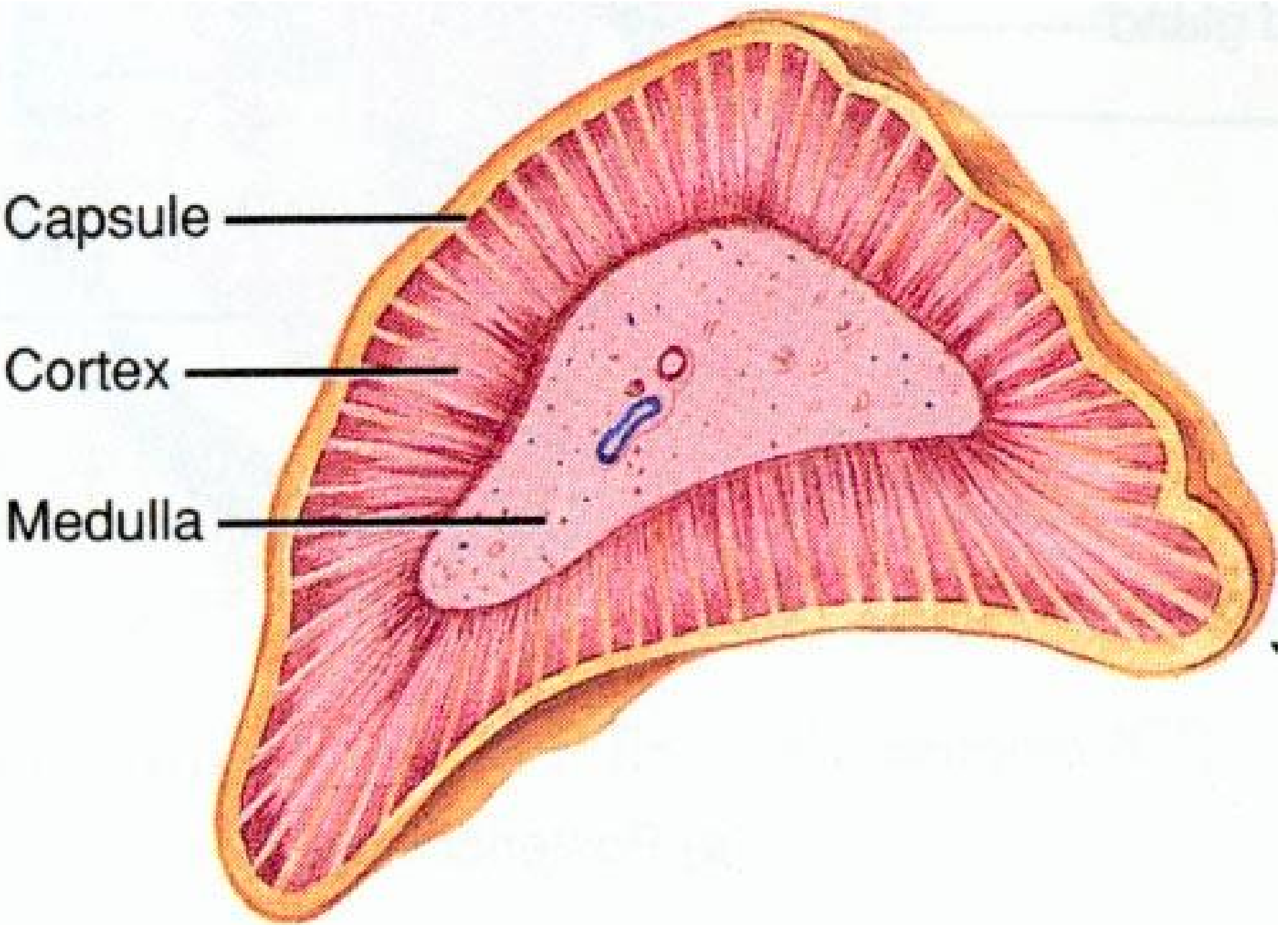
Disorders of Adrenal cortex
&
Gonads

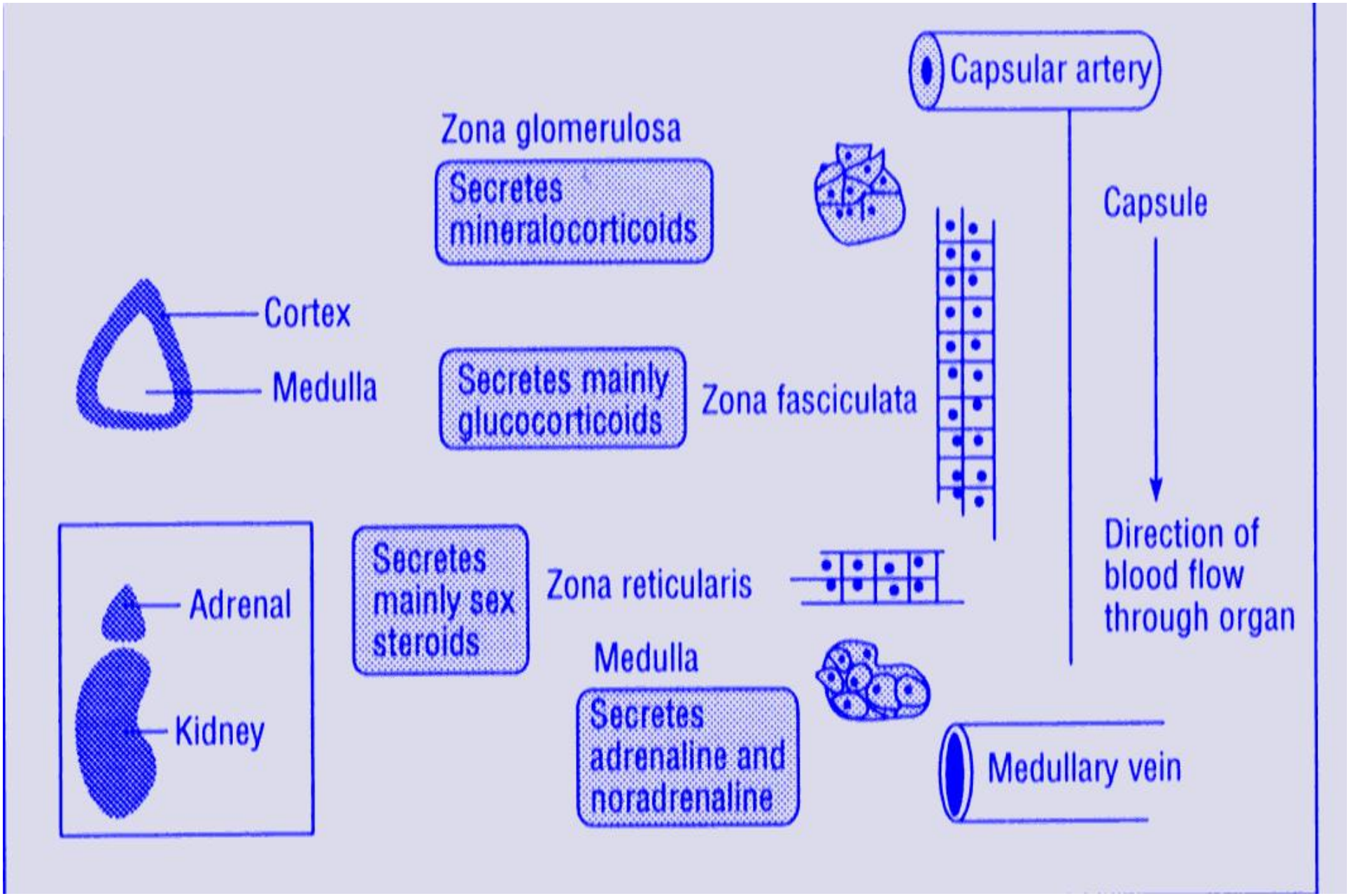
Dr Abdulmoein Al-Agha
Pediatric Endocrinologist

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
Cortex
Medulla

Adrenal gland



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 disease
- Wolman disease

Primary adrenal insufficiency

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)

Primary adrenal insufficiency Etiology

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

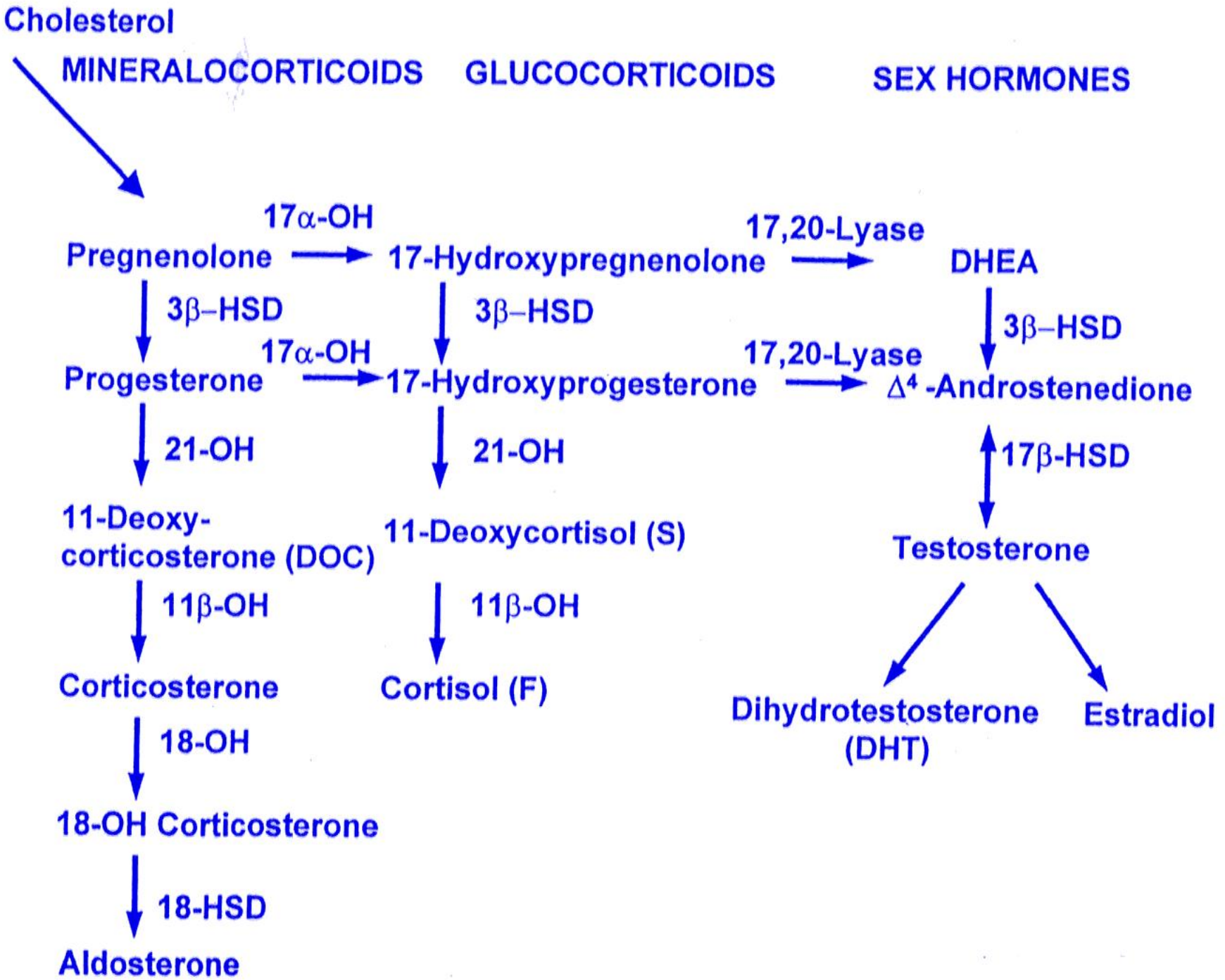
    (rifampin, phenytoin, Phenobarbital)

Secondary/Tertiary adrenal insufficiency

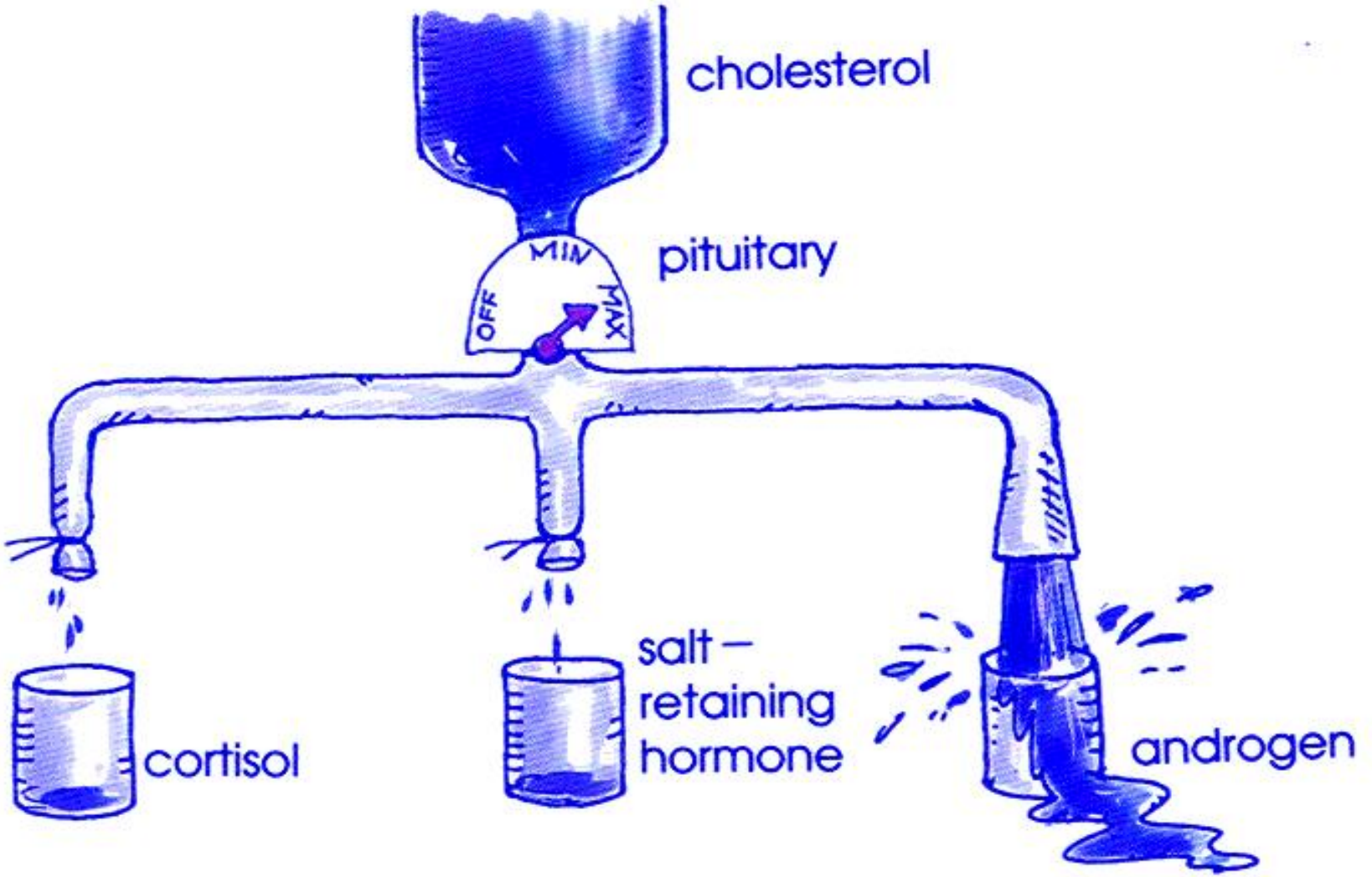
- Isolated ACTH deficiency
- Pan hypopituitarism (congenital / acquired)
- Hypothalamic / pituitary disorders
  - Tumors, surgery, radiation therapy
- Withdrawal from glucocorticoid therapy
- Inadequate glucocorticoid replacement
- Infant born to steroid-treated mother
- Surgical removal of ACTH-producing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

Congenital Adrenal Hyperplasia

- Autosomal Recessive (M=F)
- Incidence 1:1000 -15,000
- 90–95% of CAH cases are caused by 21- OHD
- Females affected with severe, classic 21- OHD are exposed to excess androgens prenatally and are born with virilized external genitalia
- Neonatal screening by filter paper on 3rd day of life (17 OHP)
- Prenatal therapy is effective in preventing genital virilization of affected females


Cholesterol
MINERALOCORTICOIDS
GLUCOCORTICOIDS
SEX HORMONES
17α-OH
Pregnenolone
17-Hydroxypregnenolone
17,20-Lyase
DHEA
3β–HSD
3β–HSD
3β–HSD
17α-OH
17,20-Lyase
Progesterone
17-Hydroxyprogesterone
Δ4 -Androstenedione
21-OH
21-OH
17β-HSD
11-Deoxy-
corticosterone (DOC)
11-Deoxycortisol (S)
Testosterone
11β-OH
11β-OH
Corticosterone
Cortisol (F)
Dihydrotestosterone
(DHT)
Estradiol
18-OH
18-OH Corticosterone
18-HSD
Aldosterone

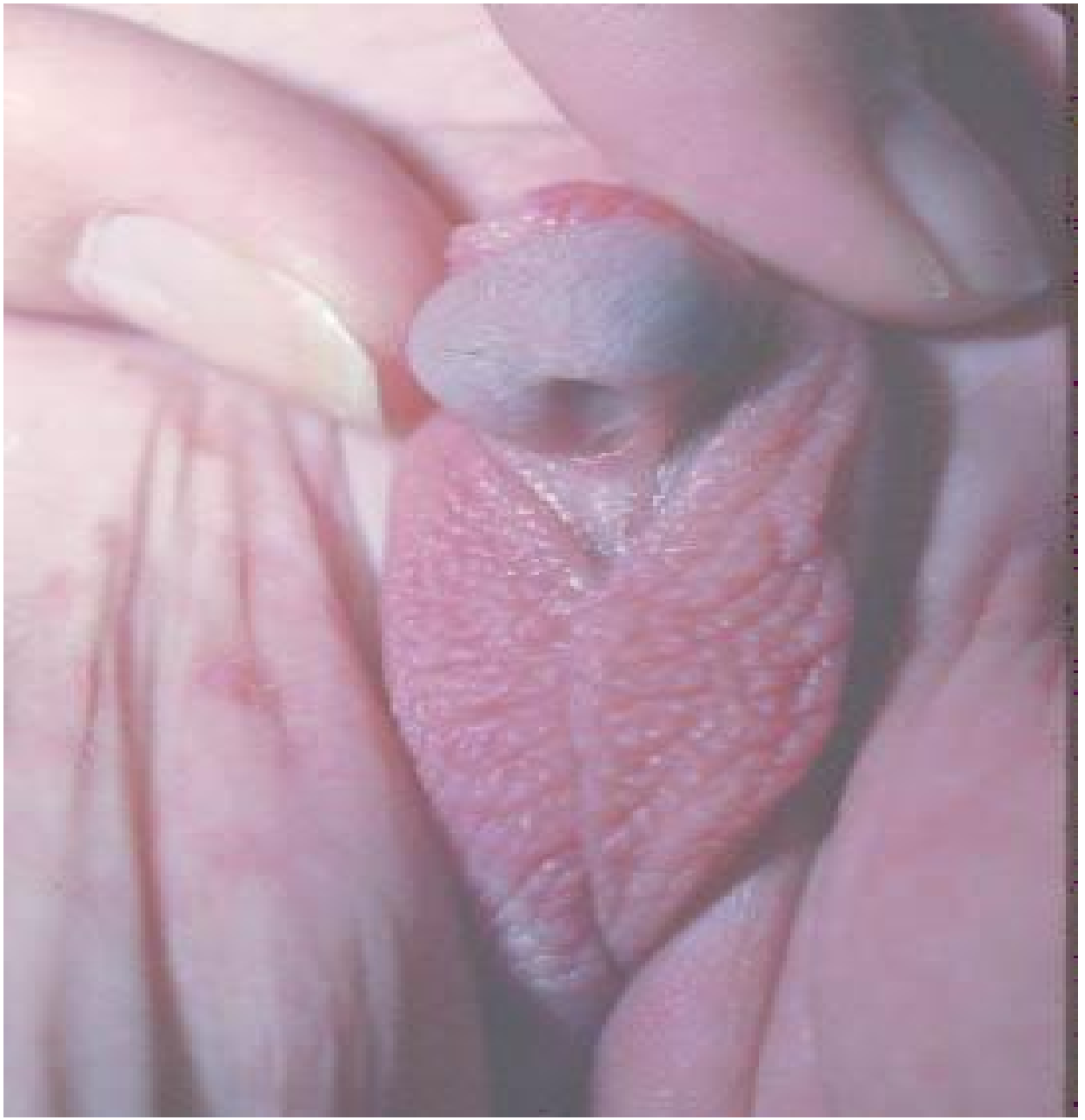
Congenital Adrenal Hyperplasia



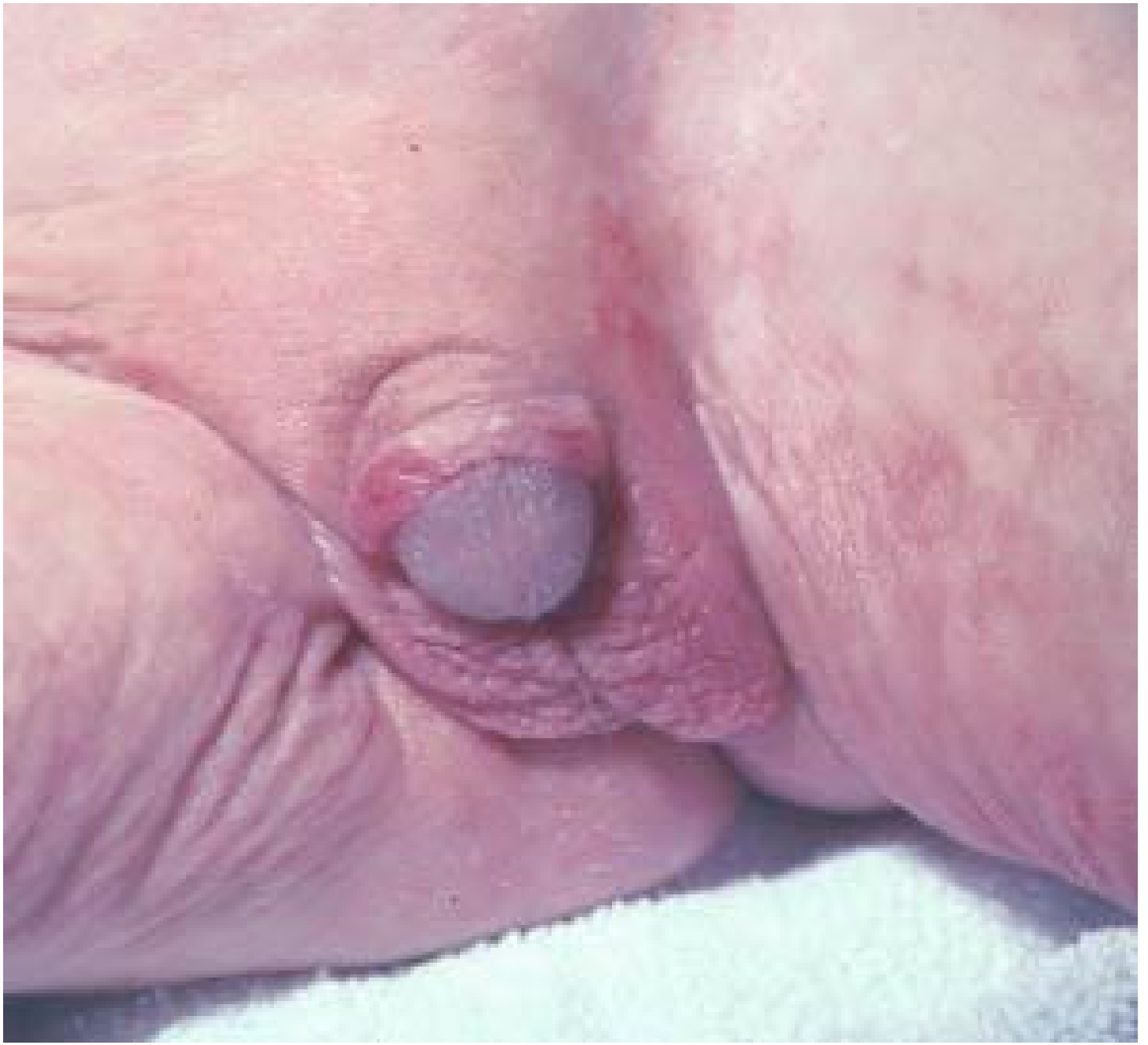
Presentations of CAH

- Ambiguous genitalia
- Failure to thrive
- Dehydration & Shock
- Salt-loss presentations with electrolytes imbalance
  - Hyponatremia
  - Hyperkalaemia
- Hypoglycemia
- Hyperpigementation

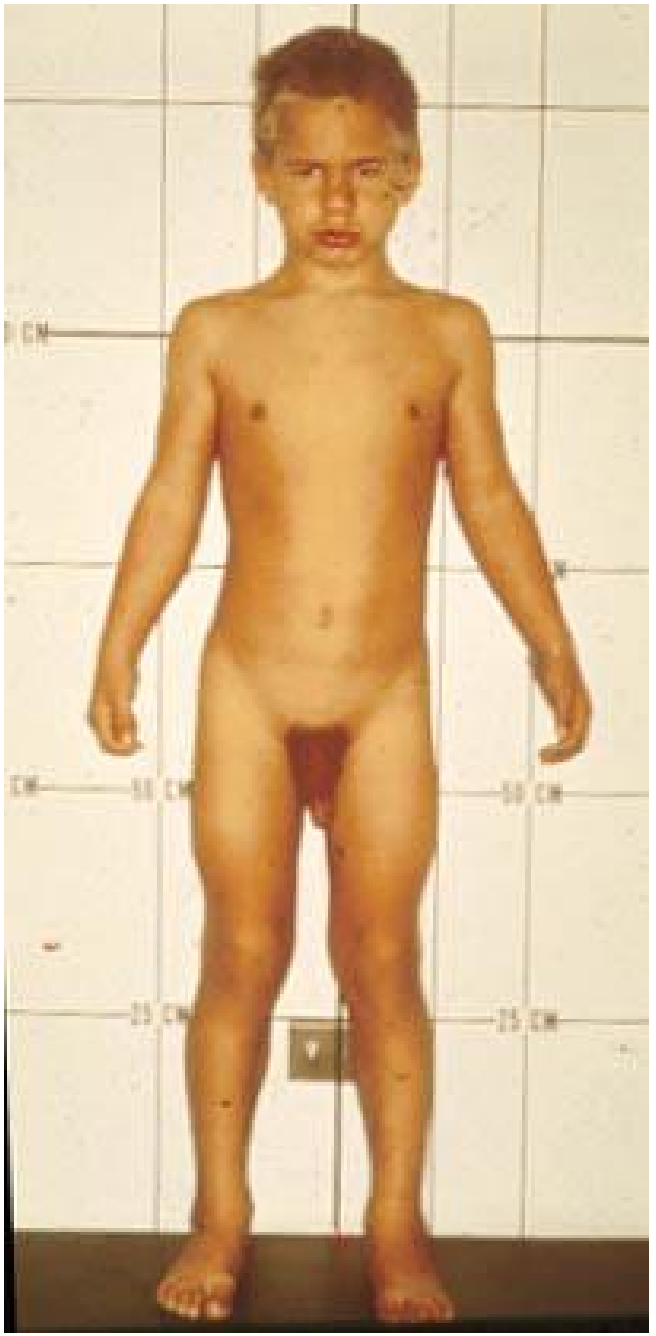
Is it a boy or a girl ?



Is it a boy or a girl ?



Non-Classical CAH



Diagnosis

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

Treatment

- Acute Adrenal Insufficiency
- Chronic Adrenal Insufficiency

- Hydrocortisone 10-20 mg/m^2/day divided into three doses
- In infancy and early childhood, sodium replacement is required
- Fludrocortisone 0.05 - 0.2 mg/day
- Monitor growth, signs of androgen excess, pubertal development and blood pressure
- During adrenal crisis intravenous hydrocortisone 50-100 mg/m2/day divided into 4 doses(6 hourly) with hydration with normal saline and dextrose
- During fever or sickness 2-3 fold increment in hydrocortisone dose
- In vomiting or diarrhea, parental therapy is indicated

Addison's disease

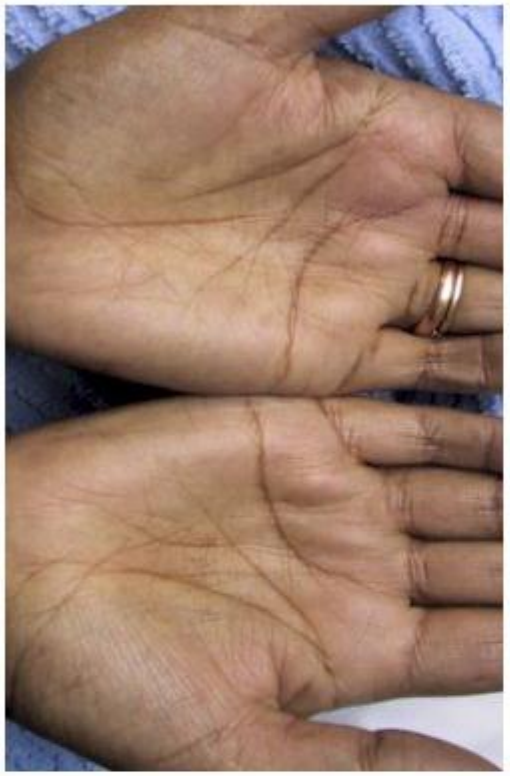
- Described by Dr Thomas Addison in 1849
- Rare endocrine disorder
- incidence 1 in 100,000 Autoimmune destruction of adrenal gland
- TB was the commonest pathology in 70-90%
- Occurs in all age groups
- Adrenal insufficiency occurs when 90 % of the adrenal cortex has been destroyed
- Often positive adrenal antibodies
- Could be an isolated problem or associated with other autoimmune diseases

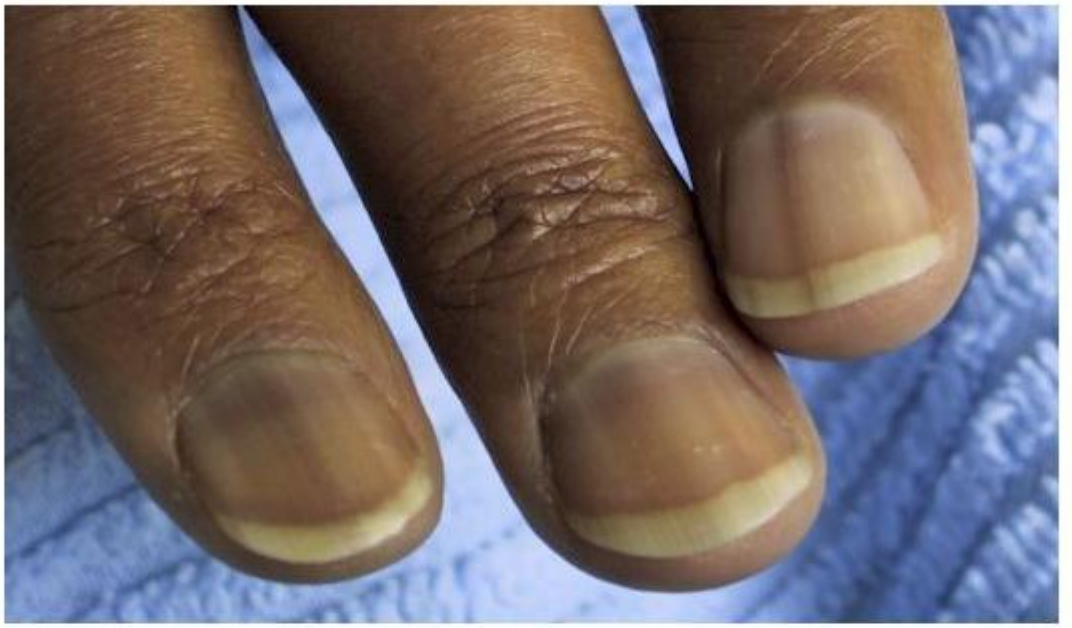
Autoimmune polyendocrinopathy

- Type I (APECED) occurs in children
- Adrenal insufficiency,hypoparathyroidism, pernicious anaemia, chronic candidiasis, chronic active hepatitis, and hair loss
- Type II “Schmidt's syndrome” usually affects young adults
- Features of type II include hypothyroidism, adrenal insufficiency and diabetes mellitus
- About 10% of patients with type II have vitiligo

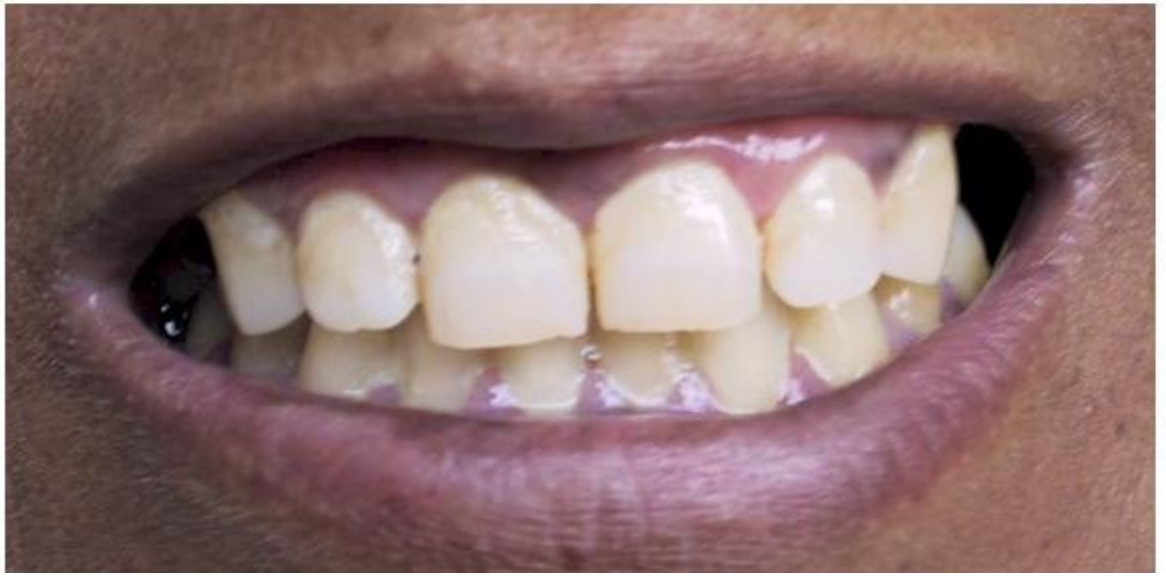
Clinical Features

- Fasting hypoglycemia
- Nausea, vomiting and diarrhea
- Weight loss, severe anorexia
- Fatigue, lethargy and muscle weakness
- Hyperpigementation
- Hypotension $\rightarrow$ Shock $\rightarrow$ Death





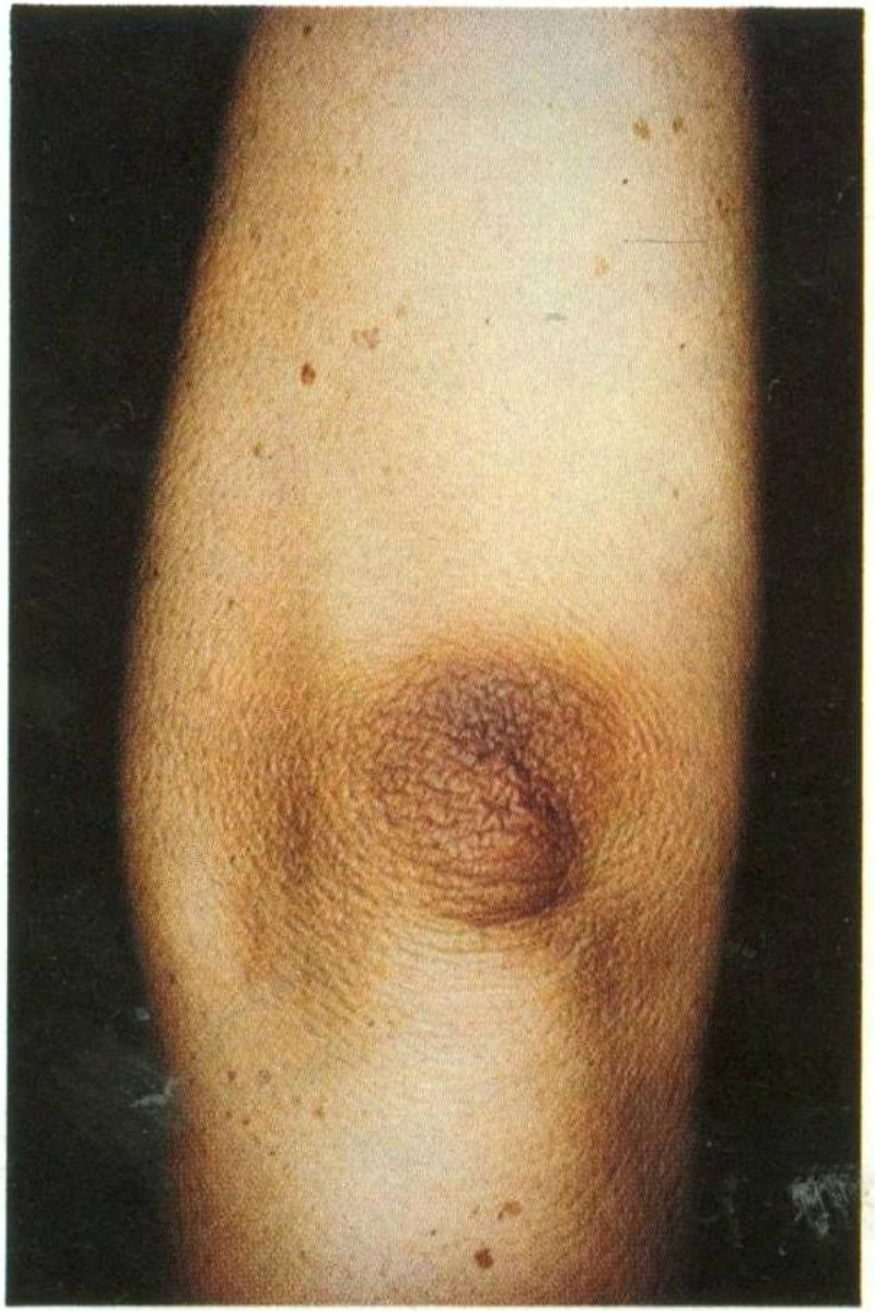
Addison's disease:



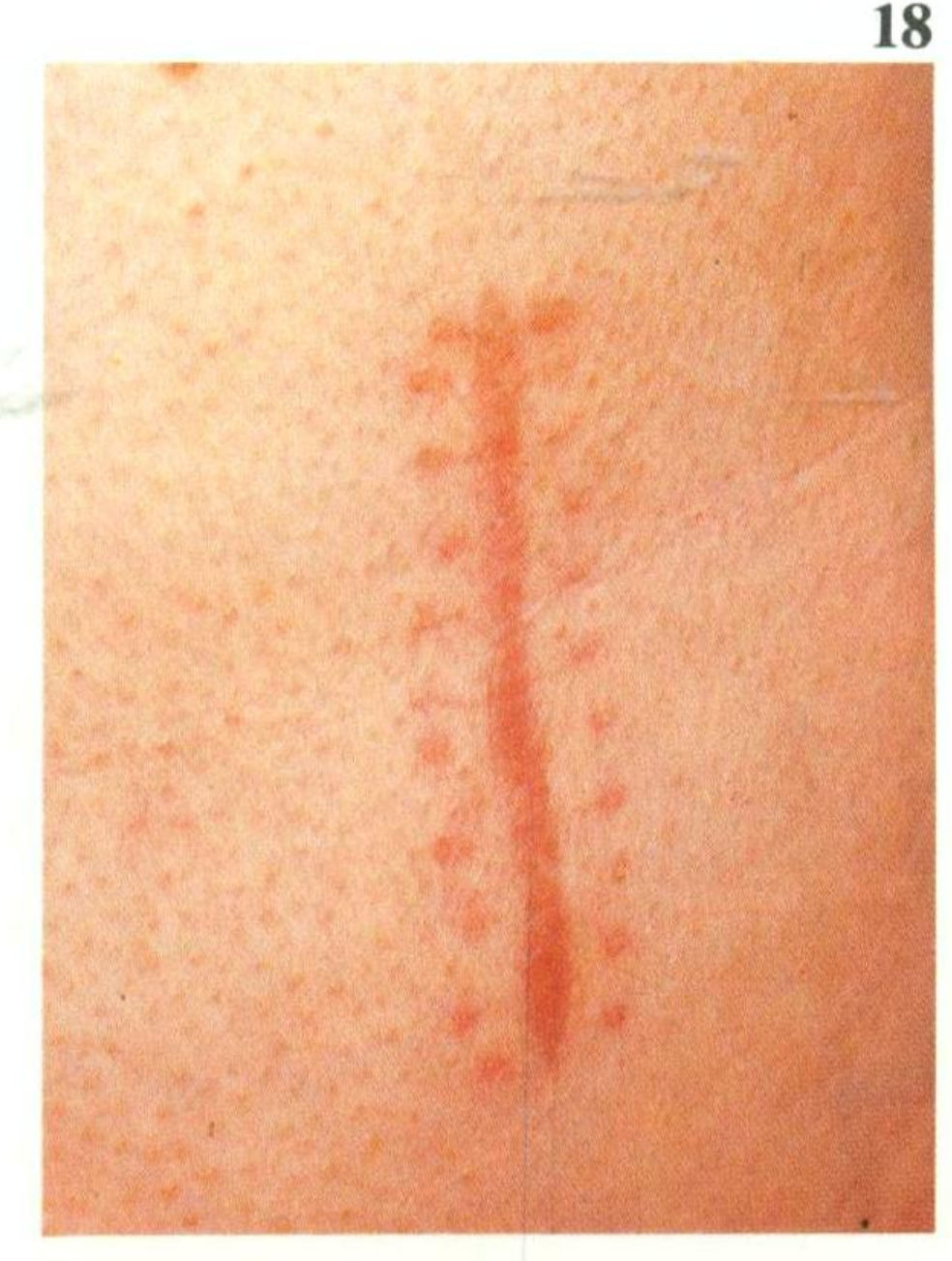
- Note the generalised skin pigmentation (in a Caucasio patient) but especially the deposition in the palmer ski creases, nails and gums.

- She was treated many year ago for pulmonary TB. What are the other causes of this condition?

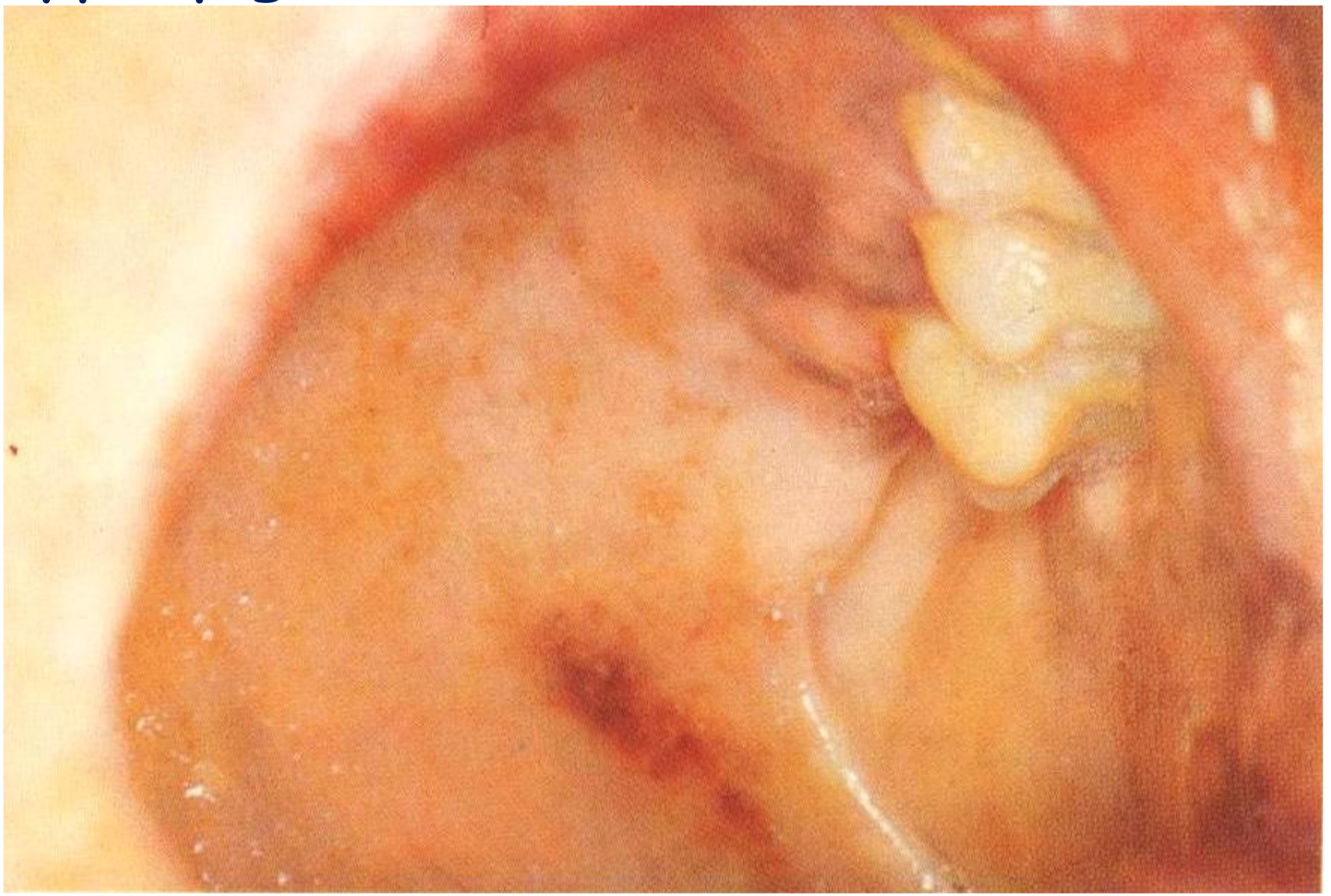
Hyperpigementation



Hyperpigmentation



Hyperpigementation

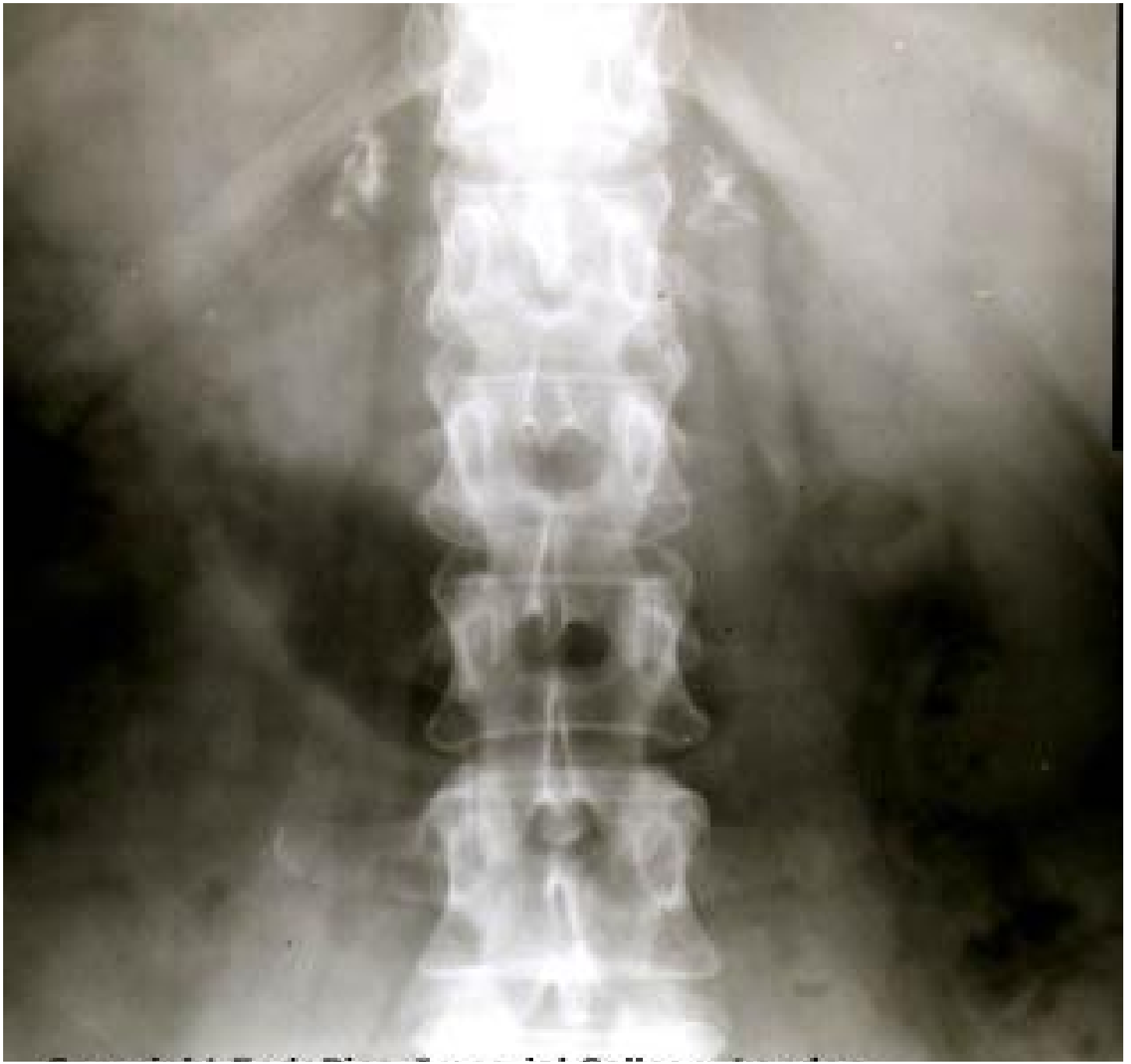


Biochemical features

- Low Na & high K with metabolic acidosis
- Elevated serum urea due to associated dehydration
- Fasting hypoglycemia
- Low serum Cortisol & Aldosterone level
- Elevated plasma Renin & ACTH levels
- Low adrenal androgen including 17-hydroxyprogestrone
- Adrenal autoantibodies are positive

ACTH Stimulation Test

- This is the most specific test for diagnosing Addison's disease
- Short ACTH test, Cortisol measurement 30 and 60 minutes after an intravenous ACTH injection
- "long" ACTH stimulation test, synthetic ACTH is given over 48- 72-hour period, and blood and urine Cortisol are measured the day before and during the 2 to 3 days of the test



Steroid Preparations

Steroid	Half Life (minutes)	Glucocorticoid Potency	Mineralocorticoid Potency
Hydrocortisone	90	1.0	1.0
Cortisone	30	0.8	0.8
Prednisolone	230	4.0	0.8
Prednisone	60	3.5-4.0	0.5
Dexamethasone	280	25.0-30.0	0.0

Adrenal Cortical Hyperfunction

Cushing's syndrome

- First described by Cushing in 1932
- A constellation of clinical abnormalities due to chronic exposure to excesses of cortisol

Aetiology

- ACTH-dependent
- ACTH - independent
  - production of cortisol by an adrenocortical adenoma or carcinoma
  - Therapeutic administration of supraphysiologic doses of cortisol or related synthetic analogues suppresses adrenocortical function and mimics ACTH-independent Hyperfunction.

ACTH dependent

- Hyperfunction of the adrenal cortex resulting from pituitary ACTH Cushing's disease
- hypersecretion of ACTH by the pituitary gland
- Patients with Cushing's disease may have a basophilic or a chromophobe adenoma of the pituitary gland
- secretion of ACTH by a non pituitary tumour
  - small cell carcinoma of the lung (ectopic ACTH syndrome)
  - administration of exogenous ACTH

Clinical manifestations

- rounded "moon" facies with a plethoric appearance
- truncal obesity with prominent supraclavicular and dorsal cervical fat pads "buffalo hump“
- distal extremities and fingers are slender
- Muscle wasting and weakness
- The skin is thin and atrophic, with poor wound healing and easy bruising
- Purple striae may appear on the abdomen
- Hypertension
- renal calculi
- osteoporosis

Clinical manifestations

- Glucose intolerance
- Reduced resistance to infection
- Cessation of linear growth
- Females usually have menstrual irregularities
- In adrenal tumours increased production of androgens in addition to cortisol lead to:
  - Hypertrichosis (hirsutism)
  - Temporal balding
  - Other signs of virilism in the female

Conn's Syndrome

- Primary aldosteronism
  - Adenoma, usually unilateral, of the glomerulosa cells of the adrenal cortex
  - rarely, adrenal carcinoma
  - Hyperplasia
- The clinical picture may mimic CAH from of 11 β-hydroxylase deficiency
- In children, Bartter's syndrome are distinguished from Conn's syndrome by the absence of hypertension in the presence of hypokalemia and hyperaldosteronism

Symptoms and Signs

- Hypersecretion of aldosterone may result in:
  - Hypernatremia
  - Hyperchlorhydria
  - Hypervolemia
  - Hypokalemic alkalosis manifested by:
    - episodic weakness
    - Paresthesias
    - transient paralysis
    - tetany
  - Diastolic hypertension
  - Hypokalemic nephropathy with polyuria and polydipsia

Aldosterone resistance Pseudohypoaldosteronism

- First described in 1958 by Cheek and Perry
- Autosomal recessive and dominant forms
- Unresponsiveness of the kidney to aldosterone
- Salt losing symptoms with poor response to Fludrocortisone but adequate response to NaCl
- Improvement wit age (by 1-2 years of age)

Gonad disorders

Puberty

BRAIN

↓ NEUROTRANSMITTERS

HYPOTHALAMUS

↓ GnRH

PITUITARY GLAND

↓ LH / FSH

GONADS ⇢ TESTOSTERONE / E2
ACTIVIN
INHIBIN

Puberty

- Period of Attainment of secondary sexual characteristics and reproductive capabilities
- Normal onset age
  - girls: 8 -12 y
  - boys: 9 -14 y
- primates
  - puberty process happened very quickly within 28 days
- Humans
  - puberty on hold for a longer period (12 y)

Disorders of Puberty

- Precocious puberty
  - Period of Attainment of secondary sexual characteristics and reproductive capabilities earlier than expected
    - girls < 8 y
    - boys < 9 y
- Delayed puberty
  - Period of Attainment of secondary sexual characteristics and reproductive capabilities later than expected
    - girls > 13 y
    - boys >14 y

Puberty

- Signs of puberty changes
  - somatic changes
    - pubic and axillary hairs
    - acne
    - perspiration and characteristic body odour (release of volatile acids= glutaric acid)
    - oily skin and hair
- All these changes happen due to increased adrenal androgens which are formed equally in both males and females
  - Adrenal androgens are
    - androstendione, DHEA,DHEAS

Puberty

- Somatic changes (Boys)
  - enlarged testes (> 4ml)
  - secondary sexual characteristics
  - increase protein and decreased adipose tissue
  - growth spurts (max. at 13.5 y)
  - sperm production (from age of 13.5 y)
  - bone mineralisation

Puberty

- Somatic changes (Girls)
  - breast enlargement
  - skeletal changes
    - widening of pelvis and carrying angle
  - increased adipose tissue in feminine pattern
  - growth spurt (max. 11.5 y)
  - menarche age of around12 y
  - E2 is important for both bone mineralisation and growth spurt

Types

- Central, True, GnRH dependent
  - 89-98% of cases (major type)
- Peripheral,Pseudo, GnRH Independent
  - 10 – 15 % of cases (not major type)
- Mixed type
  - Started with peripheral with 2ry. activation of central
- Isolated Forms
  - Thelarche
  - Adrenarche / Pubarche

The difference between types of PP

	Central type	Peripheral type
H-P-G axis	Activated axis	suppressed
LH & FSH	Adult values	Pre-pubertal
Sex steroids	High	High
Gonads	Pubertal size	Small in size (unless tumor)

Central, True, GnRH dependent

Etiology

- Idiopathic
  - most girls (90 %)
- Secondary
  - most boys (70-80%)

Etiology of CPP

CNS disorders

- Hypothalamic Hamartoma
- Glioma (NF-1)
- Astrocytoma
- Craniopharyngioma
- Ependymoma, germinoma,
- CNS radiation therapy
- Post trauma (surgery)

Etiology of CPP

- Inflammation (Brain abscesses)
- Neurological & mental retardation
- Hydrocephalus
- prolonged sex steroid exposure associated with peripheral puberty

Etiology of peripheral type

- Gonadal: McCune-Albright, tumour, cyst
- Adrenal: Virilizing CAH, tumours
- Ectopic: hCG secreting tumours
  - Germinoma, Hepatoblastoma
- Exogenous source of hormone
- Familial male dependent (Testotoxicosis)

Variants of normal puberty

- Thelarche
- Adrenarche (Pubarche)

Thelarche

- Premature breast enlargement with absence of growth spurt
- Bone age is not accelerated
- Pre pubertal pelvic U/S findings
- Onset between 6m to 4 y of age
- Increased sensitivity of the breast tissue to low levels of sex steroids
- Benign nature and need no therapy

Adrenarche

- Occurs when the adrenal androgen production is turned on prematurely in the absence of gonadal activation
- Premature appearance of pubic & axillary hair, acne, body odor & oily skin
- Idiopathic
- Benign nature with no treatment

Treatment of CPP

- GnRH agonist
- Treatment of underlying pathology

Treatment of peripheral type

- Medroxyprogestrone acetate (Provera)
- Ketoconazole
- Aromatase enzyme inhibitors
- Androgen antagonists

PCOS

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

موفقين باذن
الله تعالى