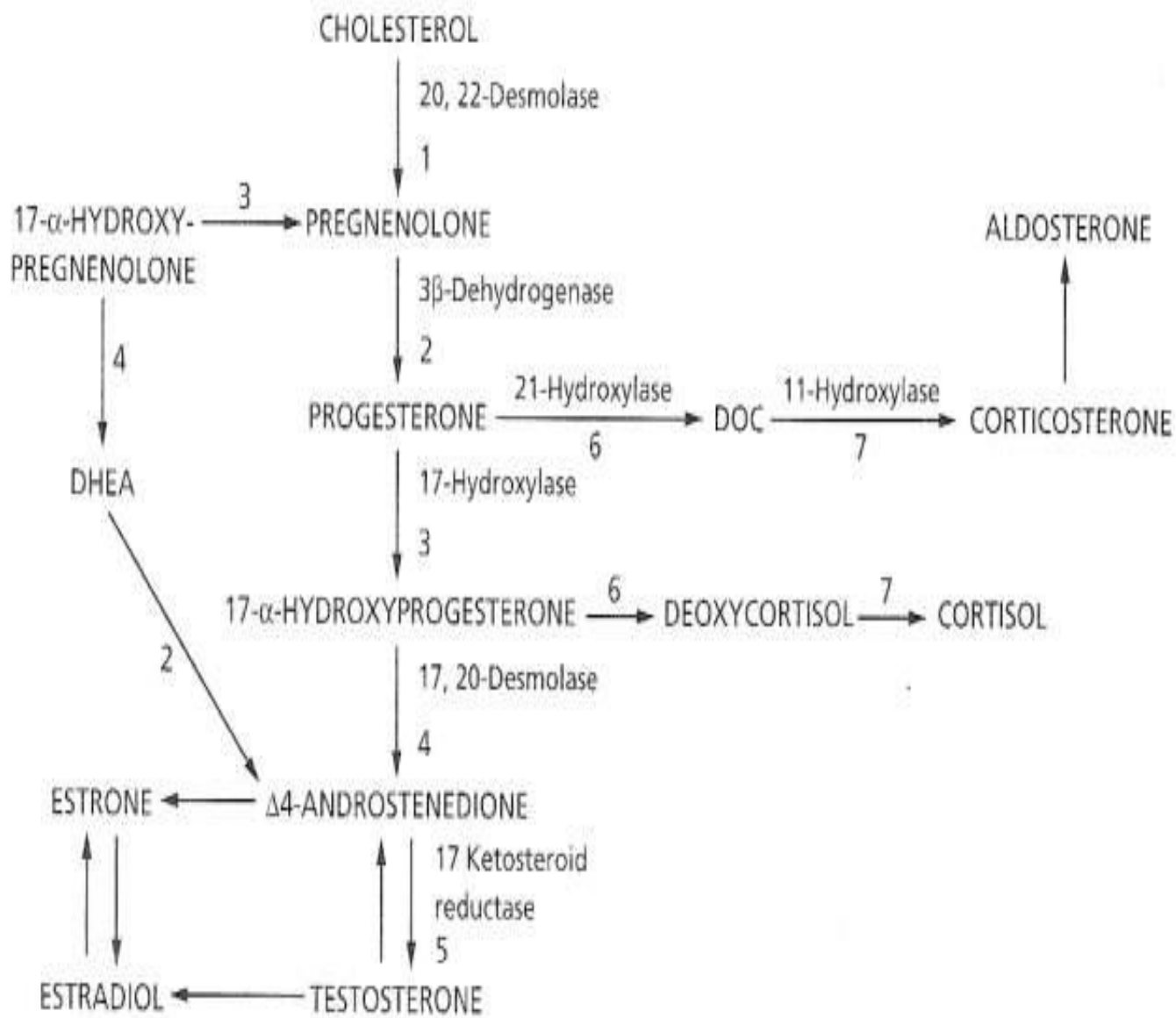


# INTERSEX DISORDERS

# DEFINITION:

- Masculinization of external genitalia in patients with normal 46XX karyotype.
  - Degree of masculinization variable:
    - mild clitoromegaly
    - complete fusion of labia folds with penile urethra



# PATHOPHYSIOLOGY:

- Female fetus exposed to elevated levels of androgens.
- Differentiation of external genitalia to male or female depends on the conversion of testosterone to dihydrotestosterone (DHT) in the tissues of the cloaca.
- ↑ DHT leads to male type development.
- Low levels of androgen → partial masculinization may occur – leading to ambiguous genitalia.
- High levels of androgens – complete male external genitalia (testis are absent)
- Androgen exposure after 12 weeks → virilization is limited to clitoral enlargement → no effect on labia.
- **Androgens no effect on internal sexual development.**
  - Remember gonadal differentiation depends on the Y-gene

# AETIOLOGY:

Due to excessive androgens:

- a.) Arising in fetus → CAH (congenital adrenal hyperplasia)
- b.) Arising in mother – androgen secreting tumor
- c.) Ingested by mother, eg. Danazol
- d.) Other cases associated with other congenital abnormalities of idiopathic
- e.). Aromatase (oestrogen synthetase) deficiency

## (A) CONGENITAL ADRENAL HYPERPLASIA:

- Common cause of female pseudohermaphroditism .
- **Autosomal recessive.**
- Enzyme deficiency in biosynthesis of cortisol.
- Cortisol production occurs in zona fasciculata zona reticularis (ACTH controlled).
- Enzyme defect in pathway → ↓ production of cortisol and ↑ ACTH
- ↑ACTH leads to ↓ steroid production and virilization in female fetus.
- 3 Enzymes – 21  $\beta$ -Hydroxylase
  - 11 $\beta$ -Hydroxylase
  - 3  $\beta$ -Dehydrogenase deficiency

# 21-HYDROXYLASE DEFICIENCY:

- 90% of cases.
- Deficiency - ↑ in progesterone and a hydroprogesterone.
- Converted to androstenedione and testosterone.
- Failure to convert progesterone to 11 deoxycorticosterone result in aldosterone deficiency.

## Presentation:

- Enlarged clitoris, fused labioscrotal folds and urogenital sinus.
- Internal genitalia development normal.
- Salt losing form and non salt losing form.

Children born with ambiguous genitalia – should be screened for CAH.

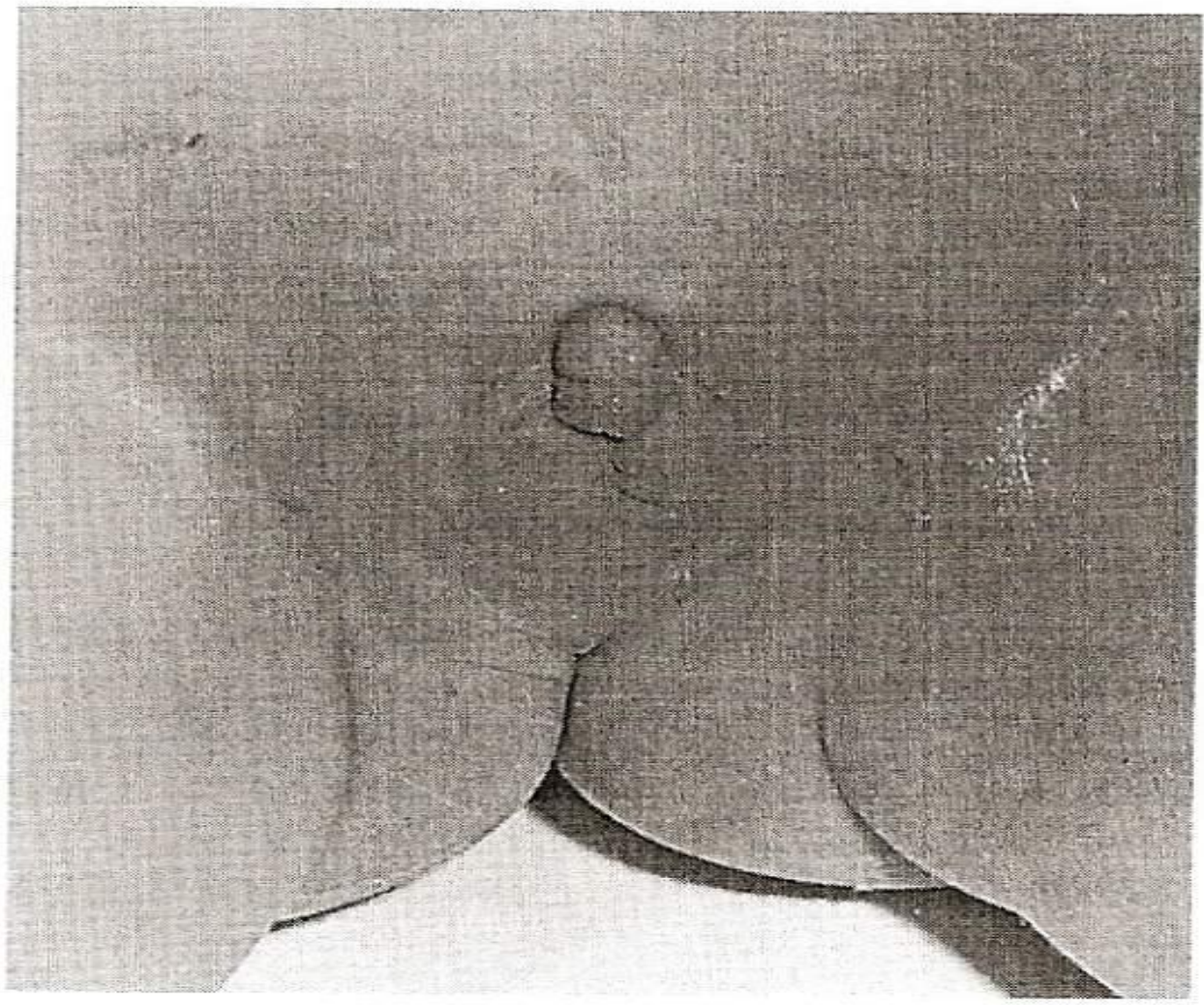
# 11-HYDROXYLOSE DEFICIENCY:

- Hypertensive form.
- 5-8% of cases.
- ↑ Levels of 11 deoxycorticosterone.

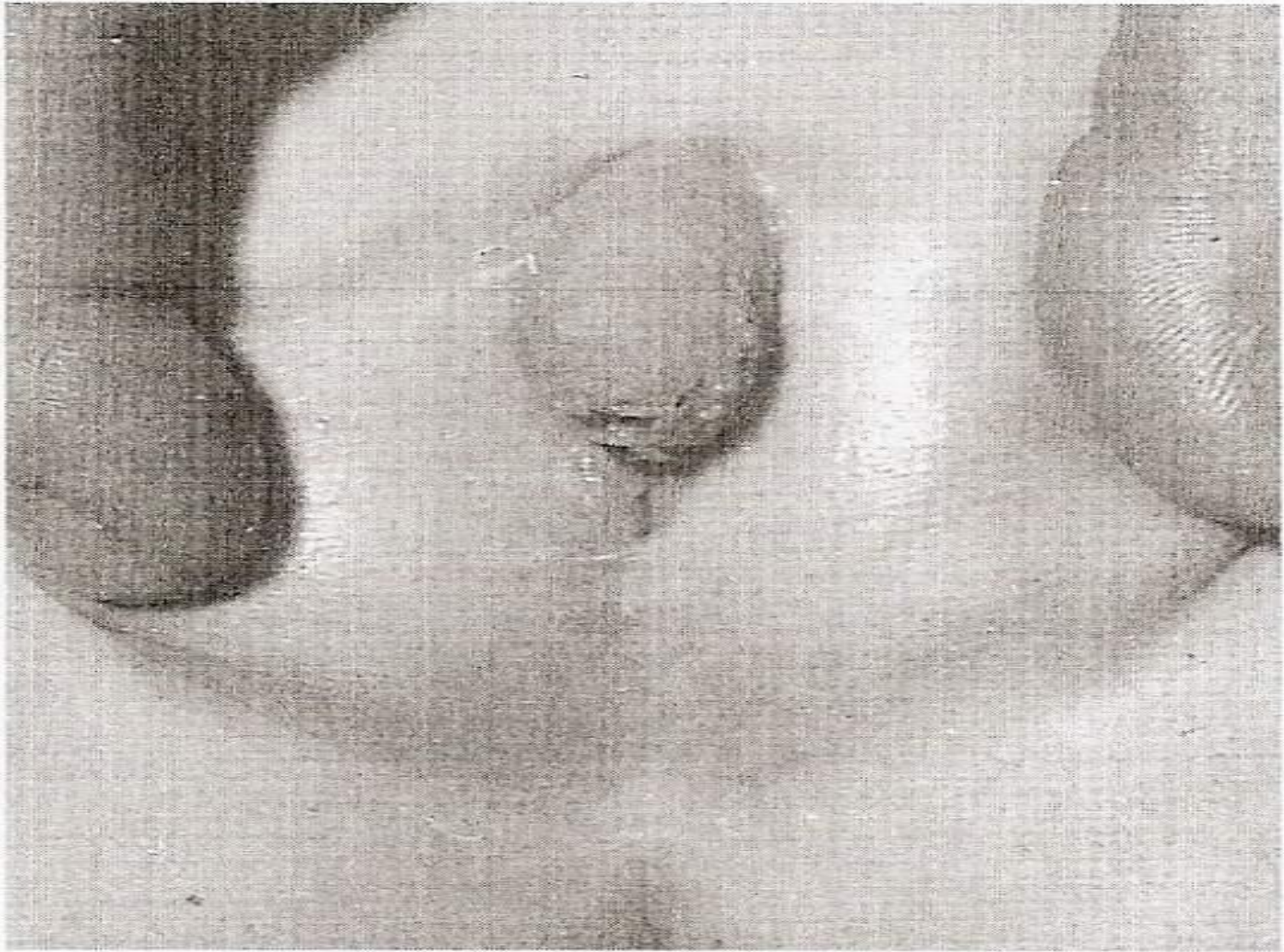


# 33 DEHYDROGENASE DEFICIENCY:

- Rare form



**Fig. 3.6** Considerable masculinization of the external genitalia of a female child whose mother was treated with methyltestosterone in early pregnancy.



**Fig. 3.2** The external genitalia of a child with CAH. Note the clitoral enlargement and the excessive fusion of labial folds which have resulted in only a single opening on the perineum.

# **(B) ANDROGEN-SECRETING TUMORS:**

## **(i) Ovary:**

→ - Luteoma

- Arrhenoblastoma

- Kruken berg tumors

→ Not all female fetuses will be affected.

→ Fetus partly protected by conversion of maternal derived androgen to estrogen in the placenta



## ii) Adrenal:

2 Reports of adrenal adenomas causing fetal masculinisation.

## C) Drugs

- Progestogen proven to have effect is ethinyl testosterone.
- Gestogens derived from testosterone and should be avoided in pregnancy.

# D. ASSOCIATED MULTIPLE CONGENITAL ABNORMALITIES:

## (A) XY FEMALE:

- Testosterone leads to development of Wolffian duct and urogenital sinus to produce normal male internal and external genitalia.
- Testosterone predominant male sex hormone.
- 2 Other processes are necessary for normal development:
  - (i) Conversion Test  $\rightarrow$  DHT ( $5\alpha$  Reductase)
  - (ii) Presence of androgen receptors in target cell.
- Normal male genotype (xy) with female phenotype will occur if:
  - (1) Failure of testicular development
  - (2) Errors in testosterone biosynthesis.
  - (3) Androgen insensitivity at target site.

# 1. Failure of testicular development:

## (a) True gonadal dysgenesis:

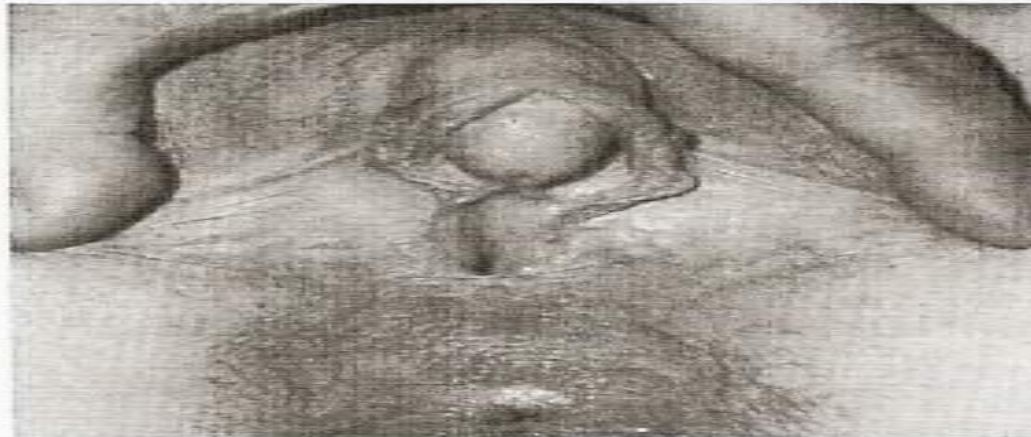
- Streak gonads, normal mullerian structures.
- Normal external female genitalia.

## (b) 46xy True hermaphroditism:

Presence of both testicular and ovarian tissue with 46xy karyotype.



(a)



(b)

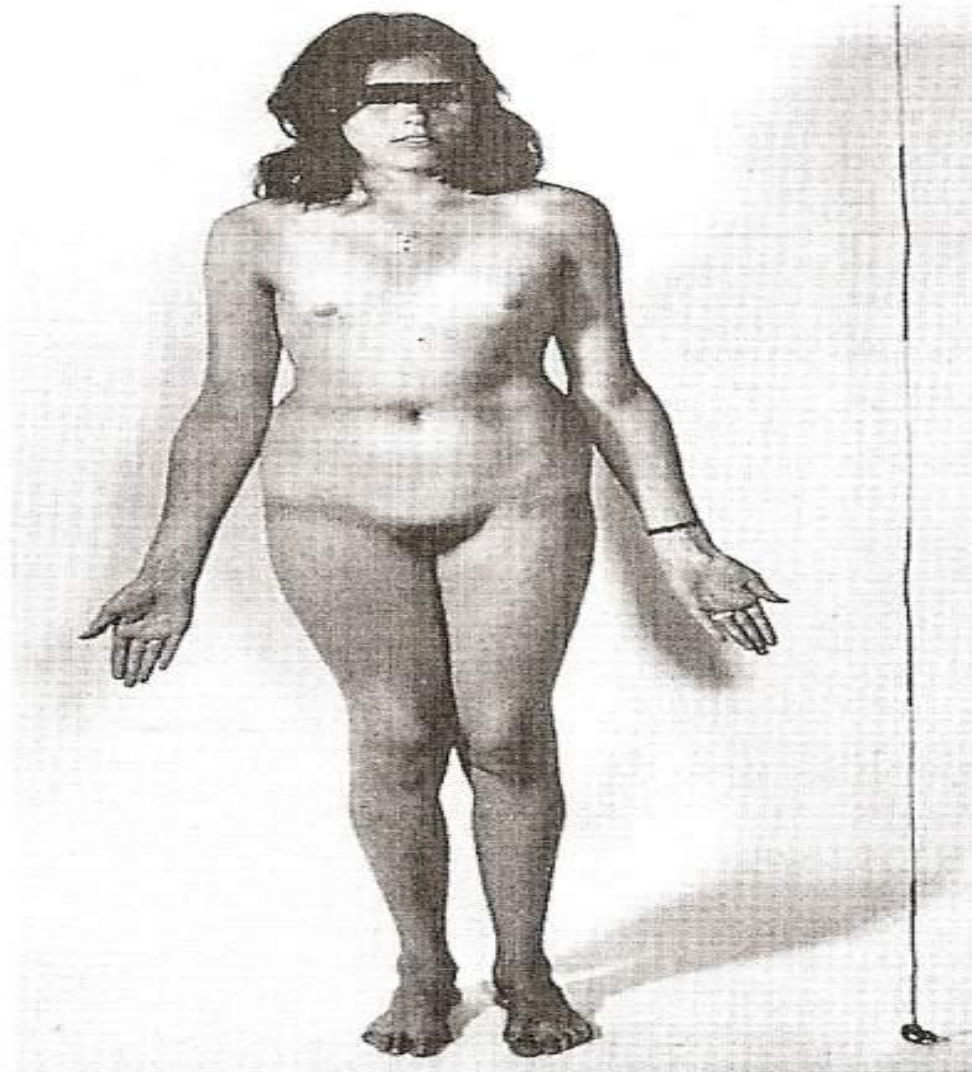
**Fig. 3.9** External genitalia in two true hermaphrodites. (a) Behind a considerable degree of clitoral enlargement it is possible to identify the urethra (not shown in the figure) and the vagina, which is illustrated. (b) An equivalent amount of clitoral enlargement, but the excessive fusion of labial folds has led to only a single perineal opening and it is not possible to identify the urethra and vagina separately.

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## II. Errors in testosterone biosynthesis:

- 4% of xy
- 20 – 22 desmolase deficiency
- 17 Hydroxylase deficiency
- 17-20 desmolase deficiency



**Fig. 3.7** A patient with enzymatic testicular failure believed to be due to 17-ketosteroid-reductase deficiency. Reproduced from Dewhurst (1980), with permission.

### III. ANDROGEN INSENSITIVITY OF TARGER SITE:

- Testicular functions is normal
  - Normal levels of circulating androgens
  - Defect – (a) Reductase deficiency.
    - (b) Complete androgen insensitivity
    - (c) Partial androgen insensitivity

## (a) 5 $\alpha$ Reductase deficiency:

- Failure to convert testosterone to DHT.
- Failure of masculinization of the site.
- Infants
  - small phallus
  - some degree of hypospadias
  - Blind vaginal pouch
  - testis in inguinal canal or in labia scrotal folds
  - mullerian structures absent- no oestrogen effect

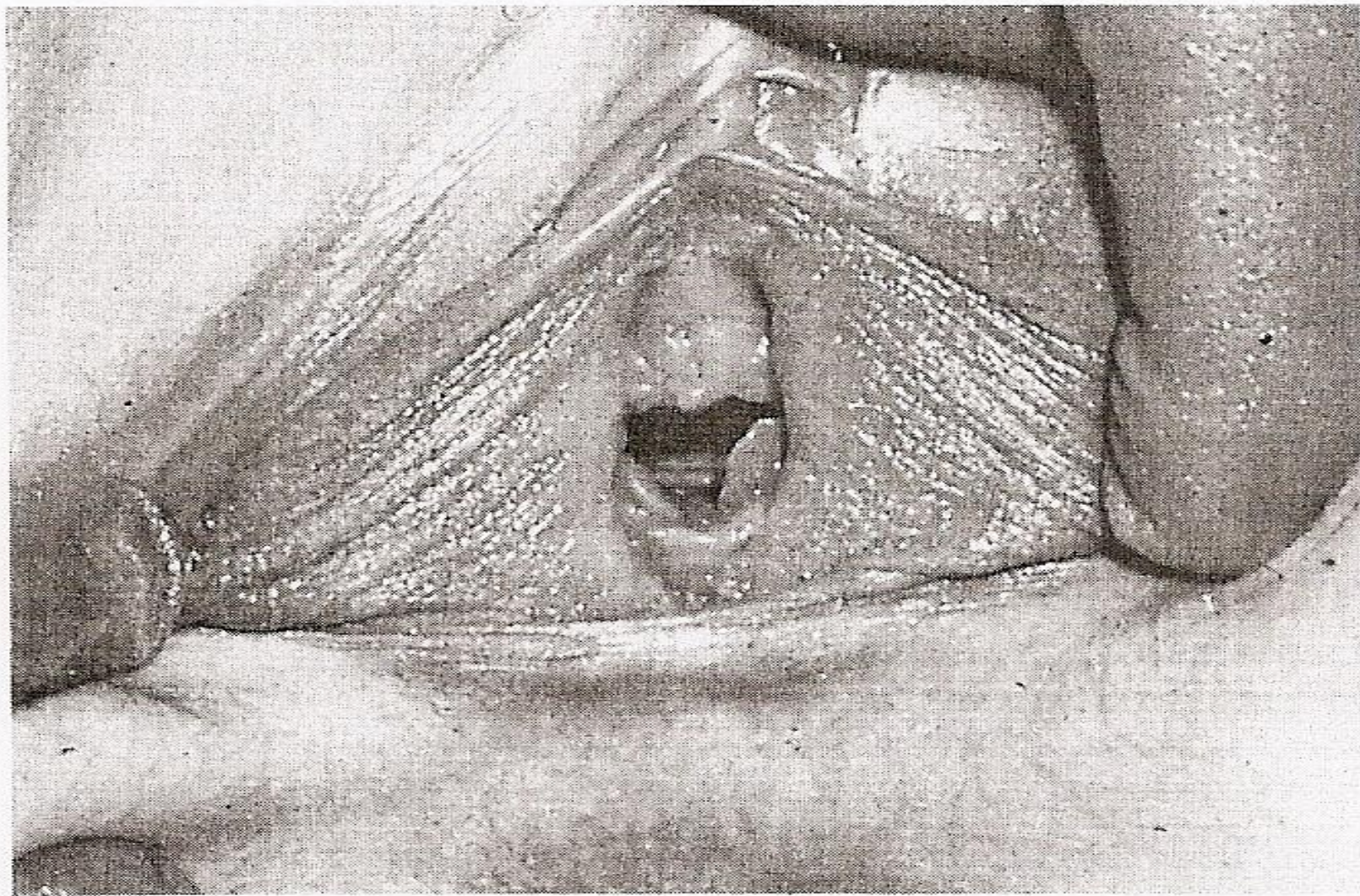


Fig. 3.8 The external genitalia of a 10-year-old 46 XY child with 5 $\alpha$ -reductase deficiency. Reproduced from Dewhurst (1980), with permission.

## (B) COMPLETE ANDROGEN INSENSITIVITY:

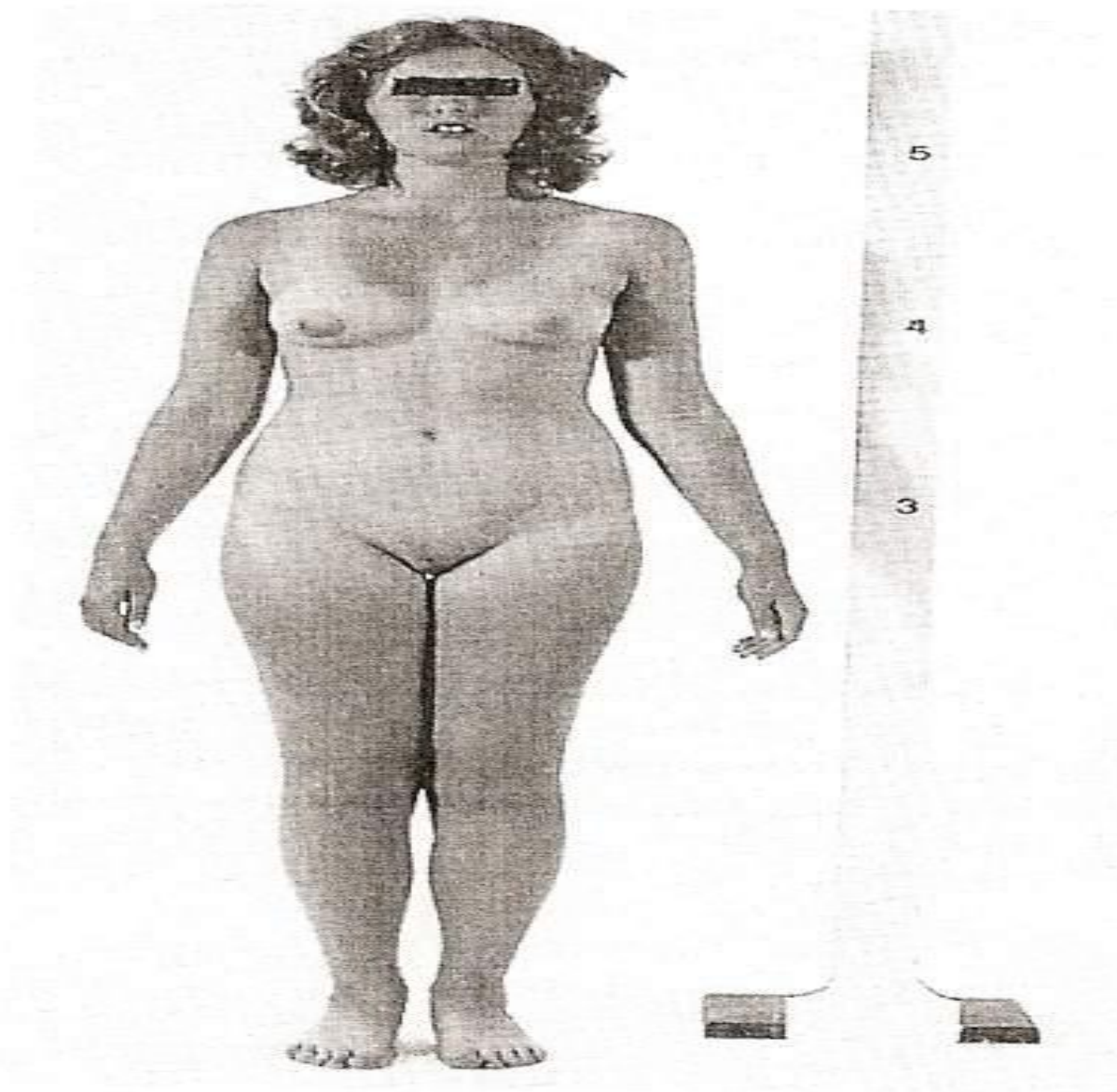
- Normal female external genitalia.
- Blind vaginal pouch.
- Absent mullerian and wolffian structures.
- Testis found in inguinal canal, labia folds. Or intra abdominal.





**Fig. 3.10** The external genitalia of a patient with androgen insensitivity.

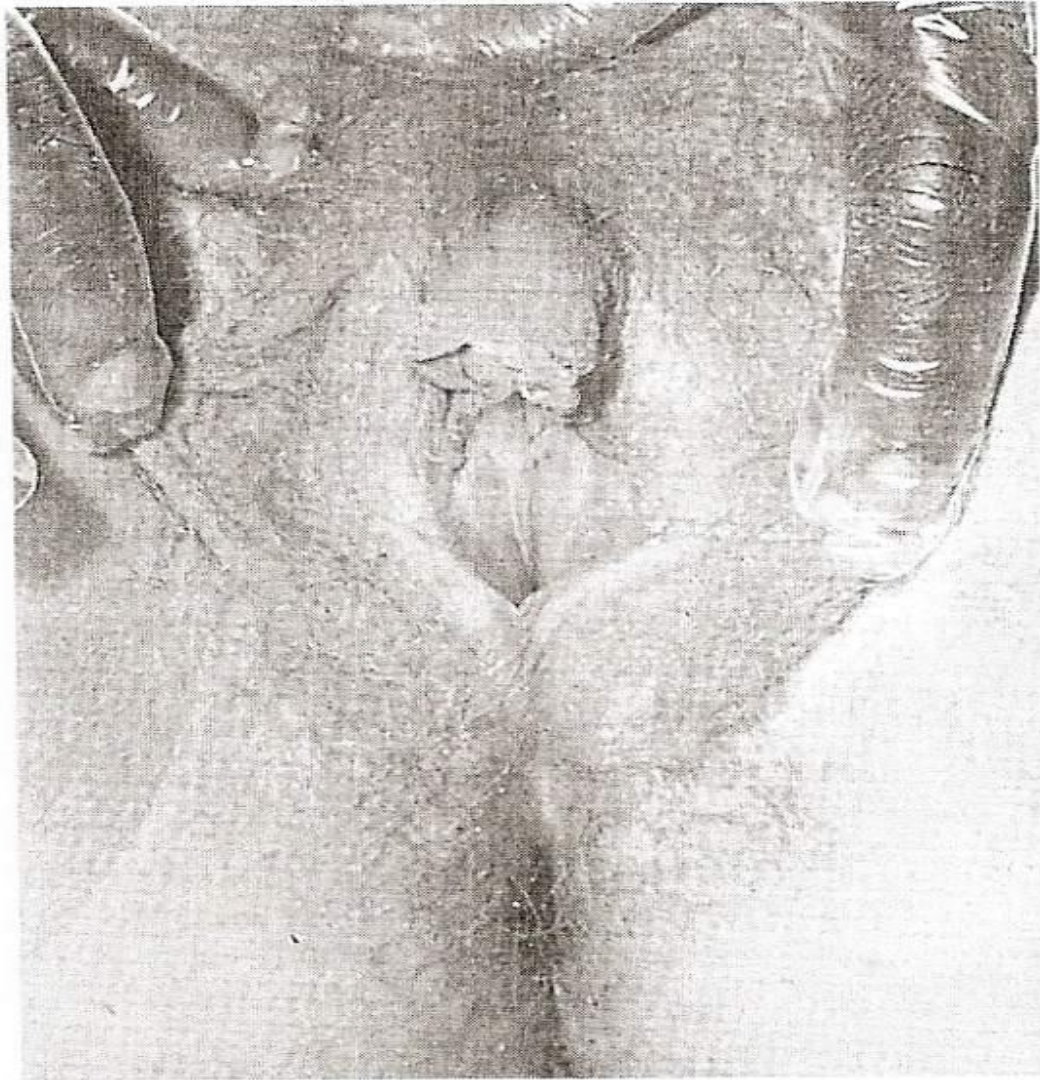




**Fig. 3.11** The external appearance of a 46 XY individual with androgen insensitivity. Note the excellent breast development and complete absence of pubic hair.

Following a similar pattern, the female sex chromosomes are





**Fig. 3.13** External genital appearance of a 46 XX individual with CAH seen for the first time at the age of 16 years.