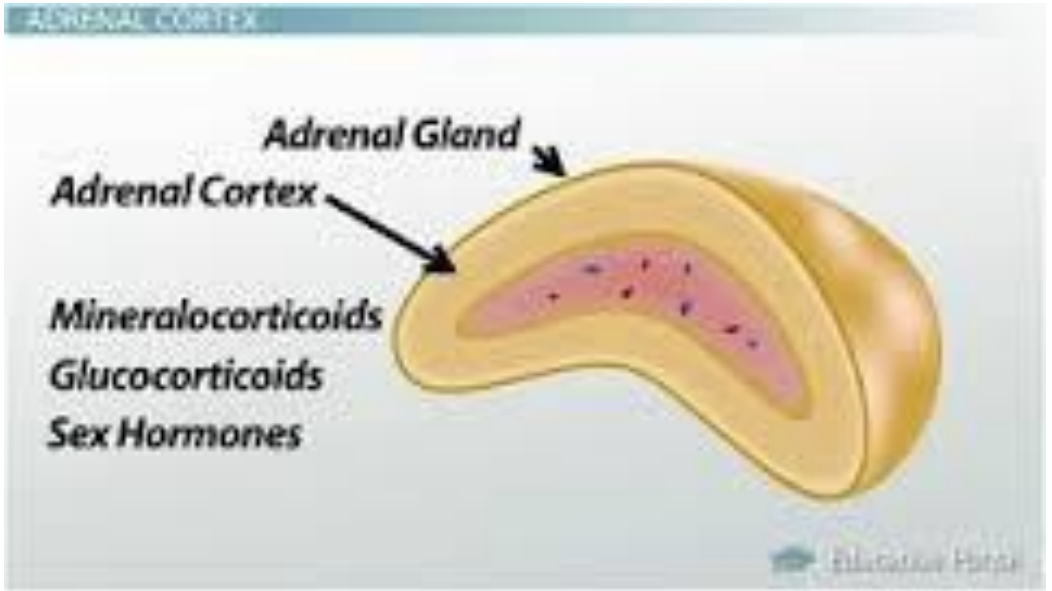
Congenital Adrenal Hyperplasia

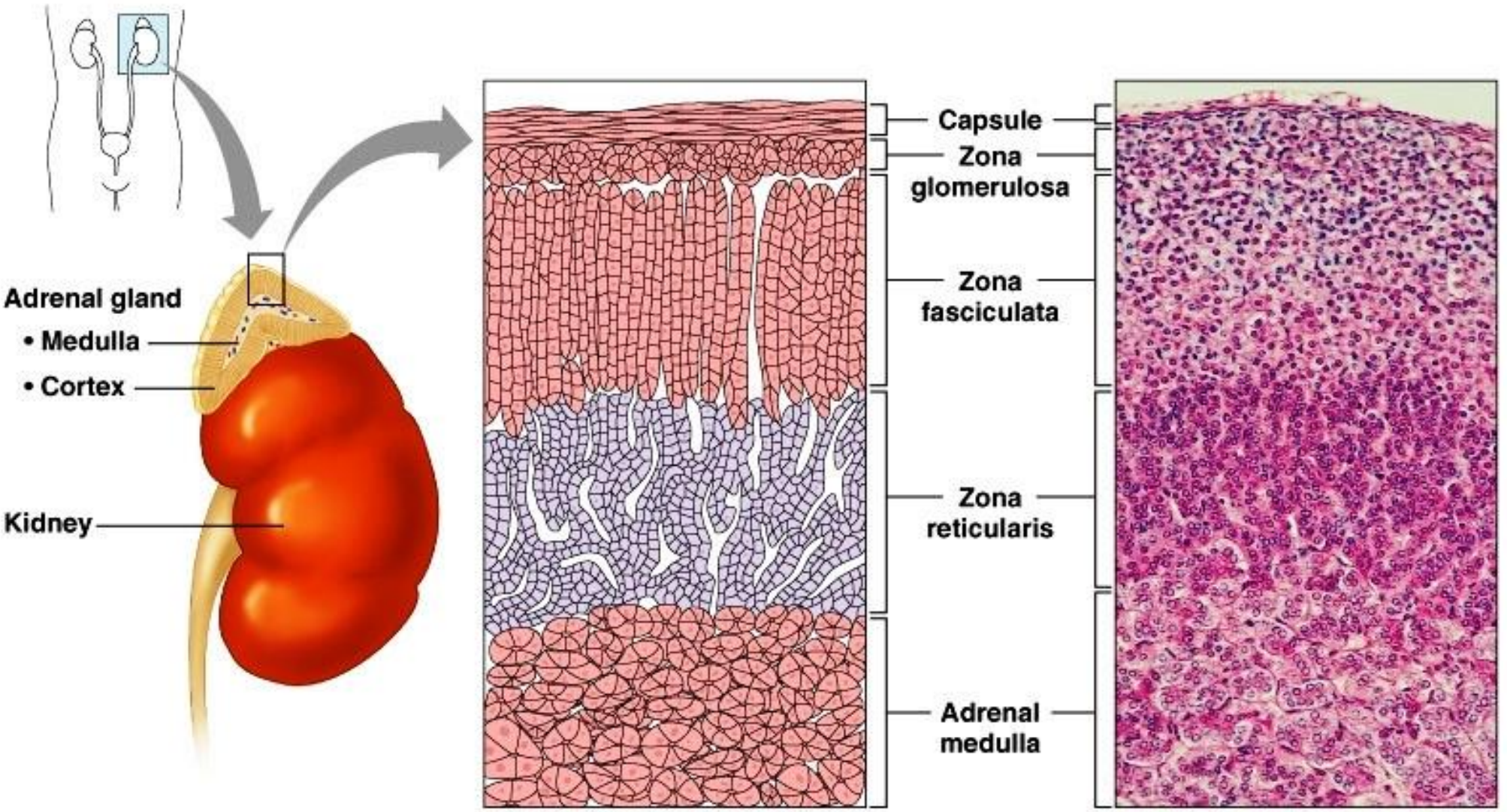


Abdulmoein Eid Al-Agha, MBBS, DCH, CABP, FRCPCH
Professor of Pediatric Endocrinology,
King Abdulaziz University Hospital,
Website: http://aagha.kau.edu.sa

Objectives

At end of this lecture, students will be able to:

- Recognize the anatomy & physiology of the adrenal gland & the related steroid hormone.
- Recognize the types and presentations of congenital adrenal hyperplasia (CAH).
- Recognize differential diagnosis of different types of CAH and the clinical findings for each.
- Formulate an approach to a child with CAH via history, clinical examination, investigation (electrolyte and acid-base imbalances), and treatment.
- Explain the management plan of an infant presenting with adrenal crises in the Emergency Department (including ABCDE) and the maintenance treatment.


Adrenal gland
• Medulla
• Cortex
Kidney
Capsule
Zona glomerulosa
Zona fasciculata
Zona reticularis
Adrenal medulla

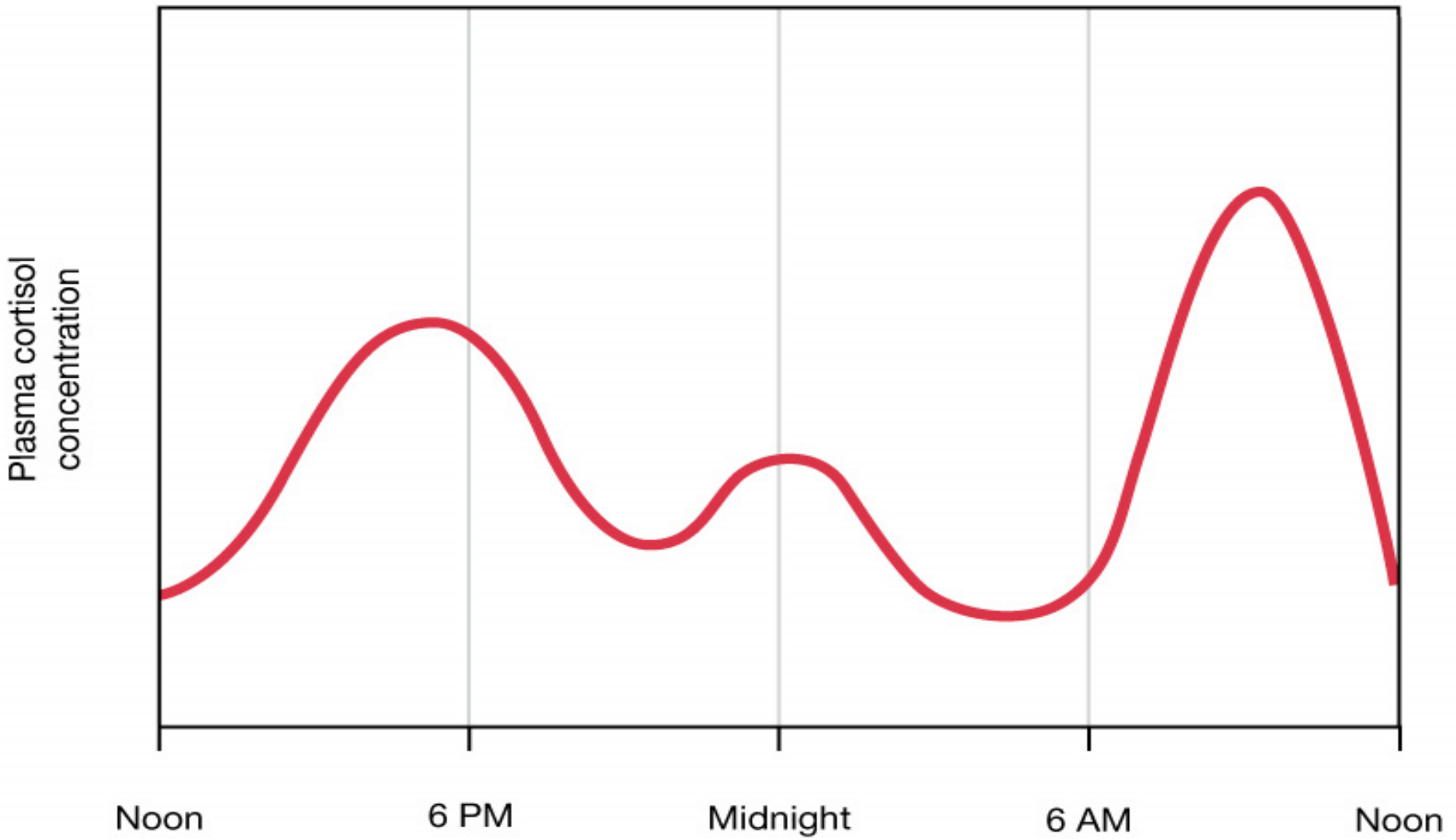
The Adrenal gland

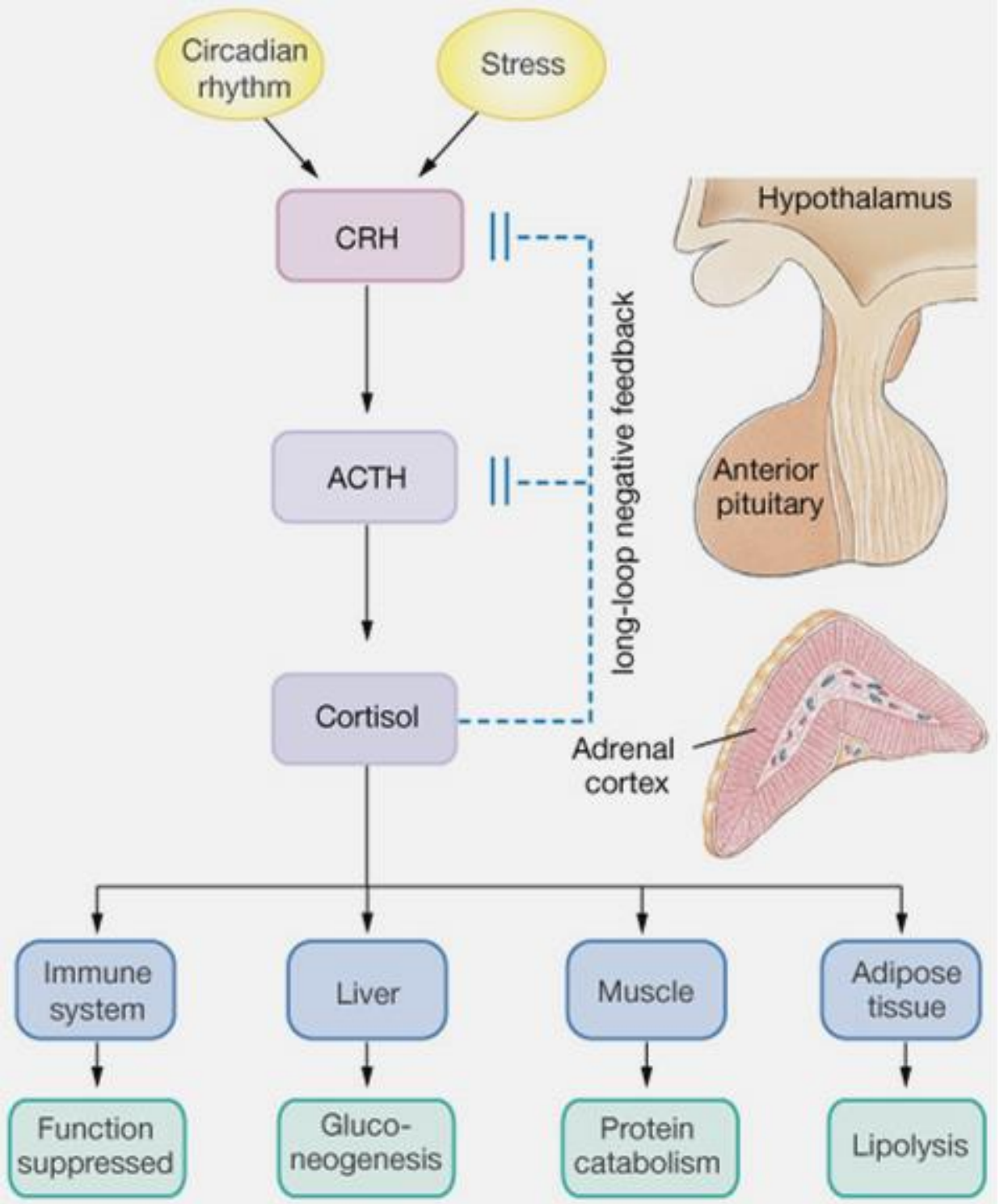
- The adrenal gland lies just above the kidneys
- Divided into two main sub-organs
  - Adrenal cortex
    - Secretes the steroid hormones
      - Glucocorticoid
      - Mineralocorticoid
      - Androgens
  - Adrenal medulla
    - Secretes Catecholamines
      - Adrenaline (epinephrine)
      - Noradrenaline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

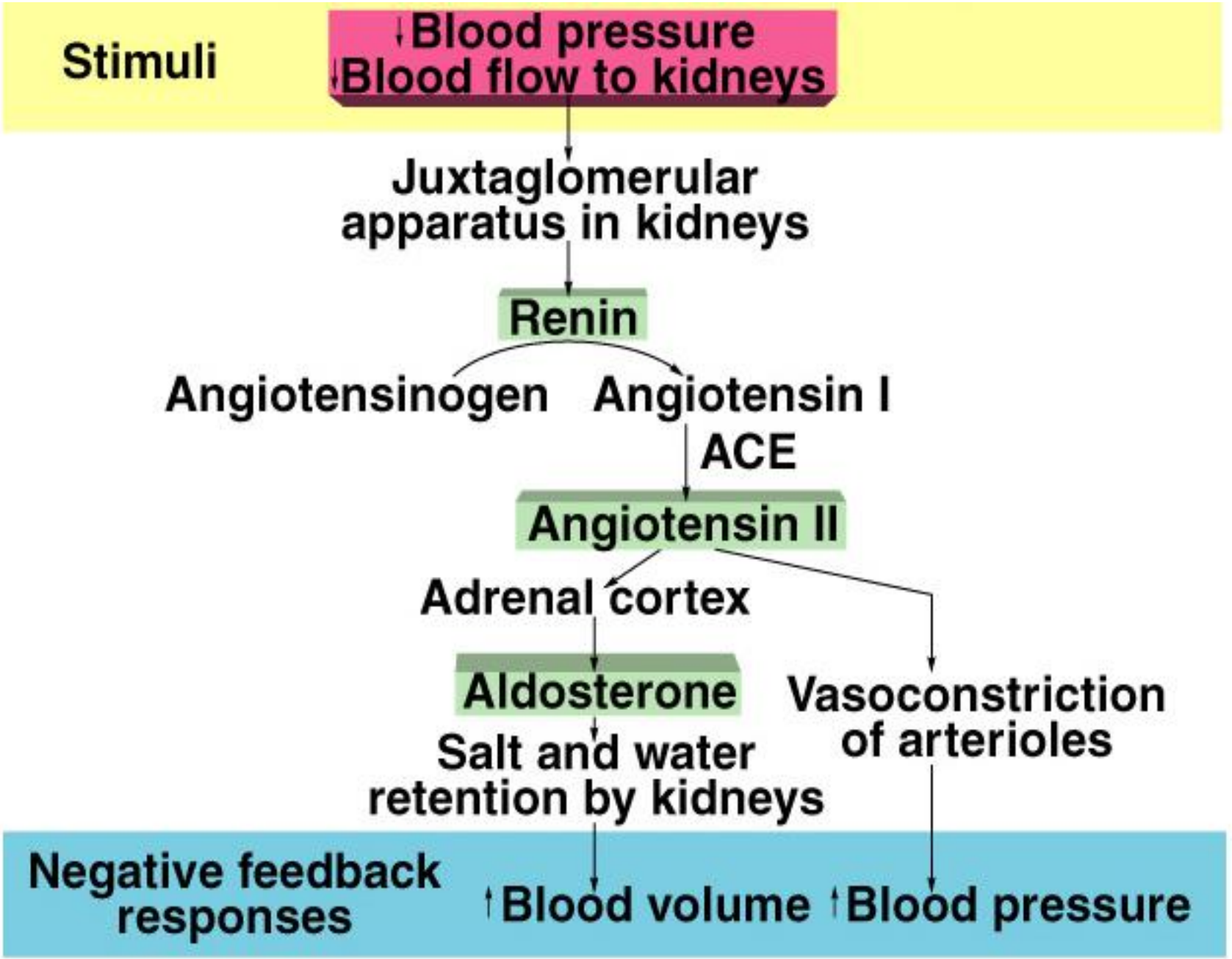
Anatomically, the adrenal gland is divided into 3 zones:

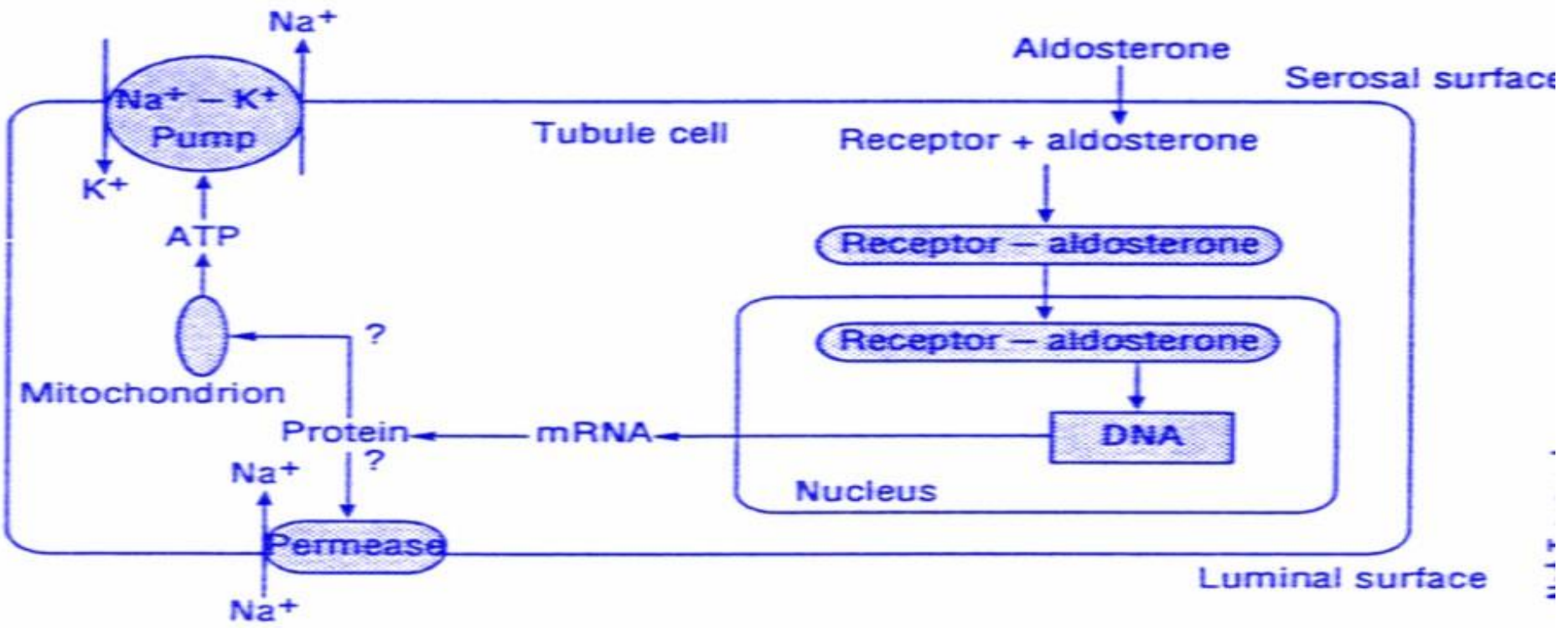
- Zona glomerulosa, which produces predominately mineralocorticoid
- Zona fasciculata, which produces predominately Glucocorticoids
- Zona reticularis, which produces predominately androgens

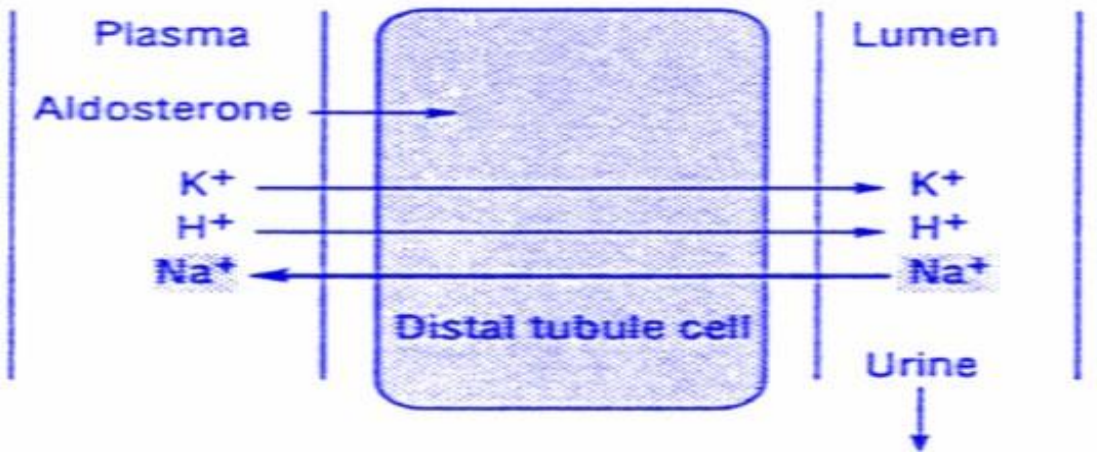
Cortisol Effects: Circadian secretion to match our daily activities




Circadian rhythm
Stress
CRH
ACTH
Cortisol
long-loop negative feedback
Hypothalamus
Anterior pituitary
Adrenal cortex
Immune system
Liver
Muscle
Adipose tissue
Function suppressed
Gluco-neogenesis
Protein catabolism
Lipolysis

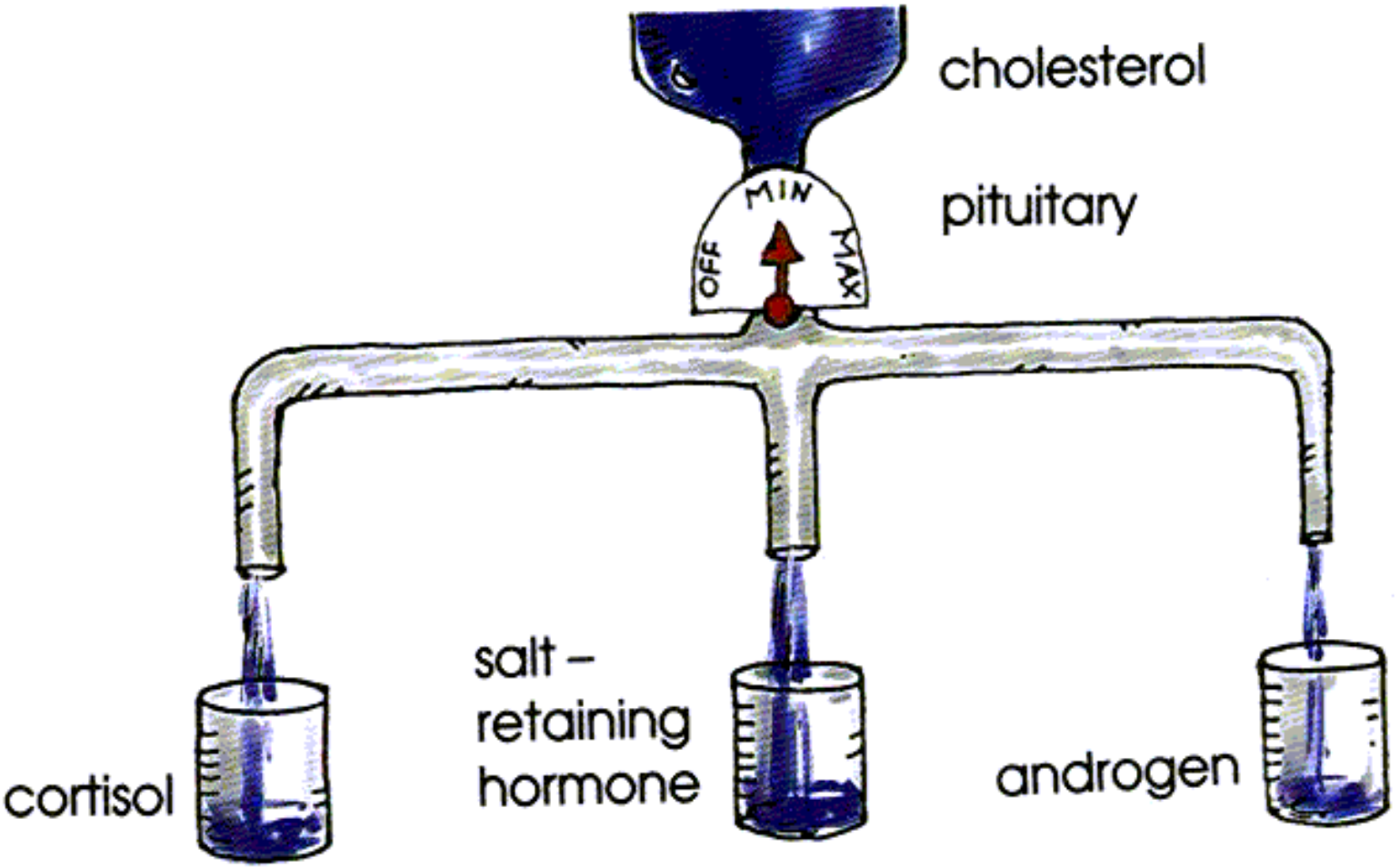

Stimuli
↓Blood pressure
↓Blood flow to kidneys
Juxtaglomerular apparatus in kidneys
Renin
Angiotensinogen
Angiotensin I
ACE
Angiotensin II
Adrenal cortex
Aldosterone
Salt and water retention by kidneys
Vasoconstriction of arterioles
Negative feedback responses
↑Blood volume
↑Blood pressure


Na+
Na+ – K+ Pump
K+
ATP
Mitochondrion
?
Protein
?
Na+
Permease
Na+
Tubule cell
Aldosterone
Serosal surface
Receptor + aldosterone
Receptor – aldosterone
Receptor – aldosterone
DNA
mRNA
Nucleus
Luminal surface

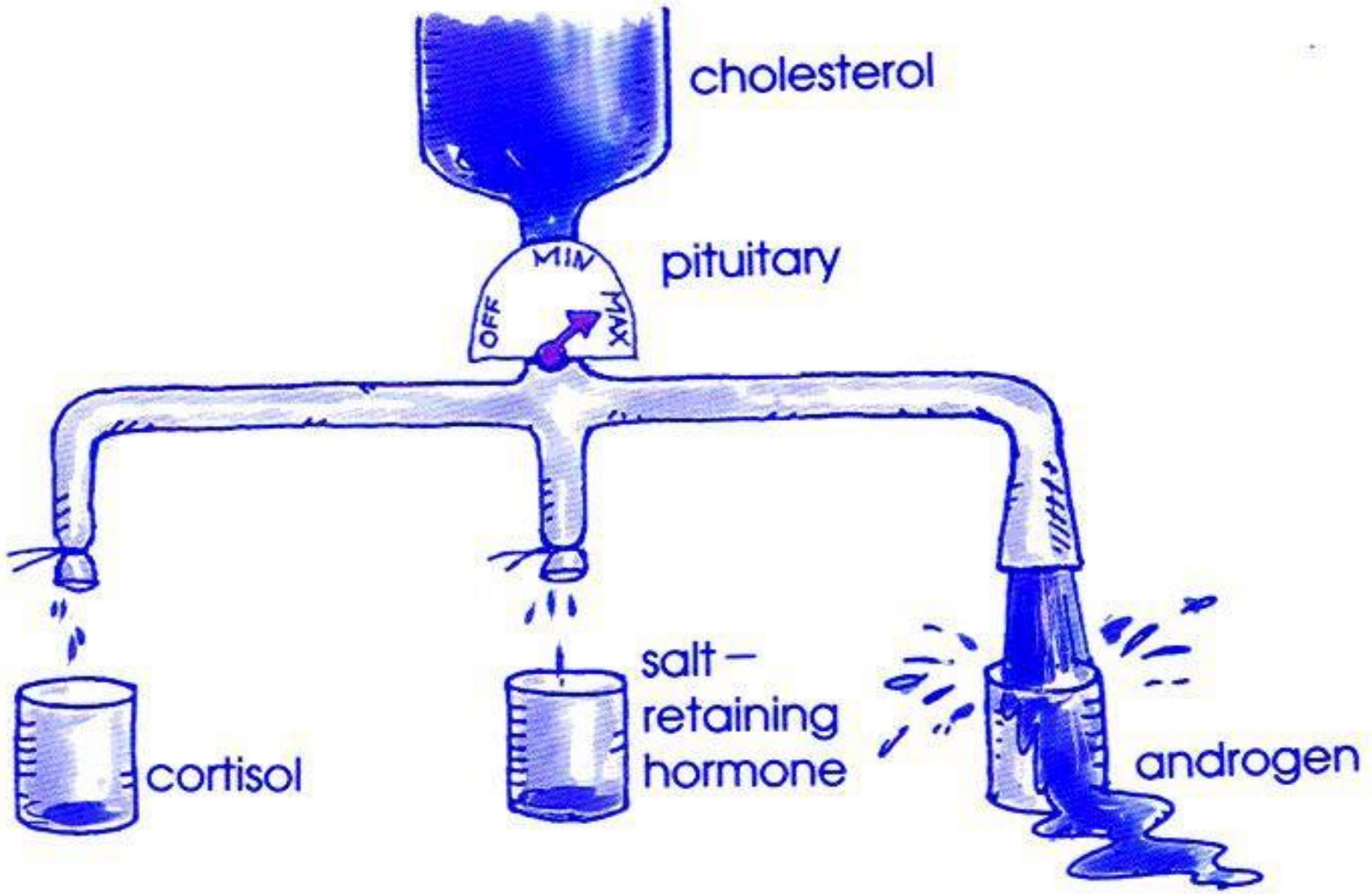

Plasma
Aldosterone
K+
H+
Na+
Distal tubule cell
Lumen
K+
H+
Na+
Urine

Congenital Adrenal Hyperplasia

Normal Adrenal Cortex Production



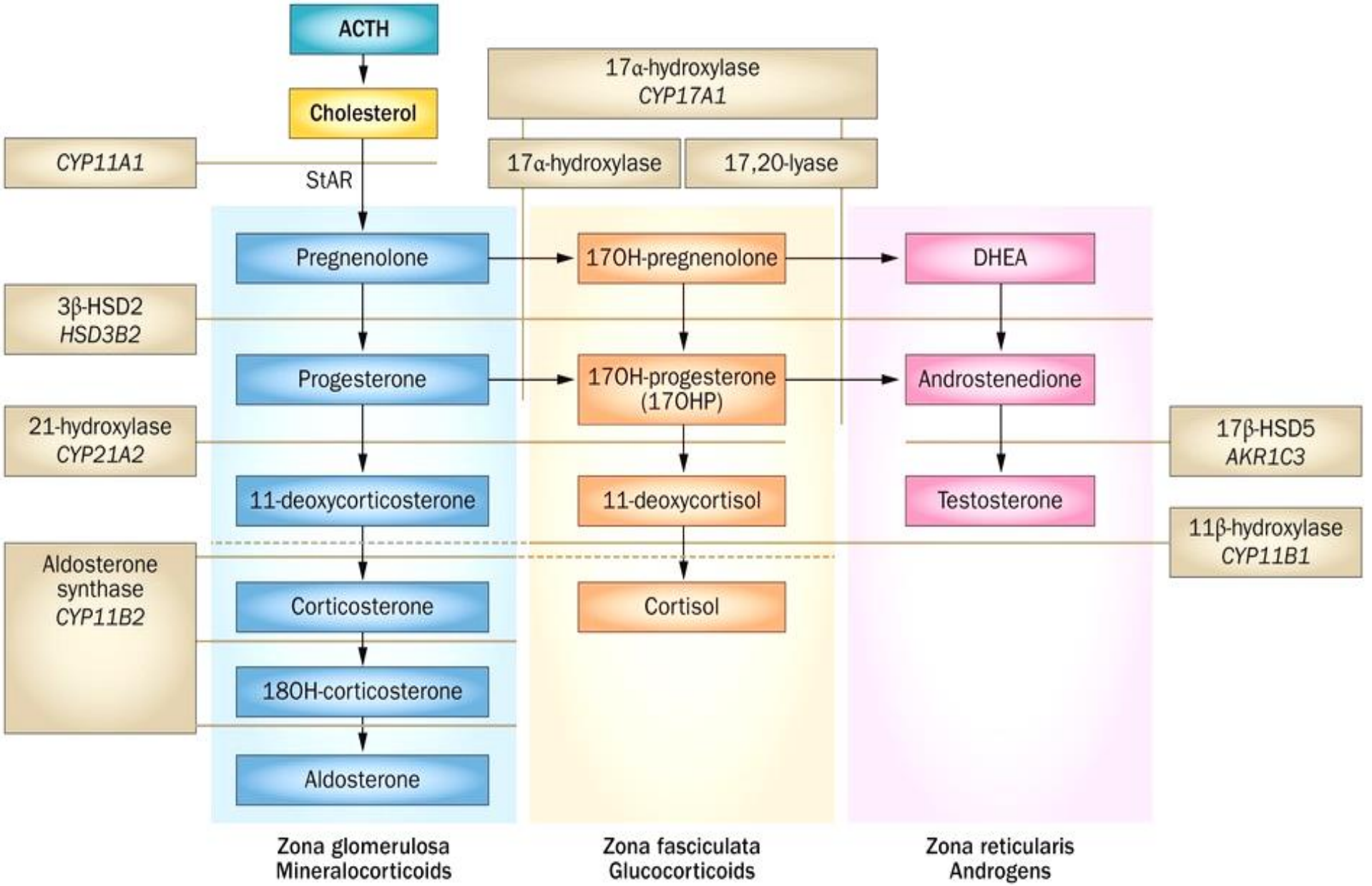
Congenital Adrenal Hyperplasia



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 but remember only one enzyme is deficient in each patient.
- 90 – 95 % of cases due to 21-Hydroxylase enzyme deficiency.
- Usual age of presentation of classical type is 7-14 days.

  - 21-Hydroxylase enzyme.
  - 11-b-Hydroxylase enzyme.
  - 17-a-Hydroxylase enzyme.
  - 3-b-Hsteroid hydrogenase enzyme.
  - 20,22 Desmolase enzyme.


ACTH
Cholesterol
CYP11A1
StAR
17α-hydroxylase
CYP17A1
17α-hydroxylase
17,20-lyase
Pregnenolone
17OH-pregnenolone
DHEA
3β-HSD2
HSD3B2
Progesterone
17OH-progesterone
(17OHP)
Androstenedione
21-hydroxylase
CYP21A2
17β-HSD5
AKR1C3
11-deoxycorticosterone
11-deoxycortisol
Testosterone
11β-hydroxylase
CYP11B1
Aldosterone
synthase
CYP11B2
Corticosterone
Cortisol
18OH-corticosterone
Aldosterone
Zona glomerulosa
Mineralocorticoids
Zona fasciculata
Glucocorticoids
Zona reticularis
Androgens

Congenital Adrenal Hyperplasia

- Autosomal Recessive disease (M=F).
- Incidence 1:1000 -15,000.
- 21-hydroxylase enzyme deficiency is the commonest cause in 90-95 % of cases.
- Gene CYP21 on Chromosome 6
- Neonatal screening on 3rd day of life by doing 17-hydroxyprogesterone (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 CAH due to 21- hydroxylase deficiency have salt wasting due to inadequate Aldosterone synthesis.
- Females are usually recognized at birth because of ambiguous genitalia.

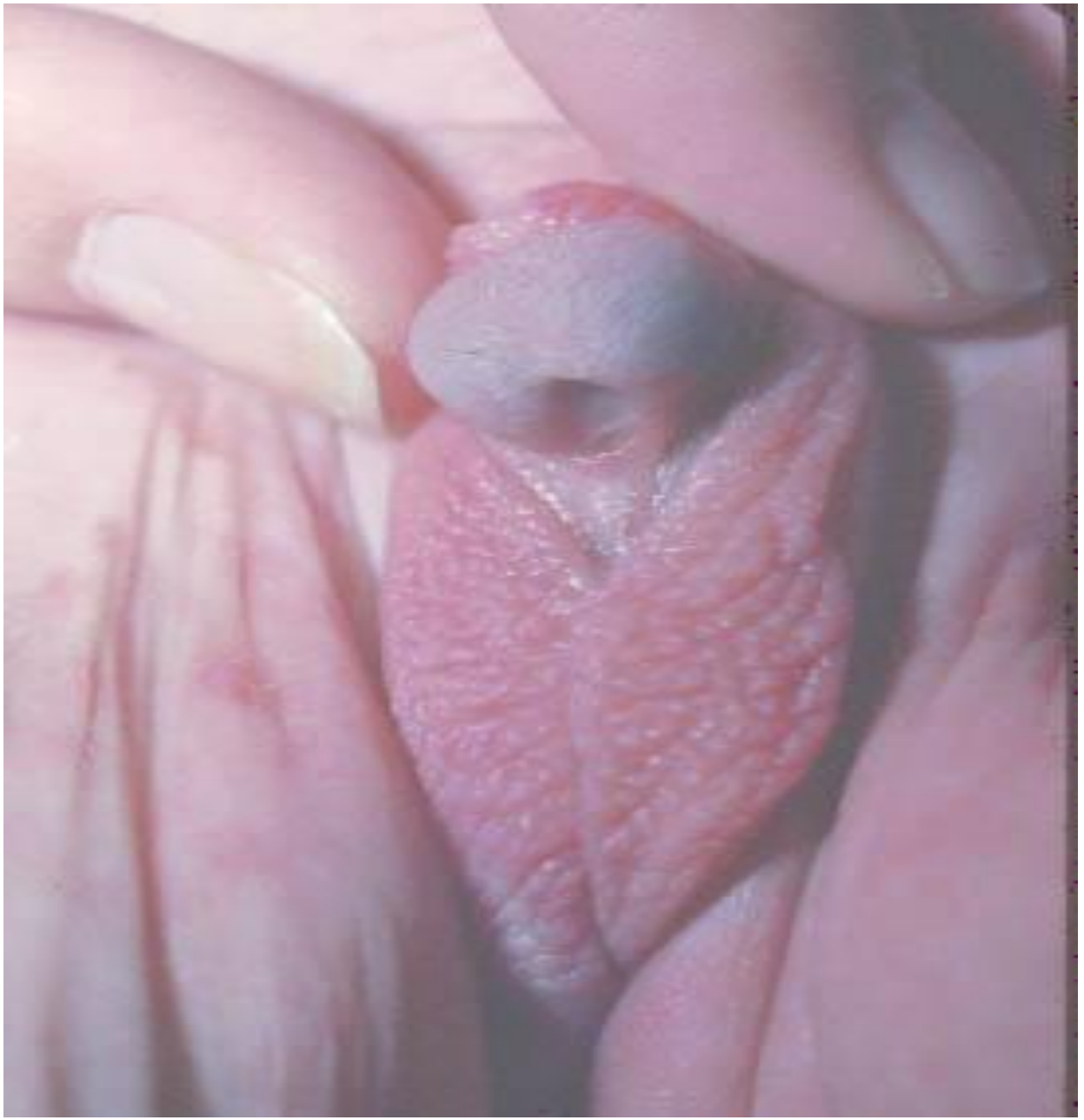
Classical Vs Non- classical CAH

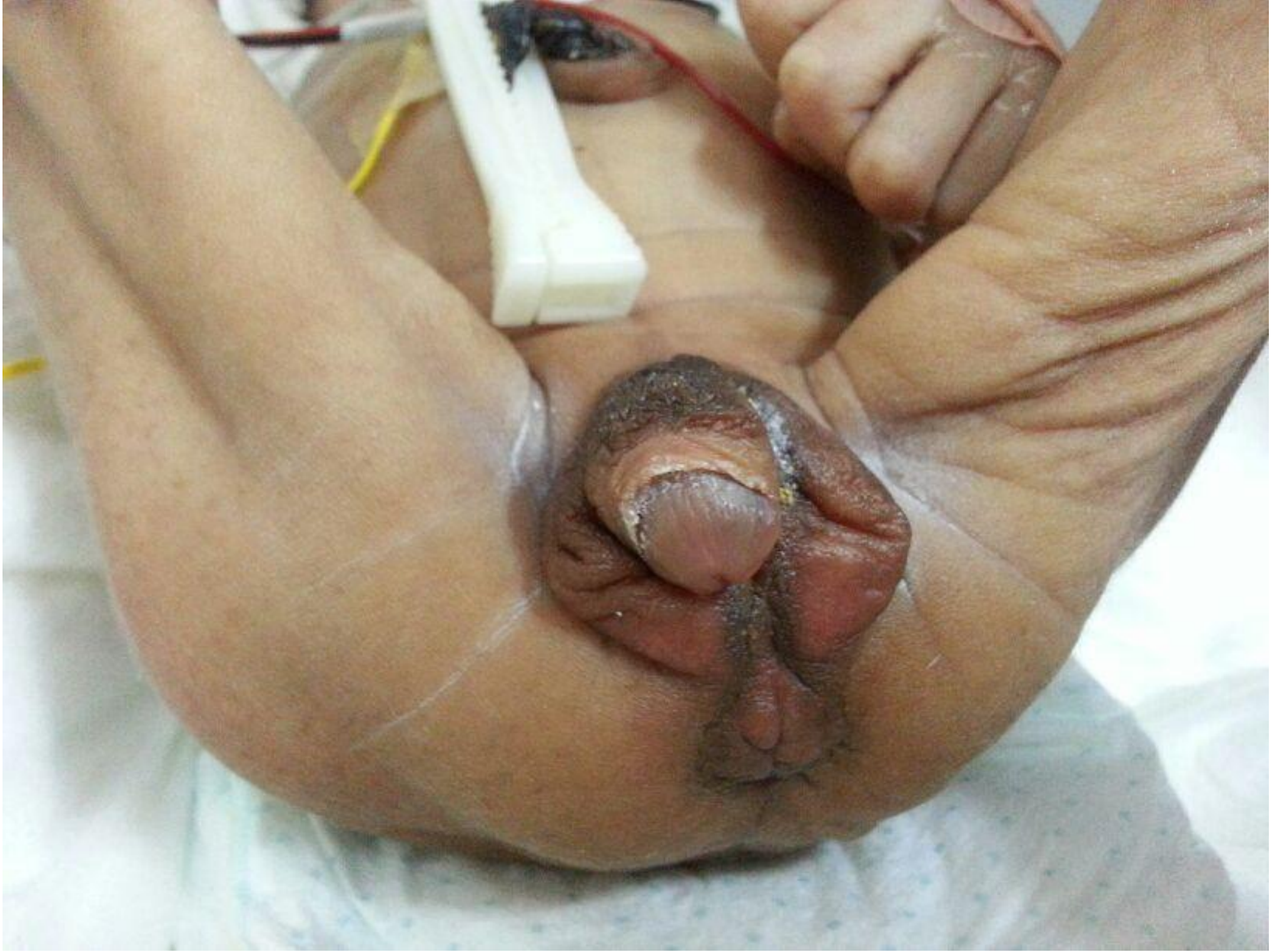
- Depending on the severity of enzyme deficiency, CAH classified into 2 forms:
  - Classicaltype with moderate – severe enzyme deficiency.
  - Non – classical type with mild enzyme deficiency.
- Classical form presents with early virilization with or without salt-losing crisis, while non-classical type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

Presentations of classical CAH

- Ambiguous genitalia (mainly in females).
- Vomiting and or diarrhea (Gastroenteritis –like).
- Failure to thrive.
- Poor feeding, decreased activity, sleepiness (sepsis –like)
- Dehydration & Shock.
- Salt-wasting presentations with electrolytes imbalance
  - Hyponatremia & hypochloremia
  - Hyperkalemia & metabolic acidosis
- Hypoglycemia.
- Seizure due to low sodium or low glucose.
- Hyperpigmentation due to high ACTH.

Is it a boy or a girl ?





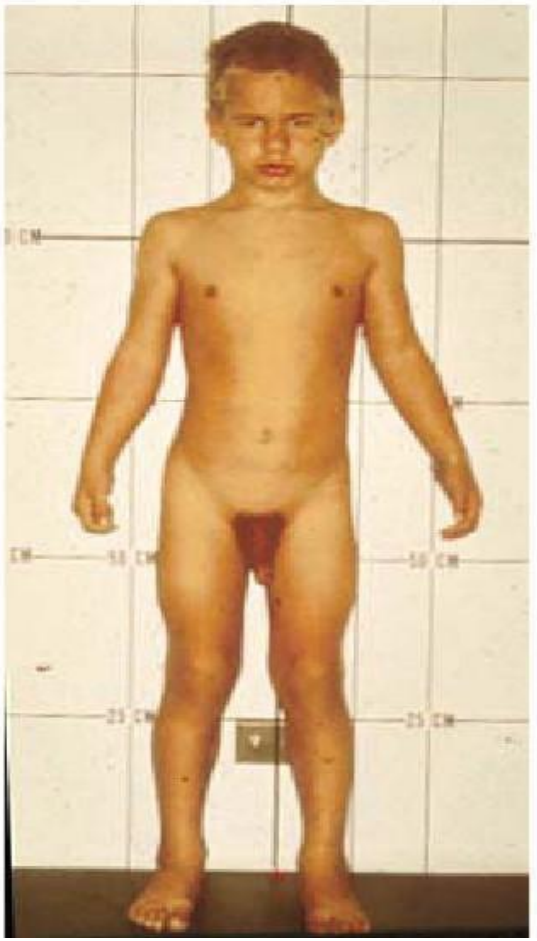
Differential diagnosis of classical CAH

- Neonates with CAH usually presents at age of 7-14 days with:
  - vomiting and electrolyte disturbances so we need to rule out gastroenteritis & pyloric stenosis.
- Poor sucking, poor feeding and sleepiness , need to rule out sepsis.
- Hyponatremia, hyperkalemia with metabolic acidosis, we need to rule out other causes e.g. congenital adrenal hypoplasia, hypoaldosteronism & pseudo hypoaldosteronism .
- Females usually presents with external genital virilization, we need to rule out other causes e.g. maternal androgenic medication intake, maternal ovarian or adrenal tumor during pregnancy and placental aromatase enzyme deficiency.

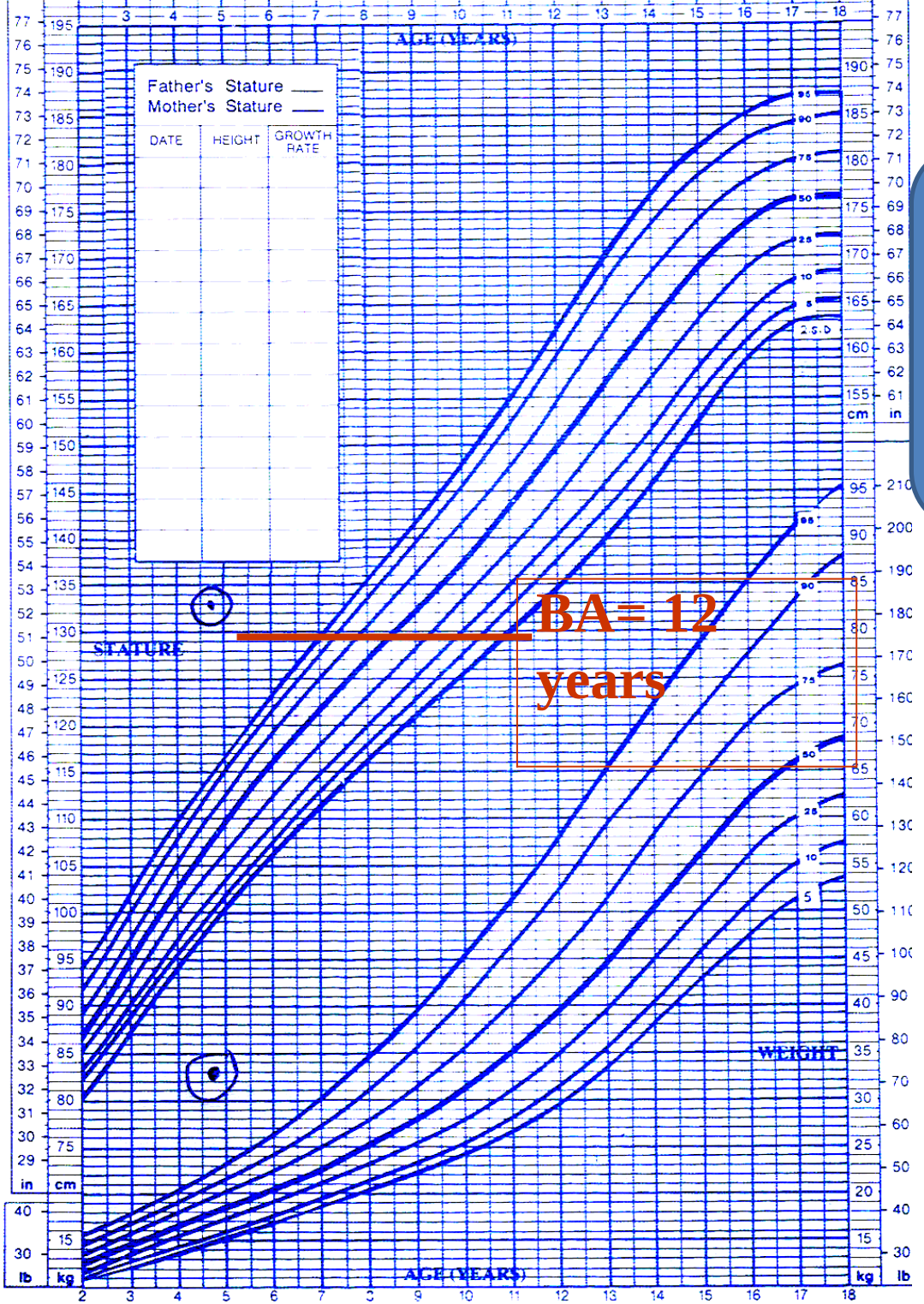
Presentation of Non- Classical CAH

- 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



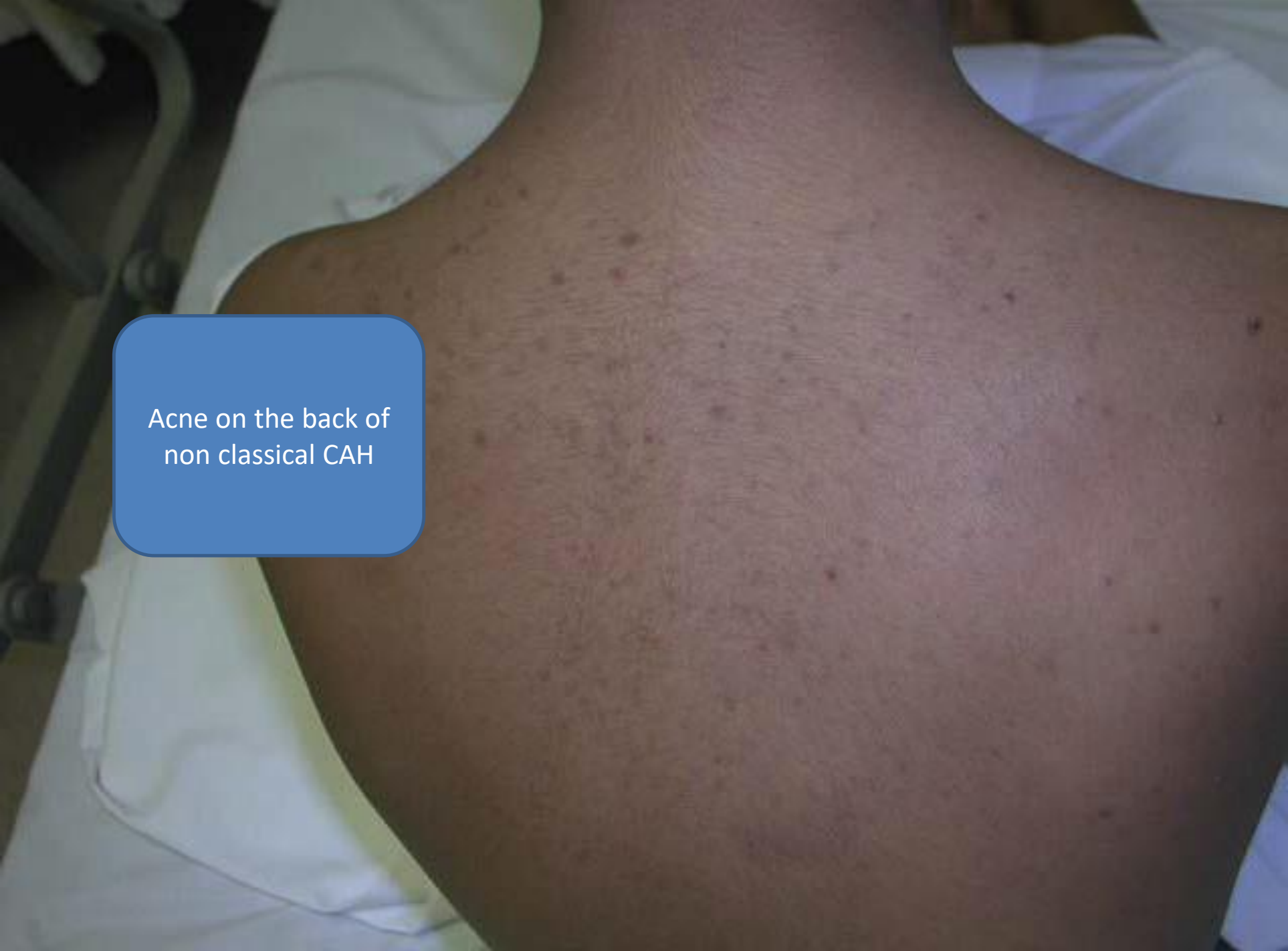
Six-year-old boy presented with peripheral precocious puberty because of Non classical CAH

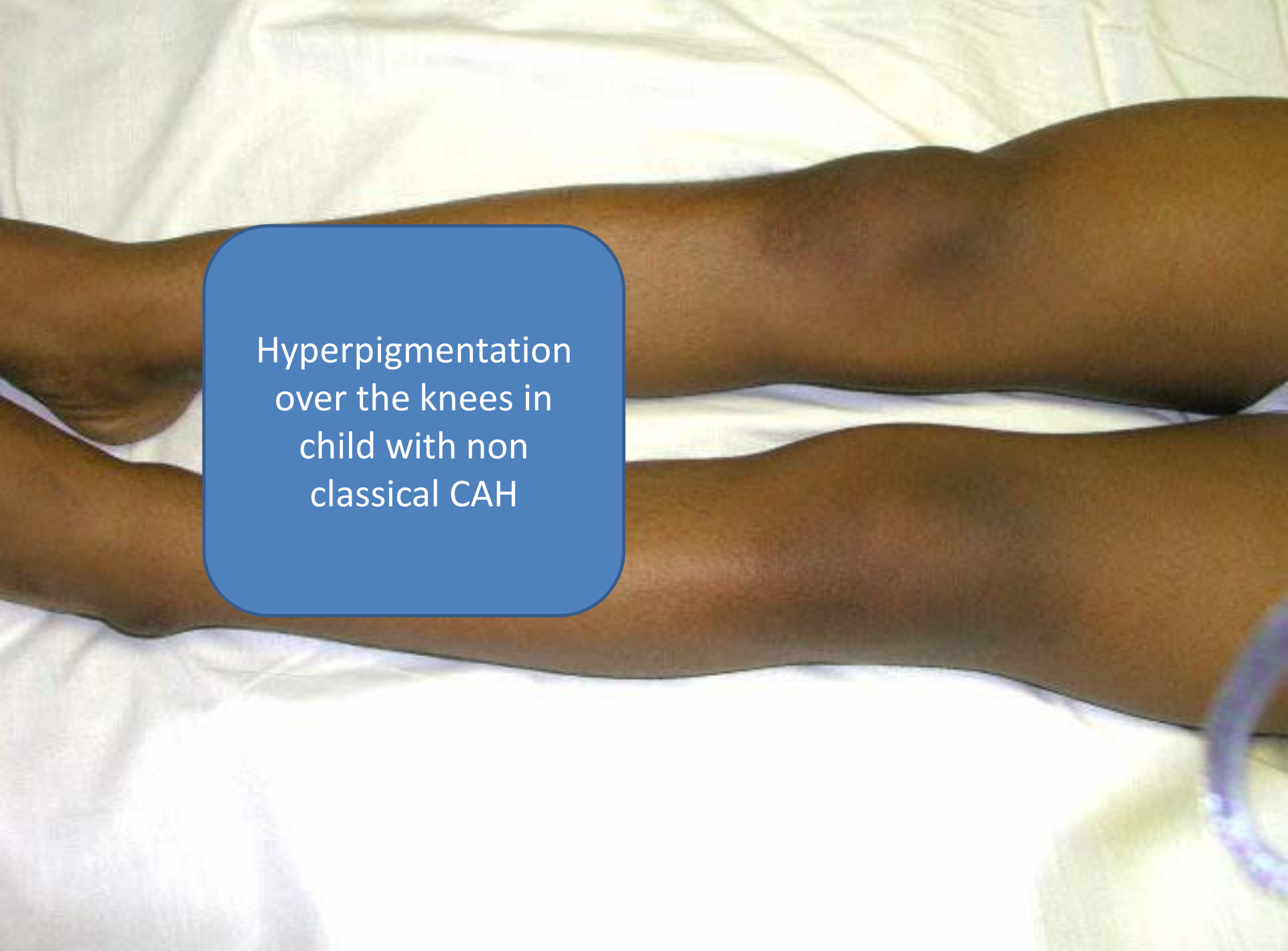


Advance growth with advance bone age in child with non classical CAH

Height = 132.8 cm

Weight = 33 kg


Acne on the back of non classical CAH


Hyperpigmentation over the knees in child with non classical CAH


Frontal Baldness in child with non classical CAH

Premature pubic hair appearance (Pubarche) in child with non classical CAH

Differential Diagnosis of non classical CAH

- Adrenal Tumor.
- Drug-Induced androgen excess.
- Hyperprolactinemia.
- Cushing Syndrome.
- Ovarian Cancer.
- Ovarian Tumor.
- Polycystic Ovarian Syndrome.

PCOS

- Usually confused with non-classical CAH.
- Adolescent onset of ovarian hyperandrogenism
  - High testosterone.
  - low SHBG.
  - High LH/FSH ratio.
- Menstrual dysfunction.
- Hirsutism & acne.
- Obesity.
- Ovarian cysts.
- Acanthosis nigricans.
- Insulin resistance.

Diagnosis of classical CAH

- A review of a patient's medical history.
- Thorough clinical examination (B.P).
- Serum electrolytes & glucose.
  - Low Na & high K.
  - Hypoglycemia.
  - Elevated serum urea due to associated dehydration.
  - Metabolic acidosis.
- Elevated plasma Renin & ACTH levels.
- Low serum cortisol.
- Low Aldosterone (in salt losing types only).
- High 17 – OHP (screening & confirmation).
- High androgens especially testosterone level.
- Urinary steroid profile.

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.

Acute emergency management of CAH

- As neonate might present with hypotension, shock and ill status, ABCD is first and important measure.

- Intravenous (IV) bolus of isotonic sodium chloride solution (20 mL/kg or 450 mL/m2) over 30-60 minutes, as needed, to restore their intravascular volume and blood pressure (Ringers lactate solution could be used as alternative to normal saline). This dosage may be repeated if the blood pressure remains low.

- Dextrose must be administered if the patient is hypoglycaemic and must be included in the rehydration fluid after the bolus dose (2-4 ml/kg of dextrose 10% slowly)to prevent hypoglycaemia.

Acute emergency management of CAH

- Give IV bolus of 50-100mg/m2 hydrocortisone immediately.

- Hyperkalaemia measures include:
  - Children with potassium > 6.0mmol/l should have an ECG and to be on cardiac monitoring.
  - If hyperkalaemia ECG changes are present (e.g. peaked T waves ± wide QRS complex ± flattened P waves), treat with calcium gluconate in order to protect the heart (10 % solution)
  - Insulin and Glucose therapy.
  - Inhaled Beta-Adrenergic Agonists (salbutamol).
  - Cation Exchange Resin (sodium polystyrene sulfonate) (keyxlyate).

Maintenance Therapy

- Lifelong therapy of Hydrocortisone 10-15 mg/m^2/day into three divided doses.
- In infancy & early childhood, sodium chloride solution replacement is required.
- Fludrocortisone dose: 0.05 - 0.2 mg/day.
- Monitor growth, signs of androgen excess, pubertal development & blood pressure.
- Please note that hydrocortisone therapy has 2 objectives (one objective is to replace cortisol deficiency and other one is to suppress high androgens by suppressing ACTH hormone).


THANKS