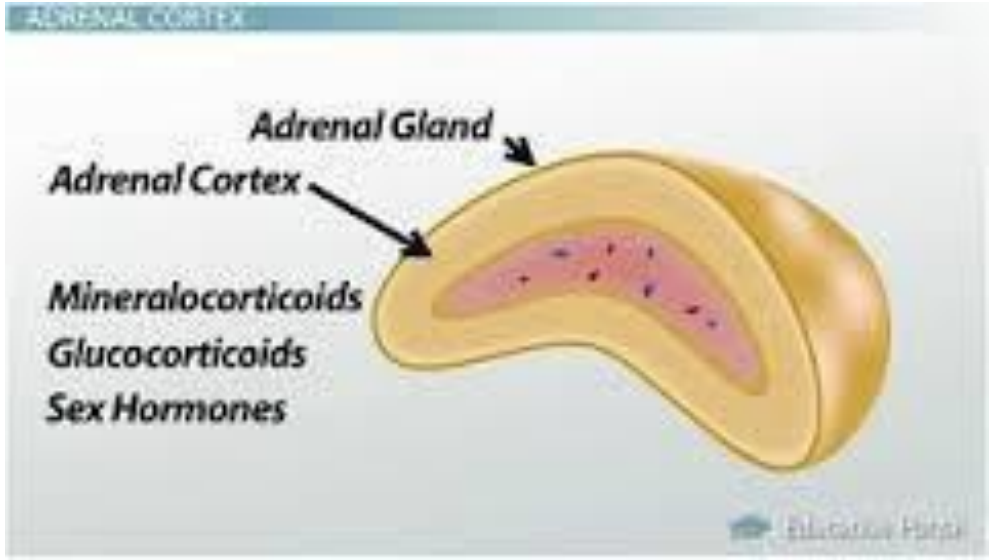
Adrenal cortex disorders in children



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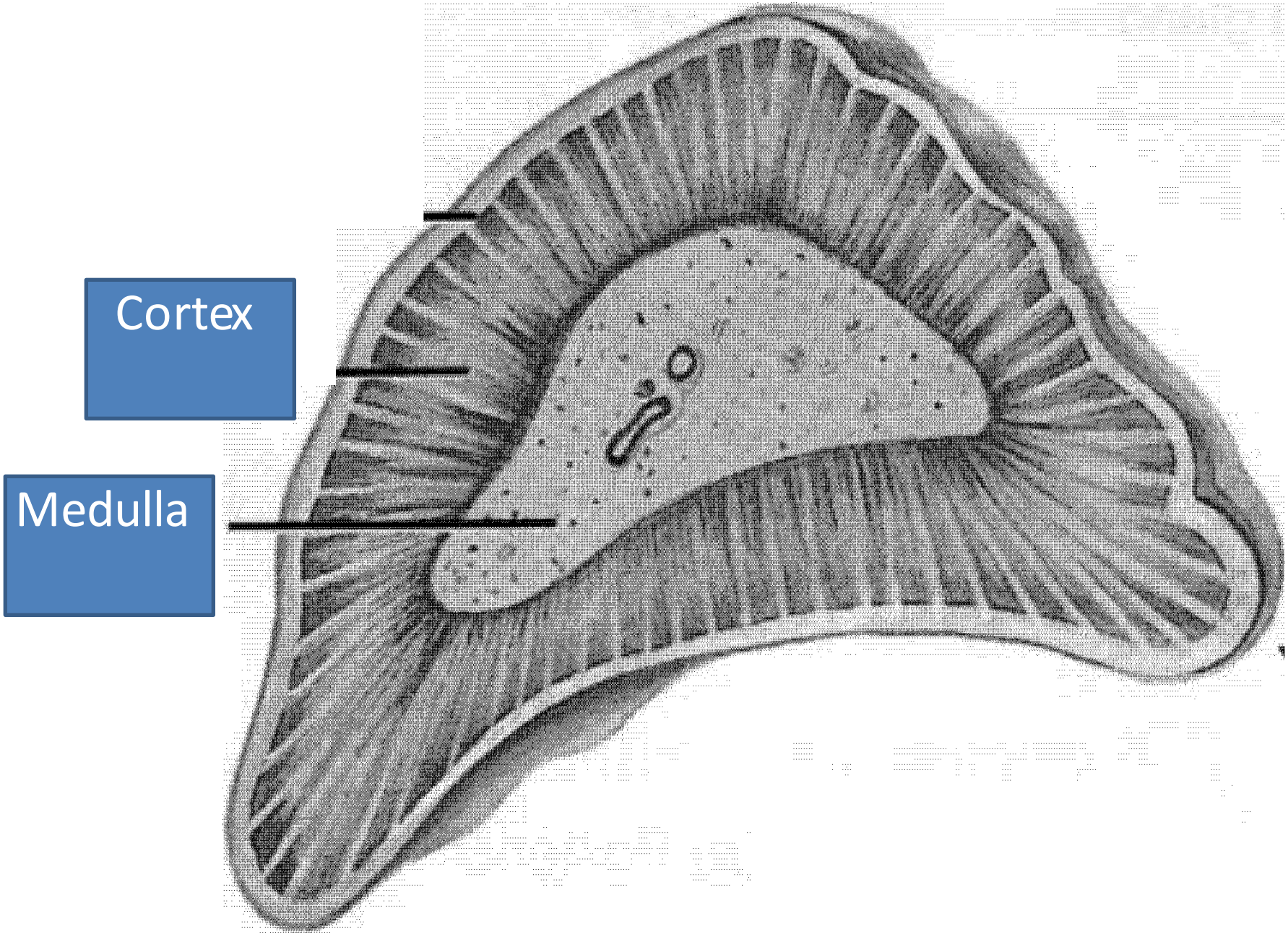
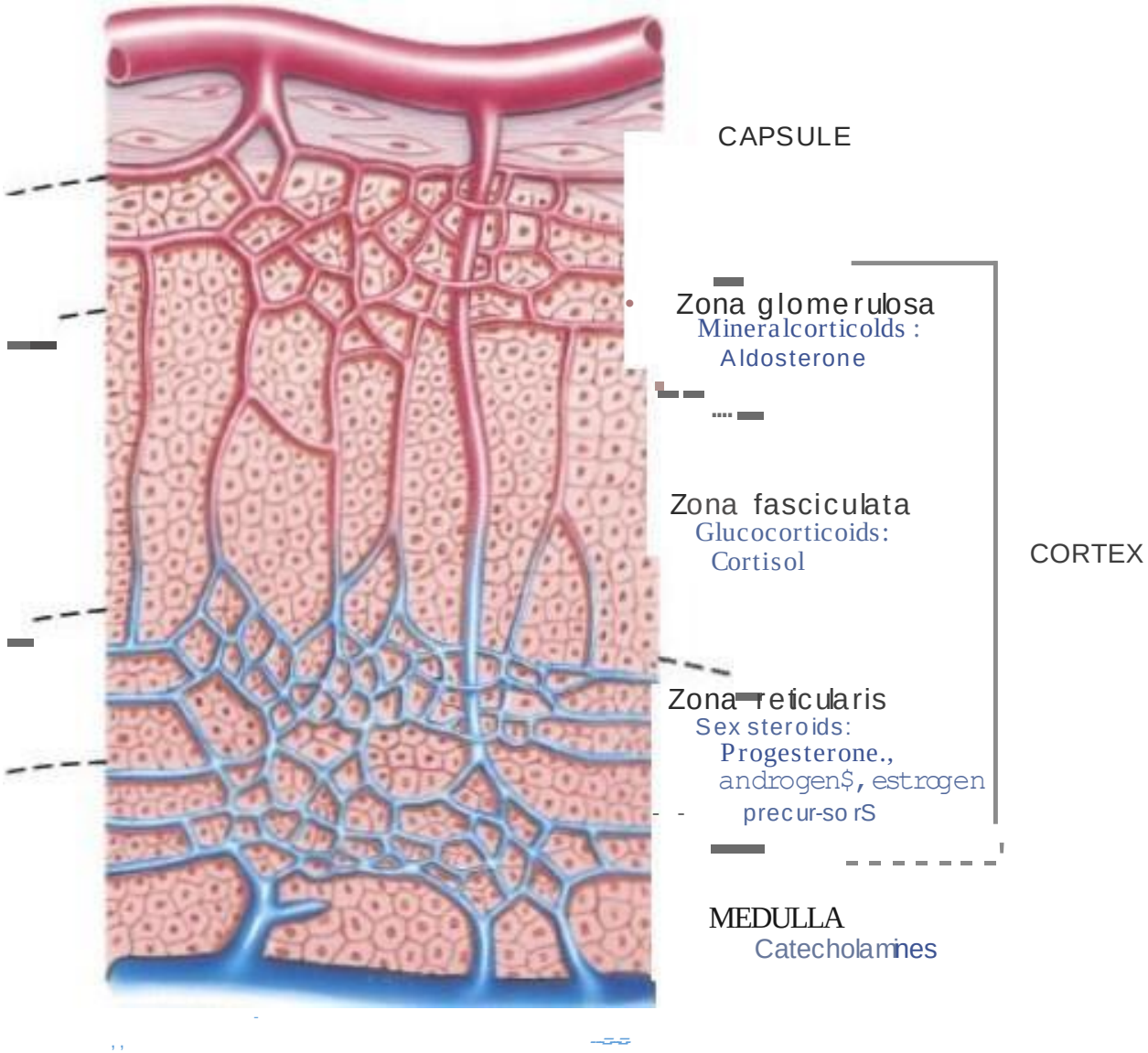
Objectives

- Recognize anatomy & physiology of the adrenal gland
- Understand the process of steroidogenesis
- Discuss various causes of adrenal insufficiency with special concentration on congenital Adrenal hyperplasia
- Clinical presentations of congenital adrenal hyperplasia (CAH)
    - Classical versus non classical CAH
- Investigations & management of adrenal insufficiency
- Management of adrenal crisis

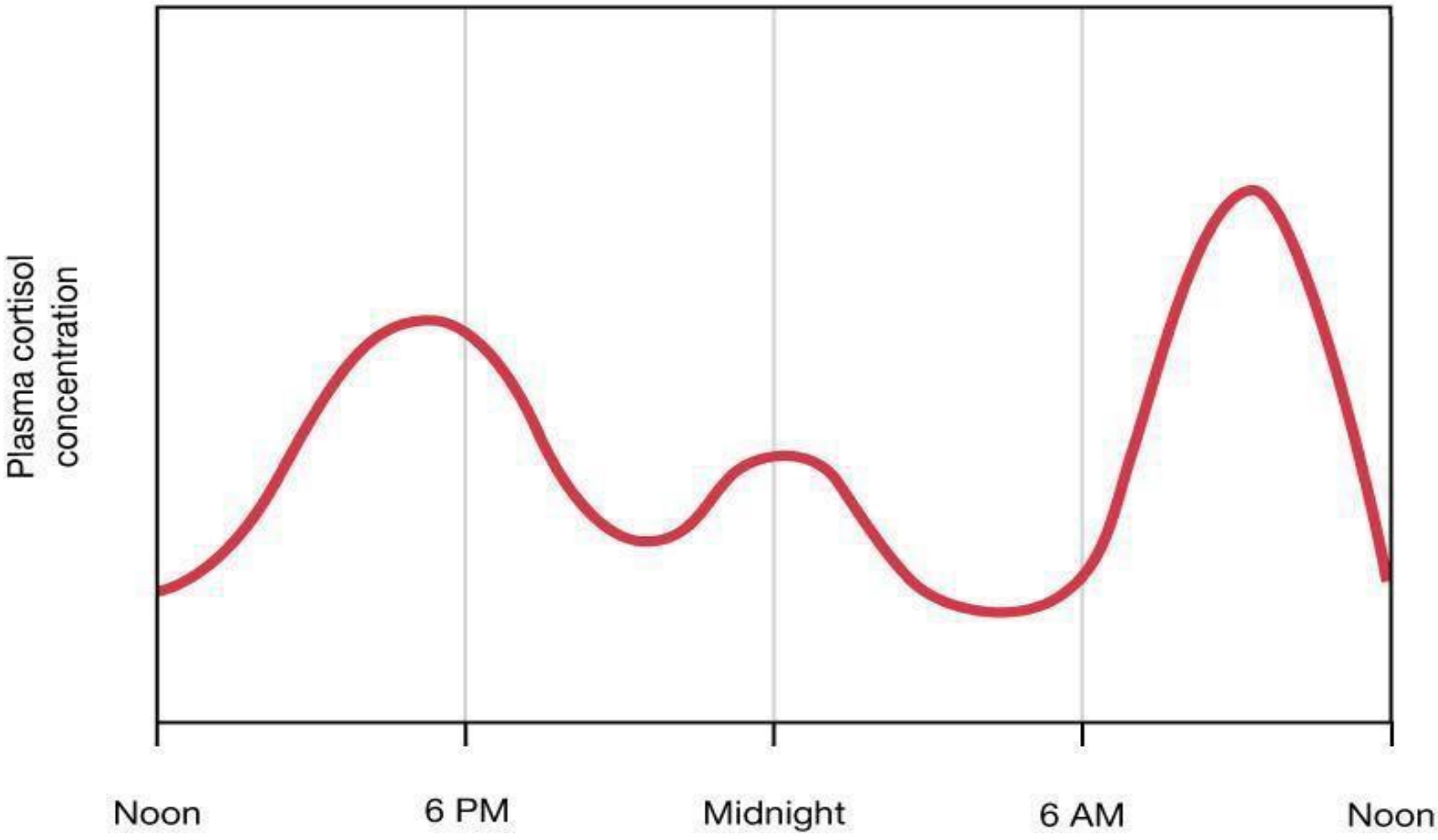

Cortex
Medulla

The Adrenal gland

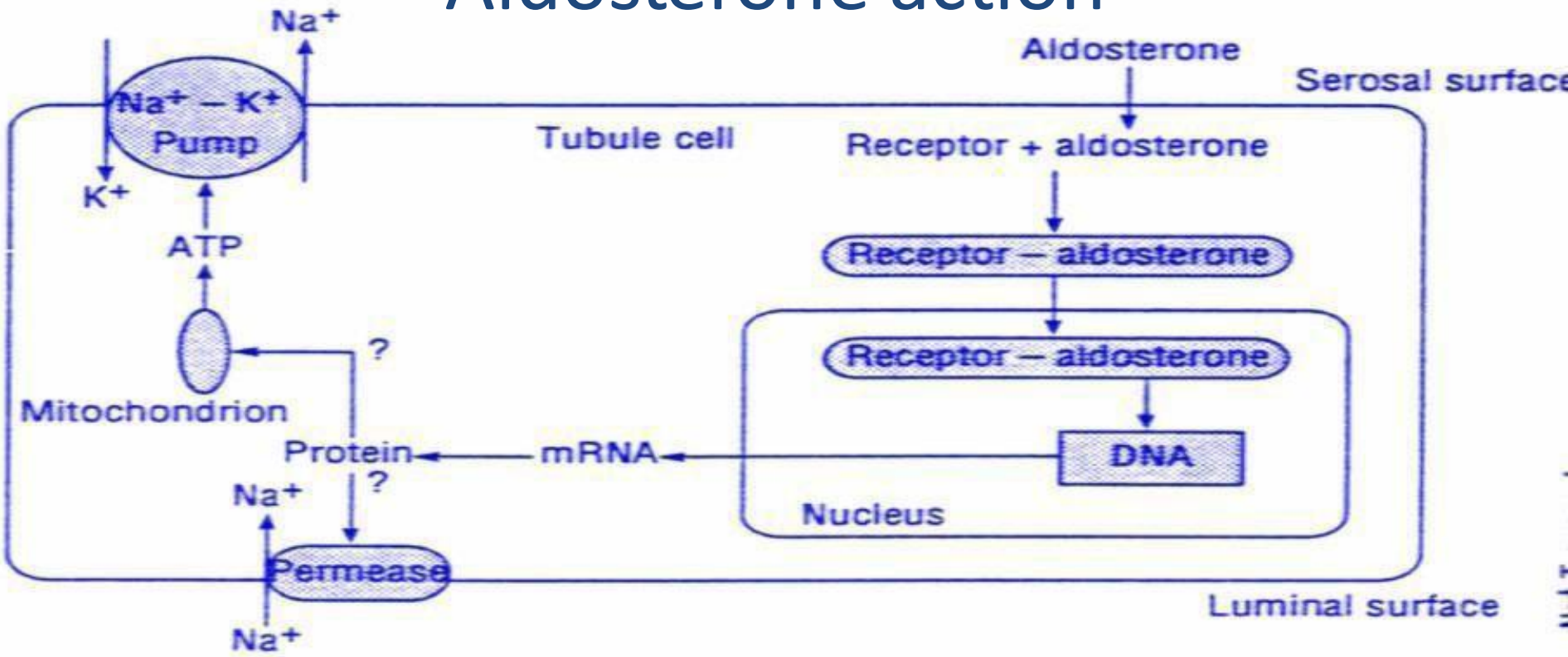
- The adrenal gland lies just above the kidneys
- Divided into two main sub-organs
  - Adrenal cortex
    - Secretes the steroid hormones
      - Glucocorticoid
      - Mineralocorticoid
      - Androgens
  - Adrenal medulla
    - Secretes Catecholamines
      - Adrenaline (epinephrine)
      - Noradrenaline (norepinephrine)

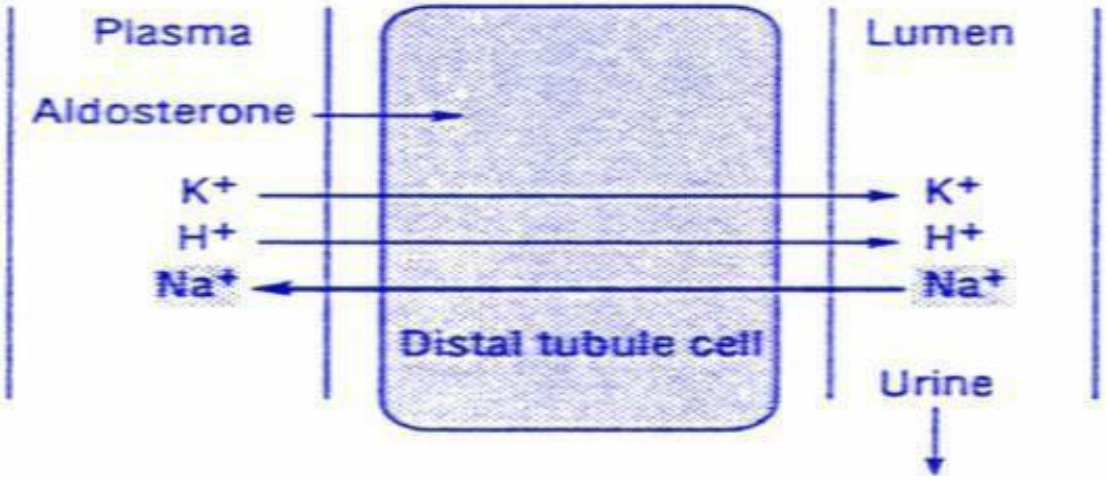

CAPSULE
Zona glomerulosa
Mineralcorticolds :
Aldosterone
Zona fasciculata
Glucocorticoids:
Cortisol
Zona reticularis
Sex steroids:
Progesterone.,
androgen$, estrogen
precur-so rS
CORTEX
MEDULLA
Catecholamines

Cortisol Effects: Circadian secretion to match our dailv activities



Aldosterone action





Disorders of Adrenal gland

Primary adrenal insufficiency

Hereditary

- Congenital adrenal hyperplasia
- Congenital adrenal hypoplasia (X-linked & A.R)
- Adrenal unresponsiveness to ACTH
- Adrenoleukodystrophy
- Adrenomyeloneuropathy
- Refsum‘s disease
- Wolman disease

Primary adrenal insufficiency

Acquired causes:

- Autoimmune
  - Isolated adrenal insufficiency (Addison's)
  - Polyglandular autoimmune syndrome type 1
    - (Addison's, hypoparathyroidism, chronic candidiasis)
  - Polyglandular autoimmune syndrome type 2
    - (Addison's, IDDM, autoimmune thyroid disease)
- Infectious
  - Tuberculosis
  - Systemic fungal infections
  - Histoplasmosis
  - HIV
  - CMV

Primary adrenal insufficiency

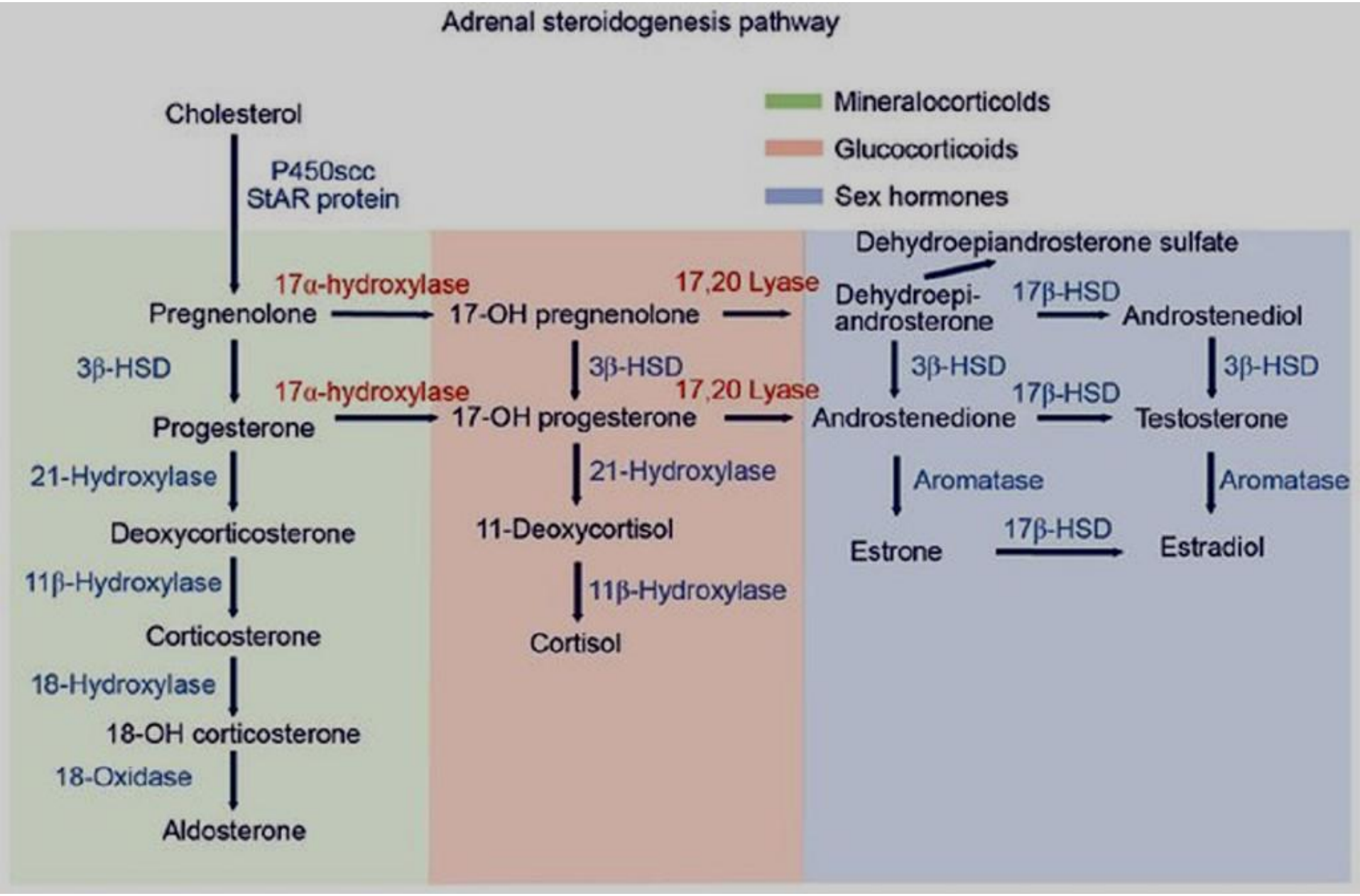
Miscellaneous

- Adrenal hemorrhage
- Triple A syndrome= Allgrove syndrome
- Medications
  - Decreased steroid synthesis (ketoconazole)
  - Increased steroid metabolism
    - (rifampin, phenytoin, Phenobarbital)

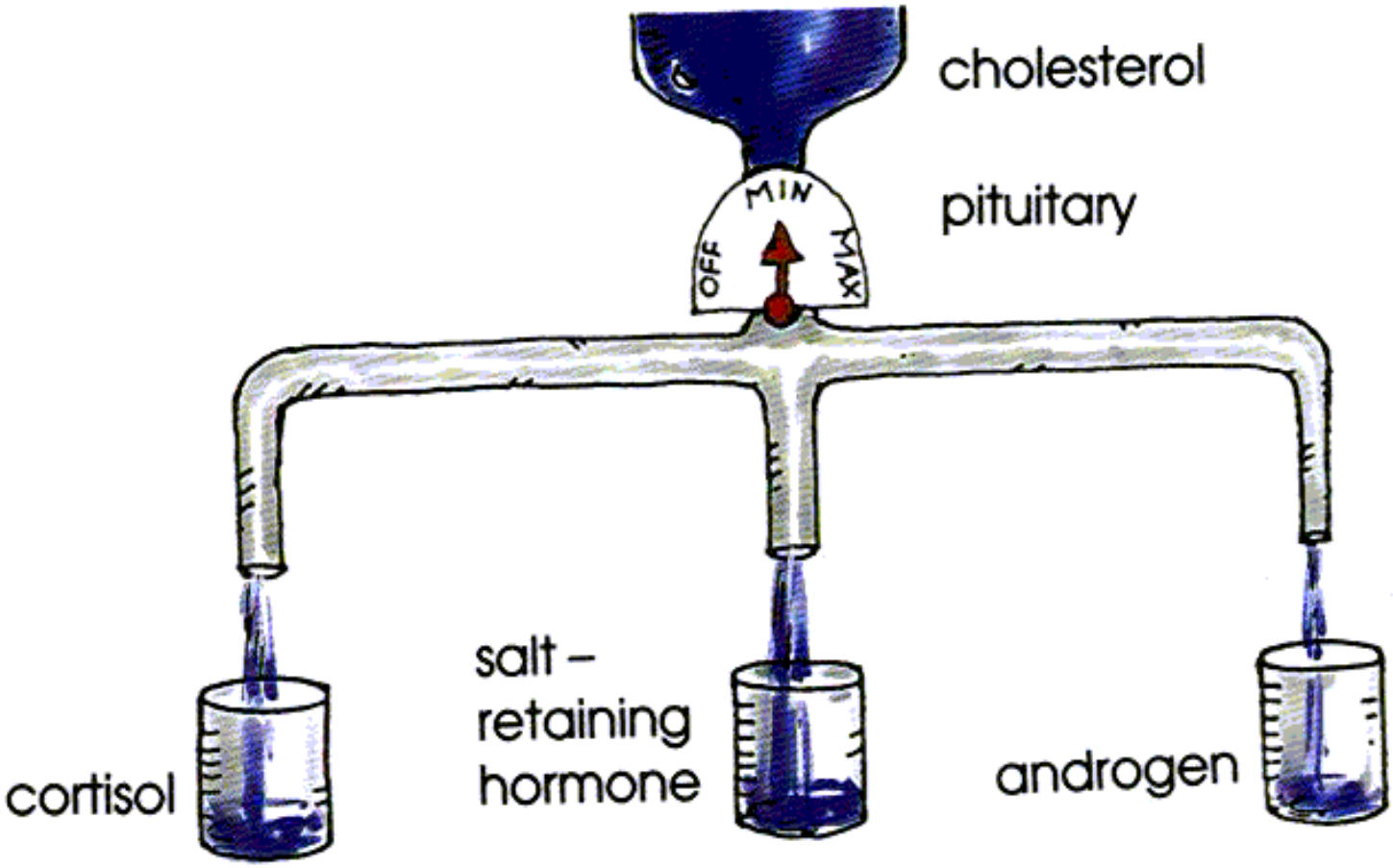
Secondary /Tertiary adrenal insufficiency

- Isolated ACTH deficiency
- Panhypopituitarism (congenital / acquired)
- Hypothalamic / pituitary disorders
  - Tumors, surgery, radiation therapy
- Withdrawal from glucocorticoid therapy
- Inadequate glucocorticoid replacement
- Infant born to steroid-treated mother
- Surgical removal of ACTH-producing tumours
  - of the pituitary gland (Cushing's disease)

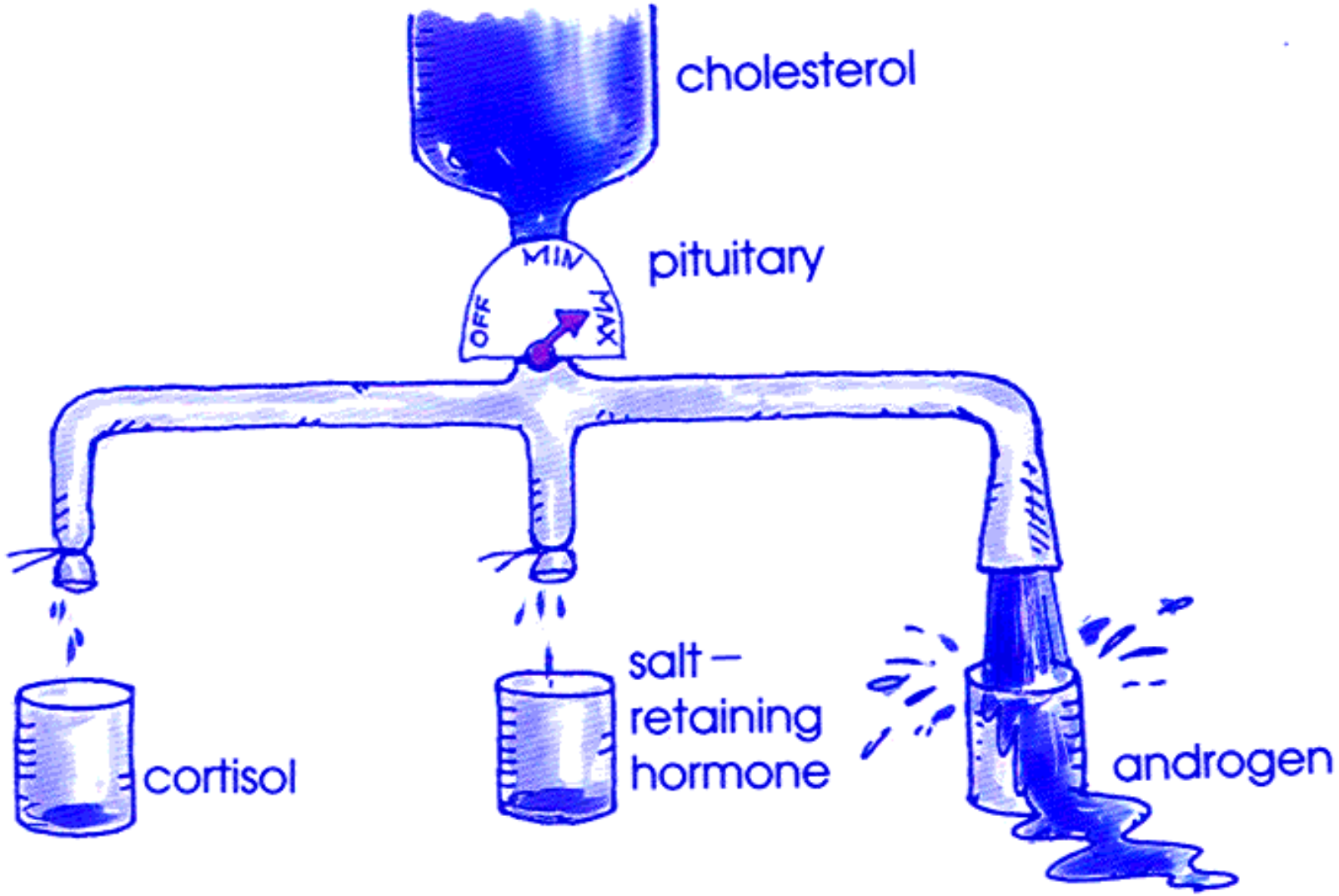
Congenital Adrenal Hyperplasia


Adrenal steroidogenesis pathway
Mineralocorticoids
Glucocorticoids
Sex hormones
Cholesterol
P450scc
StAR protein
Pregnenolone
17α-hydroxylase
17-OH pregnenolone
17,20 Lyase
Dehydroepiandrosterone sulfate
Dehydroepi-androsterone
17β-HSD
Androstenediol
3β-HSD
3β-HSD
3β-HSD
3β-HSD
Progesterone
17α-hydroxylase
17-OH progesterone
17,20 Lyase
Androstenedione
17β-HSD
Testosterone
21-Hydroxylase
21-Hydroxylase
Aromatase
Aromatase
Deoxycorticosterone
11-Deoxycortisol
Estrone
17β-HSD
Estradiol
11β-Hydroxylase
11β-Hydroxylase
Corticosterone
Cortisol
18-Hydroxylase
18-OH corticosterone
18-Oxidase
Aldosterone

Normal Adrenal Cortex Production



Congenital Adrenal Hyperplasia



Congenital Adrenal Hyperplasia

- It is a familial disorder of adrenal steroid biosynthesis with autosomal recessive mode of inheritance.
- The defect is expressed as adrenal enzyme deficiency
- 5 major Enzymes deficiency are clinically important
  - 21-Hydroxylase (90-95% cases)
  - 11-β-Hydroxylase
  - 17-α-Hydroxylase
  - 3-β-Hsteroid hydrogenese
  - 20,22 Desmolase deficiency

Congenital Adrenal Hyperplasia

- Autosomal Recessive disease (M=F)
- Incidence 1:1000 -15,000
- Carrier Rate 1 / 50
- 21-hydroxylase enzyme deficiency is the commonest cause in 90-95 % of cases
- Gene CYP21 on Chromosome 6
- Neonatal screening by filter paper on 3rd day
- of life (17 OHP)
- Prenatal therapy is effective in preventing genital virilization of affected females

Congenital Adrenal Hyperplasia

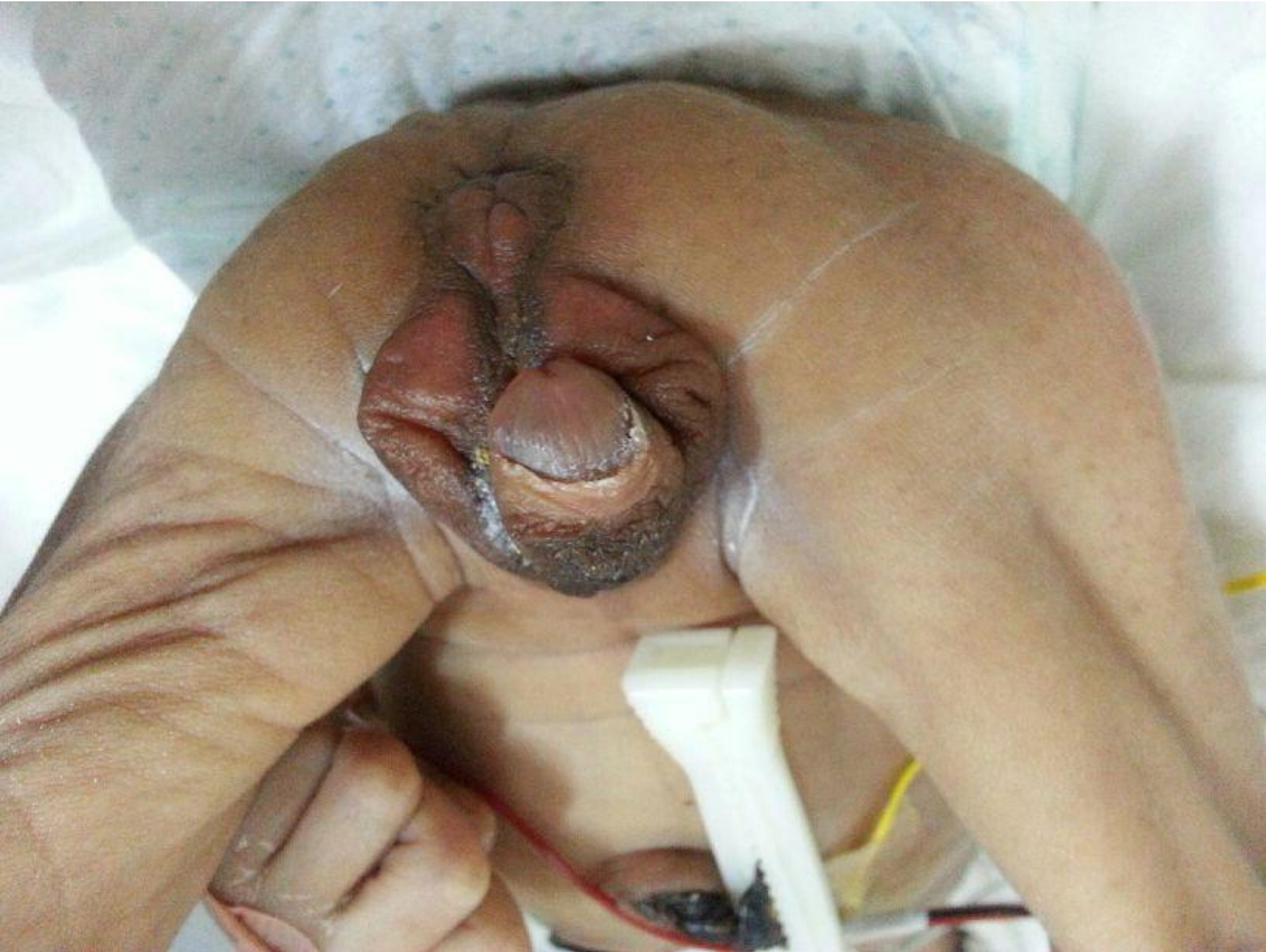
- The clinical phenotype depends upon the nature & severity of the enzyme deficiency
- Approximately 2/3 of patients with classic congenital adrenal hyperplasia due to 21- hydroxylase deficiency have salt wasting due to inadequate Aldosterone synthesis
- Females are usually recognized at birth because of ambiguous genitalia

Classical Vs Non- classical CAH

- Depending on the severity of enzyme deficiency CAH classified into 2 forms:
  - Classical type with moderate – severe enzyme deficiency
  - Non – classical type with mild enzyme deficiency
- Classical form presents with early virilization with or without salt-losing crisis, while non-classical type presents with late- onset virilization
- Non-classical type remains asymptomatic till late childhood when they may show signs of sexual precocity (peripheral precocious puberty)

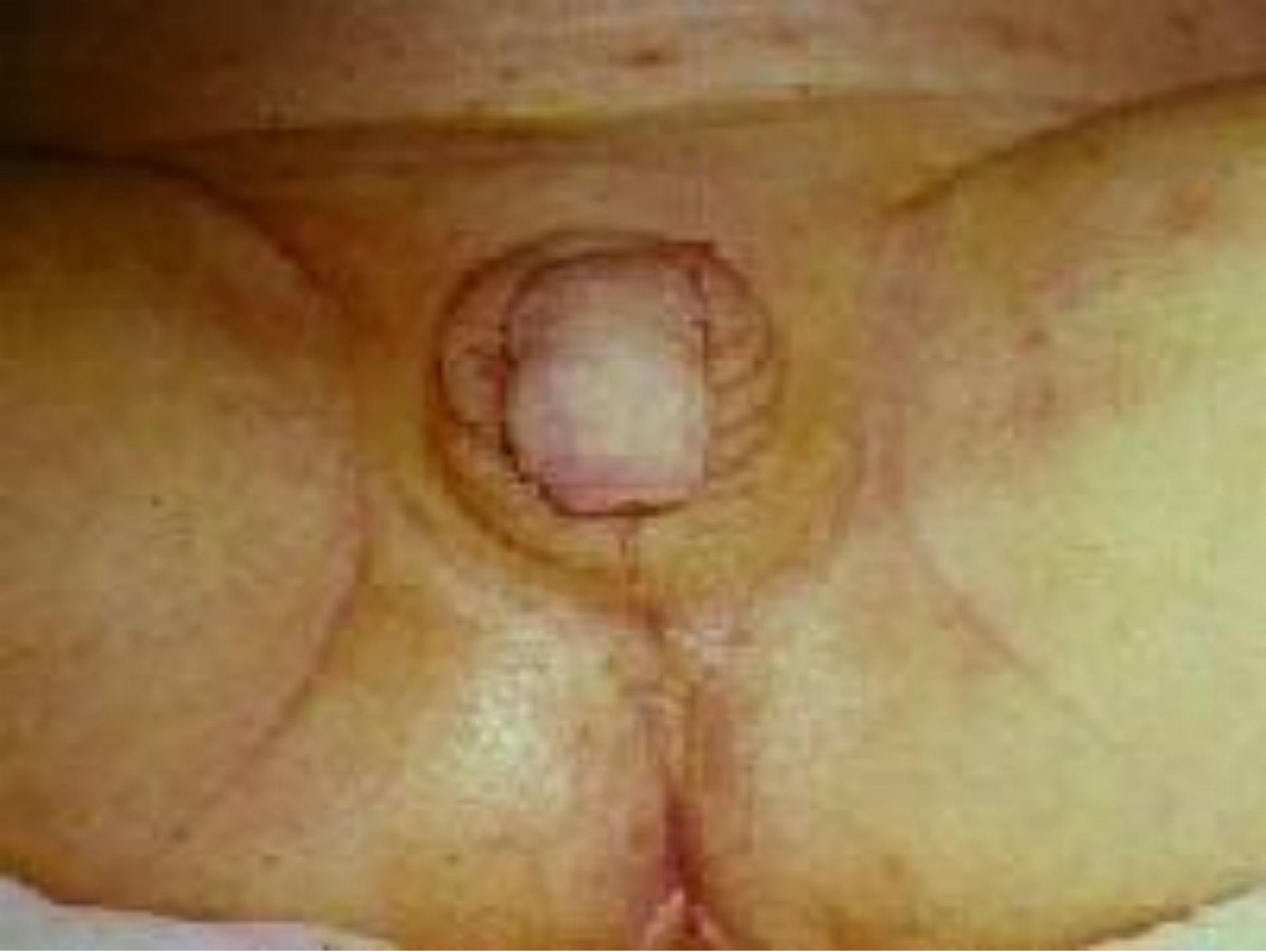
Females with CAH

- Classical form:
  - Have ambiguous genitalia at birth
  - complete fusion of the labioscrotal folds and a phallic urethra
  - clitoromegaly & partial fusion of the labioscrotal folds
- Non – classical form:
  - genitalia is normal at birth
  - Precocious pubic hair & clitoromegaly & excess facial or body hair appear early in childhood,
  - Often accompanied by tall stature



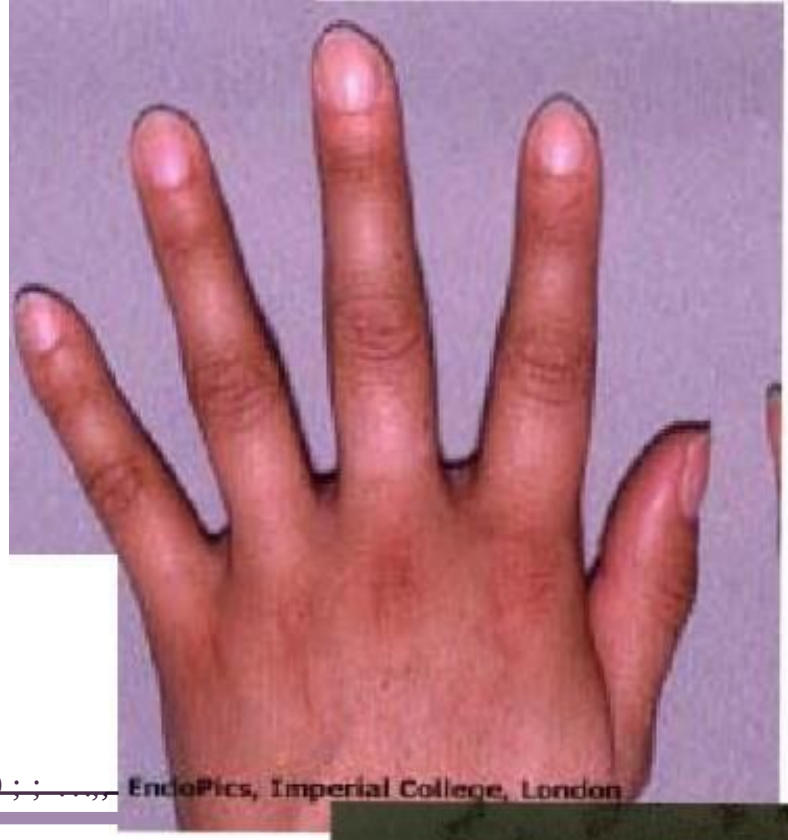
Males with CAH

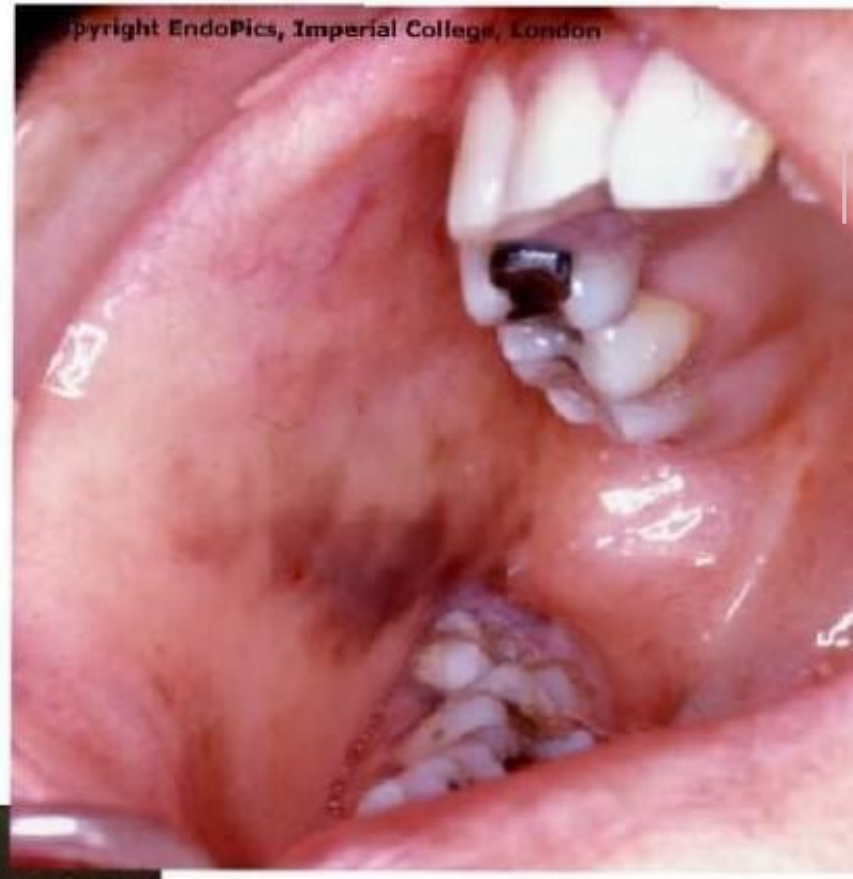
- Are not recognized at birth because their genitalia are normal
- Classical form of 21 hydroxylase enzyme:
  - They are not diagnosed until later, often with a salt wasting crisis resulting in dehydration, hypotension, or later in childhood with early pubic hair & phallic enlargement accompanied by accelerated linear growth & advancement of skeletal maturation
  - Classical form of high enzymes mild lead to feminization of external genitalia
- Non classical form:
  - Precocious pubic hair & clitoromegaly & excess facial or body hair appear early in childhood, often accompanied by tall stature



Presentations of CAH

- Ambiguous genitalia.
- Failure to thrive.
- Dehydration & Shock.
- Salt-wasting presentations with electrolytes imbalance
  - Hyponatremia & hypochloremia
  - Hyperkalemia & metabolic acidosis
- Hypoglycemia.
- Hyperpigmentation.


EndoPics, Imperial College, London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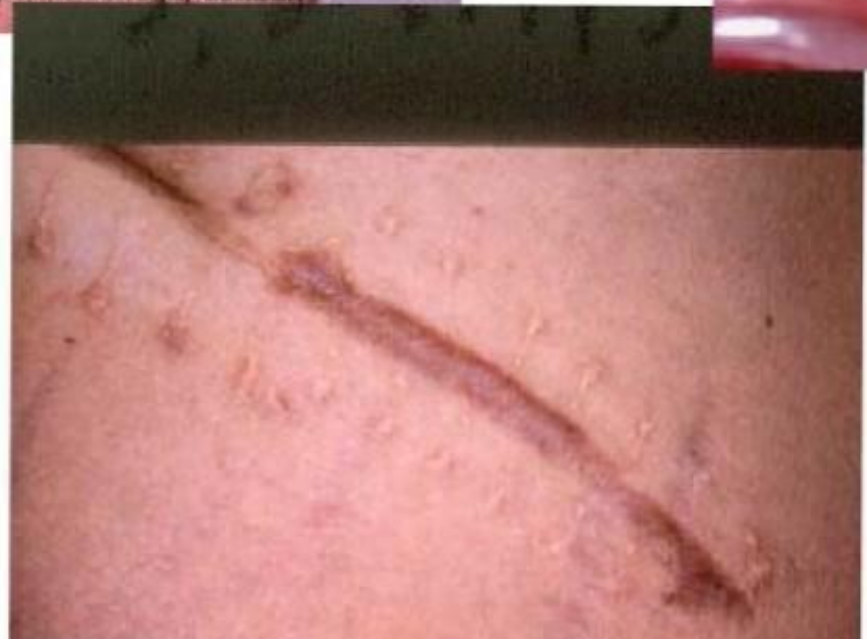
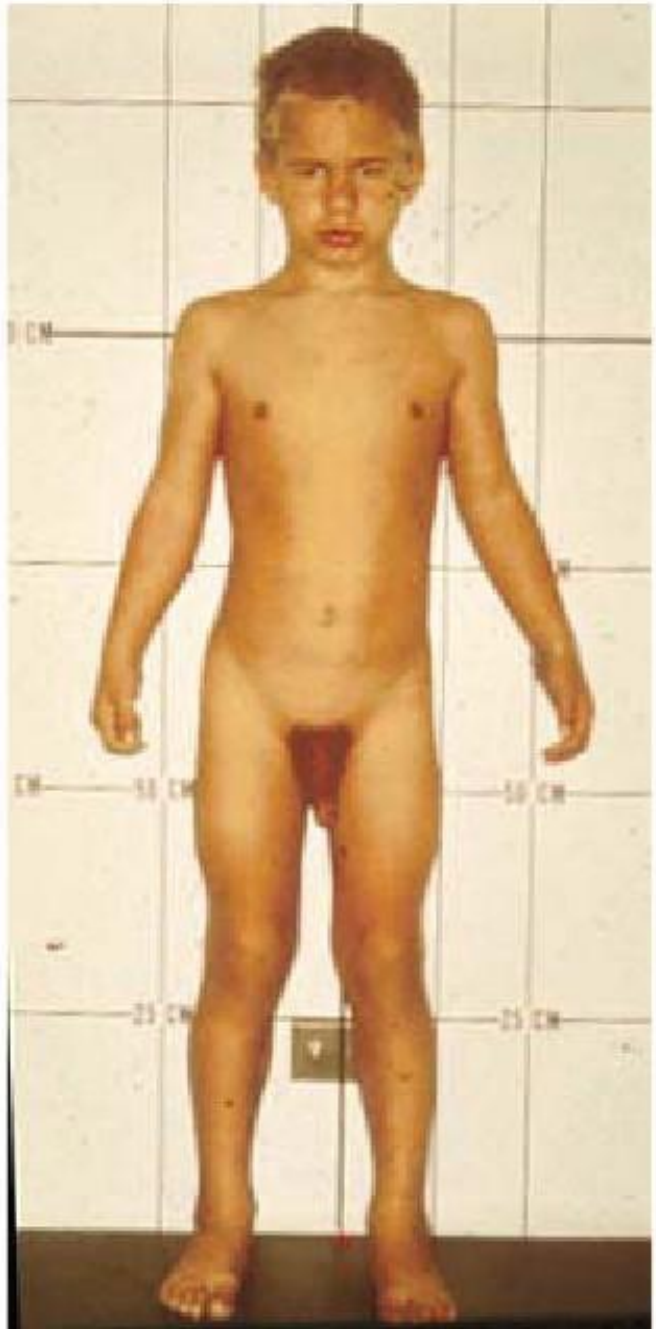
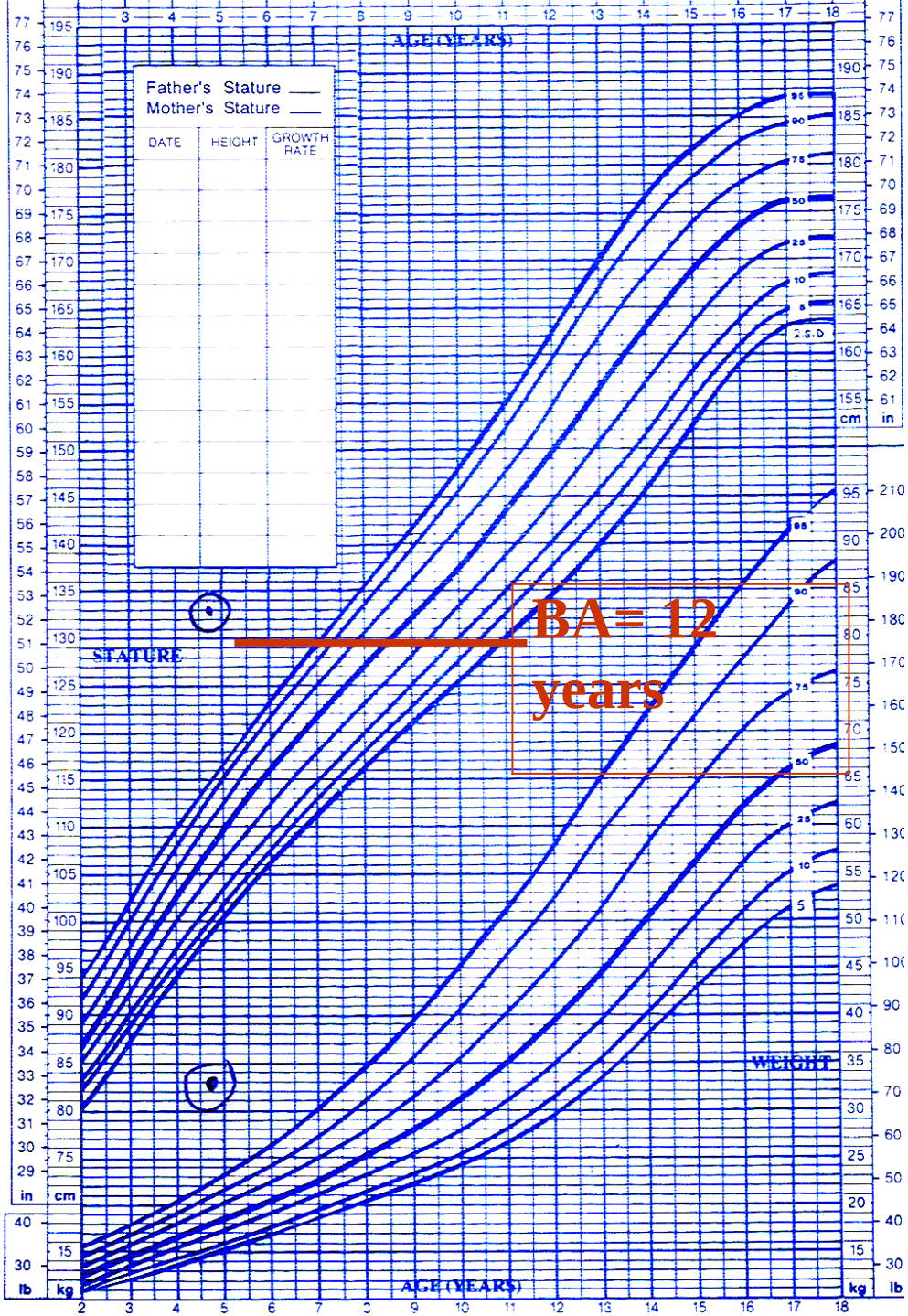


Non-Classical CAH

- Pseudo precocious puberty.
- Pubarche/ Adrenarche & advanced growth.
- Oligo- Amenorrhea & menstrual irregularity.
- Early beard hair growth, acne.
- Androgenic Alopecia.
- Infertility.
- Need hydrocortisone therapy to suppress adrenal androgens.

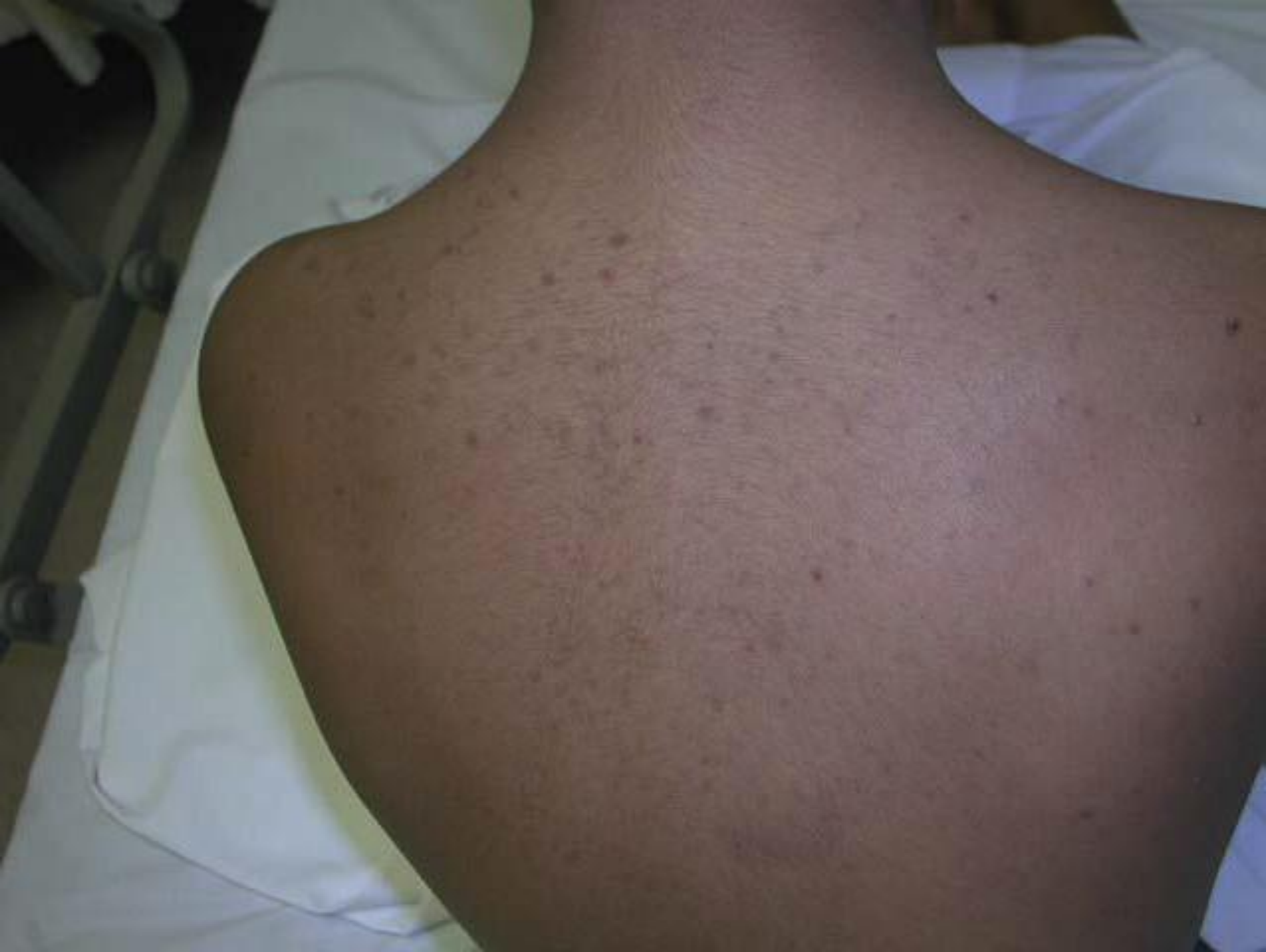
Non-Classical CAH

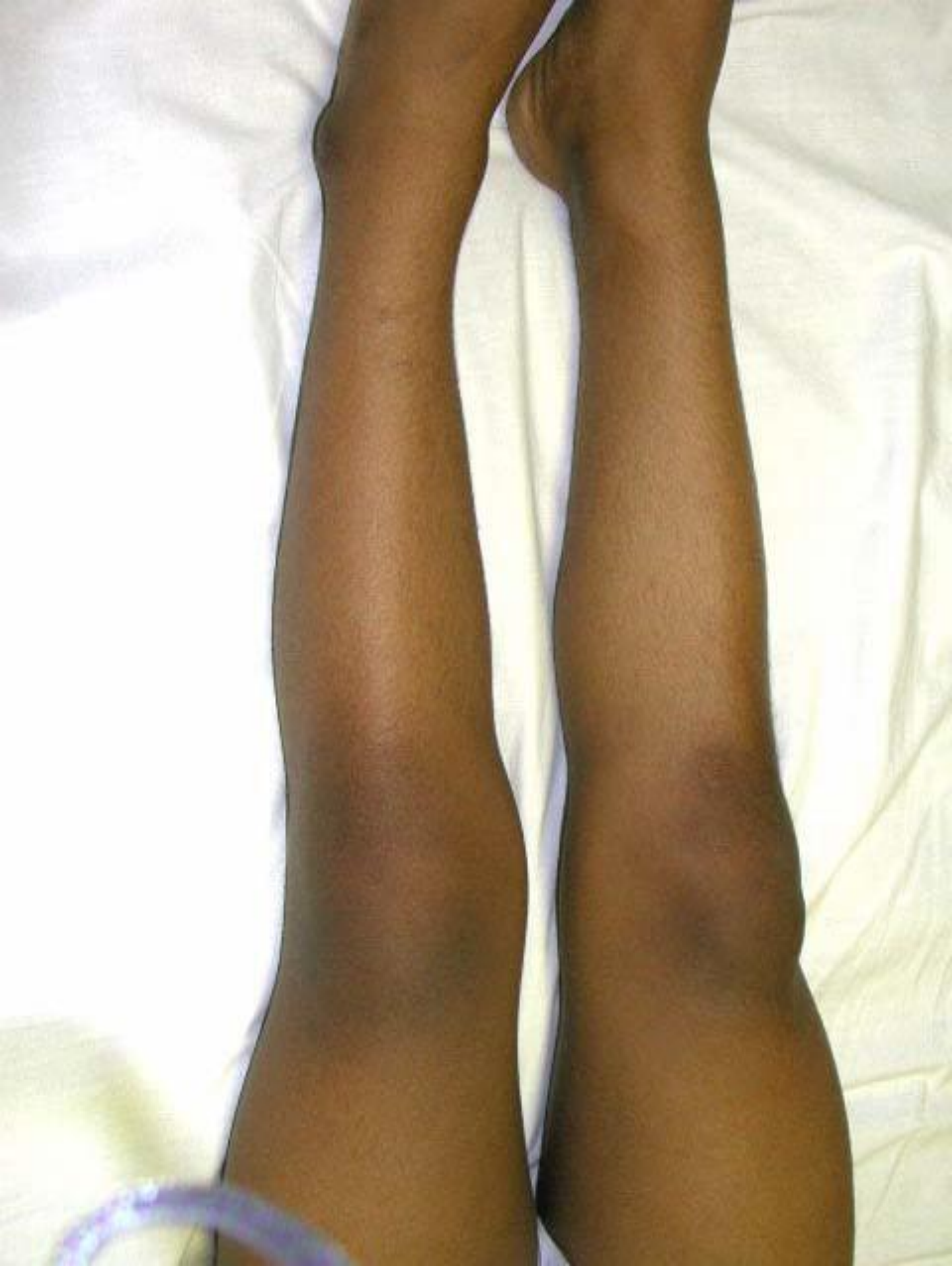


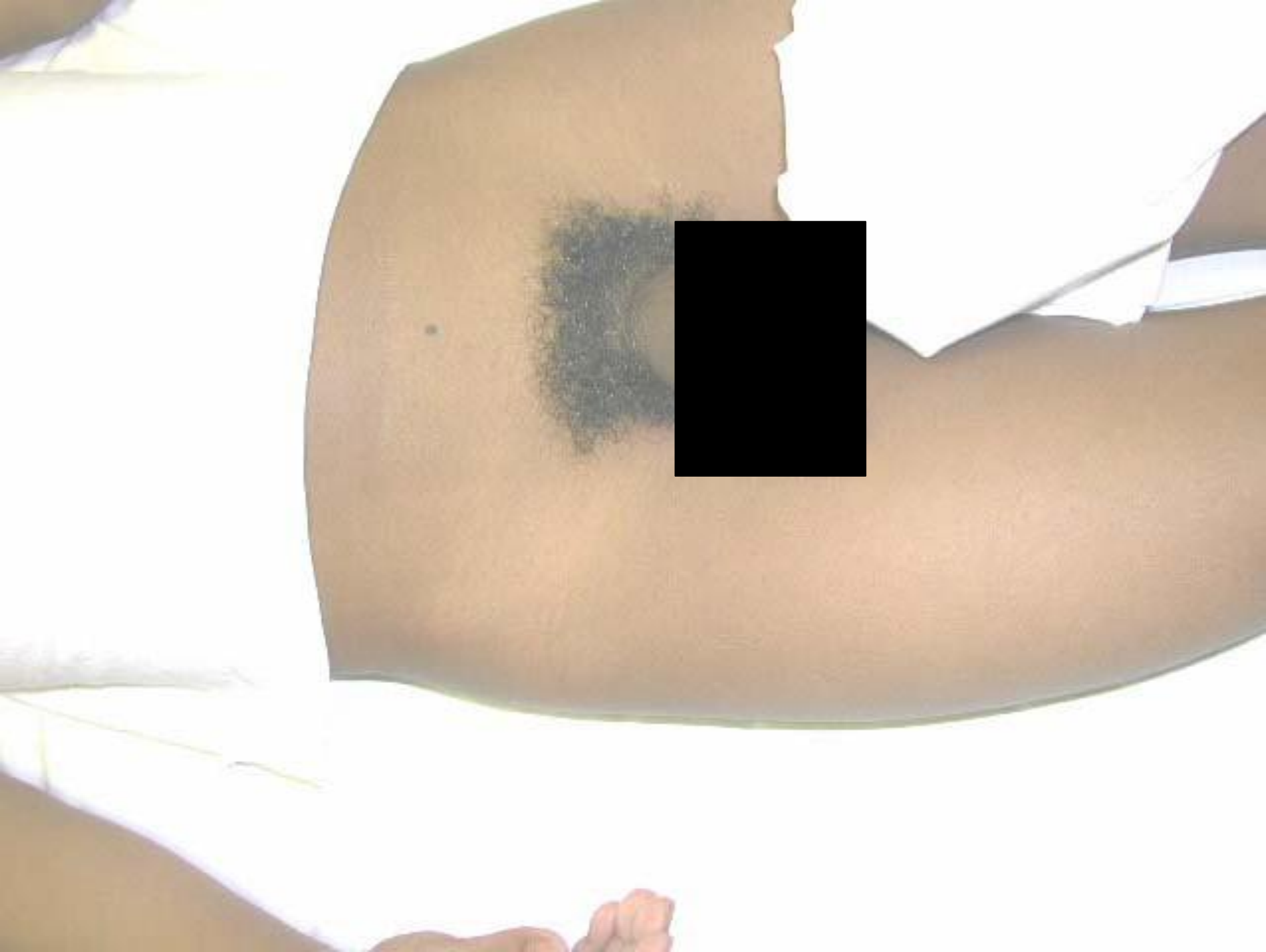


Height = 132.8 cm

Weight = 33 kg







Laboratory findings

- Low sodium & chloride
- High serum potassium.
- High serum urea.
- Metabolic acidosis.
- Hypoglycemia.
- High androgens including: 17- hydroxyprogestrone, DHEA, DHEAS & testosterone.
- High urinary 17-ketosteroid.
- Low serum Cortisol with high ACTH.
- Low serum Aldosterone with high Renin in 60-70 % of cases (salt –losing cases).

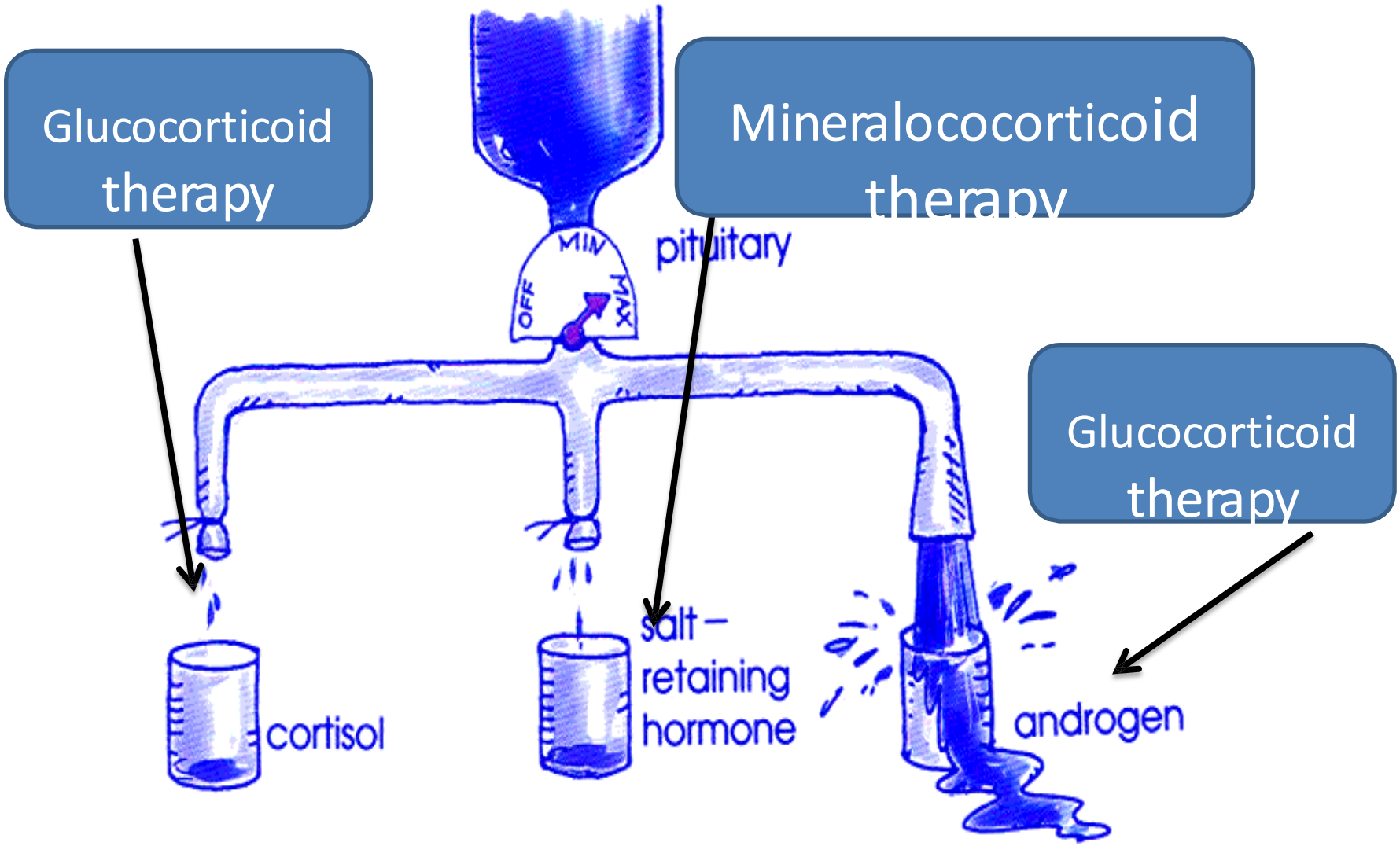
Other studies

- Karyotype is essential in the evaluation of the infant with ambiguous genitalia in order to establish the chromosomal sex
- Pelvic ultrasound: in the infant with CAH usually indicates normal internal genitalia for females & no internal structures for males
- Urogenitogram is often helpful to define the anatomy of the internal genitalia

Management

- Treatment is life-long steroid replacement
  - Hydrocortisone as glucocorticoid agent
  - Fludrocortisone as mineralocorticoid agent
- Plastic surgery for ambiguous genitalia at early age
- Genetic counseling
- Psychological support

Goals of CAH Therapies



Management

- Hydrocortisone 10-15 mg/m2/day divided into three doses orally
- In infancy & early childhood, sodium replacement is required
- Fludrocortisone 0.05 - 0.2 mg/day
- Monitor growth, signs of androgen excess, pubertal development & blood pressure