



ULTIMATE BEAUTY OF BIOCHEMISTRY

Dr. Veena Bhaskar S Gowda

Dept of Biochemistry

30th Nov 2017

SUSPECTED CASE OF CUSHING'S SYNDROME

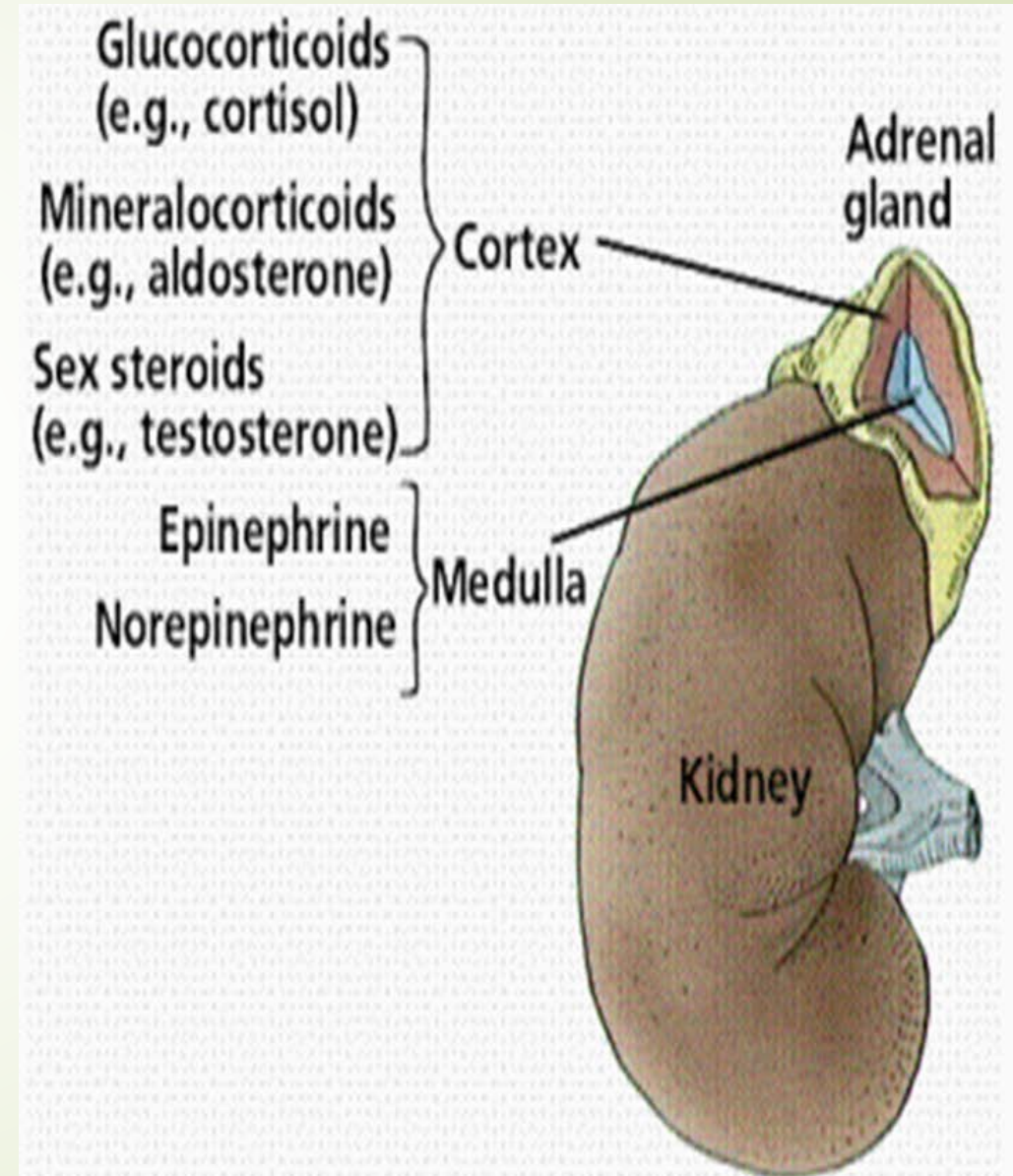
Clinical features


- ▶ Moon face
- ▶ Obesity
- ▶ Hypertension
- ▶ Hunch back
- ▶ Abdominal striae
- ▶ Reproductive problem as infertility

Supportive Biochemical investigations

- ▶ Hyperglycemia
- ▶ Hypokalemia

- Cushing's syndrome is the result of autonomous, excessive secretion of cortisol.
- Causes could be
 1. Exogenous
 2. Endogenous





Who is the
culprit??????????



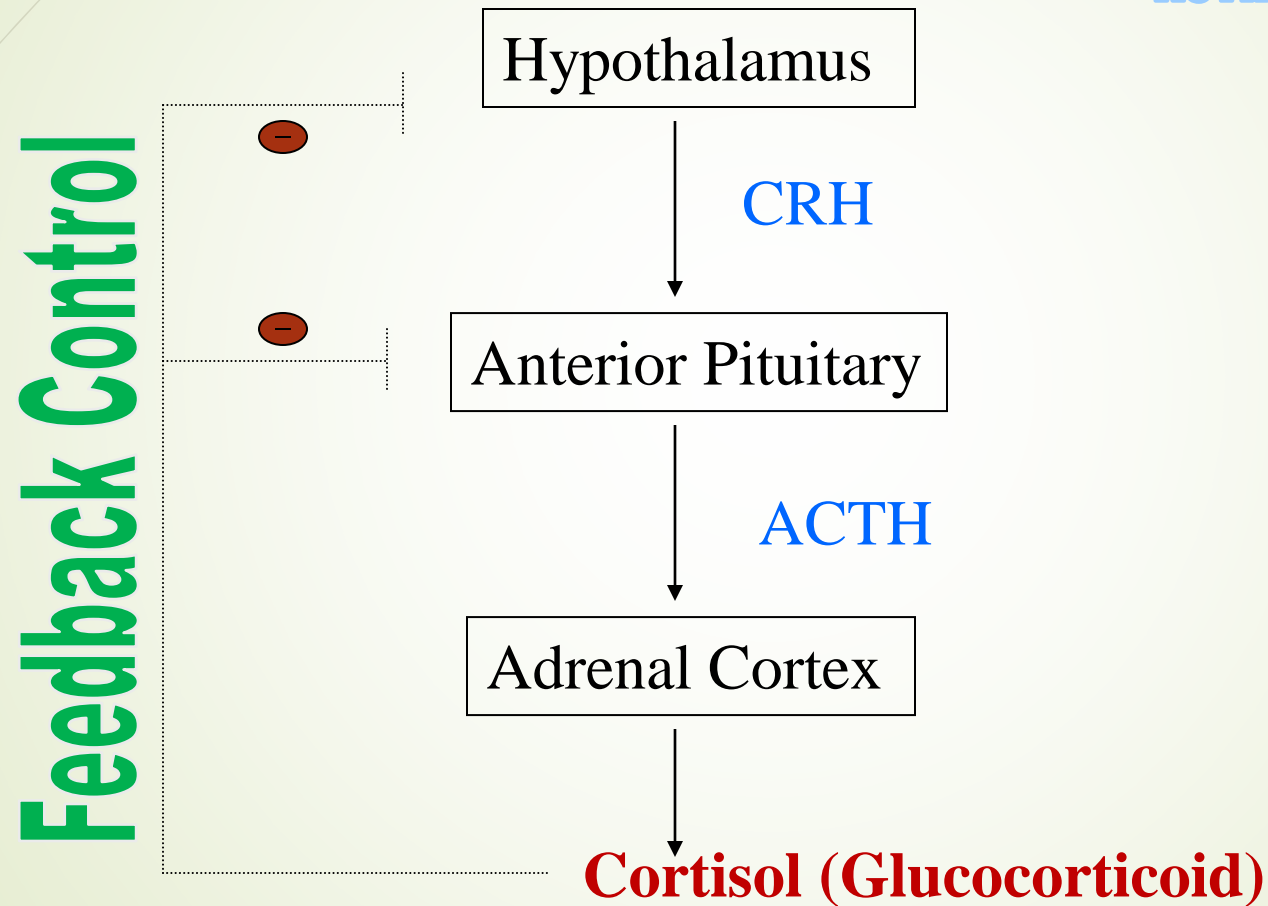
Pituitary gland

Adrenal tumor

Ectopic ACTH
producing tumor

HPA Axis

CRH: corticotrophin releasing hormone
ACTH: adenocorticotrophin



(HPA Axis = Hypothalamo Pituitary Adrenal Axis).

ENDOGENOUS CAUSES

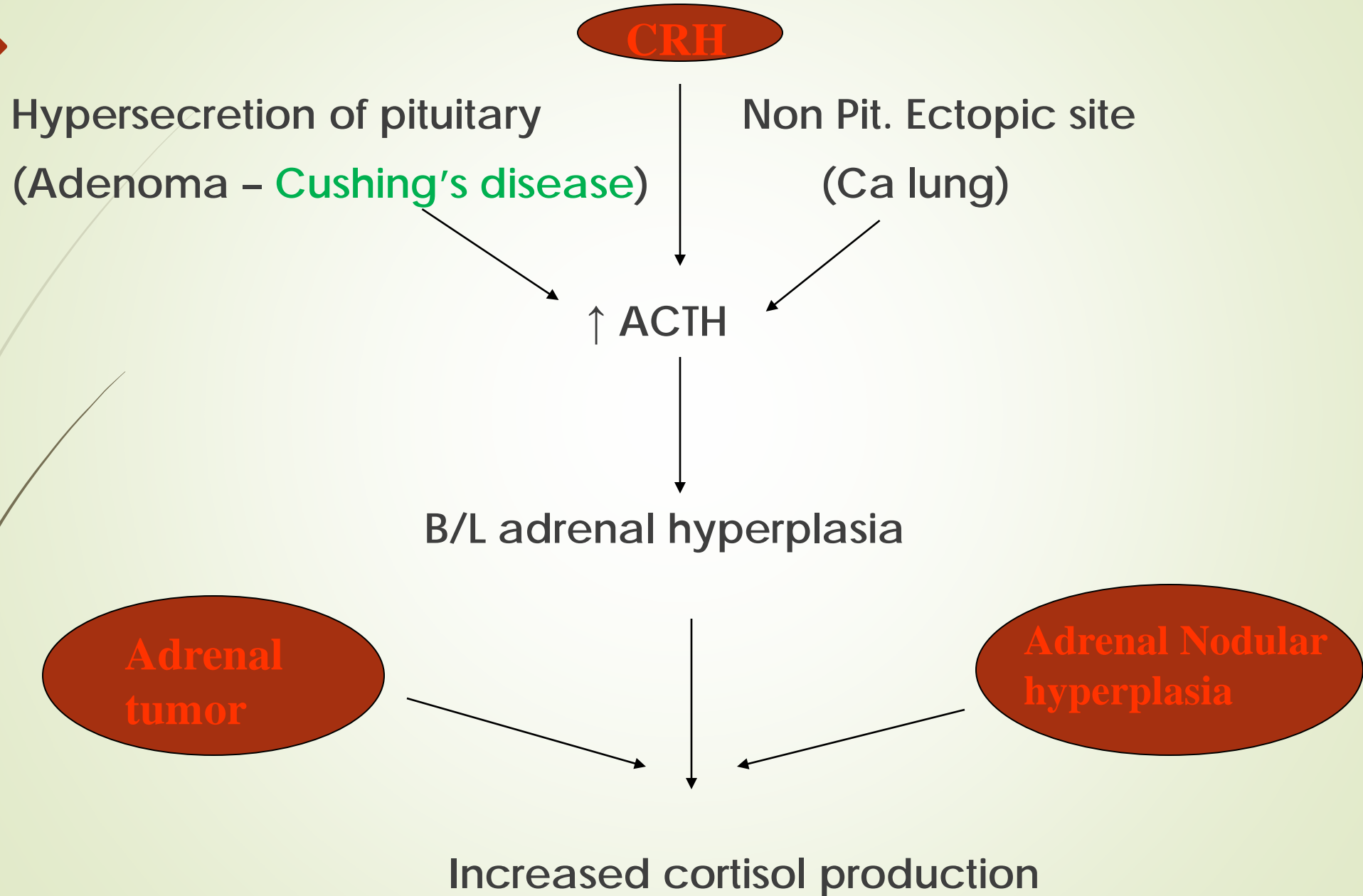
1. ACTH dependent

- a. Cushing's disease
- b. Ectopic ACTH secreting tumor

2. ACTH independent

- a. Adenoma
- b. Carcinoma
- c. Nodular adrenal hyperplasia

Endogenous Cushing Syndrome



Tests for adrenocortical functions

1. Assessment of diurnal rhythm

- ➔ Plasma cortisol levels are higher in the early morning (8AM) hours than at midnight.

Normal plasma cortisol range:

TIME	TOTAL CORTISOL	FREE CORTISOL
8 AM	5-23 µg/100ml	0.6-1.6 µg/100ml
4 PM	3-16 µg/100ml	0.2 -0.9 µg/100ml
8 PM	< 50% of 8 AM	

- ➔ Loss of this diurnal rhythmicity is an early indication of a lesion at any point in the hypothalamic-pituitary-adrenal axis.
- ➔ Stress like trauma, pain, apprehension, fever, depression & hypoglycemia can also alter this diurnal rhythm.

2. Estimation of 24 hr- urinary free cortisol

- Best Initial Screening test
- Urinary free cortisol in a 24 hr urine sample is performed
- Normal 20 -90 $\mu\text{g}/\text{day}$
- Levels more than 120 $\mu\text{g}/\text{d}$ suggest the diagnosis of Cushing's syndrome .

3. Low-Dose Dexamethasone suppression Test

Recommended if results of urinary free cortisol tests are abnormal

- ❖ **Principle:** Dexamethasone inhibits pituitary ACTH release & hence suppresses adrenal cortisol secretion, in normal persons ($< 3\mu\text{g/dl}$) at 8 AM.
- ❖ **Overnight low dose dexamethasone suppression test:** For outpatient screening, a single bed time low dose of dexamethasone (1 mg) given.
- ❖ Patients with Cushing's/ ectopic ACTH, in whom feedback control is abnormal, do not usually show cortisol suppression with low doses of dexamethasone ($>10 \mu\text{g/dl}$).

MULTIPLE LOW DOSE DEXAMETHASONE SUPPRESSION TEST

- ❖ Twenty- four- hour urine samples are collected daily for 4 consecutive days.
- ❖ Dexamethasone (0.5mg/6h) is given orally over 2 days from 8 AM of 2nd day.
- ❖ Serum cortisol on day 1 & day 5 for diurnal variation, 17-hydroxycorticosteroids (17-OHCS) & urinary free cortisol on 24 hr urine samples.
- ❖ **Interpretation:** Normal subjects have suppressed serum and urinary free cortisol on day 4 to less than 50% of baseline values.
- ❖ Patients with cushing's syndrome usually do not show diurnal rhythmicity and do not show suppression with this dose as well.

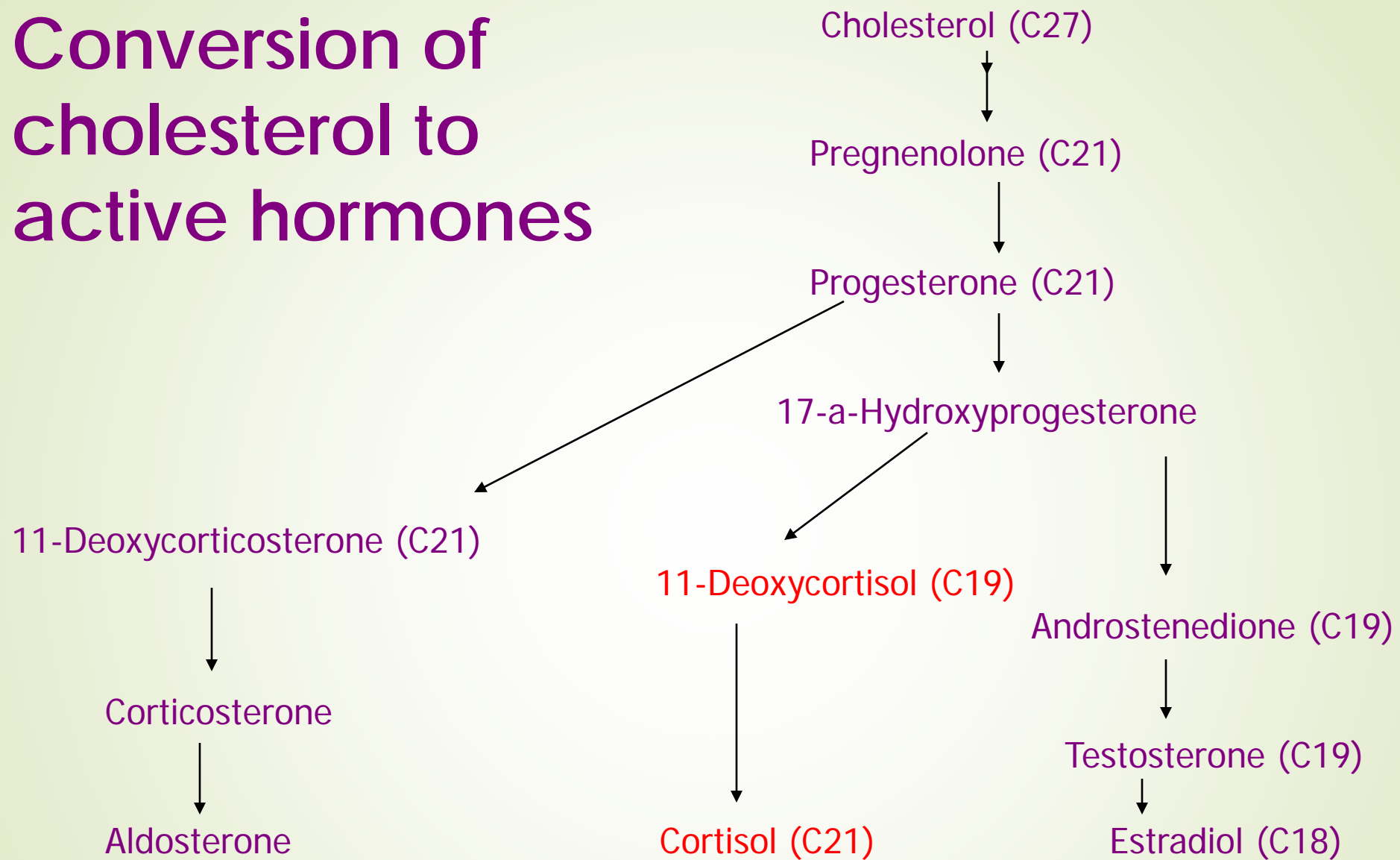
4. High-Dose Dexamethasone suppression test

- ❖ This test is performed following an abnormal low-dose dexamethasone test to establish the origin of hypercortisolism.
- ❖ Can be a single overnight test (8mg) or multiple dose test for 2 days
- ❖ A high dose of dexamethasone (2 mg/6 h for 2 days) is given over a period of 48 h, or as a single bedtime dose.
- ❖ 24-h urine samples are collected before & after dexamethasone for measurement of urinary free cortisol & 17-OHCS to determine whether there is cortisol suppression.
- This dose suppresses urinary 17-OH steroids & free cortisol as well as plasma cortisol (<10µg/dl) on day 5 in **cushing's disease (pituitary origin)**.
- If these parameters are not suppressed, adrenal tumors producing high levels of cortisol or ectopic ACTH producing tumors are the etiology.

5. Metyrapone stimulation test

- Used less frequently to delineate cause of Cushing's syndrome
- Metyrapone (given 30mg/kg body weight orally at midnight) is a potent inhibitor of 11-hydroxylase enzyme, which when administered blocks cortisol synthesis & removes the negative feedback on pituitary causing excess ACTH secretion.
- But with the pathway blocked, initially formed precursors stop at 11-deoxycortisol and alternately are diverted to androgen synthesis as well increase the urinary excretion of 17-hydroxycorticosteroids.
- In Cushing's syndrome due to pituitary tumor, ACTH response remains intact and 11-deoxycortisol show marked rise (>200nmol/L)
- In adrenal tumor or ectopic ACTH production, 11-deoxycortisol remains less than 200nmol/L.

Conversion of cholesterol to active hormones



6. CRH stimulation test

- Definitive in differentiation of pituitary causes of Cushing's syndrome from other causes.
- Exaggerated ACTH response indicates pituitary origin.
- Poor/absence of ACTH response after a CRH stimulation test, indicates adrenal or ectopic origin of the disease.
- Ratio of ACTH in blood samples drawn from inferior petrosal sinus to peripheral veins drawn simultaneously following IV administration of CRH is another variant.

