

# Adrenal Disorders

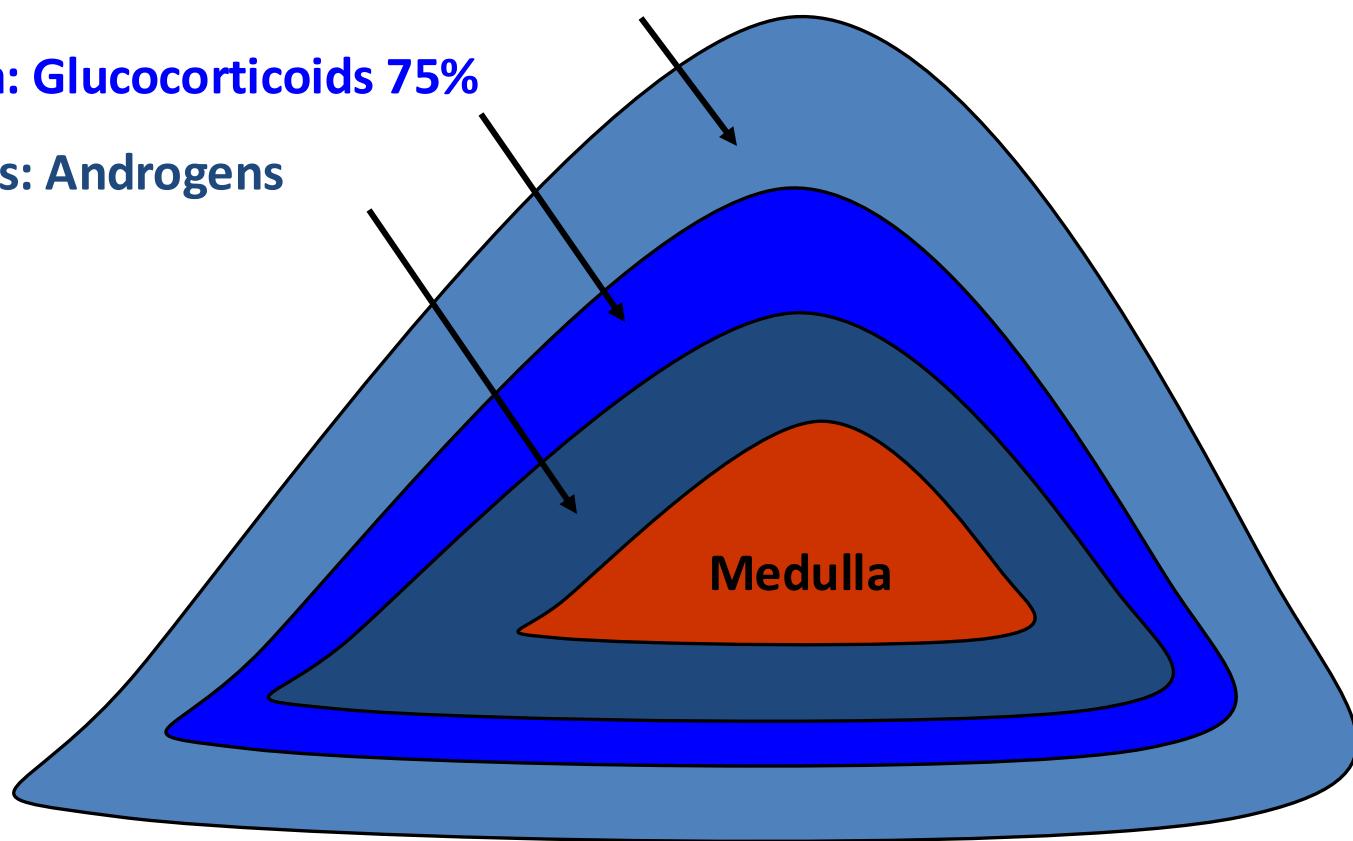
Rasha Odeh  
MB.BS,MRCPCH

# Adrenal Cortex

Zona Glomerulosa: Mineralocorticoids 5-10%

Zona Fasiculata: Glucocorticoids 75%

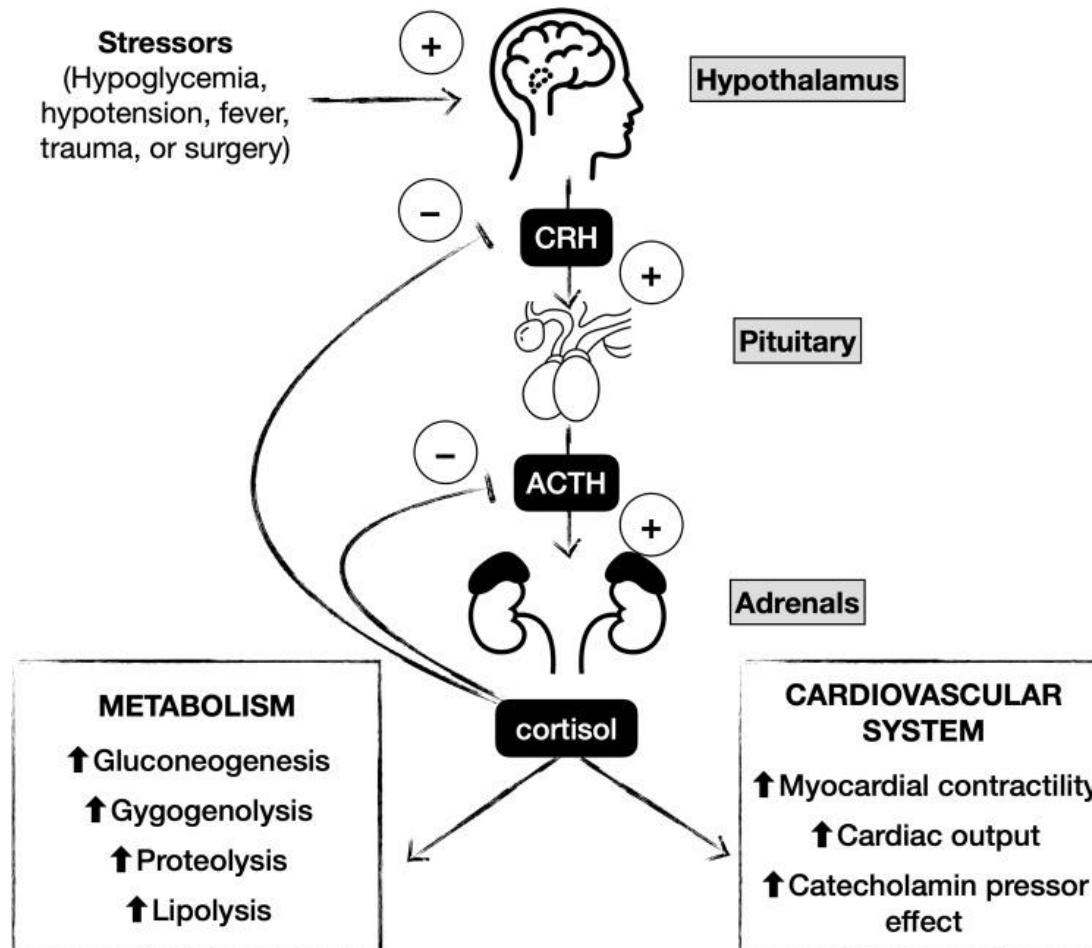
Zona Reticularis: Androgens



# Function of the adrenal cortex

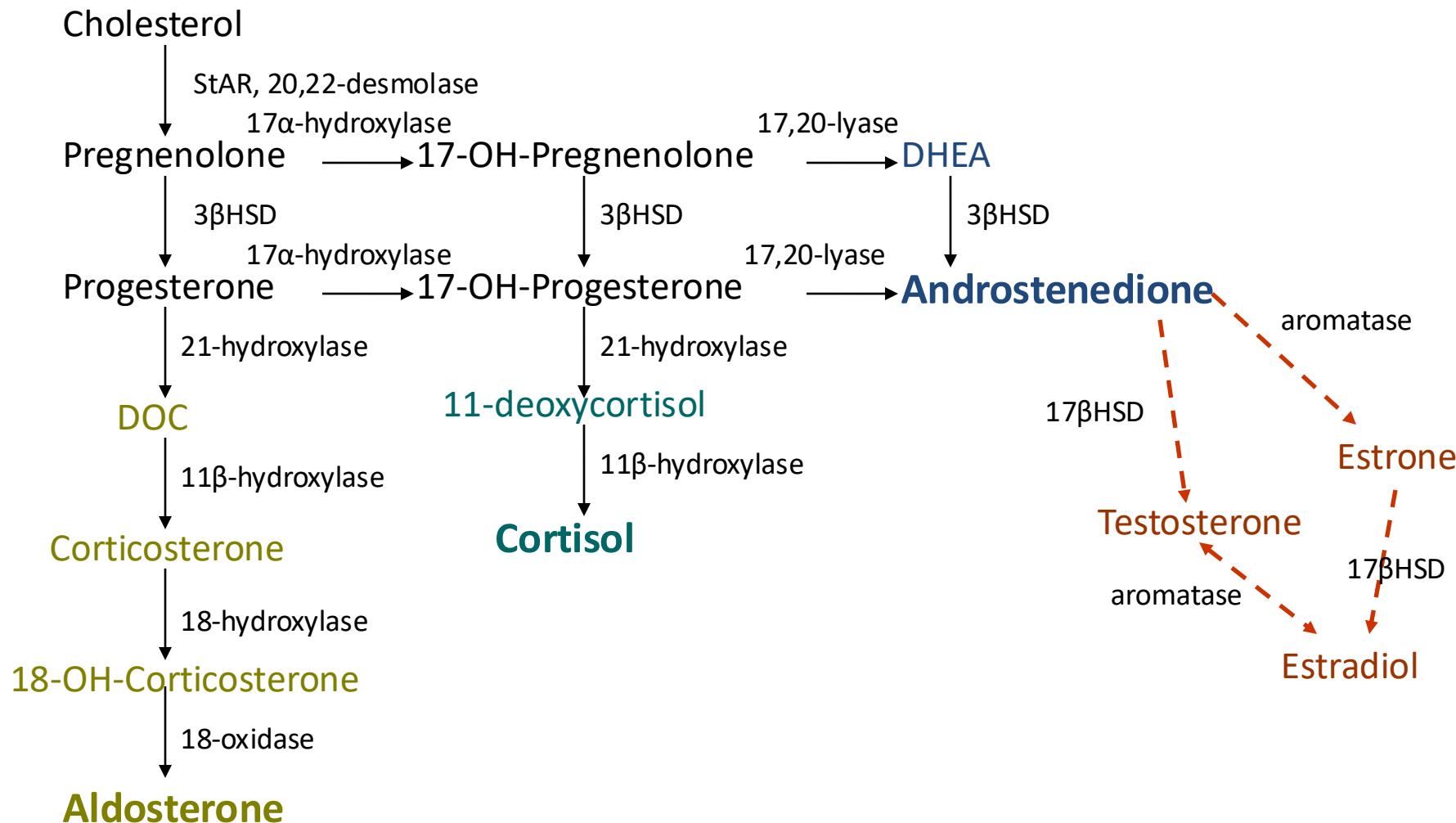
- Cholesterol is the starting point for all steroid hormone biosynthesis.
- It is obtained mostly from circulating LDL.
- It is modified by a series of hydroxylation reactions.
- The substrates have to move around the cell for the process of steroidogenesis to be complete as the the enzymes are in both the mitochondria and the endoplasmic reticulum.

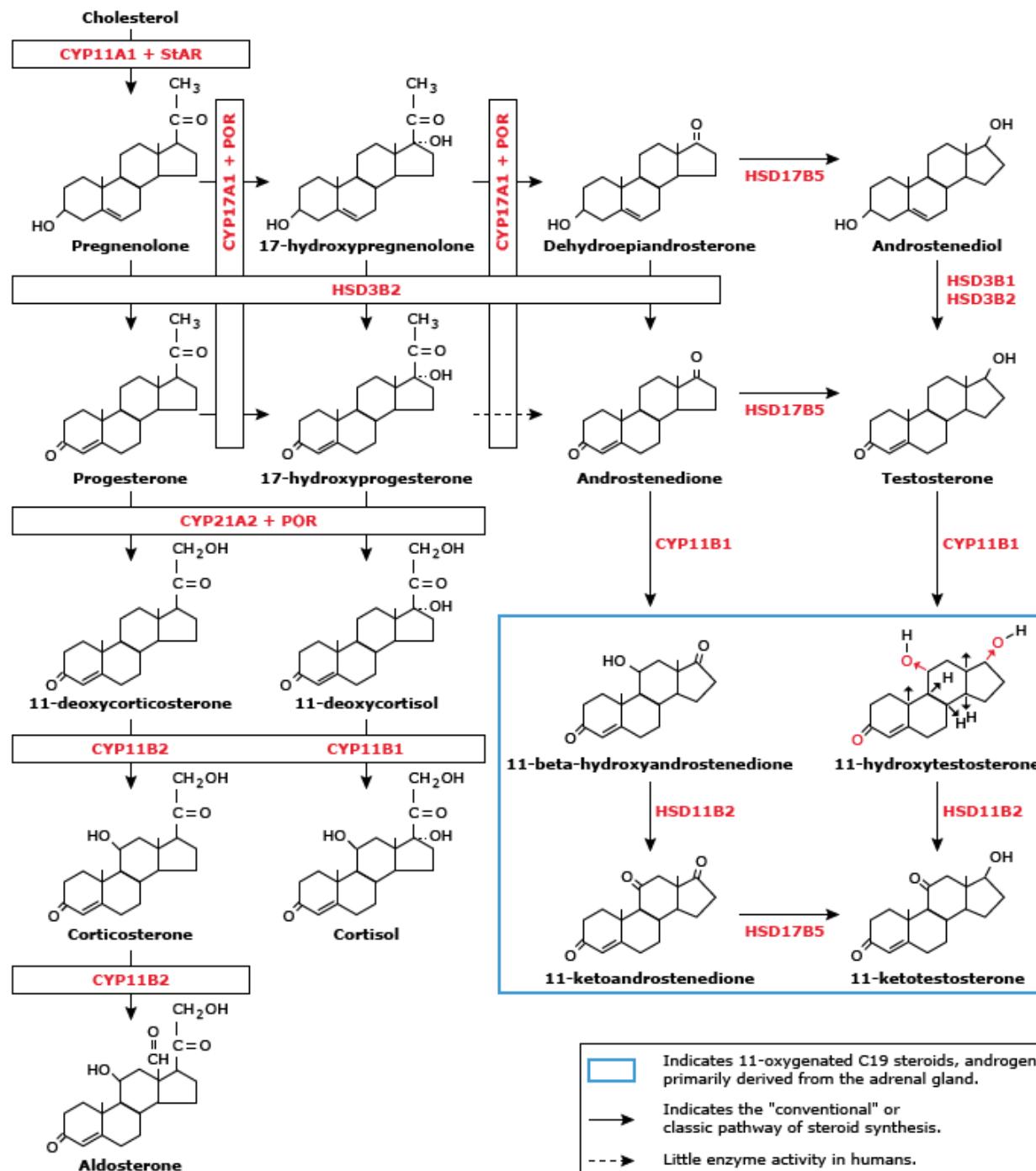
# Hypothalamic pituitary adrenal axis



ACTH

# Steroid Biosynthesis





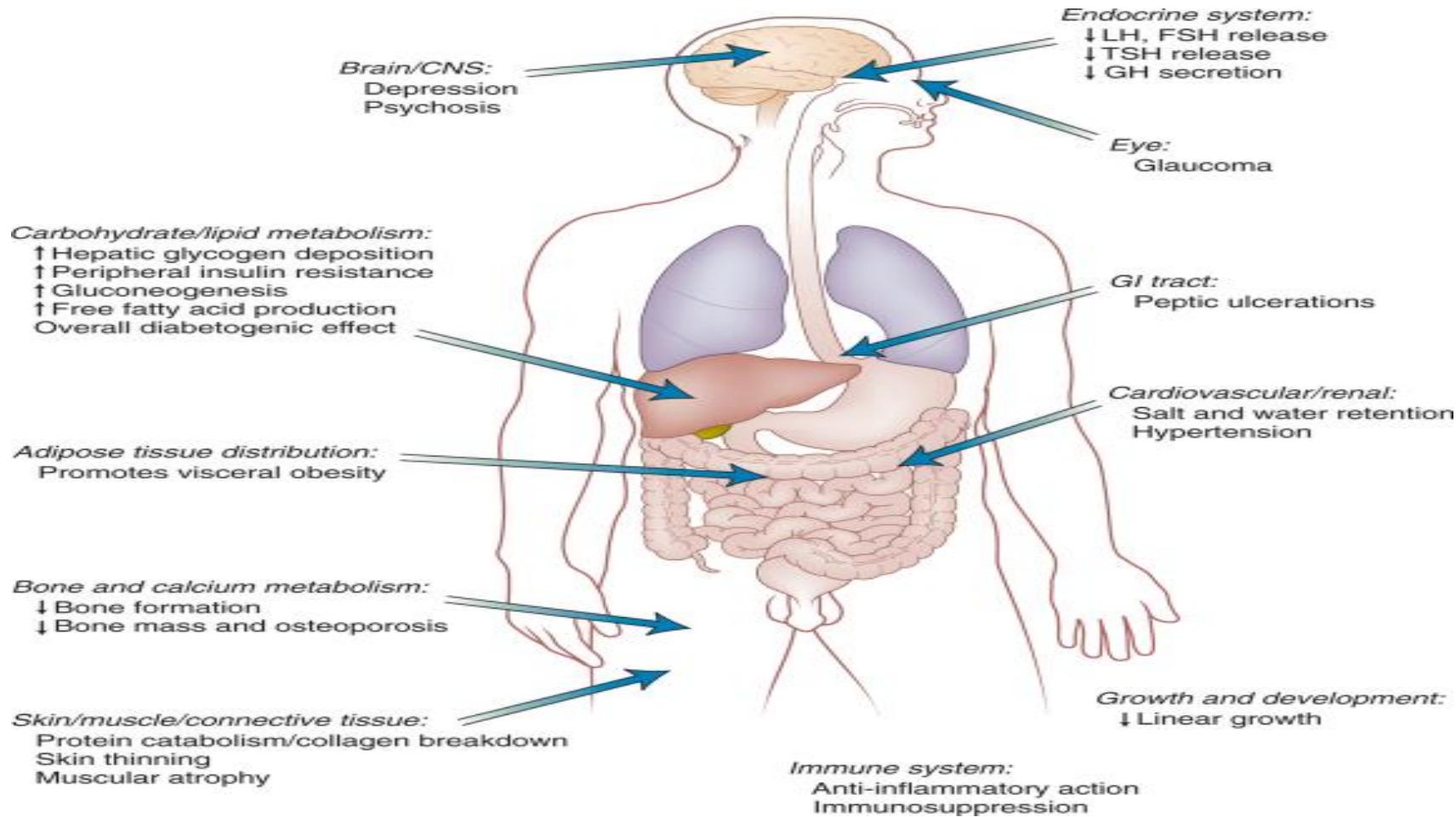
# Regulation of steroidogenesis

- **Hypothalamo-pituitary-adrenal axis:**
- Cortisol is secreted in response to ACTH, which is stimulated mainly by CRH and to lesser extent AVP !
- ACTH is derived from pro-  
opiomelanocortin(POMC).
- ACTH stimulates the production of LDL receptors and the uptake of LDL.

# Diurnal rhythms of ACTH and cortisol

- CRH hypothalamic content peaks at about 4.00 am
- Peak plasma ACTH are seen at 4.00-6.00 am
- Peak plasma level of cortisol follows at 8.00 am
- ACTH and Cortisol are released in pulses each 30-120 minutes.
- This starts at the age of 6-12 months ,well established at 3 years.

# Physiology of GCs



# Transporting cortisol

- 80% is bound to corticosteroid binding globulin(transcortin) in plasma.
- 15% to albumin.
- Transcortin does not bind dexamethasone.
- When the concentration of the binding globulin increases, the total concentration of the hormone in plasma increases.

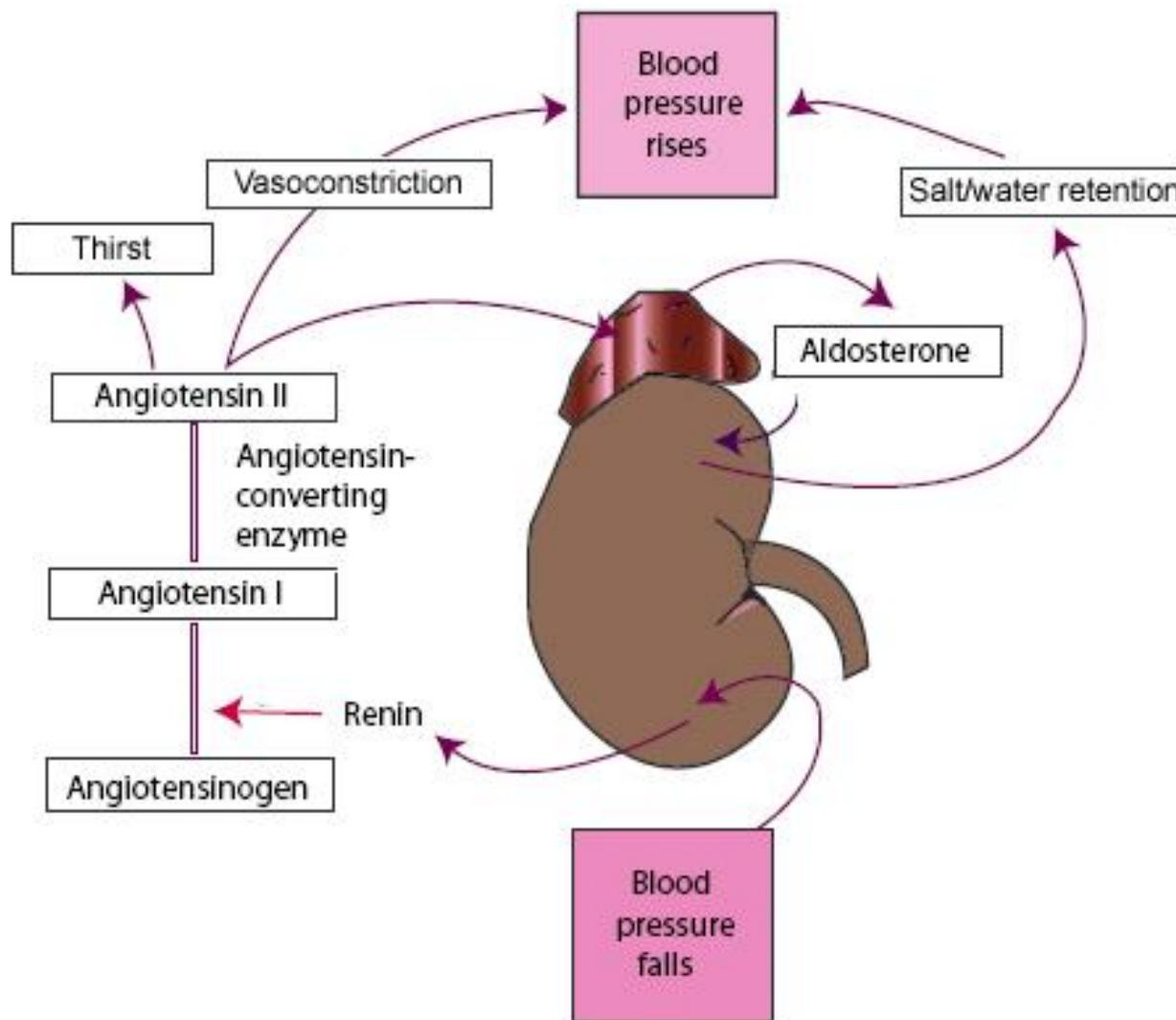
# Zona glomerulosa

- Aldosterone is the main product.
- Acts on distal tubules and collecting ducts ,increases Na reabsorption.
- Raises blood pressure by increasing plasma volume
- Present in lower concentrations and is cleared more rapidly than cortisol but is still responsible for 80% of the mineralocorticosteroid activity of the adrenal gland secretion.

# Regulation of aldosterone secretion

- The renin angiotensin system is the most important regulator.
- ACTH deficiency does not alter aldosterone production.

# Adrenal physiology 2: Renin-angiotensin system



# Zona reticularis

- Secretes DHEA,DHEAS, and androstendione.
- Can be converted peripherally to testosterone.
- Can not on their own activate androgen receptors.
- Secreted in large amounts in fetal and newborn period.
- Then it goes into rest till 7-8 years old , then adrenarche.
- It reaches a peak in young adulthood and then wanes down gradually.
- ACTH plays a permissive role in adrenarche but is not the only player.

# Catabolism of Steroids

- <1% of plasma cortisol and aldosterone are excreted unchanged in urine
- 99% are metabolized by the liver before excretion through the kidneys. -adding OH groups or linkage to sulfate or glucuronide moieties renders steroids more water soluble
- 24-hour urine samples to study the steroid hormone profile by MS -diagnostic tool-BUT analysis can be tough and needs lots of experience!

# Causes of Adrenal Insufficiency

## **Primary Adrenal Insufficiency:**

- Autoimmune adrenalitis
- Autoimmune polyglandular syndromes (type I and II)
- Tuberculosis, fungal infections
- Sepsis
- AIDS
- CAH
- Adrenal hemorrhage or infarction
- Cong. adrenal hypoplasia
- Adrenoleukodystrophy (and other metabolic disorders)
- Primary xanthomatosis
- Unresponsiveness to adrenocorticotrophic hormone

## **Secondary Adrenal Insufficiency:**

- Withdrawal from glucocorticoid therapy
- Hypopituitarism
- Hypothalamic tumors
- Irradiation or surgery of the central nervous system
- Defects in POMC synthesis or processing

# Primary adrenal insufficiency: Etiologies

## Acquired

- Autoimmune
- AIDS
- Tuberculosis
- Bilateral injury
  - Hemorrhage
  - Necrosis
  - Metastasis
- Idiopathic

## Congenital

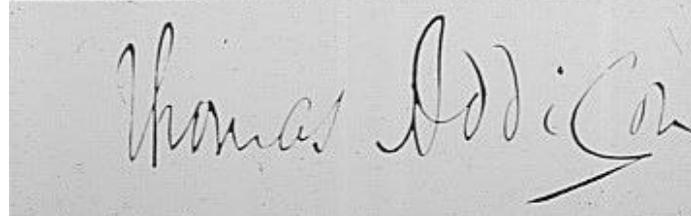
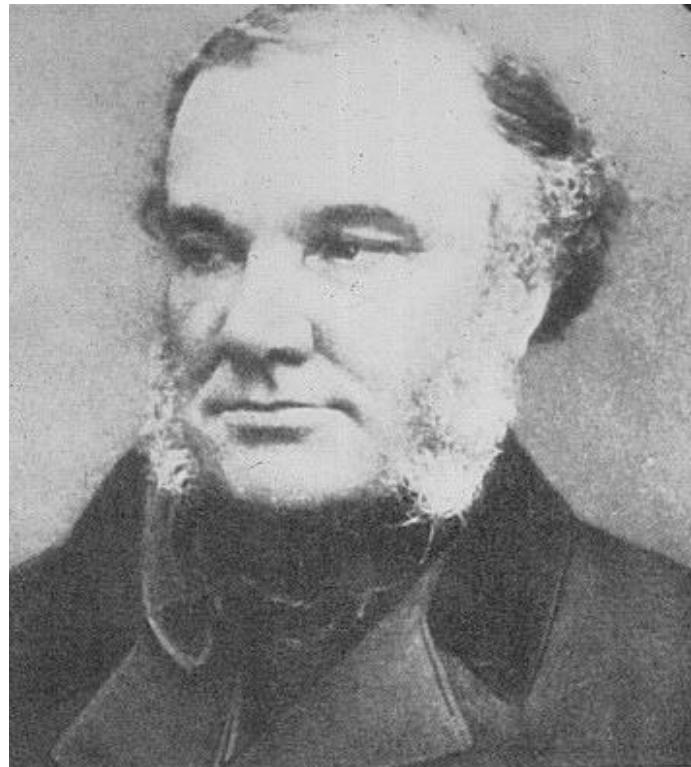
- Congenital adrenal hyperplasia
- Wolman disease
- Adrenal hypoplasia congenita
- Allgrove syndrome (AAA)

## Syndromes

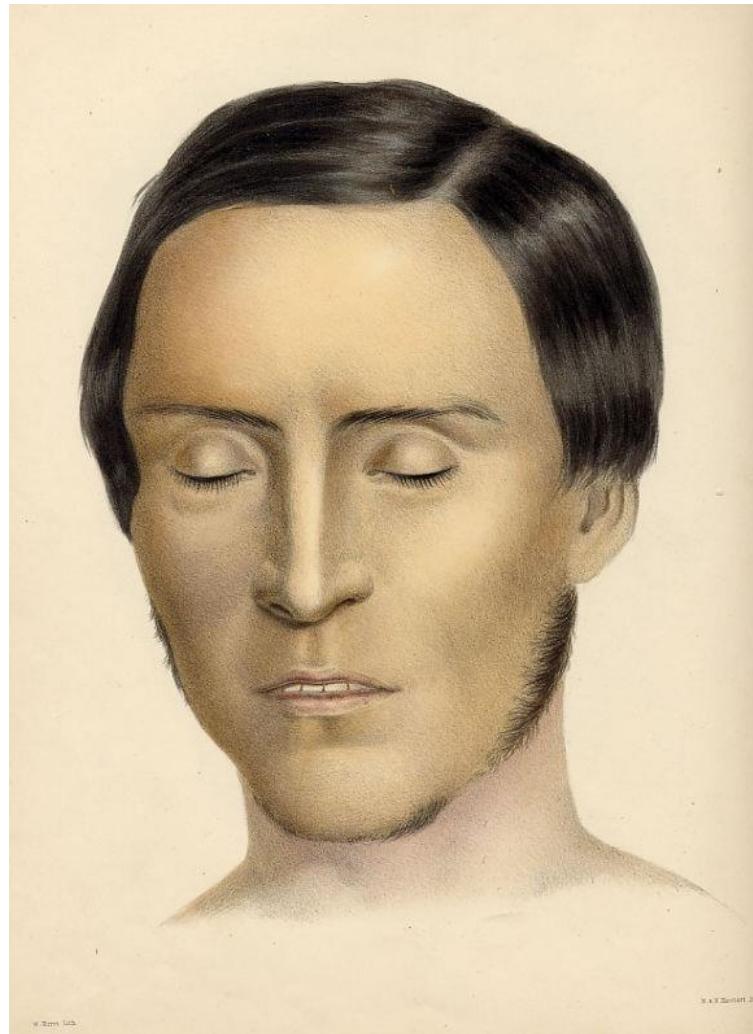
- Adrenoleukodystrophy
- Kearns-Sayre
- Autoimmune polyglandular syndrome 1 (APS1)
- APS2

# Addison's Disease

- 1<sup>st</sup> described in 1855 by Dr. Thomas Addison
- Refers to acquired primary adrenal insufficiency
- Does not confer specific etiology
  - Usually autoimmune (~80%)

A black and white photograph of a handwritten signature in cursive script. The signature reads "Thomas Addison" and is underlined at the end. The handwriting is fluid and personal.

# Primary adrenal insufficiency: Symptoms



- Fatigue
- Weakness
- Orthostasis
- Weight loss
- Poor appetite
- Neuropsychiatric
  - Apathy
  - Confusion
- Nausea, vomiting
- Abdominal pain
- Salt craving

# Primary adrenal insufficiency: Physical findings

- Hyperpigmentation
- Hypotension
- Orthostatic changes
- Weak pulses
- Shock
- Loss of axillary/pubic hair  
(women)

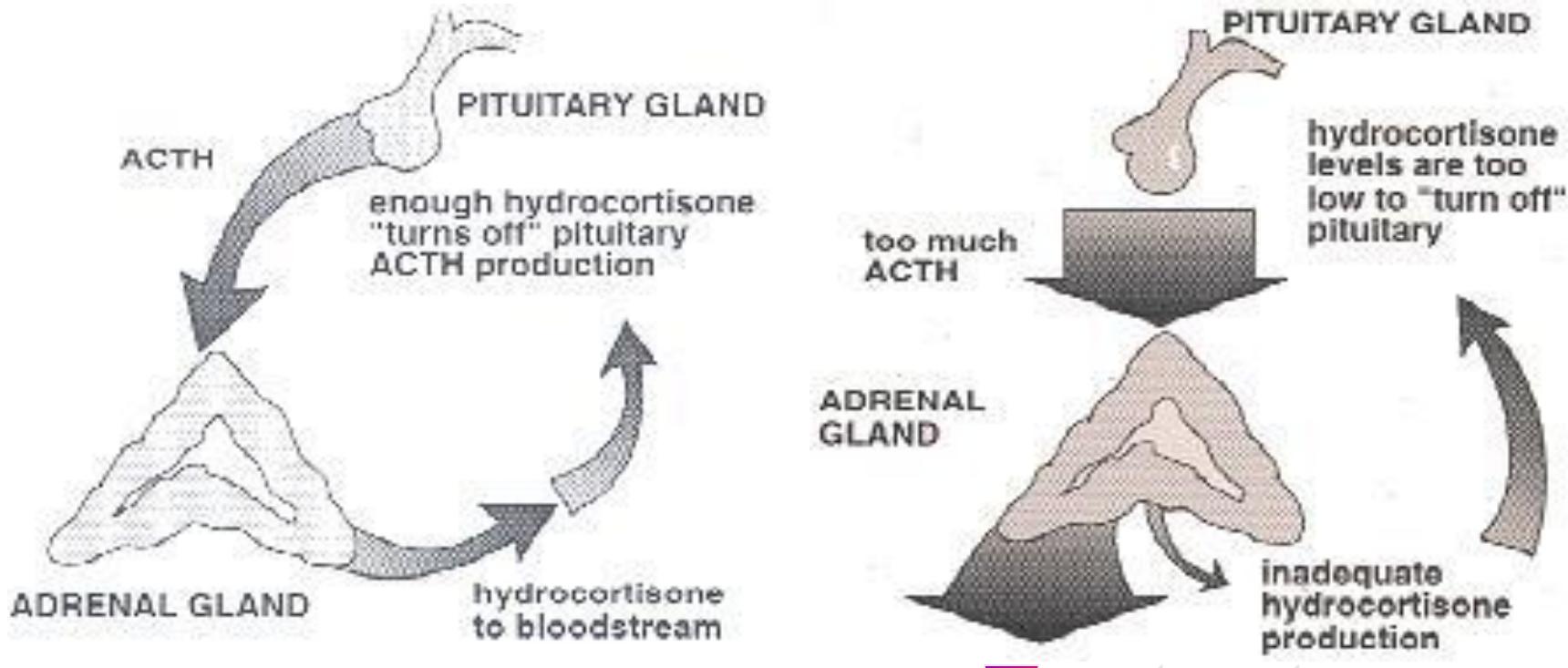


Hardin Library for the Health Sciences. John Martin Rare Book Room

# Primary adrenal insufficiency: Laboratory findings

- Hyponatremia
- Hyperkalemia
- Hypoglycemia
- Narrow cardiac silhouette on CXR
- Low voltage EKG

# 21-hydroxylase deficiency: Pathophysiology



**Testosterone**

# Prader virilization scale

Normal F

I

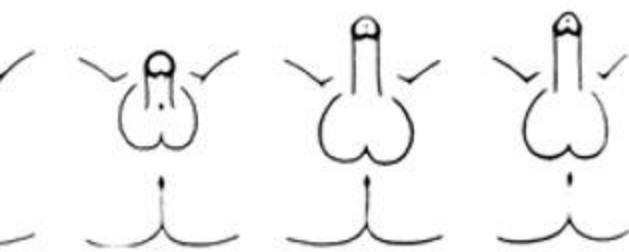
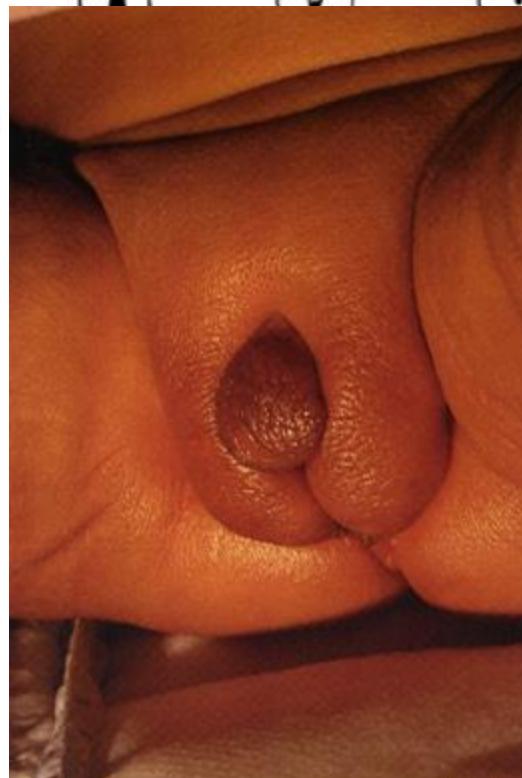
II

III

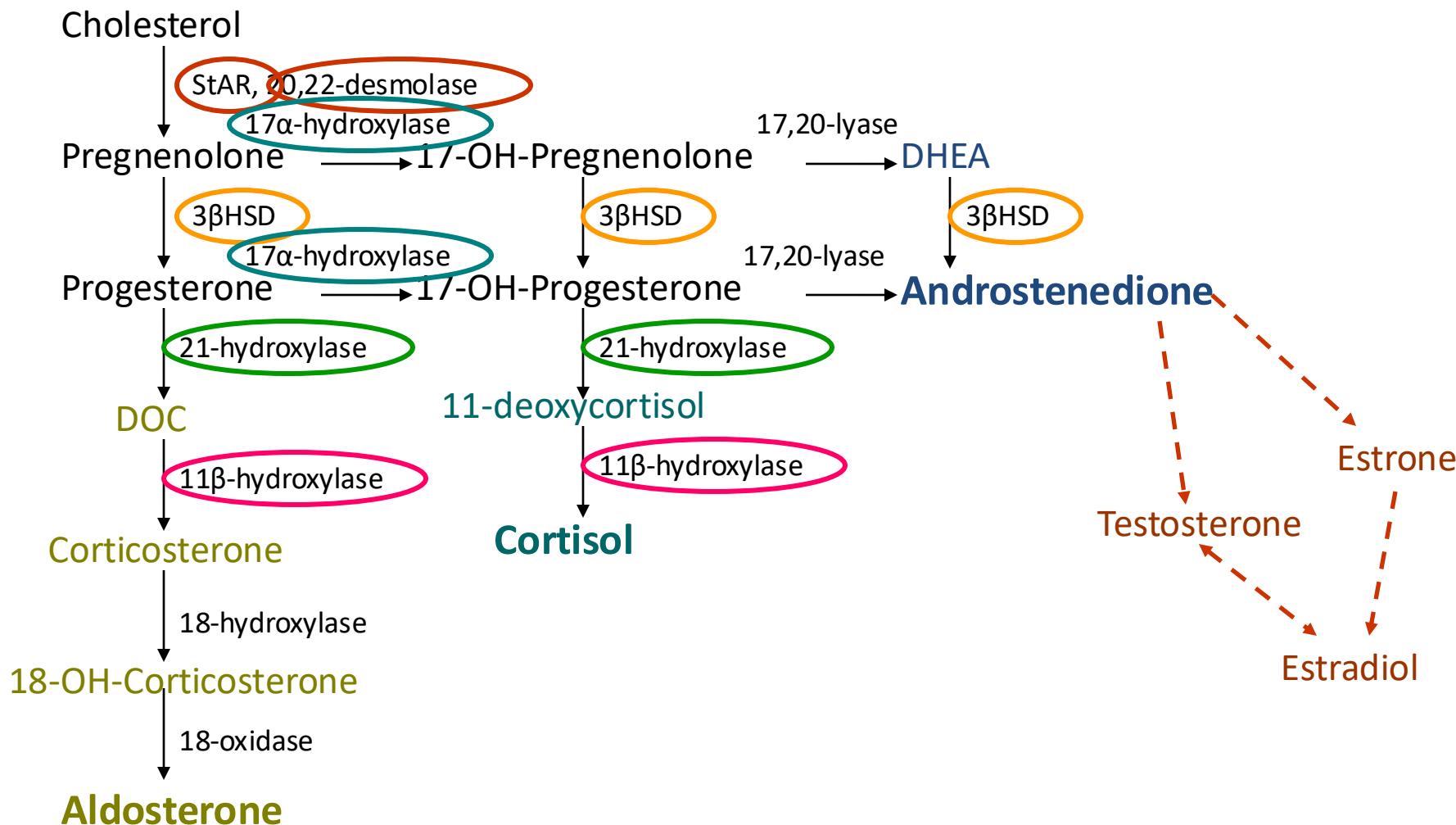
IV

V

Normal M



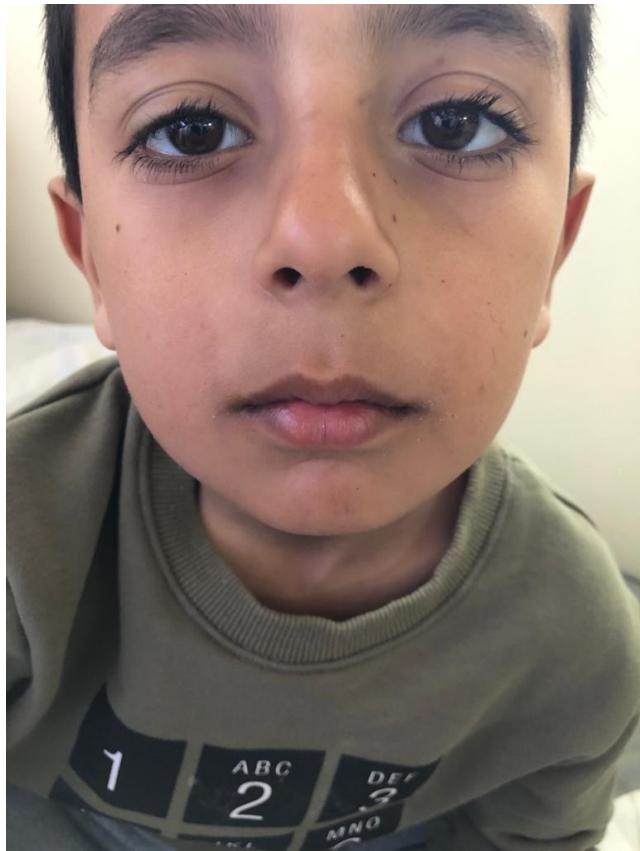
# CAH: Pathophysiology



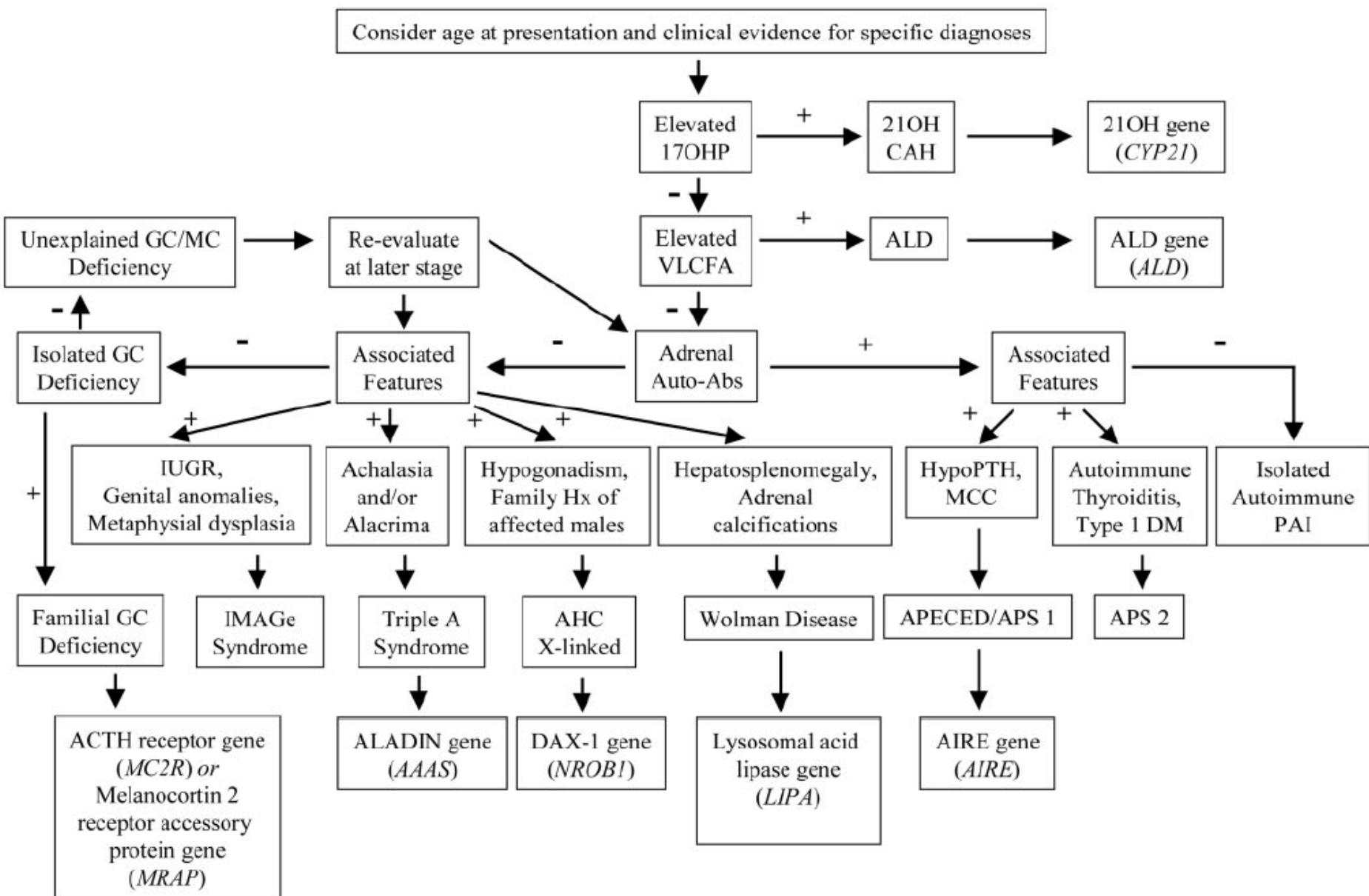
# 21-hydroxylase deficiency CAH

- Classification based on enzyme activity
  - Classic
    - Salt wasting (Complete deficiency)
    - Simple virilizing (Significant but partial defect)
  - Non Classic
    - Elevated enzyme levels (Mild deficiency)





# Primary adrenal insufficiency in children:Suggested diagnostic algorithm



# Primary adrenal insufficiency: Evaluation

- 0800 cortisol level
- ACTH level
- Random cortisol in ill patient
- ACTH stimulation test
- Suspected CAH

Needs special evaluation

- Renin and serum lytes
- Adrenal Autoantibodies
  - ACA—adrenal cortex antibody
  - Anti-21-OH-hydroxylase antibody

# Primary adrenal insufficiency: Evaluation—ACTH Stimulation

- Low dose (1 mcg) test
  - Baseline and 30 minute cortisol levels
  - More physiological ACTH level/stimulation
  - Useful in central AI
  - Useful for assessing recovery after chronic steroid treatment
- High dose (250 mcg) test
  - Baseline, 30 and 60 minute levels
  - Stronger stimulation than 1 mcg test
  - 17OHP
  - insulin/hypoglycemia test

- Imaging
- Urine collection and steroid analysis for metabolites.
- Genetic testing

# Treatment

- Stress dosing.
- Maintenance.
- Medical alerts.

# Stress dose steroids

- Loading dose
  - 50-100 mg/M2 hydrocortisone IV/IM
  - Small/medium/large approach
    - Infants: Hydrocortisone 25 mg
    - Small children: Hydrocortisone 50 mg
    - Larger children/teens: Hydrocortisone 100 mg
- Continue hydrocortisone with 50-100 mg/M2/day
  - Divide q6-8 hours
  - May be 2-3x home dose

# Primary adrenal insufficiency:

## Long term treatment

- Daily glucocorticoid replacement (hydrocortisone)
  - 10-15 mg/m<sup>2</sup>/day divided TID
  - Option to change to prednisone in teen years
- Daily mineralocorticoid replacement
  - Fludrocortisone 0.05-0.2 mg daily
- Patient education
  - Stress coverage
  - Emergency steroid administration
    - IM hydrocortisone (Solucortef Actovial)
  - Medic Alert ID

# Relative Steroid Potencies

	Glucocorticoid	Mineralocorticoid
Hydrocortisone	1	++
Prednisone/ Prednisolone	3-5	+
Methylprednisolone	5-6	0
Dexamethasone	25-50	0
Fludrocortisone	15-20	++++

# Follow up

- Serum electrolytes
- Renin
- ACTH
- 17OHP
- Androgens
- Bone age
- Growth charts

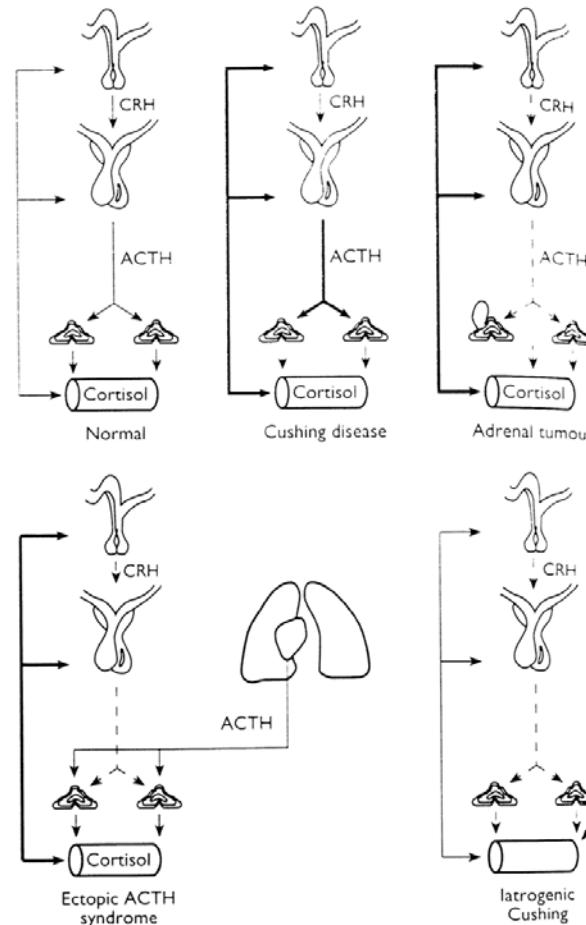
# Adrenal crisis

- IV fluids: boluses then maint. And deficit according to the severity of dehydration,during which close monitoring of blood gas and lytes.
- Steroid replacement: bolus then maint.,then shift to oral.
- Hypoglycemia: 2 ml/kg 10%dextrose bolus

- Hyperkalemia: usually normalize with fluids and steroid stress dose.
- If  $k > 6\text{mmol/L}$  cardiac monitor.
- If  $k > 7\text{mmol/L}$  either ca-gluconate or insulin with glucose iv.

# Cushing syndrome

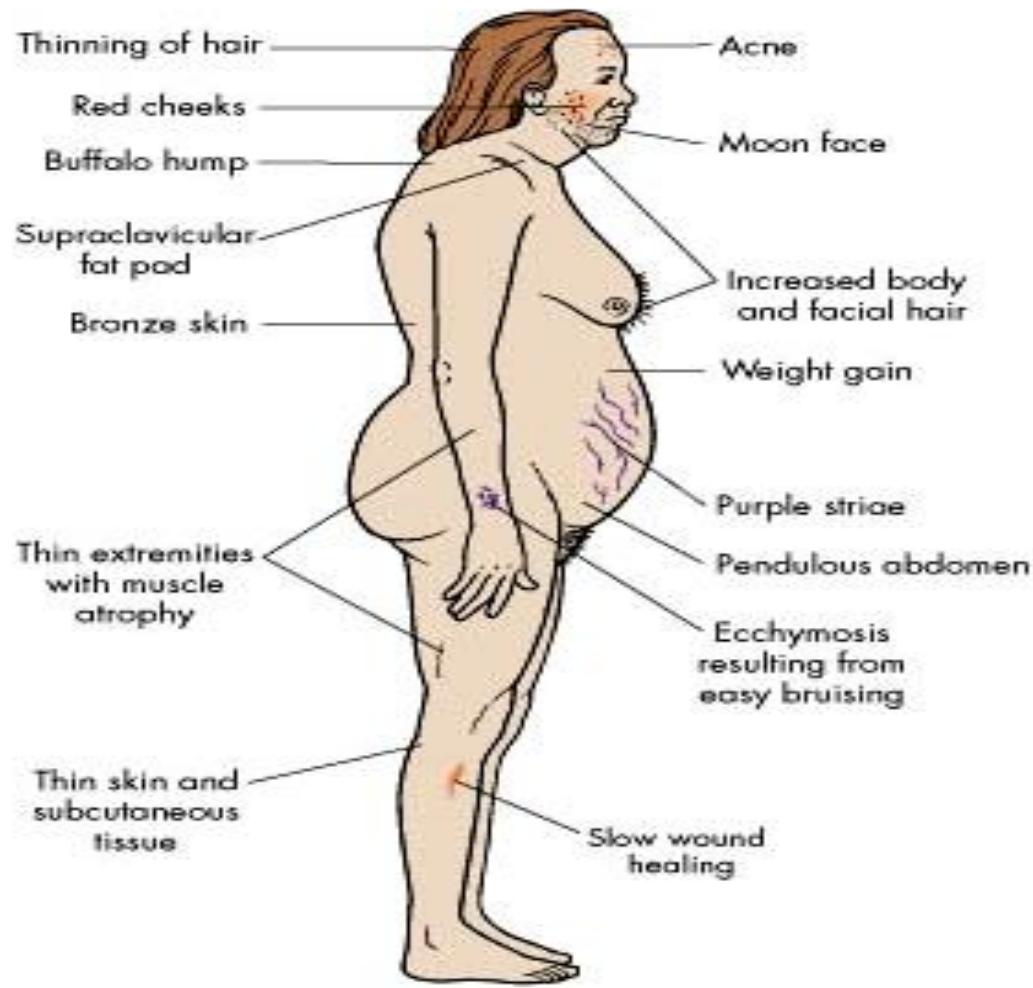
- Hypercortisolism due to pit. Overproduction of ACTH is cushing disease.
- Any other overproduction ACTH is ectopic ACTH syndrome.
- Other causes: adrenal adenoma, carcinoma or multinodular adrenal hyperplasia, mostly in infants and children < 7 yrs.
- Iatrogenic cushing syndrome.



# Clinical findings

- Hairsutism
- Facial flushing
- Striae
- Hypertension
- Muscular weakness
- Buffalo hump
- Psychological disturbances

Mostly seen in adults or late presentation in childhood.



**Figure 47-9** Common characteristics of Cushing's syndrome.

Copyright © 2000 by Mosby, Inc.

# Cont.

- Obesity(that starts generalised) and GROWTH ARREST are the important initial and alarming signs.
- Bone undermineralization.
- Puberty arrest.
- Compulsive behavior.
- In carcinomas and ectopic forms have a more fuminant coarse.

# Cushing disease

- In children , a well defined microadenoma in 80-85% of cases.
- Treatment is with trans-sphenoidal surgery.
- Minority will have high CRH, which is difficult to distinguish from 1ry pit. Adenoma.

# Other causes of Cushing syndrome

- Ectopic ACTH secretion :oat cell carcinoma.carcinoid,pancreatic islet cell carcinoma and thymoma.mostly in adults but maybe seen in infants with neuroblastoma.
- ACTH level 10-100 times in Cushing disease.
- ACTH is not suppressed by dexamethasone suppression test.

# Adrenal tumors

- More common in young children
- Adenomas secrete mainly cortisol ,minimal MCT and androgens.
- Carcinomas and nodular hyperplasia secrete cortisol and androgens.

# diagnosis

- Cortisol 8 am and 8 pm
- ACTH
- 24 hour urine collection of cortisol
- Dexamethasone suppression test.

# Pheochromocytoma

## When to suspect a pheo?

- Triad of episodic headache, diaphoresis and tachycardia ± hypertension
- Family history of pheo, VHL or MEN2 syndrome
- Clinical features of MEN2, von Hippel-Lindau disease, or pheochromocytoma/paraganglioma syndrome
- Known associated germ-line mutation in patient or family
- An undefined adrenal tumor
- Hypertension unexplained and/or poorly responsive to standard treatment
- Significant hypertension and tachycardia in response to general anesthesia, surgery or specific drugs
- **Note: 50% are caused by an underlying diagnosable genetic anomaly!**

# Diagnosis / Treatment

- **Diagnosis:**
  - Measurement of catecholamine metabolites (metanephrines) – urine/blood
  - Localization by CT imaging and MRI
  - Scintigraphy with radiolabeled metaiodobenzylguanidine (131/123I-MIBG)
- **Management:**
  - Control of blood pressure (pre-and perioperative)
  - Surgical removal
- **Prognosis:**
  - Risk for malignant pheo –12-47%