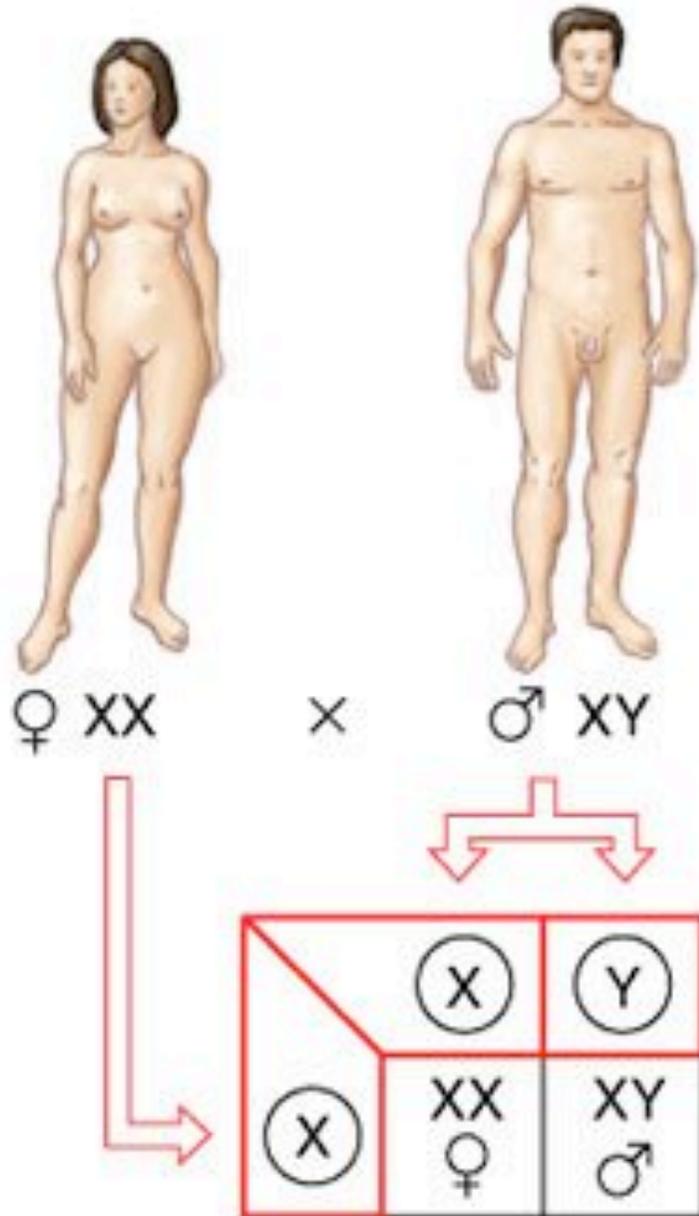


(b)



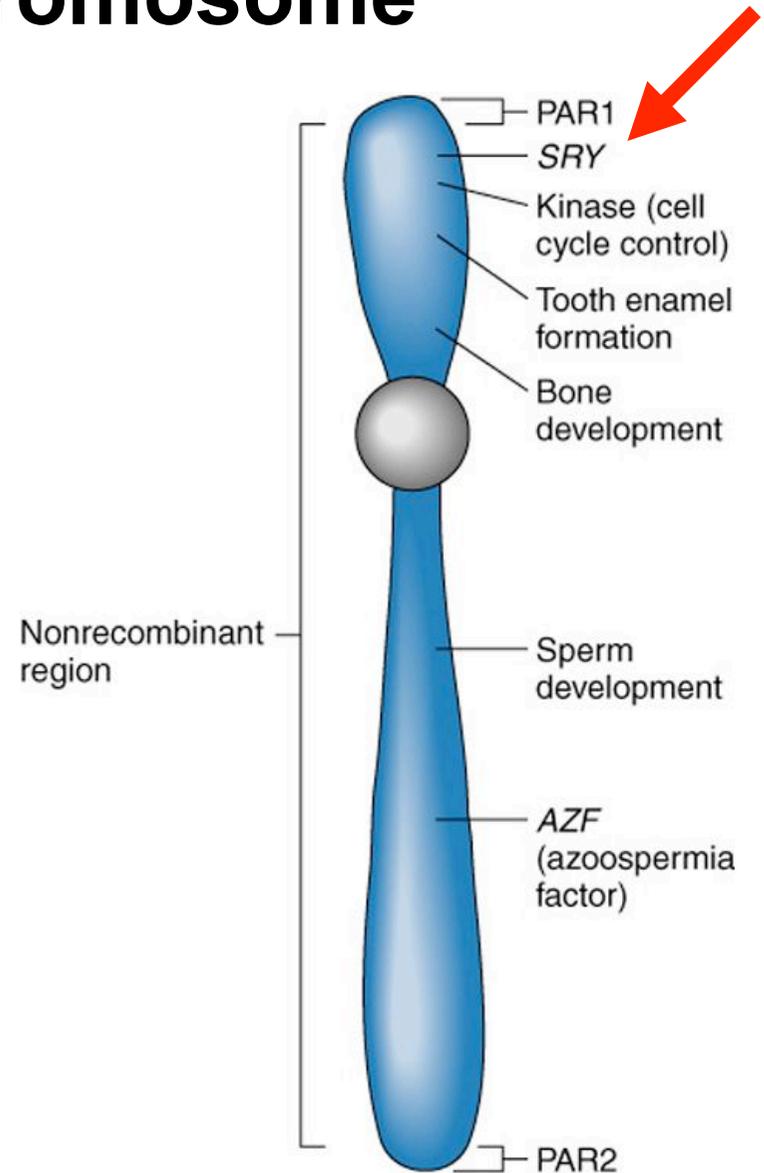
- Sex determination in humans

Genes on the Y chromosome

The Y chromosome contains 78 genes coding for 23 proteins.

The SRY gene (sex determining region Y) is unique to the Y chromosome. It codes for a DNA binding protein that's acts as a transcription factor. It starts male development by:

- - turning on testis-determining genes
- - turning off ovary-determining genes

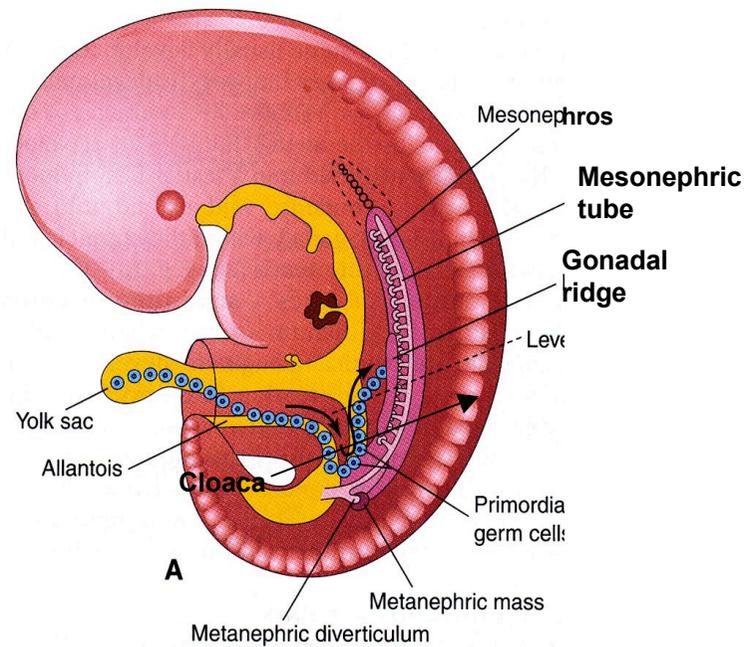


Germ cell migration

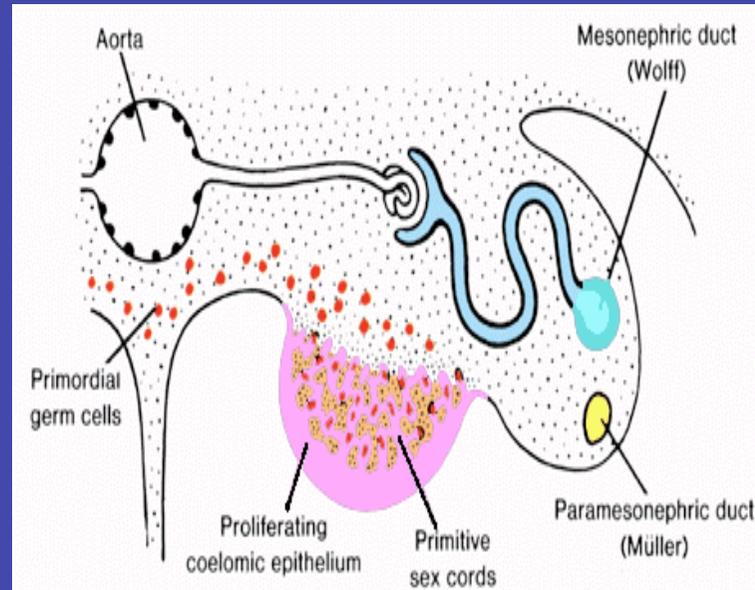
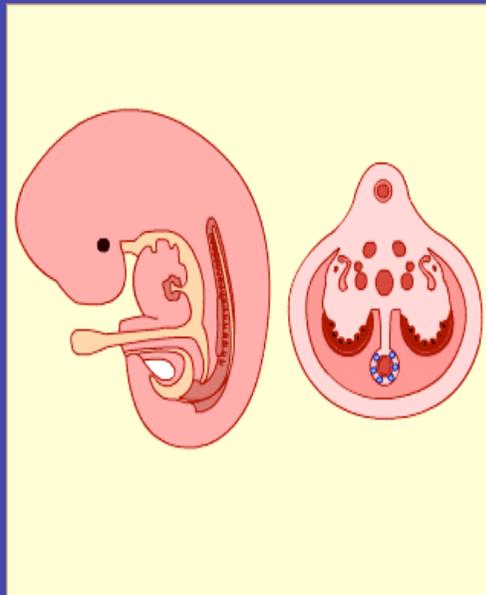
Primordial germ cells (future eggs and sperm) form in the wall of the yolk sac and migrate to the gonadal ridges which lie close to the primitive kidney (mesonephros). The gonads are the ovaries in females and testes in males.



32-day embryo



Gonadal development



During weeks 3-6 of pregnancy the germ cells enter the gonadal ridges. If they contain a Y chromosome with a SRY gene the "indifferent" gonads will develop into testes. The testes will contain (a) germ cells, (b) Sertoli cells which secrete anti-mullerian hormone and (c) Leydig cells which secrete testosterone.

If the germ cells do not contain a Y chromosome the "indifferent" gonads develop into ovaries. They do not contain Sertoli or Leydig cells.

Development of the internal genitalia (weeks 7-10)



Mullerian duct = paramesonephric duct

In the female the absence of anti-Mullerian hormone results in retention of the Mullerian ducts which partly fuse to form the uterine (fallopian) tubes, the uterus and the upper part of the vagina. The lower part of the vagina develops from tissue that grows up from part of the primitive bladder wall.

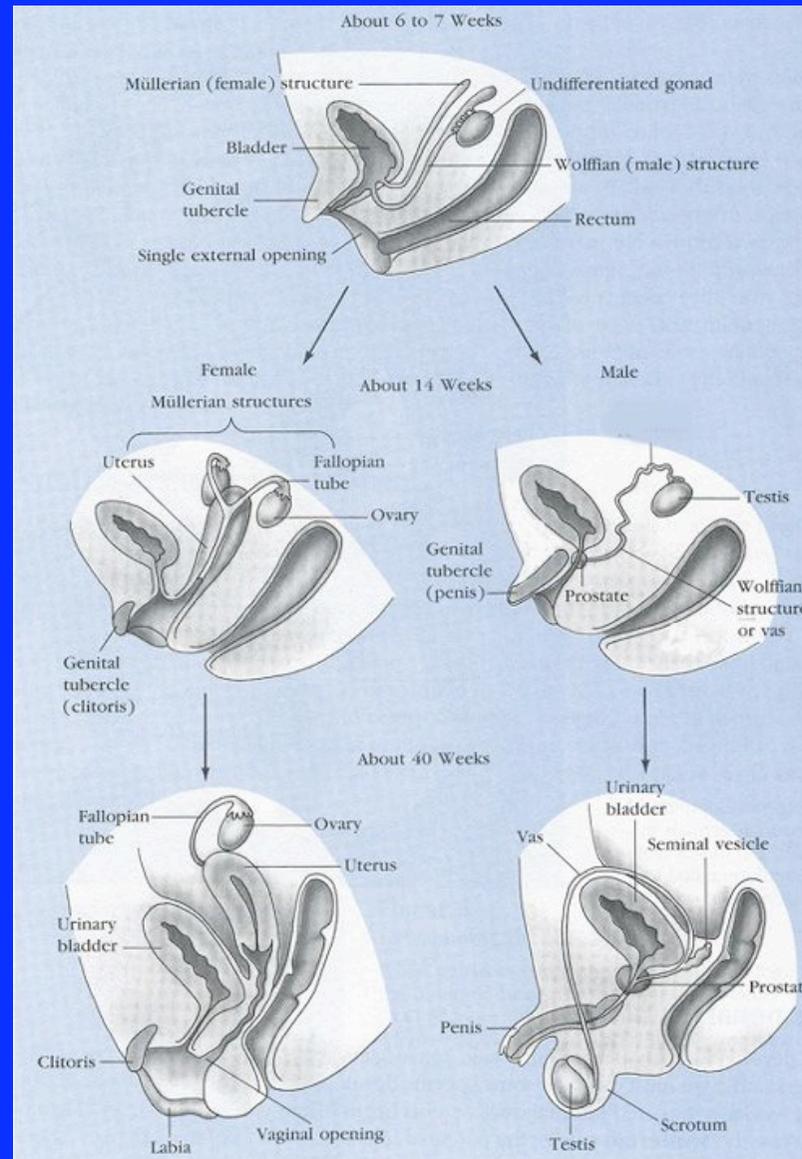
The absence of testosterone results in degeneration of the Wolffian ducts.



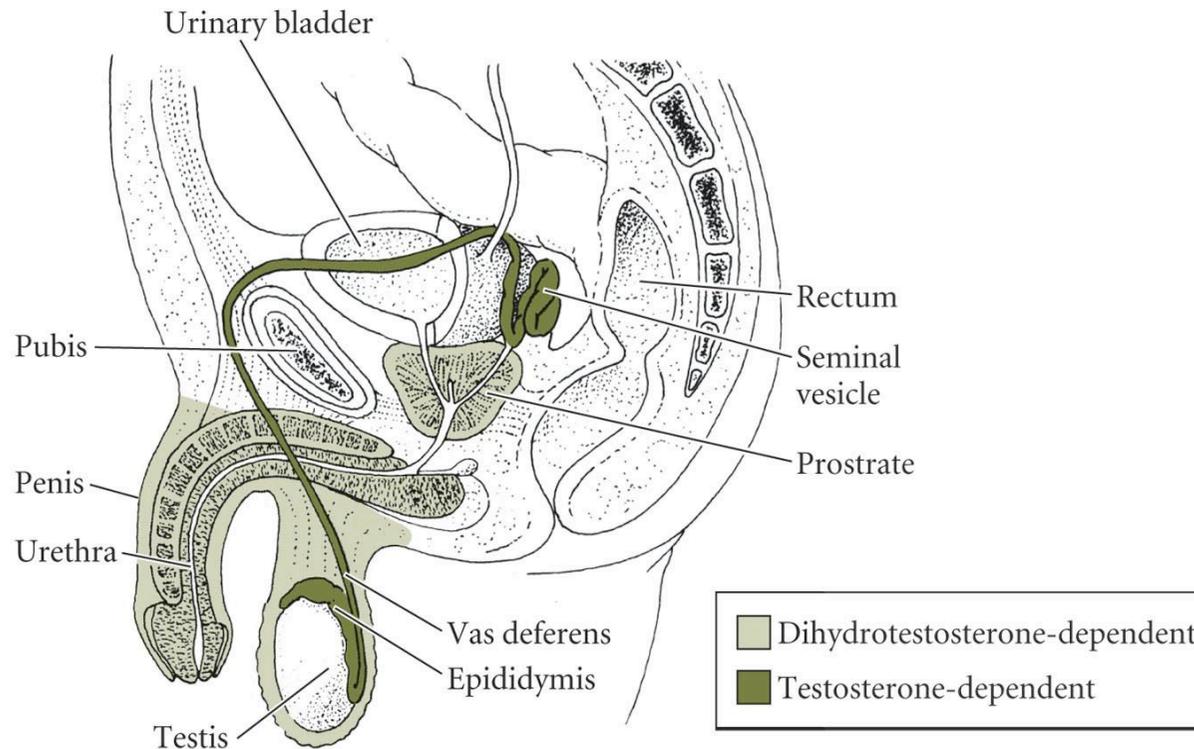
Wolffian duct = mesonephric duct

In the male the Sertoli cells in the testes (gonad) secrete anti-Mullerian hormone causing the Mullerian ducts to degenerate.

The Leydig cells in the testes (gonad) secrete testosterone and this causes the Wolffian ducts to develop into the ductus deferens (vas deferens), epididymis and seminal vesicles.

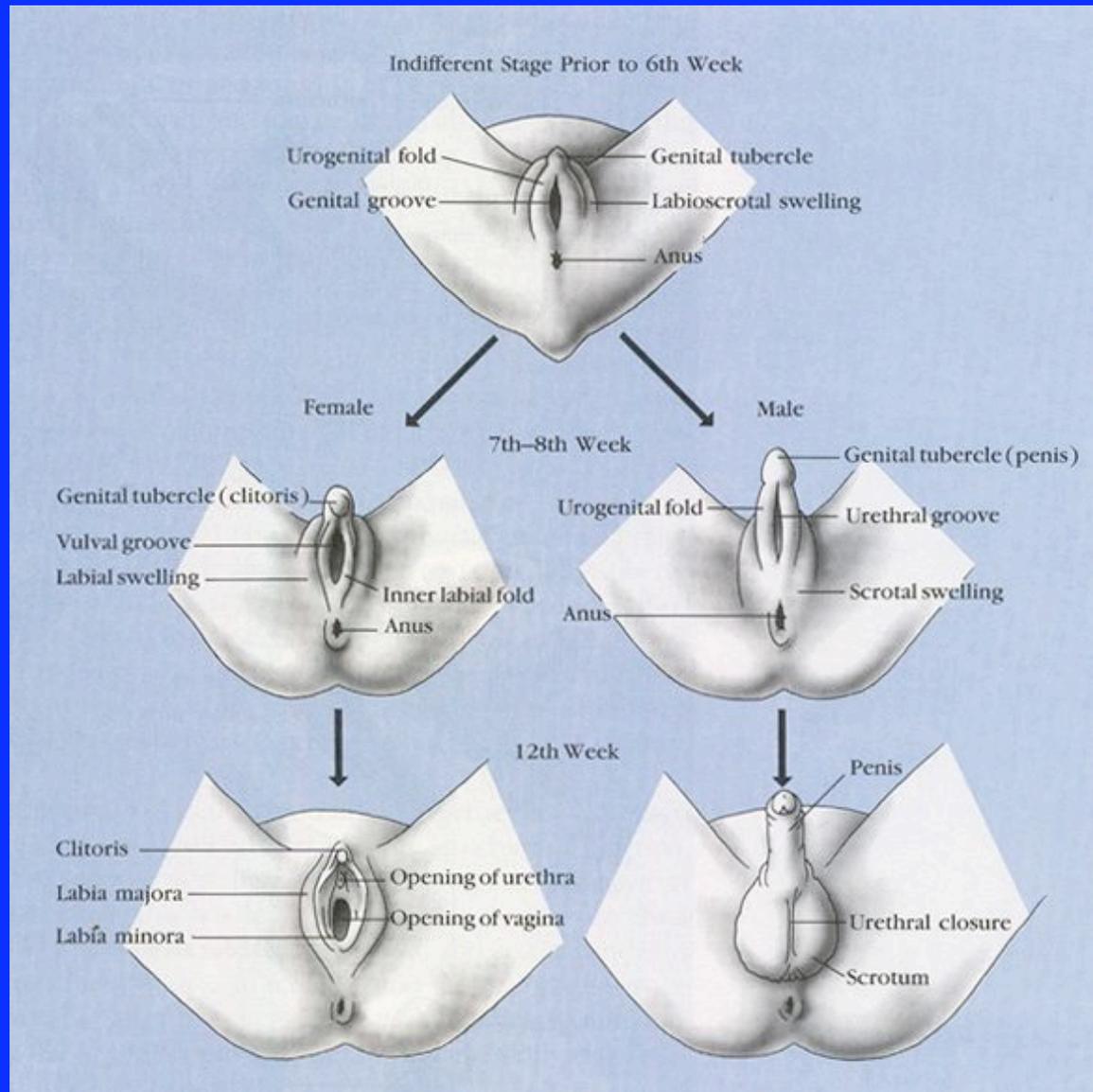


Testosterone and dihydrotestosterone



Testosterone and DHT dependent regions of the human male genital system

Development of the external genitalia



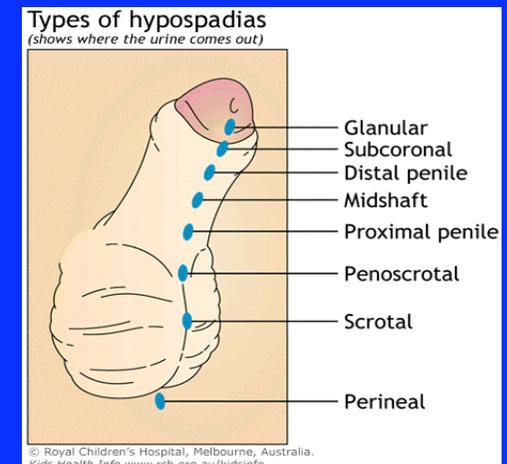
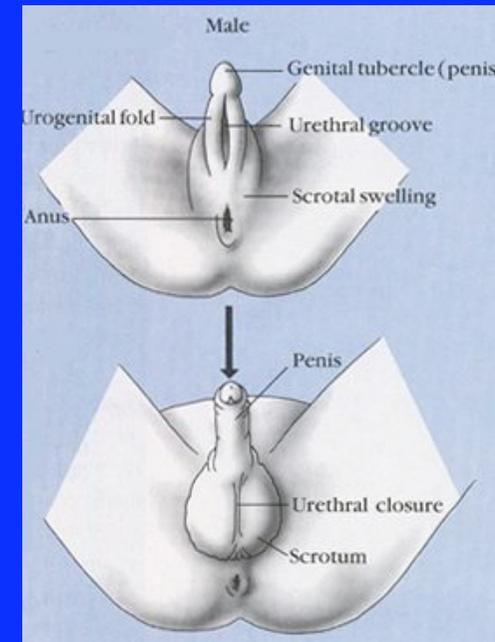
The conversion of the “indifferent” external genitalia into male is dependent on dihydrotestosterone.

This is formed from testosterone by 5α -reductase.

In the absence of this enzyme the external genitalia remain female.

Hypospadias

- If the fusion of the urethral folds fail to progress distally on the ventral penis, the urethra will be shortened.
- Hypospadias occurs when the fusion of the urethral folds stops proximal to the tip of the glans penis.
- Hypospadias can occur anywhere along the urethral groove.
- Seen in about 1:300 births with some evidence of an increase in prevalence in recent years.

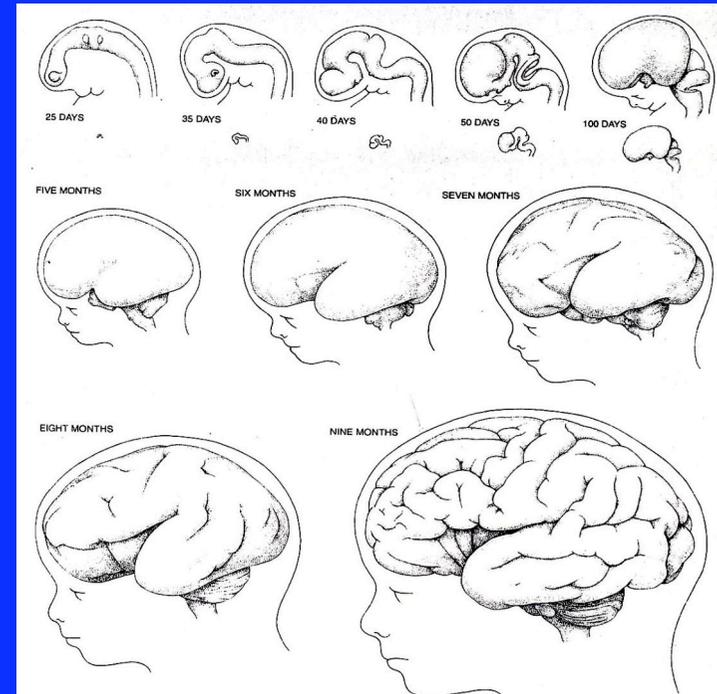


Brain development

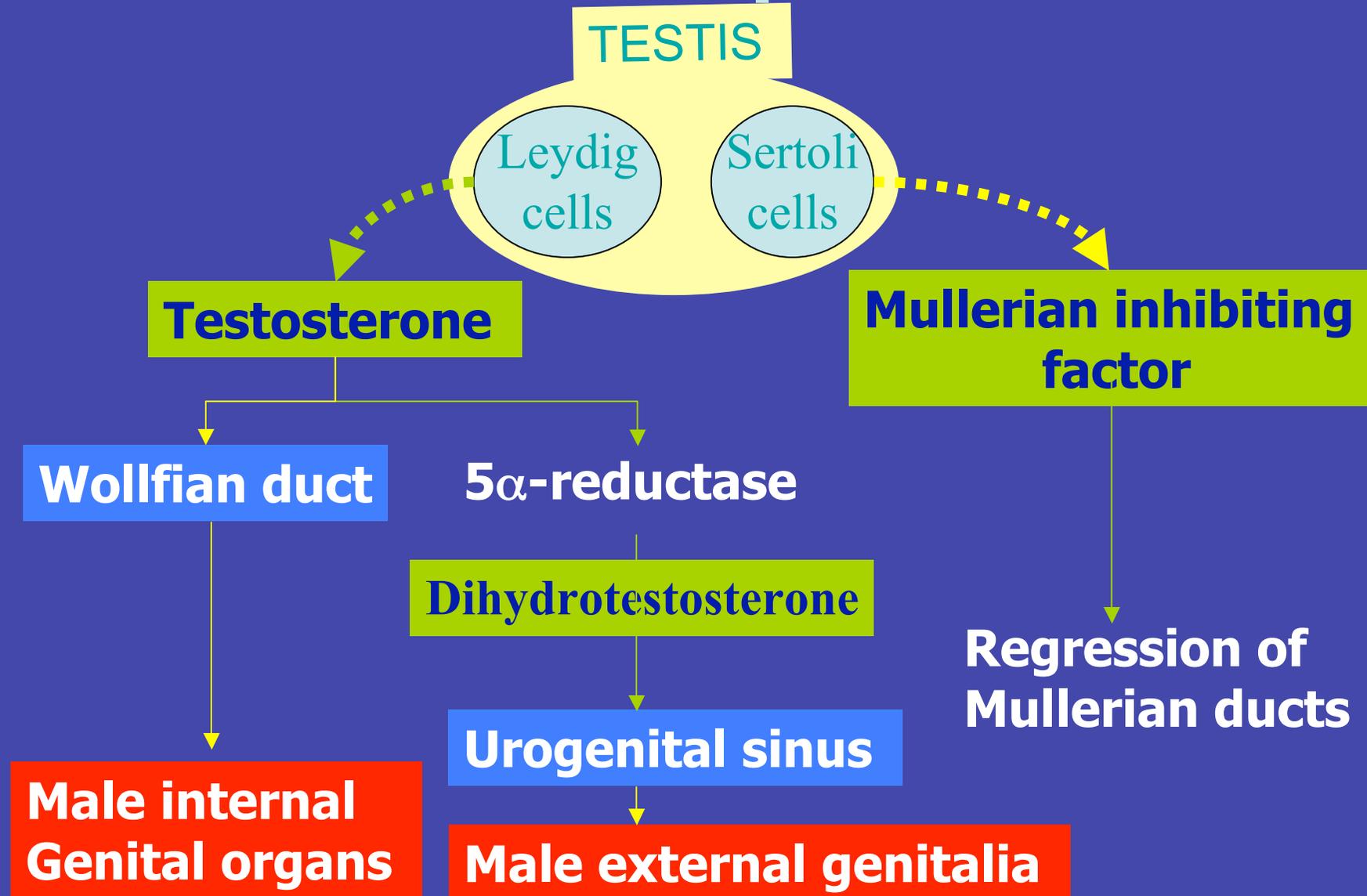
Between weeks 8 to 20 of gestation the male embryo is exposed to high levels of testosterone, peak levels are reached about week 15.

The male embryo is exposed to testosterone levels 6-fold greater than the female as determined by levels in amniotic fluid.

As well as determining internal and external genital development the testosterone is thought to "sex" the brain giving the individual gender identity.



Male development



Female development

Neutral
Development

OVARY

Urogenital sinus



Female external genitalia
· Lower part of vagina

Absence of androgen exposure

Mullerian ducts



**Female internal genital
Organs**
· Most of upper vagina
· Cervix and uterus
· Fallopian tubes

	CASE 1	CASE 2	CASE 3	CASE 4	CASE 5
GENETIC SEX	XY	XY	XY	XX	XY
MODIFYING FACTOR	Circumcision accident resulted in loss of penis at 8 months age. Testes removed 17 months. Raised as a female.	Lacks enzyme 5 alpha reductase necessary to convert testosterone to dihydrotestosterone	Abnormal androgen receptors – cannot respond to testosterone or dihydrotestosterone.	Fetal adrenals cannot make cortisol – this leads to hyperplasia of adrenals due to ACTH - excess steroids formed by adrenals diverted into testosterone	Transsexuals a person who strongly believes that he or she belongs to the opposite sex.
INTERNAL GENITALIA					
EXTERNAL GENITALIA					
RAISED AS					
GENDER IDENTITY					

1. Circumcision accident



Twin sons born 1965, circumcised 1966; Bruce's penis is badly burned and cannot be repaired. Parents see TV programme with Dr Money who claims nurture not nature determines a child's gender (theory of gender neutrality).

At age 21 months Bruce's testes removed. And he was to be raised as a girl called Brenda. At puberty placed on female hormones.



As a teenager he rebelled at suggestions that a vagina be created and threatened suicide. At this stage he was told his real story. Attempted suicide.

Further reconstructive surgery to make him a man again. Cannot father children. Married with 3 children.



Circumcision accident

In spring 2002 Bruce's twin brother Brian died of an overdose of antidepressants.

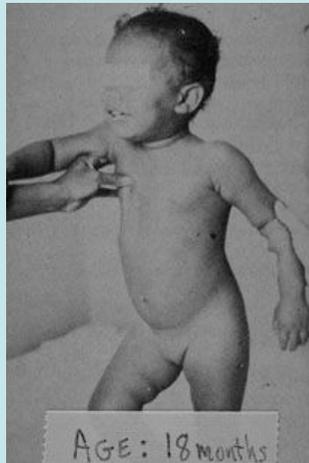
In 2004 Brian had marital difficulties. He was not easy to live with, given his explosive anger, his cyclical depressions, his fears of abandonment—all of which Jane weathered for almost 14 years. But with Brian spiralling ever deeper into sloth and despair, she told him on the weekend of May 2 that they should separate for a time. David stormed out of the house. Two days later he was found dead.

	CASE 1	CASE 2	CASE 3	CASE 4	CASE 5
GENETIC SEX	XY	XY	XY	XX	XY
MODIFYING FACTOR	Circumcision accident resulted in loss of penis at 8 months age. Testes removed 17 months. Raised as a female.	Lacks enzyme 5 alpha reductase necessary to convert testosterone to dihydrotestosterone	Abnormal androgen receptors – cannot respond to testosterone or dihydrotestosterone.	Fetal adrenals cannot make cortisol – this leads to hyperplasia of adrenals due to ACTH - excess steroids formed by adrenals diverted into testosterone	Transsexuals a person who strongly believes that he or she belongs to the opposite sex.
INTERNAL GENITALIA	♂				
EXTERNAL GENITALIA	♀				
RAISED AS	♀				
GENDER IDENTITY	♂				

2. 5- α reductase deficiency

- The enzyme 5- α reductase is necessary to convert testosterone to dihydrotestosterone (DHT). DHT is needed in the embryo to convert the genital tubercle and urethral folds into the penis and the genital folds into the scrotum.

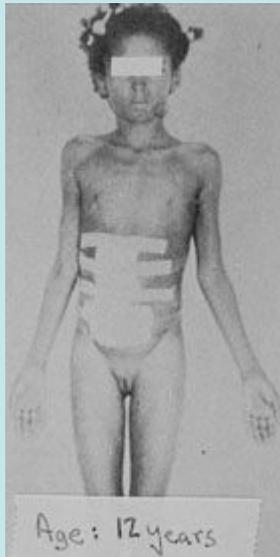
2. 5- α reductase deficiency



At 18 months, the appearance is female though undescended testes are present.



Lacking dihydrotestosterone (DHT) in utero, this boy's external genitalia develop as female. However, internally the gonadal tissue is that of normal male and his karyotype is 46 XY (normal male). In utero, DHT is essential for the normal male development of the external genitalia. After complete maturation, DHT seems to have no important biological function.

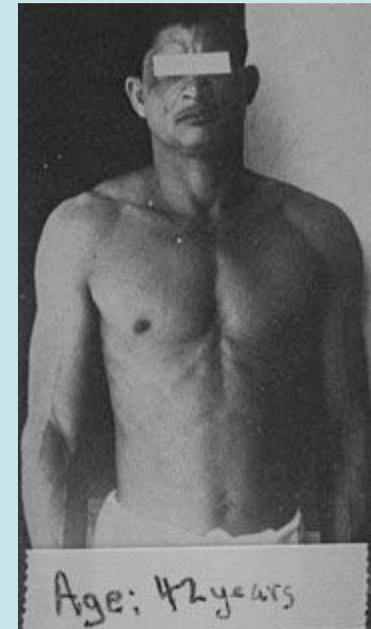


Just before puberty the phenotype is still female.



With the testosterone surge at puberty, the phenotype changes to male: the voice deepens, the testes descend, the phallus grows, erection and ejaculation begin, and a male psychosexual orientation develops.

Claim they always knew they were men.



For the rest of their lives, they resemble other Dominican men except:

- * Beard growth is scanty.
- * There is no hairline recession.
- * None has acne.
- * The prostate remains small.

The story of the guevedoces was originally presented at a Federation meeting in Atlantic City, NJ in 1973 and published in *Science* in 1974 (Imperato-McGinley J, Guerrero L, Gautier T, Peterson RE. Steroid 5alpha-reductase deficiency in man: an inherited form of male pseudohermaphroditism. *Science* 1974 Dec 27; 186 (4170): 1213-5). Specific inhibition of 5-alpha Reductase is the mechanism of action of the prostate drug, [finasteride \(Proscar\)](#), which in adults, shrinks the prostate without affecting the male phenotype.

	CASE 1	CASE 2	CASE 3	CASE 4	CASE 5
GENETIC SEX	XY	XY	XY	XX	XY
MODIFYING FACTOR	Circumcision accident resulted in loss of penis at 8 months age. Testes removed 17 months. Raised as a female.	Lacks enzyme 5 alpha reductase necessary to convert testosterone to dihydrotestosterone	Abnormal androgen receptors – cannot respond to testosterone or dihydrotestosterone.	Fetal adrenals cannot make cortisol – this leads to hyperplasia of adrenals due to ACTH - excess steroids formed by adrenals diverted into testosterone	Transsexuals a person who strongly believes that he or she belongs to the opposite sex.
INTERNAL GENITALIA	♂	♂			
EXTERNAL GENITALIA	♀	♀			
RAISED AS	♀	♀			
GENDER IDENTITY	♂	♂			

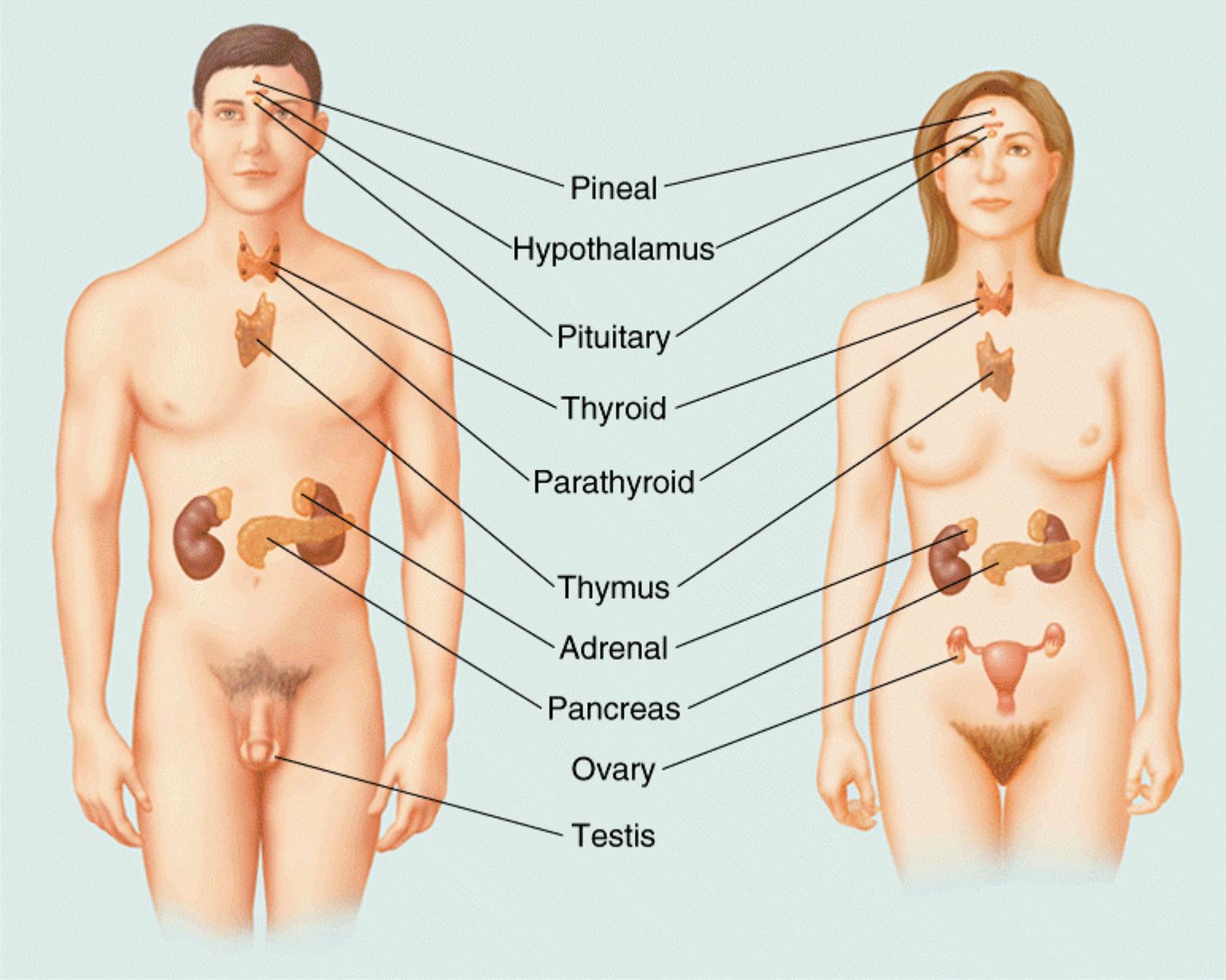
3. Androgen Insensitivity Syndrome

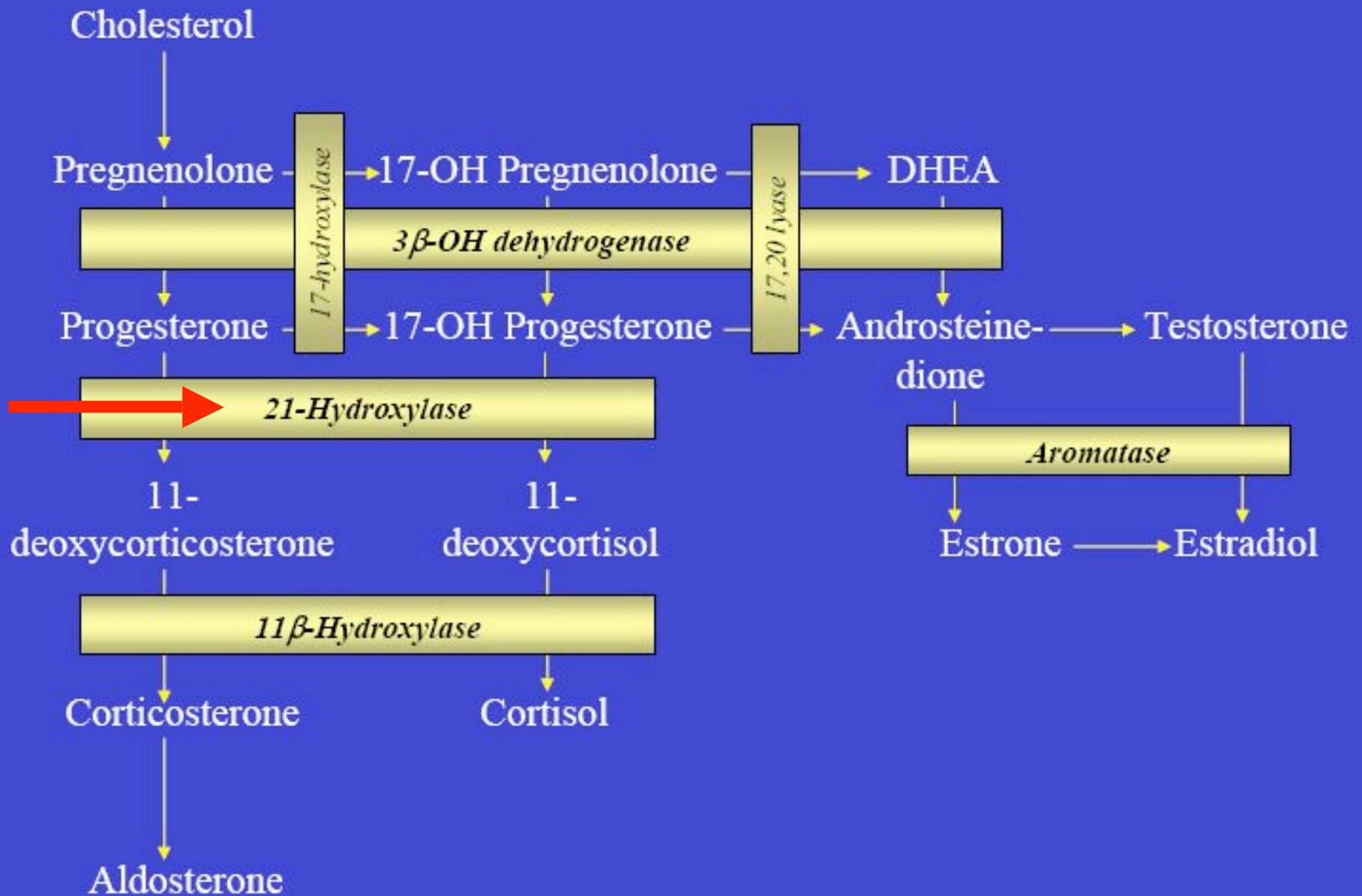
- X-linked recessive trait resulting in abnormal testosterone receptors that do not respond to testosterone. XY genotype so they have testes but they do not descend into the scrotum.
- Testosterone cannot enter cells to be converted into DHT so external genitalia are female.
- Testosterone cannot enter cells to be aromatised so the brain is female.
- Sertoli cells produce AMH so there is no uterus, uterine tubes or upper vagina but there is a short blind vagina. No internal male genitalia as no testosterone cannot activate receptors on Wolffian ducts and no male external genitalia as tissue cannot respond to testosterone or DHT.
- Unopposed estrogen (maybe some conversion of T as well). Therefore normal breast development. Raised as females and usually feel female. Do not menstruate or have pubic or underarm hair.



	CASE 1	CASE 2	CASE 3	CASE 4	CASE 5
GENETIC SEX	XY	XY	XY	XX	XY
MODIFYING FACTOR	Circumcision accident resulted in loss of penis at 8 months age. Testes removed 17 months. Raised as a female.	Lacks enzyme 5 alpha reductase necessary to convert testosterone to dihydrotestosterone	Abnormal androgen receptors – cannot respond to testosterone or dihydrotestosterone.	Fetal adrenals cannot make cortisol – this leads to hyperplasia of adrenals due to ACTH - excess steroids formed by adrenals diverted into testosterone	Transsexuals a person who strongly believes that he or she belongs to the opposite sex.
INTERNAL GENITALIA	♂	♂	absent		
EXTERNAL GENITALIA	♀	♀	♀		
RAISED AS	♀	♀	♀		
GENDER IDENTITY	♂	♂	♀		

► Endocrine Glands

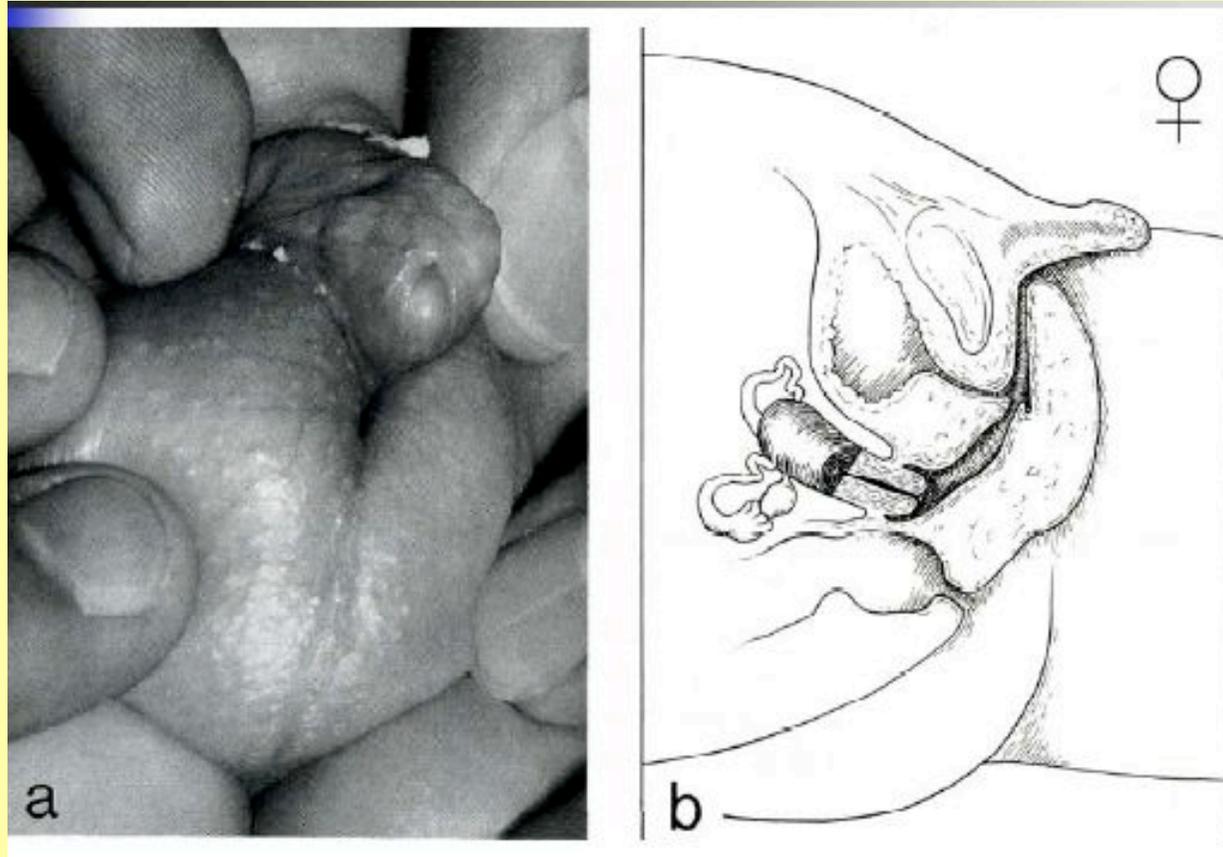




4. Congenital adrenal hyperplasia

- Genetic female with 21-hydroxylase enzyme deficiency (usually). 1:2000 children.
- Fetus is deficient in cortisol therefore the pituitary produces excess ACTH causing hyperplasia of the adrenals. This results in the adrenals producing large amounts of steroids that are diverted into testosterone by the fetal liver and/or placenta.
- Internal genitalia are normal female except the lower vagina which is androgen sensitive. Male ducts do not survive as androgen levels are too low.
- During weeks 8-13 androgens sex the brain and external genitalia to a certain extent. Enlarged clitoris and variable closing of the labia.
- Similar phenotype after maternal ingestion of androgenic drugs.
- Affected females play more with boys' toys, less interested in motherhood, more inclined to male-typical activities and careers, more likely to be attracted to women, but more hetero- than lesbian, excel in visuospatial tasks

Congenital adrenal hyperplasia



Androgenic hormones

- **Androgenic drugs** can cause masculinization (ie labioscrotal fusion) of the female fetus if administered between approximately the 8th and 13th weeks of gestation. Phallic enlargement can result from androgen exposure at any time after this period. Danazol, used to treat unexplained infertility and endometriosis (which affects 5-10% of women of childbearing age) is the drug most frequently associated with this masculinization.
- **Progestogens** can also cause masculinization by conversion into androgens in the mother and fetus. Ethisterone and norethindrone account for most of the reported cases. These drugs do not have strong androgenic properties with only 0.3-6% of girls exposed to several progestins being affected. There have also been reports of male feminization associated with progestins, such as medroxyprogesterone.
- **Oral contraceptive** use during pregnancy does not appear to influence genital development.

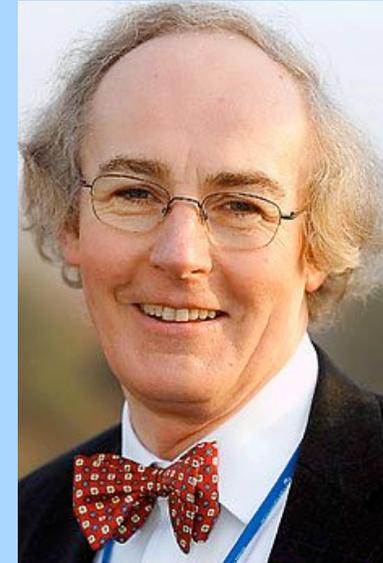


Fig. 4-10. Dizygous twins exposed throughout pregnancy to Ortho-Novum. Both infants were masculinized: **A**, the female with clitoral hypertrophy; **B**, the male with enlarged genitalia and mature scrotum.

	CASE 1	CASE 2	CASE 3	CASE 4	CASE 5
GENETIC SEX	XY	XY	XY	XX	XY
MODIFYING FACTOR	Circumcision accident resulted in loss of penis at 8 months age. Testes removed 17 months. Raised as a female.	Lacks enzyme 5 alpha reductase necessary to convert testosterone to dihydrotestosterone	Abnormal androgen receptors – cannot respond to testosterone or dihydrotestosterone.	Fetal adrenals cannot make cortisol – this leads to hyperplasia of adrenals due to ACTH - excess steroids formed by adrenals diverted into testosterone	Transsexuals a person who strongly believes that he or she belongs to the opposite sex.
INTERNAL GENITALIA	♂	♂	absent	♀	
EXTERNAL GENITALIA	♀	♀	♀	♀/♂	
RAISED AS	♀	♀	♀	♀/♂	
GENDER IDENTITY	♂	♂	♀	♀/♂	

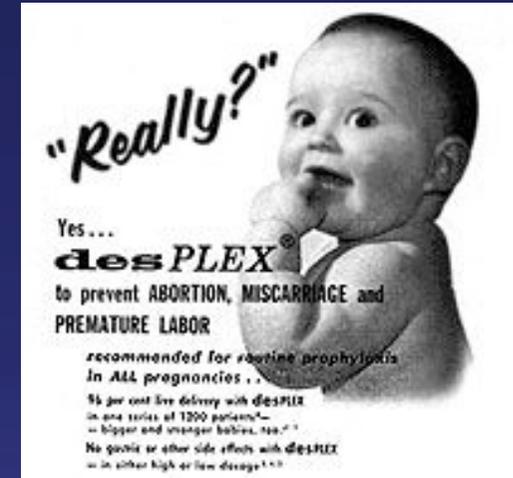
Transsexualism

- Transsexualism occurs when a person strongly believes that he or she belong to the opposite sex.
- This is typically a lifelong feeling and results in varied degrees of physical/external changes



	CASE 1	CASE 2	CASE 3	CASE 4	CASE 5
GENETIC SEX	XY	XY	XY	XX	XY
MODIFYING FACTOR	Circumcision accident resulted in loss of penis at 8 months age. Testes removed 17 months. Raised as a female.	Lacks enzyme 5 alpha reductase necessary to convert testosterone to dihydrotestosterone	Abnormal androgen receptors – cannot respond to testosterone or dihydrotestosterone.	Fetal adrenals cannot make cortisol – this leads to hyperplasia of adrenals due to ACTH - excess steroids formed by adrenals diverted into testosterone	Transsexuals a person who strongly believes that he or she belongs to the opposite sex.
INTERNAL GENITALIA	♂	♂	absent	♀	♂
EXTERNAL GENITALIA	♀	♀	♀	♀/♂	♂
RAISED AS	♀	♀	♀	♀/♂	♂
GENDER IDENTITY	♂	♂	♀	♀/♂	♀

Estrogens - Diethylstilbestrol (DES)



- Synthetic nonsteroidal estrogen prescribed to prevent miscarriage between 1938 and 1971. It was also prescribed for diabetes and high blood pressure in pregnancy. As many as 3,000,000 women may have been exposed in utero.
JAMA. 1998;280:630-634.
- Removed from the US market in 1971 after development of adenocarcinoma of the vagina and cervix in young women whose mothers had taken DES while pregnant.
- The rate of adenocarcinoma of the vagina and cervix in women exposed transplacentally is 1.4/1000 to 1/10,000. It is not normally a cancer seen in young women.

Diethylstilbestrol (DES)

- Between 18 and 33% of women exposed to DES in utero have structural abnormalities of the reproductive tract. Hypoplastic cervix, cockscomb cervix, cervical collar, pseudopolyp, T-shaped uterus, abnormal vaginal epithelium.
- **This was the first example of a human teratogen also being a transplacental carcinogen.**

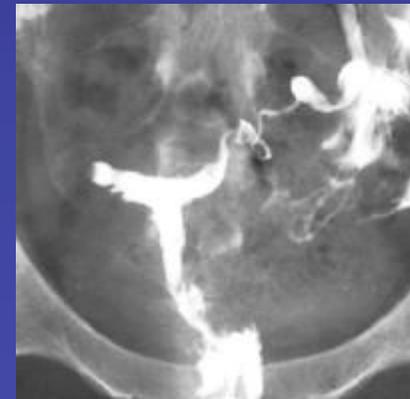
DES-exposed uterus. Myometrial hypertrophy results in a T-shaped uterine cavity. Typically, the uteri are hypoplastic..



DES T-shaped uterus



Normal uterus



DES T-shaped uterus

Diethylstilbestrol (DES)

- Males exposed to DES in utero have 3-fold increase in genital structural abnormalities.
- Most common are epididymal cysts, undescended testes and small testes. There is also sperm and semen abnormalities but no increase in infertility or sexual dysfunction.

END!