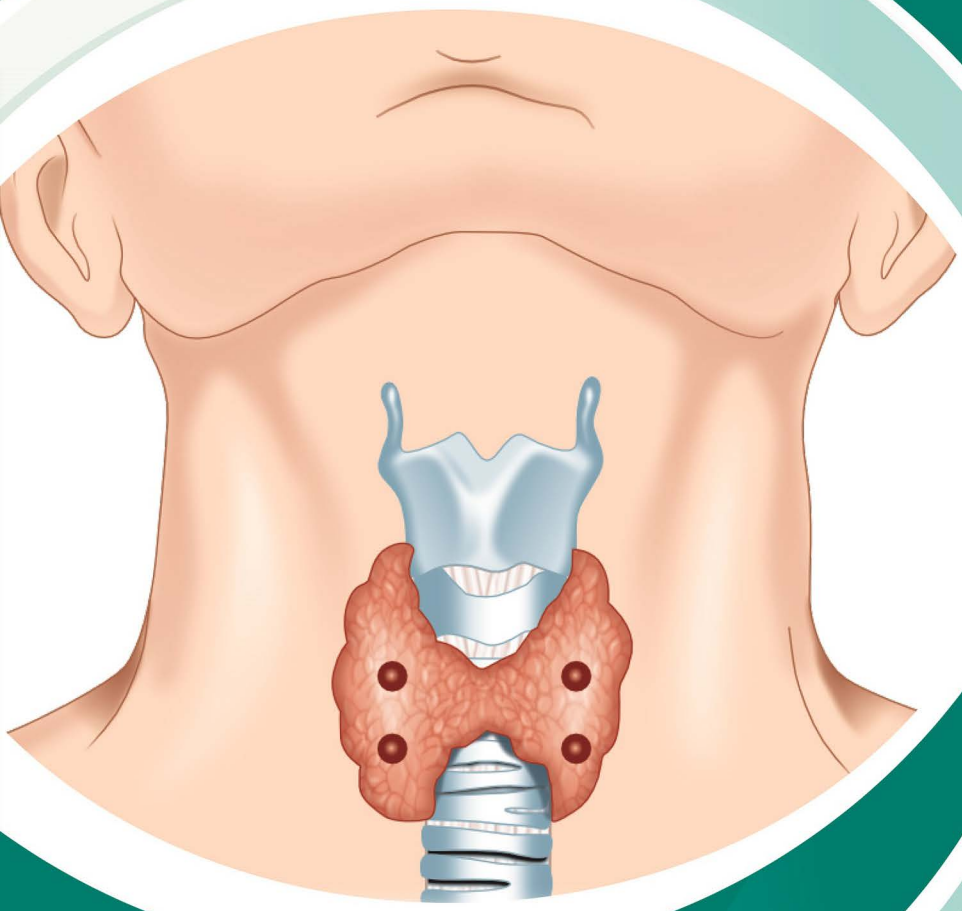

Essence of CLINICAL ENDOCRINOLOGY

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Foreword
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JAYPEE

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CHAPTER 5

Disorders of Adrenal Gland

- Introduction to the adrenal glands
  - Anatomy of adrenal glands
  - Physiology of adrenal glands
- Diseases of adrenal glands
  - Hypercortisolemia
  - Cushing's syndrome
  - Hyperaldosteronism
  - Adrenal (adrenocortical) insufficiency
  - Congenital adrenal hyperplasia
- Pheochromocytoma
  - Identification and treatment
  - Diagnosis of pheochromocytoma
- Adrenal incidentaloma

This chapter is about Adrenal Gland, which begins with an introduction to applied anatomy and physiology. It covers hyperfunctional states and hypofunctional states, adrenal cortex, congenital adrenal hyperplasia, and adrenal medullary disorder—pheochromocytoma. This chapter consists of 22 Figures, 8 Flowcharts, 18 Tables, and 1 Box to illustrate its text. This chapter ends with how to deal with Adrenal Incidentalomas.

INTRODUCTION TO THE ADRENAL GLANDS

(Anatomy and applied Embryology; Physiology)

Anatomy of Adrenal Glands

Two adrenal glands are retroperitoneum structures lie on the upper ends of the two kidneys. The right adrenal gland is pyramidal and the left one is crescentic in shape. The maximum width of right adrenal gland is 6.1 mm and that of the left adrenal gland is 7.9 mm. Glands are yellowish small and they weight about 4–5 g.

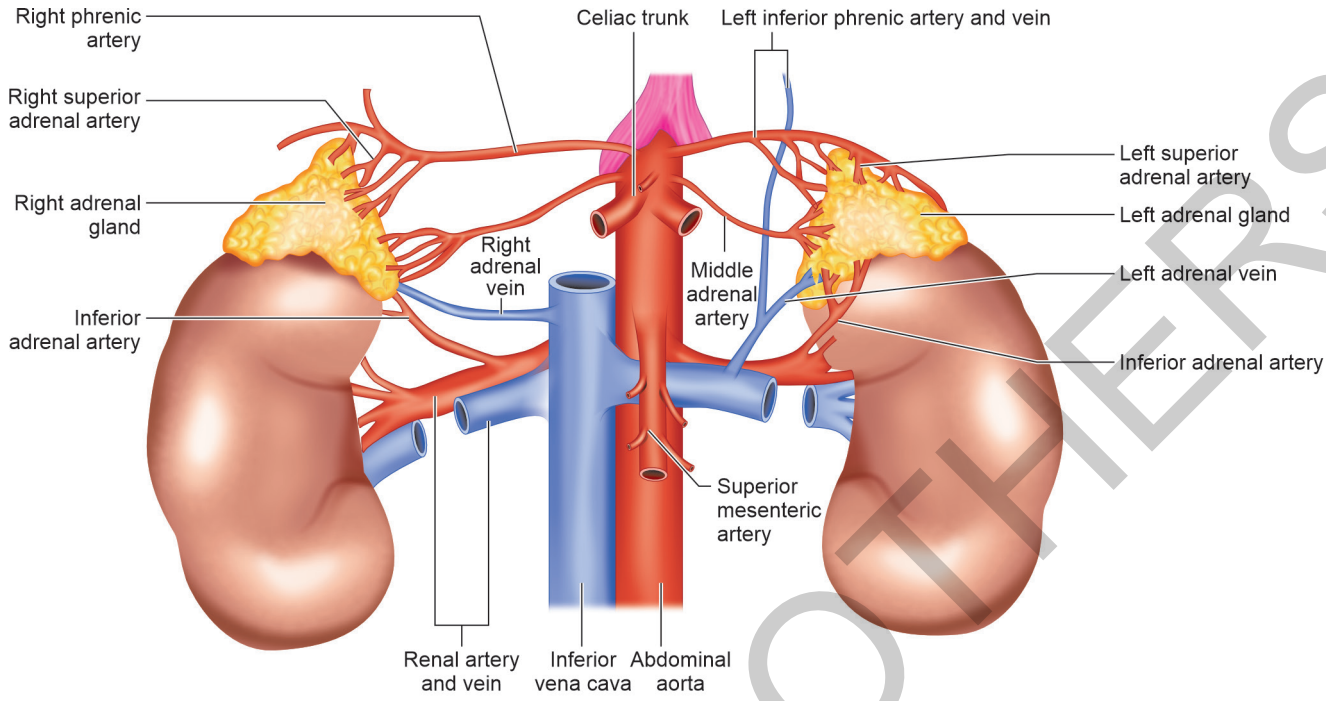
The glands have rich blood supply. Each receives three adrenal arteries arising from (1) inferior phrenic artery, (2) renal artery, and (3) abdominal aorta.

Venous drainage: The right gland flows directly into the inferior vena cava and the left gland into the left renal vein. Lymphatics drain to the aortic lymph nodes **(Fig. 1)**.

There are two distinct parts of each adrenal gland, one lie inside the other: (1) the outer one is adrenal cortex and (2) the inner one is adrenal medulla. The adrenal cortex is divided into three zones. From exterior to interior the zones are named as (1) zona glomerulosa, (2) zona fasciculata, and (3) zona reticularis **(Fig. 2)**.

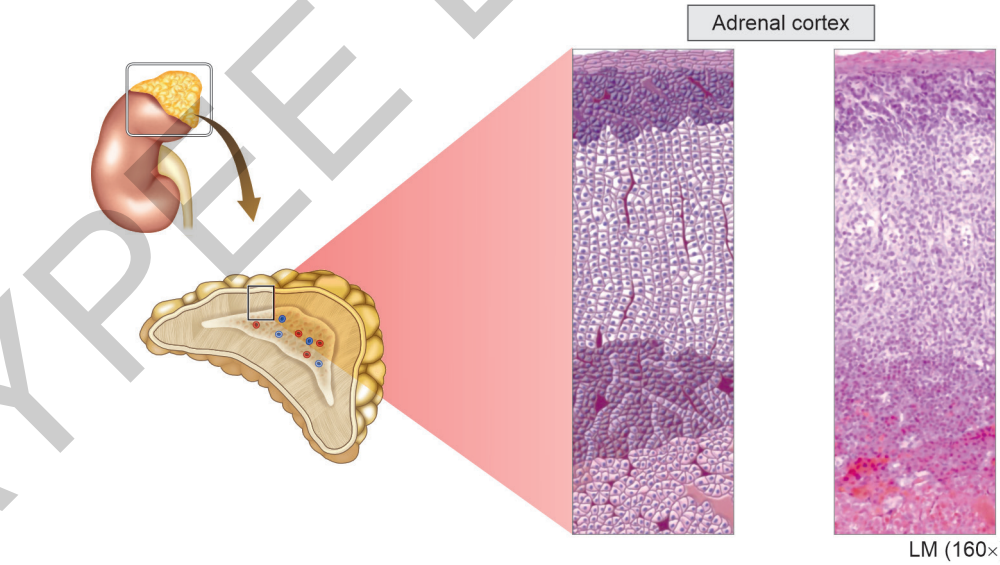
The adrenal glands are better visualized by computed tomography (CT) scan than other modalities. After contrast administration their density reaches to approximately 50–60 Hounsfield units (HU) and seen as inverted V and coma shape in right and left sides respectively.

Embryology: The adrenal cortex and medulla are mesodermal and ectodermal in origin respectively. From the mesoderm of the posterior abdominal wall at 6th week of gestation the adrenal cortex starts developing. The fetal cortex is a predominant structure during entire fetal life, it starts steroid secretion very early. At 4th month of gestation its size is four times of the kidney but at birth it is one-third of the size of the kidney. In fetal life, only a small proportion of the gland consists zona glomerulosa and fasciculata but there is no zona reticularis. After birth, the fetal cortex starts rapid regression and disappears almost



Blood supply of adrenal glands

FIG. 1: The arterial supply comes from three sources—adrenal arteries arising from (1) inferior phrenic artery, (2) renal artery, and (3) abdominal aorta. Venous drainage flows directly to two veins (1) on right side into the inferior vena cava and (2) on left side into the left renal vein.

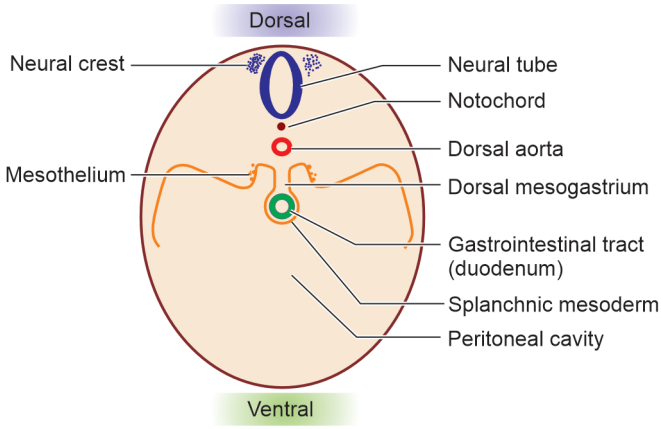


(a) Gross structure of the adrenal gland

(b) Histology of the adrenal gland—illustration (left) and light micrograph (right)

Parts of adrenal gland (Histology)

FIG. 2: There are two distinct parts of each adrenal gland: (1) the adrenal cortex and (2) the adrenal medulla. The cortex is divided into three zones. From exterior to interior the zones are: (1) zona glomerulosa, (2) zona fasciculata, and (3) zona reticularis.



Adrenal gland development

FIG. 3: Adrenal cortex starts developing from mesoderm at 6 weeks and soon begins steroid secretion. Cortex is predominant in entire fetal life; at 4 months it is four times of kidney and at birth it is one-third. Zona glomerulosa and fasciculata make up only a small proportion but zona reticularis is absent. After birth, the fetal cortex rapidly regression and disappears by age of 1 year. The permanent adult-type adrenal cortex is fully developed by age of 4–5 years. The adrenal medullas arise from neural crest cells that migrate to the medial aspect of the developing cortex. The cells have neuron-like morphology. Two cell types (1) secrete epinephrine and norepinephrine.

completely by age of 1 year. The permanent adult-type adrenal cortex is fully developed by 4–5 years of age.

The adrenal medullas develop from neural crest cells. Neural crest cells migrate to the medial aspect of the growing adrenal cortex. The cells of the medulla have neuron-like morphology. There are two cell types (1) secrete epinephrine (adrenaline) 80% and norepinephrine (noradrenaline) 20% respectively **(Fig. 3)**.

Birth Anomalies

Some anatomic anomalies of the adrenal gland may occur. Anomalies are usually associated with renal anomalies. Examples are (1) agenesis of an adrenal gland can be associated with agenesis of the kidney of same side and (2) fused adrenal glands (the two glands join across the midline posterior to the aorta) usually associated with a fused horseshoe kidney.

Physiology of Adrenal Glands

Physiology of Adrenal Cortex

Three types of steroid hormones are synthesized and secreted from the adrenal cortex. Hormones are more or less zone specific:

1. The zona glomerulosa secretes mineralocorticoids (the most important of which is aldosterone)
2. The zona fasciculata secretes mostly glucocorticoids (predominantly cortisol)
3. The zona reticularis secretes adrenal androgen [mainly dehydroepiandrosterone (DHEA)] and a small quantity of androgens also released from the zona fasciculata

About half of aldosterone is bound to protein in the blood. Most of cortisol (approximately 90%) binds to cortisol-binding globulin or transcortin. The liver is the site of degradation of all adrenocortical steroids. The degraded products are conjugated mostly to glucuronides or rest to sulfates. Excretion of approximately 75% of these degradation products form the body is in urine and the rest in the stool by means of bile.

Mineralocorticoids

Mineralocorticoid activities of adrenal steroids are provided by aldosterone, deoxycorticosterone, corticosterone, and cortisol. About 90% of mineralocorticoid activity is due to aldosterone, its concentration in the blood changes with posture and also has diurnal variation—in supine position concentration ranges from 2 to 16 ng/dL and in upright position 5 to 41 ng/dL. Its daily secretory rate is generally 150–250 μg.

Site of action of aldosterone is at the renal tubular epithelial cells of the collecting and distal tubules. It promotes sodium reabsorption and potassium excretion. Sodium is reabsorption is coupled with passive water flow in extracellular fluid. This leads to an increase in the extracellular fluid volume with little or no change in the plasma sodium concentration. The elevated extracellular fluid volumes can rise blood pressure. This high pressure helps to minimize further increases in extracellular fluid volume by causing a pressure diuresis. This phenomenon is called aldosterone escape.

In state of aldosterone lack, the kidney will lose excessive amounts of sodium and water, leading to severe dehydration. In imbalances (1) with high in aldosterone will lead to hypokalemia and muscle weakness and (2) with low in aldosterone will lead to hyperkalemia with cardiac toxicity.

Mild metabolic alkalosis may develop with aldosterone excess because there will be loss hydrogen also.

In addition to the renal tubules, other sites of aldosterone action include the sweat glands, salivary glands, and intestine, especially the colon. So, clinical manifestations of deficiency or excess of this hormone can be seen in these organ dysfunctions.

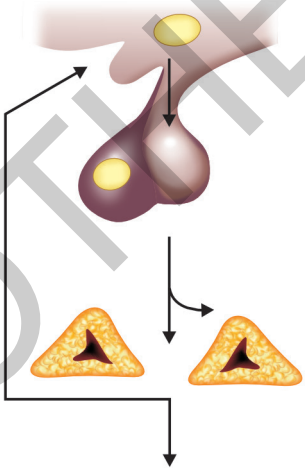
Factors affecting aldosterone secretion include the renin-angiotensin system, changes in the plasma potassium and sodium concentration, adrenocorticotropic hormone (ACTH), etc. The renin-angiotensin system and plasma potassium concentration are the most important factors.

- The renin-angiotensin system—(1) any decreased blood flow to the kidney, due to hypovolemia, hypotension, or renal artery stenosis, the juxtaglomerular apparatus to releases and enzyme called renin; (2) renin activates angiotensinogen to release a peptide hormone called angiotensin I; (3) in the lung, angiotensin-converting enzyme (ACE) converts angiotensin I to angiotensin II which is a more potent vasoconstrictor and stimulator of aldosterone release from the adrenal cortex.
- Concentration of potassium—increases in the plasma potassium concentration stimulate the release of aldosterone to encourage potassium excretion by the kidney.
- Concentration of sodium—decreases in sodium concentration stimulate aldosterone release.
- *Adrenocorticotropic hormone secretion*: It primarily causes release of glucocorticoids by the adrenal also stimulates aldosterone release to a lesser extent.

Glucocorticoids

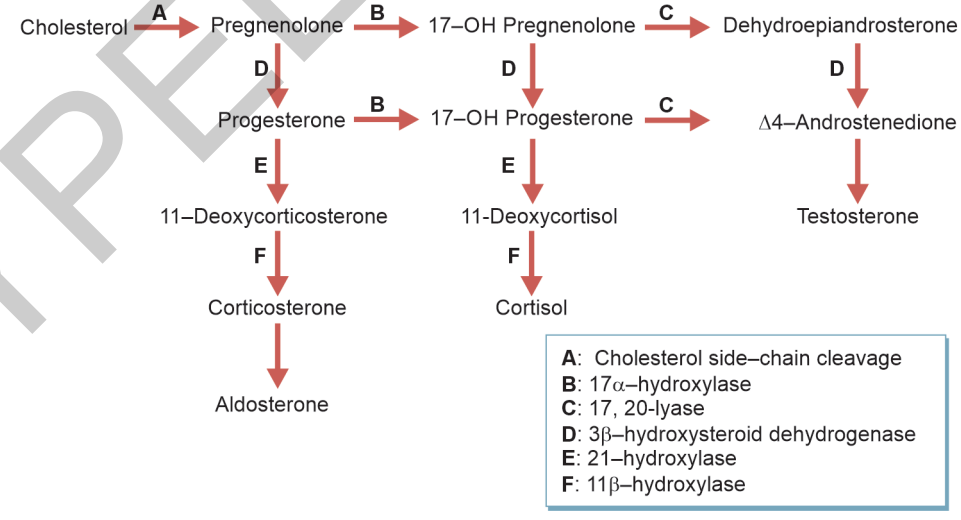
Zona fasciculata of adrenal cortex is the site of glucocorticoid hormone production. Most (approximately 95%) of glucocorticoid activity is from the cortisol hormone. Corticosterone, a glucocorticoid less potent than cortisol is also secreted by this zone of cortex. In blood averages concentration of cortisol is 12 µg/dL and average daily secretory is 5–20 mg.

Adrenocorticotropic hormone secretion of the anterior pituitary gland stimulates cortisol secretion. ACTH secretion is again controlled by corticotropin-releasing hormone (CRH) of the hypothalamus. Normally, CRH, ACTH, and cortisol secretory rates show a circadian rhythm, with peak(s) in the early morning and a nadir in the evening. Various stresses can also stimulate ACTH secretion and thereby also increase cortisol secretion. Blood cortisol level has a negative feedback effect on the anterior pituitary and the hypothalamus that helps to regulate plasma cortisol concentrations **(Figs. 4 and 5)**.



Normal relation between pituitary and adrenals

FIG. 4: Cortisol release is almost entirely controlled by the secretion of adrenocorticotropic hormone (ACTH) by the anterior pituitary gland and their negative feedback.



Steroid synthesis by adrenal cortex

FIG. 5: Adrenal cortex secretes three types of steroid hormones: (1) Zona glomerulosa secretes mineralocorticoids—aldosterone. (2) Zona fasciculata and zona reticularis secretes—glucocorticoids—predominantly cortisols. (3) Adrenal androgens are predominantly secreted by the zona reticularis, with small quantities released from the zona fasciculata.

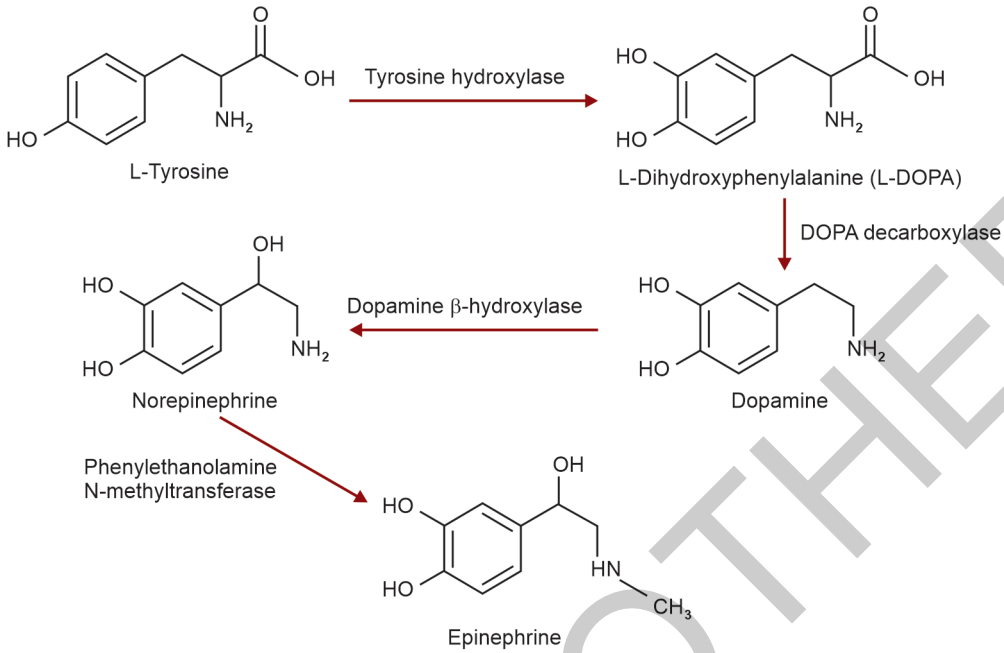


FIG. 6: Epinephrine (80%) and norepinephrine (20%), with minimal amounts of dopamine, are secreted into the bloodstream due to direct stimulation by acetylcholine release from sympathetic nerves.

Cortisol has many effects on different system/organs of the body; some of them are as follows:

- *In the liver*: Cortisol stimulates gluconeogenesis by stimulating the involved enzymes and mobilizing necessary substrates—amino acids from muscle and free fatty acids from adipose tissue. Cortisol also decreases glucose use by extrahepatic cells in the body. So, the overall result is increase in blood glucose and increased glycogen stores in the liver.
- *In body (except in the liver)*: Cortisol decreases protein stores by inhibiting protein synthesis and stimulating catabolism of muscle protein.
- *Anti-inflammatory effects*: It blocks the early stages of inflammation by stabilizing lysosomal membranes, preventing excessive release of proteolytic enzymes, decreasing capillary permeability and consequently edema and decreasing chemotaxis of leukocytes. It also induces rapid resolution of inflammation that is already in progress.
- *In blood*: Cortisol decreases eosinophil and lymphocyte counts in the blood which affects immunity adversely.

Adrenal androgens

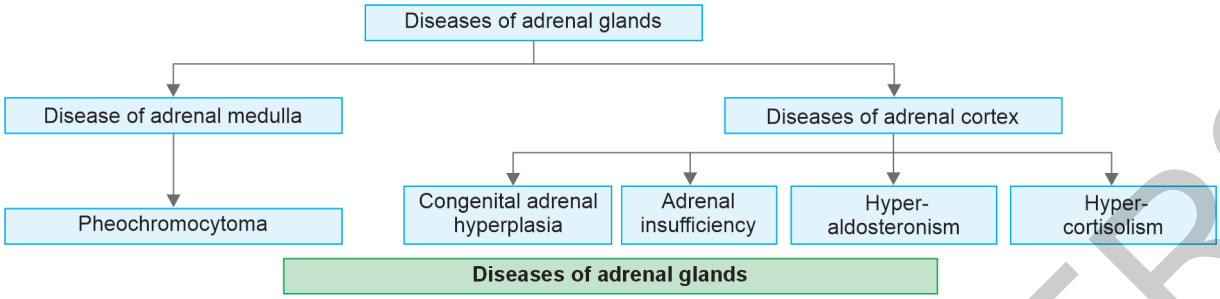
The adrenal cortex secretes several male and female sex hormones. Male sex hormones include DHEA, dehydroepiandrosterone sulfate (DHEAS), androstenedione, and 11-hydroxyandrostenedione. Female sex hormones are progesterone and estrogen—these are small in amount. Most of the androgens are converted to testosterone extra-adrenally. All these hormones have weak effects, but they play an important role in early development of the male sex organs in childhood and induction of pubarche of women. ACTH of pituitary stimulates androgen release by the adrenal.

Adrenal medulla

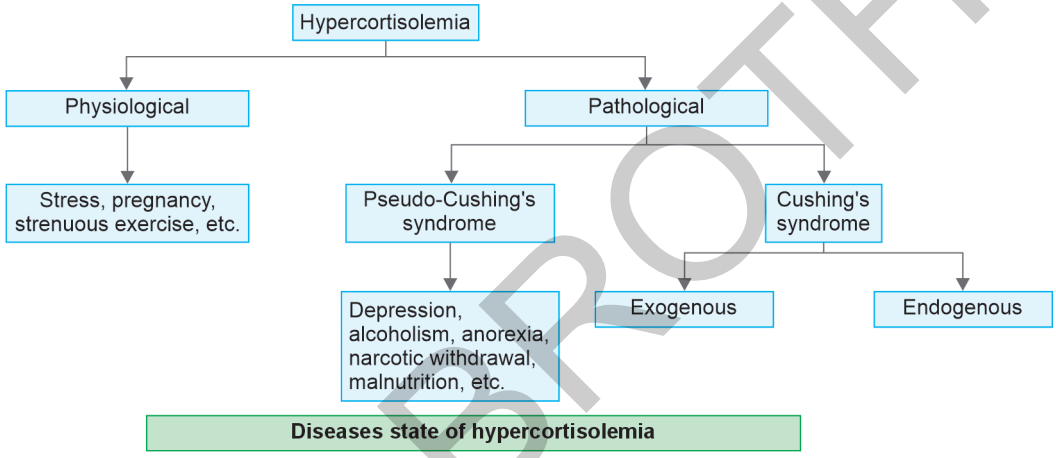
Adrenal medullary glands lie within the adrenal cortex gland but they are different in structure and function. They are of neural crest origin and secrete mainly epinephrine (80%) and norepinephrine (20%) and a minimal amount of dopamine. They are secreted into the bloodstream due to direct stimulation by acetylcholine release from sympathetic nerves. The adrenal medulla cell receives preganglionic sympathetic nerve fibers of the sympathetic chains and splanchnic nerves which pass from the intermediolateral horn cells of the spinal cord. The hormones cause increase in cardiac output and vascular resistance **(Fig. 6)**.

DISEASES OF ADRENAL GLANDS

Adrenal disorders present with hormonal disturbances. Diseases of adrenal cortex are described as hyperfunctioning states of mineralocorticoid aldosterone (hyperaldosteronism) and glucocorticoid—cortisol



FLOWCHART 1: (A) Diseases of adrenal cortex are described as (1) Hyperfunctioning states (hyperaldosteronism) and hypercortisolism, (2) Deficiency of cortisol with or without aldosterone (adrenal insufficiency), and (3) Production of abnormal steroid (CAH) and (B) Disease of adrenal medulla—pheochromocytoma.



FLOWCHART 2: Hypercortisolemia may be either a physiological response or a pathological state: (1) Pathological hypercortisolemias are Cushing's syndrome or pseudo-Cushing's syndrome and (2) Physiological hypercortisolemias are due to stress, pregnancy, strenuous exercise, etc.

(hypercortisolism), deficiency of cortisol with or without aldosterone (adrenal insufficiency), and production of abnormal steroid [congenital adrenal hyperplasia (CAH)]. Disease of adrenal medulla is excess productions of catecholamine—pheochromocytoma.

Diseases of adrenal cortex are:

1. Hypercortisolism (excess cortisol)
2. Hyperaldosteronism (excess aldosterone)
3. Adrenal insufficiency (diminish cortisol with or without diminish aldosterone)
4. Congenital adrenal hyperplasia (abnormal steroid genesis)

Disease of adrenal medulla: Pheochromocytoma (excess catecholamine) **(Flowchart 1)**.

Hypercortisolemia

A state of hypercortisolemia may be either a physiological response or a pathological state due to a wide range of causes which may be either physiological or pathological. Physiological causes include stress, pregnancy, or chronic strenuous exercise. Pathological cause includes Cushing's syndrome—endogenous or exogenous (mostly iatrogenic), psychiatric conditions, such as depression, alcoholism, anorexia, narcotic withdrawal and malnutrition **(Table 1)** of which we will study Cushing's syndrome in brief **(Flowchart 2)**.

TABLE 1: Class and causes of Cushing's syndrome.

Class (~%)	Causes (~ % within class)
Adrenocorticotropic hormone (ACTH) dependent (85%)	Pituitary ACTH-producing lesions (Cushing's disease ~80%)
	Ectopic ACTH-producing tumors (ectopic ACTH syndrome ~20%)
ACTH independent (15%)	Adrenal adenoma (~30%)
	Adrenal carcinoma (~70%)

Cushing's Syndrome

Cushing's syndrome can be defined as symptoms and signs of associated with prolong exposure to inappropriately high plasma cortisol (hypercortisolism).

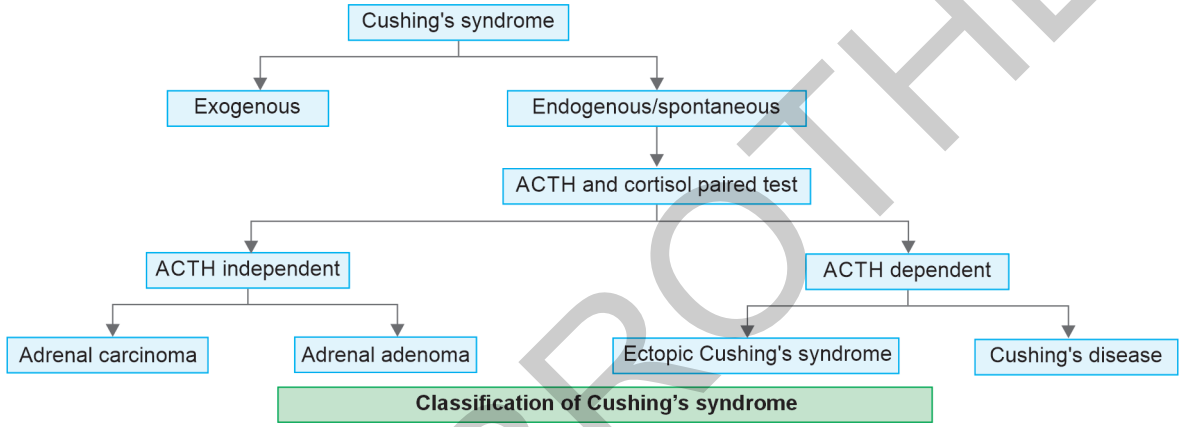
Classification of hypercortisolism is initially done as endogenous or exogenous according to the source of cortisol and then endogenous class is further on the basis of ACTH dependency **(Flowchart 3)**.

Causes of Cushing's syndrome are (1) Adrenal adenoma or carcinoma, (2) Pituitary ACTH-producing lesions, and (3) Ectopic ACTH-producing tumors **(Table 1)**.

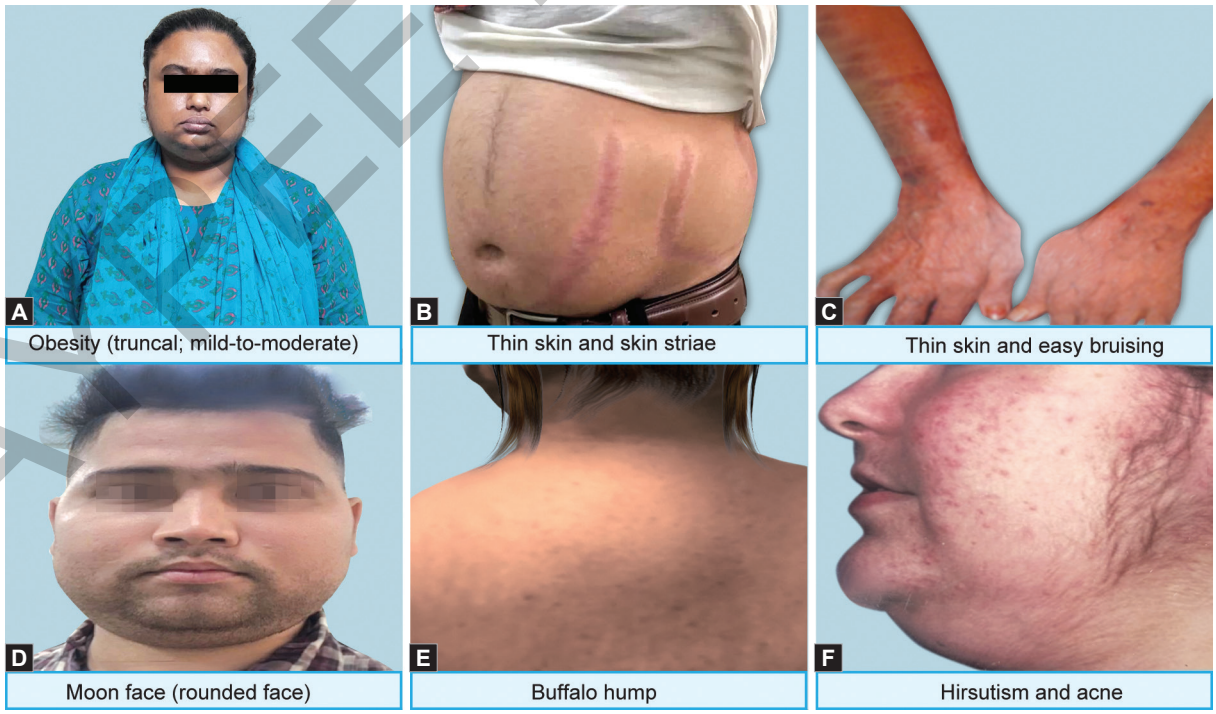
Clinical Presentation of Cushing's Syndrome (For All Age Group)

- Obesity (trunkal; mild-to-moderate)
- Thin skin, easy bruising, and purple skin striae
- Moon face, plethora, acne, and hirsutism **(Figs. 7A to F)**.

With the relative early detections (as in routine health checkup), the time-old list of presenting symptoms and



FLOWCHART 3: Spontaneous Cushing's syndrome is either adrenocorticotropic hormone (ACTH)-dependent or ACTH-independent. ACTH level is very high in ectopic Cushing's syndrome.



FIGS. 7A TO F: Presentation of Cushing's syndrome.

signs has changed nowadays. The other common features are as follows:

- Thin skin texture
- High blood sugar and pressure
- Menstrual irregularity and infertility
- Depression, emotional instability, and sleep disorders
- Undue fatigability
- Osteoporosis, etc.

Clinical Presentation of Cushing's Syndrome (For Children Age up to 18 Years)

- Growth arrest
- Rapid weight gain (obesity)
- Avascular necrosis of hip
- Fatigue/weakness
- Pubertal arrest
- Easy bruising and purple skin striae
- Moon face, plethora, acne, and hirsutism
- Hyperpigmentation
- Hypokalemic alkalosis

Tumors causing ectopic ACTH syndrome **(Table 2)**.

Useful clinical hints to etiology of Cushing's syndrome:

- *Virilization*: Adrenal carcinoma
- *Sings of aldosterone excess (hypertension and hypokalemic alkalosis)*: Ectopic ACTH
- *Severe hyperpigmentation*: Ectopic ACTH

TABLE 2: List of tumors causing ectopic adrenocorticotropic hormone (ACTH) syndrome.

Location	Tumors	Percentage
Within thorax (65%)	Oat cell carcinoma	50%
	Thymic carcinoid	10%
	Bronchial carcinoid	5%
Within abdomen and pelvis (23%)	Pancreatic islet cell tumors	10%
	Pheochromocytoma	5%
	Ovarian tumor	2%
	Prostatic carcinoma	<2%
	Cervical carcinoma	<2%
	Gastric carcinoma	<2%
	Gallbladder carcinoma	<2%
Neck and head region (7%)	Medullary carcinoma of thyroid	5%
	Parathyroid carcinoma	<2%
	Parotid carcinoma	<2%
Uncertain location (5%)		

Diagnosis of Cushing's Syndrome

Diagnosis as well as treatment of Cushing's syndrome is still representing a challenge for endocrinologist. Correct interpretations of data of diagnostic tools involving other disciplines like imaging, neurosurgery, etc. in step-by-step fashion have made remarkable progress in this regards.

There are three steps of evaluation for and management (1) Step 1: To establish spontaneous hypercortisolemia, (2) Step 2: To establish ACTH dependency of hypercortisolemia—paired ACTH and cortisol test, and (3) Step 3: Imaging study (±biochemical study) to ascertain etiology for therapeutic action.

Step 1: To establish spontaneous hypercortisolemia:

- Indicated for all cases either with clinically suspected for Cushing's syndrome after exclusion of exogenous intake of steroid (by history) or for an incidentaloma of at adrenal/pituitary.
- Biochemical test(s) for hypercortisolemia examples:
  - *Urinary free cortisol (UFC)*: UFC is measured a value more than the upper limit of normal range is considered positive of Cushing's syndrome and there may be 20–25% false negative report. Most of pseudo-Cushing's syndrome cases can be excluded by this test. But, it is not effective in detection of adrenal insufficiency.
  - *Late-night salivary cortisol*: It is a sensitive diagnostic test for Cushing's syndrome. Elevated cortisol between 11:00 PM and midnight appears to have a sensitivity of 93–100%. Normal range of <3.0–4.0 nmol/L or 0.10–0.15 μg/dL. Normal levels exclude the diagnosis of Cushing's syndrome due to an ACTH-secreting tumor; but there may be false negative for some patients with Cushing's syndrome due to an adrenal tumor.
  - *Low dose overnight dexamethasone suppression test (LODST)*: 1 mg of dexamethasone is orally given at 11 PM and cortisol is measured from next morning at 9 AM sample of blood, a value >50 mg/dL is considered positive for Cushing's syndrome. 40 out of a series of 154 cases were detected as identified as Cushing's syndrome by using LODST in our institute BIRDEM **(Fig. 8)**.

Step 2: To establish ACTH dependency of hypercortisolemia.

A simple paired ACTH and cortisol test result can provide valuable information for next step (step 3) action(s)—(1) very low or undetectable ACTH (say <10 pg/mL) with hypercortisolemia lesion(s) at adrenals,

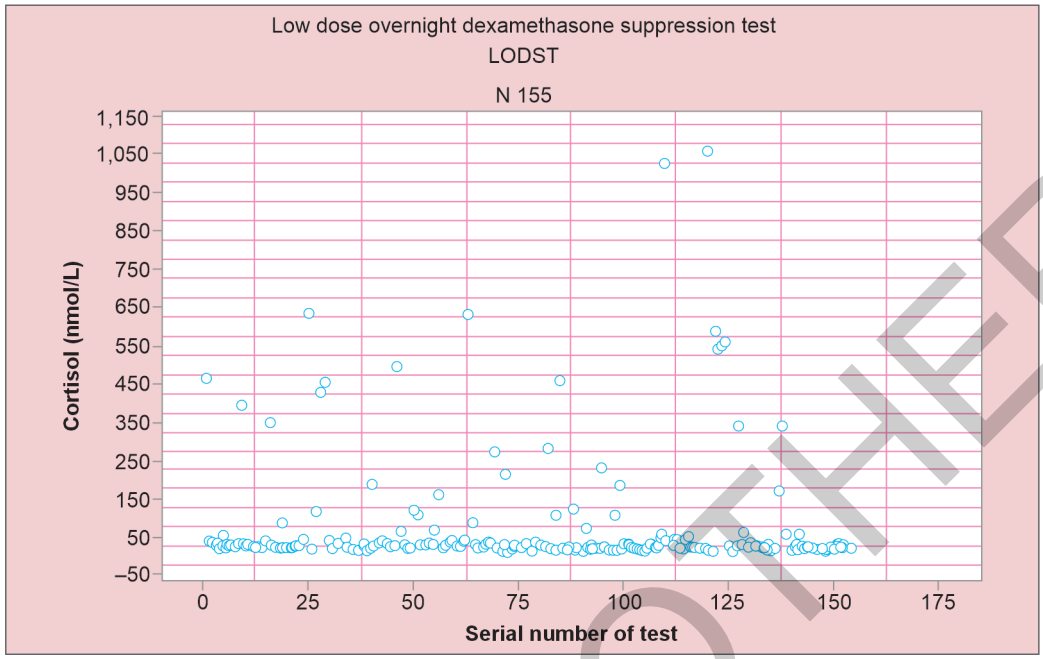


FIG. 8: 1 mg of dexamethasone is orally given at 11 PM and cortisol is measured from next morning at 9 AM sample of blood, a value >50 mg/dL is considered positive for Cushing's syndrome (CS). 40 out of a series of 154 cases were detected as identified as CS by using LODST in our institute BIRDEM.

Source: Ahmed T, Mahtab H, Tofail T, Morshed AHG, Rahman FB, Khan SA. Current status of low dose overnight dexamethasone supression test (LODST). J Obes Diabetes. 2020;4:5-8.

(2) very high ACTH (say >20 pg/mL) with hypercortisolemia lesion is likely to be ectopic ACTH syndrome, and (3) above normal or high normal ACTH (say 10–20 pg/mL) with hypercortisolemia lesion might be due to Cushing's disease (CD).

Step 3: Imaging study (+biochemical study) depending on paired ACTH and cortisol test result **(Figs. 9 to 11 and Flowchart 4)**.

- For ACTH independent cases of adrenal imaging
- Pituitary and adrenal imaging for ACTH-dependent cases
- Bilateral inferior petrosal sinus sampling combine ovine-sequence CRH stimulation test for cases of hypercortisolemia with microadenoma or negative image of pituitary region
- For cases with very high ACTH search for source of ectopic ACTH syndrome cases

Iodocholesterol scan can be used to:

- Differentiate between ACTH-dependent hypercortisolemia (bilateral high uptake—either for CD or ectopic ACTH syndrome) from ACTH-independent macronodular adrenal (unilateral adenoma/carcinoma) causing Cushing's syndrome
- Establish remnant hyperplasia after bilateral adrenalectomy
- Identify ectopic adrenal tissue

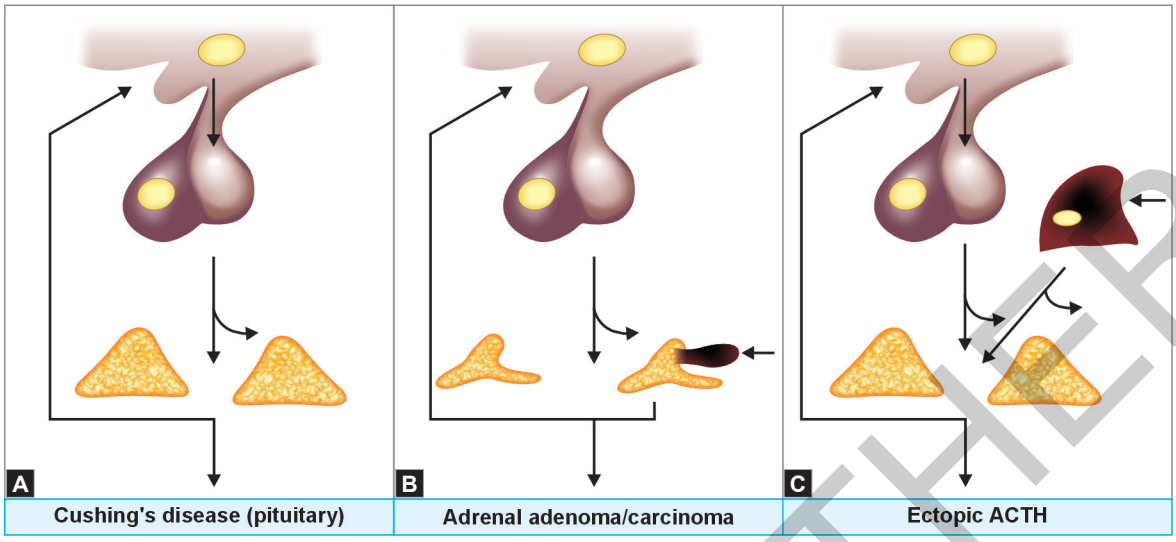
Treatment of Cushing's Syndrome

- *Surgeries for Cushing's syndrome are as follows*:
  - Unilateral adrenalectomy for unilateral adenoma or carcinoma
  - Bilateral adrenalectomy for bilateral macronodular hyperplasia, adenoma, or carcinoma
  - Surgery of primary tumor with metastasis if feasible in carcinoma.
- *Drug therapies for Cushing's syndrome are as follows*:
  - Use of mitotane, metyrapone, aminoglutethimide, trilostane, ketoconazole, or RU486 to control hypercortisolism.
  - Use of mitotane at very high dose (12 g/day) for carcinoma hypercortisolism; partial response is seen in 15–20% cases.
  - Use of Cytoxan, adriamycin, 5 Flurouracil, methotrexate (MTX), suramin, and gossypol as chemotherapy of carcinoma.

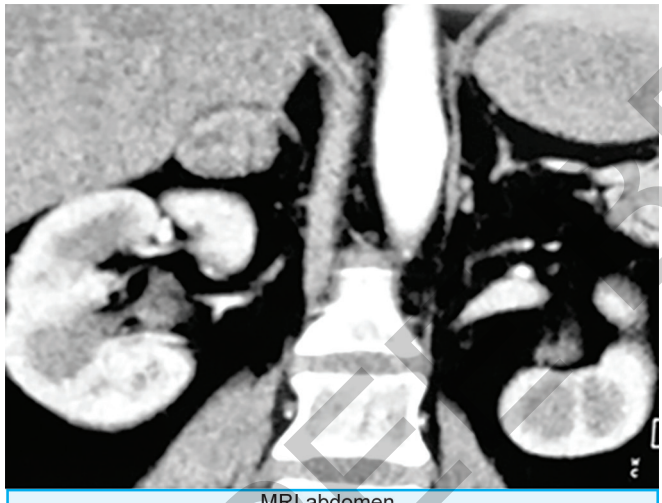
Treatment Options of Cushing's Disease

Treatment options are as follows:

- Transsphenoidal (microscopic or endoscopic) surgery or hemiphysectomy is the first line of treatment for CD by one school of thought. In events of failure resurgery or second-line options like radiotherapy (including Gamma Knife radiosurgery) or medical therapy or bilateral adrenalectomy can be tried.

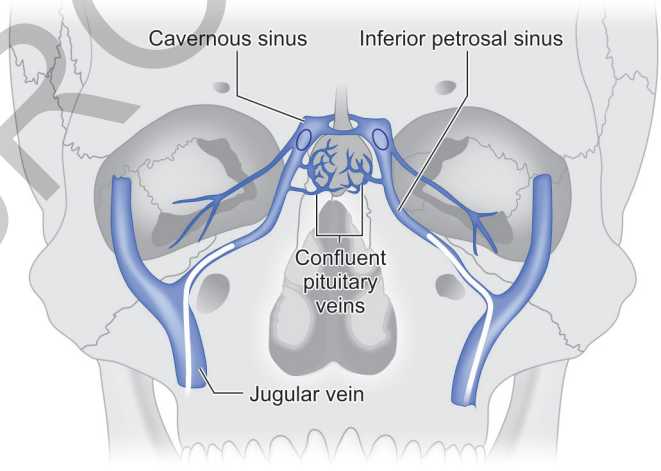


FIGS. 9A TO C: Different site of pathology in spontaneous hypercortisolemia.
(ACTH: adrenocorticotropic hormone)



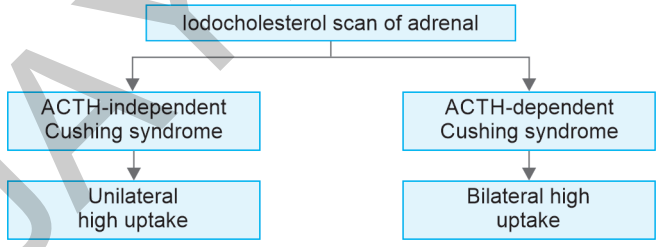
MRI abdomen
Unilateral (right) mass (adenoma)

FIG. 10: Magnetic resonance imaging (MRI) of adrenal adenoma.



Bilateral simultaneous inferior petrosal sinus sampling (BIPSS)

FIG. 11: BIPSS with corticotropin-releasing hormone (CRH) stimulation provides the "gold standard" in the differential diagnosis of Cushing's syndrome (CS). An IPS:P ratio ≥2.0 in basal samples conclusive of Cushing's disease (CD). And a peak IPS:P ratio ≥3.0 after CRH injection identified CD. In CD patients difference of ≥1.4-fold between concentrations in two sinuses ascertain location of microadenoma.



FLOWCHART 4: Iodocholesterol scan of adrenal— adrenocorticotropic hormone (ACTH)-dependent versus independent Cushing syndrome.

- Gamma Knife or stereotactic radiosurgery may become the future first line of treatment for CD.
- Pituitary external irradiation with mitotane. Total 5,000 rad in 100–200 rads fractions over 5–6 weeks (full effects may take years together). Mitotane is gradually tapered as irradiation takes effects.

- Medical therapy with ketoconazole (usual dose of 0.4–1.2 g/day), mitotane (usual dose of 1–4 g/day), metyrapone (usual dose of 1–4 g/day), aminoglutethimide (usual dose of 0.5–2 g/day), trilostane (usual dose of 0.2–1 g/day). Relapse is common after withdrawal of the drug.
- Bilateral adrenalectomy is in practice in case of nonavailability of other options or intolerance to medical therapy. But it requires lifelong steroid replacement therapy, risk to develop Nelson's syndrome in 10–15% of cases due to high ACTH level and may recur due to remnant hyperplasia.

Hyperaldosteronism

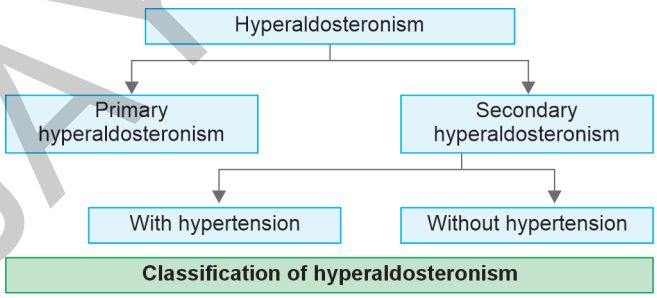
Hyperaldosteronism is characterized by salt retention, hypokalemia, and metabolic alkalosis with or without hypertension.

Hyperaldosteronism is initially classified as primary or secondary; the secondary hyperaldosteronism is further subclassified into secondary hyperaldosteronism with hypertension or secondary hyperaldosteronism without hypertension.

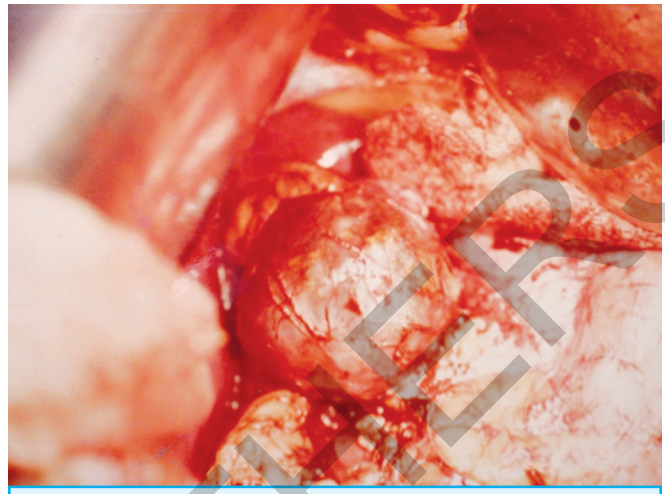
- Primary hyperaldosteronism
- *Secondary hyperaldosteronism*: (1) Secondary hyperaldosteronism with hypertension and (2) Secondary hyperaldosteronism without hypertension **(Flowchart 5)**.

Causes of hyperaldosteronism: (1) Primary hyperaldosteronism due to adrenal adenoma or carcinoma, bilateral nodular hyperplasia, and idiopathic hyperaldosteronism. (2) Secondary hyperaldosteronism with hypertension due to renovascular hypertension, accelerated hypertension, and renin-secreting tumor. (3) Secondary hyperaldosteronism without hypertension due to sodium wasting nephropathy, renal tubular acidosis (RTA), pseudohypoaldosteronism, Bartter's syndrome, and diuretic/laxative abuse **(Fig. 12)**.

Table 3 summarizes a list of hyperaldosteronism.



FLOWCHART 5: Hyperaldosteronism is initially classified as primary or secondary; the secondary hyperaldosteronism is further subclassified into two: with or without hypertension.



Hyperaldosteronism due to adrenal adenoma

FIG. 12: A large adenoma-secreting aldosterone.

TABLE 3: List of hyperaldosteronism.

Class/subclass	Causes
Primary hyperaldosteronism	• Adrenal adenoma or carcinoma • Bilateral nodular hyperplasia • Idiopathic hyperaldosteronism
Secondary hyperaldosteronism with hypertension	• Renovascular hypertension • Accelerated hypertension • Rennin-secreting tumor
Secondary hyperaldosteronism without hypertension	• Sodium wasting nephropathy • Renal tubular acidosis • Pseudohypoaldosteronism • Bartter's syndrome • Diuretic/laxative abuse

Primary Hyperaldosteronism

Clinical Presentation

- Patient seek medical attention for nonspecific complaints arise from hypokalemia:
  - Tiredness, loss of stamina, weakness, nocturia, and lassitude
  - Headache is a frequent incidental complaint.
- *When hypokalemia is severe with alkalosis*: Increased thirst, polyuria, and paresthesia may be present.
- Blood pressure ranges from borderline to severe hypertension:
  - Mean BP systolic 200 and diastolic 120 mm Hg
  - Malignant hypertension is rare (i.e., papilledema absent)
  - Clinical edema is also rare.
- Signs of subclinical tetany Trousseau's or Chvostek's sign may be present (indicating alkalosis).

Diagnosis of primary hyperaldosteronism made by documentation of hyperaldosteronism with suppressed plasma renin activity (PRA) and its cause is determined by localization of lesion by (1) CT scan, (2) adrenal venography, (3) I^{131} iodocholesterol scanning, or (4) aldosterone gradient by adrenal veins sampling with catheter **(Table 4)**.

Plasma Renin Activity Test

Plasma renin activity test estimate ability of renin to form angiotensin I from angiotensinogen in per unit of time (expressed as ng/mL/hour). Normal adult value is (0.5–4.0 ng/mL/hour with normal sodium intake and upright position). It is suppressed in (1) salt-retaining steroid therapy, (2) antidiuretic hormone (ADH) therapy, and (3) salt-sensitive essential hypertension—primary hyperaldosteronemia **(Fig. 13)**.

Decision-making investigation steps (DMIS) of primary hyperaldosteronism are shown in **Table 4**.

Treatment of Primary Hyperaldosteronism

- *For unilateral lesion*:
  Adrenalectomy: After preparing the patient with low sodium diet, potassium supplement and spironolactone. Spironolactone should be stopped a few days prior to surgery to avoid hyperkalemia. Cure rate is 50%, excellent reduction in hypertension in the rest.
- *For bilateral lesion (hyperplasia) or inoperable carcinoma*: Spironolactone and low sodium diet may control potassium wasting.

Plasma renin activity (PRA) assessment

FIG. 13: Plasma renin activity (PRA) test estimate ability of renin to form angiotensin I from angiotensinogen in per unit of time (expressed as ng/mL/hour). It is low (suppressed) in primary hyperaldosteronism but not in secondary hyperaldosteronism.

TABLE 4: Decision-making investigation steps of primary hyperaldosteronism.

Step	Investigation	Result	Action/inference
Initial step	Serum electrolyte to document hypokalemia	Hypokalemia	Go to step 4
		Normokalemia but sodium intake low	Go to step 2
		Normokalemia but on diuretic therapy	Go to step 3
Step 2	Patient is given 1 g of NaCl, i.e., 1/5 teaspoon table salt with each meal for 4 days. Then serum electrolyte is repeated on 5th day	Hypokalemia	Go to step 4
		No hypokalemia	Exclude
Step 3	Discontinue diuretics for 3 weeks and then serum electrolyte is repeated	Hypokalemia	Go to step 4
		No hypokalemia	Exclude
Step 4	Plasma renin activity (PRA) assessment	PRA suppressed	Go to step 5
		PRA not suppressed	Exclude
Step 5	Assessment of aldosterone production by 24-hour urinary aldosterone excretion and or plasma aldosterone level* (both tests are preferred if patient is on high salt diet)	High	Go to step 6
		Not high	Exclude
Step 6	*Localization of lesion by*: • CT scan • Adrenal venography • I^{131} iodocholesterol scanning • Aldosterone gradient by adrenal veins sampling with catheter	Localization—Yes	Go to step 7
		Localization—No	Follow-up
Step 7	Adrenalectomy for unilateral lesion or medical therapy for bilateral and inoperable carcinomas		

*Normal excretion of aldosterone range 5–20 mg/24 hours and normal plasma aldosterone <10 mg/L. 10–20 for hyperplasia and >20 for adenoma or carcinoma.

Secondary Hyperaldosteronism

In secondary hyperaldosteronism, aldosterone hypersecretion is due to high renin production. So, it differs from primary hyperaldosteronism by absence of PRA suppression.

It has two forms:

1. Secondary hyperaldosteronism with hypertension caused by (i) renovascular hypertension, (ii) accelerated hypertension, and (iii) rennin-secreting tumor.
2. Secondary hyperaldosteronism without hypertension due to (i) sodium wasting nephropathy, (ii) RTA, (iii) pseudohypoaldosteronism, (4) Bartter's syndrome, and (5) diuretic/laxative abuse.

Comparison of biochemical events between primary and secondary hyperaldosteronism is shown in **Table 5**.

Renal Tubular Acidosis

Inability of the kidneys to excrete acids from the blood results in high acids levels in blood resulting acidosis called renal tubular acidosis (RTA).

There are many types of RTA. Of them, three are common/main types, namely type 1, 2, and 4 RTAs.

Type 1 RTA is due to defect at distal part of the renal tubules; type 2 RTA is due to defect at proximal part of the renal tubules cause; and type 4 RTA occurs when the tubules are unable to excrete enough potassium and as well as acid from the blood, its other name is hyperkalemic RTA.

Type 3 RTA was previously described as a rare type of RTA and now it is considered as a combination of type 1 and type 2 RTA.

Type 1 RTA is associated with autoimmune diseases such as Sjögren's syndrome and lupus. Other diseases and conditions related to type 1 RTA include (1) renal medullary cystic disease, (2) sickle cell anemia, (3) a hereditary form of deafness, (4) Ehlers–Danlos syndrome, and (5) recurrent urinary tract infections. Children with type 1 RTA grow more slowly. Adults with type 1 RTA develop progressive kidney disease and bone diseases. Both adults and children with type 1 RTA may develop renal stones formation.

Type 2 RTA is associated with Fanconi syndrome and viral hepatitis. In adults, with multiple myeloma, exposure to toxins—acute lead poisoning or chronic exposure to cadmium or certain drugs to treat human immunodeficiency virus (HIV), viral hepatitis, glaucoma, migraines, and seizures. Other diseases and conditions related to type 2 RTA include (1) cystinosis, (2) hereditary fructose intolerance, and (3) Wilson disease. Children with untreated type 2 RTA may grow slowly and remain short. There may be rickets and dental disease in both children and adults.

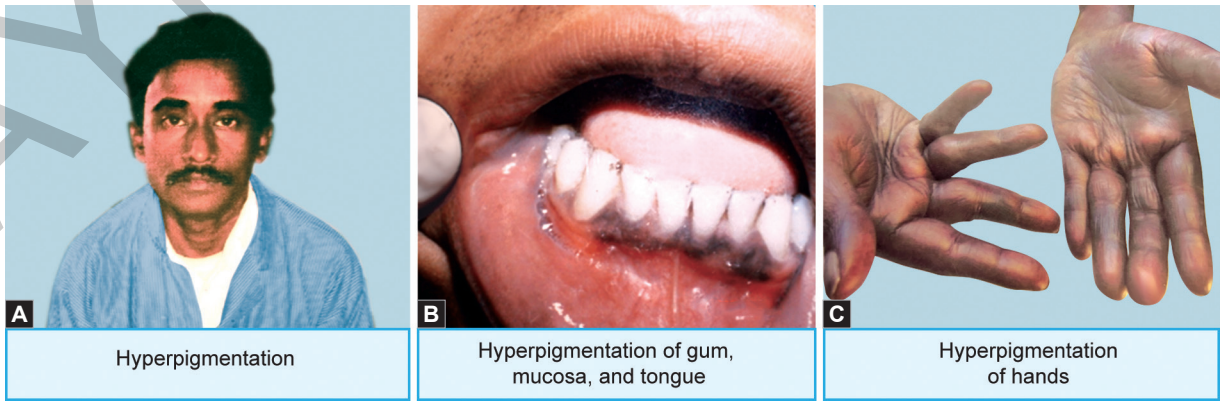
Type 4 RTA is associated with the renal transplant rejection. Due to hyperkalemia, people with type 4 RTA can have muscle weakness, heart disease, such as slow or irregular heartbeats and cardiac arrest **(Figs. 14A to C)**.

TABLE 5: Biochemical events primary versus secondary hyperaldosteronism.

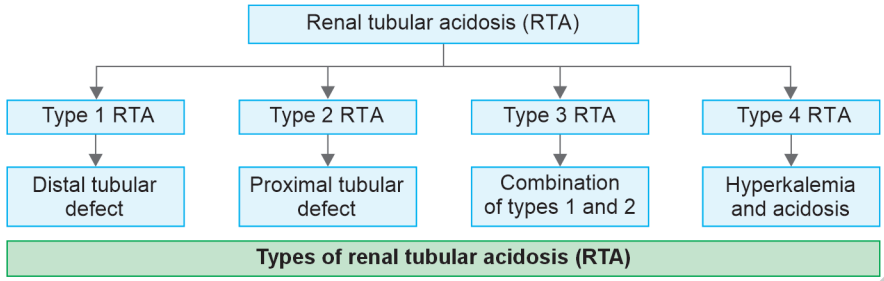
Primary hyperaldosteronism	Secondary hyperaldosteronism
High aldosterone	High renin
High sodium retention	High angiotensinogen II
High potassium loss	High aldosterone
Low renin	High sodium retention
Low angiotensinogen II	High potassium loss

Treatment of RTA

- This is called alkali therapy. Drinking a solution of sodium bicarbonate or sodium citrate is given to all types of RTA to lower the acid level in blood. It can prevent kidney stones formation.



FIGS. 14A TO C: Hyperpigmentation in chronic adrenal insufficiency.



FLOWCHART 6: Three main types of RTA are type 1, 2 and 4. And type 3 is a mixed presentation of type 1 and 2.

- Infants with type 1 RTA usually require potassium supplements. The older children and adults rarely need potassium supplement because alkali therapy prevents potassium loss into the urine.
- Alkali therapy usually keeps normal growth if initiated in childhood in type 2 RTA.
- To prevent bone problems, some adults with type 2 RTA will need vitamin D supplements.
- People with type 4 RTA usually need medicines to reduce hyperkalemia **(Flowchart 6)**.

Bartter Syndrome and Gitelman Syndrome

- These are two autosomal recessive disorders resulting in defects of renal tubular excretion and reabsorption of electrolytes.
- They are characterized by (1) salt wasting, (2) hypokalemia, and (3) metabolic alkalosis.
- The Bartter syndrome phenotype is the result of impaired sodium/chloride reabsorption in the thick ascending limb (TAL).
- The Gitelman syndrome phenotype is the result of impaired sodium/chloride reabsorption in the distal convoluted tubule (DCT).
- Common symptoms can include episodes of fatigue, muscle weakness, and muscle cramps. Sometimes, they are accompanied with gastrointestinal problems, such as abdominal pain, nausea, and vomiting and sometimes with polyuria.
- The biochemical differences are children with Bartter syndrome commonly demonstrate hypercalciuria with normal serum magnesium levels. And with Gitelman syndrome typically show low urinary calcium excretion and low serum magnesium levels.

Treatment

- Bartter syndrome is treated by:
  - Dietary measure like eating foods rich in potassium or taking potassium supplements
  - Some people also need salt and magnesium supplements
  - High doses of nonsteroidal anti-inflammatory drugs (NSAIDs) can also be used.
- Still there is no definite treatment for Gitelman syndrome. The mainstay of treatment for affected individuals is:
  - Diet with high in salt
  - Potassium-rich foods such as dried fruit
  - Magnesium supplements should be avoided because it can produce diarrhea.

Adrenal (Adrenocortical) Insufficiency

Deficiency of adrenal cortical secretion either only glucocorticoid or both glucocorticoid and mineralocorticoid produces signs and symptoms called *adrenal insufficiency syndrome*.

Adrenal insufficiency is of two types:

1. Primary adrenocortical insufficiency or high ACTH adrenal failure
2. Secondary adrenocortical insufficiency or low ACTH adrenal failure

Causes:

- Causes of primary adrenocortical insufficiency are shown in **Box 1**.
- Causes of secondary adrenocortical insufficiency are shown in **Table 6**.

BOX 1: Cause list of primary adrenocortical insufficiency.

- Addison's disease caused by autoimmunity (?Idiopathic), tuberculosis, or other (miscellaneous) causes
- Postsurgical—bilateral adrenalectomy
- Vascular as in hemorrhage [Waterhouse–Friderichsen syndrome (WFS)], sepsis, anticoagulant therapy, etc.
- Infective as in thrombosis, embolism, and vasculitis
- Fungal infection as in histoplasmosis, coccidioidomycosis, etc.
- Drugs as ketoconazole, aminoglutethimide, metyrapone, mitotane, etc.
- Others, such as hemochromatosis, acquired immunodeficiency syndrome (AIDS), metastasis, amyloidosis, sarcoidosis, and congenital adrenal hyperplasia

TABLE 6: Cause list of secondary adrenocortical insufficiency.

Pituitary lesions	Chromophobe adenoma
	Hypophysectomy
	Sheehan's syndrome
Hypothalamic lesions	Encephalitis
	Basal meningitis
	Craniopharingioma
	Trauma
	Tumor of third ventricle
	Chronic corticosteroid use
	Optic glioma
	Stalk section

TABLE 7: Features of chronic adrenal insufficiency.

Symptoms	Signs	Common biochemical features
Undue weakness (fatigue)	Weight loss	Hyponatremia
Anorexia	Growth retardation (children)	Hyperkalemia
Nausea and diarrhea	Hyperpigmentation (skin, oral cavity, and dorsum of tongue)	Hypercalciuria
Muscle and joint pain	• Hypotension • Postural dizziness • Adrenal calcification (tuberculosis) • Vitiligo (auto-immune)	Elevated plasma renin activity

Clinical Presentation of Primary Adrenocortical Insufficiency

There are three types of clinical presentation of adrenocortical insufficiency:

1. Chronic adrenocortical insufficiency
2. Acute adrenocortical insufficiency/adrenal crisis
3. Acute on chronic adrenocortical insufficiency

Chronic Presentation of Primary Adrenocortical Insufficiency

Symptoms include undue weakness (fatigue), anorexia, nausea, diarrhea, muscle, and joint pain.

Signs include weight loss, growth retardation (in children), hyperpigmentation (skin, oral mucosa, and dorsum of tongue), hypotension, postural dizziness, adrenal calcification (tuberculosis), and vitiligo (autoimmune).

Biochemical features include hyponatremia, hyperkalemia, hypercalciuria **(Fig. 14 and Table 7)**.

Diagnosis of chronic primary adrenocortical insufficiency

By documentation of plasma ACTH level elevated and ACTH is unable to stimulate serum cortisol more than the upper limit of normal range of morning sample.

- *Step 1*: To establish ACTH level elevated and cortisol low
  - *Test*: Paired cortisol and ACTH assay for all suspected cases.
  - *Result*: If ACTH level is elevated but cortisol is low, follow step 2.
- *Step 2*: To establish deficient cortisol secretary reserve
  - *Test*: Rapid ACTH stimulation test
  - *Result*: If cortisol level does not reach targets step 3
- *Step 3*: Initiate treatment
  - Look for etiology by imaging (for tuberculosis)/genetic study
  - Biochemical study for electrolytes

Paired cortisol and ACTH assay:

- *Indication*: For all suspected cases of primary adrenal insufficiency
- *Procedure*: This can be done in blood sample of any time; in cases with high clinical score an elevated ACTH plus very low/undetectable cortisol confirms the diagnosis. The reference ranges of ACTH and cortisol used are those for 9 AM sample.

Rapid ACTH stimulation test:

- *Indication*: For suspected cases of primary adrenal insufficiency, and paired ACTH and cortisol ACTH is high and cortisol is low or low normal.
- *Procedure*: IV or IM of 250 µg of ACTH is given and serum cortisol is measure at 0 minute, 30 minutes, and 60 minutes. If values are <550 nmol/L than this is a case of primary adrenal insufficiency.

Treatment of Primary Adrenocortical Insufficiency (Table 8)

There are three different component of treatment of adrenal insufficiency patients.

Secondary Adrenocortical Insufficiency

Clinical presentation of secondary adrenocortical insufficiency is shown in **Table 9**.

Workup to differentiate between primary and secondary adrenocortical insufficiency is shown in **Table 10**.

TABLE 8: Replacement/maintenance therapy.

Glucocorticoid replacement (adult)	• Hydrocorticosterone 20–30 mg/day orally • Prednisolone 5–7.5 mg/day orally • Cortisone 25–35 mg/day orally
Glucocorticoid replacement (children)	Cortisone acetate or hydrocorticosterone phosphate 12–15 mg/m^2/day orally is preferred
	This is given in two divided doses in ratio of 2:1, one in the morning and at 4–5 PM respectively
Mineralocorticoid replacement	Fludrocortisone (9α-fludrocortisones) 50–300 µg/day orally if serum sodium is not maintained
Therapy during stress	
During minor stress	Dose of glucocorticoid is doubled in nausea, vomiting, fever >100°F, and minor surgery
During major stress (including major surgery)	Dose of glucocorticoid can be given as high as 10 times in oral, IM or IV routes. Mineralocorticoid replacement is not required at that time
Patient's education	
Identification and education	Education is mandatory. Every patient should have medical alert bracelets/steroid card and emergency kit

TABLE 9: Clinical presentation of secondary adrenocortical insufficiency.

Symptoms	Signs	Common biochemical features
Similar to that of primary adrenocortical insufficiency	Similar to that of primary adrenocortical insufficiency *Except*: • No hyperpigmentation • No vitiligo • No adrenal calcification	Similar to that of primary adrenocortical insufficiency *Except*: • No hyperkalemia
And	And	And
Headache and/or other central nervous system (CNS) symptoms (according to cause)	Other CNS signs (according to cause)	Other CNS findings (according to cause)

TABLE 10: Primary versus secondary adrenocortical insufficiency.

Test/tool	Procedure	Conclusions
Long ACTH stimulation test	1 mg of depot-ACTH$^{1\text{-}24}$ is given IM and plasma cortisol is measured at 1, 4, 8, and 24 hours after injection	Any value >550 nmol/L excludes primary adrenal insufficiency
Plasma ACTH measurement	Plasma ACTH is measured at basal state	• ACTH >250 pmol/mL is conclusive of primary adrenal insufficiency • A normal/low value is compatible with secondary adrenal insufficiency
oCRH stimulation test	1 µg/kg of body weight oCRH is given IV and plasma ACTH and cortisol is measured at 0, 30, 60, 90, and 120 minutes after injection	• Mark ACTH raise but no response to cortisol is conclusive of primary adrenal insufficiency • No ACTH raise and no or minimal response to cortisol is compatible of secondary adrenal insufficiency

(ACTH: adrenocorticotropic hormone; oCRH: ovine-corticotropin-releasing hormone)

Acute Adrenal Insufficiency or Adrenal Crisis

It is a medical emergency which can be either a de novo presentation of new case or acute deterioration in a known chronic adrenal insufficiency person.

The ominous sign of adrenal crisis is hypotension and circulatory collapse. Other features will be features of adrenal insufficiency (primary/secondary) and features of precipitating factors (stress factors or sudden stoppage of steroid).

Diagnosis and treatment of adrenal crisis

- Treatment should be start without waiting for diagnostic confirmation.
- If suspected collect blood for a paired ACTH and cortisol or rapid ACTH stimulation test and start treatment.

ABC of treatment of adrenal crisis is as follows **(Table 11)**:

A. Intravenous fluid to correct volume depletion, dehydration, and hypoglycemia.
B. *Glucocorticoid therapy*:
   - Hydrocortisone phosphate 100 mg IV stat and 6 hourly
   - Reduce the dose to 50 mg IV 6 hourly, if the patient becomes stable.
C. Identify the precipitating factor(s) and treat accordingly.

Congenital Adrenal Hyperplasia

Definition: Congenital adrenal hyperplasia is a family of autosomal recessive disorder of adrenal steroid production caused by deficient or defective enzyme action for cortisol biosynthesis.

Low cortisol production of CAH results in increase production of ACTH secretion. Excess ACTH stimulation results in hyperplasia of adrenal cortex. So, why the name is CAH?

TABLE 11: ABC of treatment of adrenal crisis.

A.	Fluid therapy	Intravenous fluid (DNS/NS) to correct volume depletion, dehydration, and hypoglycemia
B.	Glucocorticoid therapy	• Hydrocortisone phosphate 100 mg IV stat and 6 hourly (classically there will be marked improvement within 4 hours of first steroid injection) • Reduce the dose to 50 mg IV 6 hourly, if the patient becomes stable
C.	Precipitating factor(s)	Identify the precipitating factor(s) and treat accordingly

(DNS: dextrose normal saline; NS: normal saline)

Clinical Presentation

Its clinical presentation varies widely. It depends on the steroid profile changed by the defective enzyme.

The triad of clinical picture is as (1) deficiency of glucocorticoids, (2) imbalance of mineralocorticoids, and (3) excess androgens as shown in **Flowchart 7**.

Classification or type of CAH (on the basis of enzyme involved) is given in **Table 12**.

21-hydroxylase Deficiency Syndrome

The steroid synthesis defects are described in **Figures 15 and 16** and clinical features in **Table 13**.

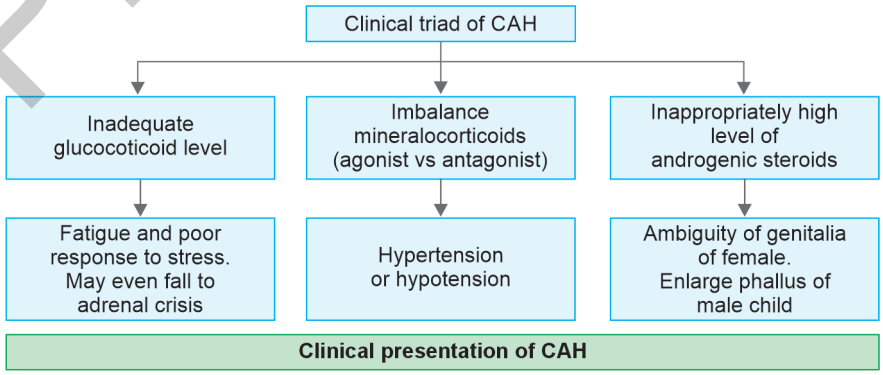
There are three different clinical presentations of 21-hydroxylase deficiency **(Table 13)**.

11β-hydroxylase Deficiency Syndrome

The steroid synthesis defects are described in **Figure 17** and clinical features in **Table 14**.

TABLE 12: Classification of congenital adrenal hyperplasia (CAH).

Clinical class	Enzyme	Type
Simple non-salt wasting CAH	21-hydroxylase deficiency	Type I CAH
Severe classic salt wasting CAH	21-hydroxylase deficiency	Type II CAH
Mild nonclassic (late onset) CAH	21-hydroxylase deficiency	
	11β-hydroxylase deficiency	Type III CAH
	3β-hydroxylase deficiency	Type IV CAH
	17α-hydroxylase deficiency	Type V CAH
Lipoid adrenal hyperplasia	Cholesterol desmolase deficiency	Type VI CAH



FLOWCHART 7: Clinical presentation of congenital adrenal hyperplasia (CAH) depends on degree of alteration in three types of steroid production.

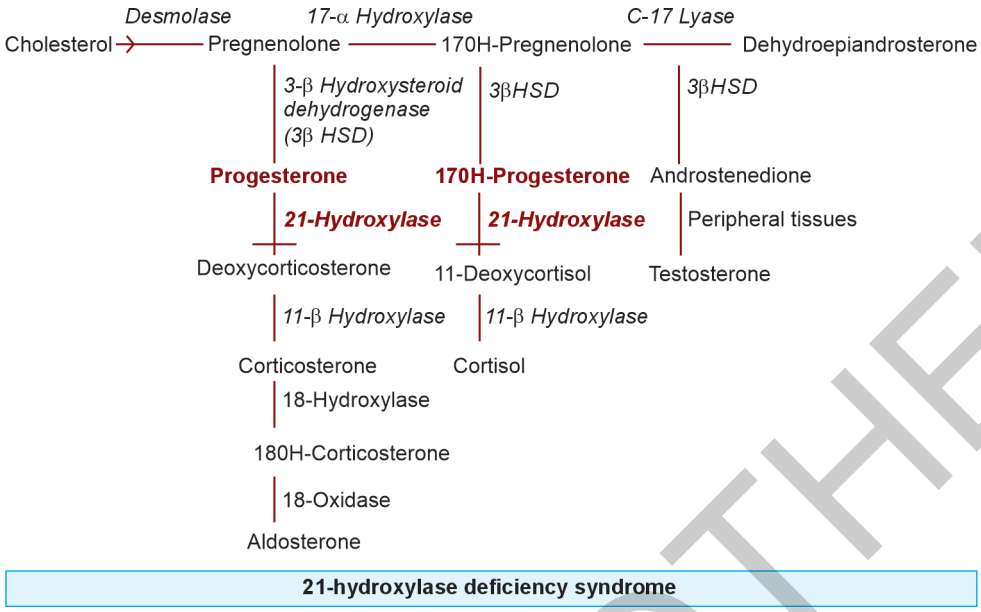


FIG. 15: 21-hydroxylase deficiency leads to deficiency of cortisol and aldosterone and excess androgens. Three clinical presentations (1) Simple non-salt wasting congenital adrenal hyperplasia (CAH) (type I); (2) Severe classic salt wasting CAH (type II), and (3) Mild nonclassic (late onset) CAH.

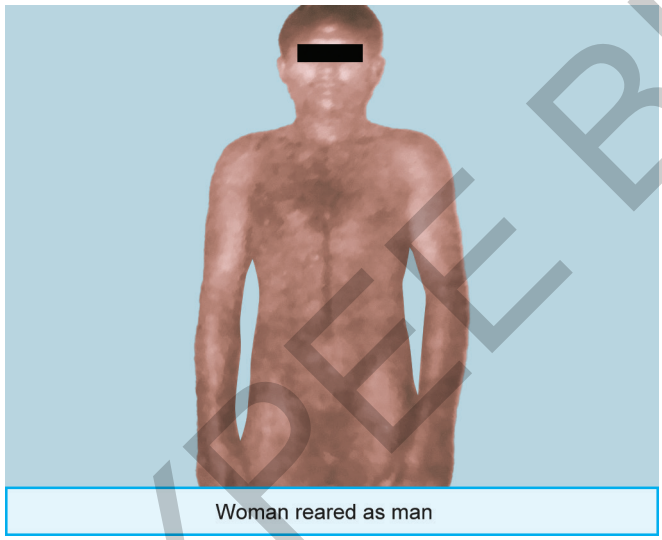


FIG. 16: An untreated adult female.

3β-hydroxysteroid Dehydrogenase Deficiency Syndrome

The steroid synthesis defects are described in **Figure 18** and clinical features in **Table 15**.

17α-hydroxylase/17,20-lyase Deficiency Syndrome

The steroid synthesis defects are described in **Figure 19** and clinical features in **Table 16**.

Cholesterol Desmolase Deficiency Syndrome

The steroid synthesis defects are described in **Figure 20** and clinical features in **Table 17**.

Treatment of CAH

Treatment of the virilizing CAHs involves hormone replacement therapy with glucocorticoids. The goal of treatment is suppression of excessive ACTH and adrenal androgen secretion without hypercortisolism. **Table 18** summarizes the treatment of CAH.

PHEOCHROMOCYTOMA

Pheochromocytoma is a catecholamine-producing tumor that typically produces labile hypertension and paroxysmal symptoms.

Common presentations are:

- *Sustained hypertension* difficult to control with usual drug and dose.
- *Hypertensive crisis*

TABLE 13: Types of 21-hydroxylase deficiency syndrome [salt losing congenital adrenal hyperplasia (CAH)].

Features	Simple non-salt wasting CAH (type I CAH)	Severe classic salt wasting CAH (type II CAH)	Mild nonclassic (late onset) CAH
Clinical features	• Ambiguous genitalia in female infants • Large erectile penis in male infants • Accelerated growth in childhood • Cliteromegaly with or without labial fusion (Prader type I or II) in female baby • Precocious puberty in male baby • Short final height due to early bone maturation	• Severe fluid and electrolyte loss due to diarrhea and vomiting within first week of life • Exaggerated features of simple non-salt wasting CAH • Features due adrenal insufficiency are dark complexion, postural hypotension, and poor tolerance to stress • Fond of taking large amount of table salt	• At birth normal external genitalia • Mild feature of androgen access around puberty, such as hirsutism in girls and oligospermia in boys • Symptom varies from asymptomatic to frank cases • Biochemical features are comparable with symptom score
Biochemical features	Serum 17-hydroxyprogesterone (17-OHP) high at basal and post-ACTH stimulation will be high	Serum 17-OHP high at basal and post-ACTH stimulation will be high	Serum 17-OHP high at basal and post-ACTH stimulation will be high
Neonatal screening	Hill prick blood spotted on filter paper on days 3–5 of life for high 17-OHP level.		

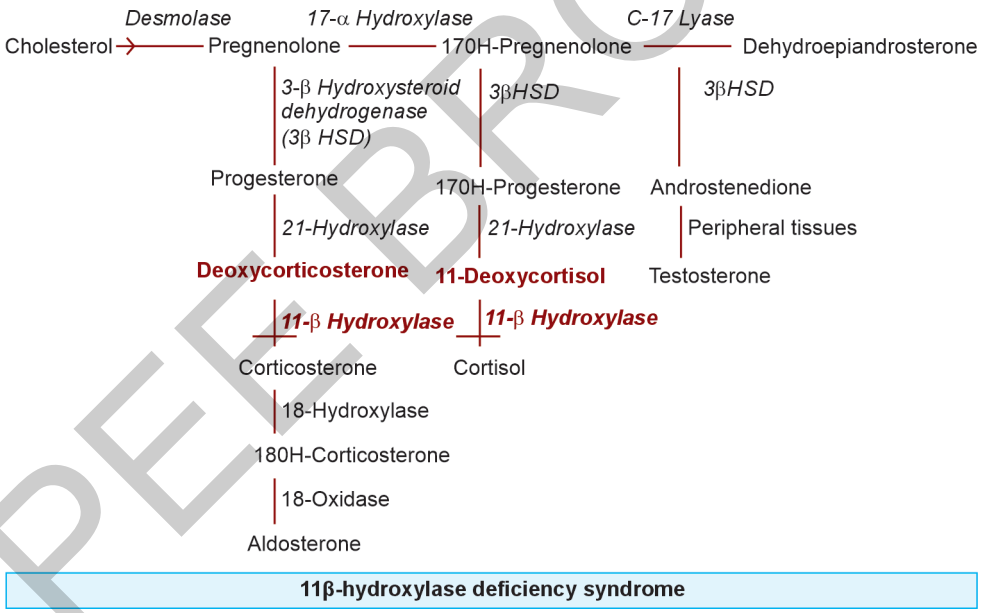
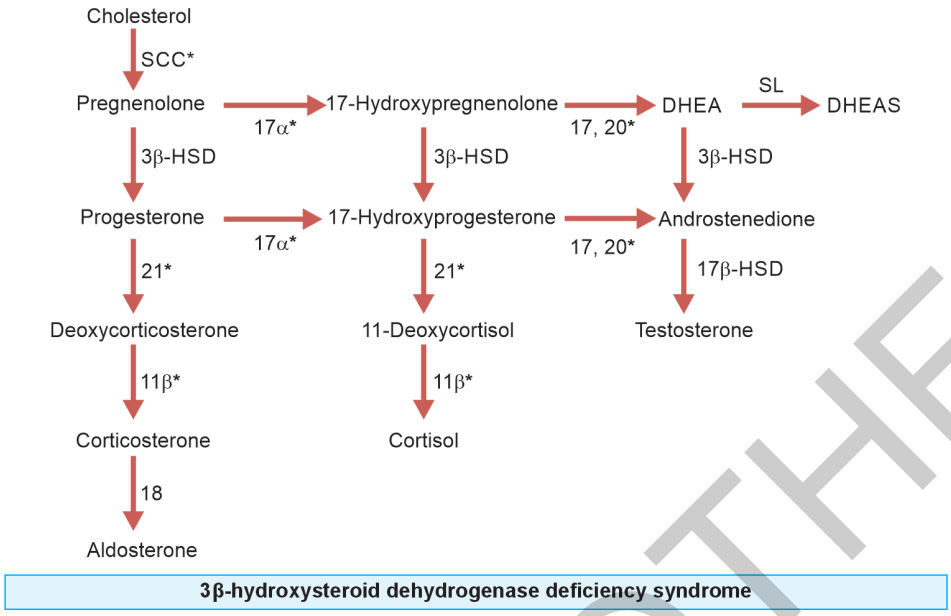


FIG. 17: 11β-hydroxylase deficiency leads to deficiency of cortisol and aldosterone and excess androgens. Two clinical presentations (1) classical congenital adrenal hyperplasia (CAH) (type III); (2) late onset/cryptic variant CAH.

TABLE 14: 11β-hydroxylase deficiency syndrome (hypertensive CAH) (type III CAH).

Clinical features	Biochemical features	Late onset/cryptic variant
• Severe hypertension • Sings of moderate virilization (cliteromagaly) in girls and precocious puberty in boys	• Low potassium, low plasma rennin activity, and there may be high sodium • Mineralocorticoid [desoxycorticosterone acetate (DOCA)] high • Androgens high	Present with hirsutism and primary amenorrhea in girls



*Hydroxylase

FIG. 18: 3β-hydroxysteroid dehydrogenase deficiency (3β-HSD) leads to deficiency of cortisol, aldosterone, and testosterone but excess dehydroepiandrosterone (DHEA). Two clinical presentations (1) classical congenital adrenal hyperplasia (CAH) (type IV); (2) late onset/non-classical form.

TABLE 15: 3β-hydroxysteroid dehydrogenase deficiency syndrome (type IV CAH).

Clinical features	Biochemical features	Late onset/nonclassical form
• Sings of androgens deficiency incomplete masculinization with hypospadias in boys but excess dehydroepiandrosterone (DHEA) clitoromegaly, and labial fusion in girls • Severe fluid and electrolyte loss due in infancy due to low aldosterone and cortisol • Frequent adrenal crisis	• Low adrenal and gonadal steroids • High DHEA	• Female present with hirsutism • Male with some degree of hypospadias

- Sign and symptoms of aortic dissection and myocardial infarction
- Paroxysmal episodes, suggestive of catecholamine release, their severity and clinical presentations are variable and generally include:
  - Frontal or occipital severe headache
  - Excessive sweating, palpitation, and apprehension for impending death along with chest and abdominal pain, nausea, and vomiting

The paroxysm last from few minutes to several hours, most episodes subside within 10 minutes.

Identification and Treatment

Such cases are important because of following characters:
- The hypertension is curable.
- The hypertensive paroxysms are sometimes lethal.
- The tumor itself may be malignant.
- Such cases can be a component of familial multiple endocrine neoplasia (MEN II and MEN III).

Findings suggestive of pheochromocytoma:
- *Clinical findings*:
  - Paroxysmal nature of attacks
  - Signs of adrenergic activity (1) tachycardia and (2) excessive sweating
  - Signs of hypermetabolism (1) raised body temperature and (2) weight loss
  - Orthostatic hypotension
  - Anxiety neurosis
  - Neurocutaneous manifestations (1) café-au-lait spots (>6), (2) neuromas of neurofibromas, (3) retinoblastoma, and (4) vertebral abnormalities.
- *Laboratory findings*:
  - Glucose intolerance
  - High hematocrit
- Family history of pheochromocytoma
- *Associated diseases*:
  - Hyperthyroidism
  - Medullary carcinoma of thyroid

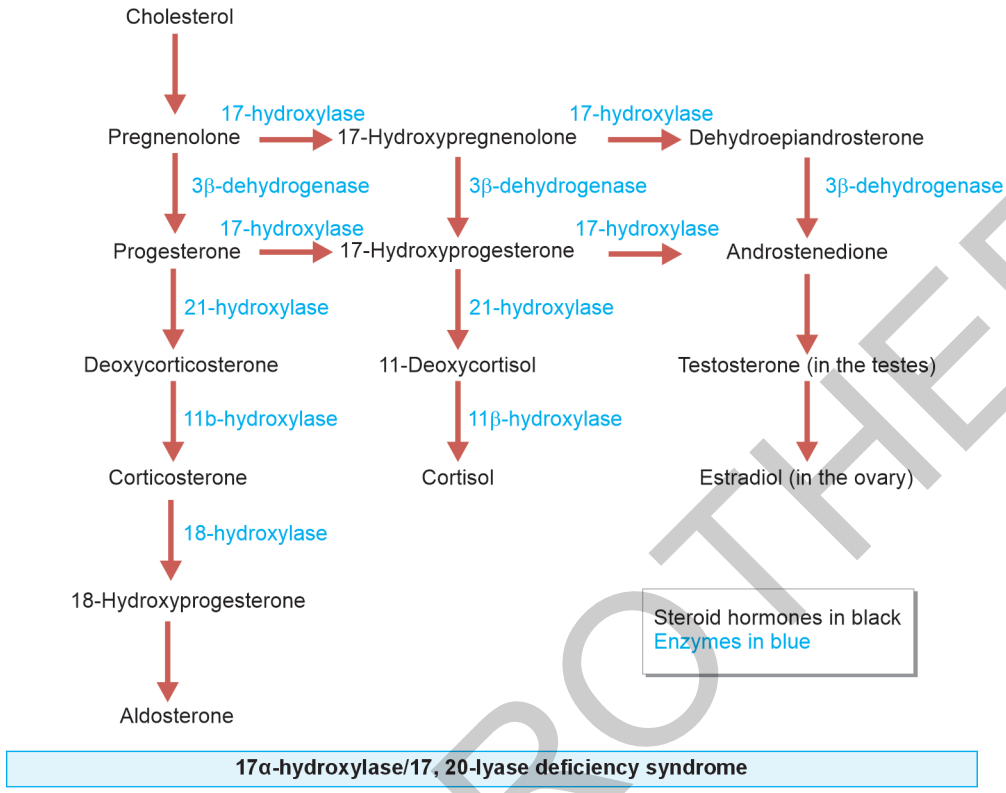


FIG. 19: 17α-hydroxylase/17,20-lyase deficiency syndrome leads to deficiency of gonadal steroids. One clinical presentation—congenital adrenal hyperplasia (CAH) type V.

TABLE 16: 17α -hydroxylase/17,20-lyase deficiency syndrome (type V CAH).

Clinical features	Biochemical features	Late onset/nonclassical form
• At birth both boy and girl are with female phenotype • At puberty primary gonadal failure with enlarge breast and primary amenorrhea • Minimum or no adrenal crisis • Hypertension	• Low potassium, plasma rennin activity, and aldosterone • High FSH and LH	Absent

(CAH: congenital adrenal hyperplasia; FSH: follicle-stimulating hormone; LH: luteinizing hormone)

- Islet cell tumor
- Neurofibromatosis

Diagnosis of Pheochromocytoma

There are two steps:

- *Step 1*: Biochemical confirmation of suspected case
- *Step 2*: Anatomical localization

Biochemical Confirmation of Suspected Case

- It is traditionally done by 24 hours urinary catecholamine by high-pressure liquid chromatography (HPLC).
- Substances are (1) dopamine (DA), (2) norepinephrine (NE), and (3) epinephrine.
- Metabolite measurement of 24 hours urinary vanillylmandelic acid (VMA) or total metanephrines is dine in most laboratories. Specific measurements of catecholamines are superior. In >90% cases of pheochromocytomas, catecholamines are more than twice of their upper limit of normal range. Most of the time, urinary catecholamine (especially norepinephrine) is elevated but occasionally they are normal if sampled when the person is normotensive or asymptomatic. Therefore, sample should be collected during a paroxysm.

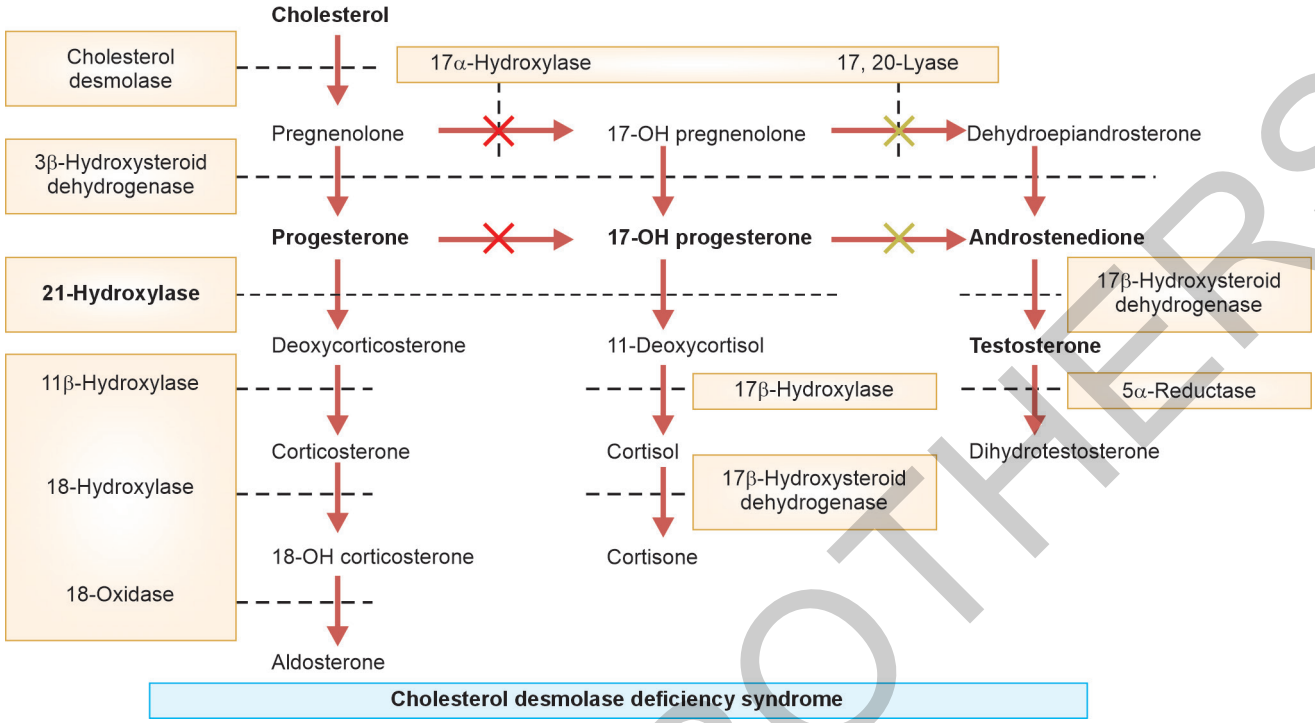


FIG. 20: Cholesterol desmolase deficiency syndrome leads to absolute deficiency of adrenal steroids. Phenotype female at birth. Usually die from adrenal crisis within first week of life (CAH type VI).

TABLE 17: Cholesterol desmolase deficiency syndrome (type VI CAH).

Clinical features	Biochemical features	Late onset/nonclassical form
• Serious disorder • All steroid synthesis is blocked • Phenotype female at birth • Usually die from adrenal crisis within first week of life • With early recognition and treatment, they can survive	Absence of all type of steroid hormone in blood	Absent

TABLE 18: Treatment of CAH.

Principle of treatment	Glucocorticoid	Mineralocorticoid
• In all forms of CAH glucocorticoid replacement with or without mineralocorticoid • It corrects all the metabolic disturbances, i.e., lower ACTH and androgens to normal; remission of hypertension, virilization, etc. improves	• In children, hydrocortisone is drug of choice (10–15 mg/day) • In adult, prednisolone or dexamethasone can be used. Dose is equivalent to 20 mg of hydrocortisone, i.e., 0.75 mg of dexamethasone or 7.5 mg of prednisolone in two divided doses in 2:1 ratio	Synthetic steroid 9α-fluorocortisone is used in salt wasting cases. Usual dose of 0.05–0.1 mg/day

(ACTH: adrenocorticotropic hormone; CAH: congenital adrenal hyperplasia)

Provocative Test

Pharmacological agents for provocation of attack, such as histamine, glucagon, or tyramine are not in use for their potential danger.

Adrenolytic (Phentolamine) Test

Intravenous bolus of phentolamine (up to 5 mg) is administered in a suspected individual after getting a stable blood pressure record. A fall in blood pressure start

in 2–3 minutes and last approximately 10 minutes. The test is considered positive if fall in systolic is >35 mm Hg and >25 mm Hg in diastolic.

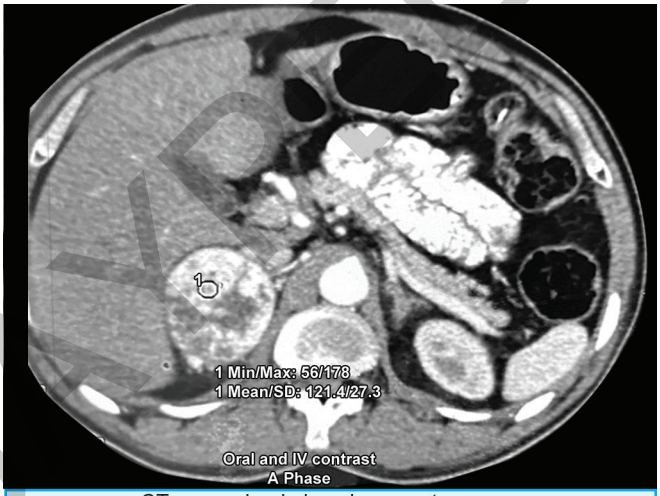
Anatomical Localization

Location of pheochromocytoma:

- Adrenal (90% is in adrenal medulla; 80% solitary, and 10% bilateral—most are having positive family history)
- Extra-adrenal (10%):
  - Cervical (2%)
  - Thoracic (10–20%)
  - Intra-abdominal (70–80%):
    - Upper abdominal (40%)
    - Organ of Zuckerkandl (30%)
    - Bladder (15%)

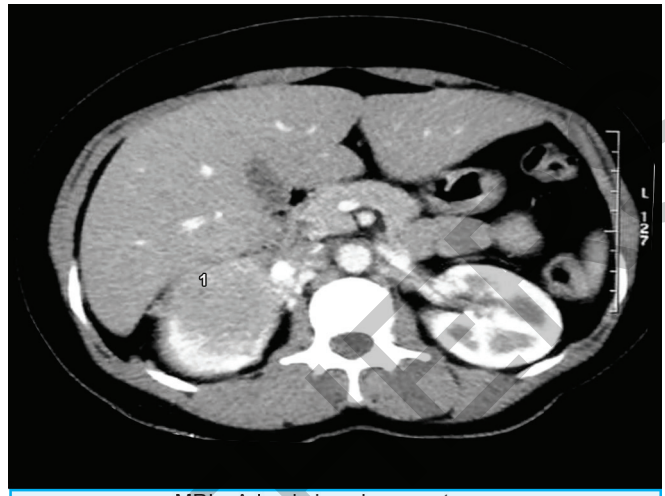
Localization procedures:

- *CT scan*: An adrenal pheochromocytoma with a diameter of >3 cm can be readily visualized with CT **(Fig. 21)**.
- It appears as a homogenous mass with a density >10 HU units on an unenhanced film and with contrast density is enhanced. Sometime hemorrhagic foci are see within the mass.
- *MRI*: Typical appearance of a pheochromocytoma in T1 image is slightly hypointense to the rest of the adrenal gland. But in T2 image, some are markedly hyperintense which called lightbulb sign **(Fig. 22)**.
- Iodobenzylguanidine scintigraphy (when CT/MRI fails to localize).
- Arteriography is also used in some specialized centers.



CT scan adreal pheochromocytoma
(right side)

FIG. 21: A 50-year man with a fairly large dense mass showing enhancement after contrast and heterogenecity.



MRI—Adreal pheochromocytoma
(right side)

FIG. 22: A 26-year-old lady having hypodense mass in right adrenal in T2 image; some are markedly hyperintense, i.e., positive lightbulb sign.

Treatment of Pheochromocytoma

Surgical Excision

Preoperative treatment of hypertension with adequate dose of α-adrenergic antagonist (phenoxybenzamine) for adequate time to expand the contracted vascular volume.

Persistent hypertension in postoperative state may be due to:

- Missed pheochromocytoma
- Adrenomedullary hyperplasia
- Renal artery ligation
- Essential hypertension

All patients should undergo clinical as well as biochemical evaluation at least after 1 month of surgery.

ADRENAL INCIDENTALOMA

Adrenal incidentaloma is defined as a clinically unapparent adrenal lesion (≥1 cm in diameter) that is detected on imaging performed for indications other than adrenal disease evaluation. This definition excludes patients who are undergoing screening and surveillance because of hereditary syndromes or those with known extra-adrenal cancer who are undergoing imaging for staging or during follow-up after treatment. They are now identified more frequently than before because of widespread use of thoracic and abdominal imaging. All of them demand evaluation for hormonal activity and potentiality for malignancy.

Adrenal incidentaloma detected on imaging study may or may not be hormonally functional. A functional

one may producing (1) cortisol (Cushing's syndrome), (2) aldosterone (primary hyperaldosteronism), or (3) pheochromocytoma. Large lesions (size >4 cm) are likely to be a malignant lesion.

Management of such a lesion requires to follow a six-step process:

1. Clinical evaluation for specific hormone excess
2. Biochemical screening study
3. Study of imaging features
4. Fine needle aspiration (FNAC) and/or surgery for cytological or histological study
5. Specific treatment
6. Follow-up of benign incidentaloma

Clinical evaluation of:

- Look for primary hyperaldosteronism in cases with resistant hypertension and hypokalemia (without papilledema and edema)
- Look for pheochromocytoma in episodic/sustain hypertension
- Look for Cushing's syndrome in cases with cushingoid features, glucose intolerance, hypertension, etc.

Biochemical screening study:

- For pheochromocytoma, either with plasma or urinary catecholamine measurements
- If negative in biochemical testing for pheochromocytoma, then for all patients should undergo biochemical testing for Cushing's syndrome and/or primary hyperaldosteronism.

Study of imaging features: A CT scan should be used to determine precontrast density, contrast washout along with its size and margins.

- A precontrast density is >10 HU; washout <50% are considered as a useful diagnostic information for suspecting malignant potentiality.
- Lesions with larger size (>4 cm) and/or irregular margin have more chance of malignancy.

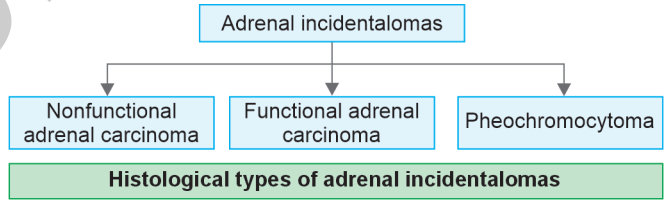
Fine needle aspiration and/or surgery for cytological or histological study: For lesions with larger size (>4 cm) and/or irregular margin have more chance of malignancy **(Flowchart 8)**.

Treatment depending on functional status and histology of the lesion:

- For hormonally active adrenal incidentalomas are according to the surgical removal protocol of the disease/syndrome.
- For malignant adrenal incidentalomas are according to the oncology protocol.
- For hormonally inactive and nonmalignant adrenal incidentalomas follow-up protocol.

Follow-up:

- For masses that likely to be benign (<10 HU; washout >50%), small (<3 cm), and nonfunctioning, imaging, and biochemical reevaluation (pheochromocytoma and hypercortisolism only) can be advised to repeat after 1–2 year or more.
- For other indeterminate lesions, repeat evaluation for growth after 3–12 months is useful, and subsequent testing intervals will be based on the rate of growth.



FLOWCHART 8: Histological types of adrenal incidentalomas fine needle aspiration (FNAC) material may of three types.

FURTHER READINGS

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Tofail Ahmed MBBS DEM PhD is a professor of endocrinology. He is retired from BIRDEM General Hospital in 2017. Now he is serving as the CEO of Distance Learning Program, Diabetic Association of Bangladesh, which provide six months' certificate course on diabetology both in online and offline mode throughout Bangladesh since 2003. He is a founder member of Bangladesh Endocrine Society and served as the President of American Association of Clinical Endocrinology (AACE), Bangladesh Chapter (2017 to 2019) and General Secretory of South Asian Federation of Endocrine Societies (SAFES) from 2015 to 2017.

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