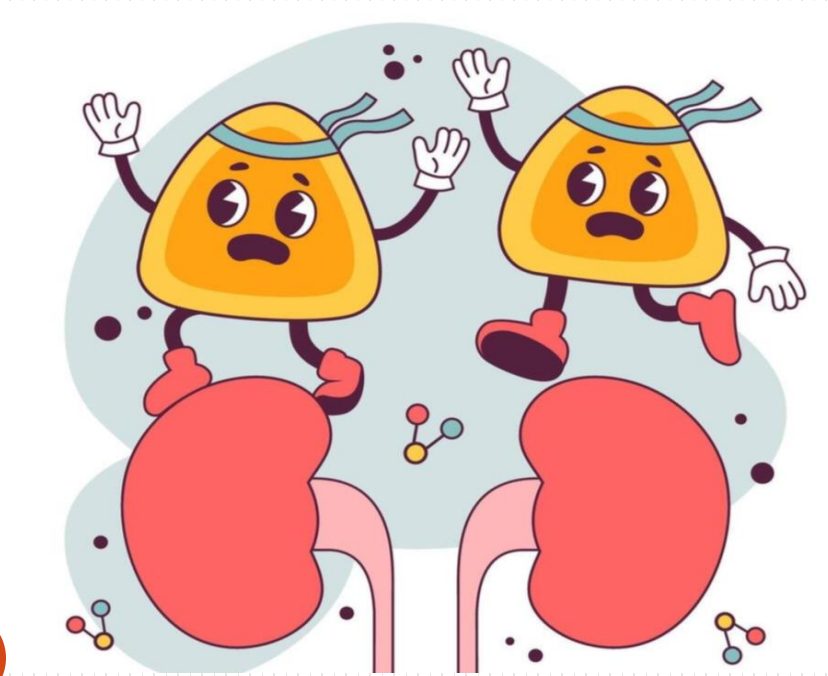
Cortisol and its clinical importance



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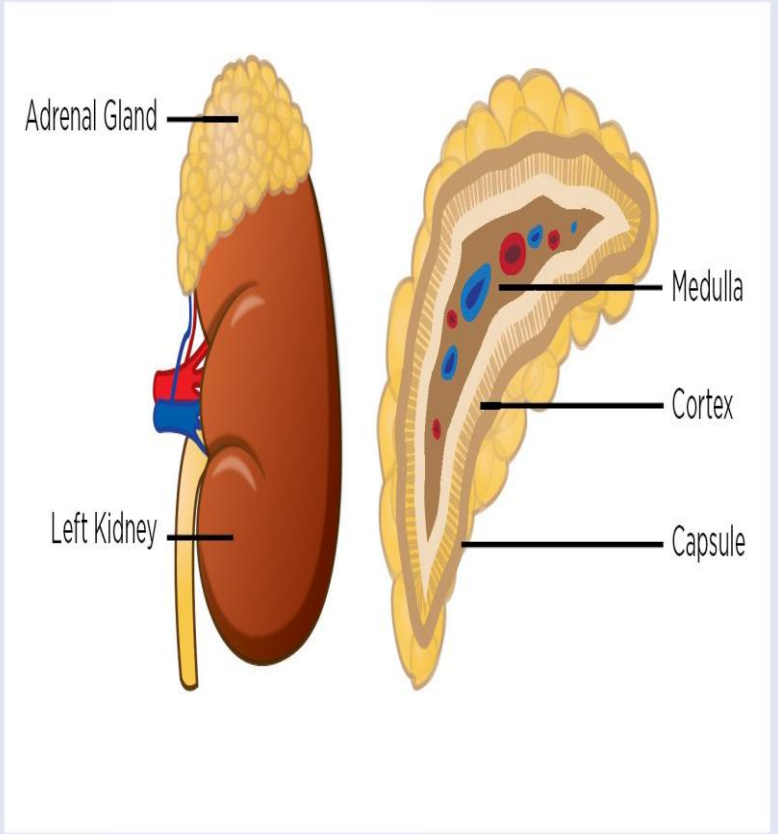
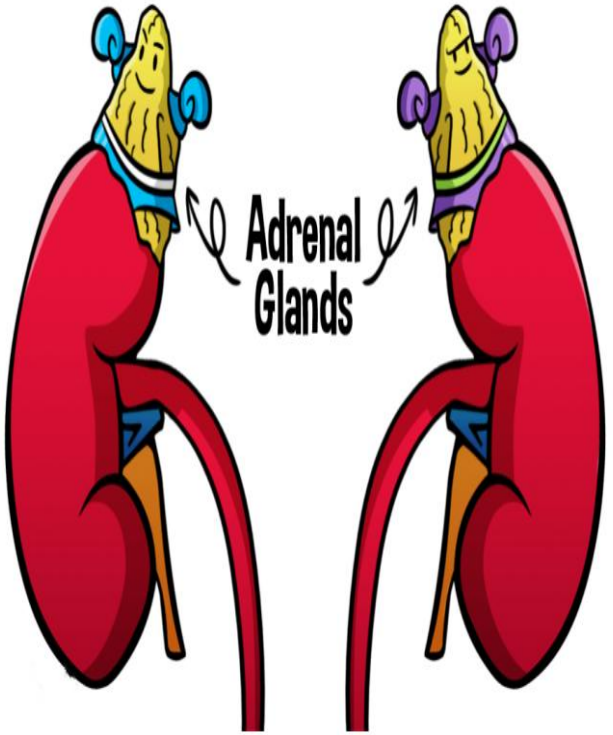
Learning Objective

1. Basic structure of adrenal gland
2. Pathway for synthesis of cortisol
3. Function of Glucocorticoids(cortisol)
4. Mechanism of action of glucocorticoids
5. Clinical aspects of glucocorticoids
6. Investigations, treatment & complications regarding cushing's syndrome.

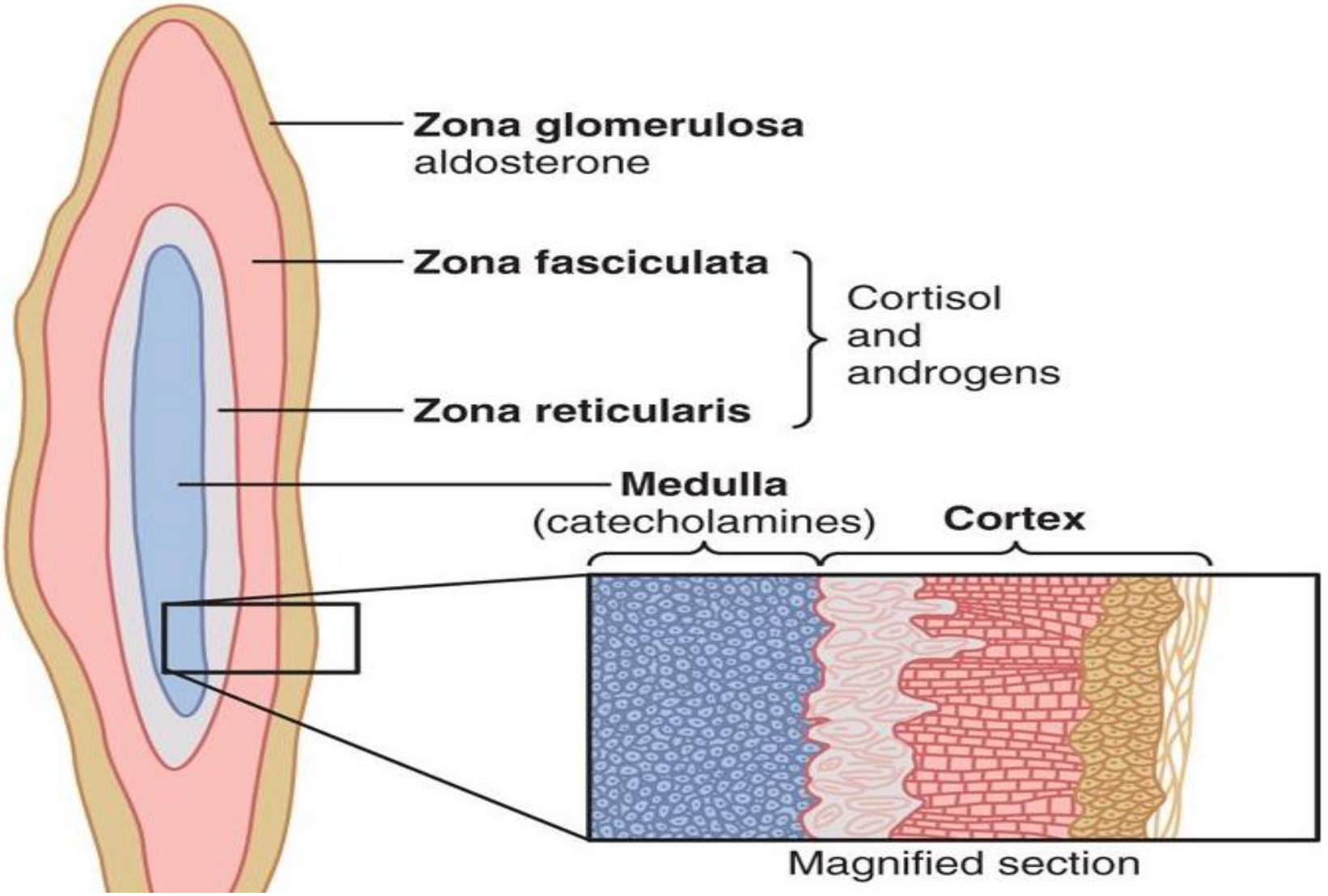
Anatomy of adrenal gland

Fig 1. **Position and structure of the adrenal gland**



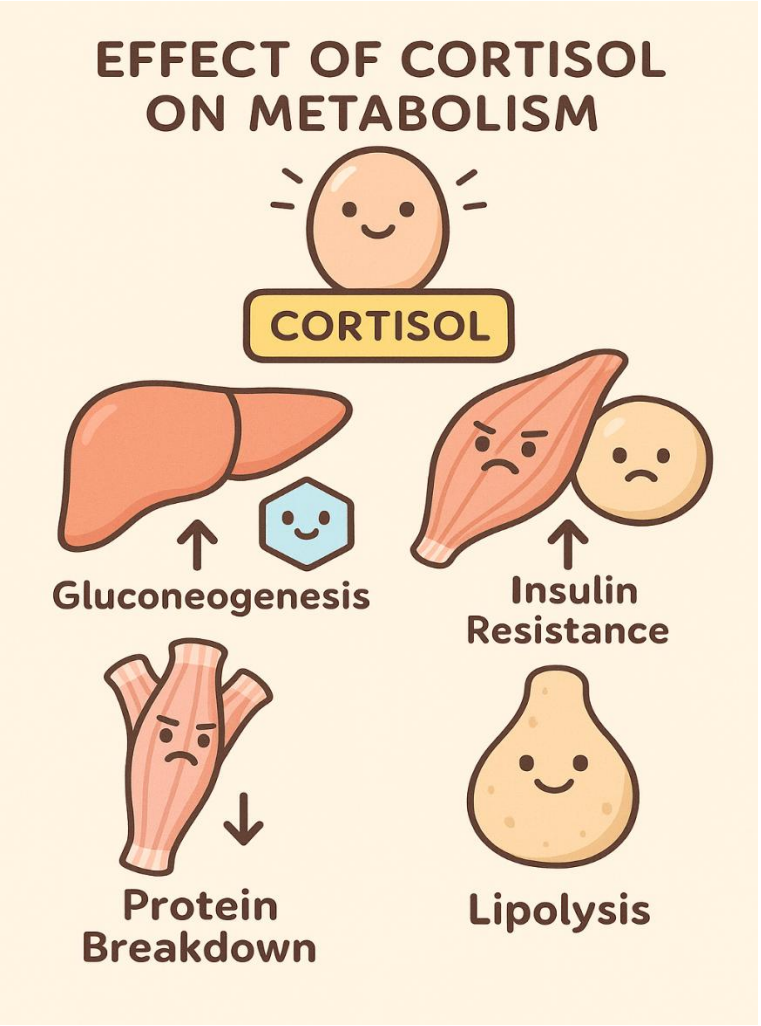


Layers of adrenal gland

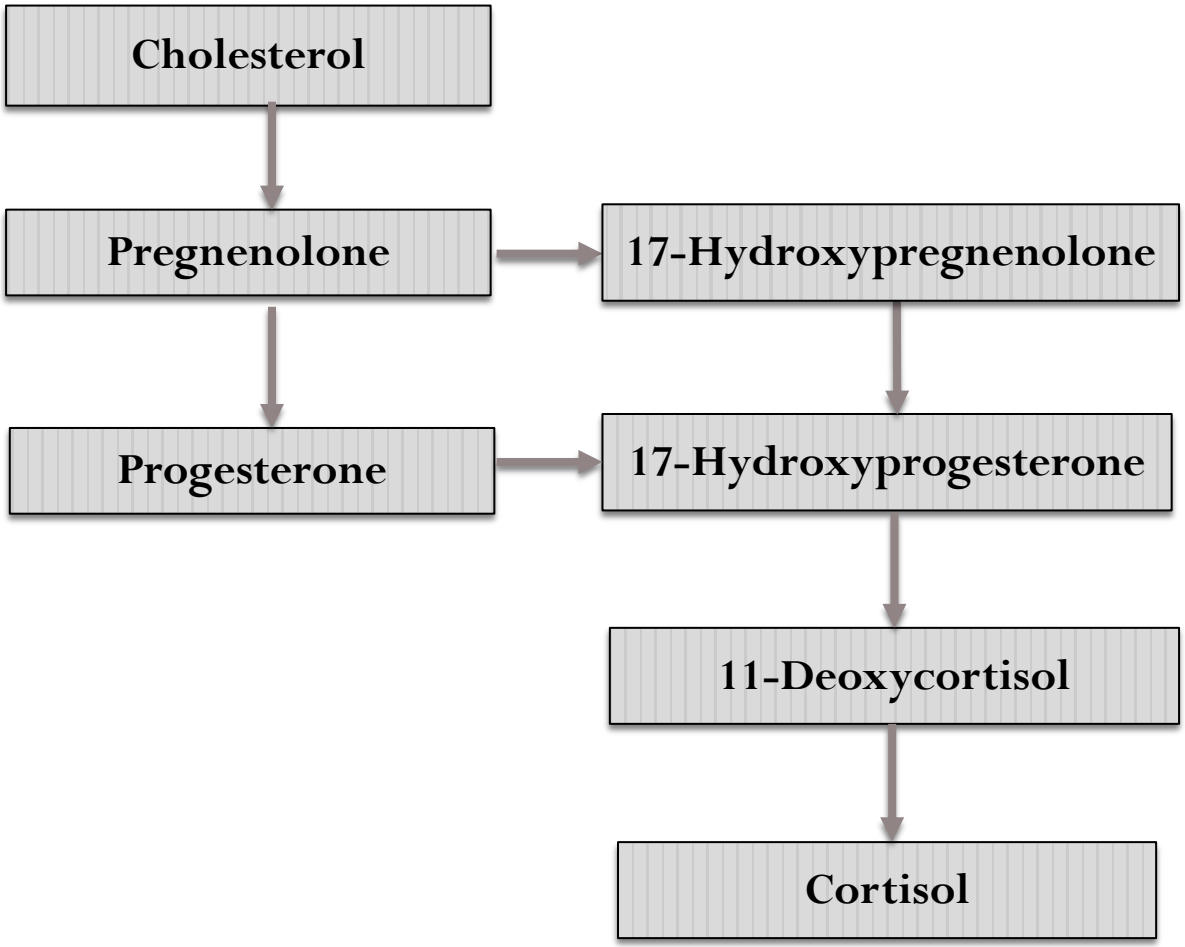


Cortisol is called Glucocorticoid

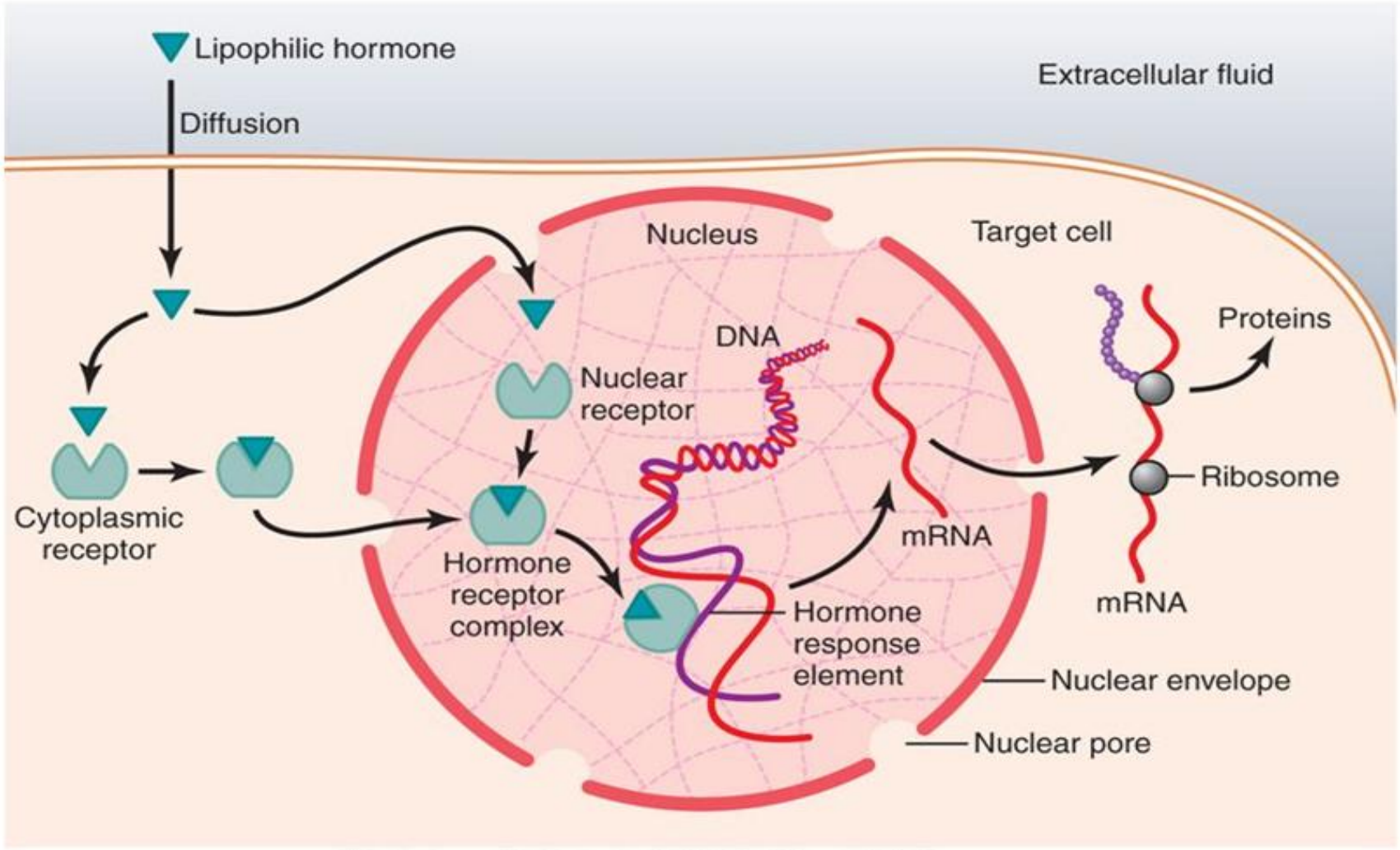
The glucocorticoids have gained their name because they exhibit important effects that increase blood glucose concentration.



Pathway for synthesis of cortisol



Mechanism of action



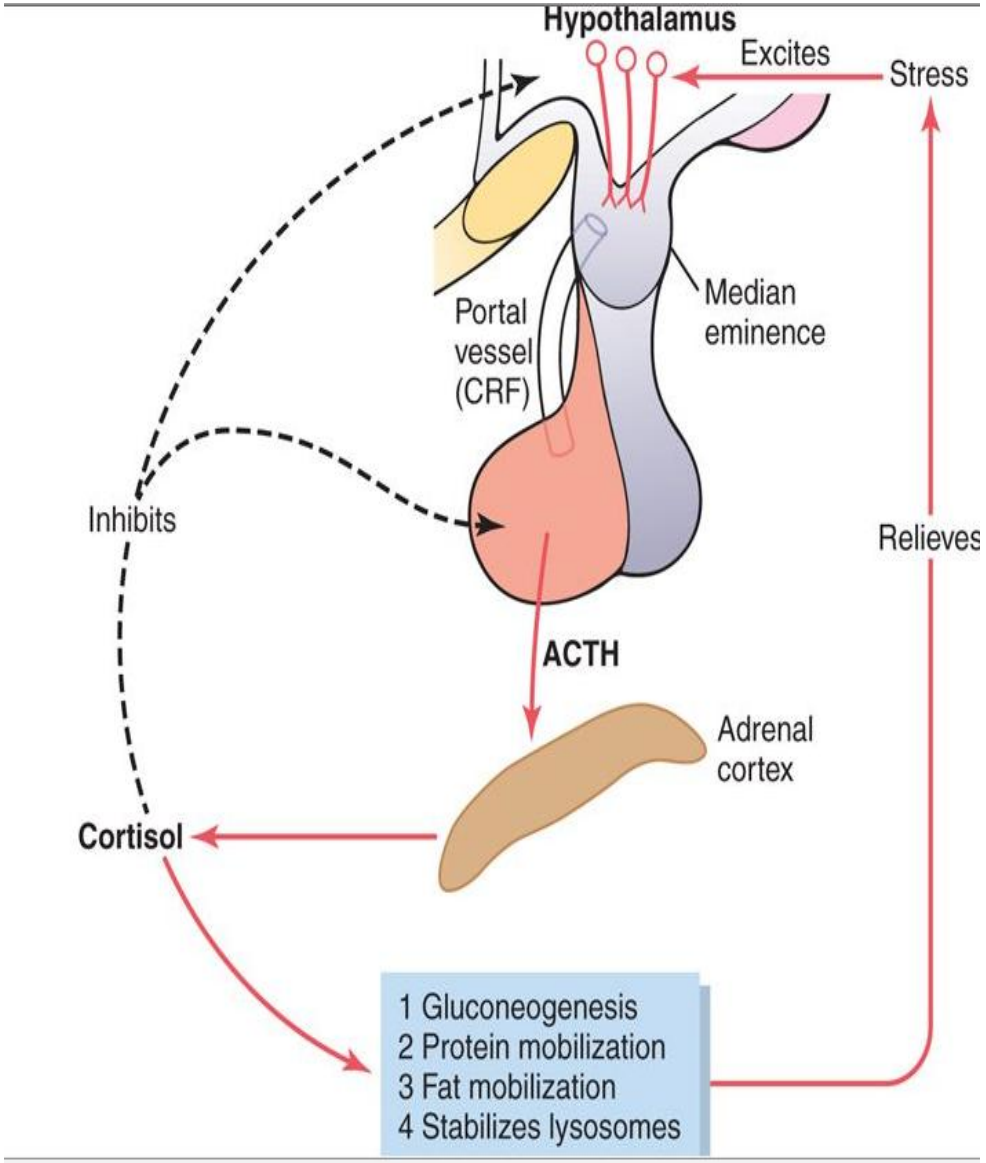
Function of Glucocorticoids(cortisol)

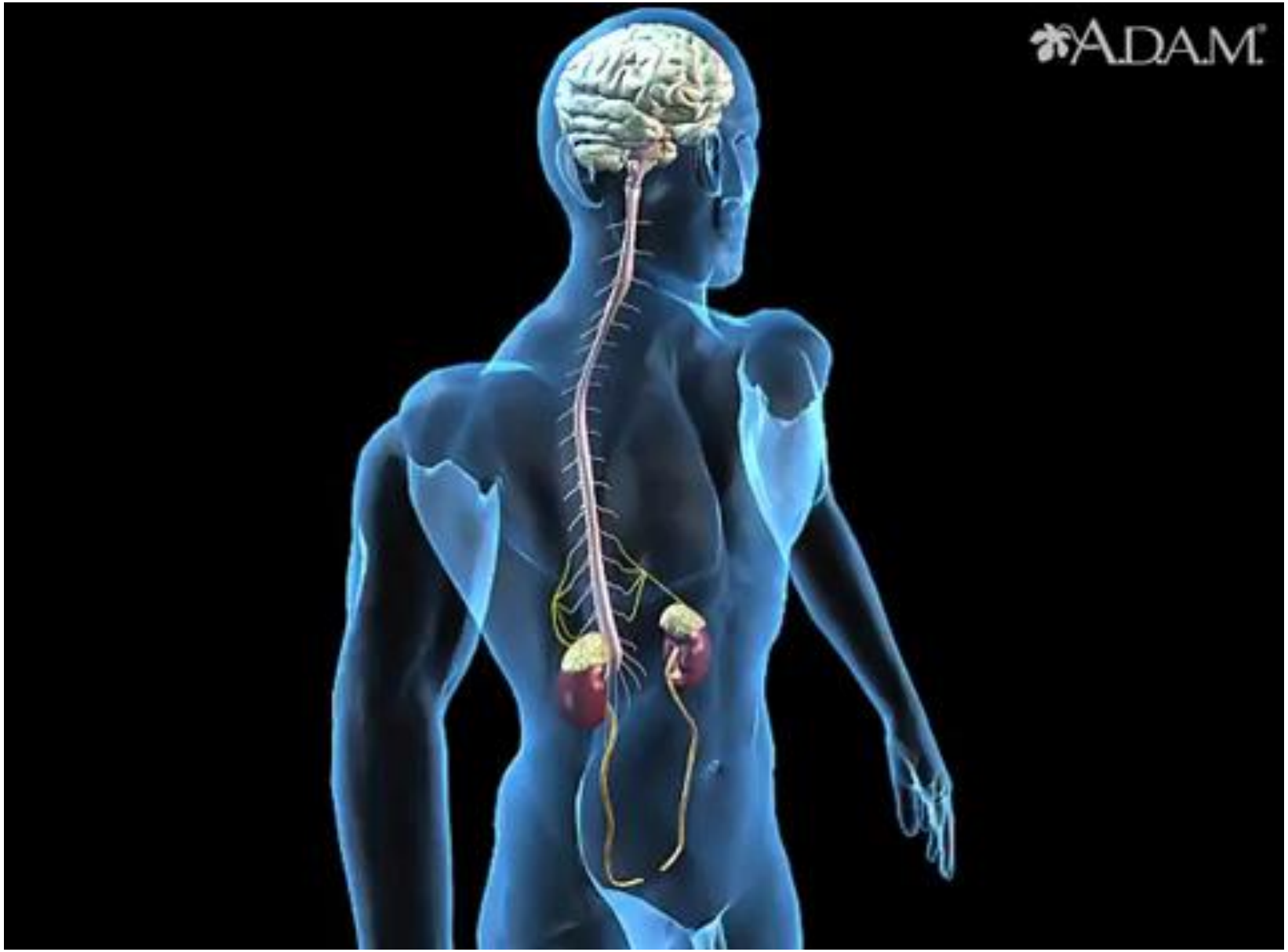
Metabolic function

CHO Metabolism	Increases gluconeogenesis Decreases glucose uptake Raises blood glucose
Protein Metabolism	Promotes protein breakdown Increases amino acid availability for gluconeogenesis
Fat Metabolism	Increases lipolysis Mobilization of fatty acid from adipose tissue

Cortisol resist stress

It supports energy availability during stress (fight or flight response) that's why it is called **emergency hormone.**




A.D.A.M.

- Cortisol decreases lymphocyte production & suppresses the immune system.
- It prevents the development of inflammation by stabilizing lysosomes.
- Cortisol lowers fever because it reduces the release of interleukin-1 from white blood cells.

Permissive action of cortisol

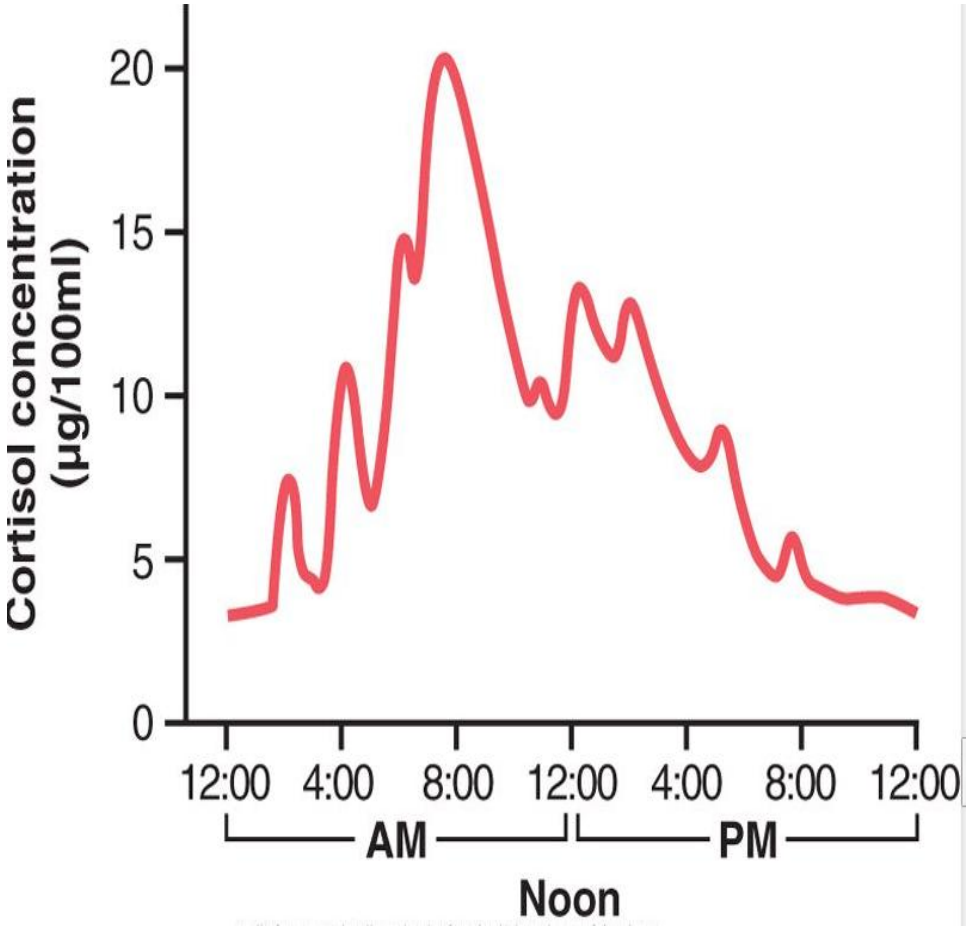
The action of some hormones are executed only in presence of glucocorticoids.This is called permissive effect of glucocorticoids.

Example :

- The presence of glucocorticoids is necessary for glucagon and catecholamines to exert their calorigenic effect.
- For catecholamines to exert their lipolytic effect.

Circadian rhythm of glucocorticoid secretion

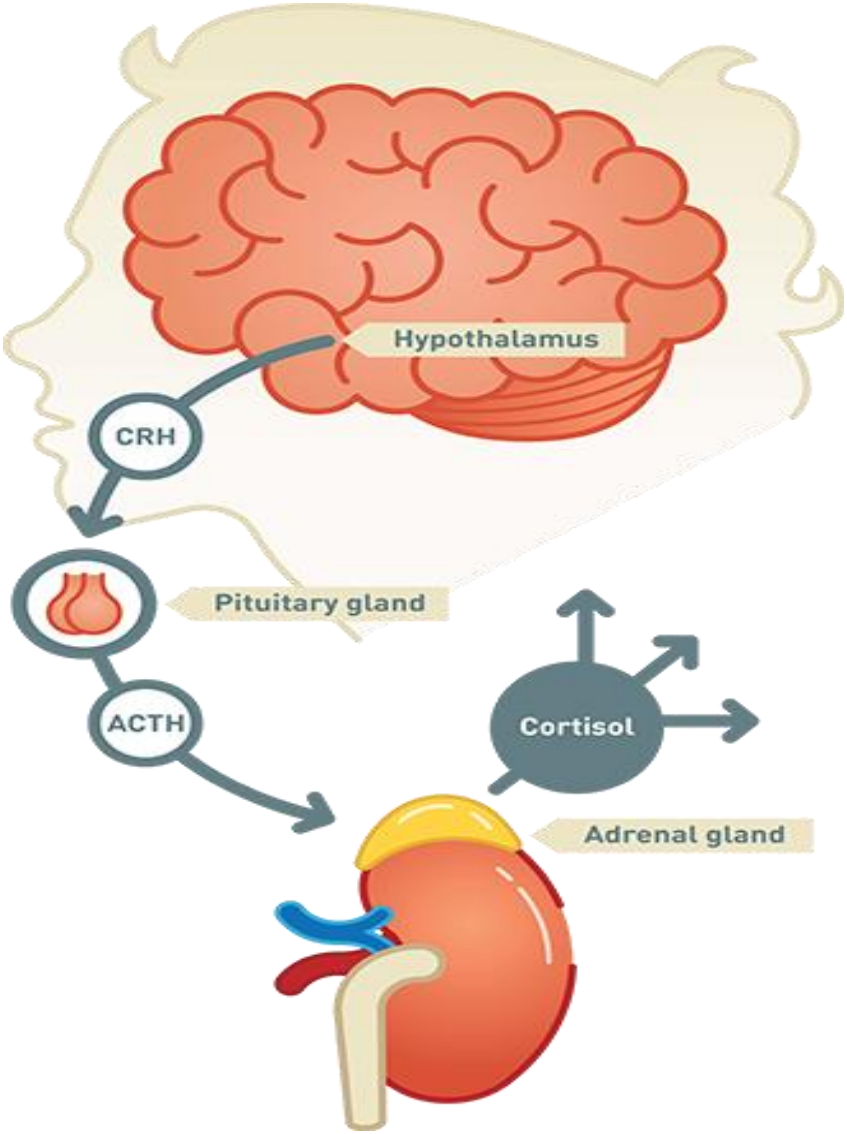
The secretory rates of CRF, ACTH, and cortisol are high in the early morning, declines by evening,& is lowest at midnight.



Clinical aspects of cortisol

- Hyper secretion of adrenal cortex causes a complex cascade of hormone effect called **Cushing's Syndrome**.

- This is caused by excessive activation of glucocorticoid receptor.



- ✓ Cushing's syndrome is named after **Dr. Harvey Cushing** (renowned American neurosurgeon).
- ✓ In 1912, he first observed the patients with this specific hormonal imbalance lead to the syndrome.

Birthday of 'Father of Neurosurgery'
DR.HARVEY CUSHING
8th April

Cushing's Awareness day

Key Statistics

Incidence: 1.8-4.5 /million /year.

Prevalence: 57-79 /million /year.

Age of diagnosis: around 40 to 45 years old.

Mortality: 2-3 times higher than general population.

Recurrence rate: Upto 20% of patients with Cushing's disease experience late recurrences.

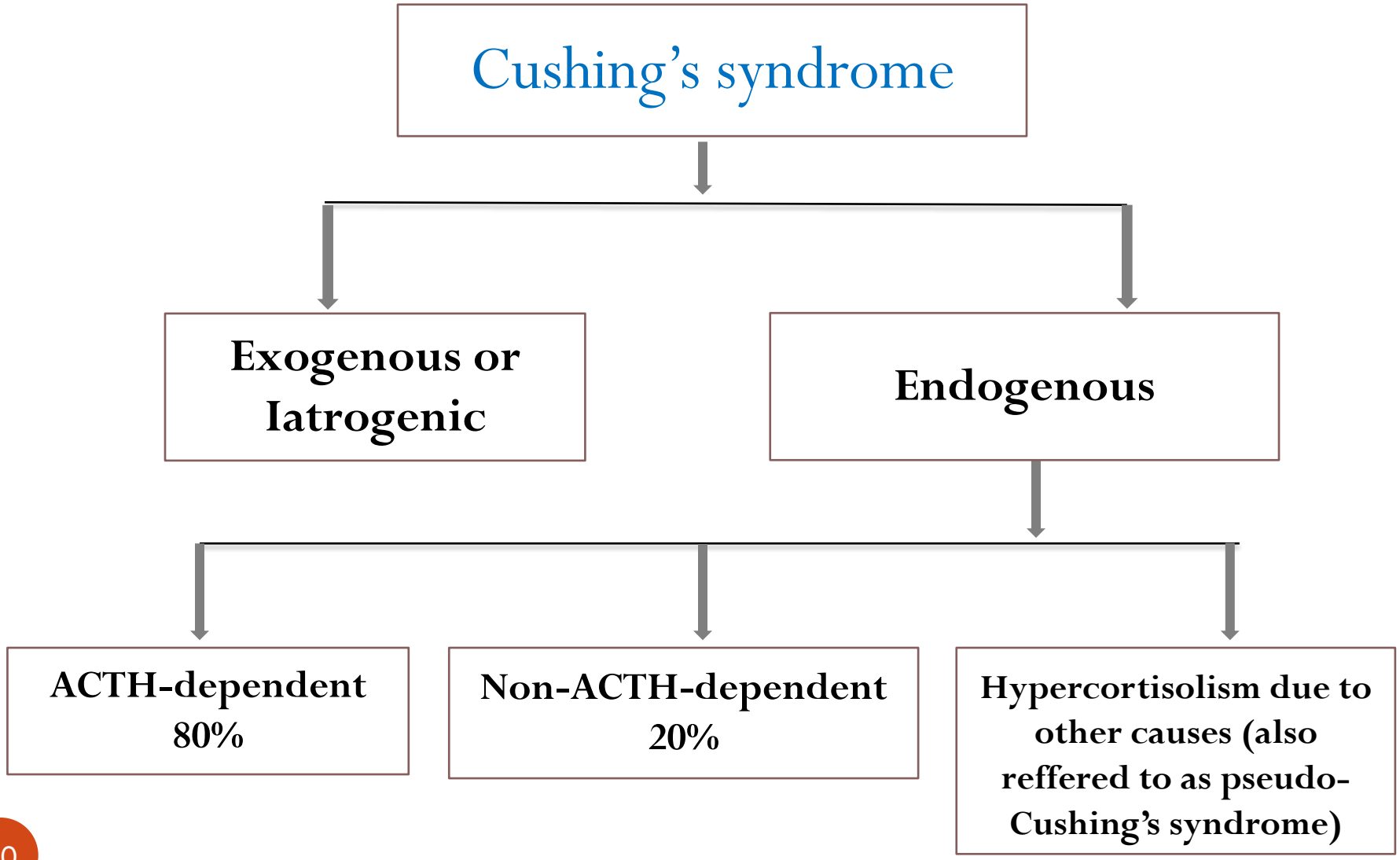
Sex Ratio: Female to male ratio of 4:1.

- Both Cushing's disease and cortisol secreting adrenal tumors are four times more common in women than men.
- In contrast, ectopic ACTH syndrome (often due to a small cell carcinoma bronchus) is more common in men.

Cushing's Disease vs Syndrome

Cushing's Disease	Cushing's Syndrome
Excess cortisol due to ACTH secreting pituitary adenoma.	Excess cortisol due to any cause.

Etiology of Cushing's syndrome



Iatrogenic Cushing's syndrome

Cushing's syndrome is most commonly iatrogenic, due to prolonged or excessive administration of exogenous glucocorticoids. Such as;

- Prednisone
- Dexamethasone
- Hydrocortisone
- Methylprednisolone

These medications are commonly prescribed for various conditions like:

- Asthma or COPD
- Autoimmune diseases (e.g. Rheumatoid arthritis)
- Organ transplantation (to prevent rejection)
- Chronic inflammation

ACTH-dependent-80%

- ACTH secreting pituitary adenoma(cushing's disease)-70%
- Ectopic ACTH syndrome (Bronchial carcinoid, Small cell lung carcinoma, other neuro-endocrine tumor)-10%

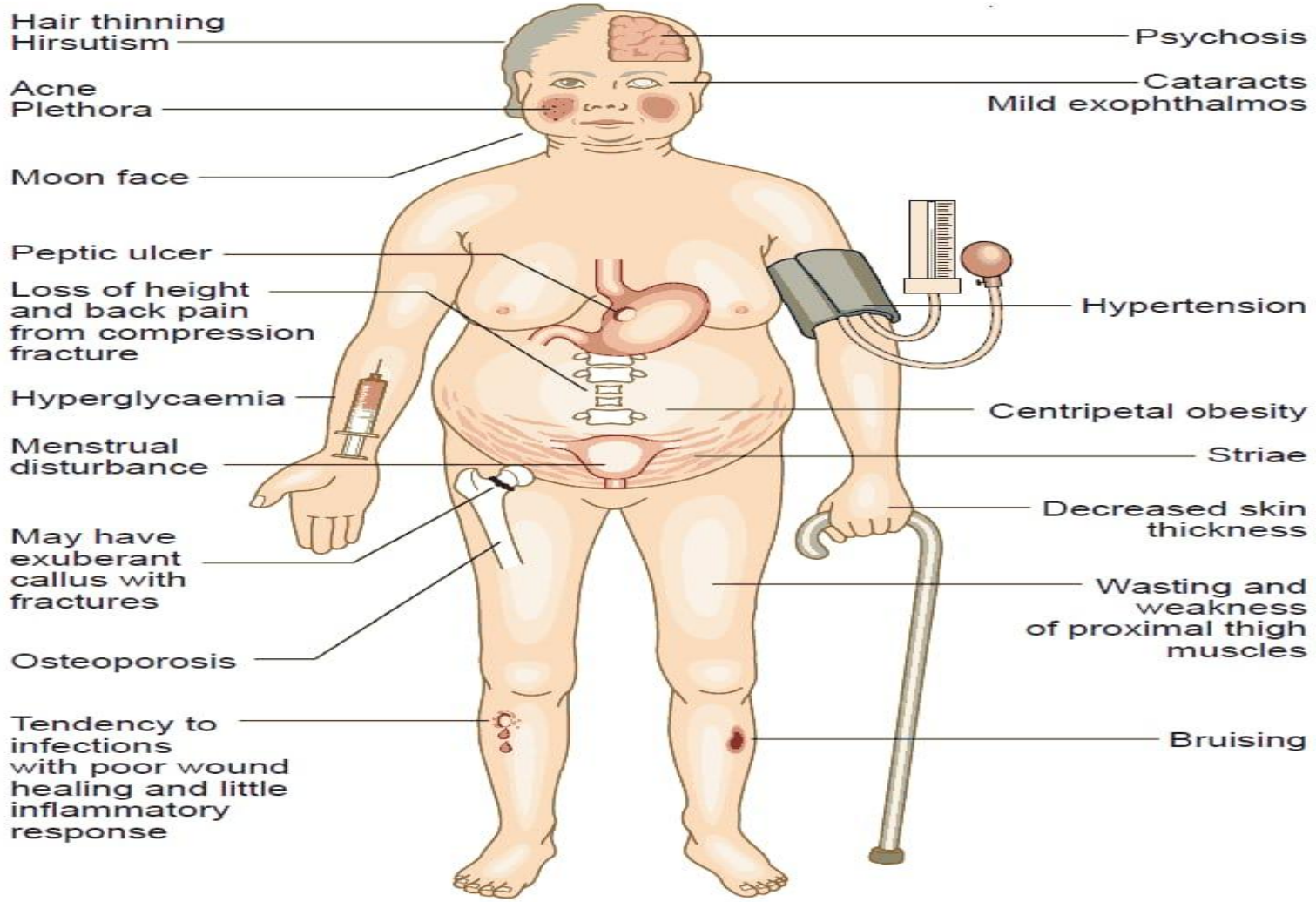
Non-ACTH-dependent-20%

- Adrenal adenoma-15%
- Adrenal carcinoma-5%
- ACTH independent macronodular hyperplasia,primary pigmented nodular adrenal disease(together <1%)

Hypercortisolism due to other causes (also reffered to as pseudo-Cushing's syndrome)

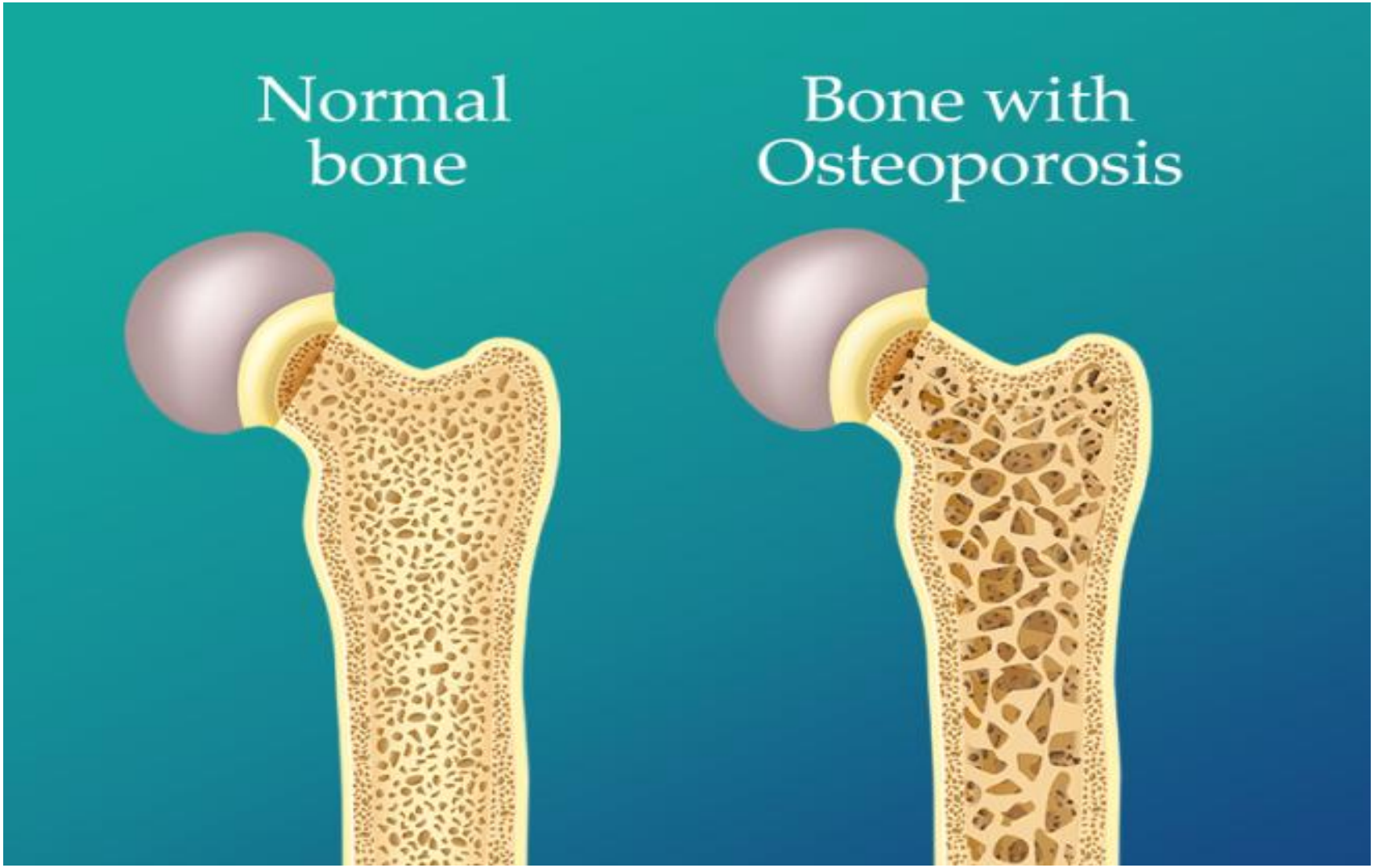
- Alcohol excess
- Major depressive illness
- Primary obesity

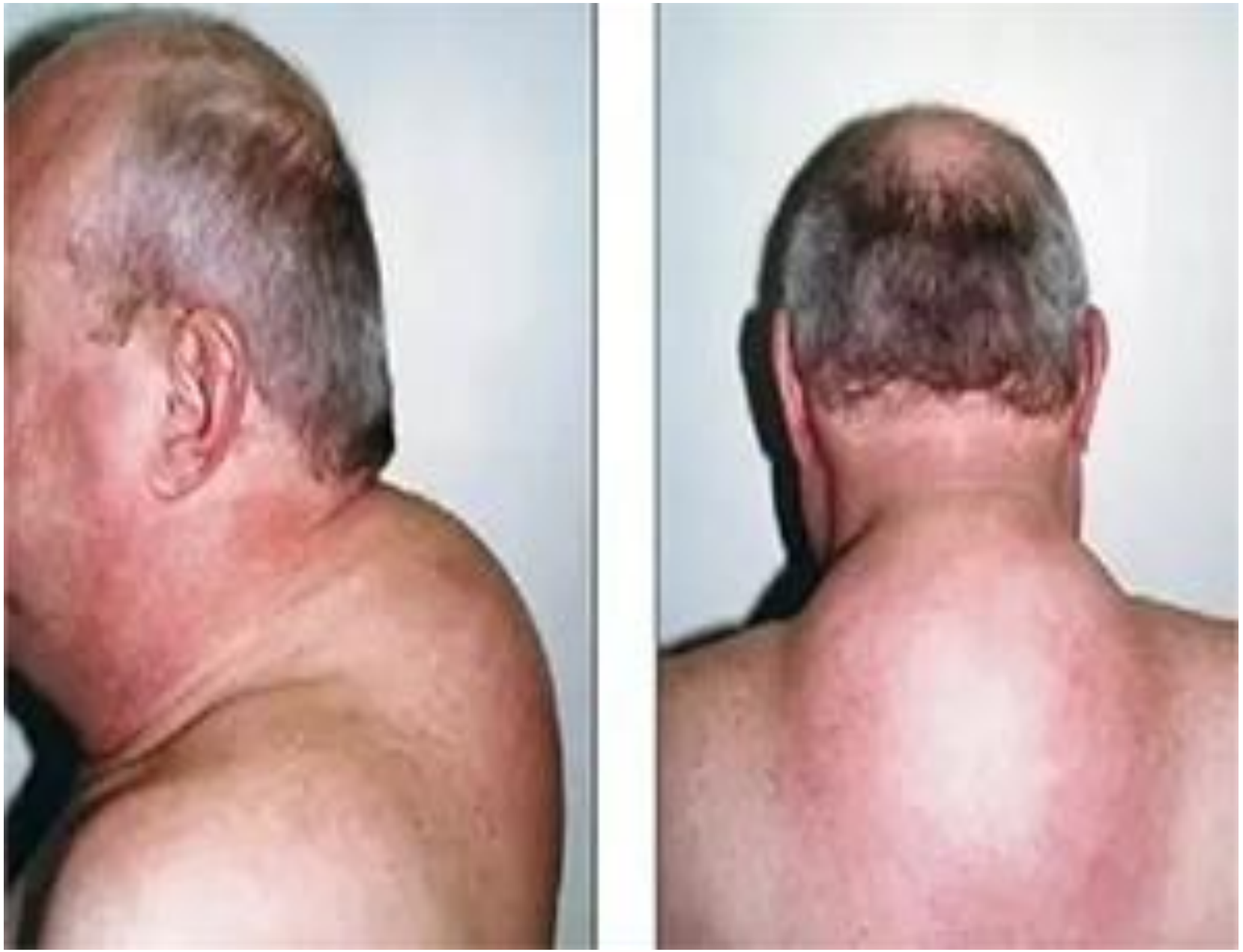
Clinical features of cushing's syndrome

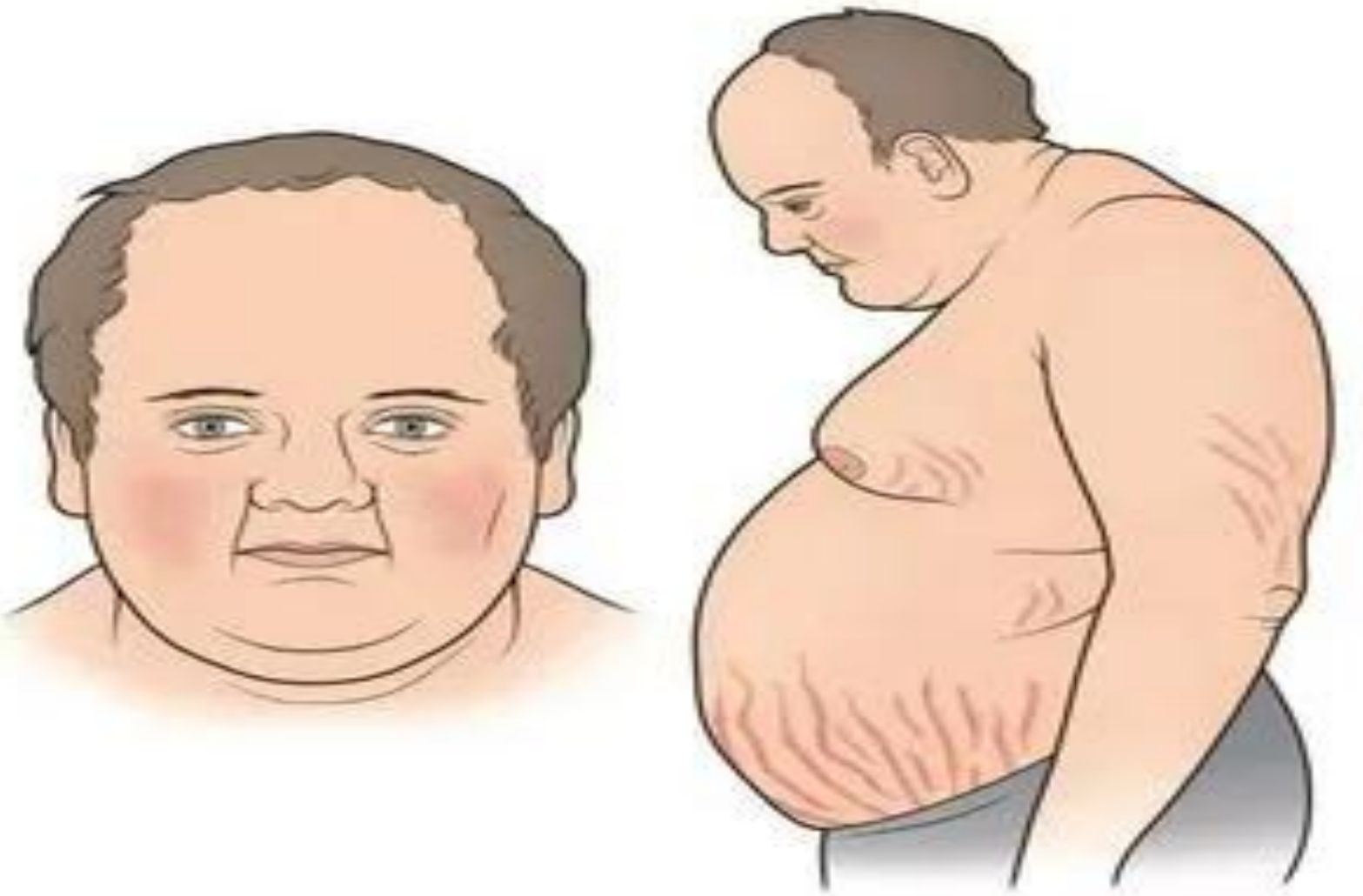


Clinical features of Cushing's syndrome.

Source : Davidsons Essentials of Medicine, 2e


Normal bone
Bone with Osteoporosis





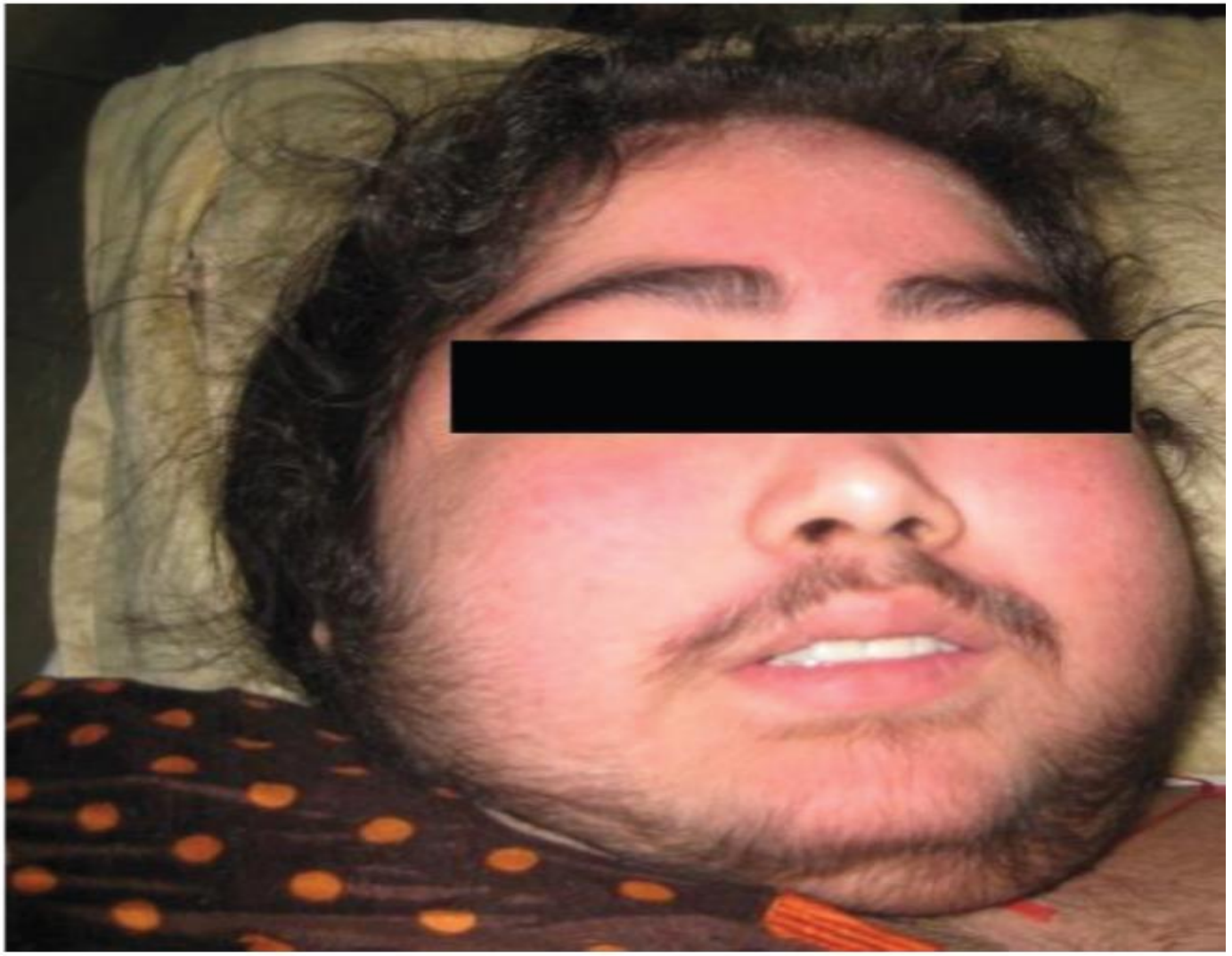
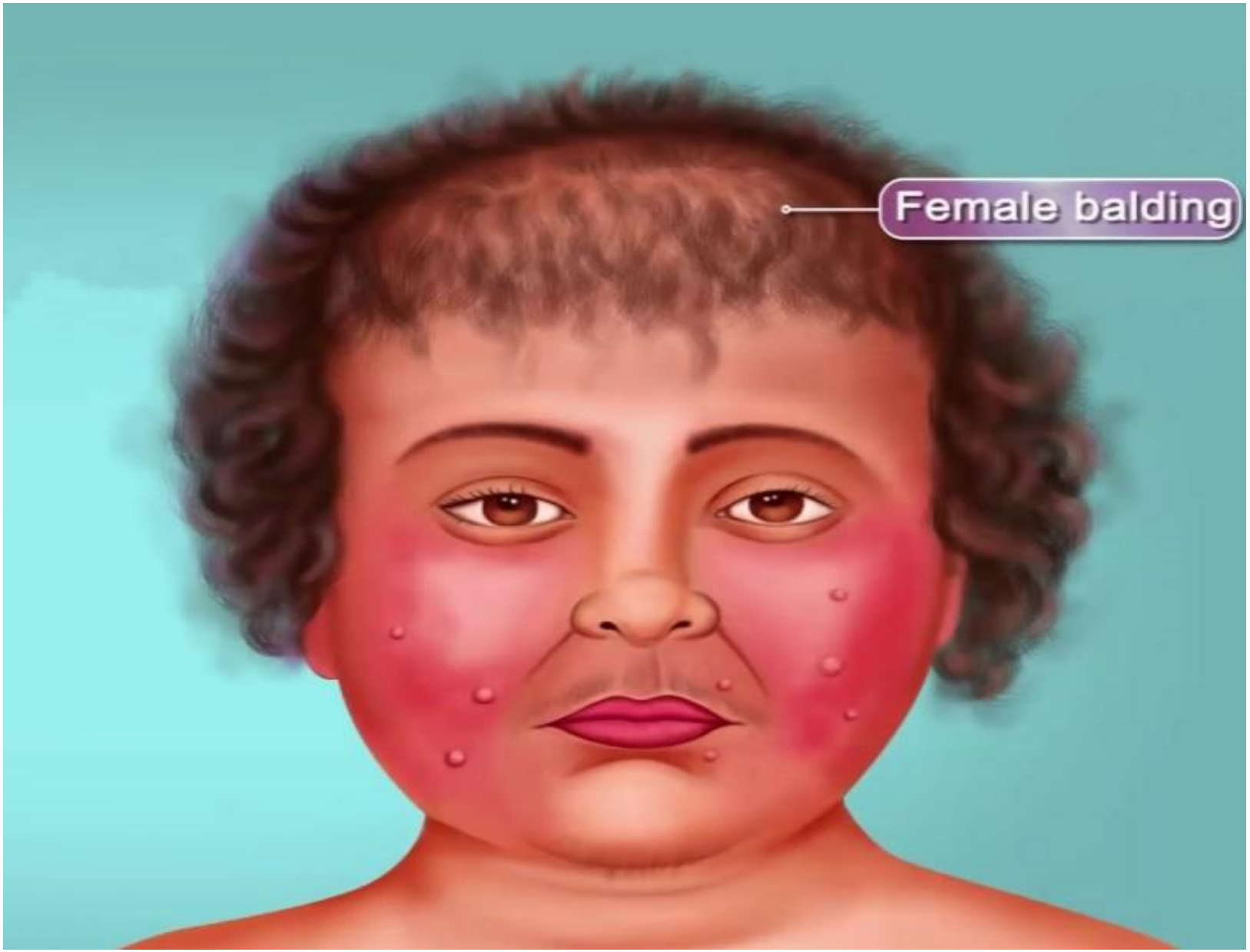


Figure 1. Figure showing marked hirsutism in a case of Cushing's syndrome


Female balding

Precautions before investigations

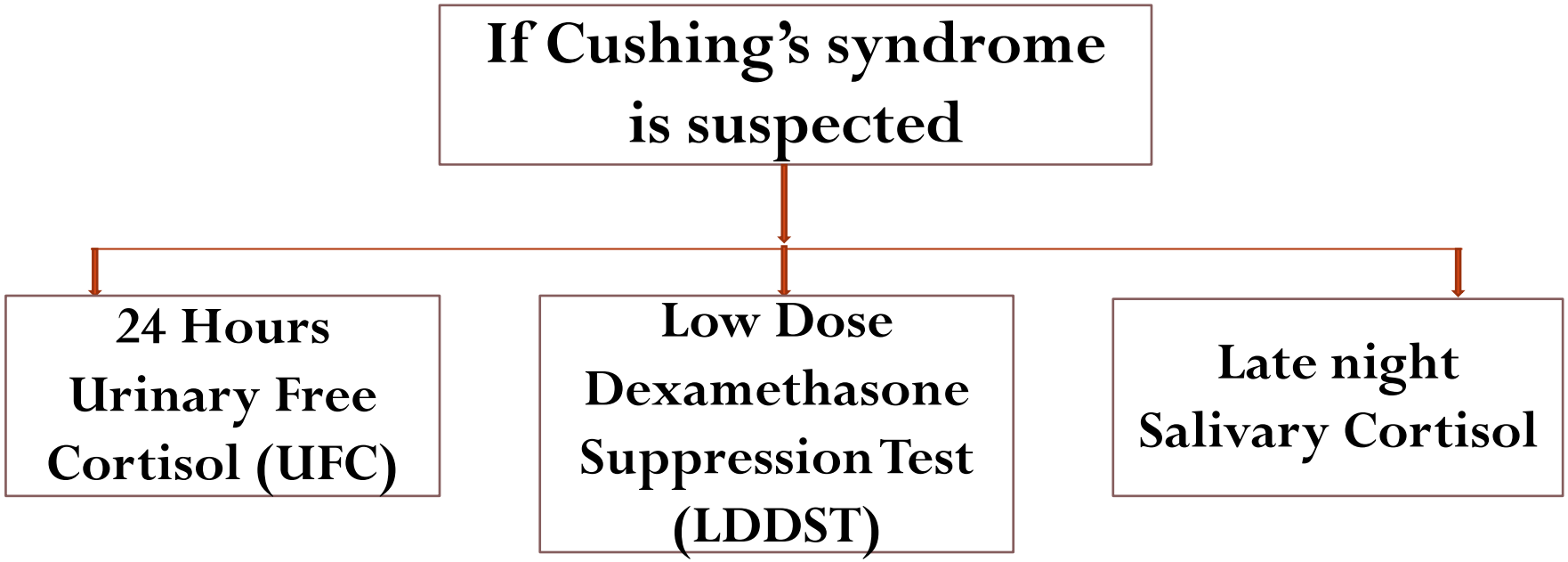
- At first we exclude exogenous glucocorticoid exposure.

- It is important for any estrogen to be stopped for 6 weeks prior to investigations to allow corticosteroid binding globulin (CBG) level to return normal and to avoid false-positive responses.

- Investigations should be avoided under the conditions of stress, because this activates HPA axis, causing potentially spurious results.

- Make sure patient is not taking medications that interfere with dexamethasone metabolism like phenytoin.

Investigations



Low Dose Dexamethasone Suppression Test (LDDST)

LDDST is more sensitive.

- Dexamethasone 0.5 mg 6 hourly for 48 hours (total 8 doses)
- Measure serum cortisol at 48 hours (or 6 hours after last dose)
- If serum cortisol > 50 nmol/L which is suggestive of Cushing's syndrome.

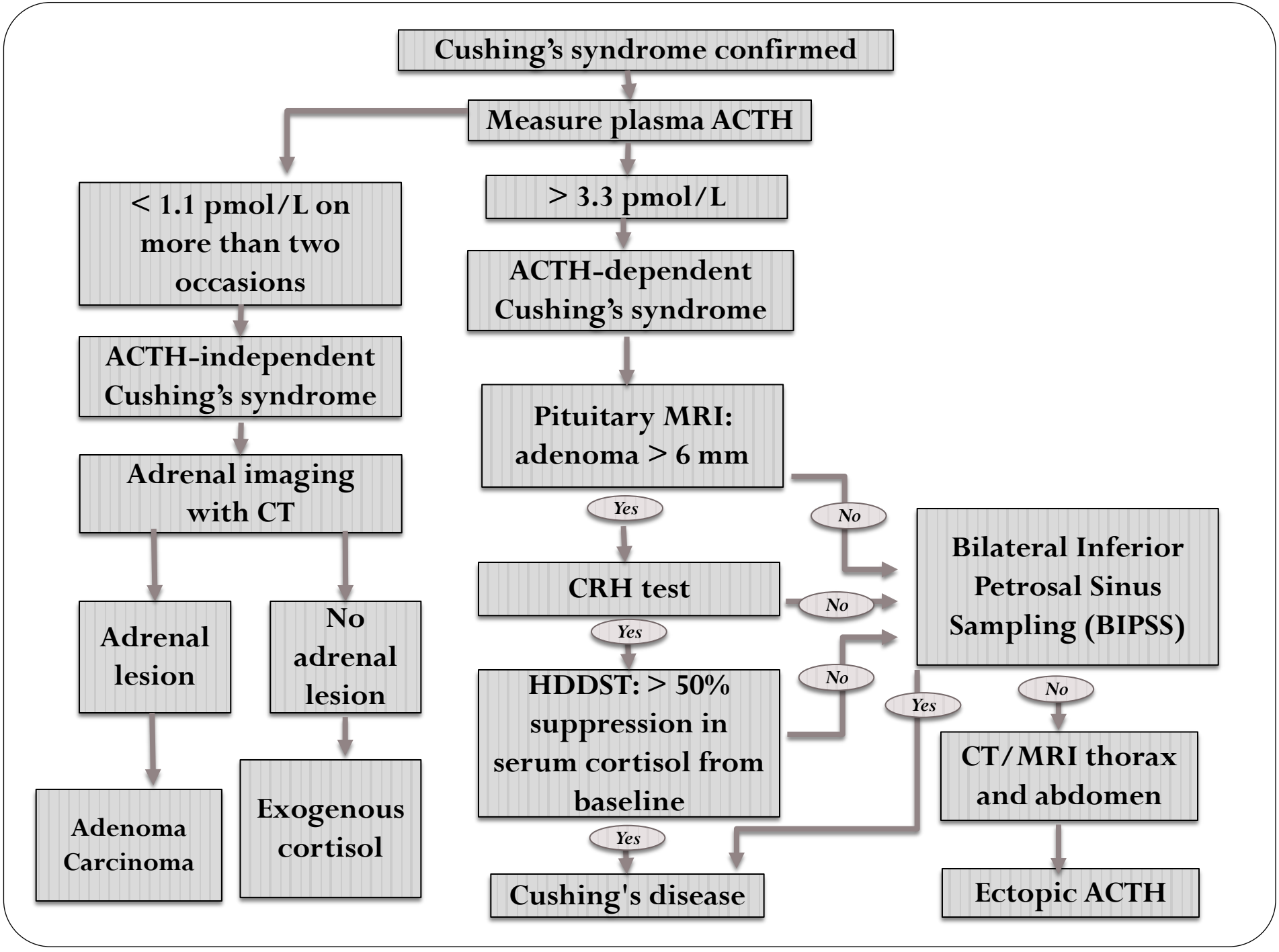
24-Hours Urinary Free Cortisol (UFC)

Incase of Cushing's syndrome ,

cortisol level is elevated (>50 µg/day)

Late-night Salivary Cortisol

Normally low at night but high in Cushing's syndrome.


Cushing's syndrome confirmed
Measure plasma ACTH
< 1.1 pmol/L on more than two occasions
> 3.3 pmol/L
ACTH-independent Cushing's syndrome
ACTH-dependent Cushing's syndrome
Adrenal imaging with CT
Pituitary MRI: adenoma > 6 mm
Yes
No
Adrenal lesion
No adrenal lesion
CRH test
No
Yes
Bilateral Inferior Petrosal Sinus Sampling (BIPSS)
HDDST: > 50% suppression in serum cortisol from baseline
No
Yes
No
Yes
Adenoma Carcinoma
Exogenous cortisol
Cushing's disease
CT/MRI thorax and abdomen
Ectopic ACTH

Other Investigations:

- RBS : Elevated blood glucose
- Serum Electrolytes : Hypokalemia, Metabolic Alkalosis (common in ectopic ACTH)
- CBC: Leukocytosis,Neutrophilia,Lymphopenia

Incase of infant, children and pregnant women,

We can do ultrasonography to see the adrenal mass (larger than 2 cm)

Treatment of Cushing's Syndrome

Cushing's disease

- Trans-sphenoidal surgery with selective removal of the adenoma is the treatment of choice.
- Laparoscopic bilateral adrenalectomy cures any type of ACTH-dependent Cushing's syndrome.
- Somatostatin analogue pasireotide is also licensed for the treatment of Cushing's disease and works by suppressing ACTH secretion by the tumor.

Adrenal tumours

- Laparoscopic adrenal surgery is the treatment of choice for adrenal adenomas.
- Radiotherapy to the tumor bed reduces the risk of local recurrence.
- Systemic therapy consists of adrenolytic drug (mitotane) and chemotherapy.

Ectopic ACTH syndrome

- Localized tumors, such as bronchial carcinoids, should be removed surgically.
- In patients with incurable malignancy, if appropriate, bilateral adrenalectomy followed by administration of adrenal steroids to make up for any insufficiency.

Iatrogenic Cushing's Syndrome

- Gradual tapering of exogenous steroids.
- Consider steroid sparing agents

  (e.g. Ketoconazole,Methotrexate,Azathioprine)
- Endocrinology referral for HPA axis evaluation

Treatment of complications

- Diabetes mellitus → Control blood sugar.
- Hypertension → Antihypertensives.
- Osteoporosis → Calcium, Vitamin D, Bisphosphonates.

Follow up

- Monitor blood pressure, blood glucose, bone mineral density.
- Measure serum cortisol, ACTH, 24 hours urinary free cortisol after treatment.

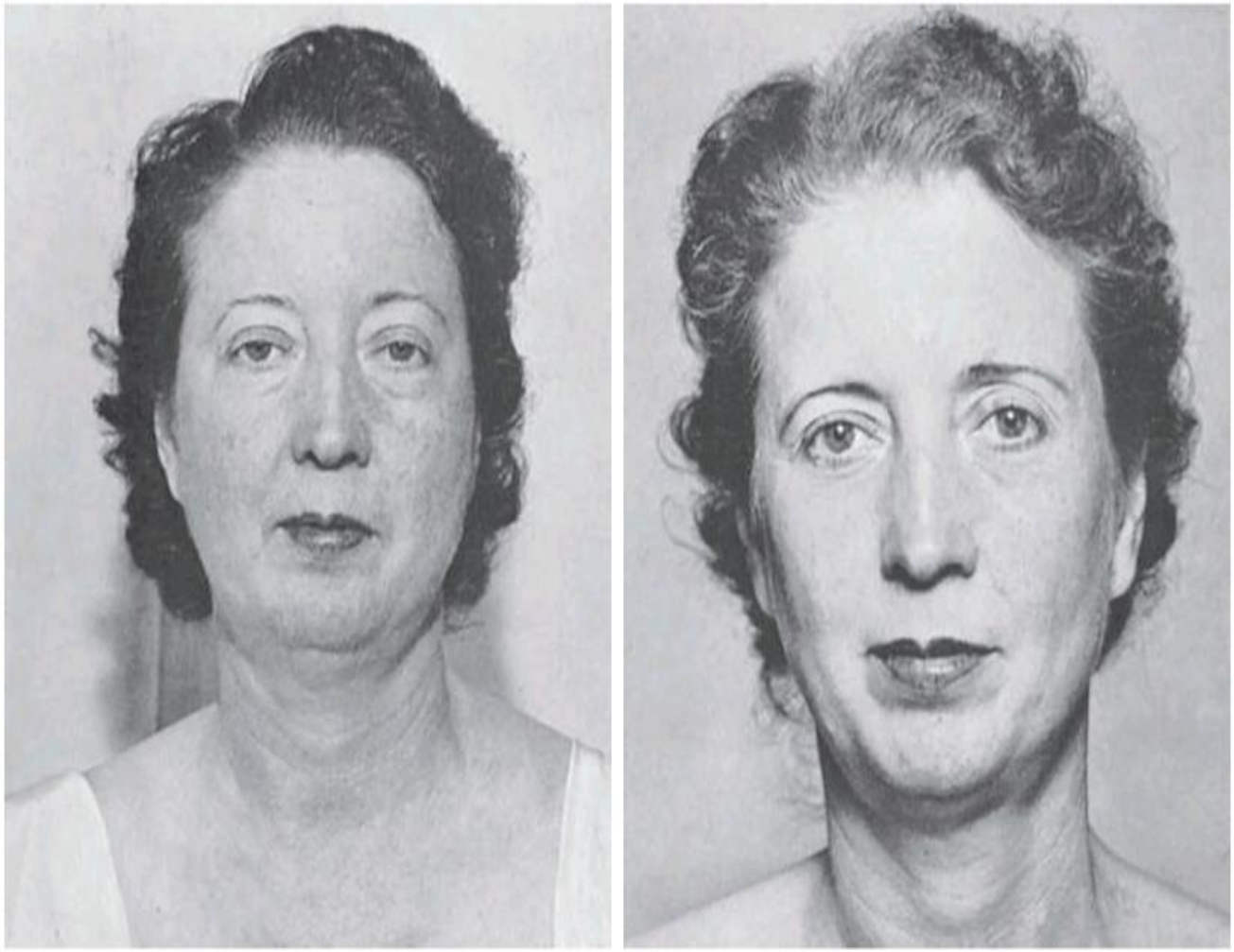


Figure 78-11. A person with Cushing's syndrome before *(left)* and after *(right)* a subtotal adrenalectomy. *(Courtesy Dr. Leonard Posey.)*

Complications

- Type 2 DM
- Hypertension
- Atherosclerosis
- Osteoporotic fractures and avascular necrosis
- Infections
- Nephrolithiasis
- Depression, Anxiety, Sleep disturbance.
- Significantly increases risk of premature death,mainly due to cardiovascular disease,infections and thromboembolic events.

Take home message

- Instruct patients not to self medicate with steroids & herbal remedies that may contain hidden steroids.
- Judicious use of glucocorticoids.
- Avoid sudden withdrawal, taper properly.
- Avoid unregulated medications.
- Increase awareness about risks of long term steroid use.

Early recognition and proper management of Cushing's syndrome can prevent life threatening complications and improve quality of life.


THANK YOU!
Thanks for your attention! Stay balanced, stay healthy.