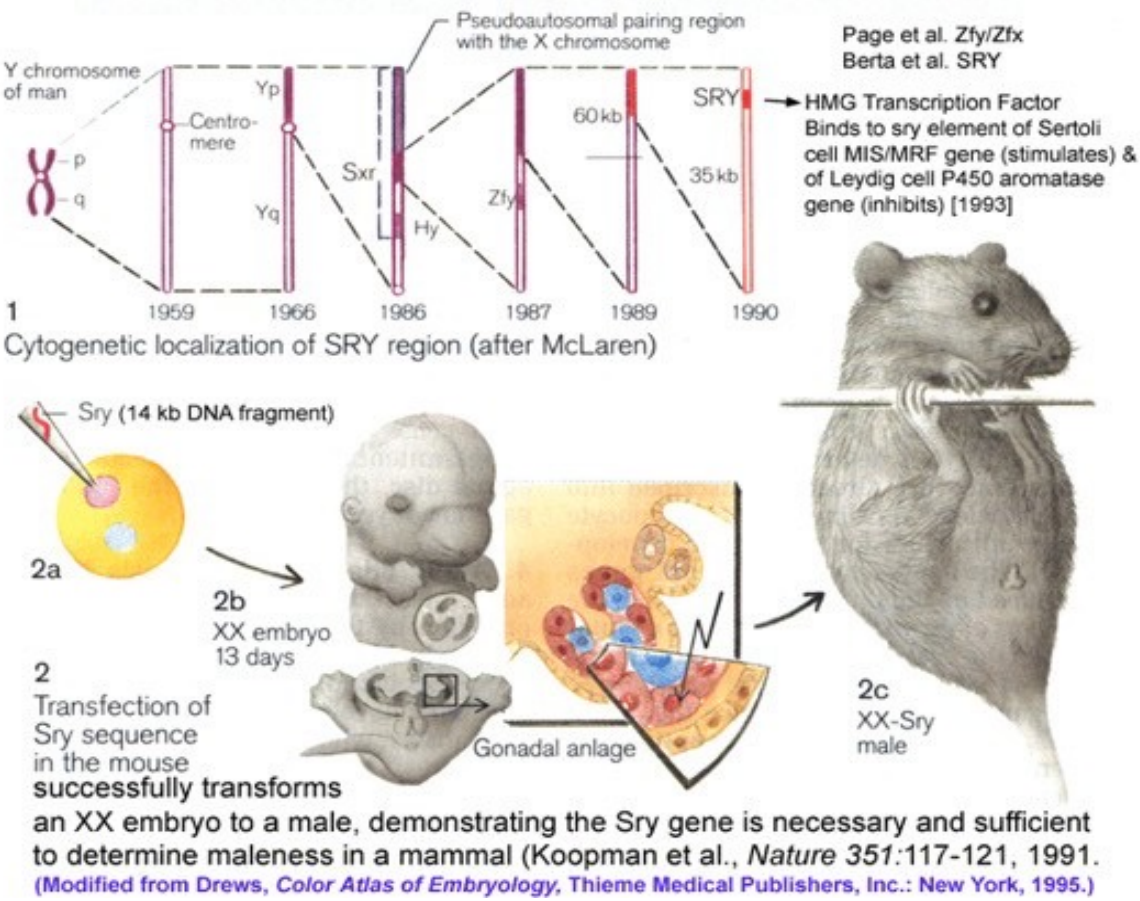
Sex reversal through abnormal X-Y exchange



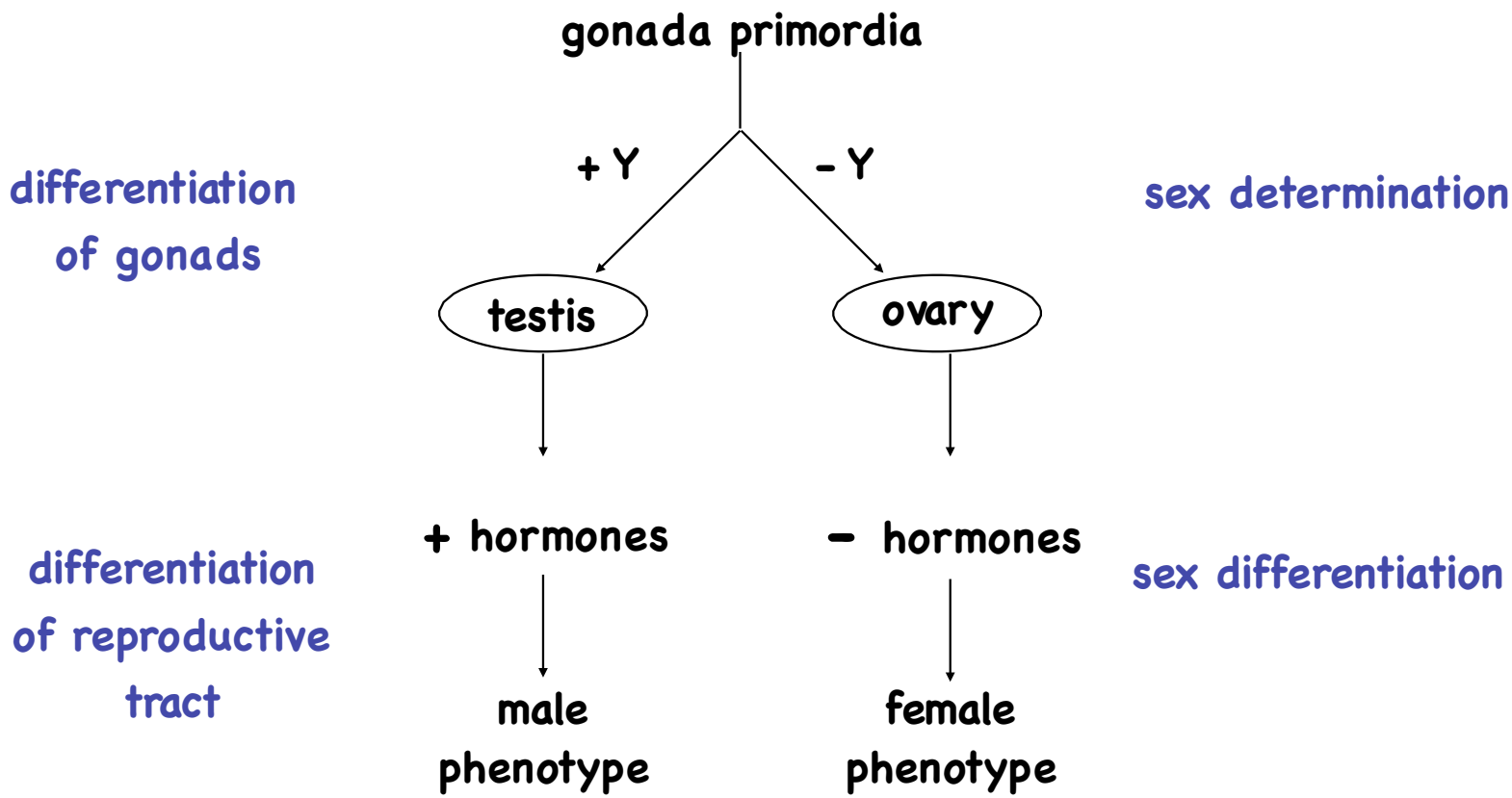
- During male meiosis, the X and the Y chromosome align and genetically recombine at the pseudoautosomal region (gray).

- Abnormal exchange, in which recombination occurs outside the pseudoautosomal region, leads to transfer of some Y chromosomal DNA to the X chromosome. If the Y chromosomal DNA contains the testis-determining gene SRY, the fertilization of an X-bearing oocyte results in and XX male.

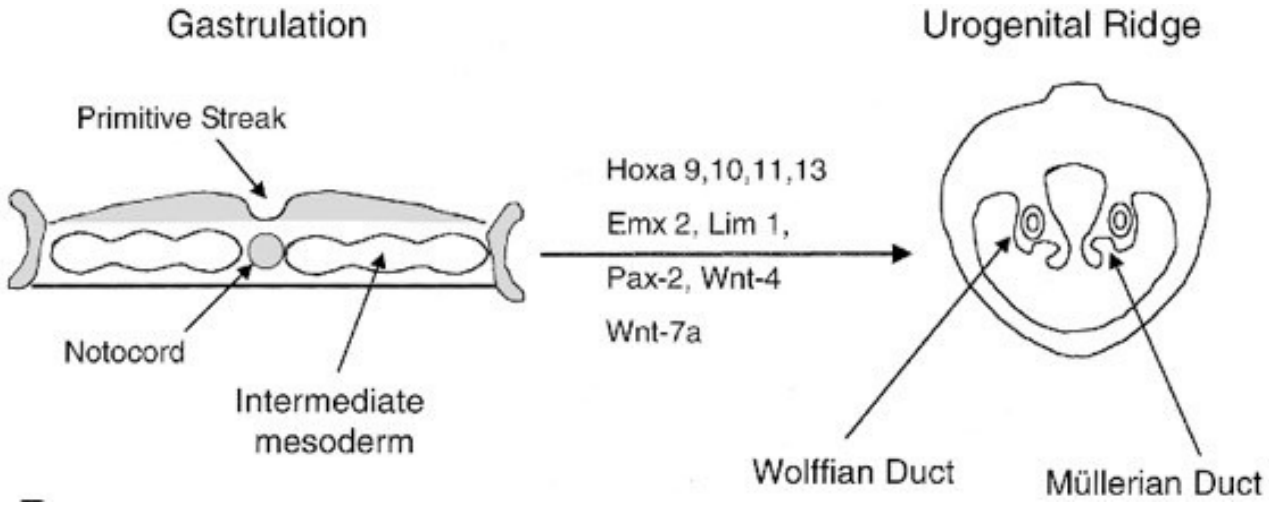
SRY is the male determination factor



SRY encodes a Zn-finger transcription factor that is expressed only in gonadal tissue, independent of the presence of germ cells


gonada primordia
+ Y
- Y
testis
ovary
+ hormones
- hormones
male phenotype
female phenotype
differentiation of gonads
sex determination
differentiation of reproductive tract
sex differentiation

Formation of the urogenital ridge in the embryo

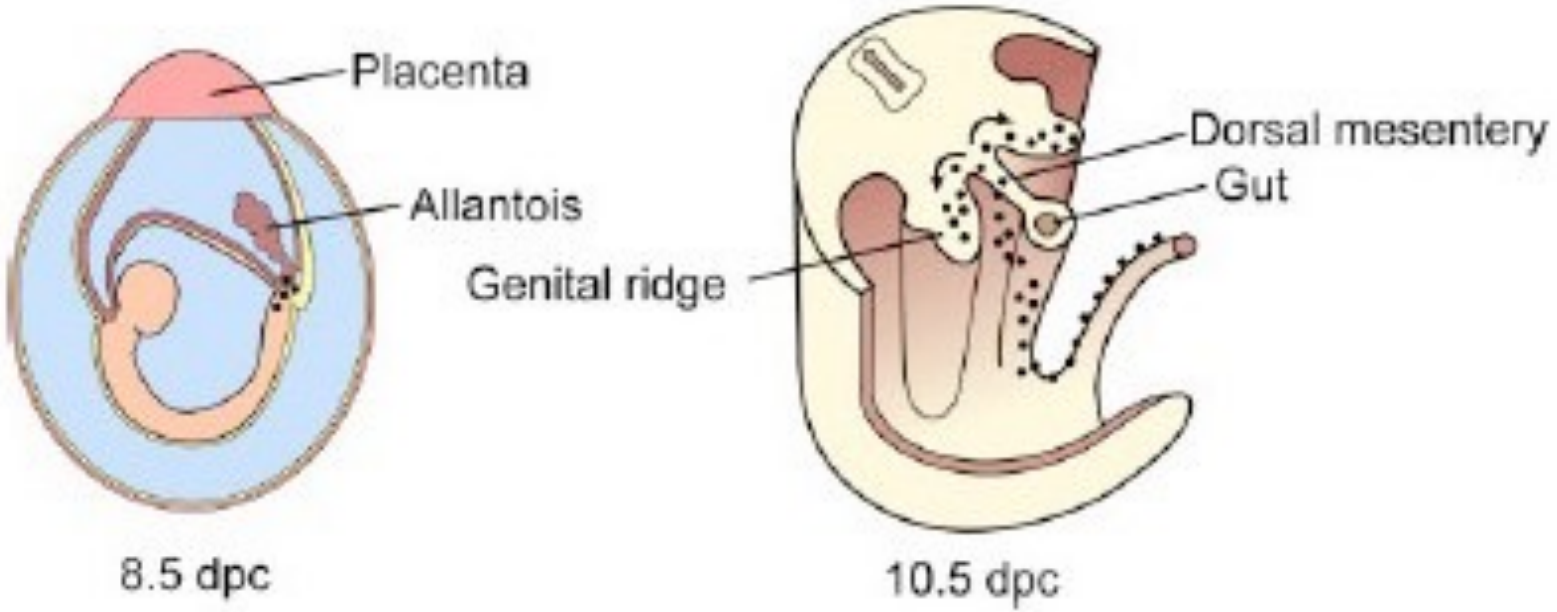


The intermediate mesoderm develops into the urogenital ridge in the embryo.

The urogenital ridge sets the stage for later differentiation into: gonads, Wolffian and Müllerian ducts.

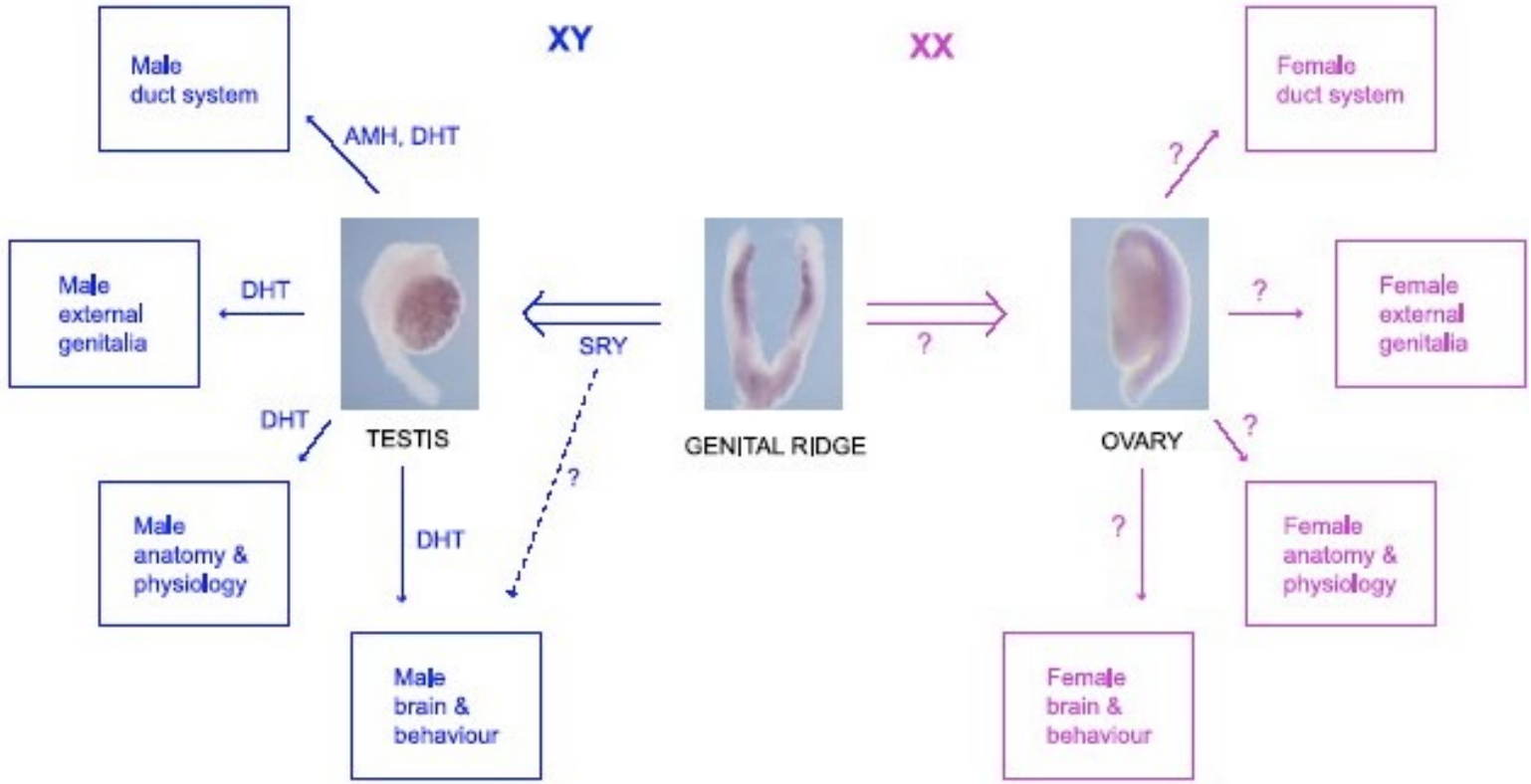
Under the control of several sex-independent genes, the ridge takes shape awaiting the sex-dependent signals that will evoke gonadal identity and the subsequent reproductive duct growth.

Migratory path of primordial germ cells



- Primordial germ cells (black dots) at the base of the allantois around the hindgut pocket in an 8.5 dpc mouse embryo and their migration along the hindgut, dorsal mesentery, and into the genital ridges in a 10.5 dpc embryo.

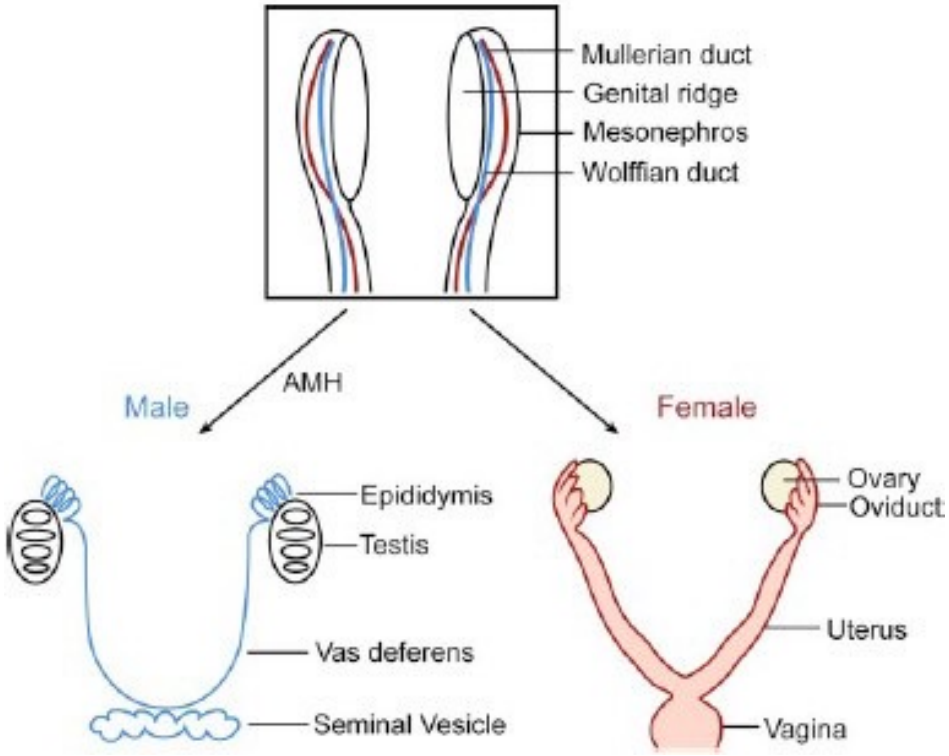
Development of sexual phenotypes



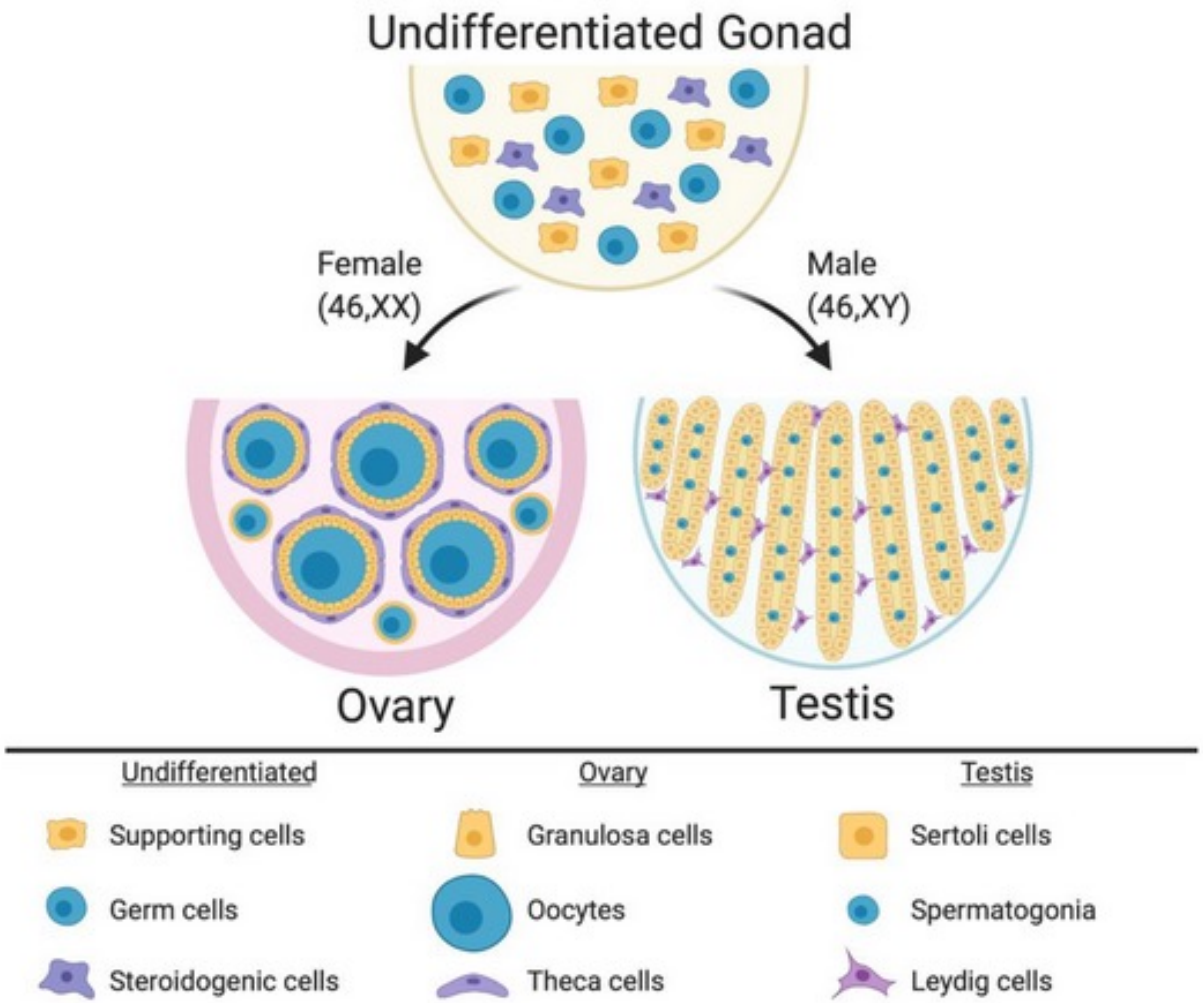
The differentiation of the bipotential genital ridge into a testis requires the Y-encoded gene SRY. Subsequently, hormones such as androgens and anti-Müllerian hormone (AMH) produced by the developing testis direct the development of all genital organs: secondary sexual differentiation. In the absence of SRY, all sexual differentiation follows the female pathway.

DHT: 5α-dihydrotestosterone

Development and Differentiation of the genital duct system



Sex Differentiation: gonads



Estermann MA, Smith, CA, Int. J. Mol. Sci. 2020, 21(18), 6614

The testis, the male primary reproductive organ, contains three types of cells

the GERM CELLS or GAMETES,

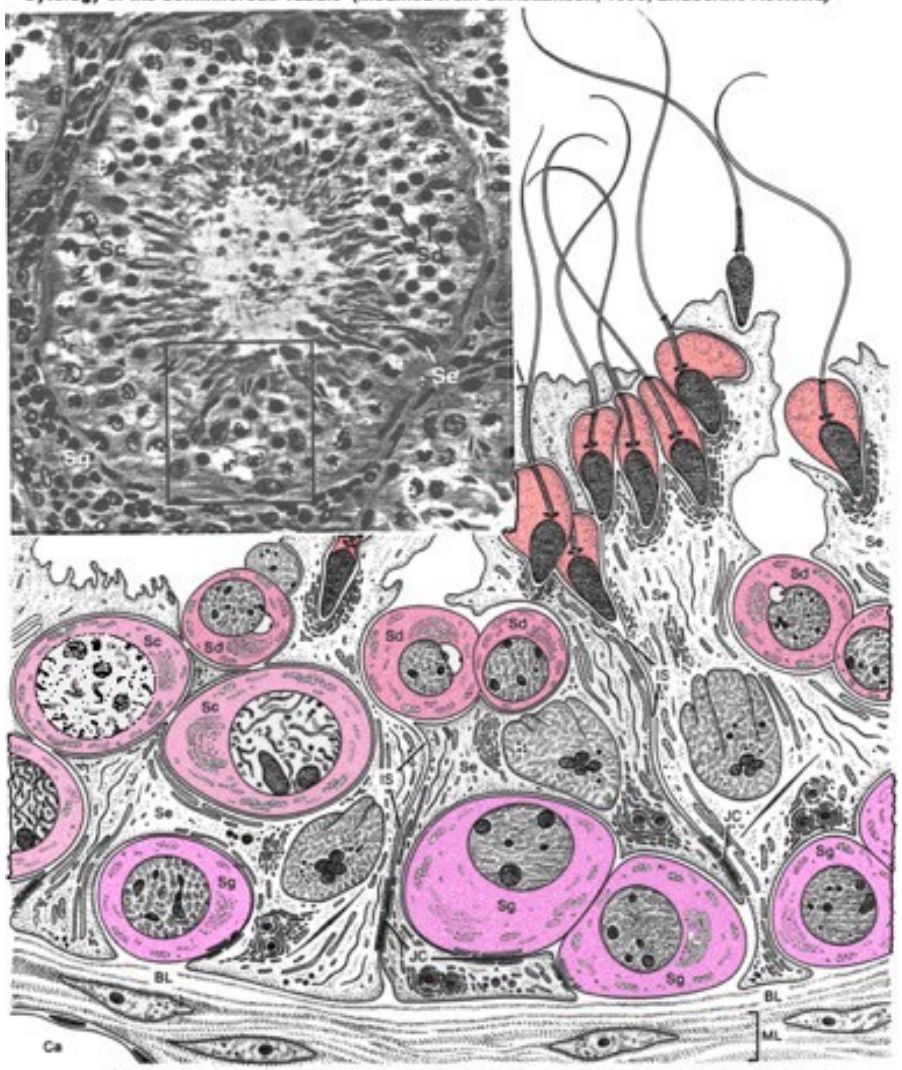
involved in fertilization.

the INTERSTITIAL CELLS of LEYDIG
that secrete testosterone, the major androgen

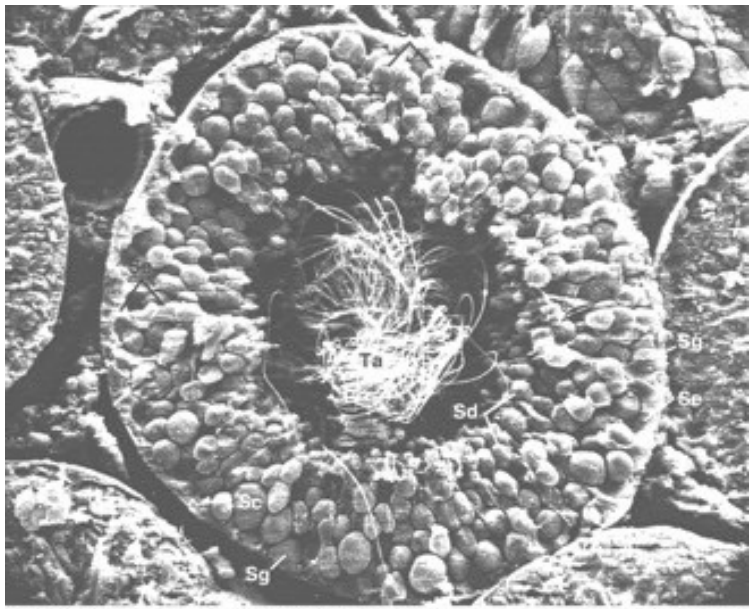
the SERTOLI CELLS
with secretory and reproductive functions

Testicular histology

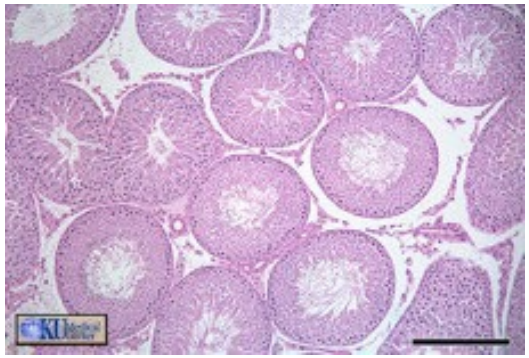
Cytology of the Seminiferous Tubule (Modified from Christiansen, 1996, *Endocrine Reviews*)



BL = Basal lamina; ML = Myoid cell layer; Ca = Capillary; JC = Junctional complex, tight junction; IS = Intercellular spaces; Se = Sertoli cell; Sg = Spermatogonia; Sc = Spermatocyte; Sd = Spermatid



Scanning electron micrograph of a transverse section of a rat seminiferous tubule. Sertoli cells, Se, serve to nuture germ cell stages from spermatogonia, Sg, through spermatocytes, Sc, and spermatids, Sd, to fully differentiated spermatozoa whose tails, Ta, can be seen in the tubule lumen. Leydig cells would lie in the spaces between tubules along with blood vessels and lymphatics. Image by Kent Christensen, University of Michigan.

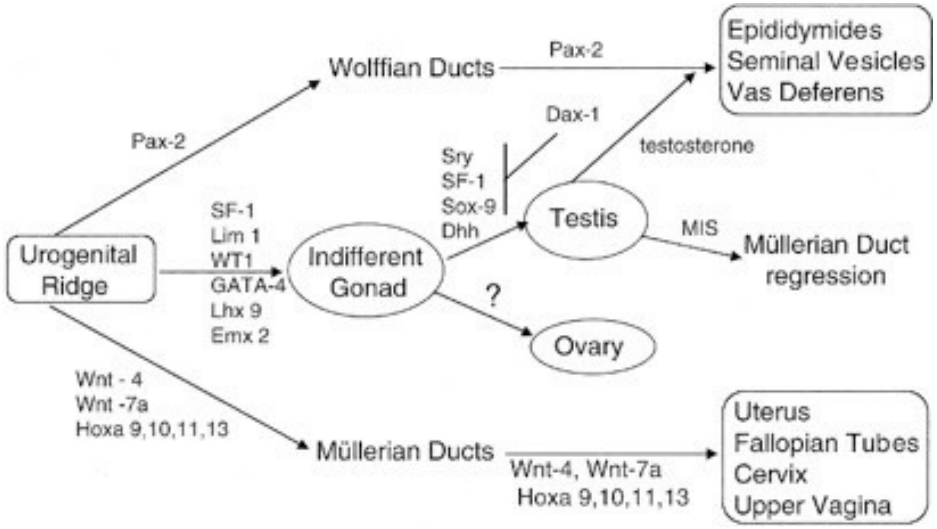


Germ Cells

- XY gonads: germ cells are not required for the development of the testis
- XX gonads: germ cells are essential for the formation and maintenance of follicles

- Differences in cell cycle stage of male and female germ cells:
  - XY gonads: primordial germ cells are in mitotic arrest until birth
  - XX gonads: primordial germ cells enter meiosis around e13.5 and are blocked in prophase until primordial follicles are formed

Gonadogenesis and reproductive duct development



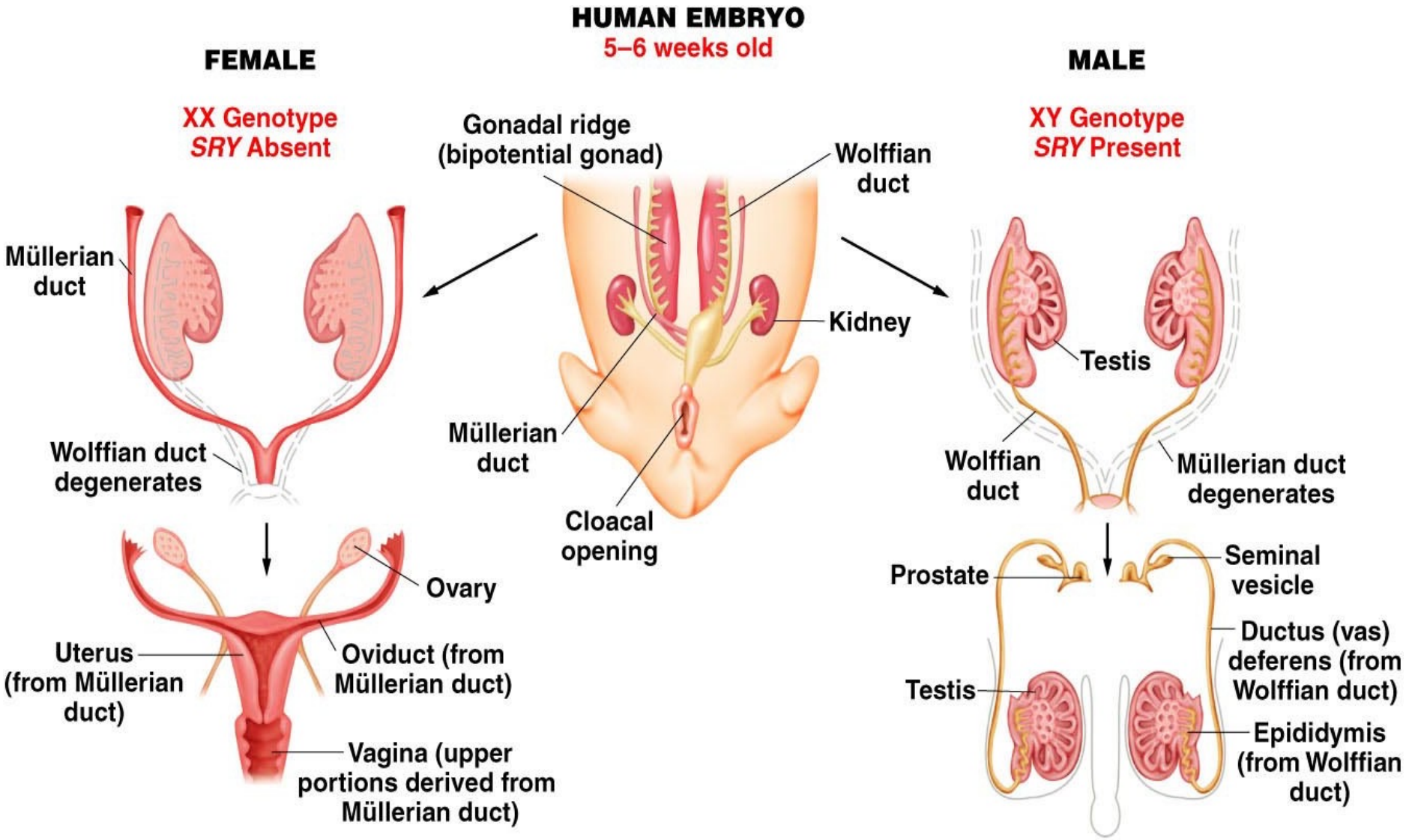
At least six gonad-determining genes (SF-1, Lim 1, WT-1, GATA-4, Lhx 9, and Emx2) direct the formation of the indifferent gonads from the intermediate mesoderm.

Absence of any of these genes blocks gonadal development.

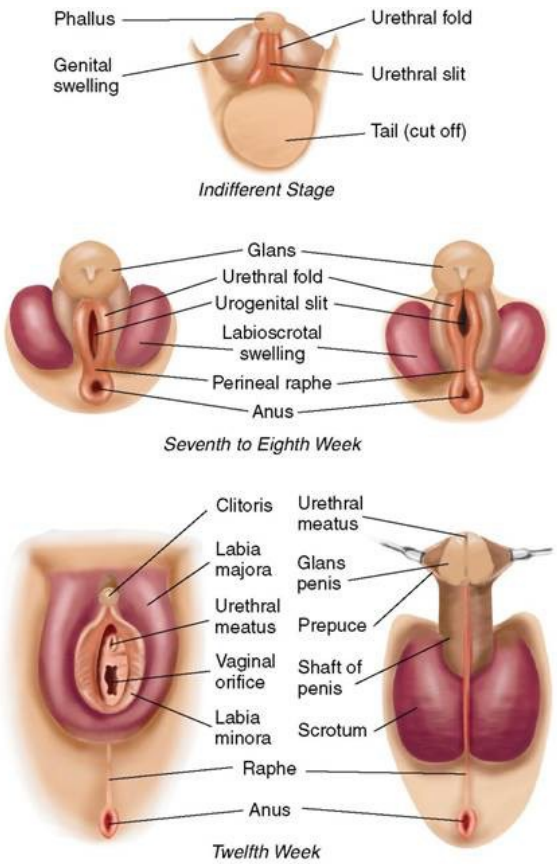
Thereafter, in males the genes necessary for normal testes, SRY, SF-1, Sox-9, and Dhh act to produce the gonad.

The secretion of testosterone and MIS ensure the development of the normal male phenotype.

In females, on the other hand, the lack of male determining genes allows for the development of ovaries. Wnt-4, -7a, and several of the Hoxa genes promote the proper growth and development of the Fallopian tubes, uterus, cervix, and vagina.


HUMAN EMBRYO
5–6 weeks old
FEMALE
XX Genotype
SRY Absent
MALE
XY Genotype
SRY Present
Gonadal ridge
(bipotential gonad)
Wolffian
duct
Müllerian
duct
Kidney
Müllerian
duct
Wolffian duct
degenerates
Cloacal
opening
Testis
Wolffian
duct
Müllerian duct
degenerates
Ovary
Uterus
(from Müllerian
duct)
Oviduct (from
Müllerian duct)
Vagina (upper
portions derived from
Müllerian duct)
Prostate
Seminal
vesicle
Ductus (vas)
deferens (from
Wolffian duct)
Testis
Epididymis
(from Wolffian
duct)

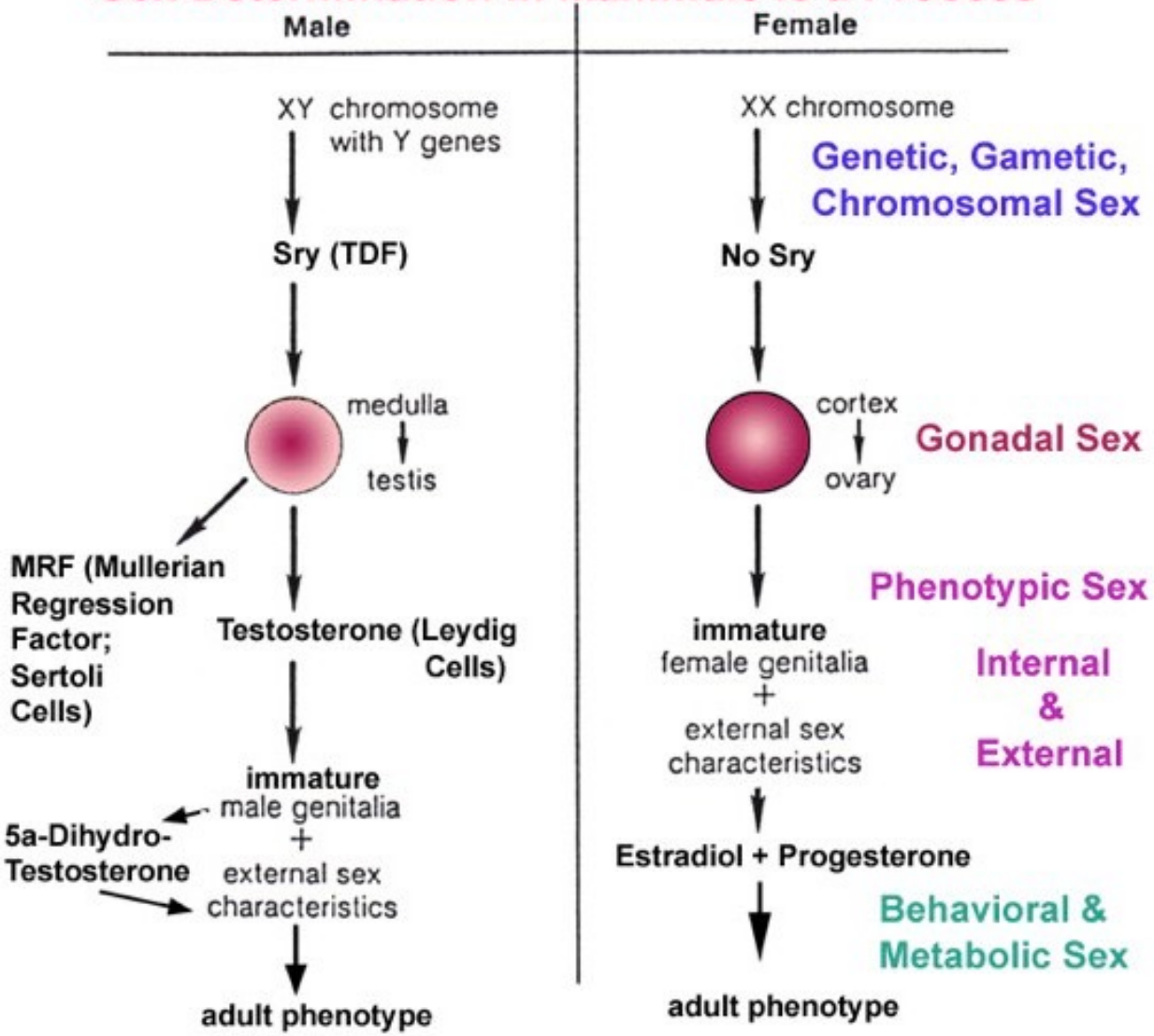
Differentiation of External Genitalia:



- Clitoris
- Labia
- Outer vagina:

- Penis
- Scrotum

Sex Determination in Mammals Is a Process



Genes of early sex differentiation

- SF1: steroidogenic factor 1, nuclear receptor which regulated expression of steroid hydroxylases
- WT1 Wilm' s tumor locus (Chr 11p13)
- SOX-9
- Müllerian inhibiting substance (MIS) product of Sertoli cells
- Dosage sensitive sex (DSS) reversal locus on the X chromosome contains DAX-1
- DAX-1 nuclear hormone receptor

Development of external genitalia in males

Testosterone

↓ 5 α-reductase

DHT

(dehydrotestosterone)

↓

Development of penis and scrotum

16-week- old fetus

Male Urogenital System

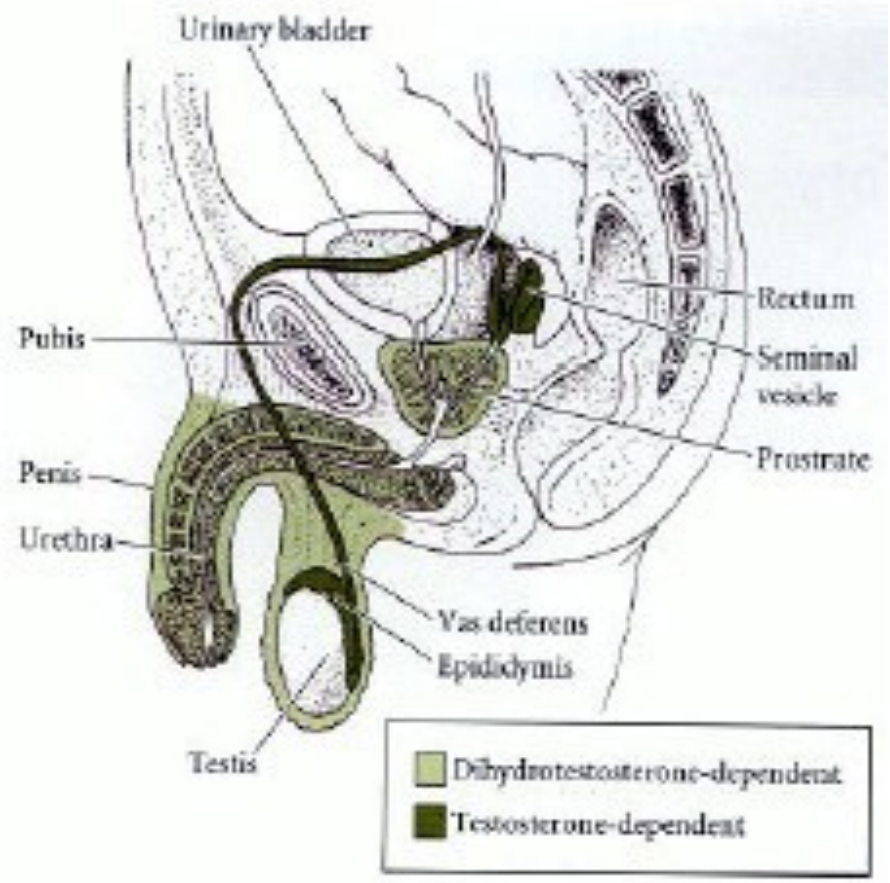
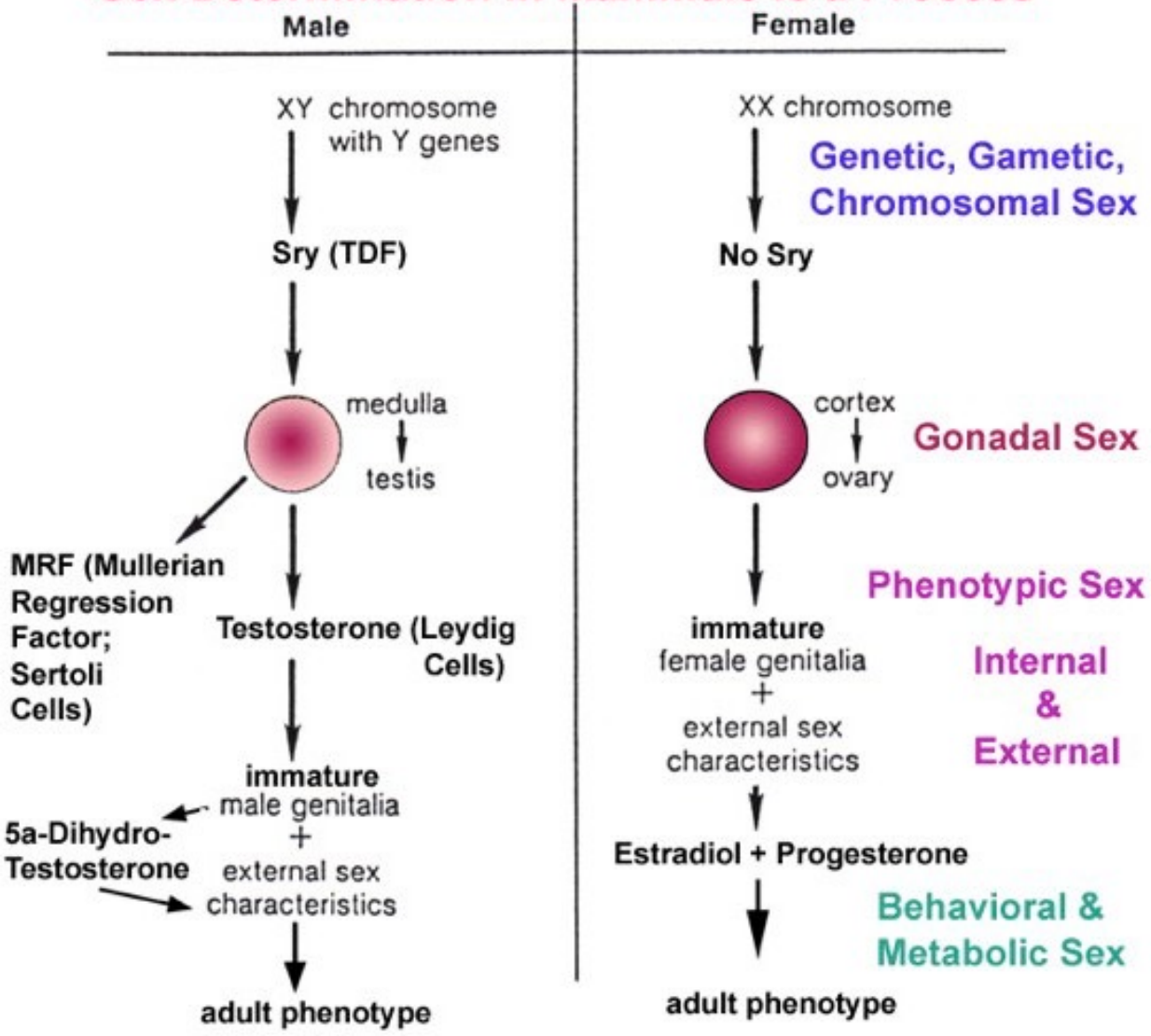


Figure Testosterone- and dihydrotestosterone-dependent regions of the human male genital system. (After Imperato-McGinley et al. 1974.)

Testosterone (T) and Dihydroxytestosterone (DHT)

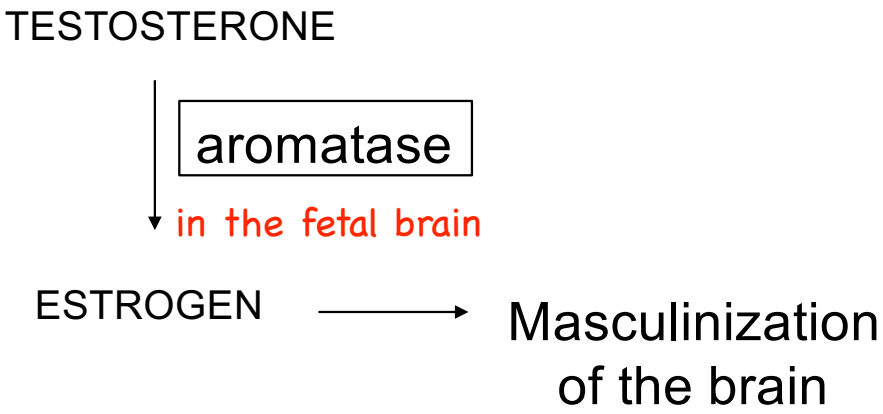
- DHT is synthesized from testosterone in target tissues by 5α reductase type II
- T and DHT bind to AR
- DHT is 3-5x as potent as T
- Wolffian derivatives are T-dependent
- External genitalia require DHT for masculinization

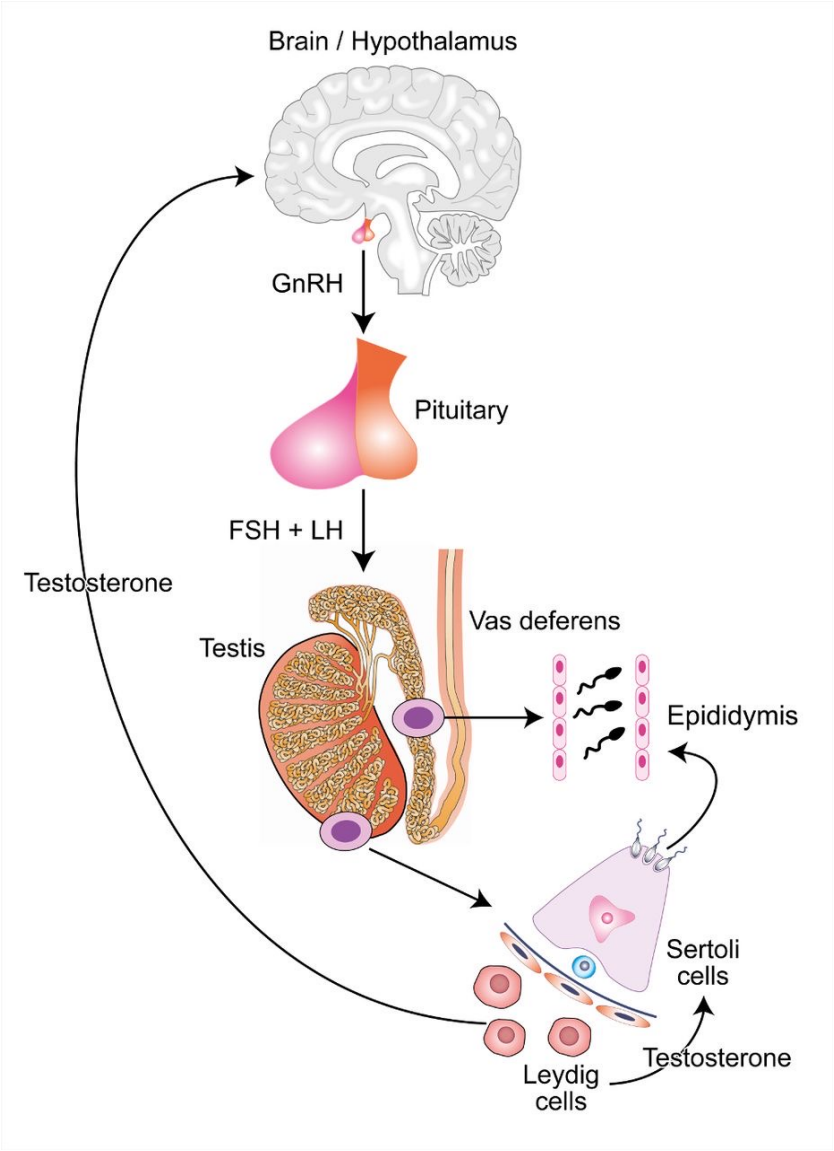
Sex Determination in Mammals Is a Process



Sexual differentiation of the brain

at 6 months of gestation



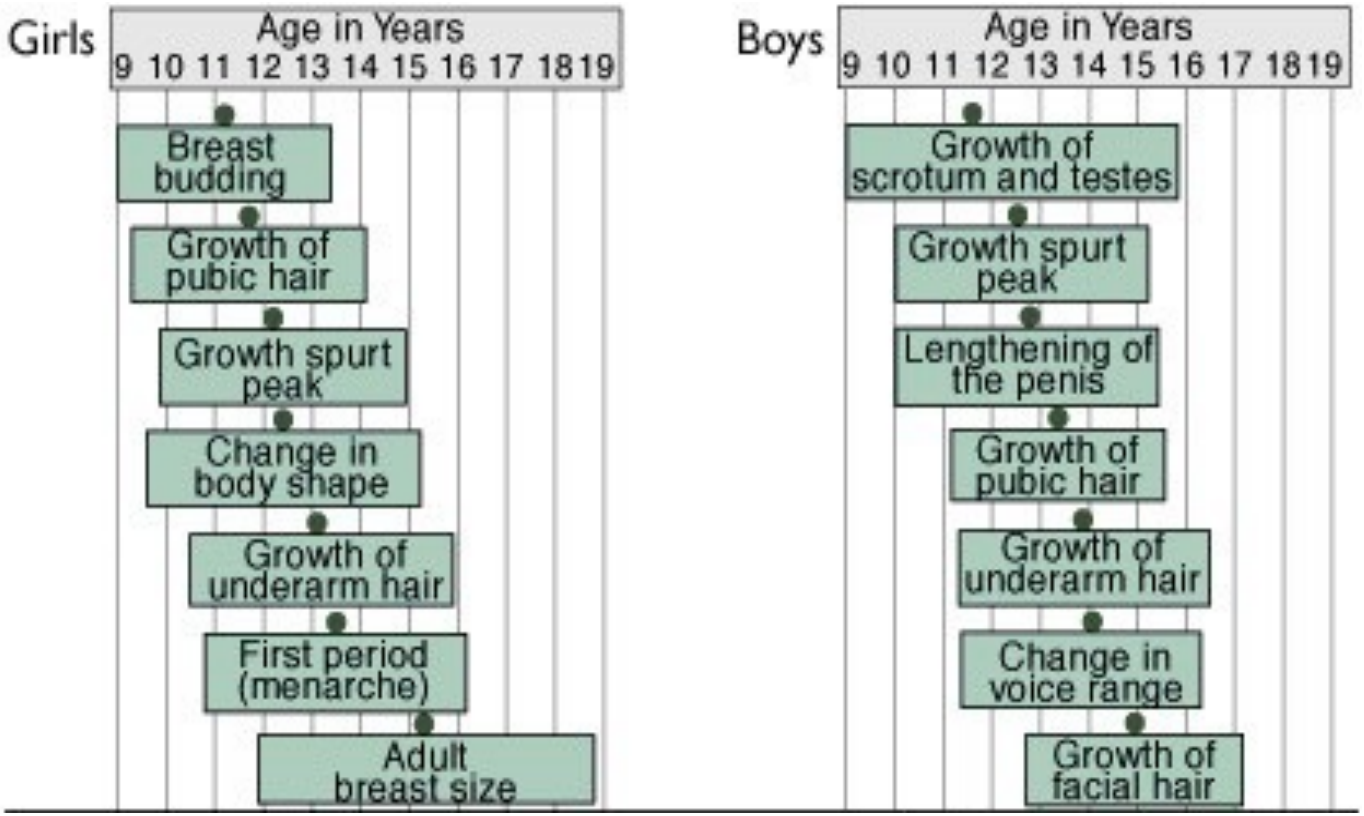


Male reproductive endocrinology:

The hypothalamus releases GnRH into the circulatory system and, through blood, directly into the pituitary.

GnRH triggers the release of the pituitary LH and FSH that stimulate the testes to testosterone secretion and sperm production.

Changes during puberty



Normal Pubertal Milestones

Females:

Breasts: age 9-11

Pubic hair: age 8-9

Growth spurt: 12

Menses: age 12

Males:

Testes: age 10-11

Pubic hair: age 10-11

Penile growth: age 13

Growth spurt: age 14

Delayed Puberty

No breast development: age 13

No menses: age 15

No testes development: age 14

Chromosomal mutations and nondisjunctions

Mistakes of meiosis

- 1 in 200 infants has a chromosomal abnormality
- 28% of first trimester miscarriages have a chromosomal abnormality
- abnormalities in larger chromosomes are not compatible with survival

Down syndrome Trisomy 21

Cri-du-chat syndrome Microdeletion 5p15.2

Cytogenetic Abnormalities

- 45 0X, Turner syndrome
  - Ovarian agenesis, dysgenesis
- 47 XXY Klinefelter syndrome
  - Testicular dysgenesis, hypogonadism
- 47 XYY or 48 XYYY supermales (1/1000)
  - Normal sexual development
- 47 XXX, 48 XXXX, 49 XXXXX super females
  - Normal ovarian function

Turner Sydrome

45 X karyotype

1 in 5000 women

No germ cells, abnormal ovaries

Genetic transmission during meiosis or mitosis

Female genitals

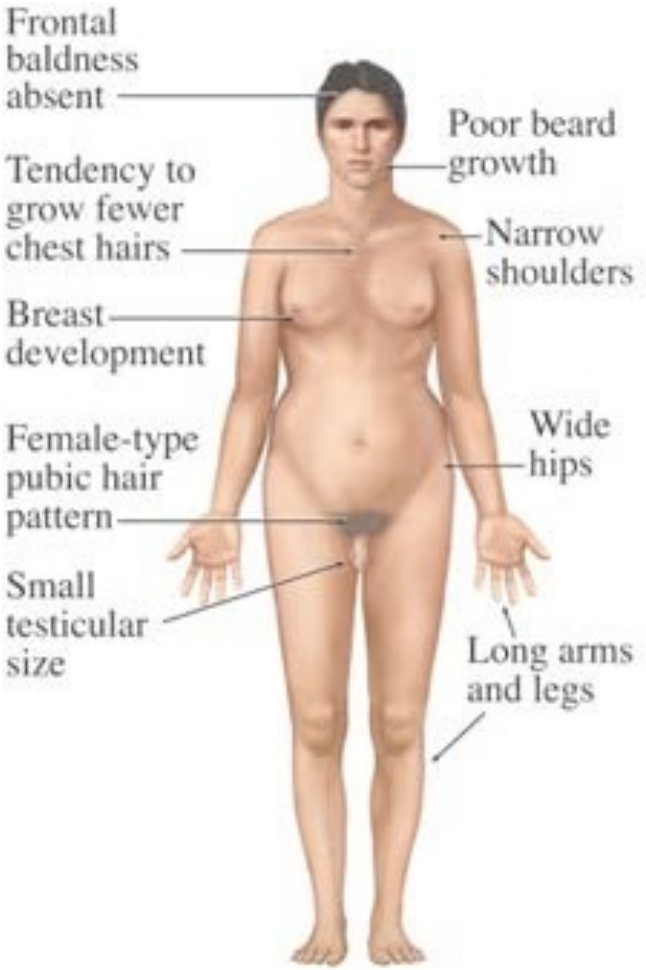
Reduced height

Webneck

Decreased estrogen levels

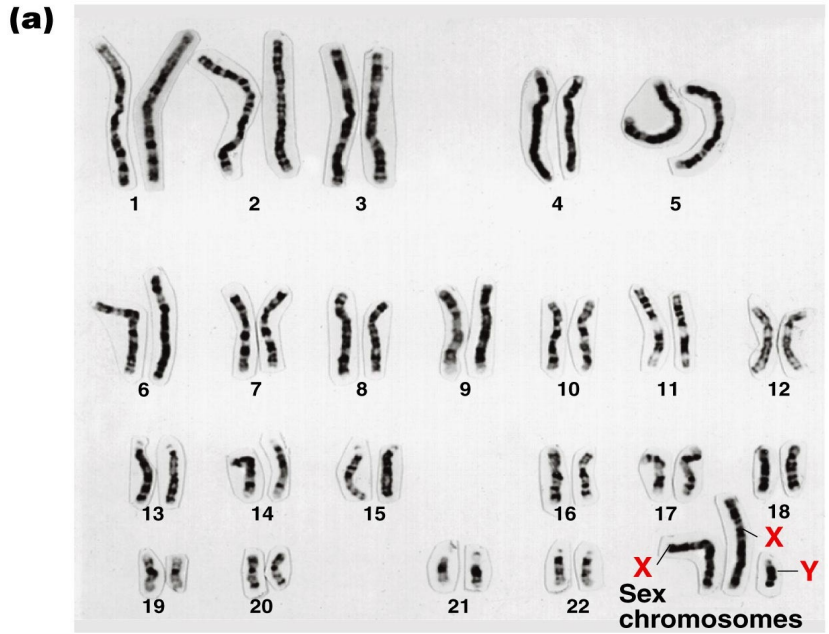
Increased LH and FSH levels

Klinefelter Syndrome



http://all4freehere.com/2009/07/what-is-klinefelters-syndrome/

- male genitalia
- more than 1X chromosome



Abnormalities of sex differentiation

- Hermaphrodism (rare):
  - Presence of both functional testicular and ovarian tissue.
  - True intersex: possess both male and female sexual development.

- Pseudohermaphrodism:
  - Describes either abnormal male or female sexual development!

Hermaphrodism with mosaicism 46XX/XY

- normal male sex hormone levels!
- phallus 3 cm
- hypospadia
- left; half-uterus, ampulla, ovary
- right: ovotestis

Female pseudohermaphroditism

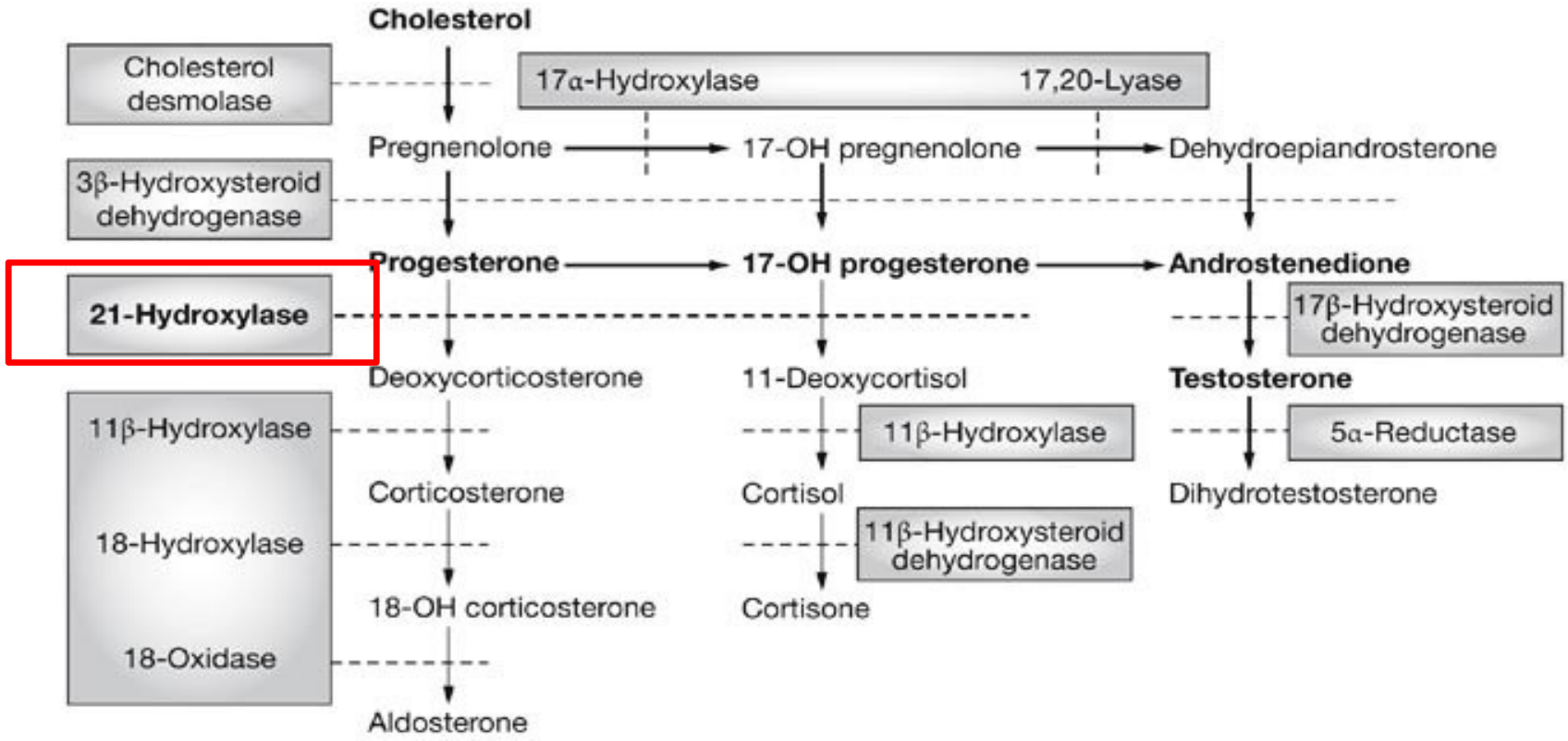
male phenotype in 46, XX individual

- excess fetal androgens : congenital adrenal hyperplasia
- – 21-hydroxylase deficiency
- - 11 β–hydroxylase deficiency
- - 3 β–hydroxysteroid dehydrogenase deficiency

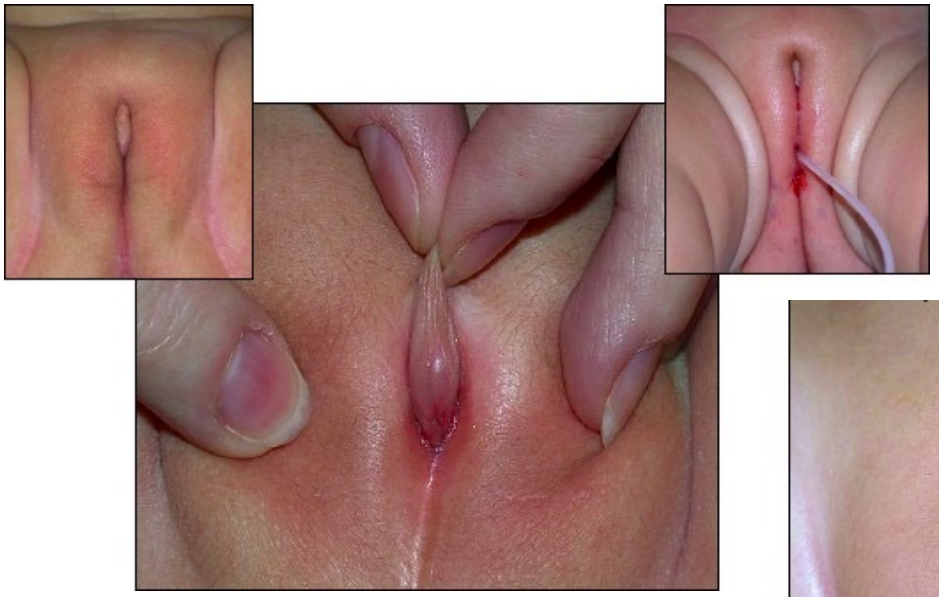
- increased androgen production from maternal origin

- excess androgen production by placenta: aromatase defect

Congenital Adrenal Hyperplasia
21-Hydroxylase Deficiency:



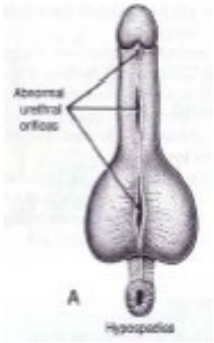
Female pseudohermaphrodism due to congenital adrenal hyperplasia



Female pseudohermaphrodism due to congenital adrenal hyperplasia

Incomplete masculinization of external genital organs

MacLaughlin and Donahoe 2004 New Engl. J. of Med.



hypospadias

(1/300)

Male pseudohermaphroditism:
female phenotype in 46, XY individual

-Gonads = testicles

-external organs incompletely masculinized

*Causes

abnormalities of testis hormone secretion

anti Müllerian hormone/Müllerian inhibiting substance defects

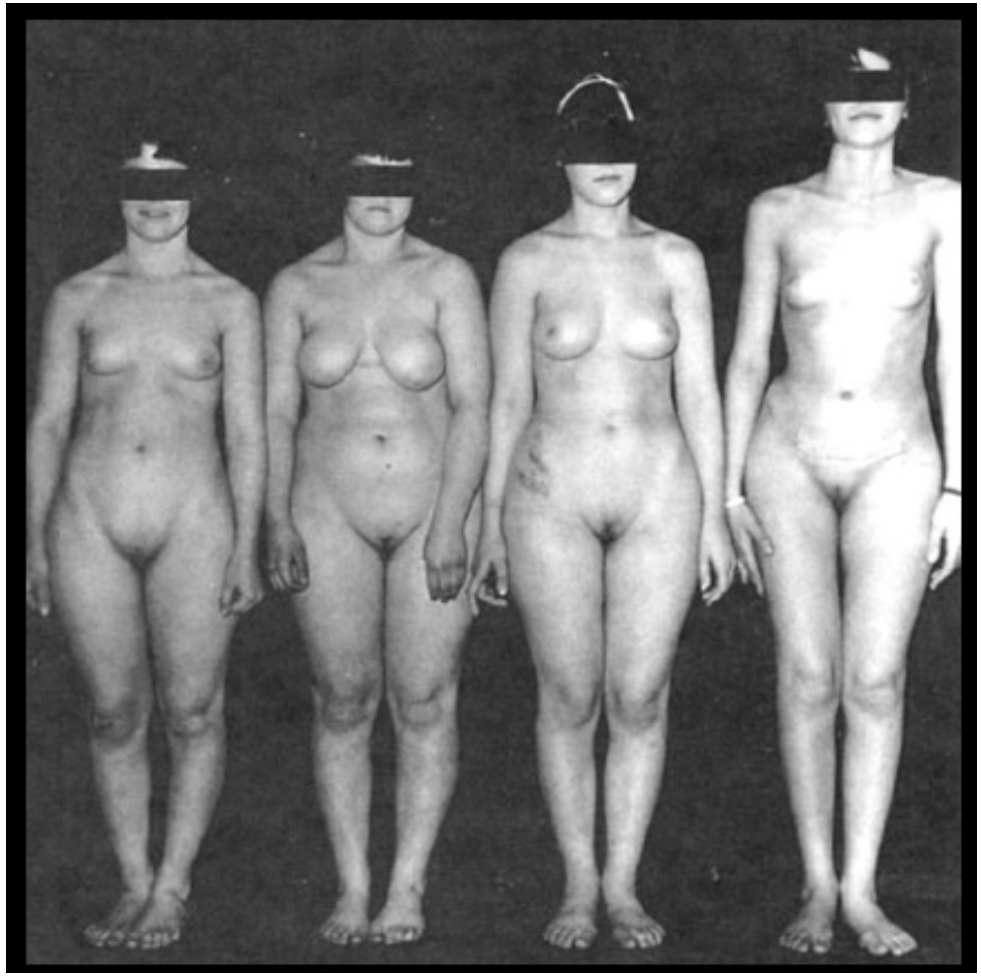
5α reductase deficiency

androgen insensitivity syndrome

maternal consumption of antiandrogenic drugs (e.g. spironolactone)

environmental agents

Testicular Feminization

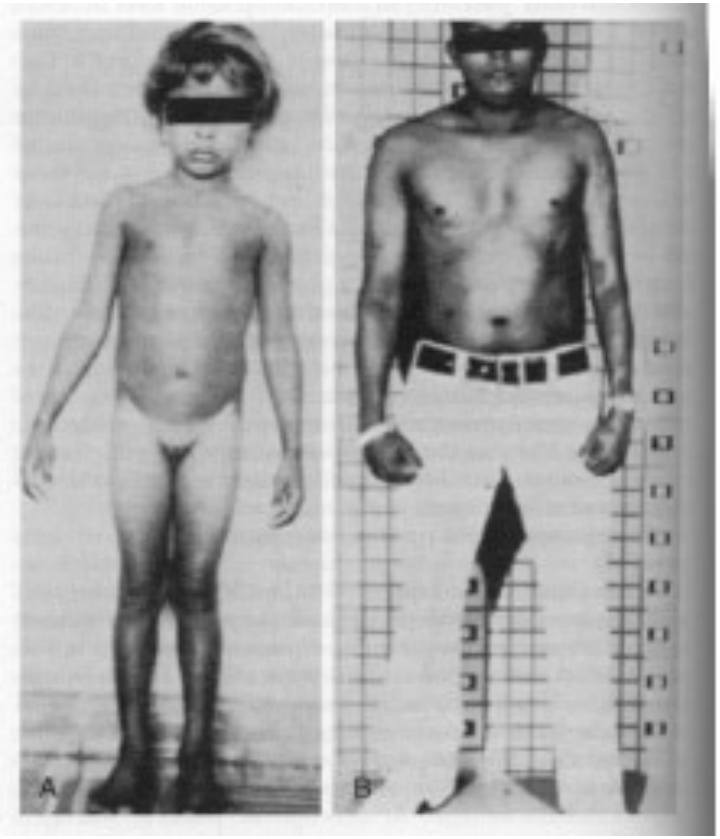


- Testicles
- Cryptorchidism
- Absence of Müllerian duct derivatives
- Secondary female sex characteristics

- Complete resistance
  - androgen receptor not functional
- Partial resistance
  - androgen receptor shows altered function

5α-reductase deficiency

Guevedoche (huevo a las doce)



- female phenotype of external genitalia until puberty
- post pubertal virilization, in cluding in behaviour
- no DHT
- at puberty increased testosterone levels
- Jeffrey Eugenides: Middlesex
- Rolando Sanchez, Guevote (director) The way I feel is how I am Documentary 1996, Caraibes

Cryptorchidism (undescended testes)

- Intraabdominal temperature is toxic for the germ cells
- Testicles descend into the scrotum through the inguinal canal
- Cryptorchidism most common malformation in young boys
- Consequences:
  - Infertility
  - Increased risk of testicular cancer