"He who studies medicine without books sails an uncharted sea, but he who studies medicine without patients does not go to sea at all." – William Osler

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MEDICINE
TEAMWORK

ADRENAL DISORDERS

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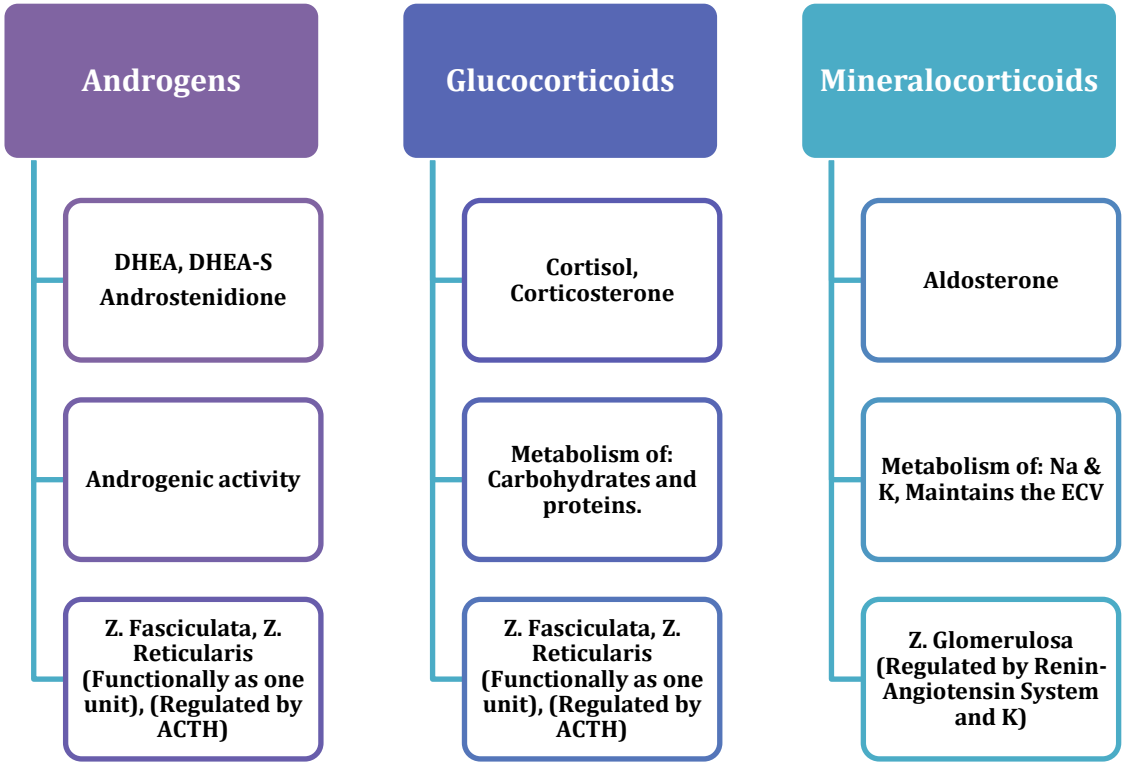
Anatomy:

- -Located in the **retroperitoneum** above or medial to the upper poles of the kidneys.
- -Weight 4-5gm.
- -Surrounded by a fibrous capsule.
- -Highly vascularized.
- -Consists of:
  1. Cortex: comprise 90% of the adrenals weight
  2. Medulla: "modified Sympathetic ganglion" comprises 10% of adrenal weight.

Physiology:

- The adrenals function as several separate endocrine glands within one anatomical structure, regulating fluid volume and stress response.
- The outer layer is the cortex, which secretes 3 different kinds of steroids from 3 cell lines.



- The adrenal medulla is an extension of the sympathetic nervous system which secretes catecholamines (Adrenaline & Nor-Adrenaline).

Embryology of Adrenal Cortex:

- Adrenal Cortex is of **mesodermal origin** and composed of:

1. **Fetal zone**:
   - Additional zone in fetus
   - Produces mainly DHEA & DHEA-S (precursors of maternal-placental estrogen).
2. **Definitive zone**:
   - The origin of the adult adrenal cortex.
   - Synthesizes many steroids mainly cortisol.

- Adrenocortical weight decreases gradually until the fetal zone disappears **3 months** after delivery.
- Larger than the kidney at **mid gestation** and much larger than adult gland in relation to total body mass.
- During the **first 3 years**, the adult adrenal cortex develops and differentiates into 3 adult zones:
  - Glomerulosa.
  - Fasciculata.
  - Reticularis.

Embryology of Adrenal Medulla:

- **Medullary chromaffin cells** (the principal cells of adrenal medulla) are from the **neural crest**.
- During development, the medullary cells migrate and lie surrounded by the cortex.

Adrenal Disorders:

- Cortex:
  - Adrenal Insufficiency.
  - Cushing's syndrome.
  - Hyperaldosteronism.
  - Congenital adrenal hyperplasia.
- Medulla:
  - Pheochromocytoa.

Types of Adrenal Insufficiency:

- Primary adrenal insufficiency (Addison's diease):
  - Primary hypofunction of the adrenal cortex.
- Secondary adrenal insufficiency:
  - Deficient secretion of ACTH from the pituitary gland.

Etiology of Primary Adrenal Insufficiency:

- Anatomic destruction of gland (chronic & acute)
  - Adrenocortical atrophy. (Autoimmune or TB)(The most common cause of 1ry Adrenal Insufficiency)
  - Surgical removal.
  - Infection.
  - Adrenal Hemorrhage.
  - Invasion (rare): metastasis, amyloidosis, sarcoidosis.
- Metabolic failure in hormone production:
  - Congenital adrenal hyperplasia (CAH).
  - Enzyme inhibitors: (metyrapone, ketoconazole, aminoglutethemide).
  - Cytotoxic agents: (mitotane).
- ACTH-blocking Antibodies.

Etiology of Secondary Adrenal Insufficiency:

- Hypopituitarism due to hypothalamic-pituitary disease.
- Suppression of hypothalamic-pituitary axis by excess steroids:
  - Exogenous steroids (Iatrogenic e.g. steroidal medications)
  - Endogenous steroids (secreting tumors)

Incidence:

- Primary adrenal insufficiency is relatively rare
- Secondary adrenal insufficiency is more common due to the common therapeutic use of steroids.

Addison's Disease:

- Progressive destruction of adrenal cortex.
- At least 90% of gland is destroyed before signs of insufficiency appear.
- 50% of patients have +ve circulating adrenal Abs.
- More common in women 2.6:1. It is usually diagonsed in the 3rd to 5th decade.

Primary adenocortical insufficiency (Addison's disease):
Major causes:
Autoimmune → 80%
Tuberculosis → 20%

Common Sign & Symptoms in chronic primary adrenal insufficiency:

-Symptoms:	**Frequency**
Asthenia (weakness, tiredness, fatigue)	100
Anorexia	100
Gastrointestinal symptoms	90
Nausea	85
Vomiting	75
Constipation	30
Abdominal pain	30
Diarrhea	15
Salt craving	15
Postural dizziness	10
Muscular or joint pains	10
-Signs:	
Weight loss	100
Hyperpigmentation of skin	95
Pigmentation of mucous membrane	80
Decreased axillary and pubic hair (in women only *adrenals are the only source of androgens for females)	60
Hypotention (systolic BP <110 mm Hg) with postural accentuation	15
Vitiligo (with autoimmune)	10
-Lab findings:	
Hyponatremia	90
Hyperkalemia	65
Hypercalcemia	5
Azotemia	55
Anemia	40
Eosinophilia	15

-Hyperpigmentation:

1. Formed after onset of ACTH excess.
2. Generalized hyperpigmentation of the skin and mucous membranes.
3. Classical and one of the earliest findings of Addison's disease.
4. Skin precedes buccal mucosa in pigmentation.

Diagnostic Tests

- Since basal levels of adrenocorticol steroids may be normal in partial adrenal insufficiency, test of adrenocortical reserves are necessary to establish the diagnosis.

Rapid ACTH stimulation test:

- After a baseline cortisol sample is obtained and synthetic ACTH called tetracosactrin is given in a dose of 0.25mg 1m. Or i.v. and additional cortisol samples are obtained at 30 and 60 min following the injection.
- Subnormal responses to exogenous ACTH is an indication of decreased adrenal reserve and establish the diagnosis of adrenocortical insufficiency.
- However, this test does not differenciate between primary and secondary adrenal insufficiency and ACTH level has to be done.

Plasma ACTH Levels

- It differentiates between primary and secondary states being high in the primary form and low normal or low in secondary forms.

Metyraphone Testing

- Metyraphone blocks cortisol synthesis by inhibiting 11B hydroxylase enzymes that converts 11 deoxy cortisol to cortisol. This stimulates ACTH which in turn increases levels of 11 deoxycortisol. Urinary 17 hydroxycorticosteroid levels also increases. It is used as an overnight test. A normal response indicates normal ACTH secretion and adrenal function.

Acute Adrenal Crisis:

- A state of acute adrenal insufficiency occurring in patients with Addison's disease who are exposed to any form of stress.
- Precipitating stress factors:
    - Infection.
    - Trauma.
    - Surgery.
    - Dehydration. (Salt deprivation, vomiting, diarrhea)
    - Discontinuation of steroids replacement therapy.

-Common clinical features:

- Hypotension & Shock.
- Fever.
- Dehydration & Volume depletion.
- Nausea & Vomiting.
- Abdominal pain (may mimic acute abdomen).

-Shock and coma may rapidly lead to death in untreated patients.

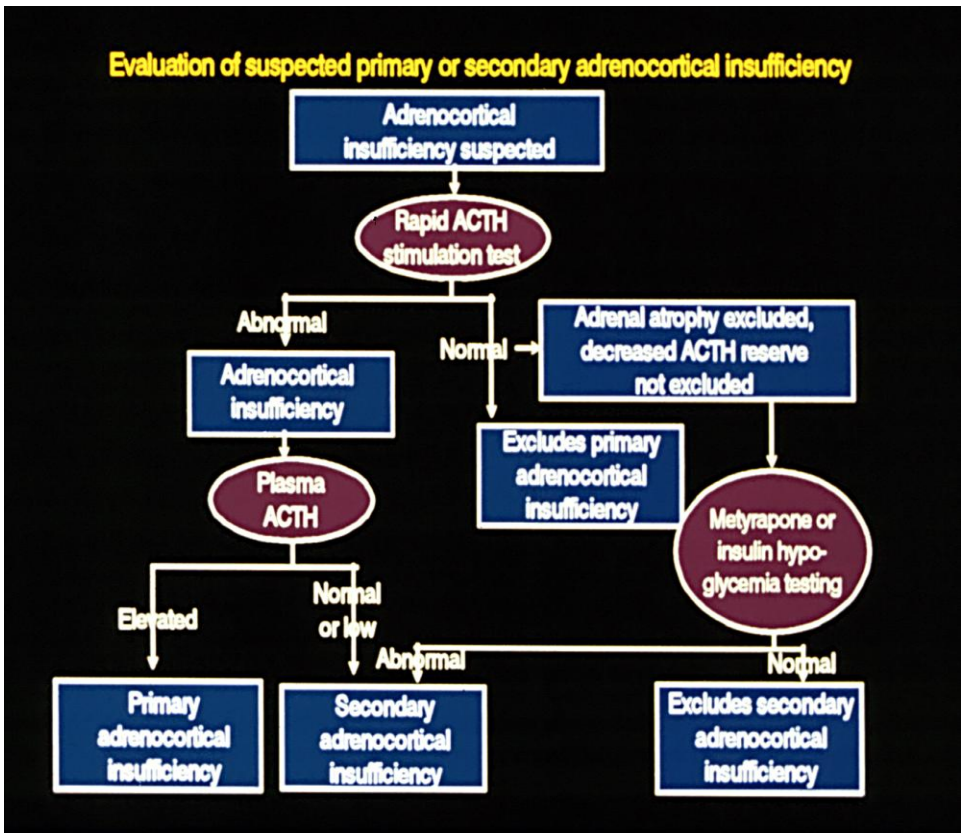
Treatment:

- It should be started as soon as possible once diagnosis suspected.
- Parenteral cortisol is commonly used and it has sufficient mineralocorticoid activity so additional treatment is not required. **The dose begin as 100 mg every 6 hrs**, and the dose is gradually tapered when condition is stable.
- Maintenance therapy with oral cortisol with or without a mineralcorticoid is then given.
- Intravenous fluids including glucose and saline are required to correct volume depletion, hypotension and hypoglycemia as well as the acidosis and hyperkalaemia but the shock may not respond to vasopressors unless glucocorticoids are administered.
- **Adrenal crisis can be prevented in an already diagnosed patient by proper education on dosage of drugs during illness.**
- The patient should be informed about life-long therapy and the need to increase the dose of steroids during illness(it should be atleast doubled for minor illnesses) and if symptoms continue, a physician should be called.
- If oral therapy cannot be taken because of vomiting or diarrhoea, then medical assistance should be sought for parenteral therapy

Secondary Adrenal Insufficiency:

- Causes:
  - Hypothalamic-pituitary disease causing inadequate ACTH production.
  - Long-term steroid therapy suppressing ACTH production (**the most common cause)**.
- Vague symptoms of feeling unwell.
- In early stages: Basal ACTH & cortisol levels may be normal.
- Further loss of basal ACTH leads to atrophy of Z. Fasciculata & Z. Reticularis.
- Associated with: History of glucocorticoid therapy, Features of loss of other pituitary hormones.

Note: Since **ACTH does not control Zona glomurulosa**, the features related to aldosterone imbalance in primary adrenal insufficiency (Volume depletion, dehydration & hyperkalemia) would **not appear** in secondary adrenal insufficiency. Also there will be **no pigmentation** because there is **no increase in ACTH**.



Adrenal Imaging:

- CT is the gold standard.
- MRI
- X-Ray (rare)
- Causes of adrenal enlargement: TB (granulomas), Adrenal Hemorrhage and infiltrative diseases.
- Abdominal radiograph reveal adrenal calcification in half of patients with tuberculosis adrenilitis and in some patients with other invasive or hemorrhagic causes of adrenal insufficiency.

Diagnosis of Adrenal Insufficiency:

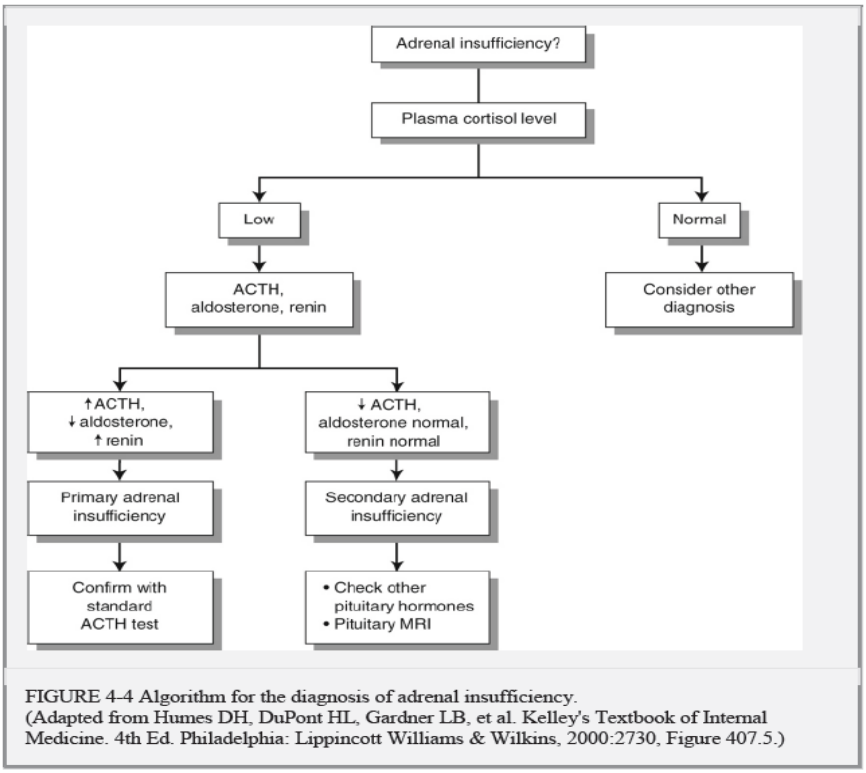


FIGURE 4-4 Algorithm for the diagnosis of adrenal insufficiency.
(Adapted from Humes DH, DuPont HL, Gardner LB, et al. Kelley's Textbook of Internal Medicine. 4th Ed. Philadelphia: Lippincott Williams & Wilkins, 2000:2730, Figure 407.5.)

- ACTH Stimulation test: give an IV infusion of ACTH, and measure plasma cortisol at the end of the infusion.
    - Primary adrenal insufficiency: no increase in cortisol after ACTH infusion. No increase in cortisol could be due to atrophied adrenals from 2ry insufficiency. Measure plasma ACTH, if increased = 1ry insufficiency / normal or low = 2ry insufficiency.
    - Secondary adrenal insufficiency: cortisol does not increase sufficiently (the adrenals are not used to stimulation) at first. Repeat the test for 4 or 5 days and the adrenals will respond normally.
- Long ACTH stimulation test: can exclude adrenal suppression by steroids or ACTH deficiency.
- Imaging: MRI of (brain-pituitary/hypothalamus) if secondary or tertiary (related to hypothalamus and CRH) adrenal insufficiency is diagnosed.

Treatment:

- Patients with Addison's disease require **life long therapy** usually with both glucocorticoids and mineralocorticoids.
- **Hydrocortisone (glucocorticoid) 25-30 mg/day** usually given twice per day.
- **Fludrocortisone (mineralocorticoid) 0.05-0.1 mg/day** dose in the morning (In secondary adrenal insufficiency fludrocortisone is rarely required).
- **Increase cortisol dose** during stress and illness (at least double the dose for minor illnesses).
- **Parenteral cortisol** used in **Adrenal Crisis**, the dose begins as **100 mg every 6 hrs** then gradually tapered when condition is stable & add mineralocorticoid as required.
- **IV fluids** including **glucose** to correct volume depletion and hypoglycemia.

Cushing's Syndrome:

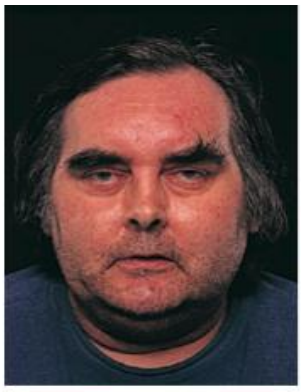
- Cushing's **syndrome** is the term used to describe the clinical state of **increased** free circulating **glucocorticoid**.
- It occurs most often following the therapeutic administration of synthetic steroids or ACTH. All the spontaneous forms of the syndrome are rare.

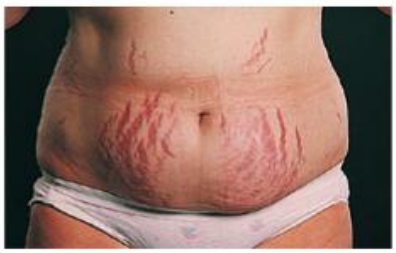
Causes:

- ACTH-dependent disease:
  - **Pituitary**-dependent (Cushing's **disease**).
  - Ectopic ACTH-producing tumors.
  - ACTH administration.
- Non-ACTH-dependent causes:
  - **Adrenal adenomas.**
  - **Adrenal carcinomas.**
  - **Glucocorticoid administration. (Most common)**

Clinical Features:

Symptoms
Weight gain (central)
Change of appearance
Depression
Insomnia
Amenorrhoea/ oligomenorrhoea
Poor libido
Thin skin/easy bruising
Hair growth/acne
Muscular weakness
Growth arrest in children
Back pain
Polyuria/polydipsia
Psychosis
Old photographs may be useful





Signs	
Moon face	Kyphosis
Plethora	'Buffalo hump' (dorsal fat pad)
Depression/psychosis	Central obesity
Acne	**Striae (purple or red)**
Hirsutism	Rib fractures
Frontal balding (female)	Oedema
Thin skin	**Proximal myopathy**
Bruising	Proximal muscle wasting
Poor wound healing	Glycosuria
Pigmentation	
Skin infections	
Hypertension	
Osteoporosis	
Pathological fractures (especially vertebrae and ribs)	

- Pigmentation occurs only with ACTH-dependent causes.
- Impaired glucose tolerance or frank diabetes is common, especially in the ectopic ACTH syndrome.
- Hypokalemia due to the mineralocorticoid activity of cortisol is common with ectopic ACTH secretion.
- In Cushing's disease: ACTH is normal or modestly elevated while in the ectopic syndrome: markedly elevated. In adrenal tumours: ACTH is undetectable.

Diagnosis:

- Confirmation rests on demonstrating inappropriate cortisol secretion, not suppressed by exogenous glucocorticoids: difficulties occur with obesity and depression where cortisol dynamics are often abnormal. Random cortisol measurements are of no value. Occasional patients are seen with so-called (cyclical Cushing's) where the abnormalities come and go.
- Investigations to confirm the diagnosis include:
  1. **48-hour low-dose dexamethasone test:** Normal individuals suppress plasma cortisol to 50 nmol/L. Patients with Cushing's syndrome fail to show complete suppression of plasma cortisol levels
  2. **Circadianrhythm**: After 48 hours in hospital, cortisol samples are taken at 0900 h and 2400 h (without warning the patient). Those with Cushing's syndrome have high midnight cortisol levels (100 nmol/L).

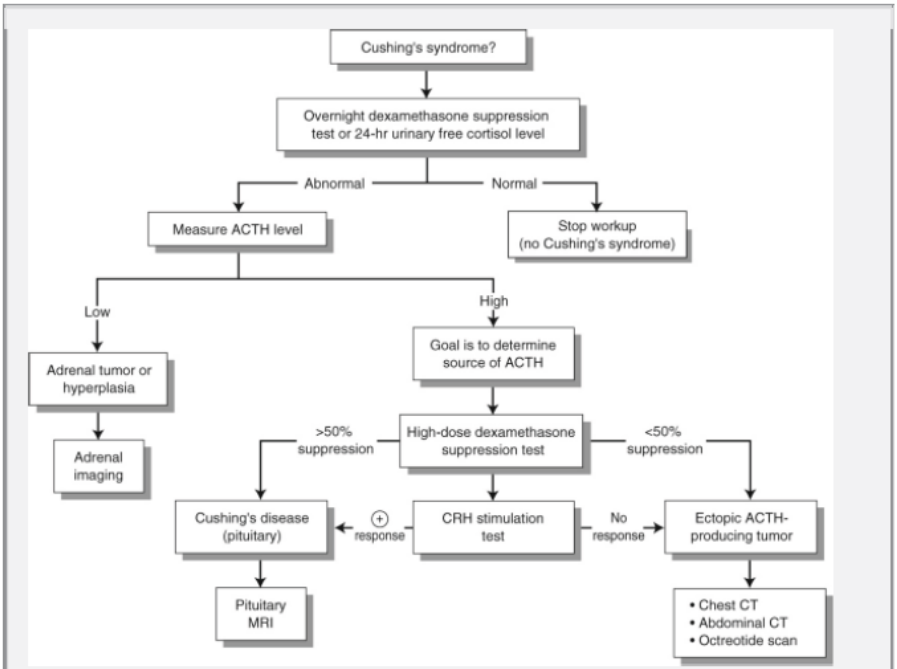


FIGURE 4-3 Algorithm for the diagnosis of Cushing's syndrome and its cause. (ACTH, adrenocorticotropic hormone; DM, dexamethasone)
(Adapted from Humes DH, DuPont HL, Gardner LB, et al. Kelley's Textbook of Internal Medicine. 4th Ed. Philadelphia: Lippincott Williams & Wilkins, 2000:2725, Figure 407.3.)

Determining the cause:

1. **Adrenal CT or MRI scan:** Adrenal adenomas and carcinomas. **Bilateral** adrenal hyperplasia may be seen in **ACTH-dependent causes** or in **ACTH-independent nodular hyperplasia**.
2. **Pituitary MRI:** shows Pituitary Adenomas
3. **Plasma potassium levels:** Hypokalemia is common with **ectopic ACTH secretion**. (All diuretics must be stopped.)
4. **High-dose dexamethasone:** Failure of significant plasma cortisol suppression suggests an **ectopic source of ACTH or an adrenal tumor**.
5. **Plasma ACTH levels:** Low or undetectable ACTH levels (< 10 ng/L) on two or more occasions are a reliable indicator of **non-ACTH-dependent disease**.
6. **CRH test:** An exaggerated ACTH and cortisol response to exogenous CRH suggests pituitary-dependent **Cushing's disease**, as ectopic sources rarely respond.
7. **Chest X-ray**: to look for a carcinoma of the bronchus or a bronchial carcinoid. If ectopic ACTH is suspected, whole-lung, mediastinal and abdominal CT scanning should be performed.
8. **Radiolabelled octreotide (111In octreotide):** is occasionally helpful in locating ectopic ACTH sites.

Treatment:

- Untreated Cushing's syndrome has a very bad prognosis, with death from hypertension, myocardial infarction, infection and heart failure.
- Whatever the underlying cause, cortisol hypersecretion should be controlled prior to surgery or radiotherapy with metyrapone, an 11 beta-hydroxylase blocker.

-Cushing's disease (pituitary-dependent hyperadrenalism):

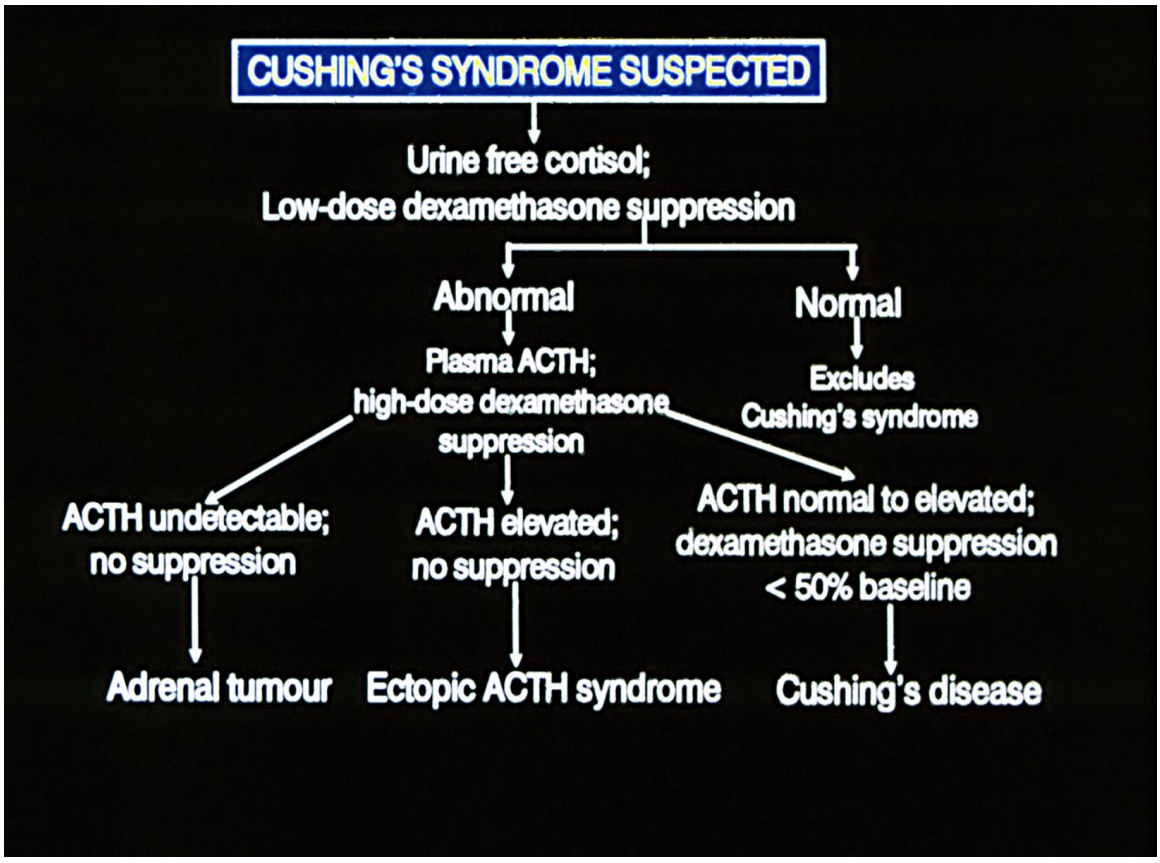
1. Trans-sphenoidal removal of the tumour is the treatment.
2. External pituitary irradiation alone is slow acting, only effective in 50–60% even after prolonged follow-up and mainly used after failed pituitary surgery. Children, however, respond much better to radiotherapy.
3. Medical therapy to reduce ACTH (e.g. bromocriptine, cyproheptadine) is rarely effective.
4. Bilateral adrenalectomy is an effective last resort if other measures fail to control the disease.

Drugs:

- Mitotane acts by inhibiting cortisol synthesis through inhibiting the P450 enzyme responsible for 11B hydroxylation.
- Metyrapone also blocks cortisol synthesis by inhibiting 11B hydroxylase action and also the cholesterol side-chain cleavage.
- Ketocenazole is a potent inhibition of the P450 enzymes with a principle effect on the 17-20 lyase enzymes but it also inhibits 11B hydroxylase, 18 hydroxylase and cholesterol side-chain cleavage.
- Aminoglutethimide acts to inhibit the conversion of cholesterol to pregnenolone.
- RU486 (Mifepristone) is a potent glucocorticoid receptor antagonist.
- They all have major side effects which limit their usefulness as medical therapy except in individual cases.

-Other causes:

1. **Adrenal adenomas** should be resected after achievement of clinical remission with metyrapone.
2. **Adrenal carcinomas** are highly aggressive and the prognosis is poor. If there are no widespread metastases, tumor bulk should be reduced surgically. The adrenolytic drug mitotane may inhibit growth of the tumor and prolong survival, though it can cause nausea and ataxia.
3. **Tumors secreting ACTH ectopically** should be removed if possible. Otherwise chemotherapy/radiotherapy may be used, depending on the tumor.
4. **Control of the Cushing's syndrome** with metyrapone or ketoconazole is beneficial for symptoms, and bilateral adrenalectomy may be appropriate to give complete control of the Cushing's syndrome if prognosis from the tumor itself is reasonable.
5. If the source of ACTH is not clear, cortisol hypersecretion should be controlled with medical therapy until a diagnosis can be made.



Incidental adrenal tumors (incidentalomas):

- It is unsuspected adrenal masses discovered in 3–10% of scans (CT, MRI, X-RAY and US for other purposes) incidentally.
- Functional tests to exclude secretory activity should be performed if none is found it is recommended to remove large (> 4–5 cm) and functional tumors but observation for smaller hormonally inactive lesions.

Primary Mineralocorticoid Excess

- The principle mineralocorticoid hormone is aldosterone. It is produced in the zona glomerulosa exclusively and is primarily controlled by the renin-orgiotensin system.
- Other regulators include:
  - Potassium level
  - ACTH and
  - Neural Components of the adrenergic and dopomenergic systems.
- There is increased production of aldosterone by abnormal zona glomerulosa tissue (adenoma or hyperplasia) which leads to :
- Increased sodium retention
- Expansion of the extracellular fluid volume
- Increased total body sodium content that leads to suppression of renin production.
- Potassium depletion occur decreasing the total body and plasma concentration of potassium and producing alkalosis.
- With moderate potassium depletion there is decreased carbohydrate tolerance and resistance to antidiuretic hormone.
- Because aldosterone biosynthesis is intensified, the entire biosynthetic pathway becomes activated and precursors like DOC corticosterone and 18-hydroxycorticosterone are present in increased amount in person with an aldosterone producing tumour.
- There is no abnormalities in cortisol production, plasma cortisol levels or cortisol metabolism.

CAUSES

- Aldosterone producing adenoma (APA)
- Bilateral adrenal hyperplasia; idiopathic AH
- Indeterminate hyperaldosteronism
- Dexamethasone suppressible hyperaldoesteronism
- Adrenocortical carcinoma.

Clinical Features

- Patient usually come to medical attention because of symptoms of **hypokalaemia and/or detection of previously unsuspected hypertension.**
- There are no characteristic symptoms and often nonspecific complaints, e.g. tiredness, lethargy, weakness, noctoria and symptoms of potassium depletion.
- If potassium depletion is severe with alkalosis, there is increased thirst and polyuria and maybe parasthesia.
- A positive trousseau or chvostek sign may suggest alkalosis with severe potassium depletion.
- Headache is a frequent complaint.
- Blood pressure can range from borderline to severe hypertensive levels.Accelerated/malignant hypertension is rare and a postural fall in blood pressure without reflex tachycardia is observed in severe potassium depletion because of blunting of the baroreceptors. Retinopathy is mild with haemorrhages being rare.
- The ECG shows signs of modest LVH and potassium depletion.

Laboratory & Radiological Diagnosis

- Diuretics should be stopped three weeks prior to potassium measurement. Other features include:
  - A high serum sodium in the presence of reduced haematocrit value (due to increased extracellular fluid and plasma volume from sodium retention)
  - There is also failure to concentrate urine.
  - Abnormal glucose tolerance
  - Alkalosis
  - All features of potassium depletion.

- If hypokalaemia is documented, the next step is to assess the renin angiotensin system by doing a random plasma renin activity level and if normal or high in the absence of diuretics therapy, then primary aldosteronism is very unlikely but if it is suppressed, then primary aldosteronism is a likely diagnosis.

Measurement of Aldosterone & Other Steroid

- Aldosterone – both plasma and urinary aldosterone measurement should be performed while the patient is taking a high salt diet with sodium chloride supplementation.
- Assessment of aldosterone production can be best done by measurement of urinary aldosterone excretion over 24 hour period and it is superior to plasma aldosterone measurement in detecting abnormal production of aldosterone but cannot discriminate between adenoma and hyperplasia. While the plasma levels can differentiate between the two conditions in most cases.
- It is important to distinguish between adenoma and hyperplasia because surgery is indicated in the former but not in the latter. After at least 4 days of high salt intake and after an overnight recumbency, the 8:00 am aldosterone level is usually greater than 20 mg/dl in adenoma and less than 20 mg/dl in hyperplasia. After 2-4 hours of upright posture (which normally activates the renin system with a rise in aldosterone) the plasma aldosterone level shows no significant change in most patients with adenoma but is almost always increased in hyperplasia.

Other Steroids:

- Plasma DOC and corticosterone are frequently increased in 8:00 AM in patients with adenoma whereas they are rarely elevated in hyperplasia.
- 18-Hydroxycorticosterone is invariably increased in patients with adenoma to greater than 85 mg/dl and shows no overlap with the normal or slightly high values in patients with hyperplasia.
- In patients, where the above tests are equivocal, further tests can help to establish the diagnosis and also help in further defining the hyperplasia.
- I.SALINE INFUSION TEST: Saline loading establishes aldosterone unresponsiveness to volume expansion and thereby identifies autonomy in patients with adenoma or hyperplasia while aldosterone suppresses in indeterminate hyperplasia.
- IITHE DEOXYCORTICOSTERONE ACETATE MANOUVER (DOC): Aldosterone is suppressed minimally or not at all by DOC or fludrocortisone in patients with adenoma or hyperplasia but indeterminate hyperaldosteronism can suppress with this manouver.
- III GLUCOCORTICOID TREATMENT: The glucocortoid remediable hyperaldoesteronism responds well to administration of ACTH suppressive doses of glucocorticoids (1-2 mg of dexamethasone daily).

Localization of Adenoma/Carcinoma

- Scanning using i.v. Administered 1^3 iodocholesterol locates tumour in 80% of the cases depending on the size of the tumour.
- NP59 scan is another scan which consumes less time. CT scanning is also useful with less radiation hazard.
- Other methods include adrenal venography, adrenal vein catheterization and bilateral sampling of blood for aldosterone measurements.

Treatment:

- In aldosterone producing adenoma, unilateral adrenalectomy is recommended provided there is adequate potassium replacement and adequate extracellular volume expansion with adequate control of BP before surgery all of which can be achieved by spironolactone with or without other medications which should be given for some time before surgery.
- The surgical cure of hypertension associated with adenoma is excellent as is reported to be over 50% in many series with reduction of hypertension in the remainder.
- In hyperplasia, antihypertensive medication should be given as surgery will not ameliorate the hypertension.

Pheochromocytoma

- Pheochromocytomas are tumours arising from the **chromaffin cells** in the sympathetic nervous system. They release epinephrin or norepinephrin (or both) and in some cases, dopamine into the circulation causing hypertension as well as other signs and symptoms.

- Only 0.1% of hypertensive patients have pheochromocytoma but recognition is important because it can be fatal during delivery or surgery if unrecognized and not properly treated.
- Pheochromocytoma may occur as a heritable disorder either alone or in combination with other endocrine tumours, e.g. MEN type II A – hyperparathyroidism, pituitary adenoma and medullary thyroid carcinoma or MEN Type II B – pheochromocytoma with mucosal neuroma.

The Rule of 10

- 10% bilateral
- 10% Familial
- 10% Malignant
- 10% Extra adrenal
- Common extra adrenal sites and near the kidneys and the organ of Zuckerkandl. They can also occur in the posterior mediastinal region.

Clinical Manifestations:

- Most patients have symptoms that vary in intensity and are perceived to be mainly episodic or paroxysmal by about half the patients. Most patients with persistent hypertension also have superimposed paroxysms and only few patients are entirely free of symptoms and hypertension between attacks and give no evidence of catecholamine excess during these intervals.

COMMONLY REPORTED SYMPTOMS AND SIGNS

Symptoms during or following paroxysms:

- Headache
- Sweating
- Forceful heart beat with or without tachycardia
- Anxiety or fear of impending death
- Tremor
- Fatigue or exhaustion
- Nausea and vomiting
- Abdominal or chest pain
- Visual disturbances

Symptoms between Paroxysm

- Increased sweating, cold hands and feet, weight loss, constipation
- In the attack, the symptoms resemble those produced by injection of epinephrine or norepinephrin.
- An episode usually starts with a sensation of something deep inside the chest and a stimulus to deepen breathing is noted. The patient then becomes aware of a pounding or forceful heartbeat caused by the baroreceptor-mediated increase in cardiac output. This throbbing spreads to the rest of the trunk and head causing a headache or a pounding sensation in the head.
- The intense alpha receptor-mediated peripheral vasoconstriction causes cool, moist hands and feet and facial pallor.
- This combination of increased cardiac output and vasoconstriction causes marked elevation of the blood pressure.
- The decreased heat loss and increased metabolism cause a rise in temperature and flushing and leads to reflex sweating which may be profuse and usually follows the cardiovascular effects.
- The increased glycolysis and alpha receptor-mediated inhibition of insulin release cause an increase in blood sugar levels.
- Patient experience anxiety and when episodes are prolonged there may be nausea, vomiting, chest or abdominal pain, visual disturbances, parasthesia or seizures. A feeling of fatigue or exhaustion usually

follows the attack. Most of these symptoms can be elicited in all patients but the variability of presenting complaints maybe confusing and is sometimes misleading.

Other causes of increased sympathetic activity must be thought of:

- Angina due to coronary vasospasm
- Severe anxiety state
- Hypertension
- Hypertensive crises associated with
    - Paraplegia
    - Tabesansalis
    - Lead poisoning
    - Acute porphyria
- Menopausal hot flushes
- Thyrotoxicosis, etc.
- The attacks in pheochromocytoma in those patients with paroxysmal symptoms occur several times a week or oftener and last 15 minutes or less but they may occur at intervals of months or as often as 25 times a day and may last minutes to days. With time the attacks usually increase in frequency but do not change much in character. They are usually precipitated by activities that compress the tumour, e.g changes in position, exercise lifting, defecation or eating and by emotional distress or anxiety.
- On the other hand, patients with persistently secreting tumours and chronic symptoms usually experience the symptoms complex in response to transient increases in the release of catecholamines. In addition, they have increased metabolic rate with heat intolerance, increased sweating with weight loss. There is also hyperglycaemia and glucose intolerance.
- Hypertension is usually present and characteristically there is wide fluctuations and an episode of marked hypertension might be followed by hypotension and shock.
- The blood pressure typically does not respond to commonly used antihypertensive medications. Chronic constriction of the arterial and venous beds leads to reduction in plasma volume and the inability to further constrict the bed upon arising causes the postural hypotension that is characteristically observed.
- A mass might be felt in the neck or abdomen and palpation may produce a typical paroxysm.
- Patients with persistent symptoms and hypertension may develop hypertensive retinopathy or nephropathy as well as the other sequelae of hypertension. CVA, CCF and MI are all observed. A significant number were found to have myocarditis post partum.

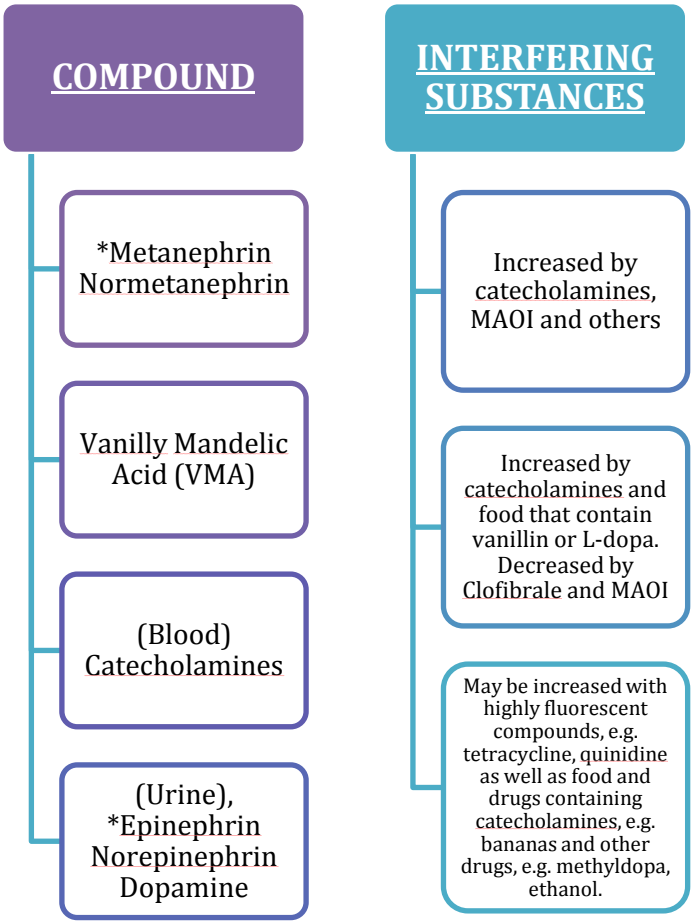
Clinical Diagnosis:

The diagnosis of pheochromocytoma should be considered in the following patients.

- Patients with paroxysmal symptoms
- Children with hypertension
- Adults with severe hypertension not responding to therapy.
- Hypertensive patients with diabetes or hypermetabolism.
- Hypertensive patients with symptoms resembling the symptom complex described above or can be evoked by exercise position change .. ect. or certain antihypertensive medications.
- Patients who become severely hypertensive or go into shock during anesthesia, surgery or obstetric delivery,
- Patients who have disorders sometimes associated with pheochromocytoma, e.g. neurofibromatosis, mucosal adenomes, medulary carcinoma of thyroid or those who have first degree relatives who have rheochromocytomas or other manifestations of MEN.
- Ganglioneuromas and neuroblastomas can produce catecholamines with dopamine being the major product leading to a similar picture resembling pheochromocytoma.

Laboratory Diagnostic Tests & Radiological Investigations

- In patients with continous hypertension or symptoms**, levels of plasma or urinary catecholamines and their metabolites are usually clearly increased,** the difficulty arises in patients having brief and infrequent paroxysms with symptom-free intervals and in such cases, sampling of blood or urine should be done during a carefully observed episode to confirm the diagnosis.



In patients with infrequent episodes, it may be useful to induce a paroxysm under supervision (it should not be done for those with angina or other severe symptoms). The infusion of glucagons can induce an attack in 90% of patients with pheochromocytoma, Histamin can also be used for the same purpose. Once the diagnosis has been established, the tumour must be located prior to surgical removal. CT scanning gives better results than sonography or other radiological tests. MRI is evolving as very specific and excellent technique for detecting pheochromocytomas. Analysis of blood samples obtained for venous drainage can be of great value in locating small tumours in unusal locations. MIBG(meta iodobenzylguanidine) can detect even the smallest tumour but not all pheochromocytomas produce detectable images and other tumours e.g. neuroblastoma give positive **images.**

Treatment is directed toward:

- Reduction of symptoms
- Lowering of BP
- Amelioration of paroxysms
- Therapy with alpha adrenergic antagonists should be instituted. Such treatment will allow expansion of the vascular bed and plasma volume.
- Agents commonly used include phentolamine and phenoxybenzamine, small doses of propranolol maybe required for marked tachycardia or arrthymia prior or during surgery.
- Therapy with phenoxybenzamine can be used as a diagnostic test in the occasional patient in whom the chemical tests are inconclusive. A good response in the nature and frequency of attacks as well as on BP indicates the need for re-evaluation of the patient with a strong suspicion for pheochromocytoma.

Surgery:

- Patients should be fully, prepared medically prior to surgery to avoid intra and post operative complications. Once the tumour is removed, the blood pressure usually falls and i.v. fluids and / or blood might be needed to restore circulatory volume. Persistence of high BP after surgery should alert physician to look for other causes, e.g. renal vascular hypertension.

Dexamethasone suppression Tests

- Low Dose test:
    - Dexamethasone 0.5 mg is given every 6 hrs. for two days, and 17-hydroxysteroids excretion and free cortisol are measured on the second day of the test. The level should be suppressed to below 4mg/day and >50% respectively. Also serum cortisol level will suppress to <5 mcg/dcl.
- Screening test:
    - Dexamethasone 1 mg overnight test will suppress morning cortisol to less then 3 mcg/dcl in normal patients. This will need other confirmatory tests e.g. UFC.
    - False positive results have been seen in depression, with certain medications (Phenytoin and barbiturates) and in patients undergoing stressful events or serious illnesses.

References:

- Dr. Alruhaily's Lecture Slides.
- Step-Up To Medicine.
- Kumar & Clark Clinical Medicine.