

Adrenal Disorders

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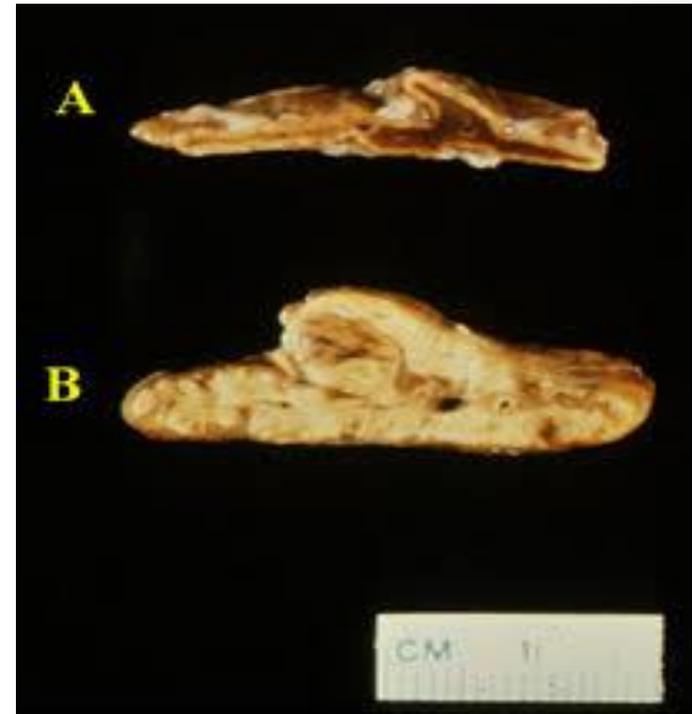
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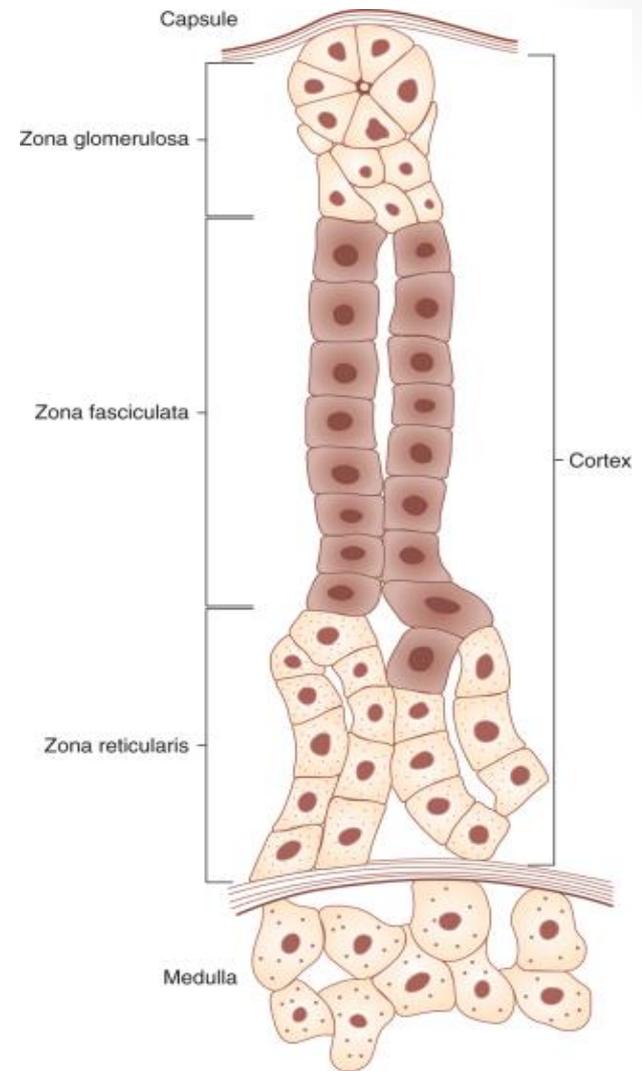
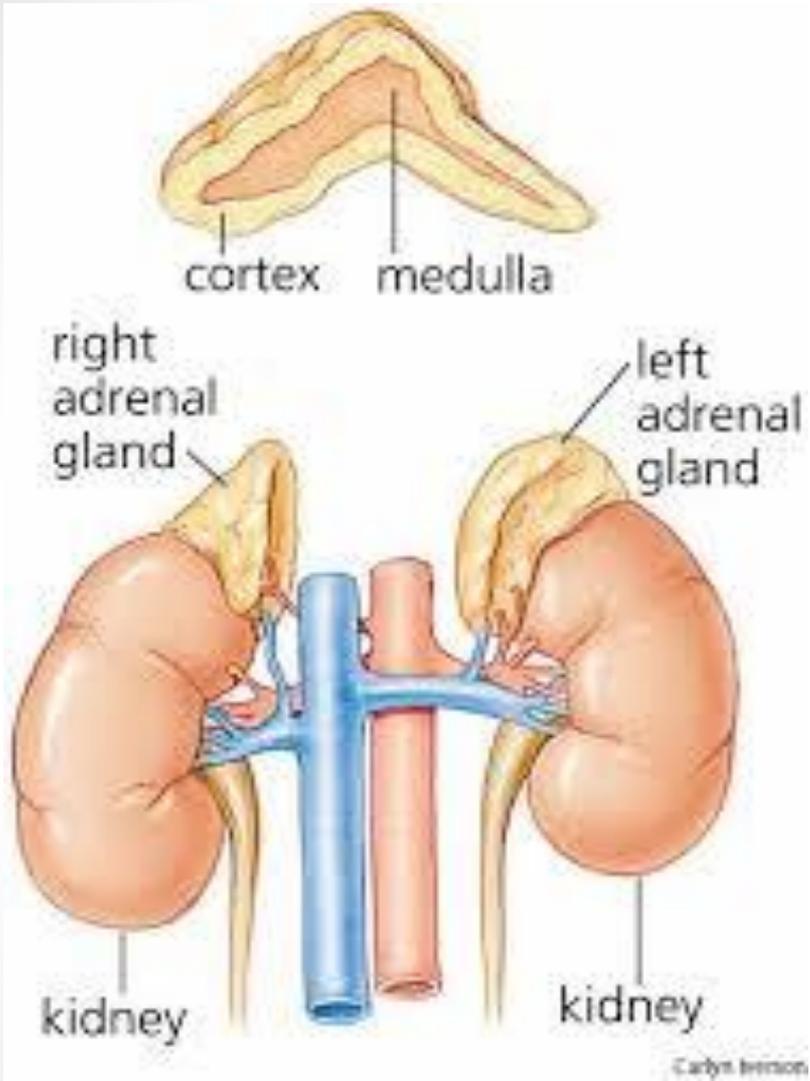
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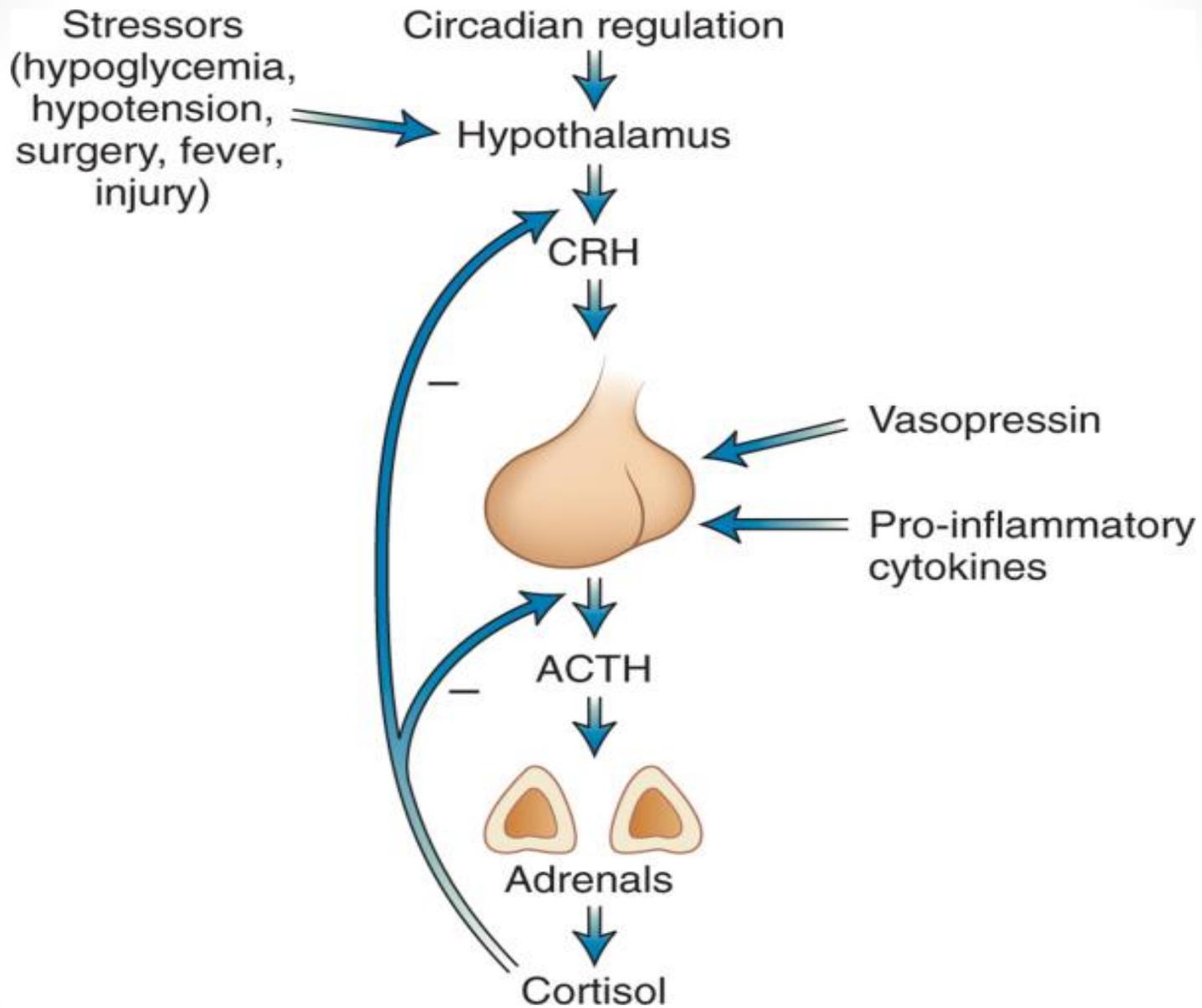
Introduction

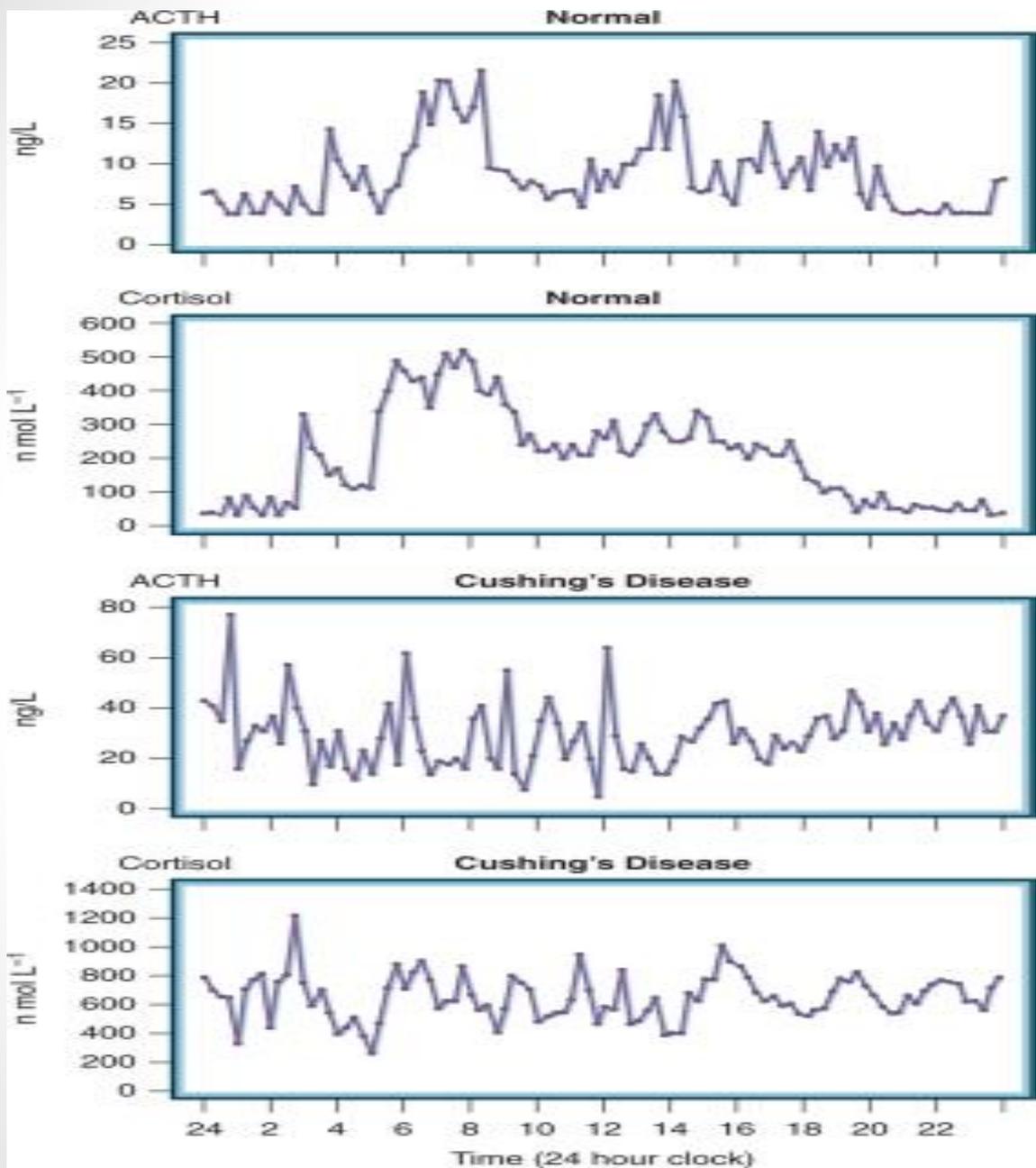
- The adult adrenal gland is a pyramidal structure.
- Approximately 4 g in weight.
- 2 cm wide, 5 cm long, and 1 cm thick.
- Lying immediately above the kidney on its posteromedial surface.



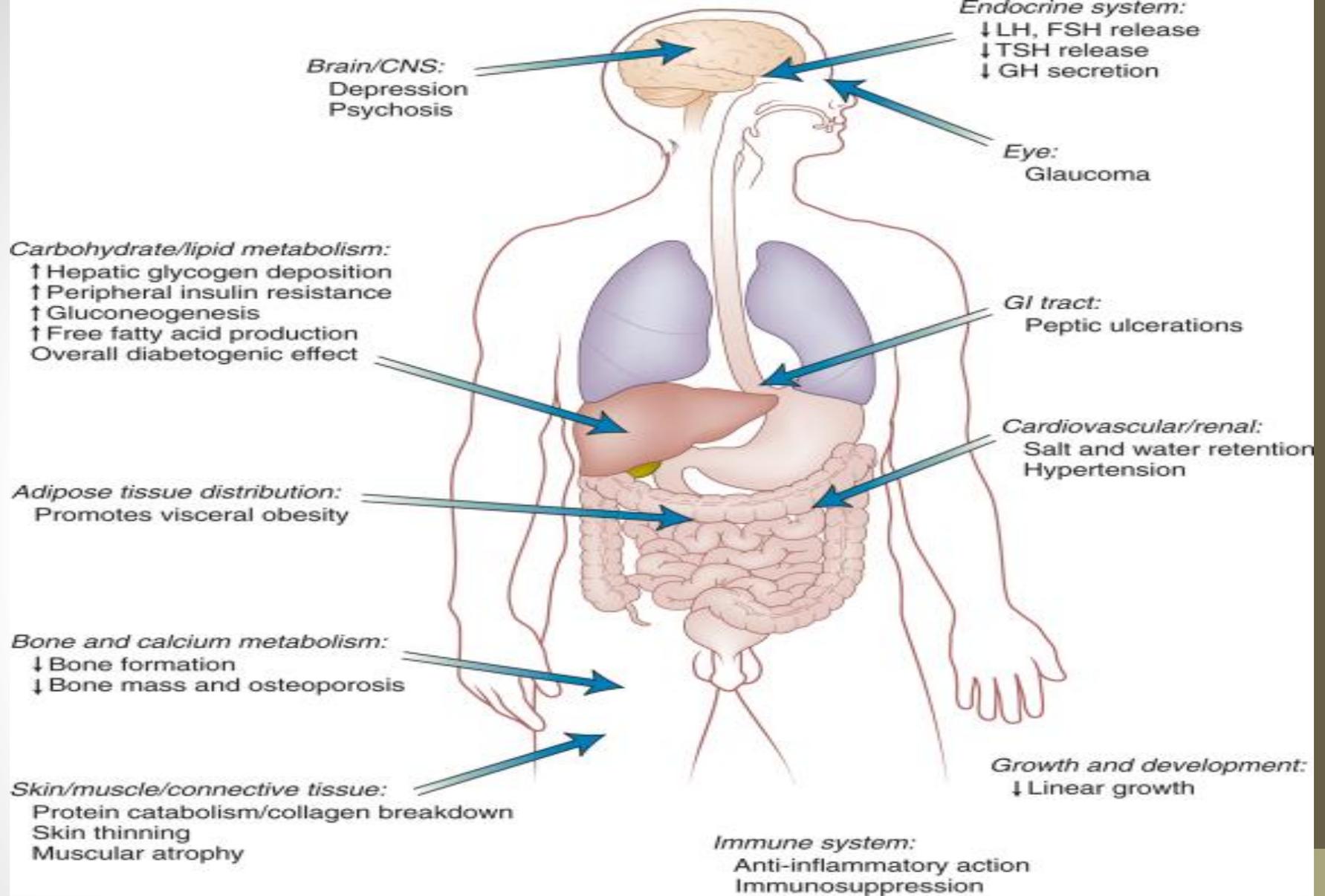
specimens consist of cut sections of a normal adrenal gland (upper) and an adrenal gland in which the cortex (yellow) is hyperplastic.







Circadian and pulsatile secretion of adrenocorticotrophic hormone (ACTH) and cortisol in a normal subject (*top two panels*) and in a patient with Cushing's disease. In a normal subject, secretion of ACTH and cortisol is highest in early morning and falls to a nadir at midnight. ACTH pulse frequency and pulse amplitude are increased in Cushing's disease, and circadian rhythm secretion is lost.



The principal sites of action of glucocorticoids in humans highlighting some of the consequences of glucocorticoid excess

Therapeutic use of corticosteroids

- **Endocrine:** Replacement therapy (Addison's disease, pituitary disease, congenital adrenal hyperplasia), Grave's ophthalmopathy
- **Skin:** Dermatitis, pemphigus
- **Hematology:** Leukemia, lymphoma, hemolytic anemia, idiopathic thrombocytopenic purpura
- **Gastrointestinal:** Inflammatory bowel disease (ulcerative colitis, Crohn's disease)
- **Liver:** Chronic active hepatitis, transplantation, organ rejection
- **Renal:** Nephrotic syndrome, vasculitides, transplantation, rejection
- **Central nervous system:** Cerebral edema, raised intracranial pressure
- **Respiratory:** Angioedema, anaphylaxis, asthma, sarcoidosis, tuberculosis, obstructive airway disease
- **Rheumatology:** Systemic lupus erythematosus, polyarteritis, temporal arteritis, rheumatoid arthritis
- **Muscle:** polymyalgia rheumatica, myasthenia gravis

RELATIVE BIOLOGIC POTENCIES OF SYNTHETIC STEROIDS IN BIOASSAY SYSTEMS

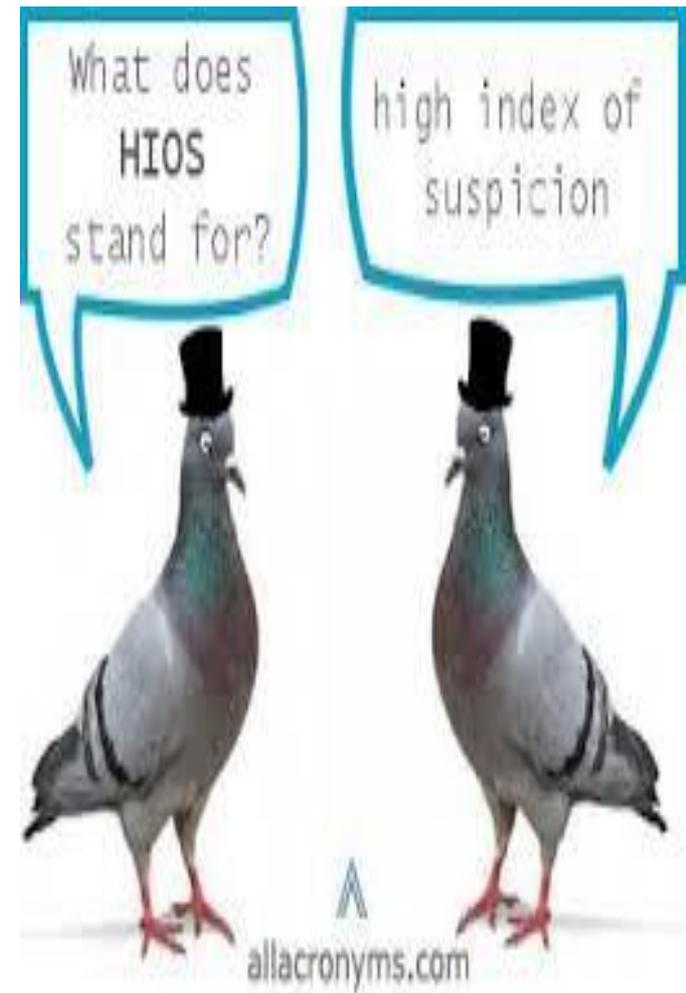
Steroid	Anti-inflammatory Action	Hypothalamic- Pituitary-Adrenal Suppression	Salt Retention
Cortisol	1	1	1
Prednisolone	3	4	0.75
Methylprednisolone	6.2	4	0.5
Fludrocortisone	12	12	125
Fludrocortisone	14		225
Triamcinolone	5	4	0
Dexamethasone	26	17	0

Adrenocortical diseases

- **Glucocorticoid Excess**
 - Cushing's syndrome
 - Pseudo-Cushing's syndromes
- **Glucocorticoid Resistance**
- **Glucocorticoid Deficiency**
 - Primary hypoadrenalism
 - Secondary hypoadrenalism
 - Post-chronic corticosteroid replacement therapy
- **Congenital Adrenal Hyperplasia**
 - 21-Hydroxylase, 3 β -hydroxysteroid dehydrogenase, 17 α -hydroxylase, 11 β -hydroxylase, and StAR deficiencies
 - **Mineralocorticoid Excess**
 - **Mineralocorticoid Deficiency**
 - Defects in aldosterone synthesis
 - Defects in aldosterone action
 - Hyporeninemic hypoaldosteronism
 - **Adrenal Incidentalomas, Adenomas, and Carcinomas**

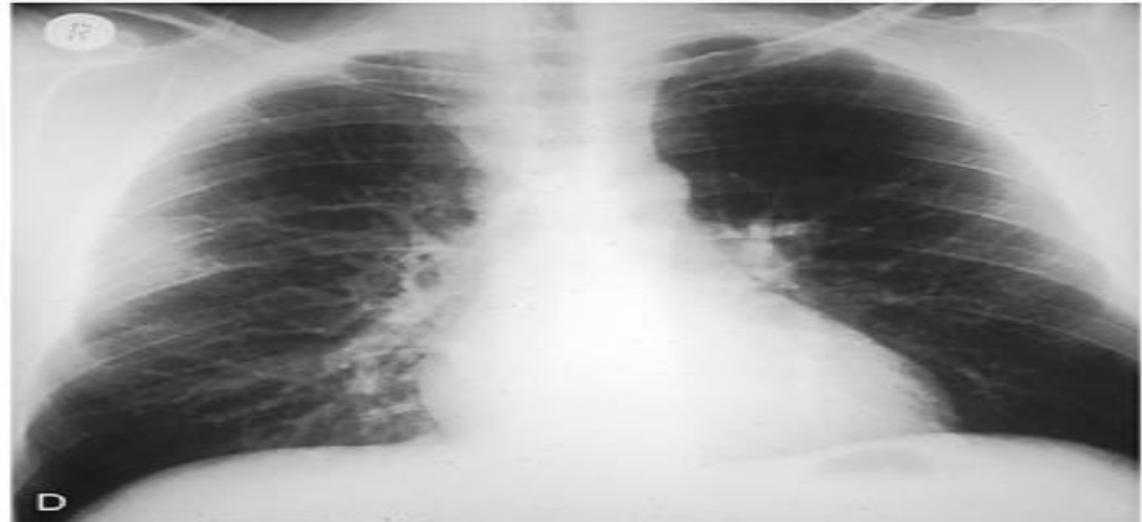
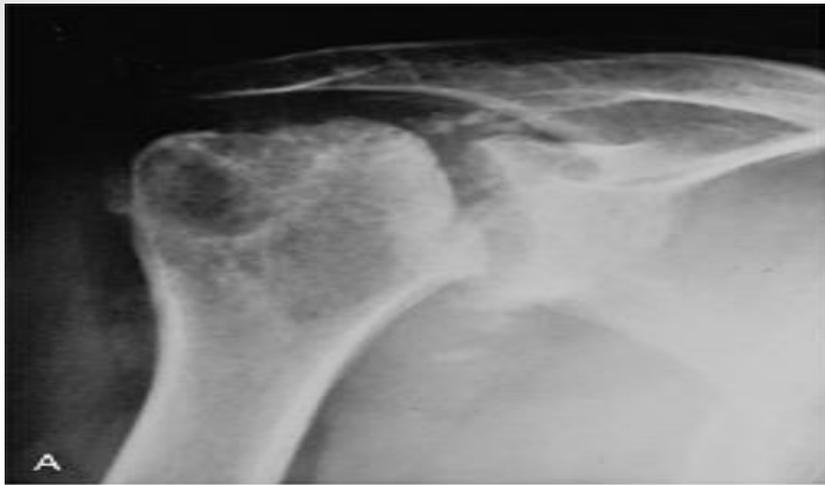
Cushing's Syndrome

- The classic features of Cushing's syndrome of centripetal obesity, moon face, hirsutism, and plethora are well known. However, this gross clinical picture is not always present and a high index of suspicion is required in many cases.





A, Centripetal and some generalized obesity and dorsal kyphosis in a 30-year-old woman with Cushing's disease. **B**, Same woman as in **A**, showing moon facies, **plethora**, hirsutism, and enlarged supraclavicular fat pads. **C**, Facial rounding, hirsutism, and acne in a 14-year-old girl with Cushing's disease. **D**, Central and generalized obesity and moon facies in a 14-year-old boy with Cushing's disease. **E** and **F**, Typical centripetal obesity with **livid abdominal striae** seen in a 41-year-old woman (**E**) and a 40-year-old man (**F**) with Cushing's syndrome. **G**, Striae in a 24-year-old patient with congenital adrenal hyperplasia treated with excessive doses of dexamethasone as "replacement" therapy. **H**, **Typical bruising** and thin skin of Cushing's syndrome. In this case, the bruising has occurred without obvious injury.



Bone abnormalities in Cushing's disease. **A**, Aseptic necrosis of the right humeral head of a 43-year-old woman with Cushing's disease of about 8 months' duration. **B**, Aseptic necrosis of the right femoral head in a 24-year-old woman with Cushing's disease of about 4½ years' duration. The *arrows* indicate the crescent subchondral radiolucency, best seen in this lateral view. **C**, Diffuse osteoporosis, vertebral collapse, and subchondral sclerosis in the patient whose shoulder is shown in **A**. **D**, Rib fracture in a 38-year-old man with Cushing's disease.

CLASSIFICATION OF CAUSES OF CUSHING'S SYNDROME

- **ACTH dependent:**
 1. Cushing's disease (pituitary dependent)
 2. Ectopic ACTH syndrome
 3. Ectopic CRH syndrome
 4. Macronodular adrenal hyperplasia



- **ACTH independent:**

1. Adrenal adenoma and carcinoma
2. Primary pigmented nodular adrenal hyperplasia and Carney's syndrome.
3. Iatrogenic (e.g., pharmacologic doses of prednisolone, dexamethasone)



- **Pseudo-cushing's syndrome:**

1. Depression
2. Obesity
3. Physical stress
4. Malnutrition
5. Eating disorders
6. PCOS
7. Uncontrolled diabetes
8. Obstructive sleep apnea
9. Chronic alcoholism



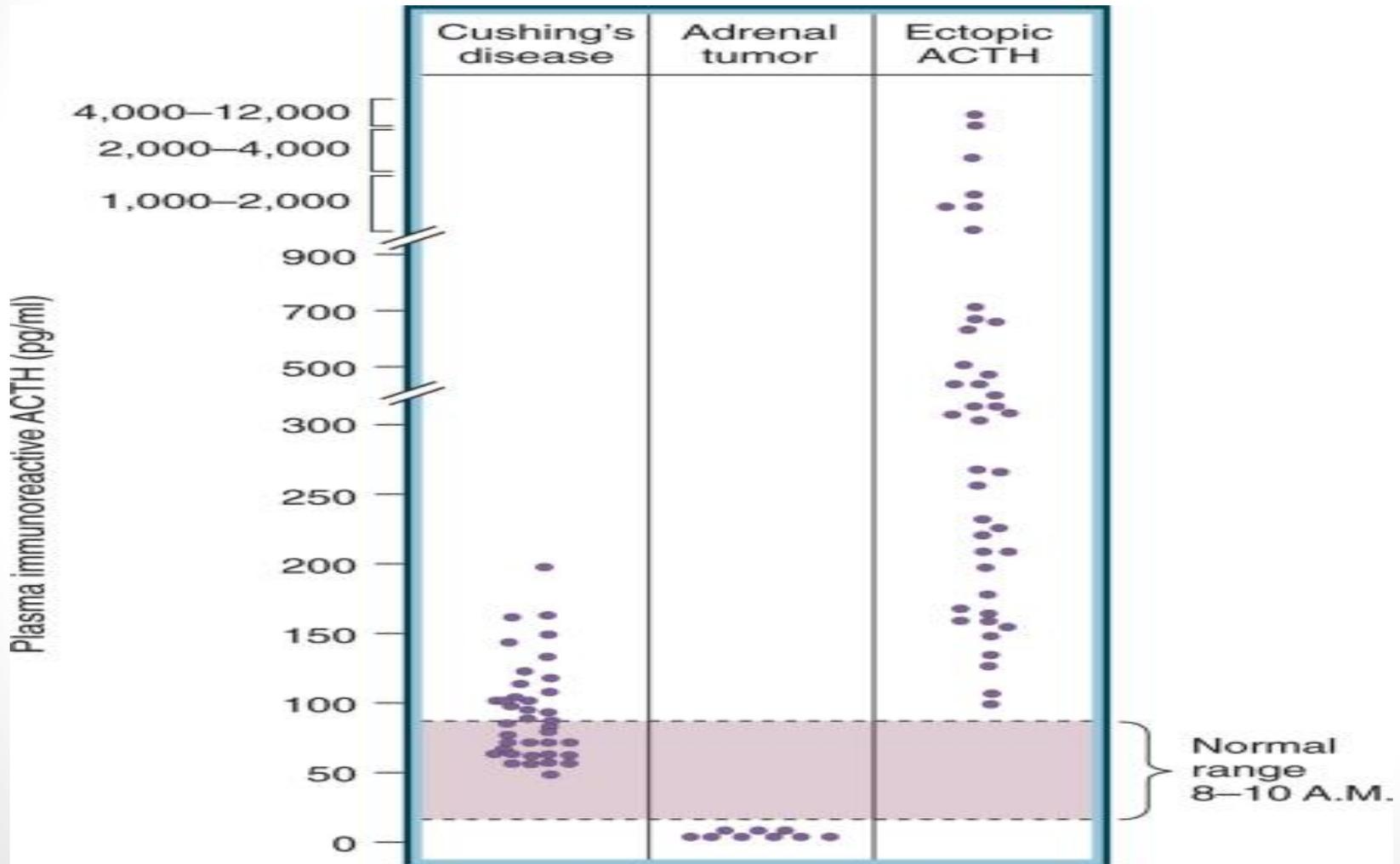
Investigation of patients with suspected Cushing's syndrome

- **Question 1: “Does the patient have Cushing's syndrome?”**
- 24 hour urine free cortisol
- Low dose Dexamethasone suppression test
- Late night salivary cortisol



- **Question 2: Having Confirmed Cushing's Syndrome Clinically and Biochemically, "What is the cause?"**

1. Check serum ACTH



Clinical Suspicion Cushing's Syndrome

Screening tests:

24 hour urinary free cortisol
Overnight 1mg dexamethasone suppression test or
Low dose dexamethasone suppression test (0.5mg 6-hourly for 48 hours)
24 hour salivary cortisol

? Pseudo-Cushing's ? Clinical suspicion

Consider additional testing
Insulin hypoglycemia tests
Combined low dose dexamethasone/CRH stimulation test
Loperamide test

Diagnosis of hypercortisolism confirmed

Differential diagnosis

ACTH

Suppressed

Detectable

CT Adrenals (consider macronodular hyperplasia)

ACTH dependent disease

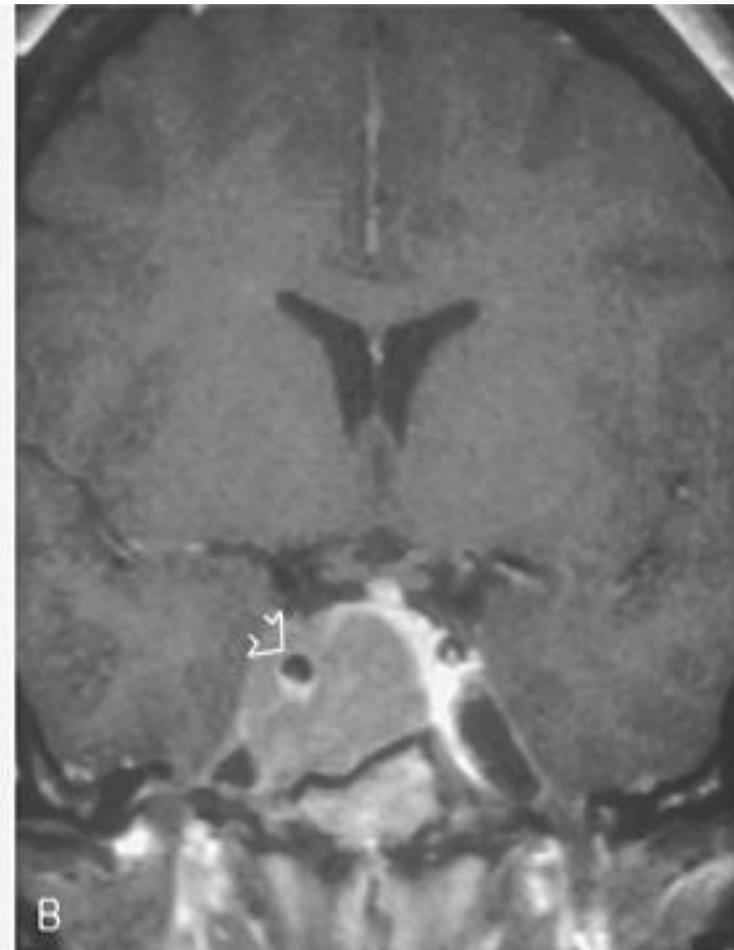
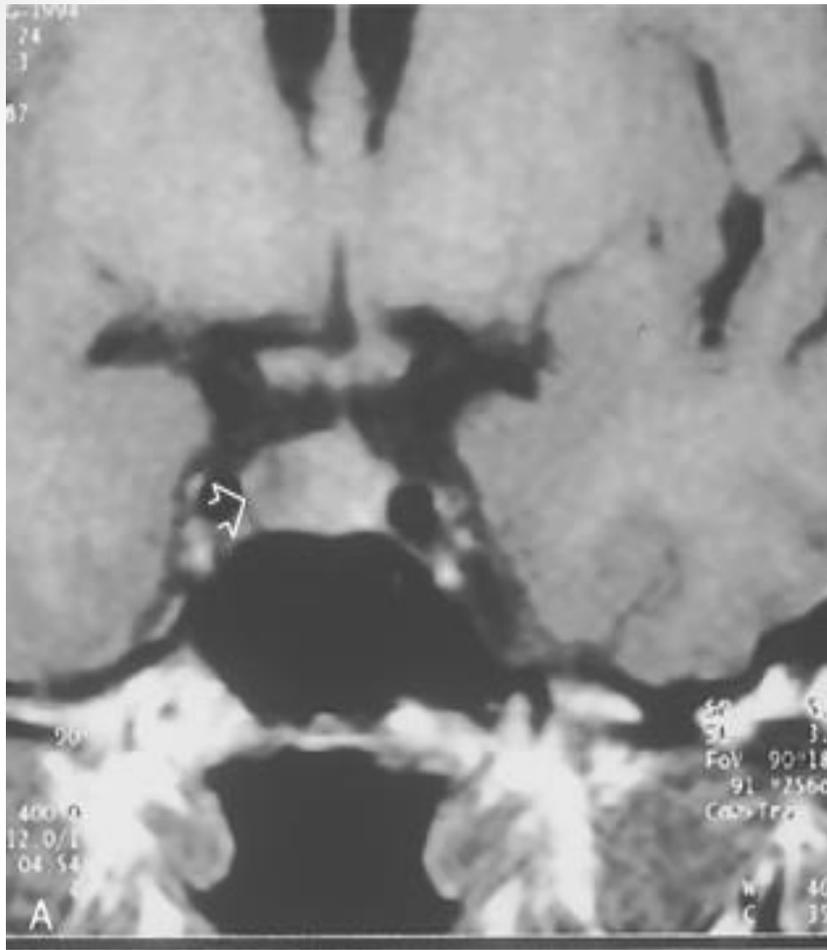
- 50% cortisol suppression following high dose dexamethasone suppression test (2mg 6 hourly for 48 hours)
- >50% increase serum cortisol post CRH stimulation test
- Normal potassium and bicarbonate
- Positive MRI scan pituitary

Then proceed to transphenoidal hypophysectomy

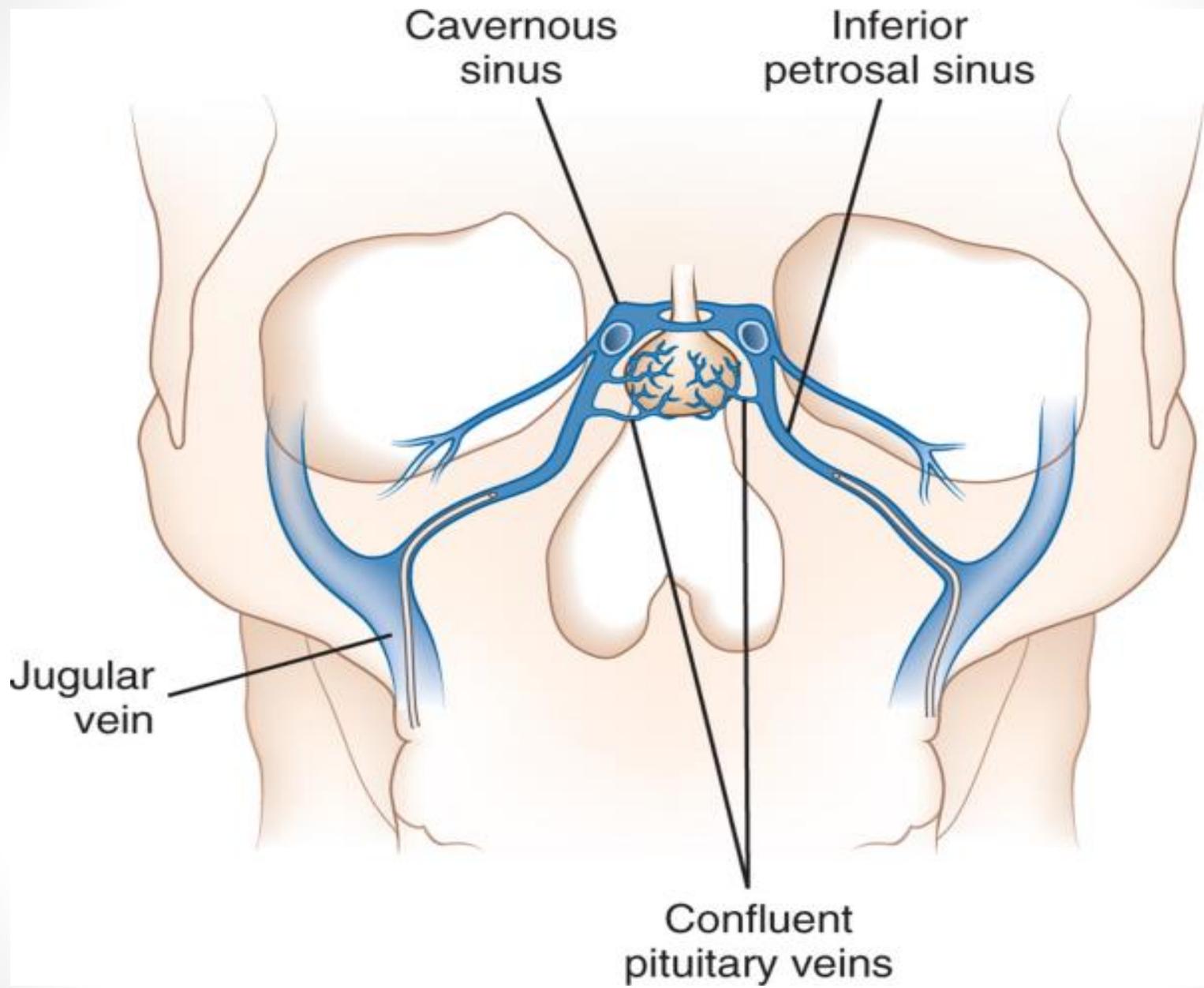
If tests inconclusive (i.e. failure of any above criteria)

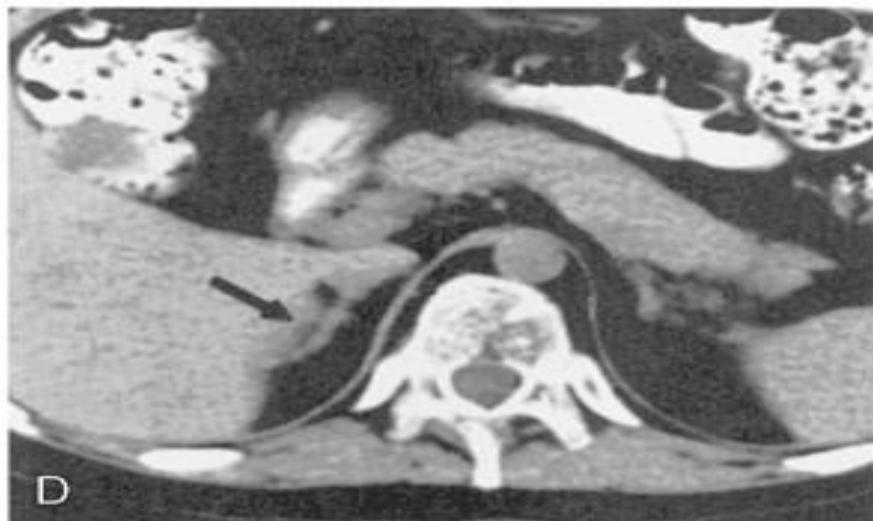
Inferior petrosal sinus sampling with CRH
Positive ACTH gradient
Cushing's disease
Transphenoidal hypophysectomy

No ACTH gradient
Ectopic ACTH syndrome
Appropriate radiology ± venous sampling

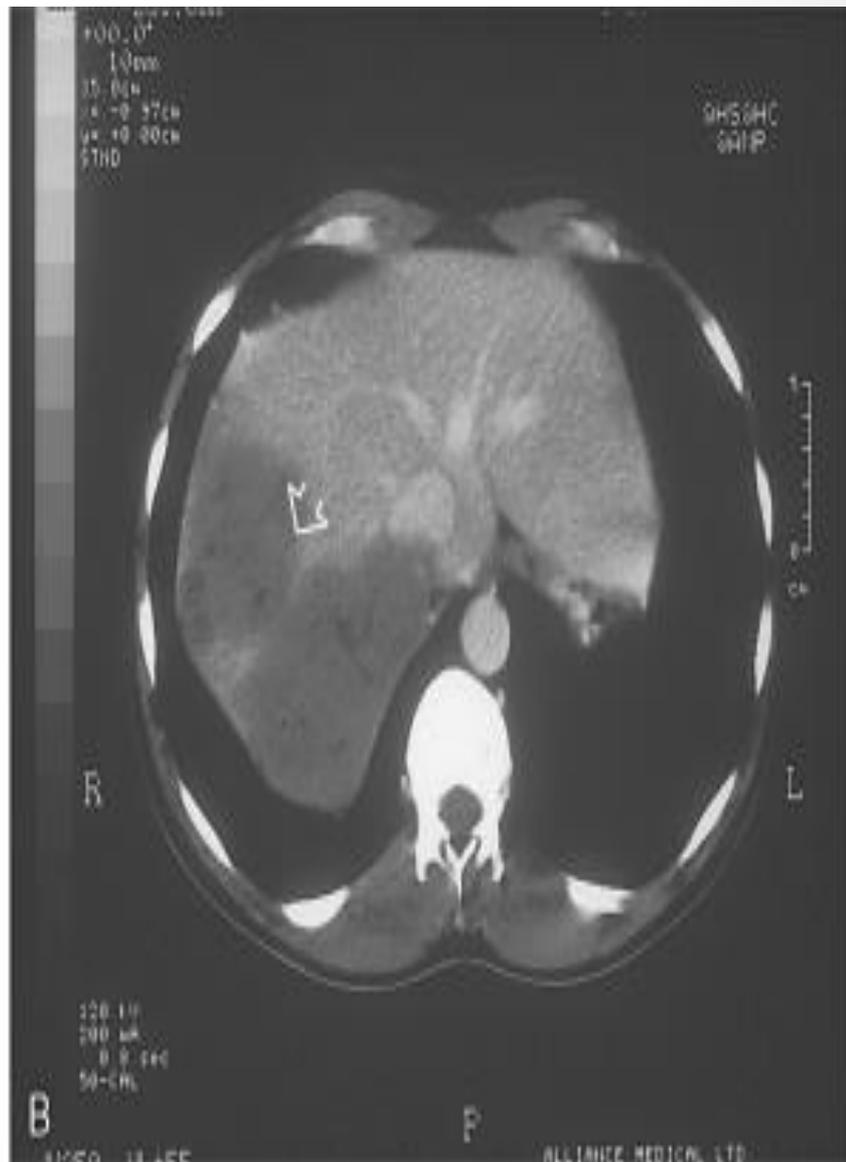


MRI scan of pituitary demonstrating the typical appearance of a pituitary microadenoma. A hypodense lesion is seen in the right side of the gland with deviation of the pituitary stalk away from the lesion. **B**, MRI scan of the pituitary gland demonstrating a large macroadenoma in a patient with Cushing's disease. In contrast to smaller tumors, these tumors are invariably invasive and recur after surgery.





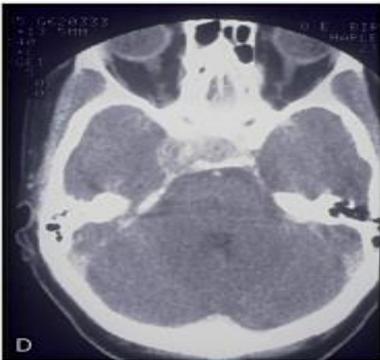
A, Adrenal computed tomographic (CT) scan demonstrating bilateral adrenal hyperplasia in a patient with Cushing's disease. B, CT scan of a typical solitary left adrenal adenoma causing Cushing's syndrome. C, Cushing's syndrome caused by massive macronodular hyperplasia. Adrenal glands are replaced by multiple nodules (arrows). Combined weight of adrenal glands was over 100 g. D, Cushing's syndrome caused by surgically proven primary pigmented nodular adrenal disease in a 21-year-old patient. Notice the multiple small nodules with the relatively atrophic internodular adrenocortical tissue involving the medial limb of the right adrenal gland (arrow).



Computed tomographic scan of a patient with rapidly progressing Cushing's syndrome caused by an adrenal carcinoma. An irregular right adrenal mass is shown (A) with a large liver metastasis (B).

Treatment

1. Adrenal source → Unilateral or bilateral adrenalectomy
2. Pituitary source → Pituitary surgery, rarely have to do bilateral adrenalectomy



A young woman with Cushing's disease, photographed initially beside her identical twin sister (A). In this case, treatment with bilateral adrenalectomy was undertaken. Several years later, the patient presented with Nelson's syndrome and a right third cranial nerve palsy (B and C) related to cavernous sinus infiltration from a locally invasive corticotropinoma (D). Hypophysectomy and radiotherapy were performed with reversal of the third nerve palsy (E). Note the advancing skin pigmentation of Nelson's syndrome.

3. Ectopic ACTH secretion → Treat the primary cancer+-medical therapy.

4. Medical treatment if patient refuses surgery, or surgery is contraindicated or failed to achieve a complete cure.



"When I yell 'CLEAR' that doesn't mean you."

Glucocorticoid deficiency

- **Primary hypoadrenalism causes:**

1. Autoimmune (Addison's disease)
2. Autoimmune polyendocrine syndrome type I (Addison's disease, chronic mucocutaneous candidiasis, hypoparathyroidism, dental enamel hypoplasia, alopecia, primary gonadal failure, see Chapter 41)
3. Autoimmune polyendocrine syndrome type II (Schmidt's syndrome) (Addison's disease, primary hypothyroidism, primary hypogonadism, insulin-dependent diabetes, pernicious anemia, vitiligo, Chapter 41)
4. Infections (Tuberculosis, Fungal infections, CMV, HIV)
5. Metastatic tumor
6. Infiltrations (Amyloid, Hemochromatosis)
7. Intra-adrenal hemorrhage (Waterhouse-Friderichsen syndrome) after meningococcal septicemia
8. Adrenoleukodystrophies
9. Congenital adrenal hypoplasia
10. Congenital adrenal hypoplasia, i.e. DAX-1 mutations and SF-1 mutation
11. Bilateral adrenalectomy

- **Secondary hypoadrenalism causes:**

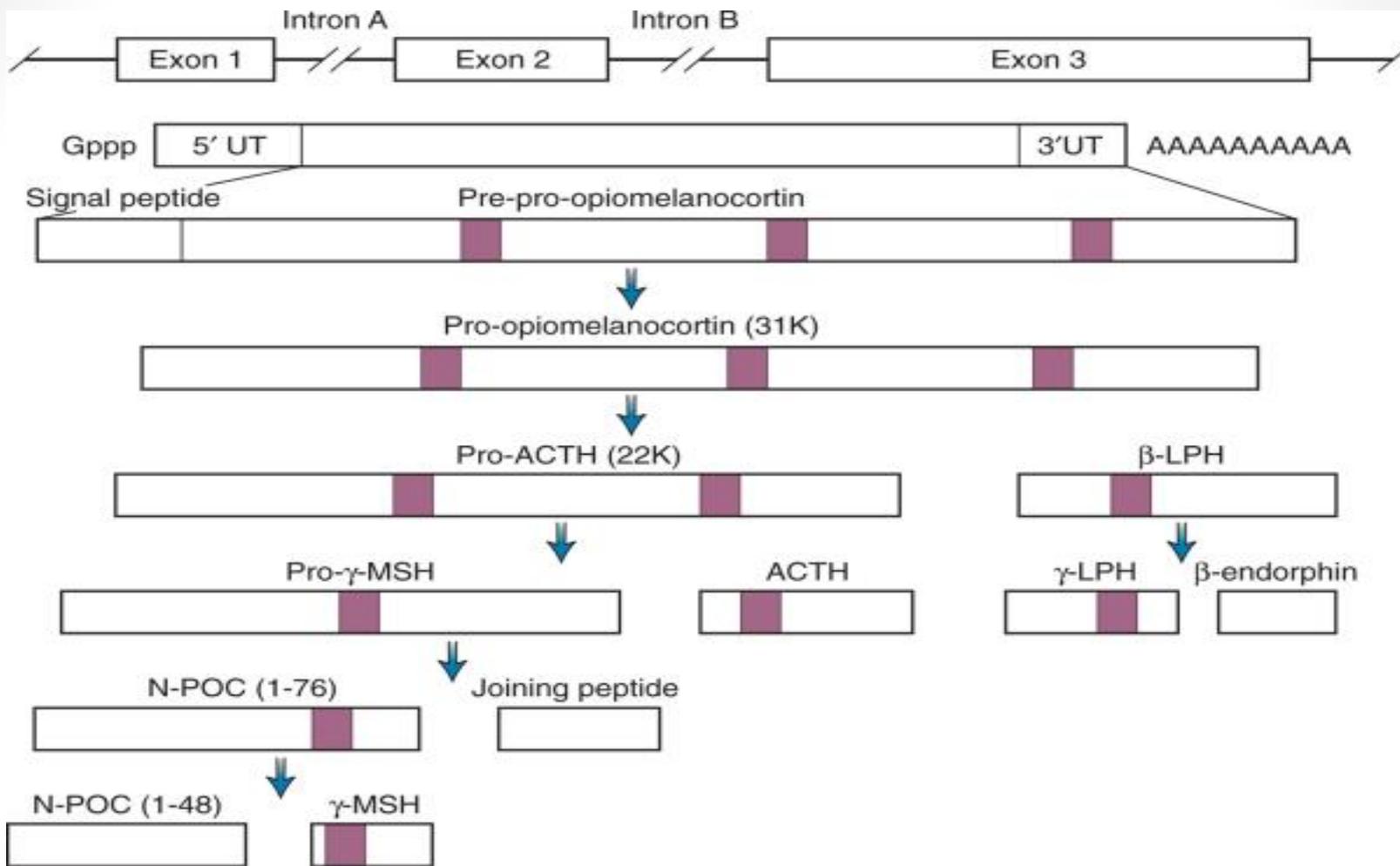
1. Exogenous glucocorticoid therapy
2. Hypopituitarism
3. Selective removal of ACTH-secreting pituitary adenoma
4. Pituitary tumors and pituitary surgery, craniopharyngiomas
5. Pituitary apoplexy
6. Granulomatous disease (tuberculosis, sarcoid, eosinophilic granuloma)
7. Secondary tumor deposits (breast, bronchus)
8. Postpartum pituitary infarction (Sheehan's syndrome)
9. Pituitary irradiation (effect usually delayed for several years)
10. Isolated ACTH deficiency
11. Idiopathic
12. Lymphocytic hypophysitis
13. TRIT gene mutations
14. POMC processing defect
15. POMC gene mutations

Type of Adrenal Insufficiency	Manifestation
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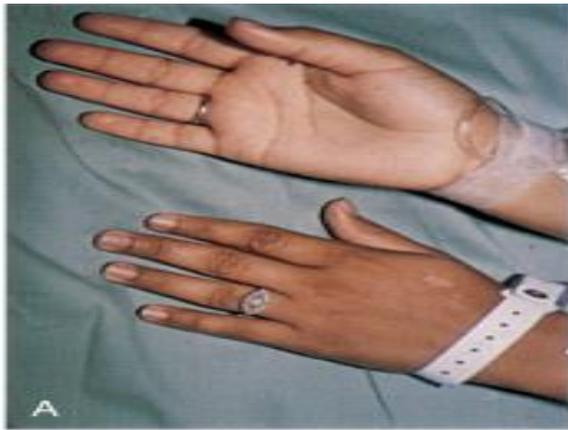
Primary	Hyperpigmentation, hyperkalemia, vitiligo, adrenal calcification, orthostatic hypotension, craving for salt
Secondary	Pale skin not due to anemia, decreased libido and impotence, diabetes insipidus, delayed puberty, loss of axillary or pubic hair
Both	Nausea, vomiting, and diarrhea; hyponatremia, orthostatic hypotension; shock; anorexia; weight loss; hypoglycemia; lymphocytosis; normocytic anemia; tiredness, depression



United States [president John F. Kennedy](#) (1917-1963), probably the single most famous case of Addison's disease



Synthesis and cleavage of pro-opiomelanocortin (POMC) within the human anterior pituitary gland. Prohormone convertase enzymes sequentially cleave POMC to adrenocorticotrophic hormone (ACTH).



Pigmentation in Addison's disease. **A**, Hands of an 18-year-old woman with autoimmune polyendocrine syndrome and Addison's disease. Pigmentation in a patient with Addison's disease before (**B**) and after (**C**) treatment with hydrocortisone and fludrocortisone. Note the additional presence of vitiligo. **D**, Similar changes also seen in a 60-year-old man with tuberculous Addison's disease before and after corticosteroid therapy. **E**, Buccal pigmentation in the same patient.

Work up?

- Routine labs including kidney function & electrolytes
- Cosyntropin stimulation test with baseline cortisol and ACTH.
- Insulin Tolerance test if suspecting an acute secondary hypoadrenalism
- 21 hydroxylase antibodies
- Imaging:

Primary hypoadrenalism → Adrenal CT

Secondary hypoadrenalism → Pituitary MRI

Adrenal crises

- **Similar symptoms and signs of adrenal insufficiency but are more severe, including but not limited to: severe hypotension, hyperkalemia, fever & decreased level of consciousness.**



Treatment

- **Establish intravenous access with a large-gauge needle.**
- **Draw blood for stat serum electrolytes and glucose and routine measurement of plasma cortisol and ACTH. Do not wait for laboratory results.**
- **Infuse 2 to 3 L of 154 mmol/L NaCl (0.9% saline) solution or 50 g/L (5%) dextrose in 154 mmol/L NaCl (0.9% saline) solution as quickly as possible.**
- **Inject intravenous hydrocortisone (100 mg immediately and every 6 hr)**
- **Use supportive measures as needed.**

Long term replacement therapy

Glucocorticoid Replacement

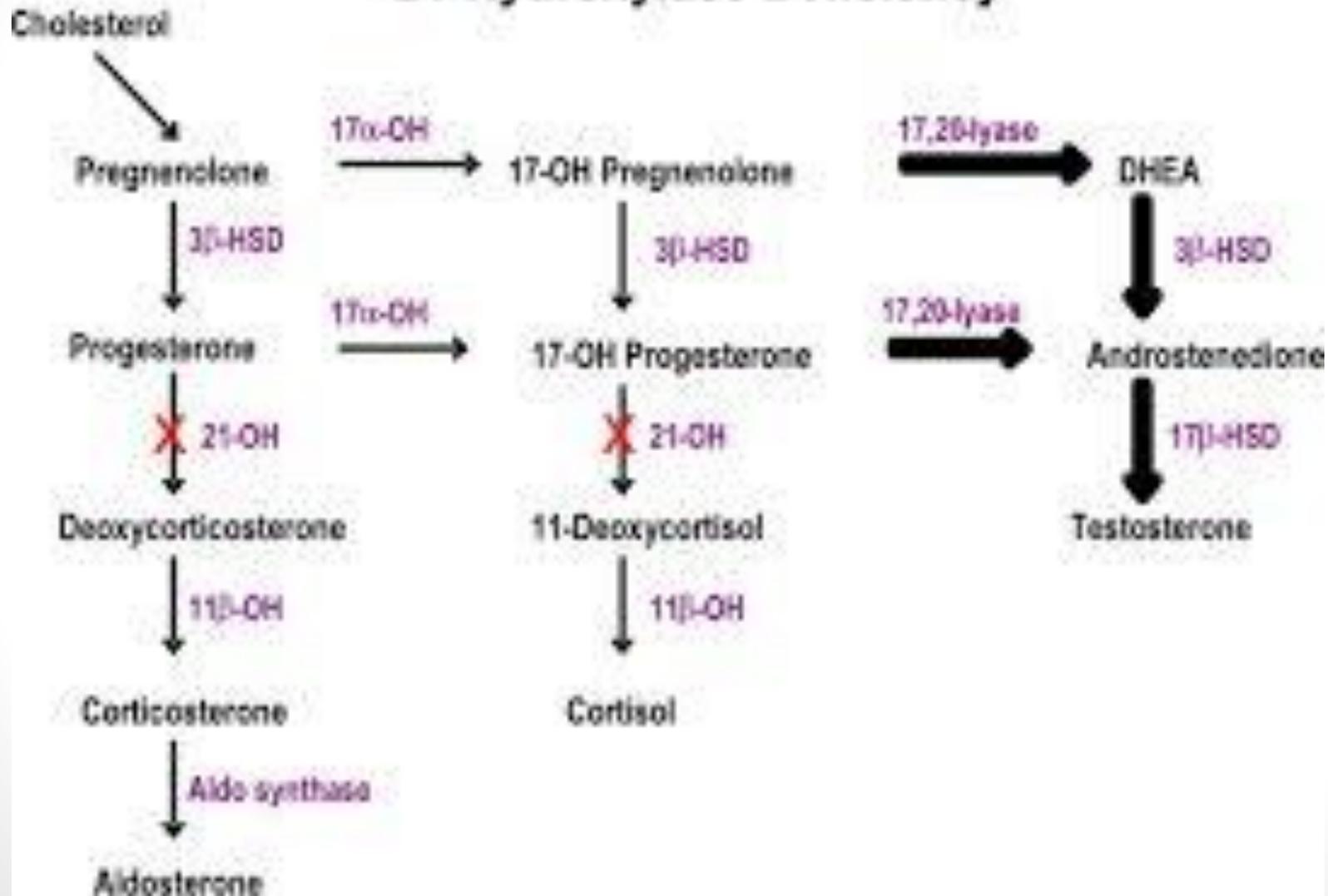
- Hydrocortisone 10 mg on awakening and 5 to 10 mg in early afternoon.
- Monitor clinical symptoms and morning plasma ACTH.

Mineralocorticoid Replacement

- Fludrocortisone 0.1 (0.05 to 0.2) mg orally.
- Liberal salt intake.
- Monitor lying and standing blood pressure and pulse, edema, serum potassium, and plasma renin activity.
 - Educate patient about the disease, how to manage minor illnesses and major stresses, and how to inject steroid intramuscularly.
 - Obtain Medical Alert bracelet/necklace, Emergency Medical Information Card.

Congenital adrenal hyperplasia

21-Hydroxylase Deficiency



21-hydroxylase deficiency

- 90% of cases of CAH are due to 21-hydroxylase deficiency.
- The condition arises because of defective conversion of 17α -hydroxyprogesterone to 11-deoxycortisol.
- Reduced cortisol biosynthesis results in reduced negative feedback drive and increased ACTH secretion; as a consequence, adrenal androgens are produced in excess
- 75% of cases have mineralocorticoid deficiency because of failure to convert progesterone to deoxycorticosterone in the zona glomerulosa.
- Clinically, several distinct variants of 21 hydroxylase deficiency have been recognized

1. Simple Virilizing Form →

Females → clitoral enlargement, labial fusion, and development of a urogenital sinus → sexual ambiguity at birth and even inappropriate sex assignment.

Males → are phenotypically normal at birth and are at risk of not being diagnosed; may present in early childhood with signs of precocious pseudopuberty such as sexual precocity, pubic hair development, and/or growth acceleration due to premature androgen excess.

2. **Salt-Wasting Form** → 75% of cases of both sexes also have concomitant deficiency of aldosterone deficiency. In addition to the described features, neonates may present within the first week of life with a salt-wasting crisis and hypotension. This condition carries a significant neonatal mortality rate.

3. Nonclassic or “Late-Onset” 21-Hydroxylase Deficiency:

Patients present in childhood or early adulthood with premature pubarche or with a phenotype that may masquerade as polycystic ovary syndrome (PCOS). Females present with hirsutism, primary or secondary amenorrhea, or anovulatory infertility. Androgenic alopecia and acne may be other presenting features.



Pheochromocytoma and paraganglioma

- Catecholamine-secreting tumors that arise from chromaffin cells of the adrenal medulla and the sympathetic ganglia are referred to as pheochromocytomas and extraadrenal catecholamine-secreting paragangliomas (extraadrenal pheochromocytomas), respectively.
- Rare tumors, with an annual incidence of 2 to 8 cases per million people.¹
- From screening for secondary causes of hypertension in outpatients, the prevalence of pheochromocytoma has been estimated at 5.0%.

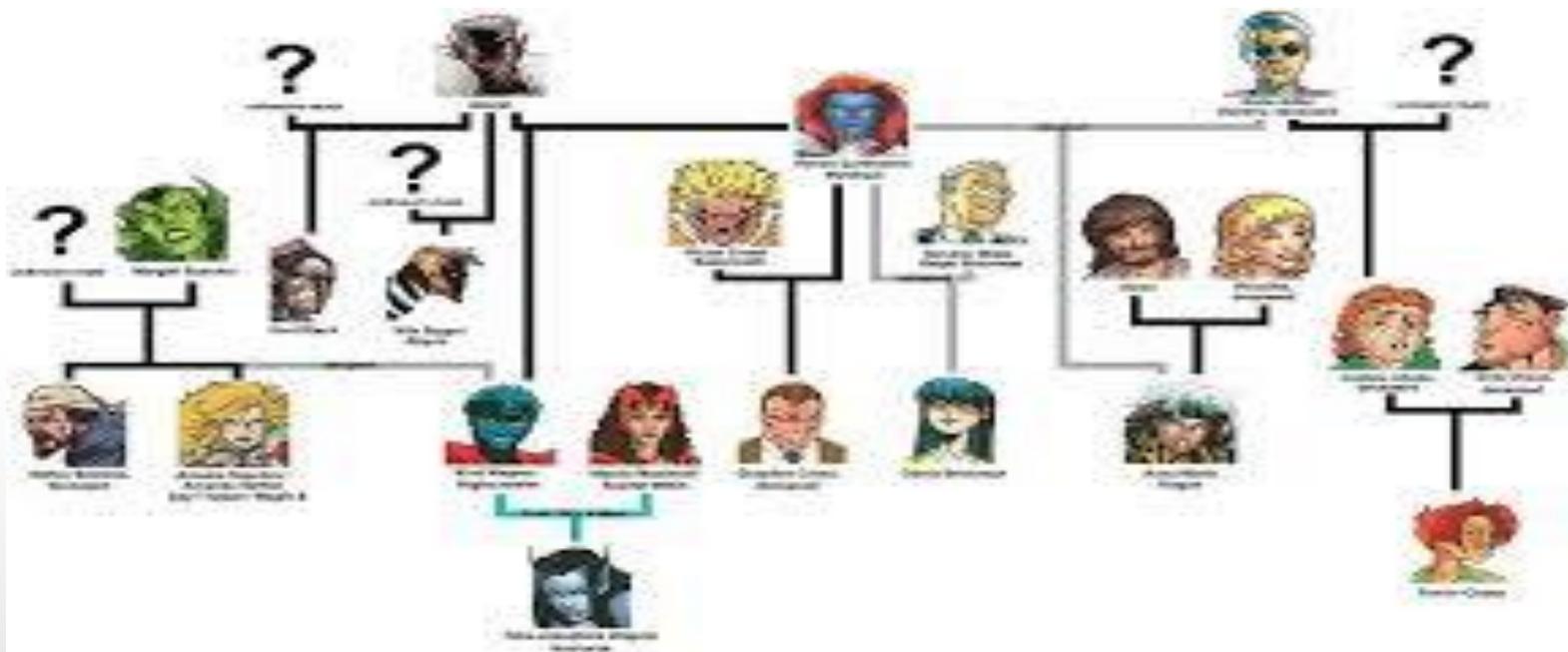
- It is important to suspect, confirm, localize, and resect these tumors because:

(1) the associated hypertension is curable with surgical removal of the tumor

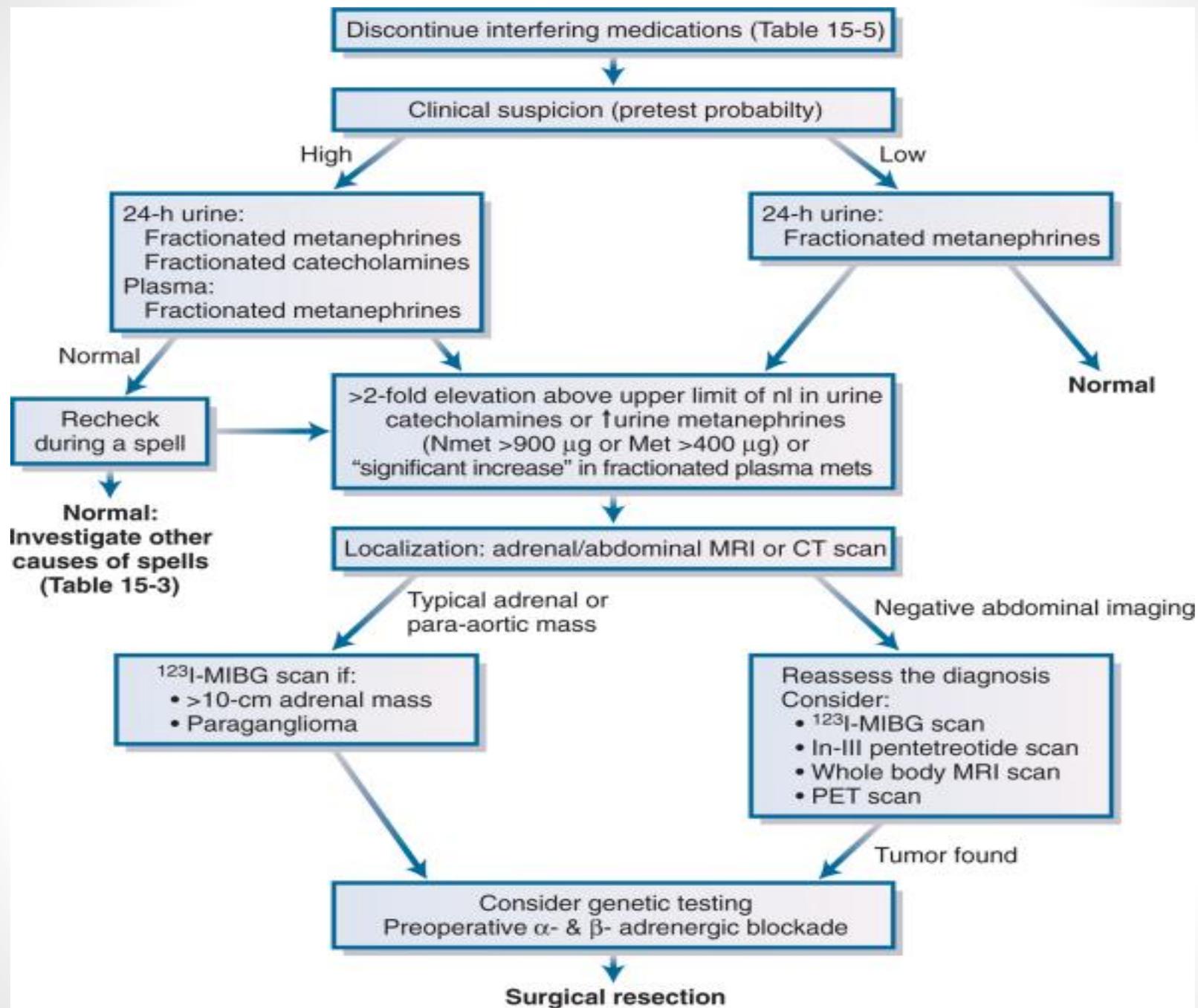
(2) a risk of lethal paroxysm exists

(3) at least 10% of the tumors are malignant

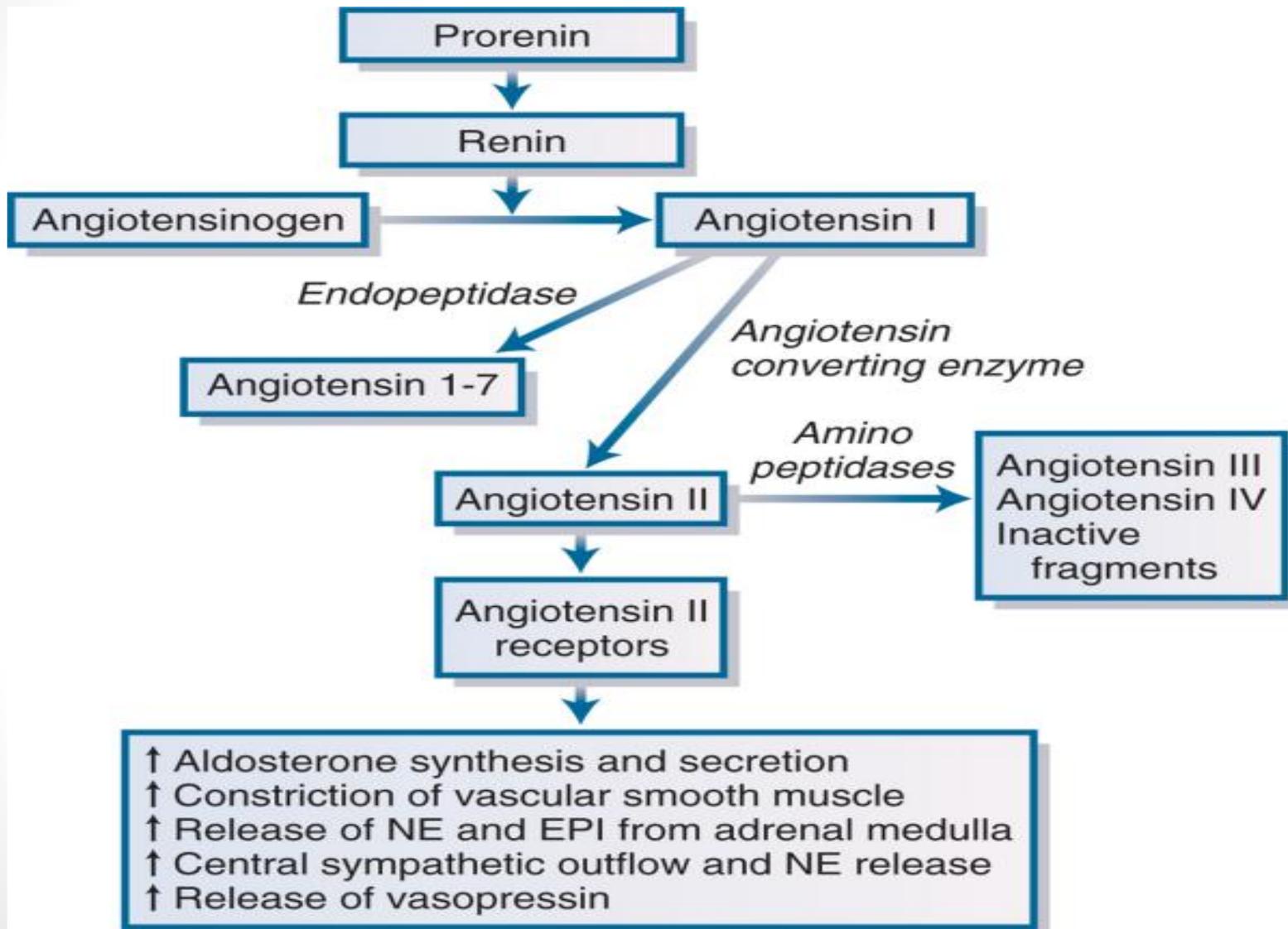
(4) 10% to 20% are familial and detection of this tumor in the proband may result in early diagnosis in other family members.



Signs/symptoms	Patient percentage
Classic triad (headache+diaphoresis+tachycardia)	21 (5/24)
Hypertension	33 (8/24)
Labile blood pressure	4 (1/24)
Palpitations	8 (2/24)
Headache	8 (2/24)
Abdominal pain	4 (1/24)
Adrenal hemorrhage	4 (1/24)
Asymptomatic	25 (6/24)



RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

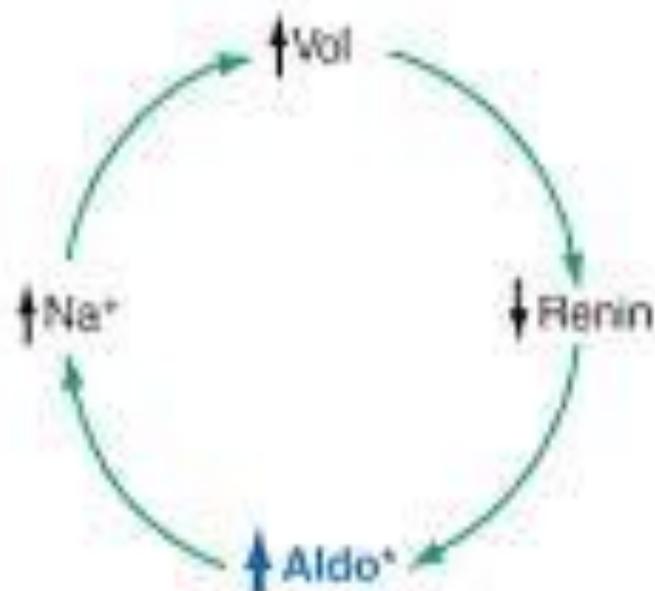


Primary hyperaldosteronism (Conn's Syndrome)

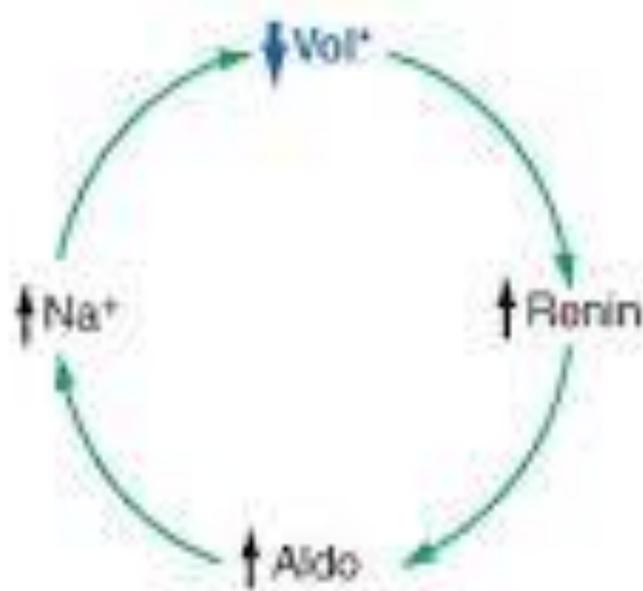
- **Causes:**

1. Aldosterone-producing adenoma (APA)—35% of cases
2. Bilateral idiopathic hyperplasia (IHA)—60% of cases
3. Primary (unilateral) adrenal hyperplasia—2% of cases
4. Aldosterone-producing adrenocortical carcinoma—<1% of cases
5. Familial Hyperaldosteronism (FH)
6. Glucocorticoid-remediable aldosteronism (FH type I)—<1% of cases
7. Ectopic aldosterone-producing adenoma or carcinoma—<0.1% of cases

Primary aldosteronism



Secondary aldosteronism



* Initiating event

Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition; <http://www.accessmedicine.com>

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When to consider testing for primary aldosteronism:

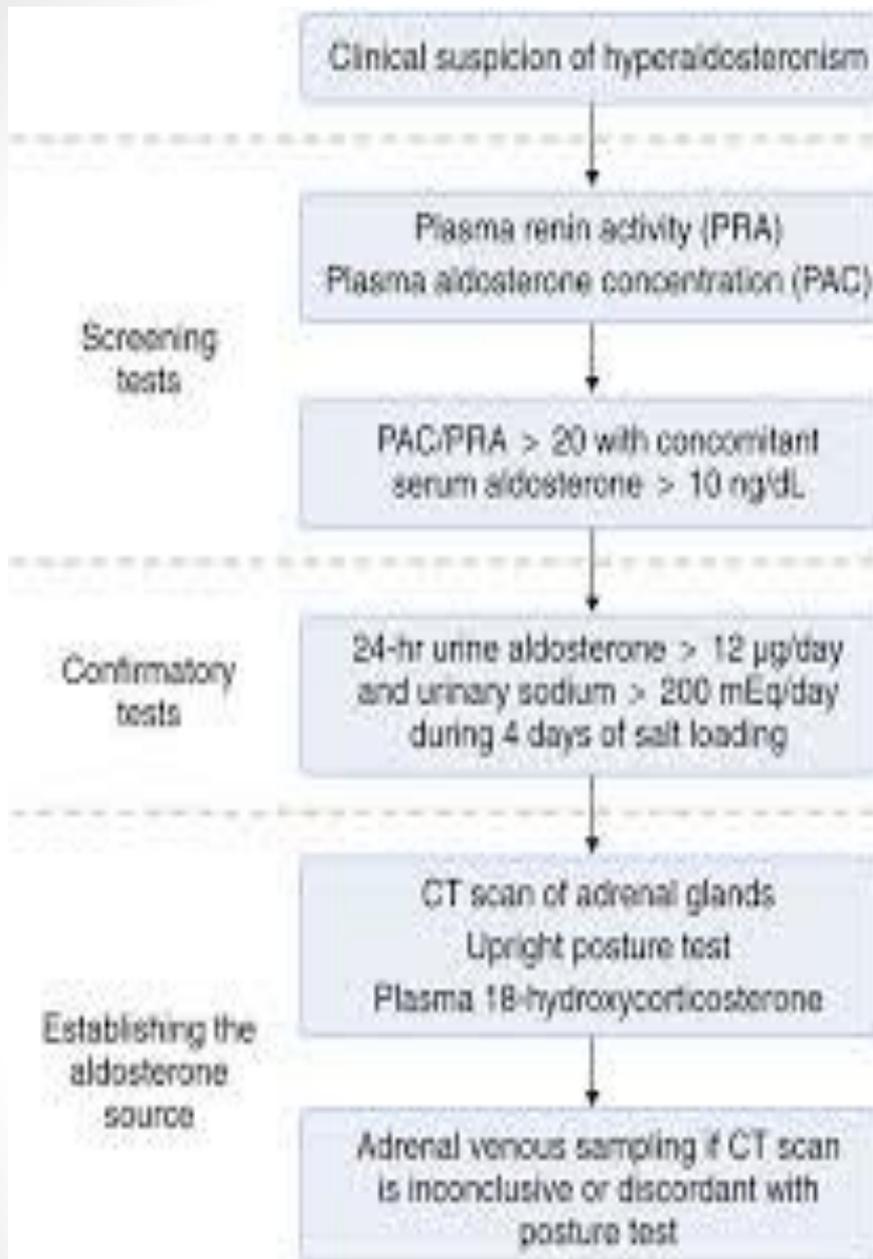
- Hypertension and hypokalemia
- Resistant hypertension
- Adrenal incidentaloma and hypertension
- Onset of hypertension at a young age (<20 y)
- Severe hypertension (≥ 160 mm Hg systolic or ≥ 100 mm Hg diastolic)
- Whenever considering secondary hypertension

Morning blood sample in seated ambulant patient

- Plasma aldosterone concentration (PAC)
- Plasma renin activity (PRA or PRC)

\uparrow PAC (≥ 15 ng/dL)
 \downarrow PRA (< 1.0 ng/mL per hour) or
 \downarrow PRC ($<$ lower limit of detection for the assay)
and
PAC/PRA ratio ≥ 20 ng/dL per ng/mL per hour

Investigate for primary aldosteronism





Confirmed primary aldosteronism

Adrenal CT scan

Normal
Micronodularity
Bilateral masses

Unilateral
hypodense
nodule >1 cm

Low
probability
APA

High
probability
APA

>40 y
consider

<40 y
consider

AVS

No
lateralization
with AVS

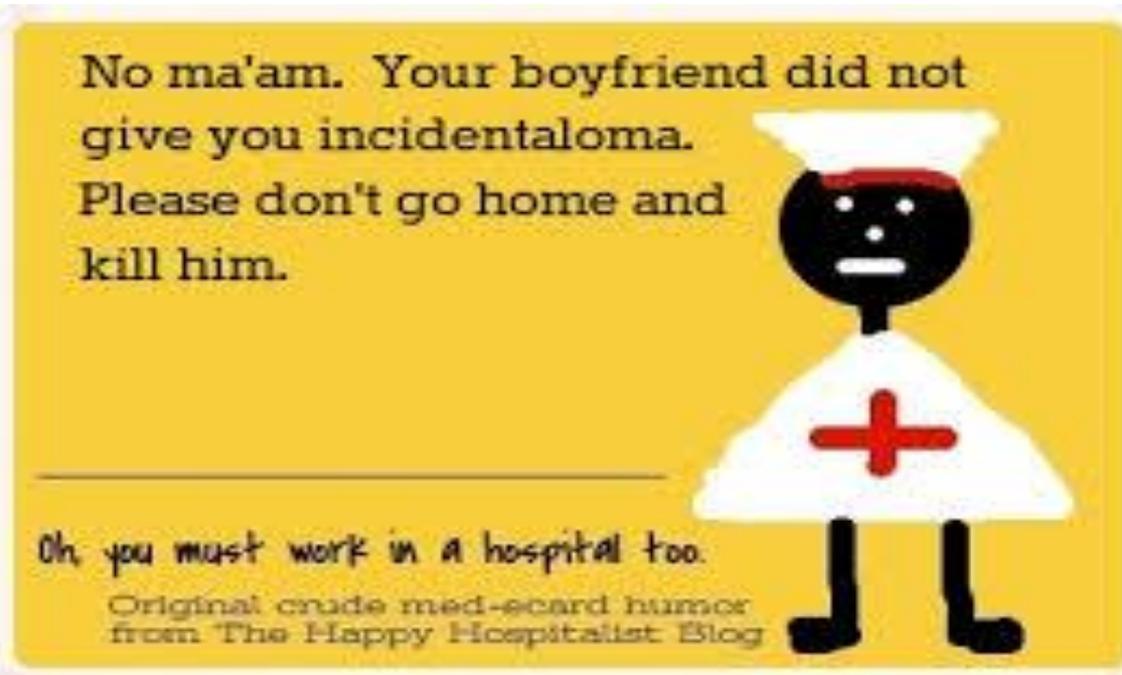
Lateralization
with AVS

IHA:
Pharmacologic
therapy

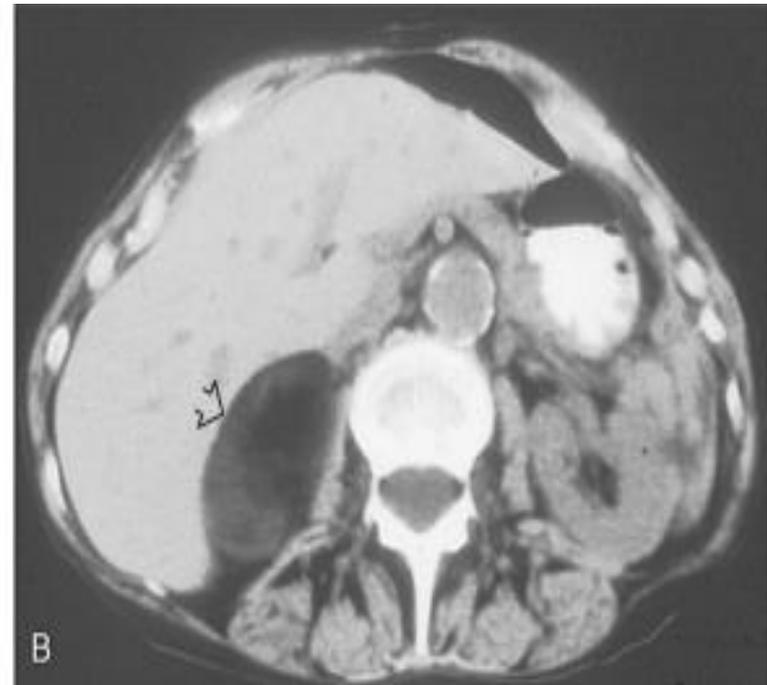
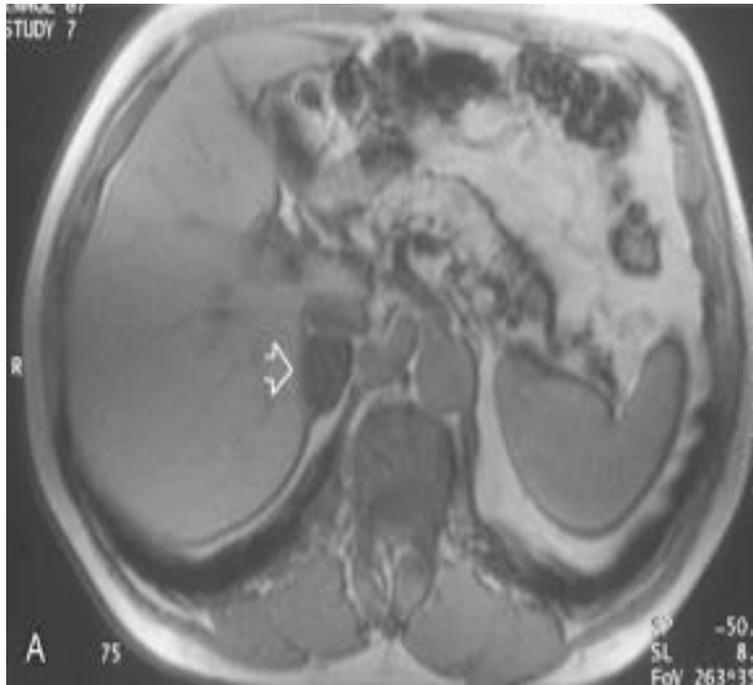
APA or PAH:
Unilateral
laparoscopic
adrenalectomy

ADRENAL INCIDENTALOMAS

- An adrenal mass will be uncovered in up to 4% of patients imaged for nonadrenal pathology.
- Incidentalomas are uncommon in patients younger than 30 years of age but increase in frequency with age.
- They occur equally in males and females.



- In more than 85% of cases these lesions are nonfunctioning, benign adenomas. Occasionally they may represent myelolipomas, hamartomas, or granulomatous infiltrations of the adrenal. Functioning tumors (pheochromocytomas or those secreting cortisol, aldosterone, or sex steroids) and carcinomas comprise the remainder.



A, Adrenal incidentaloma discovered in a woman undergoing investigation for abdominal pain. **B**, Incidentally discovered right adrenal myelolipoma



Figure 1: Gross appearance of Adrenal Myeloid tumor specimen. On cut section, a solid tumor showing waxy appearance of yellowish areas with few hemorrhagic areas.

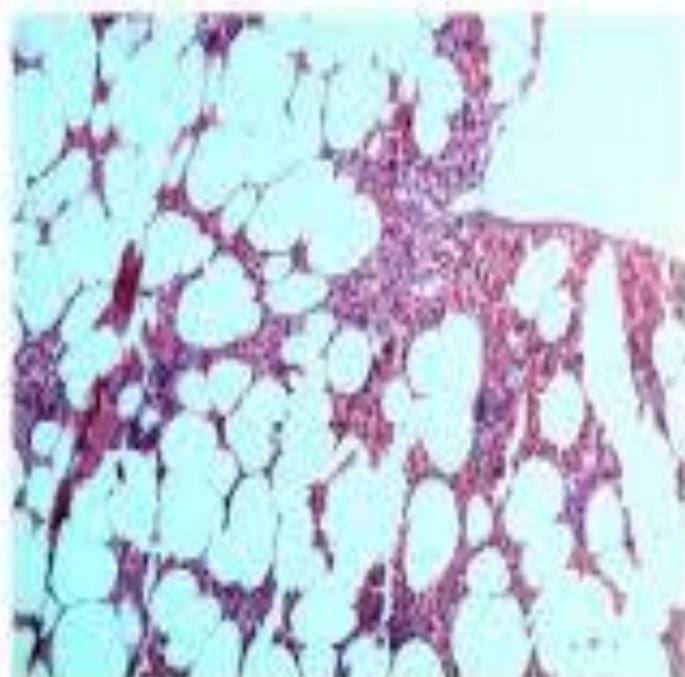


Figure 2: Microscopic examination: Section revealed characteristic admixture of mature adipose tissue with normal hematopoietic tissue (H&E stain, 4X)

- Some “incidentalomas” may cause abnormal hormone secretion without obvious clinical manifestations of a hormone excess state; the best example of this relates to “preclinical” Cushing's syndrome, which may occur in up to 20% of all cases → All patients with incidentally discovered adrenal masses should undergo appropriate endocrine screening tests:
 - **24-hour urinary catecholamine collection**
 - **Low dose DST**
 - **If history of HTN, check supine circulating PRA/aldosterone levels.**
 - **DHEAS should be measured as a marker of adrenal androgen secretion based on the clinical picture.**

- The possibility of malignancy should be considered in each case.
- In patients with a known extraadrenal primary, the incidence of malignancy is obviously much higher (up to 20% of patients with lung cancer, for example, have adrenal metastases on CT scanning).
- In those with no evidence of malignancy, adrenal carcinoma is rare.
- In true incidentalomas, size appears to be predictive of malignancy—a lesion less than 4 cm in diameter in size is most unlikely to be malignant. The majority of nonfunctioning lesions less than 4 cm can therefore be treated conservatively, and patients followed up with annual imaging.
- Even incidentalomas greater than 6 cm are more likely to be benign than malignant, but because of an increased risk of malignancy (about 30%), many centers recommend removal of tumors greater than 6 cm in diameter.

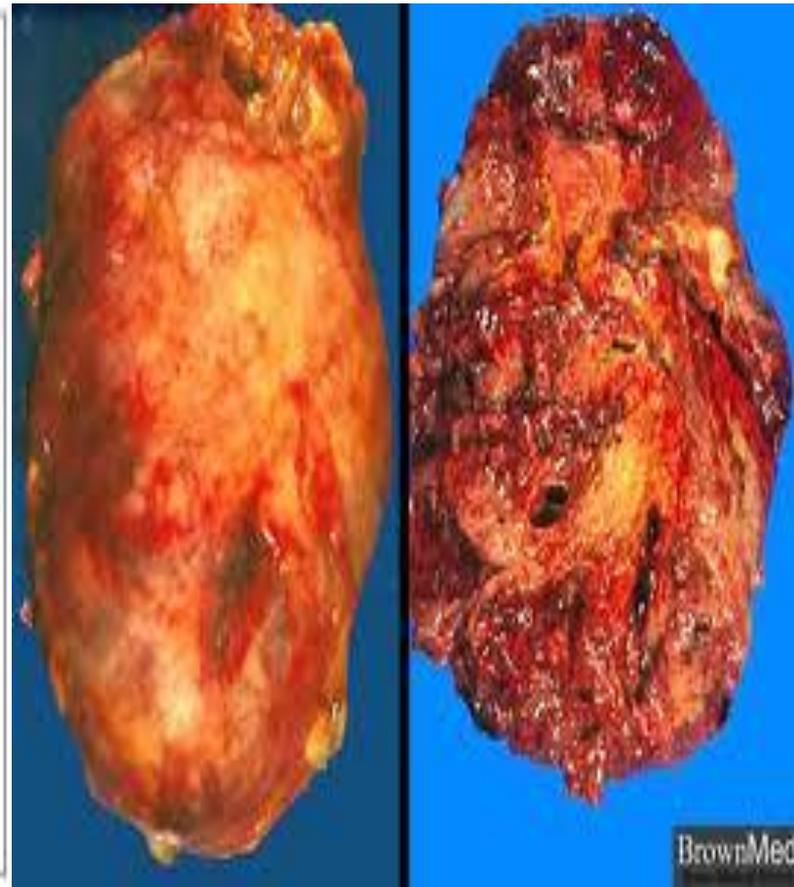
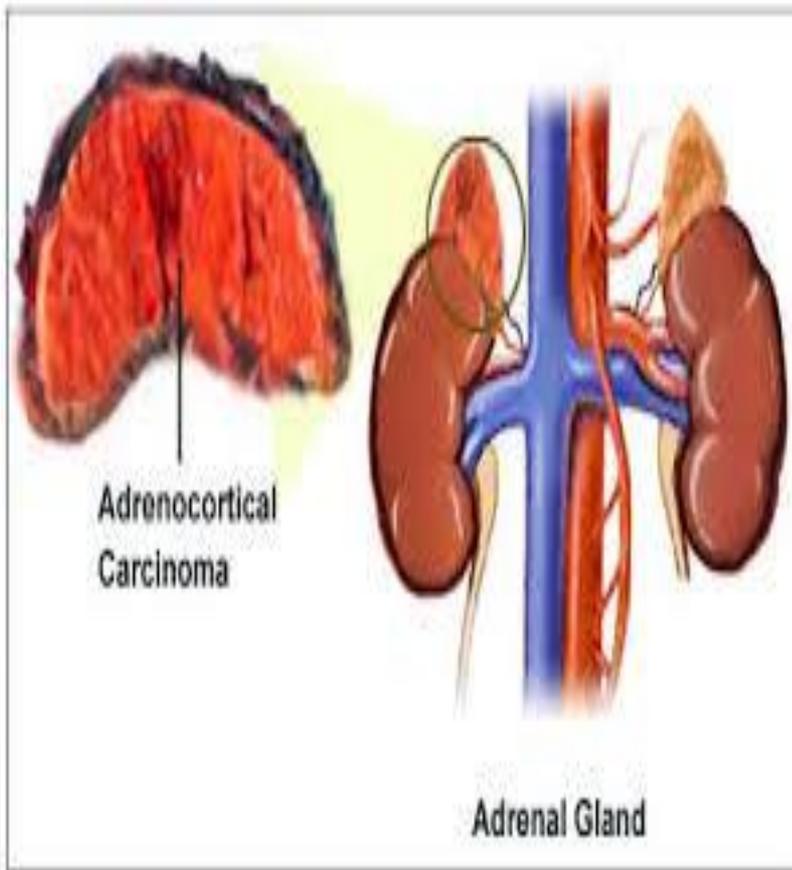
- Additional characteristic CT or MRI appearances studies may aid in differentiating malignant from nonmalignant lesions. If malignancy is suspected on imaging or clinical predictors, then open adrenalectomy rather than a laparoscopic approach is advised.
- CT-guided biopsy is useful in differentiating adrenal from nonadrenal tissue in the case of a suspected metastasis, but is poor in differentiating benign adenomas from malignant adrenal lesions.



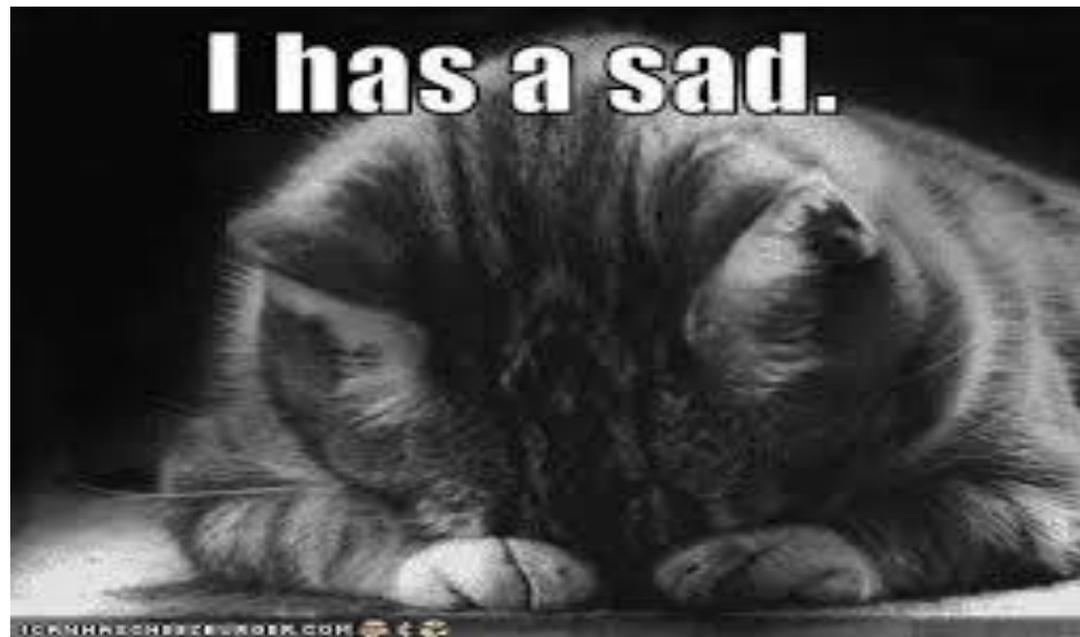
Adrenocortical carcinoma

- Primary adrenal carcinoma is very rare with an incidence of 1/million population/year.
- Women are more commonly affected than men (2.5:1)
- Mean age of onset is between 40 and 50 years of age, although males tend to be older at presentation.
- 80% of tumors are functional, most commonly secreting glucocorticoids alone (45%), glucocorticoids and androgens (45%), or androgens alone (10%). Less than 1% of all cases secrete aldosterone.

- Patients present with features of the hormone excess state (glucocorticoid and/or androgen excess) but abdominal pain, weight loss, anorexia, and fever occur in 25% of cases. An abdominal mass may be palpable.



- Current treatments for what is often an aggressive tumor are poor. Surgery offers the only chance of cure for patients with local disease, but metastatic spread is evident in 75% of cases at presentation. Radiotherapy is ineffective, as are most chemotherapeutic regimens. Mitotane in high doses offers transient benefit in reducing tumor growth in 25% to 30% of cases and controlling hormonal hypersecretion in 75% of cases.
- Overall, the prognosis is poor, with 5-year survival rates of less than 20%.





1. Williams Textbook of Endocrinology
2. Medscape.com
3. UpToDate.com

