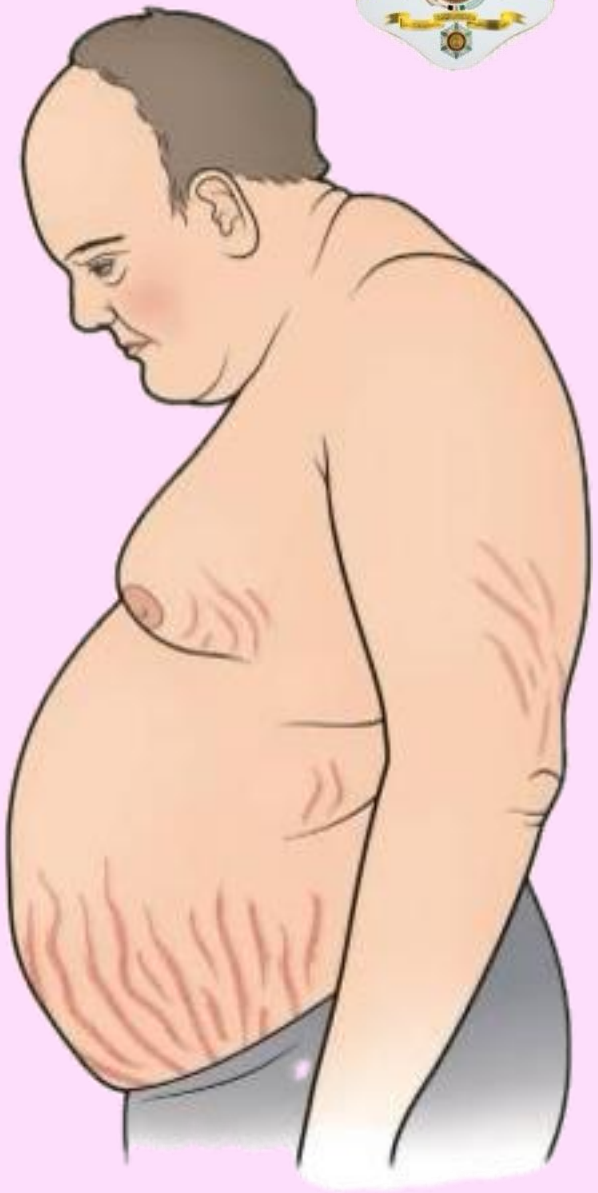
Cushing disease

- **Done by:**

- Batoul Al-obaidyeen
- Lama Khashashneh
- Raneem Abu hamdeh

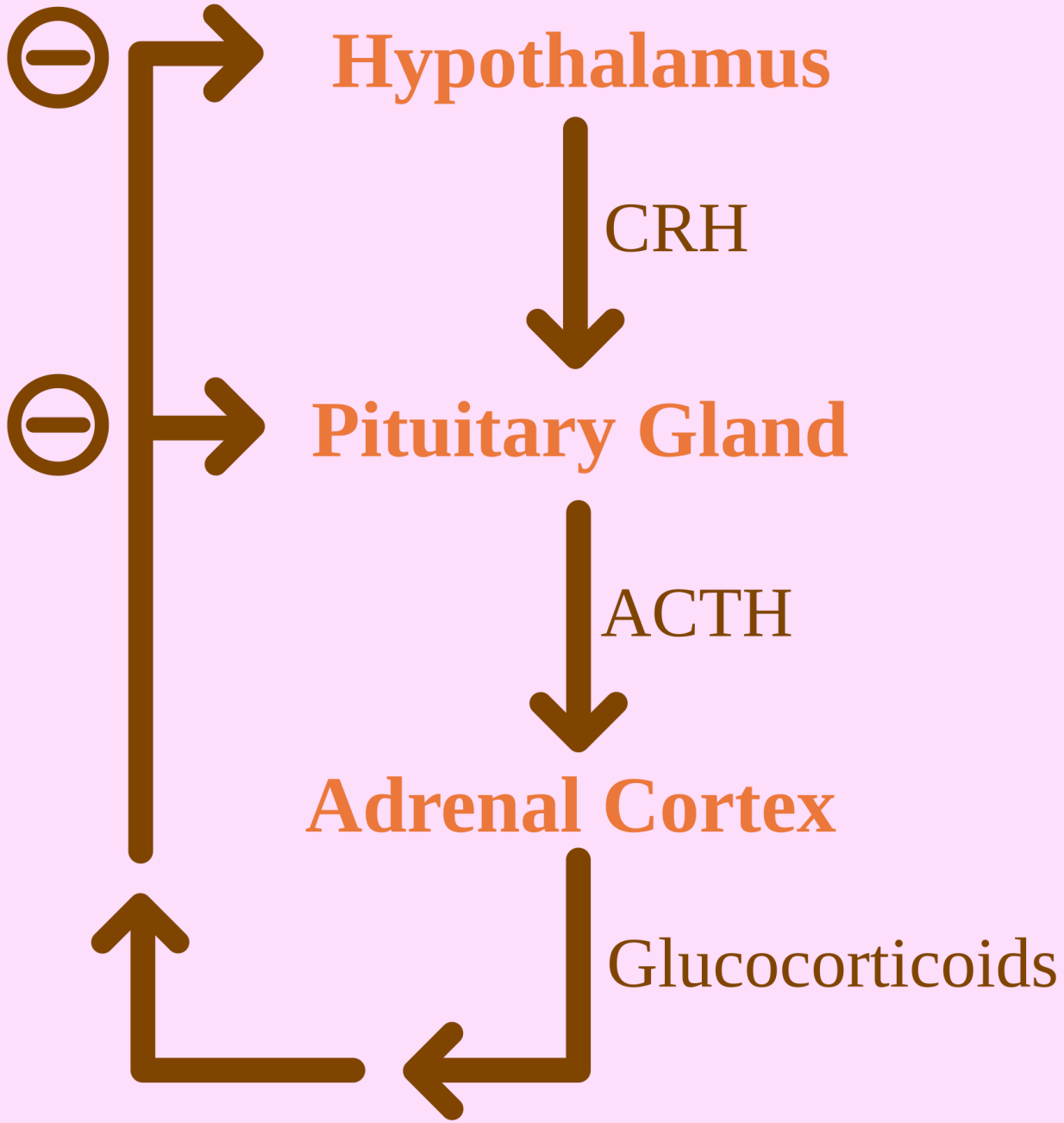


Types if Cushing syndrome:

- **Exogenous:** iatrogenic cushing syndrome

- **Endogenous hypercortisolism**:

- **A-**primary: an issue in the adrenal gland
- **B**-secondary hypercortisolism: an issue outside the adrenal gland


Hypothalamus
CRH
Pituitary Gland
ACTH
Adrenal Cortex
Glucocorticoids

Causes and pathophysiology:

- 1. Iatrogenic Cushing syndrome is the most common cause, and is due to prescribed glucocorticoids. Androgen excess is absent because the exogenous steroid suppresses androgen production by the adrenals

- 2. Adrenal adenomas and carcinomas (20% of cases): the adrenal gland produces too much cortisol {primary endogenous}

Causes and pathophysiology

- 3. Ectopic ACTH production (10% to 15%){secondary endogenous} ACTH-secreting neuroendocrine tumor stimulates the cortisol release from the adrenal glands without the normal negative feedback loop because the source of the ACTH is outside the pituitary gland

- Most often caused by neuroendocrine tumors of the lung (e.g., smallCell carcinoma), pancreas, or thymus

Effects of cortisol:

- **Metabolic:** ↑ Gluconeogenesi : hyperglycemia
- ↓ Glucose uptake in muscle and fat → insulin resistance
- ↑ Protein catabolism → breakdown of muscle protein into amino acids
- ↑ Lipolysis → breakdown of fat

Effects of cortisol

- Anti-inflammatory and immunosuressant

- Cardiovascular Effects:
- ↑ Vascular sensitivity to catecholamines (epinephrine, norepinephrine) → helps maintain blood pressure

- **Fluid and electrolyte balance:** by binding to mineralocorticoid receptors

Effects of cortisol

- Central Nervous System

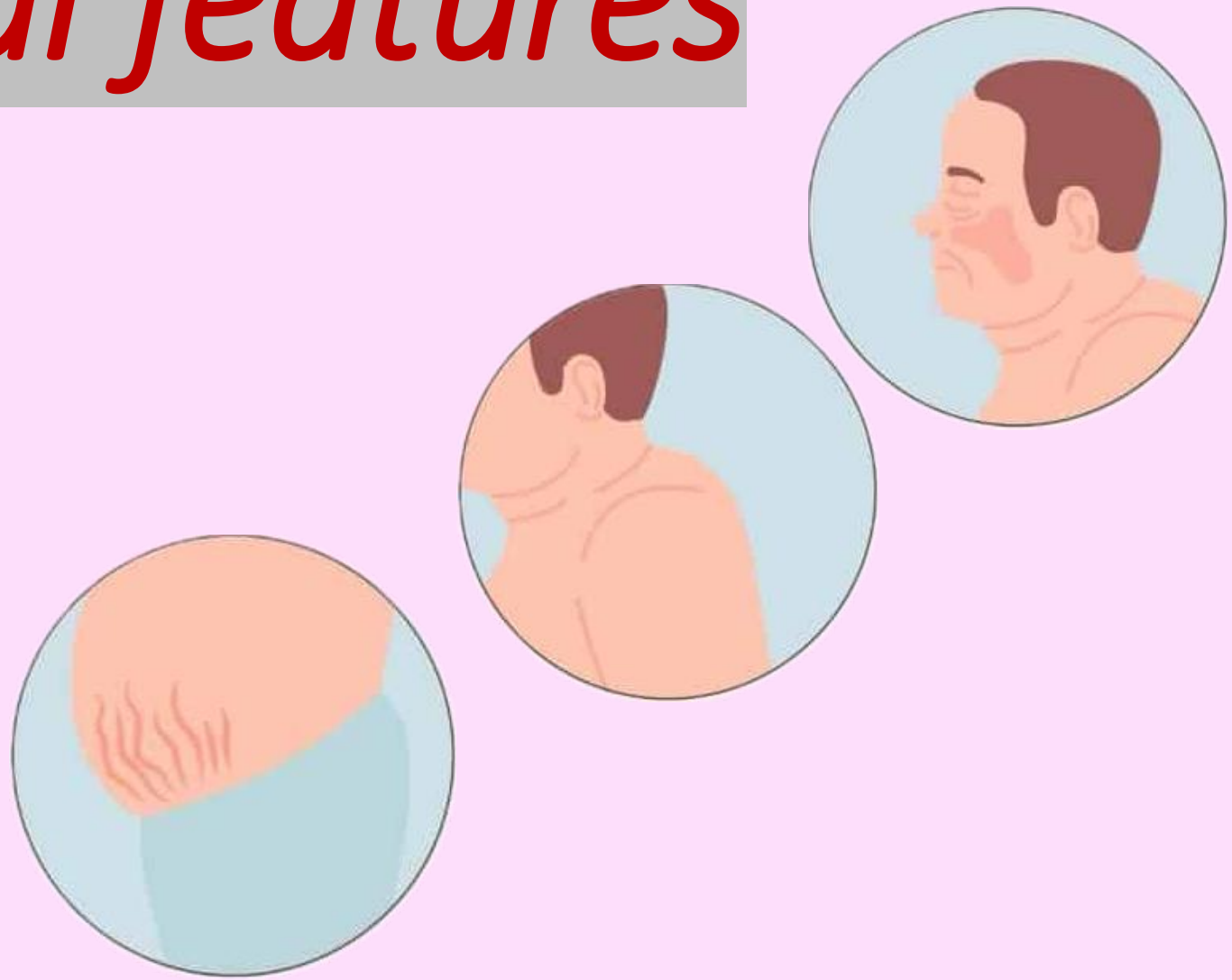
- Affects mood, memory, and alertness
- Most commonly depression anxiety and sleep disturbances by alternation of neurotransmitters such as serotonin dopamine and NE

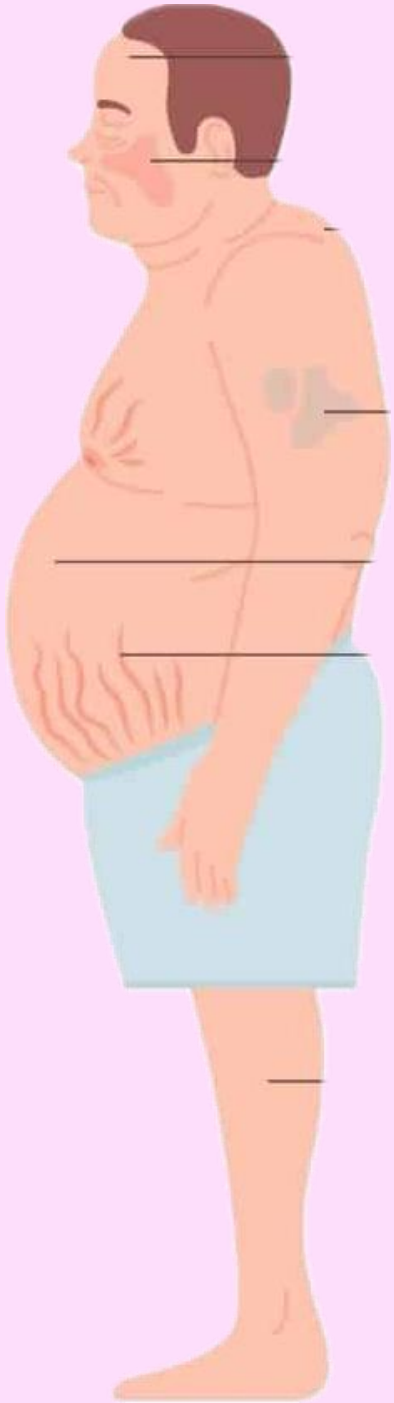
Effects of cortisol

- ***Stress Response***
- Cortisol is a key “stress hormone” — helps body handle stress (infection, trauma)

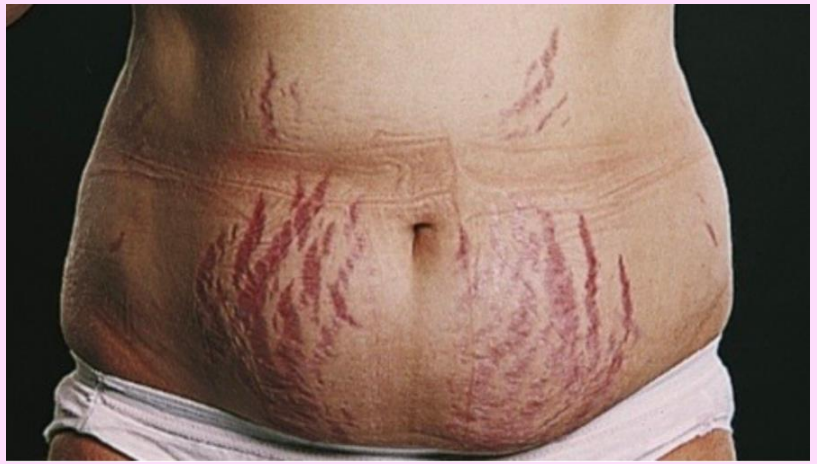
- **Bone and Skin**
- ↓ Osteoblast activity → osteoporosis with long-term use
- ↓ Collagen synthesis → thin skin, easy bruising, poor wound healing

Clinical features





Skin



- Thin, easily bruisable skin with ecchymoses
- Stretch marks (classically purple abdominal striae)
- Hirsutism
- Acne
- If secondary hypercortisolism : often hyperpigmentation:
- darkening of the skin due to an overproduction of melanin.
- especially in areas that are not normally exposed to the sun (palm creases, oral cavity).
- Caused by excessive ACTH production because melanocyte-stimulating hormone (MSH)
- cleaved from the same precursor as ACTH called proopiomelamocortin (POMC) .
- Not a feature of primary hypercortisolism.
- Delayed wound healing.
- Flushing of the face.

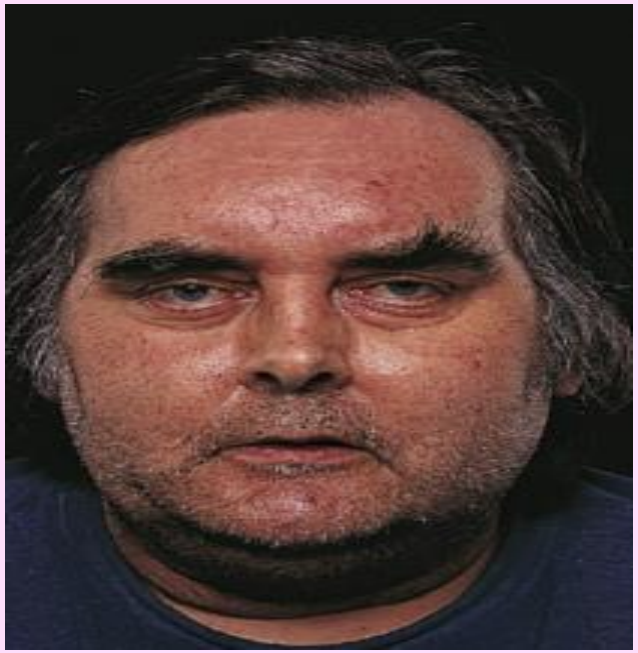
Neuropsychological & musculoskeletal

- Anxiety, irritability, fatigue, sleep disturbance, memory deficits,
- depression, psychosis.
- Osteopenia, osteoporosis, pathological fractures, avascular necrosis of the
- femoral head, muscle atrophy/weakness

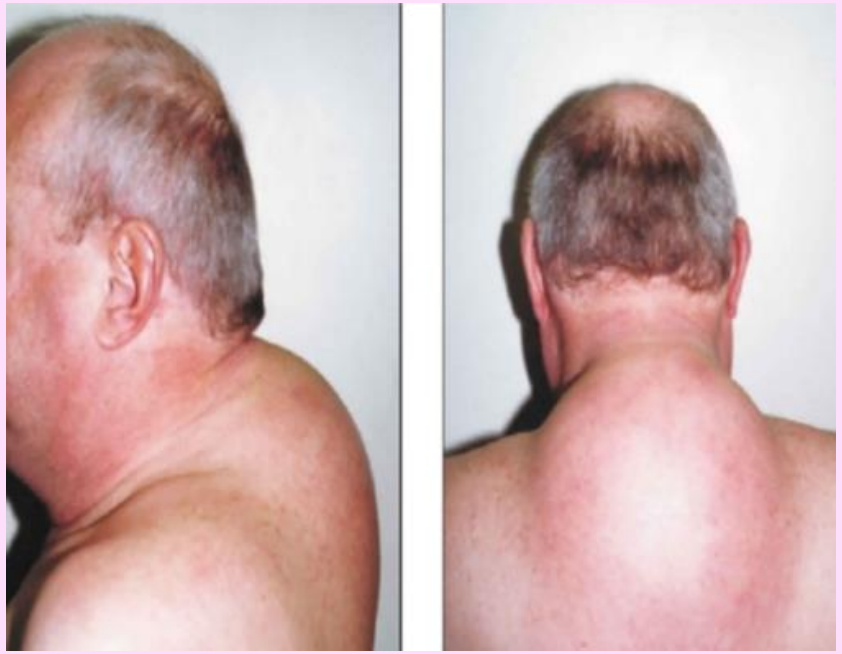
Endocrine and metabolic

- Insulin resistance hyperglycemia.
- Dyslipidemia
- Weight gain characterized by central obesity, moon facies, and a
- dorsocervical fat pad (buffalo hump)
- M: Decreased libido
- F: Decreased libido, virilization, and/or irregular menstrual cycles (e.g.,
- amenorrhea)
- Growth delay (in children)

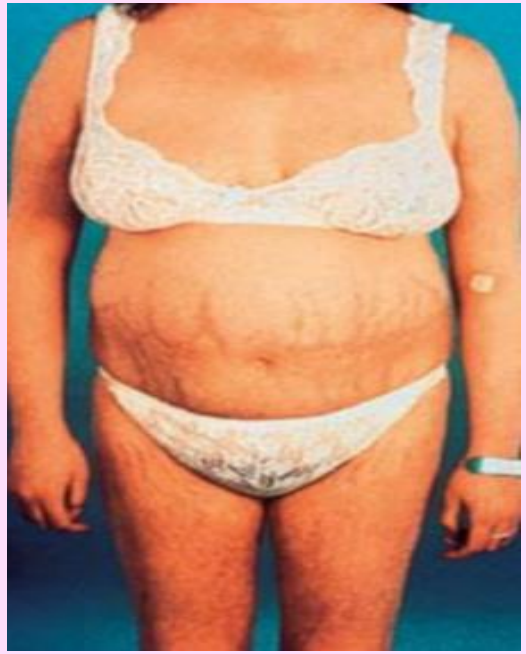
Weight gain



Moon face



Buffalo Hump



Central obesity

Other features

- Secondary hypertension (~90% of cases)
- Increased susceptibility to infections (due to immunosuppression)
- Peptic ulcer disease
- Cataracts

“CUSHINGOID”

is the acronym for side effects of corticosteroids:

- **C**ataract
- **U**lcer (peptic)
- **S**traie/**S**kin thinning
- **H**ypertension/**H**irsutism/**H**yperglycemia
- **I**nfection
- **N**ecrosis (avascular head of the femur)
- **G**lucose elevation
- **O**steoporosis/**O**besity
- **I**mmunosuppression
- **D**epression/**D**iabetes

Note

- -Patients with secondary hypercortisolism due to ectopic ACTH production
- may present with rapid onset of hypertension and hypokalemia without
- other typical features of Cushing syndrome.
- -Consider a diagnosis of hypercortisolism in patients who present with
- proximal muscle weakness. central obesity, thinning skin, weight gain, sleep
- disturbance, and/or depression

Diagnosis

Diagnosis

- ***Prolonged glucocorticoid therapy*** is the most common cause of hypercortisolism (exogenousCushing syndrome); further testing is not required in these patients.

- ***Routine laboratory studies:*** Not required to establish the diagnosis, but if performed,may show the following typical findings:-

- Hypernatremia, hypokalemia, metabolic alkalosis .
- Hyperglycemia:due to stimulation of gluconeogenic enzymes (e.g., glucose-6-phosphatase) and inhibition of glucose uptake in peripheral tissue.
- Hyperlipidemia (hypercholesterolemia and hypertriglyceridemia) .
- CBC : leukocytosis (predominantly neutrophilic), eosinopenia.

- ***Identifying the causes :***

Testing for hypercortisolism

Urine free cortisol

- Free cortisol is measured in a complete 24-hour urine collection.
- Supportive finding: T urine free cortisol.

Low- dose dexamethasone suppression test

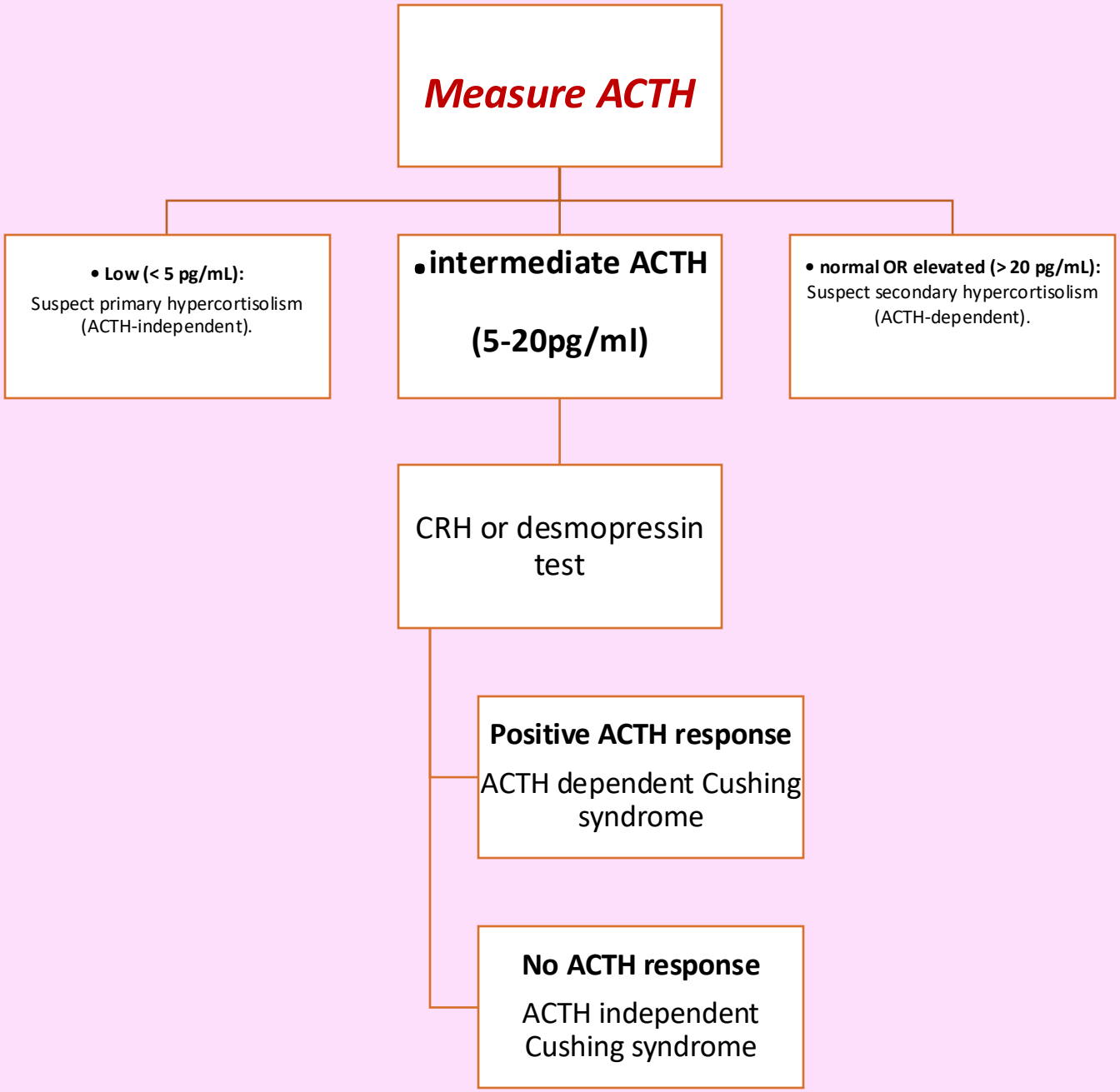
- 1 mg of dexamethasone is administered between 11 pm at midnight and serum cortisol is measured the following morning between 8 and 9 am.
- Supportive finding: 1 early morning serum cortisol level (> 50 nmol/L) .

Late-night salivary cortisol

- A saliva sample is collected at the patient's usual bedtime.
- Supportive finding: 1 salivary cortisol (> 4 nmol/L).

Late-night serum cortisol:

- A serum sample is taken from the patient (awake or asleep).
- Supportive finding: 1 serum cortisol (> 7.5 mcg/dL).


Measure ACTH
• Low (< 5 pg/mL):
Suspect primary hypercortisolism (ACTH-independent).
•intermediate ACTH
(5-20pg/ml)
• normal OR elevated (> 20 pg/mL):
Suspect secondary hypercortisolism (ACTH-dependent).
CRH or desmopressin test
Positive ACTH response
ACTH dependent Cushing syndrome
No ACTH response
ACTH independent Cushing syndrome

3) Proceed based on the results.

- ***If ACTH-independent hypercortisolism is suspected:***

  Obtain adrenal MRI and /or CT.

  Assess for an adrenal tumor (e.g., adrenal adenoma, carcinoma, hyperplasia).

- ***If ACTH-dependent hypercortisolism is suspected:***

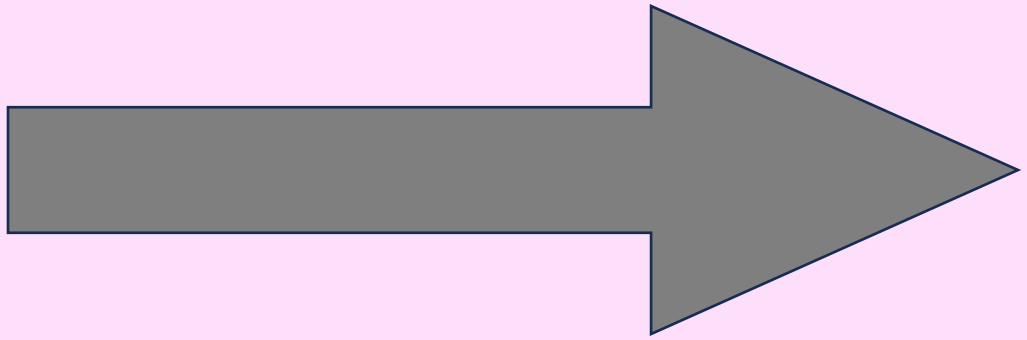
  Obtain further testing.

Further testing in patients with ACTH-dependent hypercortisolism:

- The goal is to differentiate between Cushing disease and ectopic ACTH production. Acombination of tests is often necessary.

- ***Obtain a pituitary MRI to evaluate for Cushing disease***

- **1. Pituitary adenoma** > 6 mm confirms Cushing disease.
- **2**. If there is no evidence of a pituitary adenoma or findings are unclear, obtain either:
- - Bilateral inferior petrosal sinus sampling (IPSS)
- - Hormone testing in ACTH-dependent hypercortisolism



1. CRHstimulationtest + Desmopressin stimulation test

- ACTH and cortisol levels increase further:
  Cushing disease is likely.
- No increase in ACTH or cortisol levels:
  Ectopic ACTH production is likely.

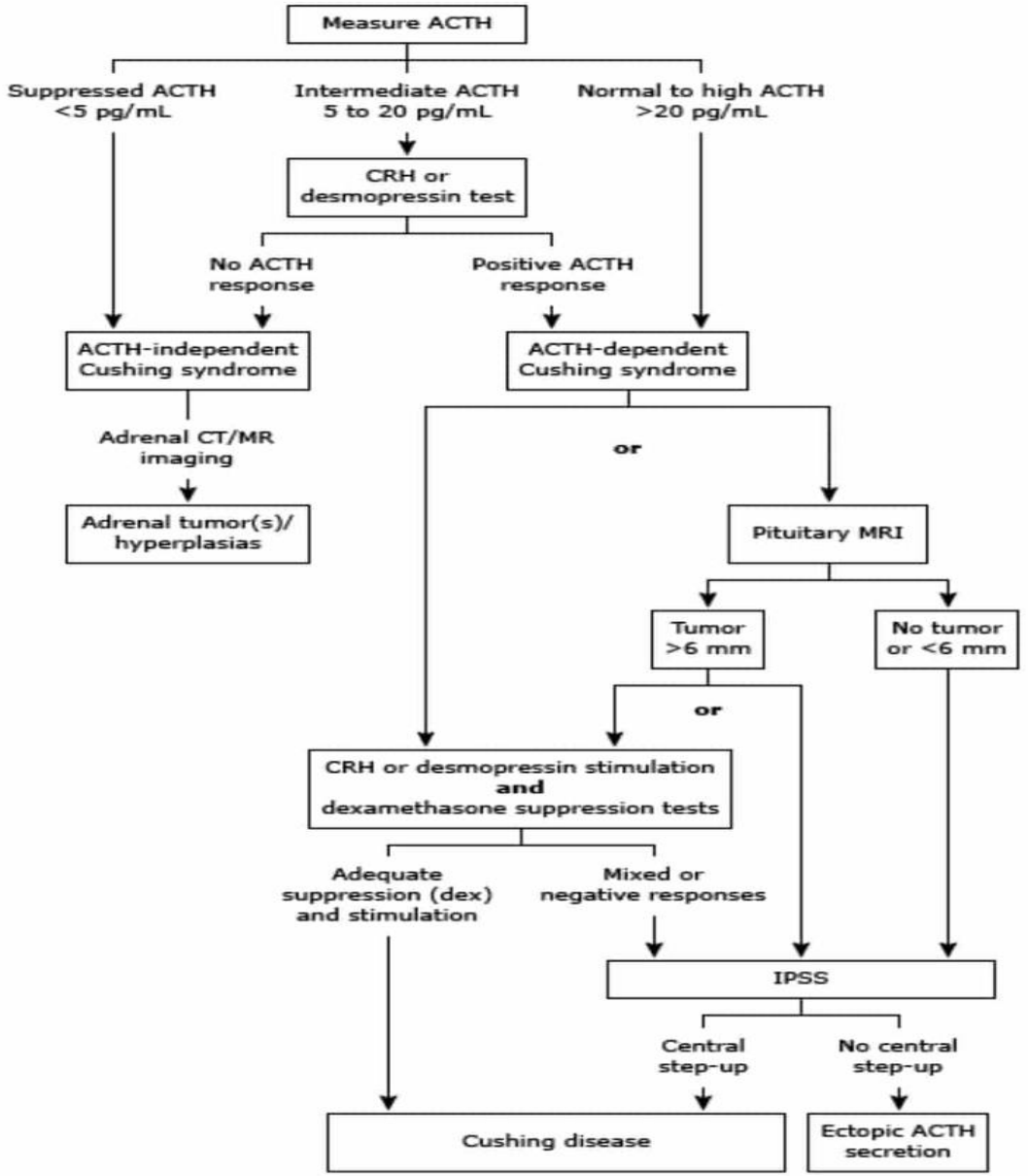
2. High-dose dexamethasone suppression test

- Adequate suppression, i.e., 1 cortisol (< 50% of baseline): Cushing disease is likely.
- No or inadequate suppression:
  Ectopic ACTH production is likely.

- ***If ectopic ACTH production is suspected:***

- imaging to locate the ACTH-producing primary malignancy (e.g., SCLC, RCC, carcinoid).

Testing to establish the cause of Cushing syndrome*



Treatment:

- The following section applies to endogenous Cushing syndrome. For patients with exogenousCushing syndrome, consider lowering the dose of glucocorticoids or replacing them

- **First-line treatment**: tumor resection.
- **Second-line or adjunctive therapy**: pharmacological treatment.
- Patients who develop adrenal insufficiency after surgery require lifelong glucocorticoidreplacement therapy.

First line: curative surgery

- **1) Primary hypercortisolism:** unilateral or bilateral laparoscopic or open adrenalectomy for adrenocortical tumors

- **2) Cushing disease:** transsphenoidal hypophysectomy.

- **3) Ectopic ACTH production:** tumor resection with node dissection.

Follow-up:• Patients should receive lifelong monitoring for recurrence.
• Glucocorticoid replacement therapy is often necessary after surgery.

Second line : pharmacological treatment

- **Metyranone (** an 11B-hydroxylase blocker)
- **Ketoconazole**
- **Aminoglutethimide**
- **Trilo-stane**
- **Etomidate (** in sever cases**)**

• *Complication: Nelson syndrome (post adrenalectomy syndrome)*

- • **Etiology**: bilateral adrenalectomy in patients with a previously undetected pituitary adenoma
- • **Pathophysiology**:bilateral adrenalectomy no endogenous cortisol production no negative feedback from cortisol on the hypothalamus T CRH production uncontrolled enlargement of preexisting but undetected ACTH-secreting pituitary adenoma 1 secretion of ACTH and MSH manifestation of symptoms due to pituitary adenoma and T MSH
- • **Clinical features**:headache, bitemporal hemianopia (mass effect), cutaneous hyperpigmentation
- • **Diagnostics**:- High levels of B-MSH and ACTH.Medica- Pituitary adenoma on MRI confirms the diagnosis.
- • **Treatment**:surgery (e.g., transsphenoidal resection) and/or pituitary radiation therapy(e.g., if the tumor cannot be fully resected).

Thank you