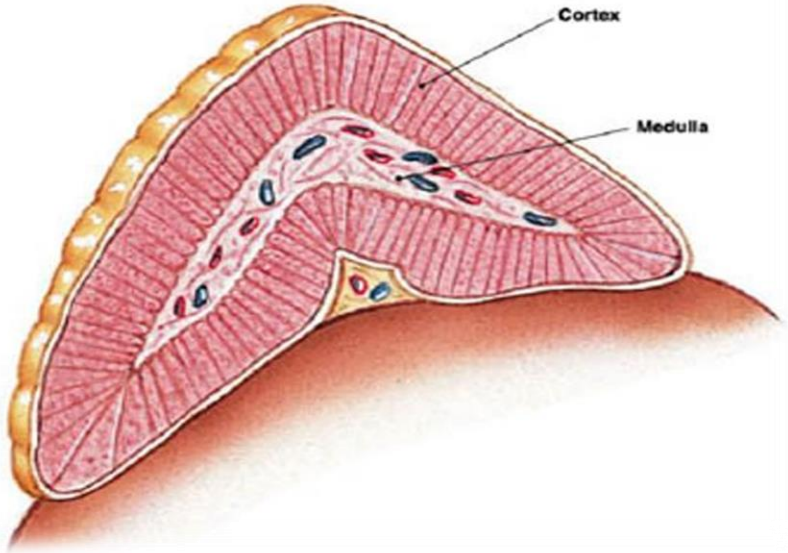
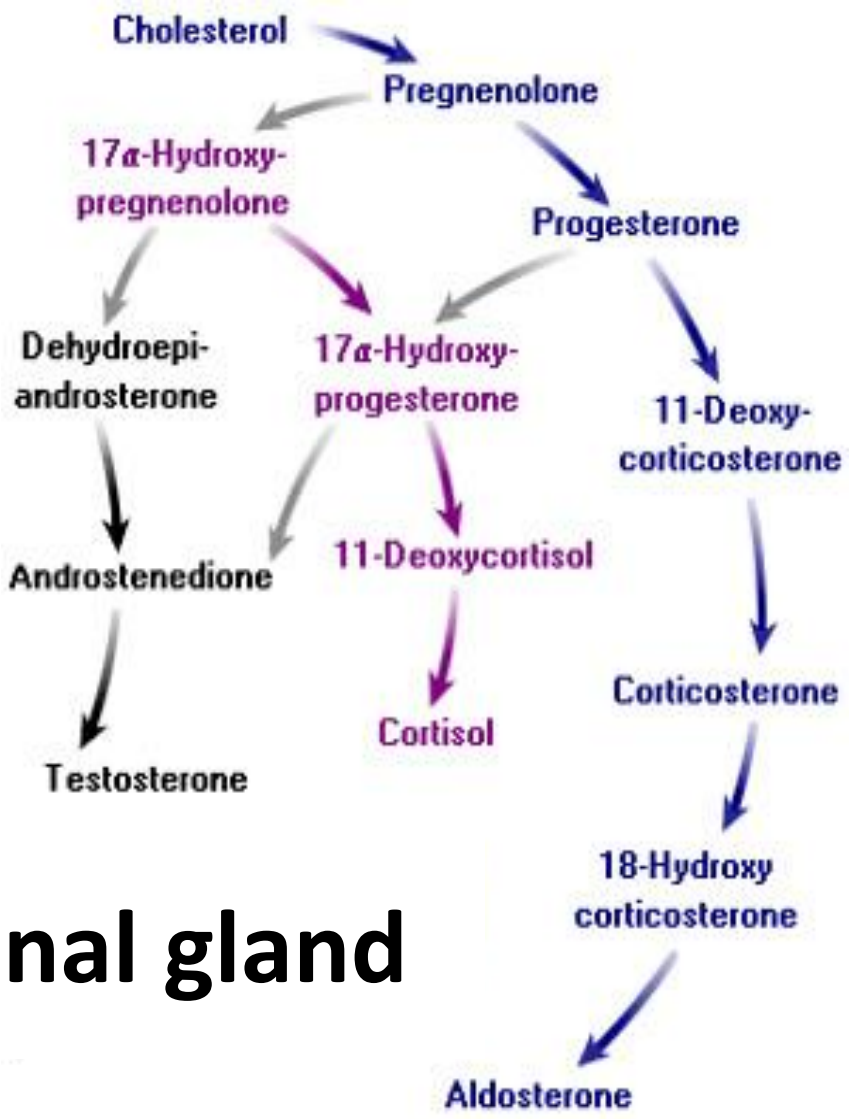


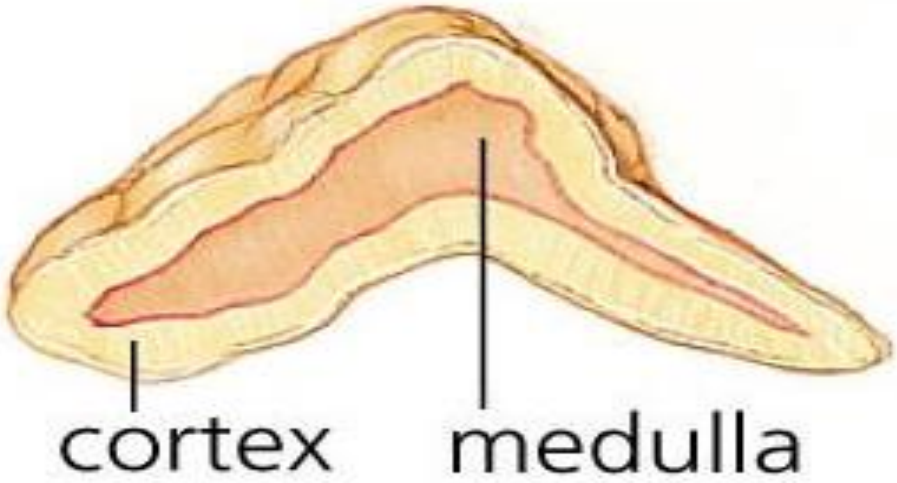


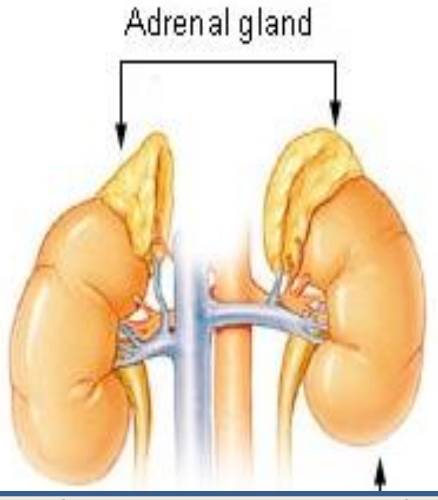
The disorders of adrenal gland

Harea Dumitru

2023

Adrenal glands



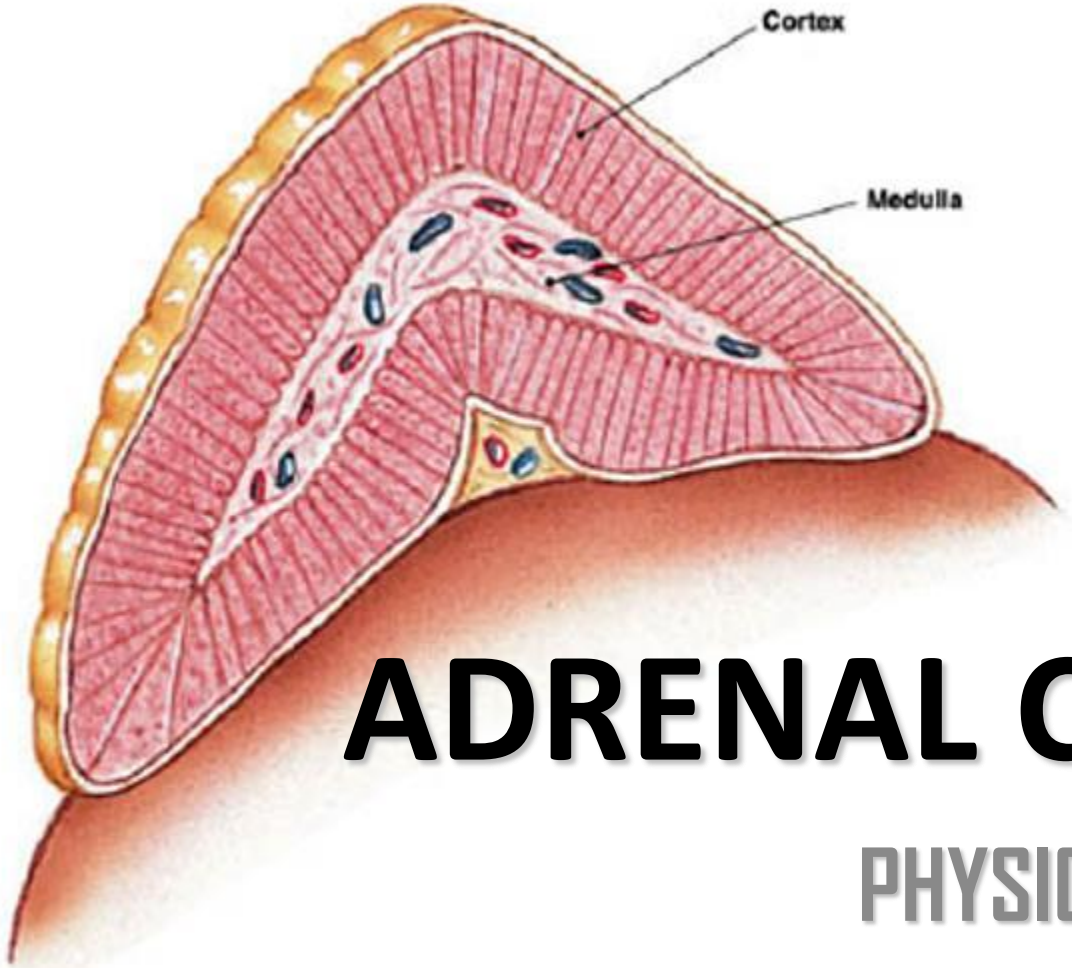


- Bilateral structures located immediately superior to the kidney;
- Derived from both neuronal tissue and epitelial (epithelial-like) tissue;
- is a hybrid gland consisting of a cortex and a medulla;

80-90%
Steroids hormones

10-20%
Catecholamines
Chromaffin cells
Epinephrine – 80%
Norepinephrine – 20%

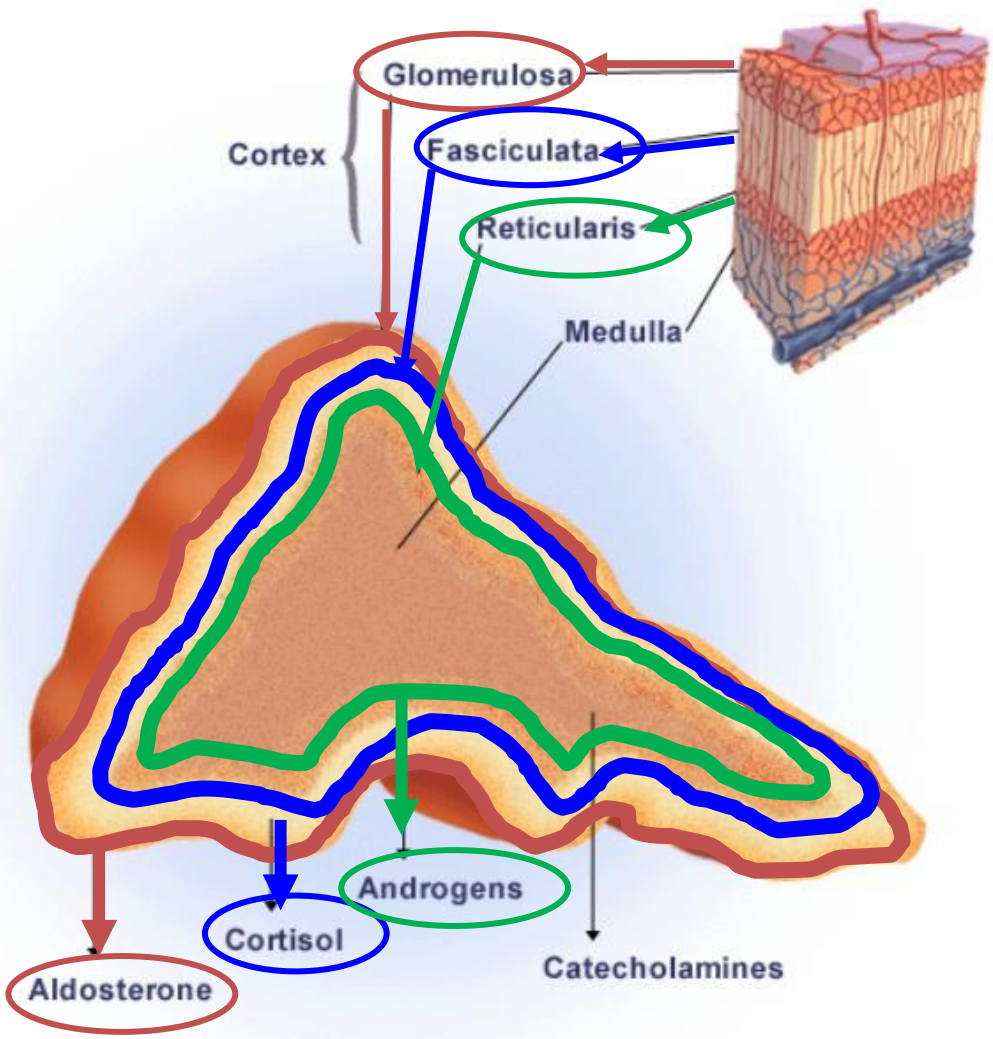
Acts as rapid responder to stress
Regulate energy metabolism and cardiac output



ADRENAL CORTEX

PHYSIOLOGY

Adrenal cortex



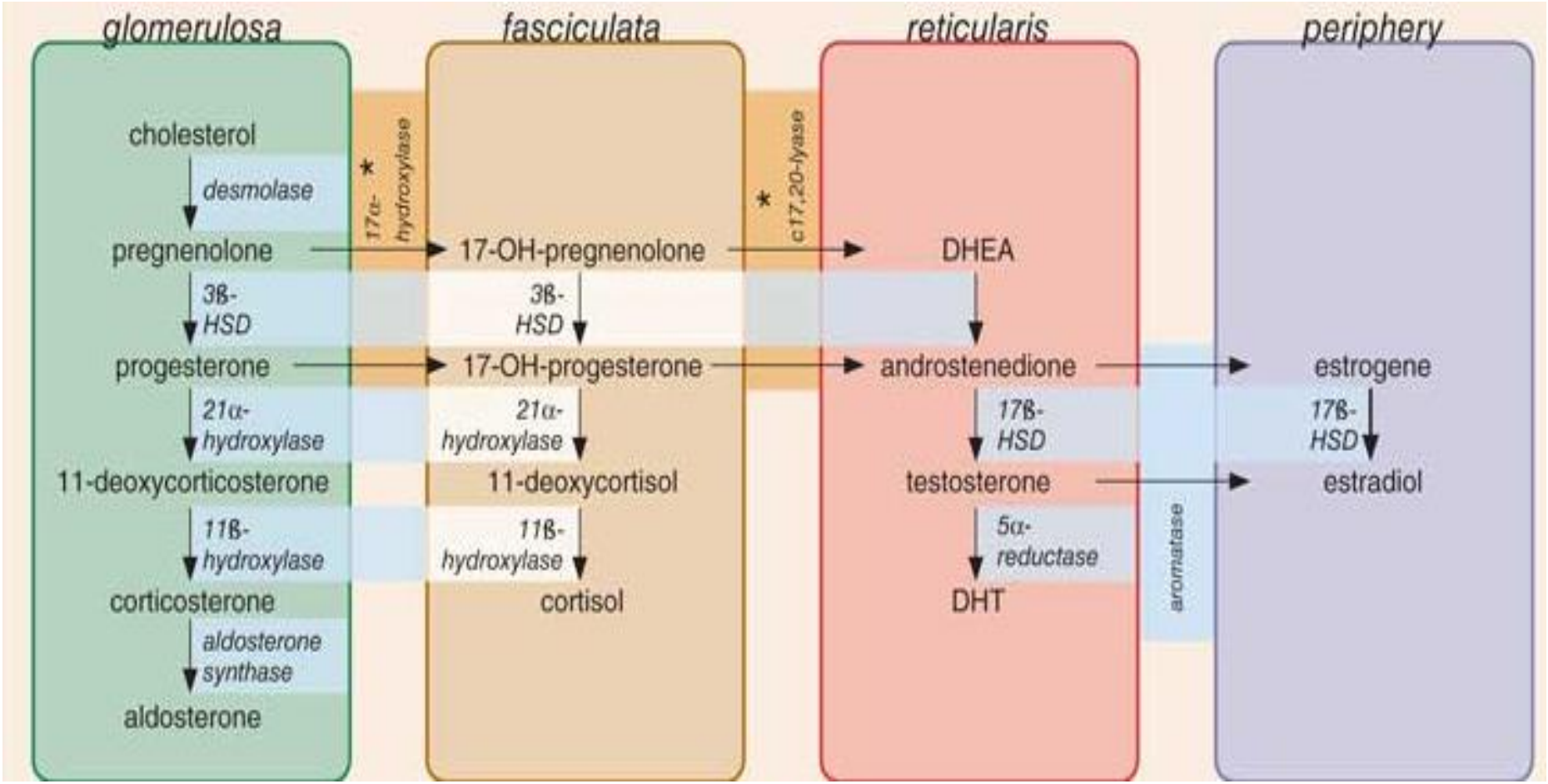
The adrenal cortex produces **three classes** of corticosteroid hormones:

•**mineralocorticoids** (e.g., ***aldosterone***) – regulate salt and water balance ;

•**glucocorticoids** (e.g., ***cortisol***) – regulate glucose use, immune and inflamatory homeostasis and other processes

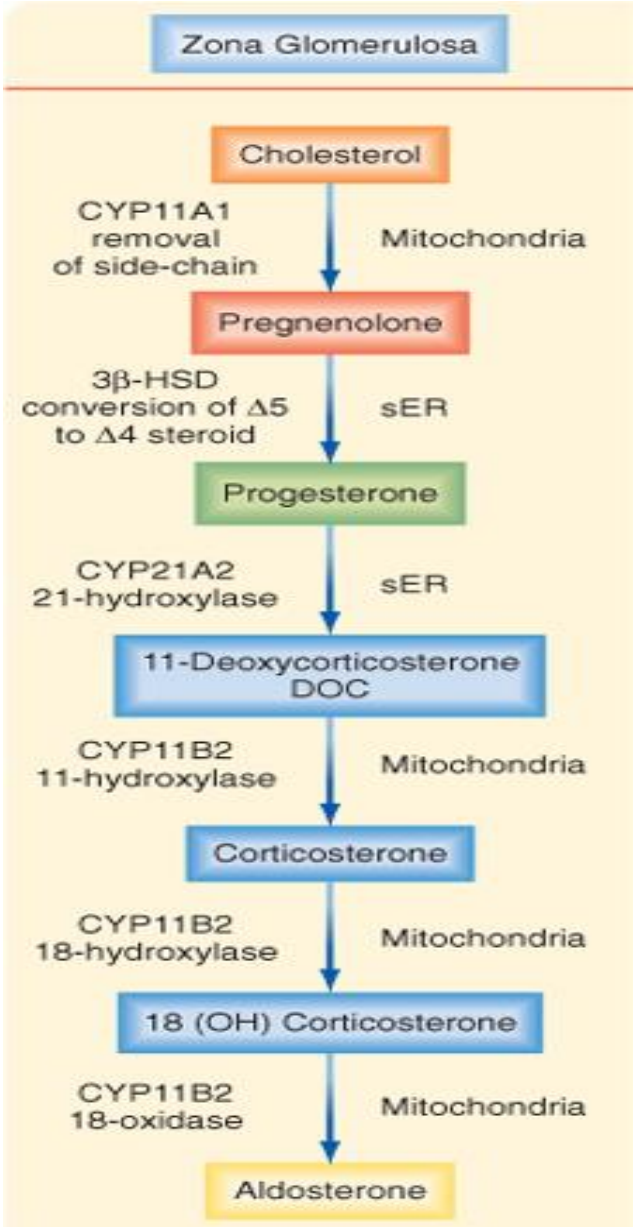
• **adrenal androgen precursors** (e.g., ***dehydroepiandrosterone***, •DHEA) – major role for fetoplacental estrogen synthesis and as a substrate for peripheral androgen synthesis in women

Adrenal cortex - synthesis of hormone



- The steroid hormones derived from **colesterol**
- Steroidogenic endocrine cells are characterized by the steroidogenic enzimes they express, as well as their final hormonal product

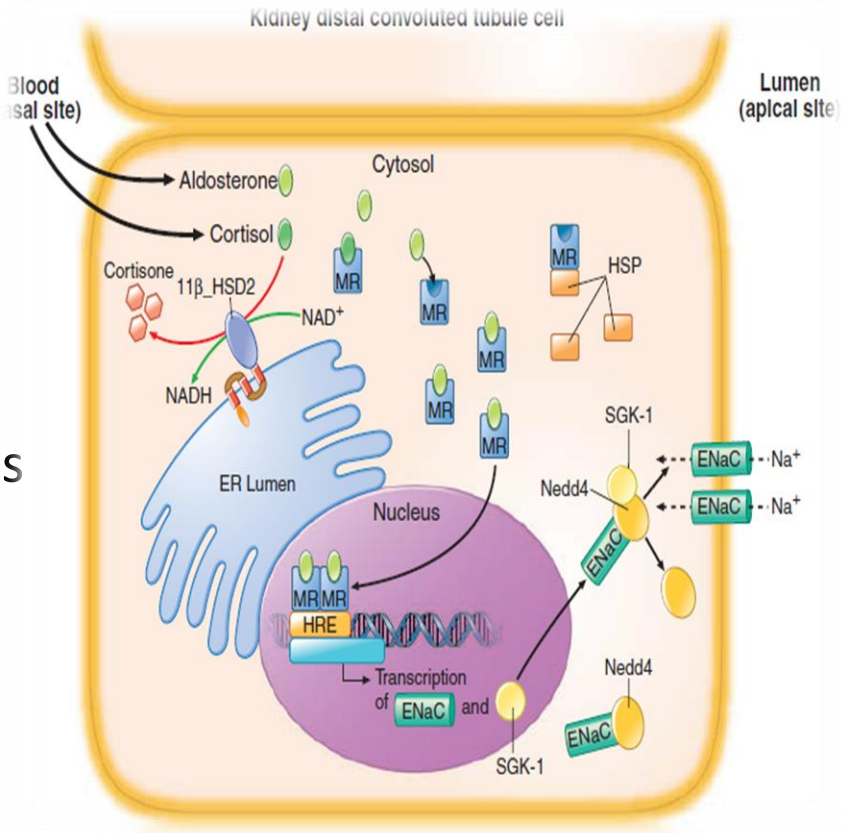
Zona glomerulosa



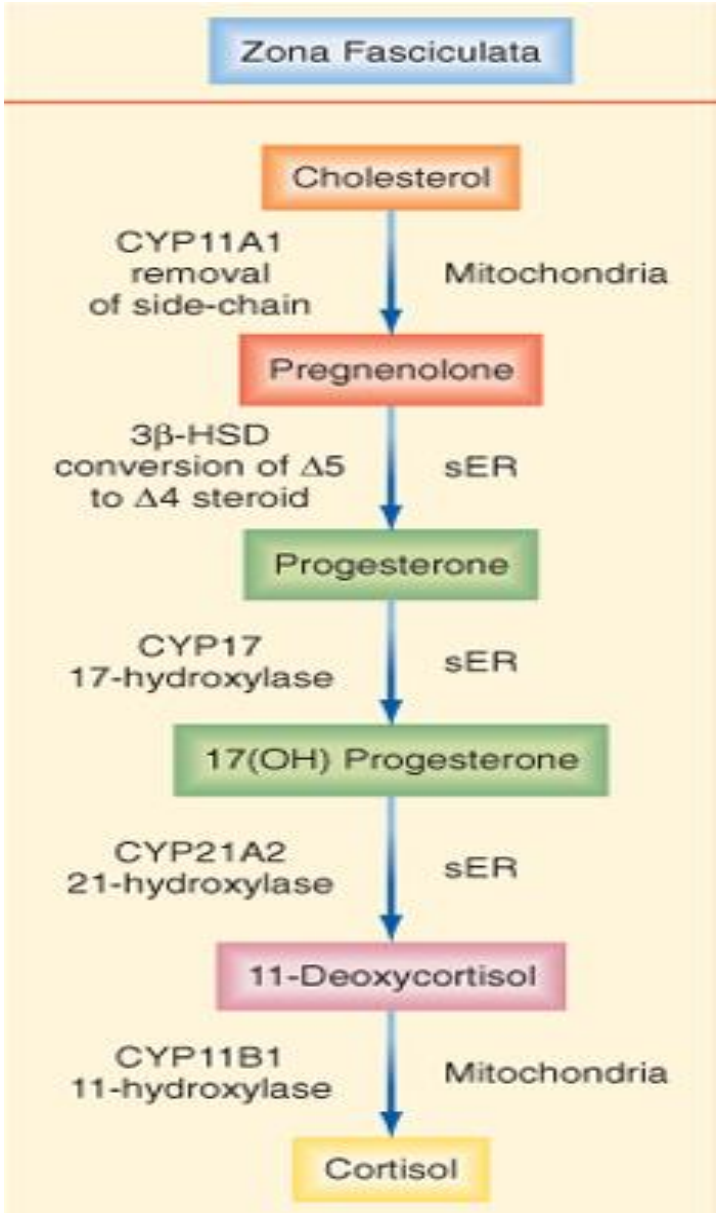
- Produces mineralocorticoid – **aldosterone,**
- **Regulate salt and volume homeostasis;**
- **Primarly regulated** by the
  - renin-angiotensin system,
  - extracellular K and
  - atrial natriuretic peptide;
- Is only ***secondarily influenced*** by ACTH;
- The zona glomerulosa is that it does **not express CYP 17**, therefore, these cells **never make cortisol and androgens;**
- **A completely unique features** of the zona glomerulosa is the expression of **CYP 11B2 – aldosterone synthase** – catalyzes the last three reactions from DOC to aldosterone.

Physiologic actions of Aldosterone

- **Kidney:**
  - ↑ the reabsorbtion **of Na^+** , followed by **H_2O** by **the distal nephron** (*95% of reabsorption Na^+ in the nephron occurs before the distal nephron, independently of Aldosterone regulation*)**;**
  - **Na^+** uptake at the distal nephron is accompanied by Cl^- and H_2O ;
  - Stimulates **K^+ and H^+ excretion**



Steroidogenic pathway



- The **largest** and most **actively** steroidogenic zone;
- Produces the **glucocorticoid** hormone, *cortizol;*
- **5 reaction**
  - The side chain of **cholesterol** is removed by CYP 11A1 to generate – **pregnenolone**;
  - **Pregnenolone** is a substrate for the enzyme 3βHSD2 and convert to **progesterone**;
  - **Progesterone** is then hydroxilated to **17 hydroxiprogesterone** by CYP 17 – it is indispensable step for the formation of cortizol;
  - **17 hydroxiprogesterone** is hydroxilated by CYP 21 producing **11deoxicortisol** and
  - then is hydroxilated by CYP 11B1 producing **cortisol**

Physiologic action of cortisol

- Hyperglycemic
  - Gluconeogenic
  - Insulin antagonist in muscle and in adipose tissue
- Lypolitic
- Protein catabolic
- Anti-inflamatory
- Suppress immune system
- Inhibits ADH secretion and action
- Permissive for calorigenic, lypolitic effects of catecholamines

Metabolic action

- Cortisol – regulates blood glucose – Hyperglycemic;
  - **Stimulating gluconeogenesis**:
    - **Direct** – enhances the gene expresion of phosphoenolpiruvate carboxykinase (PEPCK) and glucose6phospatase
    - **Indirect** – increasing responsivness to glucagon and catcholamines
  - Insulin antagonist in muscle and in adipose tissue. **Decreases GLUT 4** mediated glucose uptake in skeletal muscle and adipose tissue;

Actions on bone, connective tissue

- increase bone resorption;
- decrease intestinal calcium absorption and decrease renal calcium reabsorbtion;
- direct inhibit osteoblast - Inhibits bone formation
- inhibits fibroblast proliferation and collagen formation

Actions on CVS and GI

- **Cortisol** is ***permissive on the actions of catecholamines*** – **increases cardiac output and blood pressure;**

- Necessary for vascular response to catecholamines

- **Cortisol** **stimulates erythropoietin** synthesis, Stimulates red blood cell production

- Necessary for function GIT

Actions on CNC

- Alters mood and behavior
- **Cortisol** reinforces the enhancement of the delivery of blood glucose to the brain by its positive efects on the CVS;

Anti-inflammatory and immunosuppressive action

- **Cortisol, along epinephrine and norepinephrine**, **represses the production of proinflamatory cytokines** and stimulate the production of anti-inflamatory cytokines;

- **Cortisol inhibits phospholipase A2** a key enzime in prostoglandin, leukotriens and thromboxane syntesis.

- **Cortisol stabilizes lysososmal membranes**, thereby decreasing the release of the proteolitic enzymes that augment local swelling;

- **Cortisol inhibits** migration of leukocytes to the site of injury;

- **Cortisol stimulates** release of the neutrophils from bone marrow;

- **Cortisol decreases** number of circulating eosinophils

- **Cortizol inhibits proliferation of connective tissue** fibroblasts, inhibits the immune response;

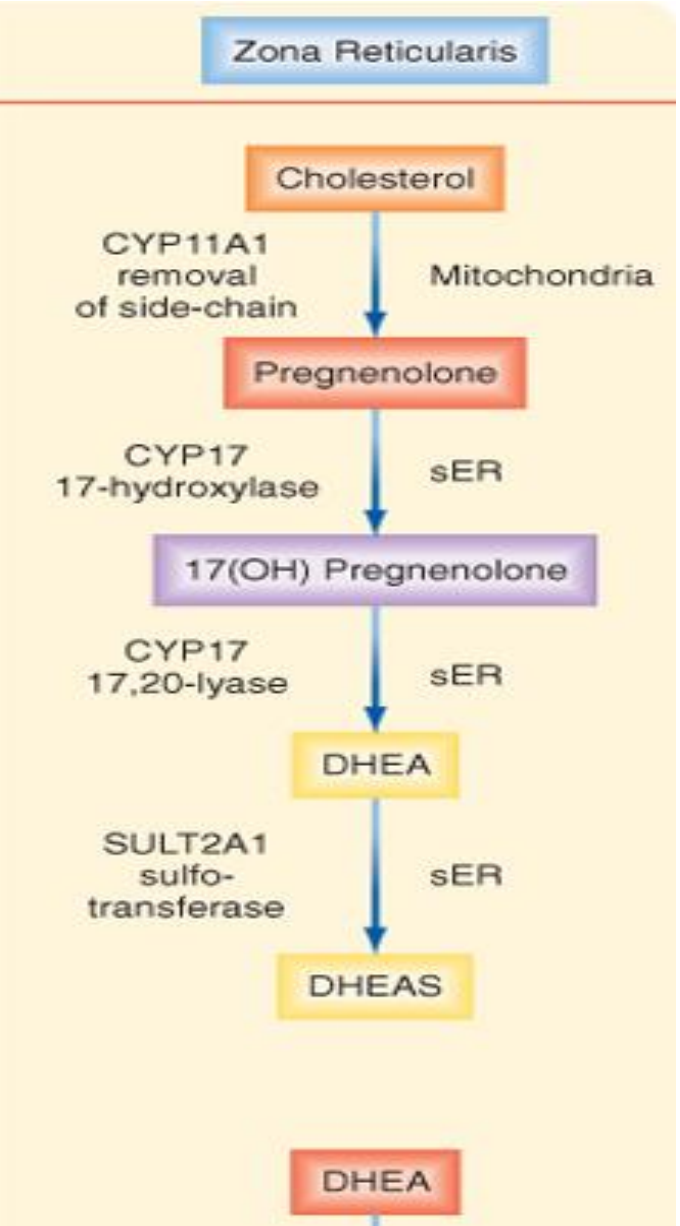
- **High cortisol levels decrease the number of circulating Tlymphocytes** (Thelper) and decrease their ability to migrate to the site of antigenic stimulation

	Physiologic function	Cushing Syndrome	Addison Disease
Liver	Increased expression of gluconeogenic enzymes,	Increased **hepatic glucose output**; together with insulin, increased hepatic glycogen stores	Diminished hepatic glucose output and glycogen stores
Adipose tissue	Permissive for lipolytic signals (catecholamines, GH) leading to elevated plasma FFA to fuel gluconeogenesis	Overall effect (together with insulin): **central obesity** (truncal obesity, moon facies, and buffalo hump)	**Decreased adiposity** and decreased lipolysis
Skeletal muscle	Degradation of fibrillar muscle proteins by activating the ubiquitin pathway, thereby providing amino acid substrates for gluconeogenesis	Muscle weakness and wasting mainly in proximal muscles; increased urinary nitrogen excretion (urea from amino acids)	Muscle weakness, decreased muscle glycogen stores; decreased urinary nitrogen excretion
Glucose	Maintains plasma glucose during fasting (antihypoglycemic action); increases plasma glucose during stress (hyperglycemic action)	Impaired glucose tolerance, insulin-resistant diabetes mellitus; increased plasma glucose is due to decreased peripheral glucose utilization and increased hepatic glucose output	**Hypoglycemia,** increased insulin sensitivity

	Physiologic effects	Cushing Syndrome	Addison Disease
Heart	Increased contractility	Hypertension	Lower peripheral resistance; postural decrease in blood pressure (orthostatic hypotension); low-voltage ECG
Skin	Antiproliferative for fibroblasts and keratinocytes	Easy bruisability due to dermal atrophy; striae or sites of increased tension, especially sites of adipose tissue accumulation; poor wound healing; hirsutism and acne are due to ACTH-mediated increase of adrenal androgens; hyperpigmentation is a direct effect of ACTH on melanocortin 1 receptors	Darkening of the skin is due to ACTH mediated stimulation of epidermal melanocortin 1 receptors; vitiligo may occur due to direct autoimmune destruction of melanocytes in circumscribed areas

		Cushing Syndrome	Addison Disease
Gastrointestinal tract	trophic effect on the gastrintestinal mucosa	Weight gain; stimulation of gastric acid and pepsin secretion increases the risk for ulcer	GI motility decreases; GI mucosa degenerates; GI acid and enzymes production decrease
Kidney	inhibits ADH secretion and action; Increased GFR and nonphysiologic actions on mineralocorticoid receptors	Hyponatremia due to SIADH Hypokalemic alkalosis, increased ECF volume due to mineralocorticoid activity (increased DOC, saturation of type 2 11 - hydroxysteroid dehydrogenase by high levels of cortisol)	Action of ADH is po tentiated, Hyponatremia, hyperkalemic acidosis, and decreased ECF volume are mainly due to loss of mineralocorticoid activity

Zona reticularis



- The innermost zone – begins to appear after birth at about age 5 years;
- Produces the **androgen** hormones
- **DHEAS –** become detectable at about 6 years of age;
- Onset of adrenal androgen production is called adrenarche, contributes to appearance of axillary and pubic hair;
- limited amount of androstendione is made in z reticularis

Physiologic actions of adrenal androgens

Men

- Peripheral conversion of adrenal androgen to active androgens is much lower than testicular production

Women

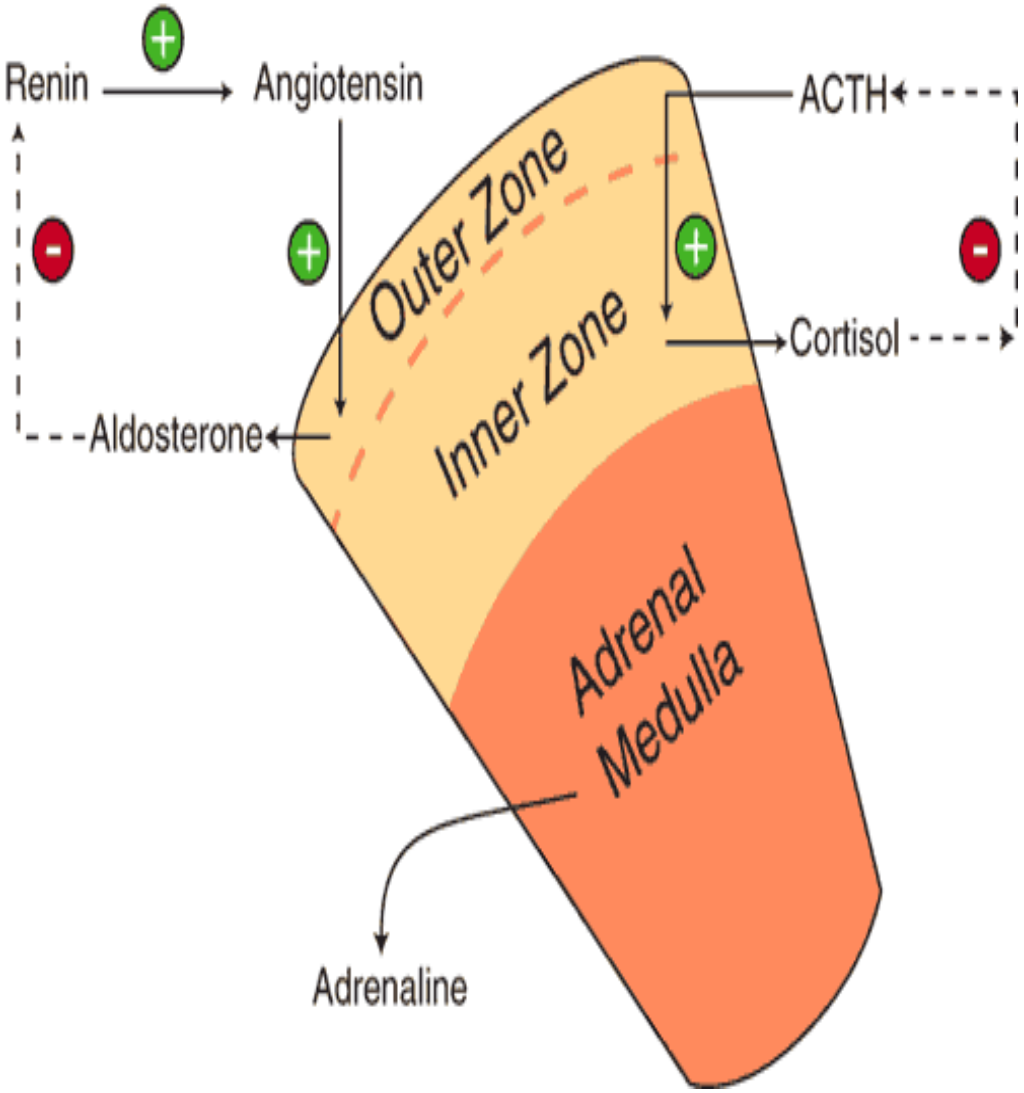
- Adrenal androgen contributes to about 50% of circulating active androgens – requiered for axillary and pubic hair growth and libido;

- **Excess** – involve **masculinization** of women (enlarged clitoris, hirsutism, ovarian dysovulation)

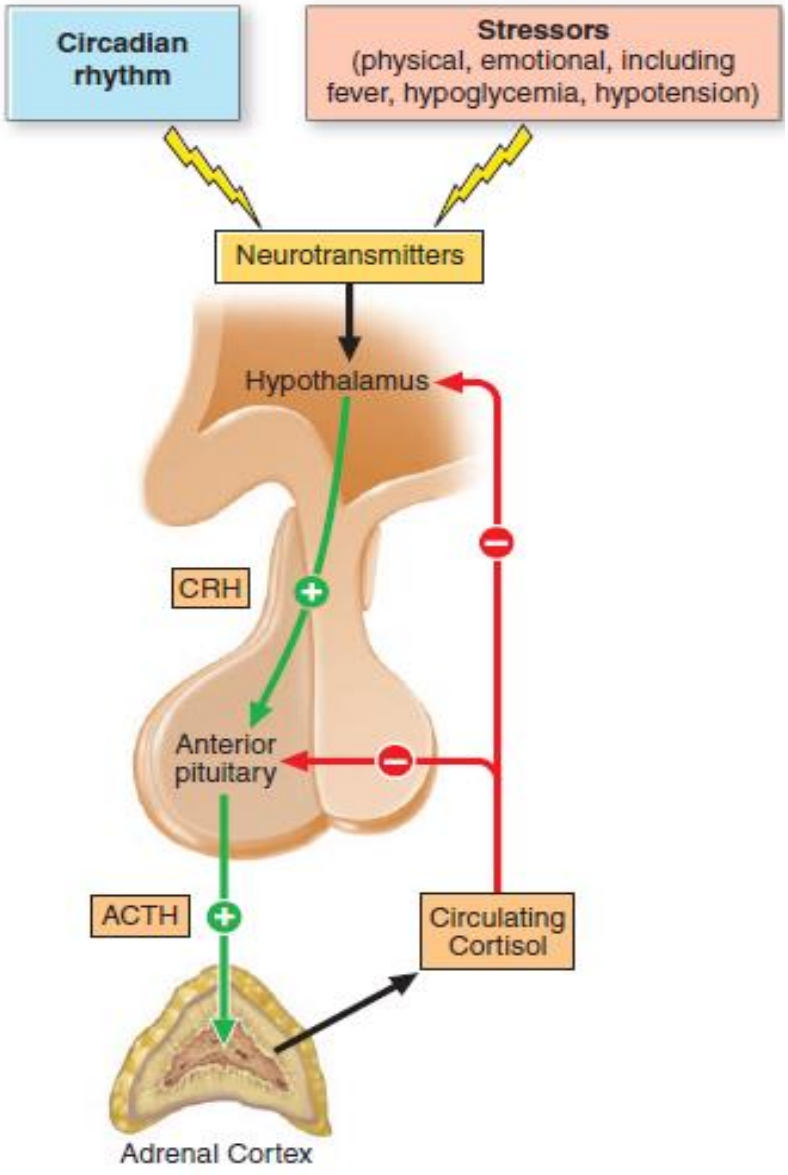
Regulation

•Production of **glucocorticoids and adrenal androgens** is under the control of the **hypothalamic-pituitary-adrenal (HPA) axis**,

•whereas **mineralocorticoids** are regulated by the **renin-angiotensinaldosterone** (RAA) system.



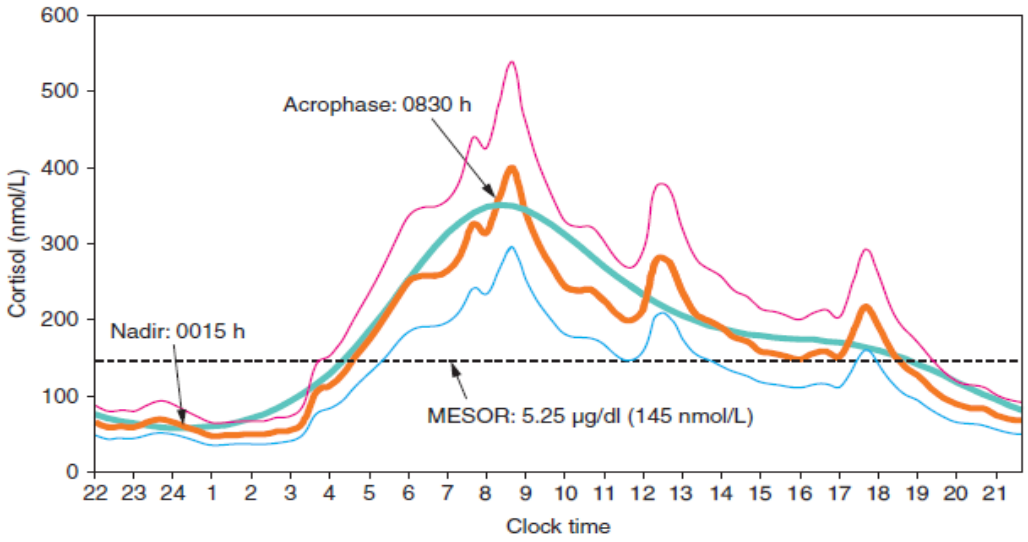
Regulation of the hypothalamic-pituitary-adrenal axis



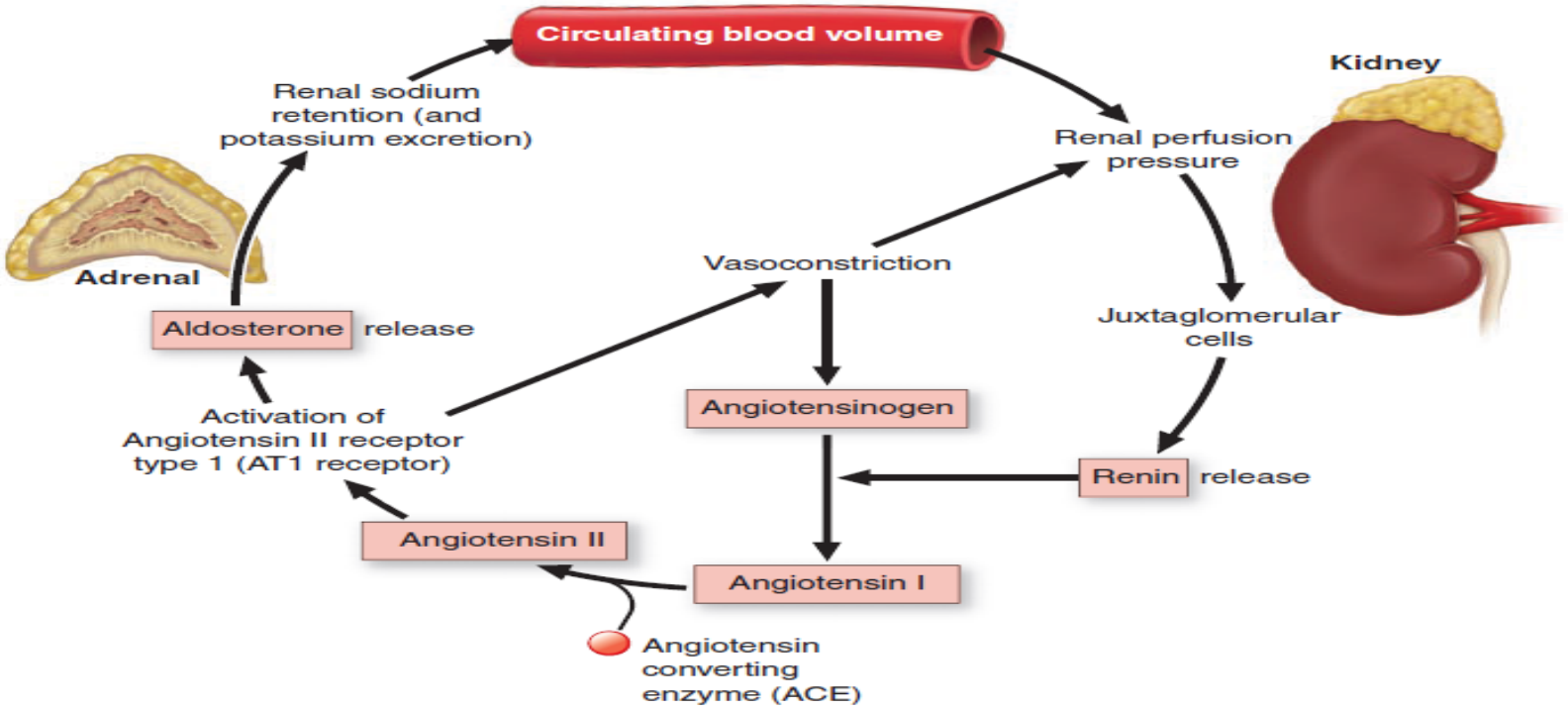
•**Endogenous or exogenous stress** → corticotropin-releasing hormone **(CRH**).

•**CRH stimulates** the cleavage of the pro opiomelanocortin (POMC) →**adrenocorticotropic hormone (ACTH)**.

•**ACTH →cortisol synthesis**, with additional short-term effects on mineralocorticoid and adrenal androgen synthesis. **Trophic actions**



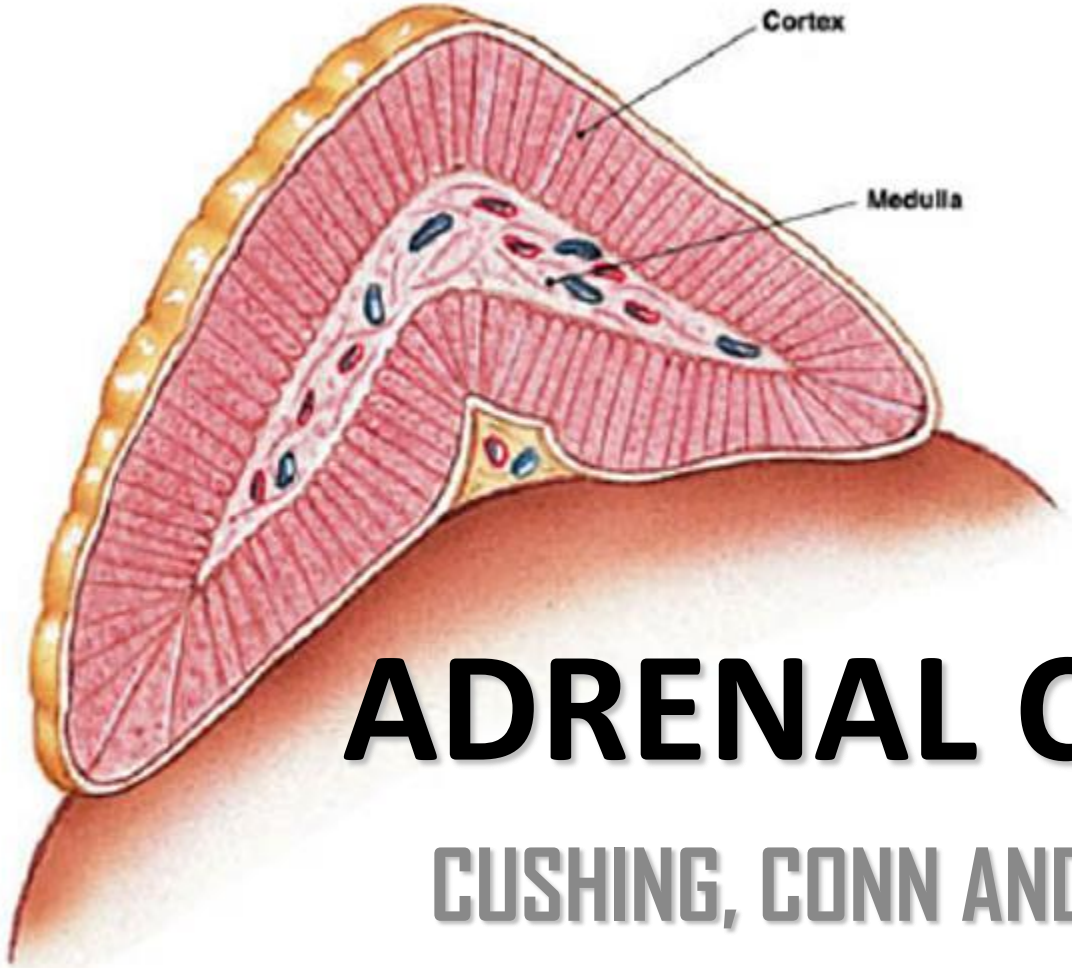
Regulation of the renin-angiotensin-aldosterone system



•**Mineralocorticoid production** is controlled by the RAA regulatory cycle, which is initiated by the release of renin from the juxtaglomerular cells in the kidney, resulting in cleavage of angiotensinogen to angiotensin I in the liver**.**

•**Angiotensinconverting enzyme (ACE)** cleaves angiotensin I to angiotensin II, which binds and activates AT1 receptor, resulting in increased aldosterone production and vasoconstriction.

•**Aldosterone enhances sodium retention and potassium excretion**, and increases the arterial perfusion pressure, which in turn regulates renin release.



ADRENAL CORTEX

CUSHING, CONN AND ADDISON DISEASE

CUSHING'S SYNDROME

reflects a

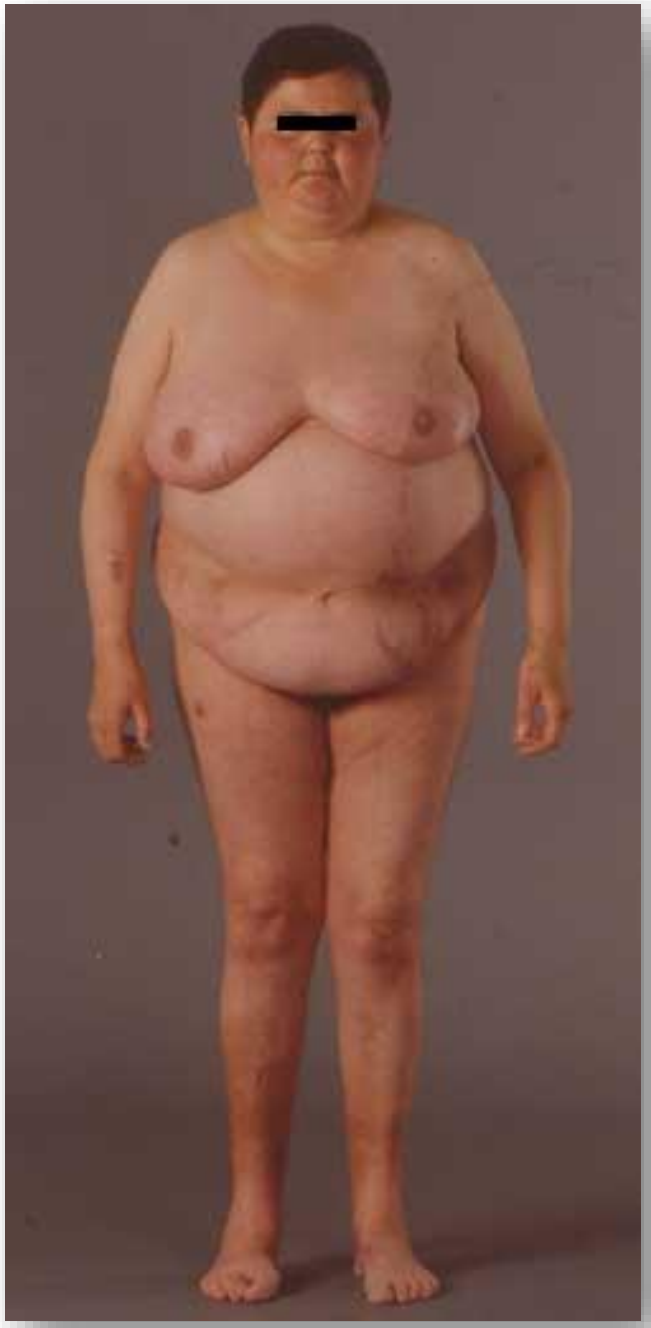
constellation of clinical features

that result from

chronic exposure to excess glucocorticoids

of any etiology.

- **ACTH-dependent**
  - pituitary corticotrope adenoma,
  - ectopic secretion of ACTH by nonpituitary tumor
- **ACTH-independent**
  - Adrenocortical adenoma,
  - adrenocortical carcinoma,
  - nodular adrenal hyperplasia
- **iatrogenic**
  - administration of exogenous glucocorticoids to treat various inflammatory conditions



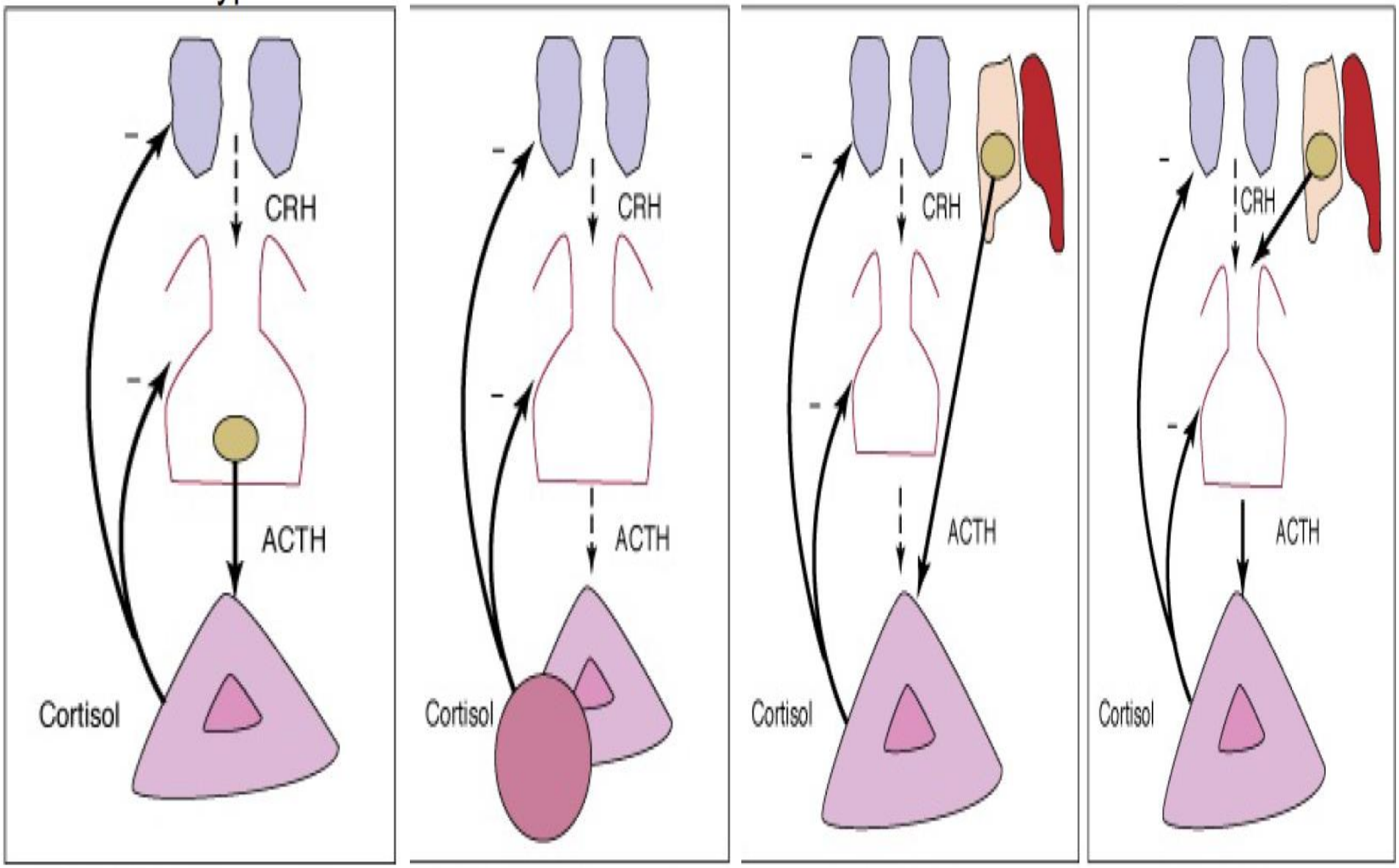
Etiology

ACTH dependent Cushing's Syndrome 90%

- **pituitary corticotrope adenoma 75% Cushing's Disease** (F/M 4/1)
  - Microadenoma 90%
  - Macroadenoma 5-10%
- **ectopic secretion of ACTH by nonpituitary tumor 15%** (F/M 1/1)
  - Small Carcinoid tumor (*lung, thymus, pancreas)*
  - Medullary thyroid cancer
  - Pheochromacytoma

ACTH independent Cushing's Syndrome 10%

Adrenocortical adenoma 5-10
Adrenocortical carcinoma 1%
Rare causes: PPNAD, primary pigmented nodular adrenal disease; AIMAH, ACTHindependent massive adrenal hyperplasia; McCune-Albright syndrome
<1%

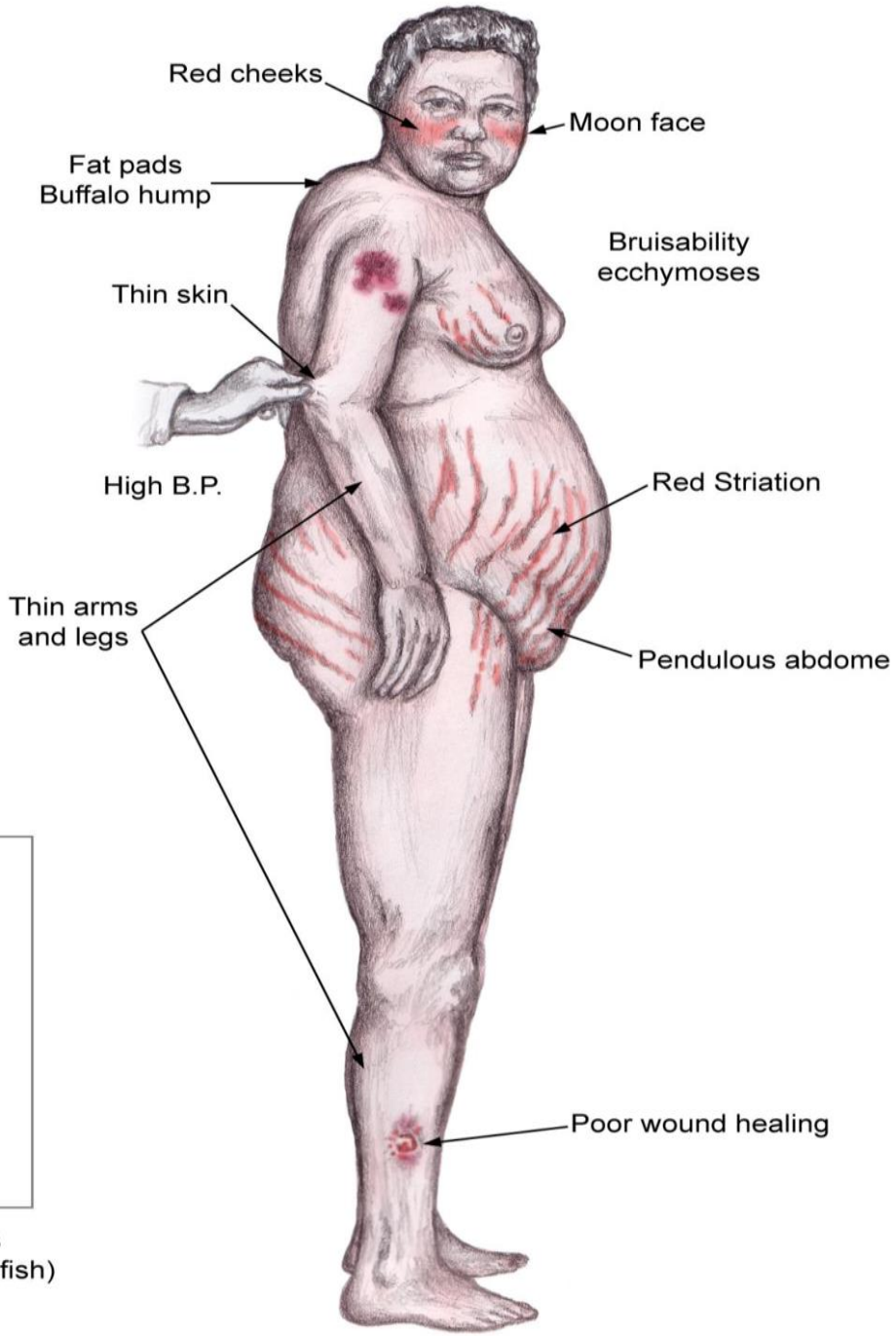


Pituitary ACTH-dependent Cushing syndrome

Adrenal adenoma with ACTH-independent Cushing syndrome

Ectopic ACTH syndrome

Ectopic CRH syndrome



Body Compartment/System	Signs and Symptoms
Body fat	Weight gain, central obesity, rounded face, fat pad on back of neck ("buffalo hump")
Skin	Facial plethora, thin and brittle skin, easy bruising, broad and purple stretch marks, acne, hirsutism
Bone	Osteopenia, osteoporosis (vertebral fractures), decreased linear growth in children
Muscle	Weakness, proximal myopathy (prominent atrophy of gluteal and upper leg muscles)
Cardiovascular system	Hypertension, hypokalemia, edema, atherosclerosis
Metabolism	Glucose intolerance/diabetes, dyslipidemia
Reproductive system	Decreased libido, in women amenorrhea (due to cortisol-mediated inhibition of gonadotropin release)
Central nervous system	Irritability, emotional lability, depression, sometimes cognitive defects, in severe cases, paranoid psychosis
Blood and immune system	Increased susceptibility to infections, increased white blood cell count, eosinopenia, hypercoagulation with increased risk of deep vein thrombosis and pulmonary embolism

DIAGNOSIS

There are two stages in the investigation of suspected Cushing syndrome:

(1) Does this patient have Cushing syndrome?
(2) If so, what is the cause?

QUESTION 1:
DOES THIS PATIENT HAVE CUSHING SYNDROME?

Cushing syndrome suspected

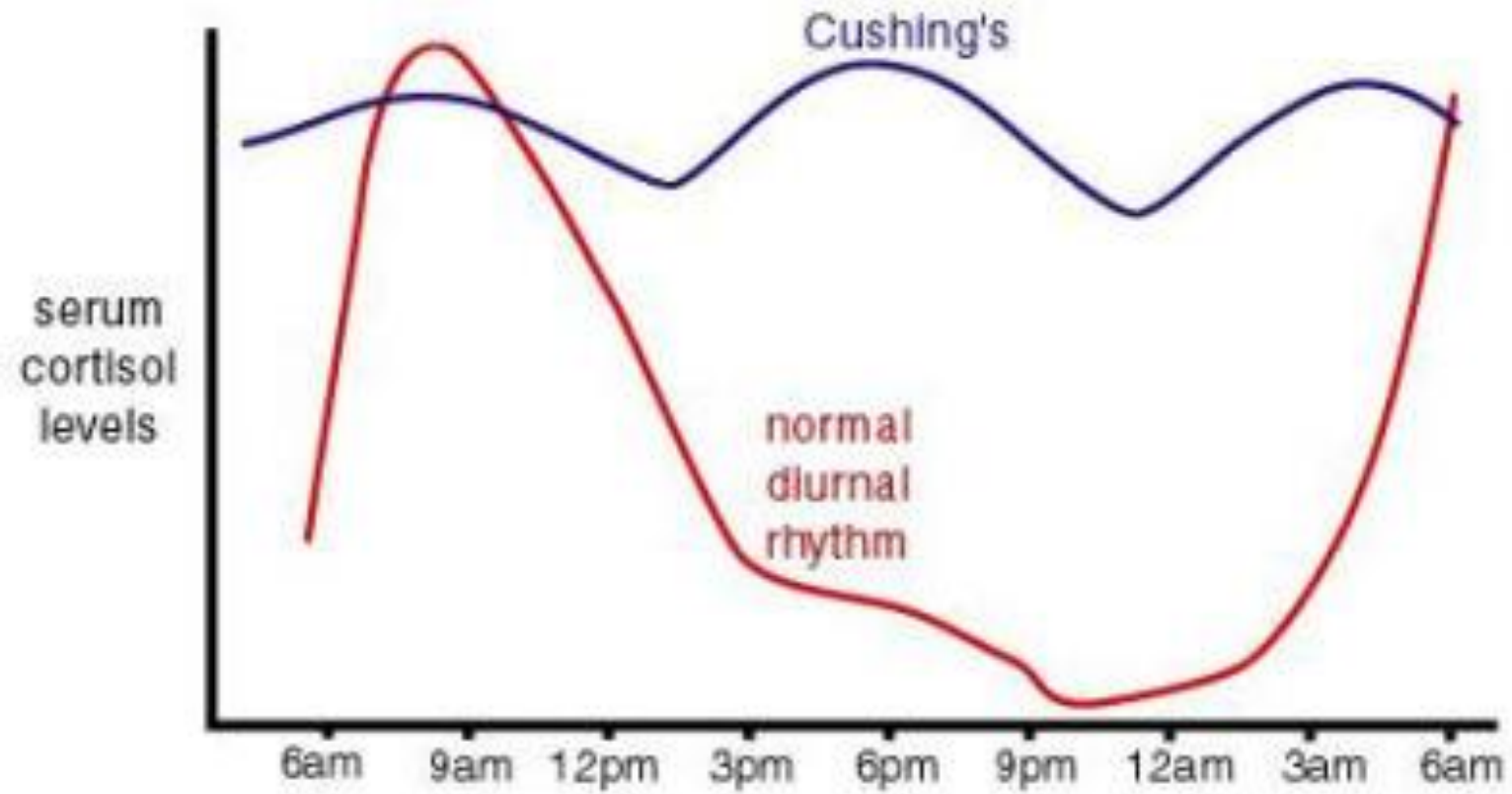
Exclude exogenous glucocorticoid exposure

Plasma cortisol

- **The diagnostic utility of single plasma cortisol concentrations is limited** by the episodic nature of cortisol secretion and *its appropriate elevations during stress* (such as stress of venipuncture, intercurrent illness, admission to hospital, during surgery, and following trauma)

- **Total cortisol concentrations may also be increased** in severe anxiety, endogenous depression, starvation, anorexia nervosa, alcoholism, chronic kidney disease, high-estrogen state (eg, during pregnancy and when exogenous estrogens or oral contraceptives are being used - increased CBG-binding capacity).

- **In normal subjects**, plasma cortisol levels are at their highest early in the morning and reach a nadir (<50 nmol/L [<2 µg/dL] in a nonstressed subject) at about midnight.



- This circadian rhythm is lost in patients with Cushing syndrome; in the majority, the 9 am plasma cortisol is normal but nocturnal levels are raised.
- Random morning plasma cortisol levels are therefore of little value in making the diagnosis, whereas a midnight cortisol level greater than 200 nmol/L (>7.5 µg/dL) indicates Cushing syndrome. Conversely, if a serum cortisol value is less than 50 nmol/L at midnight, Cushing syndrome is excluded at that time.

Salivary Cortisol

- **Cortisol in the saliva is in equilibrium with the free and biologically active cortisol in the blood**.

- **Salivary cortisol concentrations are not affected by changes in serum cortisol–binding proteins**, by salivary flow or composition, and they are stable at room temperature for many days.

- **Measurements of salivary cortisol can be obtained from late-night, ambulatory saliva** samples, which are used as a means of establishing the presence or absence of Cushing syndrome.

- Salivary cortisol may also be used to obtain accurate free cortisol levels in patients with abnormal serum-binding proteins.

- However, plasma and salivary cortisol in normal individuals reach a nadir from 10 pm to 2 am. **Patients with Cushing syndrome do not reach a normal nadir at this time**, and several studies have shown **that elevated late-night time salivary cortisol is a sensitive and specific diagnostic test for Cushing syndrome.**

Free urinary cortisol

- **The assay of unbound cortisol excreted in the urine is an excellent method for the diagnosis of Cushing syndrome**.

- **Urine free cortisol is measured in a 24-hour urine collection**

- **Diagnostic utility**—This method is particularly **useful in differentiating simple obesity from Cushing syndrome**, because urine free cortisol levels are not elevated in obesity.

- The levels may be elevated in the same conditions that increase plasma cortisol including a slight elevation during pregnancy.

Low-Dose Overnight Dexamethasone Suppression Tests

Dexamethasone, a potent glucocorticoid, **normally suppresses pituitary ACTH release** with a **resulting fall in plasma and urine cortisol**, thus assessing feedback inhibition of the HPA axis

- The **overnight 1-mg Dx suppression test** is commonly used as a screening test for Cushing syndrome.

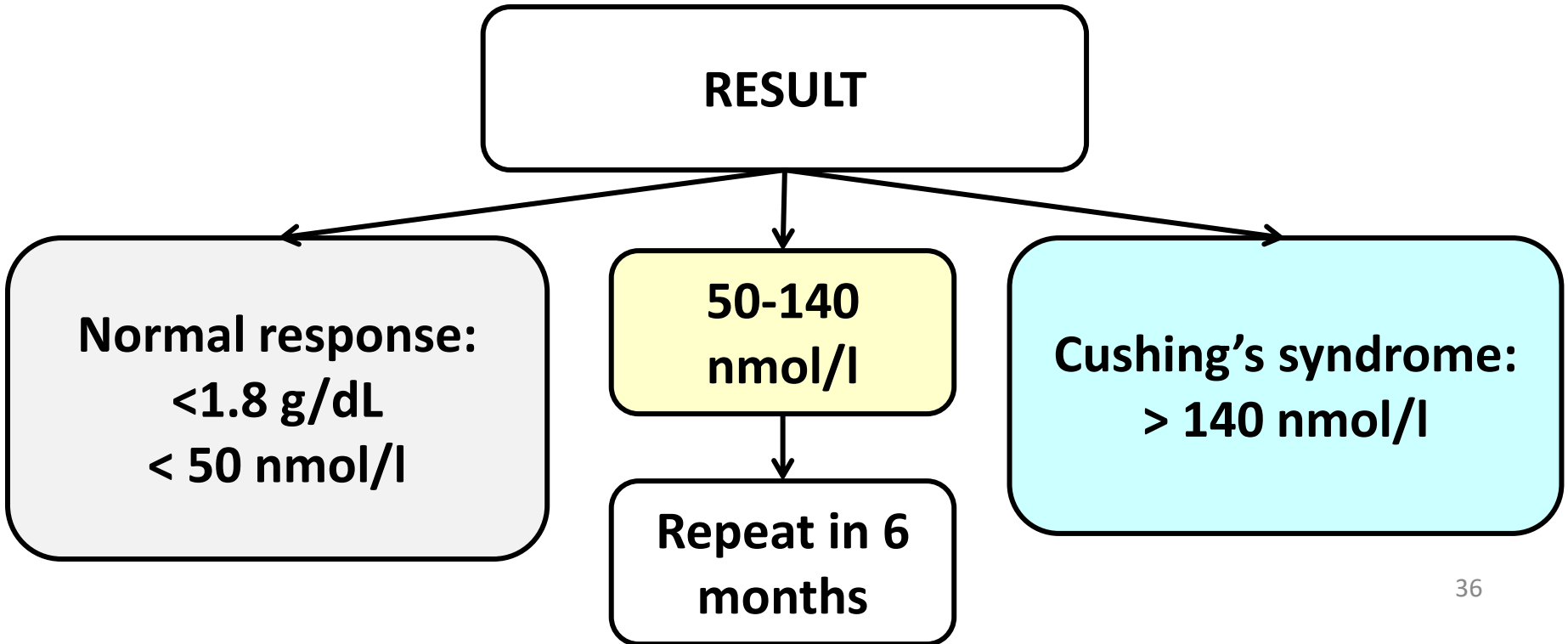
Low-Dose Overnight Dexamethasone Suppression Tests

I – day:

- Dexamethasone 1 mg is administered orally between 11 PM and midnight

II – day:

- Serum cortisol levels are drawn the next morning between 8 and 9 AM.



QUESTION 2:
WHAT IS THE CAUSE OF CUSHING SYNDROME IN THIS PATIENT?

Morning Plasma ACTH

- normal reference range 2–11 pmol/L (9–52 pg/mL);

- Such a test differentiates ACTH-dependent from ACTH-independent causes.

- In patients with **ACTH-independent Cushing syndrome** (primary glucocorticoid-secreting adrenal tumors) plasma **ACTH is suppressed**, and a level less than 5 pg/mL (1.1 pmol/L) is diagnostic.

- In patients with **ACTH-dependent Cushing syndrome:**

  - in the **Cushing disease** (pituitary ACTH hypersecretion), plasma **ACTH levels are inappropriately normal or modestly elevated**.

  - in the **ectopic ACTH syndrome**, **Plasma ACTH levels are high** (usually >20 pmol/L; >90 pg/mL)

Differential Diagnosis of ACTH-Dependent Cushing's Syndrome (between Cushing disease and ectopic ACTH syndrome):

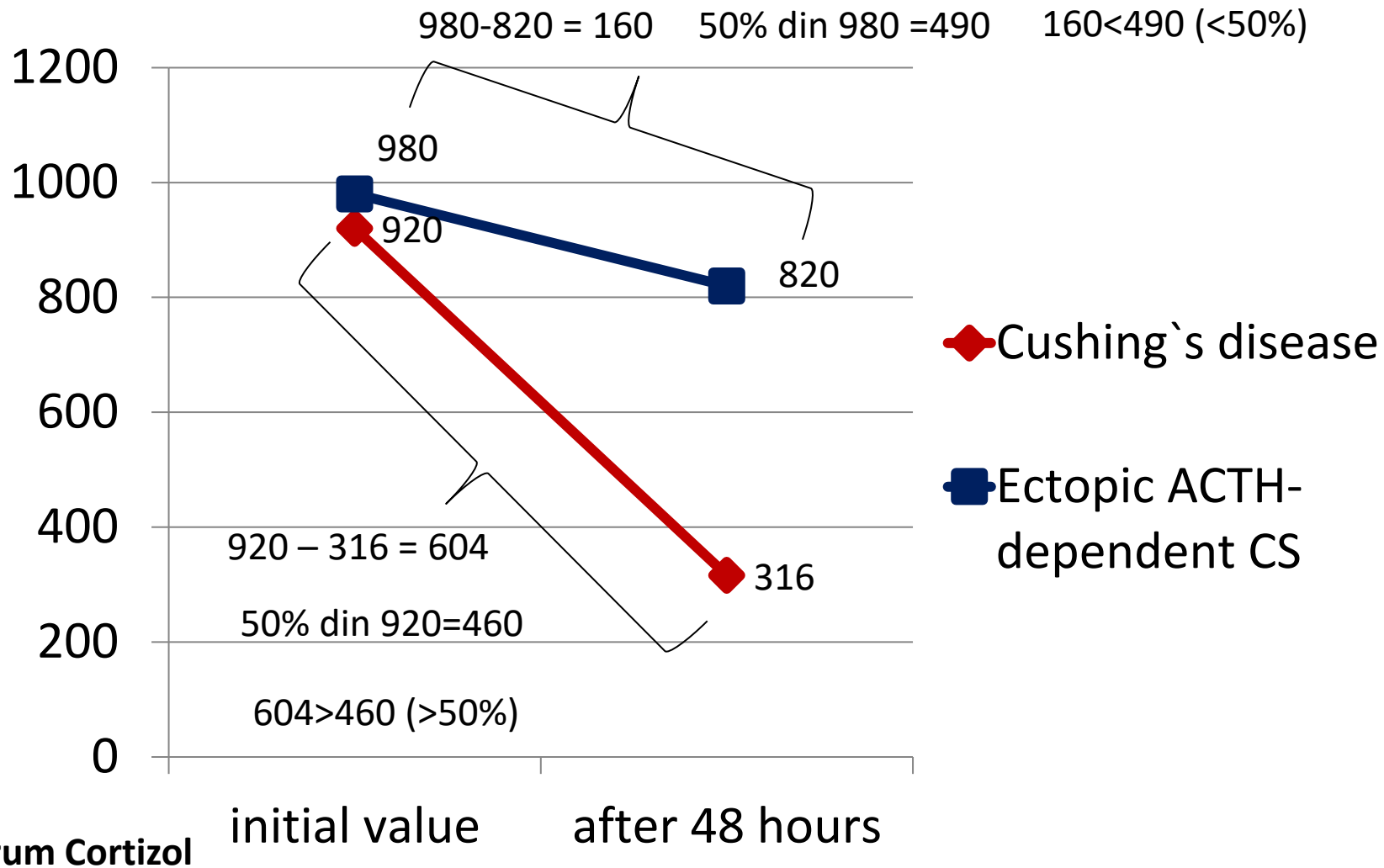
- High-Dose Dexamethasone Suppression Test
- Corticotropin-Releasing Hormone Test
- Inferior Petrosal Sinus Sampling and Selective Venous Catheterization

High-Dose Dexamethasone Suppression Test

- **Overnight high-dose Dx suppression** - Baseline morning serum cortisol is measured, and oral dexamethasone 8 mg is administered between 11 PM and midnight. Repeat serum cortisol is drawn the next morning (between 8 and 9 AM). Generally, **patients with Cushing disease suppress plasma cortisol level to less than 50%** of baseline values—in contrast to patients with the ectopic ACTH syndrome

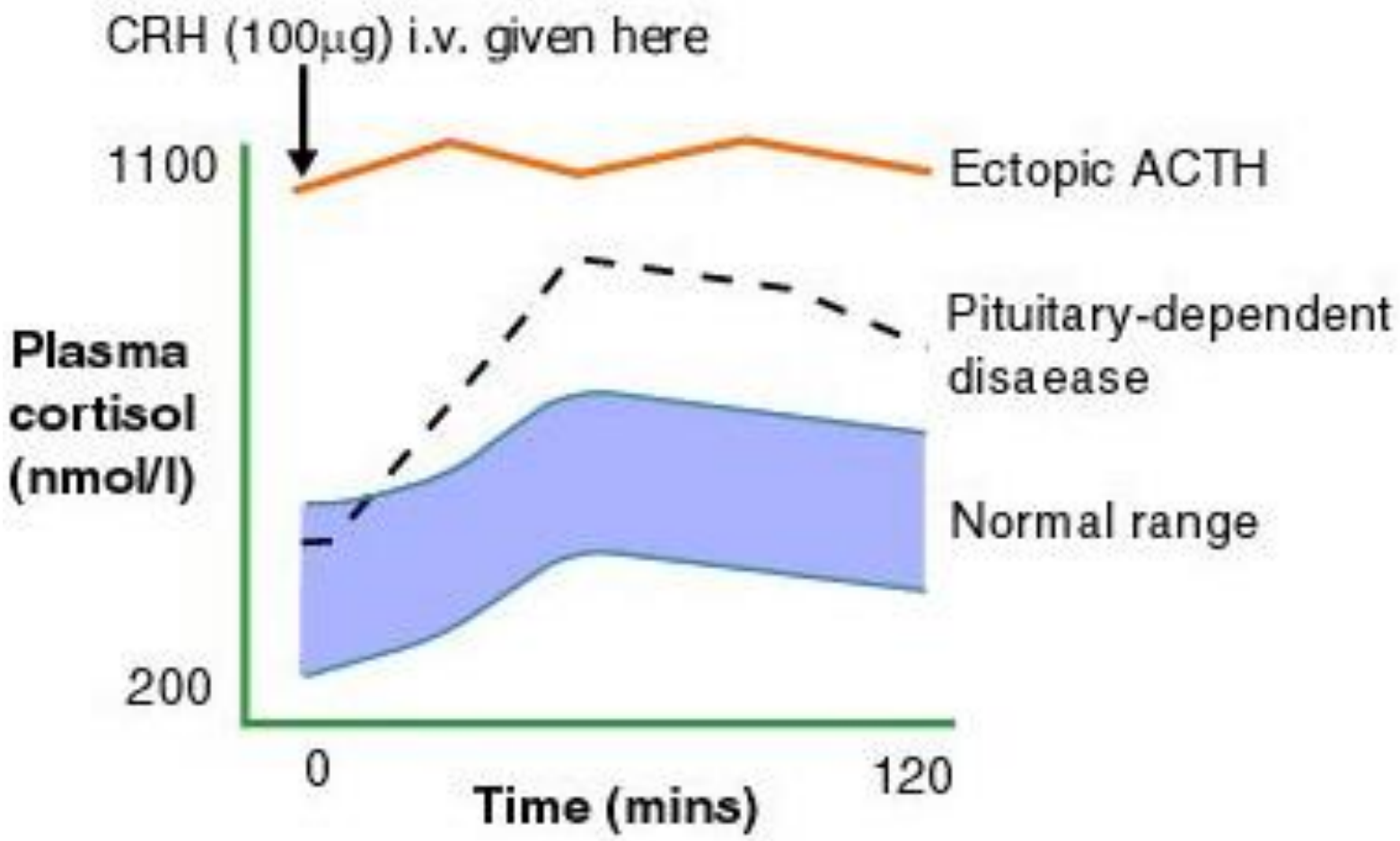
- **Two-day high-dose Dx suppression test—**2 mg orally every 6 hours for 2 days. The plasma or urinary free cortisol (or both) is measured at 0 and +48 hours, and a greater than 50% suppression of plasma cortisol from the basal value has been used to define a positive response (**Cushing disease**).

- **High-Dose Dexamethasone Suppression Test**



Serum Cortizol normal level 200-660

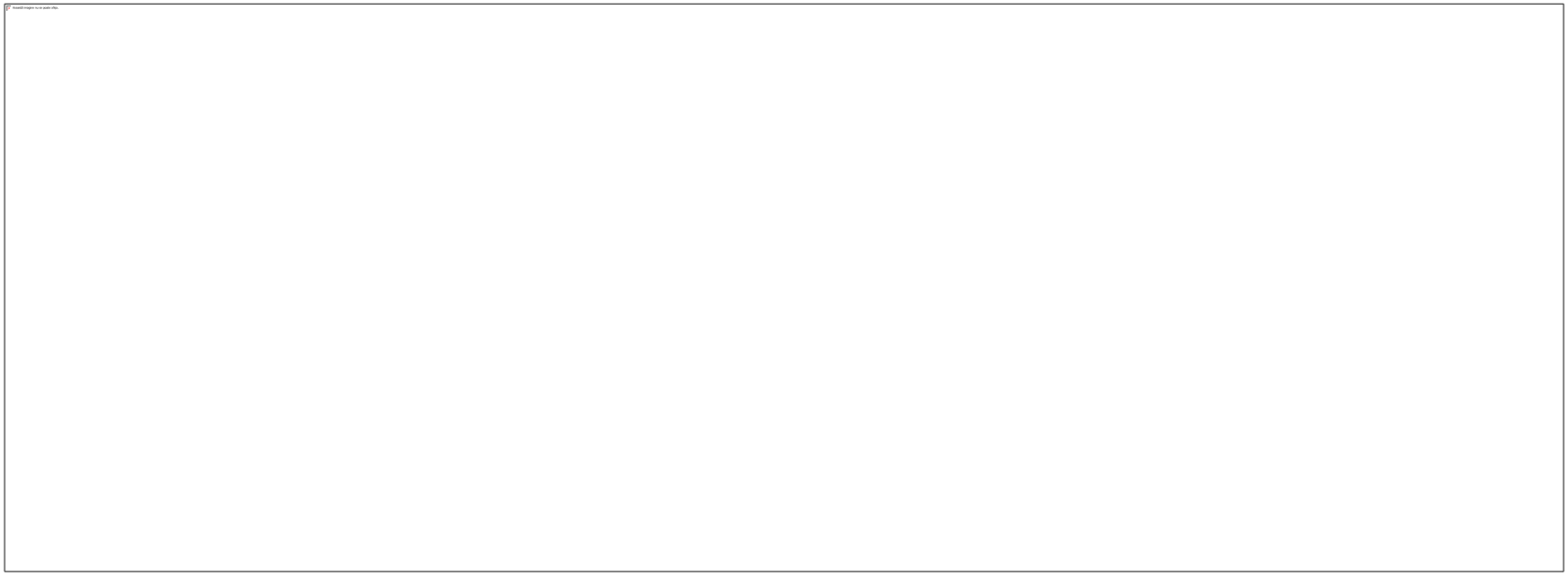
Corticotropin-Releasing Hormone Test



- **INFERIOR PETROSAL SINUS SAMPLING**
- The most definitive means of accurately distinguishing pituitary from nonpituitary ACTH-dependent Cushing syndrome is the use of bilateral simultaneous IPSS with CRH stimulation, and this procedure is the next step in the evaluation of patients with ACTH-dependent Cushing syndrome when MRI does not reveal a definite adenoma.
- Blood leaves the anterior lobe of the pituitary and drains into the cavernous sinuses, which then empty into the inferior petrosal sinuses and subsequently into the jugular bulb and vein. Simultaneous inferior petrosal sinus and peripheral ACTH measurement before and after CRH stimulation can reliably confirm the presence or absence of an ACTH-secreting pituitary tumor.

Imaging

- CT/MRI Scanning of Pituitary and Adrenal Glands

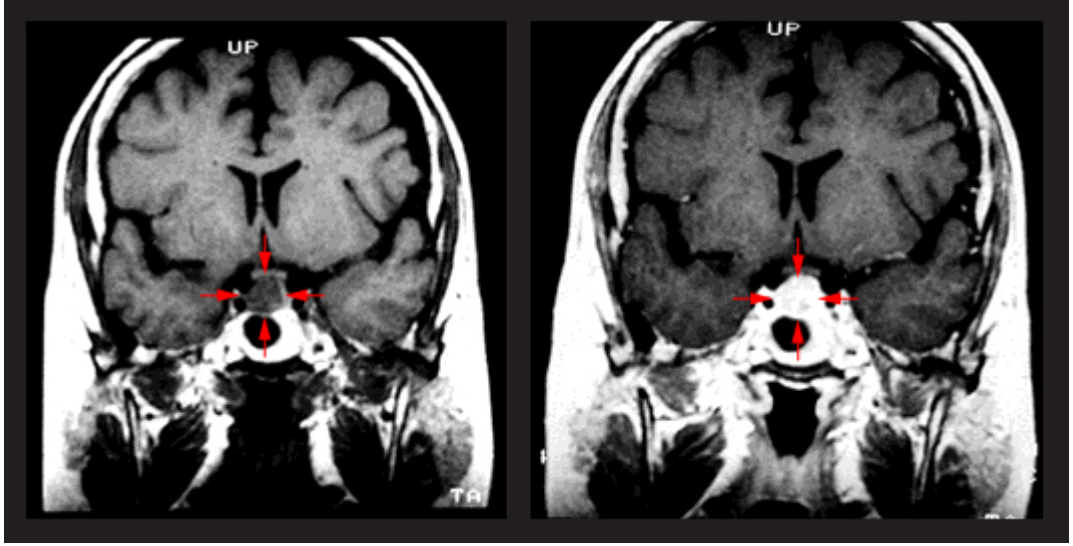


Normal

Pituitary ACTH-dependent Cushing syndrome – Cushing disease

Ectopic ACTH-dependent Cushing syndrome

ACTH-independent Cushing syndrome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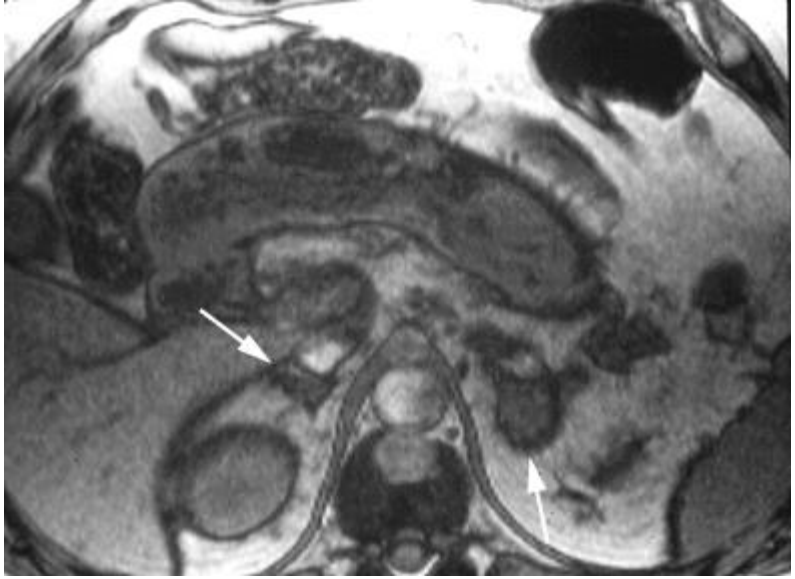

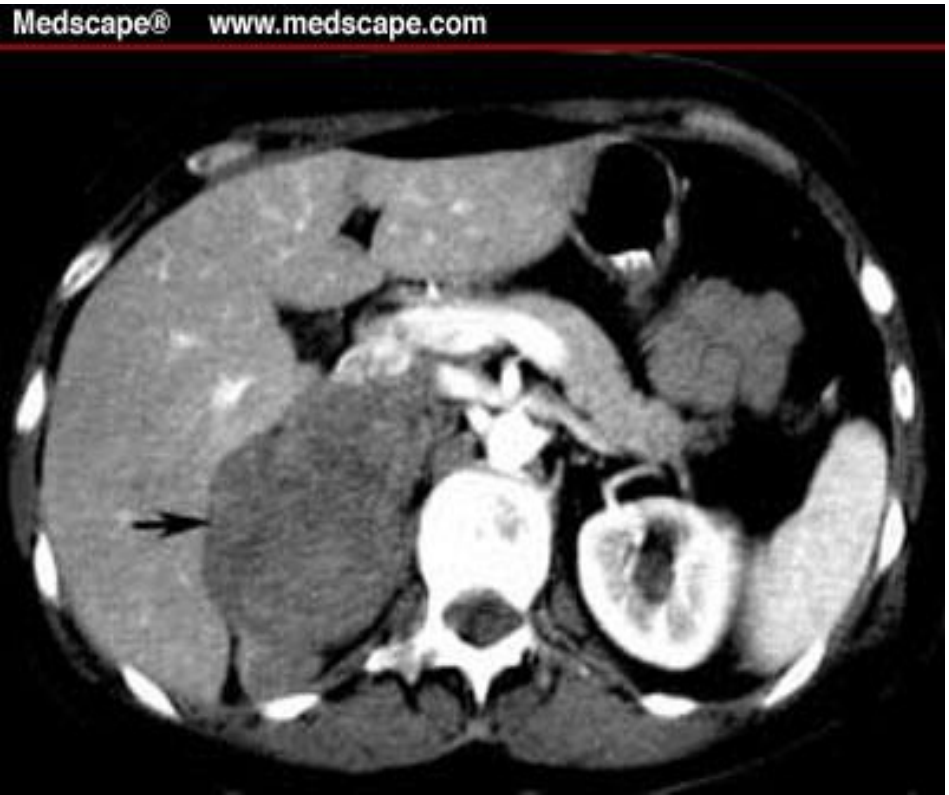
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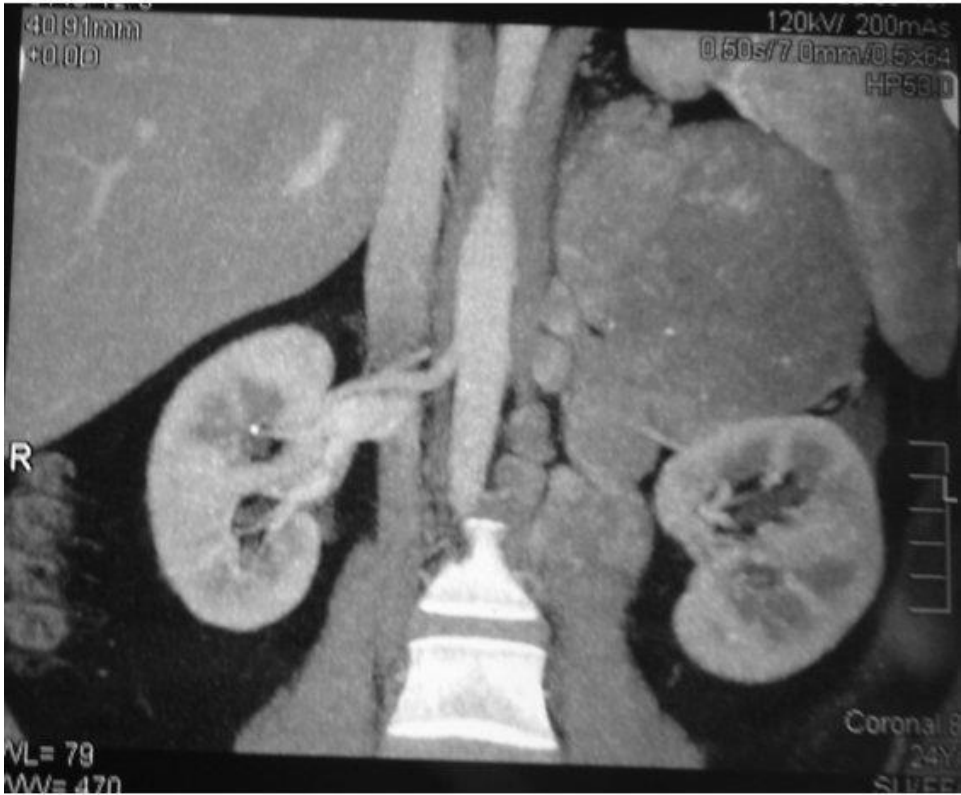
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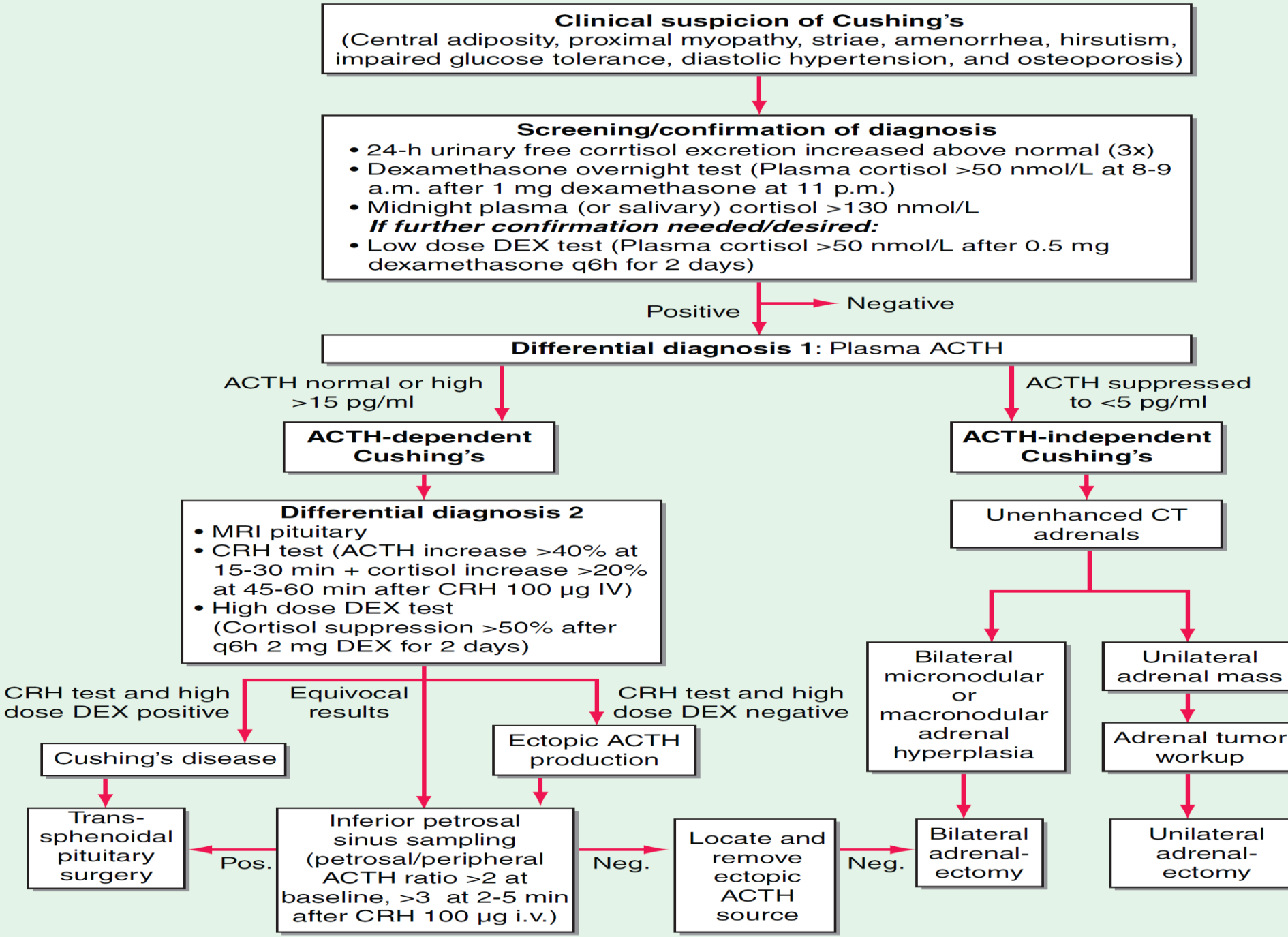
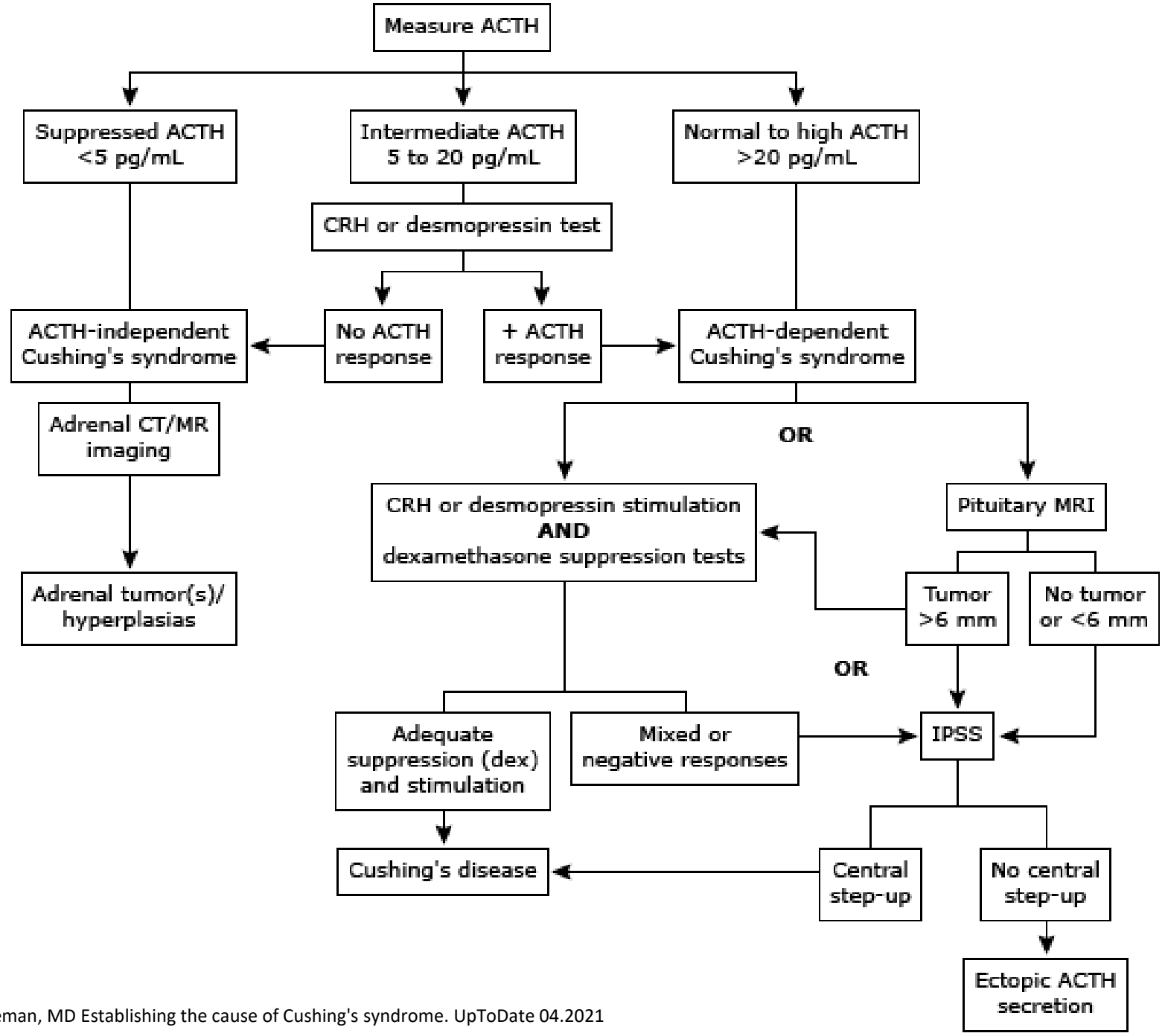
Algorithm for Management of the Patient with Suspected Cushing's Syndrome





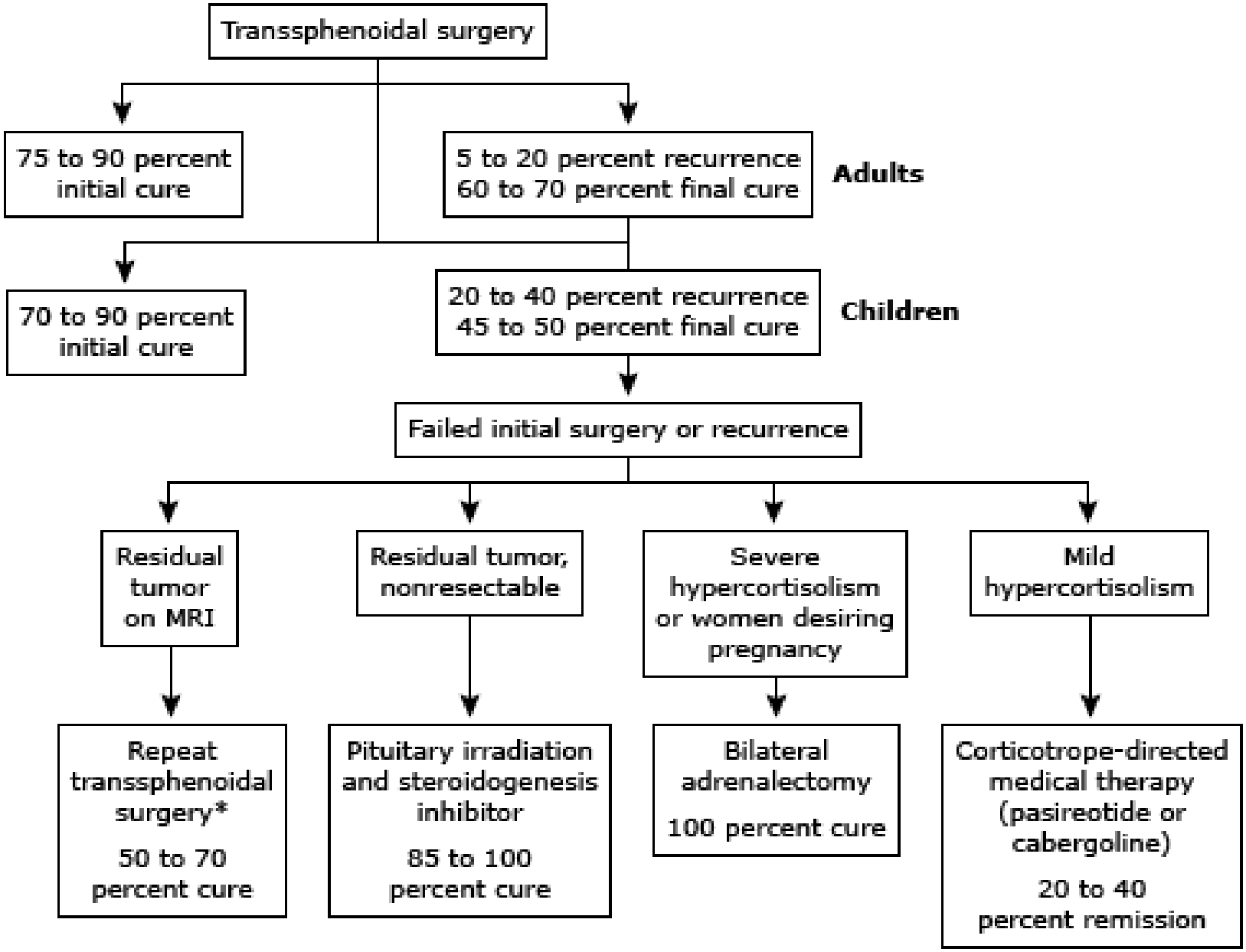
Lynnette K Nieman, MD Establishing the cause of Cushing's syndrome. UpToDate 04.2021

Treatment

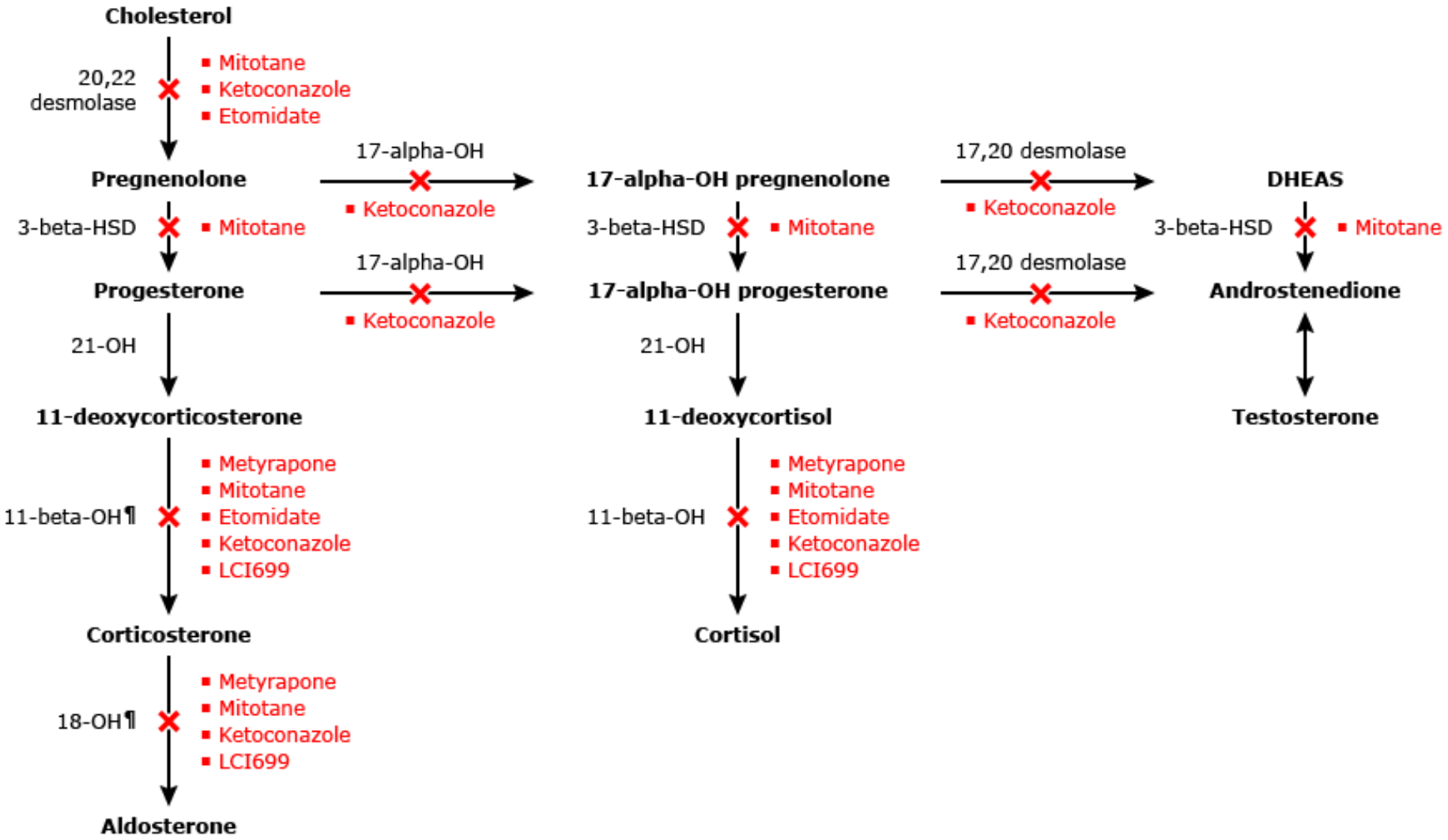
- **In ACTH-independent disease**, treatment consists of surgical removal of the adrenal tumor. For smaller tumors, a minimally invasive approach can be employed, whereas for larger tumors and those suspected of malignancy, an open approach is preferred.

- **In Cushing's disease**, the treatment of choice is selective removal of the pituitary corticotrope tumor, usually via a transsphenoidal approach.
  - This results in an initial cure rate of 70–80%
  - If pituitary disease recurs, there are several options, including second surgery, radiotherapy, stereotactic radiosurgery, and bilateral adrenalectomy. These options need to be applied in a highly individualized fashion.

Treatment of Cushing's disease



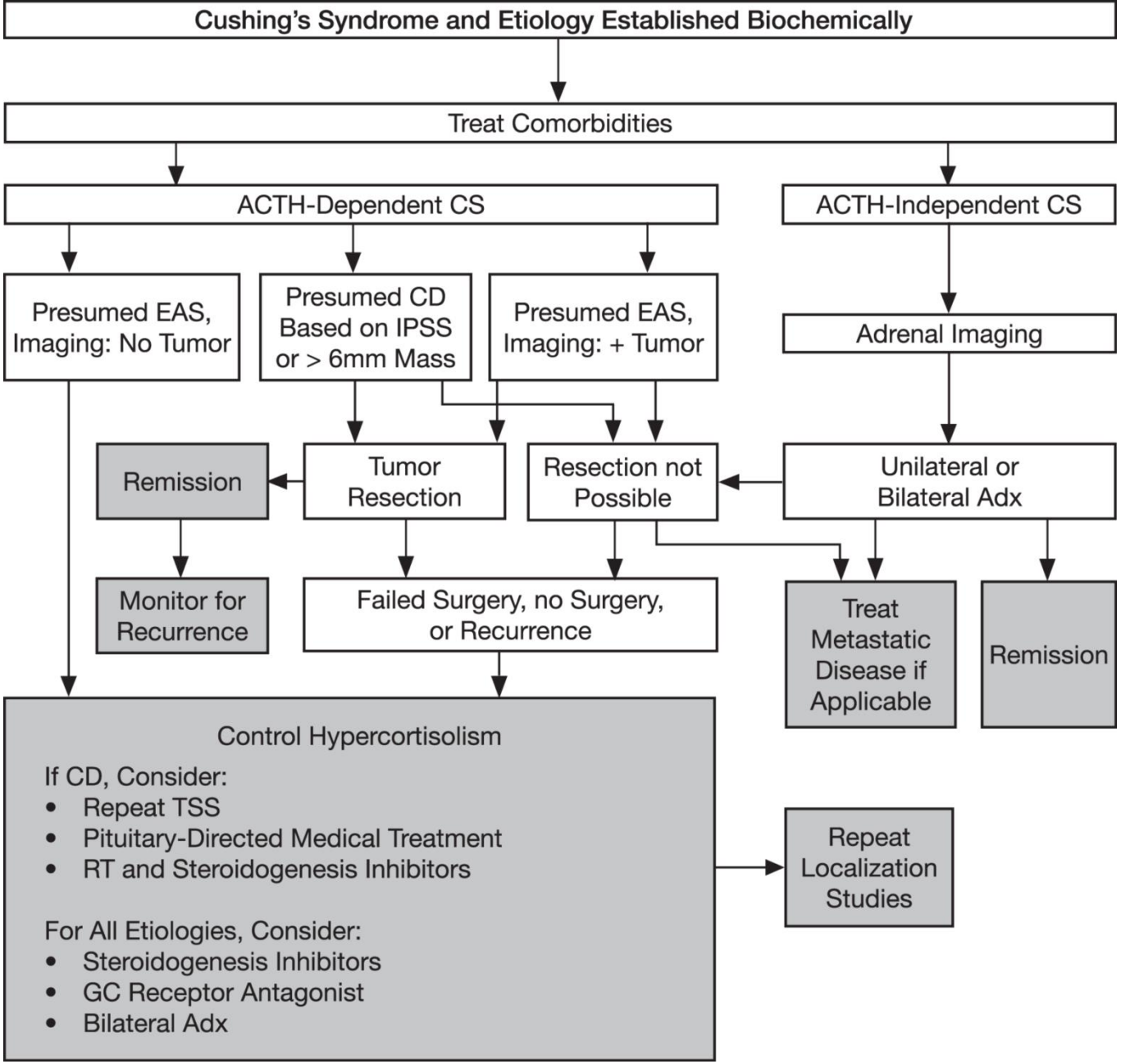
Adrenal steroidogenesis inhibitor				
Ketoconazole[179,181–187]	400–1600 mg total per day, orally, given twice or three times a day	Retrospective studies: approximately 65% of patients had UFC normalisation initially, but 15–25% escape	Gastrointestinal disturbances, increased liver enzymes, gynecomastia, skin rash, adrenal insufficiency	EMA-approved for treatment of endogenous Cushing's syndrome, off-label use in USA; increasing doses may be needed to counter escape; needs gastric acid for absorption (avoid proton-pump inhibitors); decrease in testosterone would be preferred in women, men need follow-up for hypogonadism; risk of serious hepatotoxicity, mostly transient but regular liver function test monitoring required; risk of QTc prolongation; careful review of other medications for potential drug–drug interactions is essential
Osilodrostat[181–183,188–192]	4–14 mg total per day, orally, given twice a day as maintenance dose; some patients require lower starting doses at 2 mg per day; 30 mg, twice a day maximum	Phase 3 randomised withdrawal study showed 86% UFC normalisation	Increased androgenic and mineralocorticoid precursors (hirsutism, hypertension, hypokalaemia), gastrointestinal disturbances, asthenia, adrenal insufficiency	FDA-approved for patients with Cushing's disease in whom pituitary surgery is not an option or has not been curative; EMA and Japan have approved for treatment of endogenous Cushing's syndrome; not yet widely available; rapid decrease in UFC; risk of hypocortisolism, hypokalaemia, and QTc prolongation; 11-deoxycortisol can cross-react in cortisol immunoassays; careful monitoring for hyperandrogenism in women
Metyrapone[179,181,182,193–197]	500 mg to 6 g total per day, orally, given three or four times a day	UFC normalisation in retrospective studies approximately 70%; in a prospective study, 47% at week 12	Increased androgenic and mineralocorticoid precursors (hirsutism, hypertension, hypokalaemia), gastrointestinal disturbances, adrenal insufficiency	EMA-approved for treatment of endogenous Cushing's syndrome, off-label use in USA; rapid decrease in UFC, typically in first month; 11-deoxycortisol can cross-react in cortisol immunoassays; hyperandrogenism needs to be monitored with long-term use in women
Mitotane[179,181,182,198]	500 mg to 4 g total per day, orally, up to 5 g in Cushing's disease per day given three times a day	Retrospective studies show approximately 80% UFC normalisation	Gastrointestinal disturbances, dizziness, cognitive alterations, adrenal insufficiency; increased liver enzymes; treatment should be stopped if elevations are >5 × ULN	Approved by the FDA and EMA for treatment of adrenal cancer with endogenous Cushing's syndrome; slow onset of action, highly variable bioavailability; narrow therapeutic window (dose titration based on mitotane plasma concentrations); 11-deoxycortisol can cross-react in cortisol immunoassays; neurological toxicity could be a limiting factor; teratogenicity and abortifacient activity, coupled with a long half-life, could limit use in women who desire future pregnancy
Etomidate[179,199–201]	0·04–0·1 mg/kg/h intravenously for patients in the intensive care unit; 0·025 mg/kg/h for patients not in the intensive care unit	Retrospective studies show approximately 100% serum cortisol control (10–20 µg/dL)	Sedation or anaesthesia; adrenal insufficiency, myoclonus, nausea, vomiting, and dystonic reactions at higher anaesthetic doses	Off-label use only; very rapid onset of action, appropriate for acute treatment of severe hypercortisolism; intravenous hydrocortisone required at high doses to avoid adrenal insufficiency
Levoketoconazole*[202,203]	300–1200 mg total per day, orally, given twice a day	Phase 3 open label study showed 31% UFC normalisation (primary endpoint), 42% normalisation when using imputed data (comparable with other studies); phase 3 randomised withdrawal study showed that 41% lost response with drug vs 96% with placebo; clinical signs and symptoms of hypercortisolism improved	Gastrointestinal disturbances, headache, oedema, increased liver enzymes, adrenal insufficiency	Investigational; FDA and EMA orphan drug status for treatment of endogenous Cushing's syndrome; possible lower risk for hepatotoxicity than with ketoconazole based on animal models, although no head-to-head studies in humans available; needs gastric acid for absorption (avoid proton-pump inhibitors); risk of QTc prolongation; careful review of other medications for potential drug–drug interactions is essential



Steroidogenesis in the adrenal cortex denoting the specific pathways inhibited by ketoconazole (KTZ), metyetomidate, and newer steroidogenesis inhibitors.

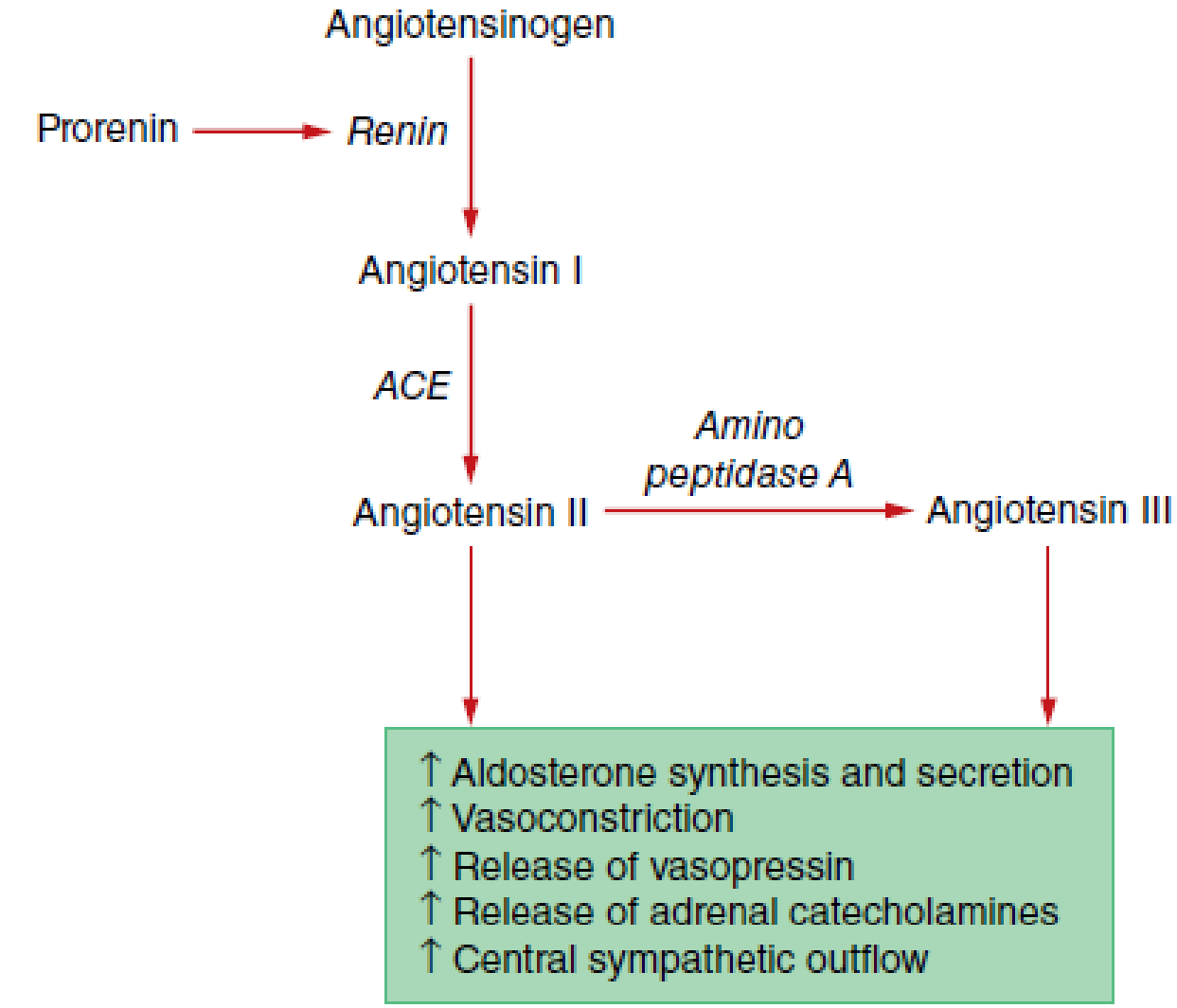
Somatostatin receptor ligands				
Pasireotide[179,181,204–206]	0·6–1·8 mg/mL subcutaneously total per day, given twice a day	Phase 3 study showed 15–26% UFC normalisation	Hyperglycaemia, type 2 diabetes, diarrhoea, nausea, abdominal pain, cholelithiasis, fatigue	Widely approved for patients with Cushing's disease in whom pituitary surgery is not an option or has not been curative; may decrease tumour volume; high risk of hyperglycaemia requires careful patient selection; risk of QTc prolongation
Pasireotide long-acting release[181,207–209]	10–30 mg per month, intramuscularly	Phase 3 study showed 40% UFC normalisation; clinical signs and symptoms of hypercortisolism improved	Hyperglycaemia, type 2 diabetes, diarrhoea, nausea, abdominal pain, cholelithiasis, fatigue	Widely approved for patients with Cushing's disease in whom pituitary surgery is not an option or has not been curative; decreases tumour volume; high risk of hyperglycaemia requires careful patient selection; risk of QTc prolongation
Dopamine receptor agonists				
Cabergoline[179,181,210–214]	0·5–7 mg total per week, orally	Retrospective studies showed approximately 40% UFC normalisation initially, but roughly 25–40% escape; clinical signs and symptoms of hypercortisolism improved	Headache, nasal congestion, hypotension, depression, dizziness	Off-label use only for Cushing's disease; decreases tumour volume in up to 50% of the patients evaluated; poor response could be due to under-titration; risk of treatment-induced impulse-control disorder; unclear risk for cardiac valvulopathy
Glucocorticoid receptor blocker				
Mifepristone[179,181,215–218]	300–1200 mg total per day orally, given once a day	Open-label phase 3 study showed significant improvement in glycaemia (approximately 60% of patients) and blood pressure; clinical signs and symptoms of hypercortisolism improved	Gastrointestinal disturbances, headache, hypokalaemia, arthralgia, peripheral oedema, hypertension, vaginal bleeding, adrenal insufficiency	FDA-approved for hyperglycaemia associated with Cushing's syndrome; no cortisol markers of efficacy; challenging to use outside specialised clinical practice; risk of hypokalaemia and adrenal insufficiency, needs close monitoring; careful review of other medications for potential drug–drug interactions is essential

EMA=European Medicines Agency. FDA=US Food and Drug Administration. ULN=upper limit of normal. UFC=urinary-free cortisol. *Investigational drug with completed phase 3 clinical trials.

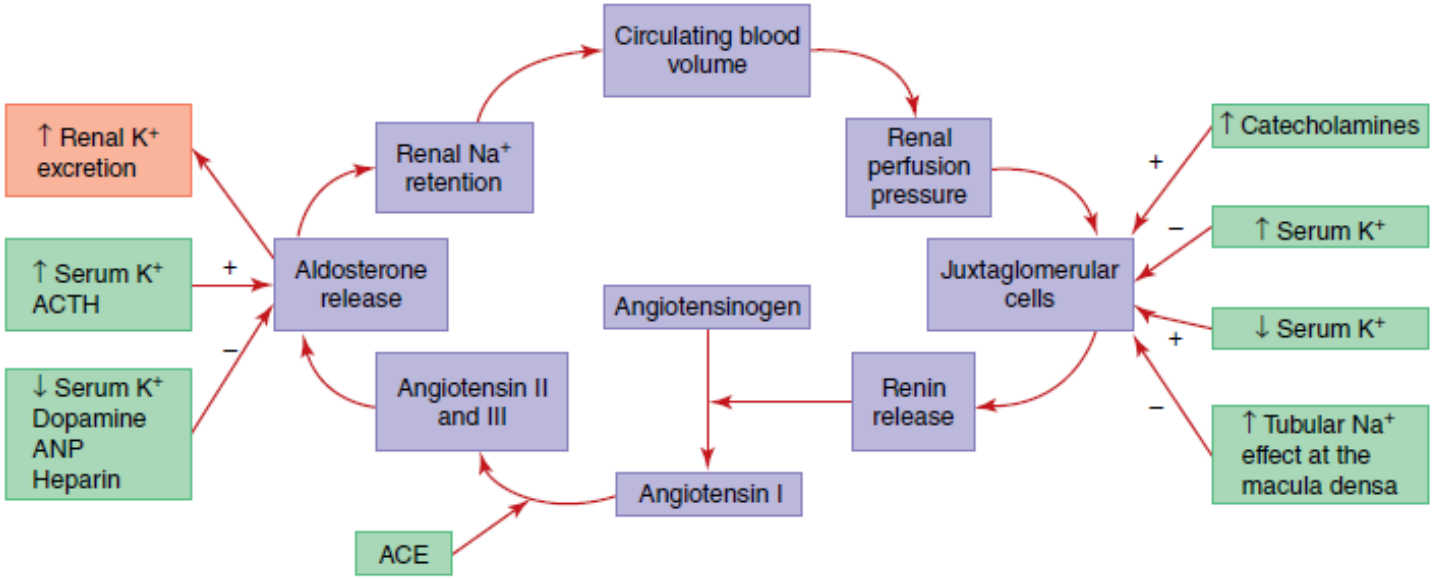


Treatment of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2015;100(8):2807-2831. doi:10.1210/jc.2015-1818

CONN'S SYNDROME – PRIMARY HYPERALDOSTERONISM



Steps in the production of angiotensin peptides by the renin-angiotensin system (ACE, angiotensin-converting enzyme).



Renin-angiotensin-aldosterone and potassium-aldosterone feedback loops. Zona glomerulosa aldosterone production and secretion are determined by input from each loop (ACE, angiotensin-converting enzyme; ACTH, corticotropin; ANP, atrial natriuretic peptide; BP, blood pressure; K^+, potassium; Na^+, sodium).

Conn's syndrome – primary hyperaldosteronism

- **Hypertension,**
- **suppressed plasma renin activity (PRA),**
- **increased aldosterone excretion**

characterize the syndrome of **primary aldosteronism.**

Causes

- Aldosterone-producing adenoma (APA) 35%
- Bilateral idiopathic hyperplasia (IHA) 60%
- Unilateral (primary) adrenal hyperplasia 2%
- Aldosterone-producing adrenocortical carcinoma < 1%
- Familial hyperaldosteronism (FH) –
  - Glucocorticoid-remediable aldosteronism (FH type I) < 1%
  - FH type II (APA or IHA) < 2%
- Ectopic aldosterone-producing adenoma or carcinoma < 0.1%

Clinical manifestations

- **Excess activation of the mineralocorticoid receptor** leads to **potassium depletion** and **increased sodium retention**, with the **latter causing an expansion of extracellular and plasma volume**.

- **hydrogen depletion** can cause **metabolic alkalosis**.

- **Aldosterone** also has **direct effects** on the vascular system, where it **increases cardiac remodeling and decreases compliance**.

- **Aldosterone excess** may cause **direct damage to the myocardium** and the kidney glomeruli, in addition to secondary damage due to **systemic hypertension**.

Clinical presentation

- The diagnosis of primary aldosteronism is usually made in patients who are in the third to sixth decade of life.

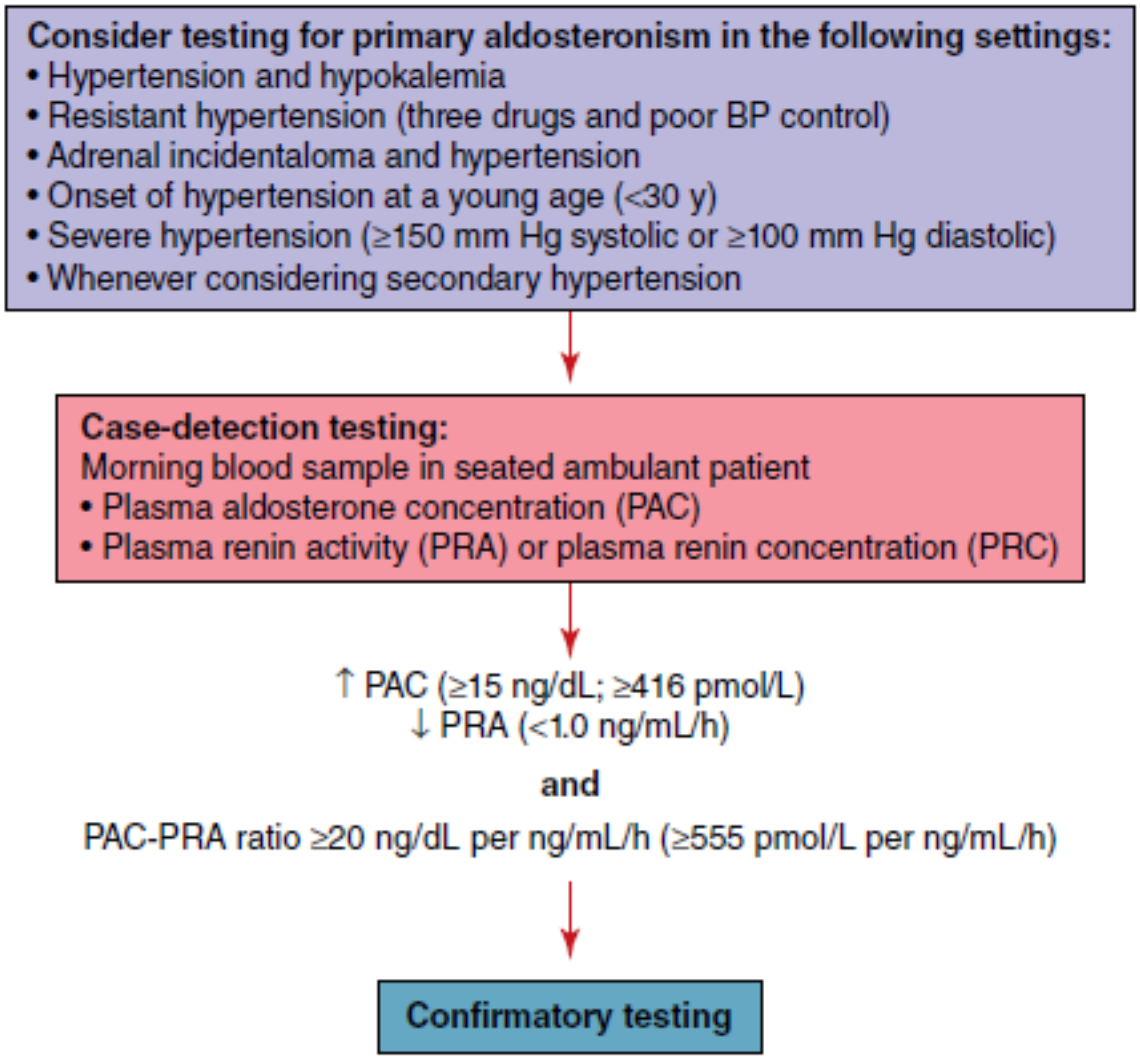
- **Few symptoms are specific to the syndrome.**
  - Patients with marked hypokalemia may have **muscle weakness and cramping,** headaches, palpitations, **polydipsia, polyuria,** nocturia, or a combination of these.
  - The polyuria and nocturia are a result of a hypokalemia-induced renal concentrating defect and the presentation is frequently mistaken for prostatism in men.

- There are no specific physical findings.
- Edema is not a common finding because of mineralocorticoid escape.
- The degree of **hypertension** is usually moderate to severe and may be resistant to usual pharmacologic treatments.

Diagnosis

- **Diagnostic screening** for mineralocorticoid excess **is not currently recommended for all patients with hypertension**, **but should be restricted to those** who exhibit
  - hypertension associated with drug resistance,
  - hypokalemia,
  - an adrenal mass, or
  - hypertension before the age of 40 years.

- **The accepted screening test** is concurrent measurement of **plasma renin and aldosterone with subsequent calculation of the aldosterone-renin ratio (ARR)**; serum potassium needs to be normalized prior to testing.



When to consider testing for primary aldosteronism and use of the plasma aldosterone concentration to plasma renin activity ratio as a case-finding tool (BP, blood pressure; PAC, plasma aldosterone concentration; PRA, plasma renin activity; PRC, plasma renin concentration).

Confirmatory tests

Oral sodium loading test.

- patients should receive a high sodium diet (supplemented with sodium chloride tablets if needed) for 3 days, with a goal sodium intake of 5000 mg (equivalent to 12.8 g sodium chloride or 218 mEq of sodium).
- On the third day of the high sodium diet, a 24-hour urine specimen is collected for measurement of aldosterone, sodium, and creatinine.
- Urinary aldosterone excretion more than 12 µg/24 h is consistent with autonomous aldosterone secretion.

Confirmatory tests

Intravenous saline infusion test

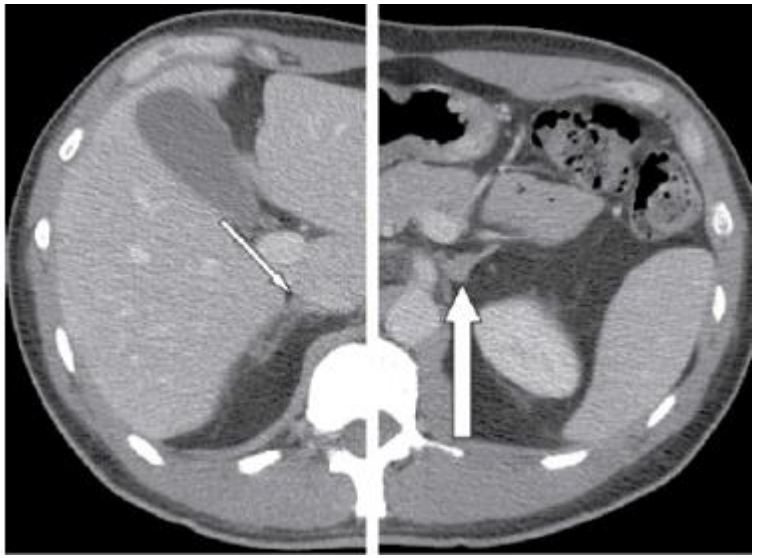
- Normal subjects show suppression of PAC after volume expansion with isotonic saline; subjects with primary aldosteronism do not show this suppression.
- Two liters of 0.9% sodium chloride solution are infused intravenously with an infusion pump over 4 hours into the recumbent patient.
- At the completion of the infusion, blood is drawn for measurement of plasma aldosterone concentration. plasma aldosterone concentration levels in normal subjects decrease to less than 5 ng/dL; most patients with primary aldosteronism do not suppress to less than 10 ng/dL

Confirmatory tests

Fludrocortisone Suppression Test

- fludrocortisone acetate is administered for 4 days (0.1 mg every 6 hours) in combination with sodium chloride tablets (2 g three times daily with food).
- In the setting of low plasma renin activity, failure to suppress the upright 10 am plasma aldosterone concentration to less than 6 ng/dL on day 4 is diagnostic of primary aldosteronism

Diagnosis

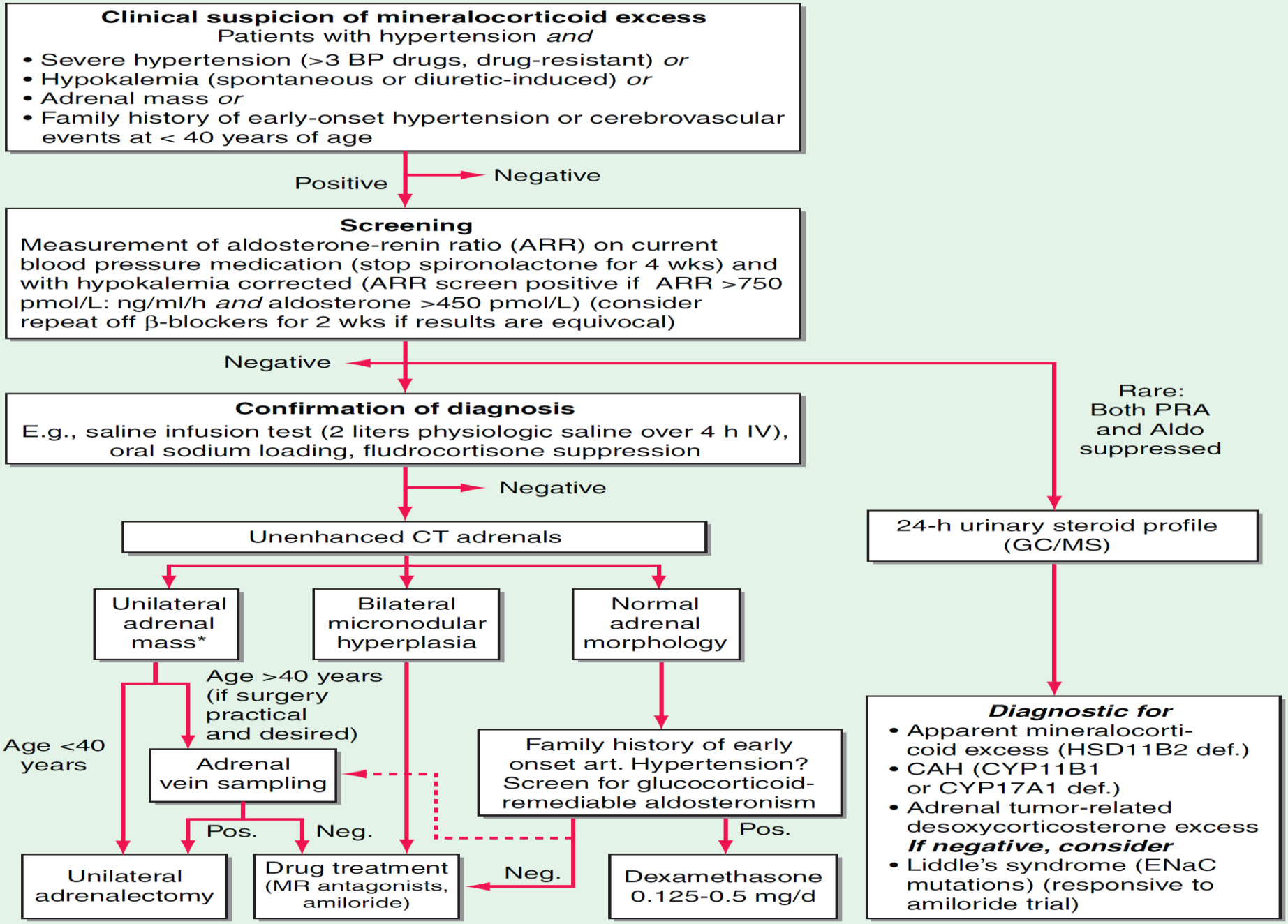


- **After the diagnosis of hyperaldosteronism** is established, the **next step** is to use **adrenal imaging to further assess the cause**

- **Fine-cut CT scanning of the adrenal regio**n is the **method of choice** as it provides excellent visualization of adrenal morphology and identify larger tumors suspicious of malignancy but may miss lesions smaller than 5 mm.

- **Selective adrenal vein sampling (AVS)** should only be carried out in surgical candidates with either no obvious lesion on CT or evidence of a unilateral lesion in patients older than 40 years, as the latter patients have a high likelihood of harboring a coincidental, endocrine inactive adrenal adenoma .

Algorithm for the Management of Patients with Suspected Mineralocorticoid Excess



Pharmacological treatment

- IHA and GRA should be treated medically. APA patients may be treated medically if the medical treatment includes mineralocorticoid receptor blockade.

- A sodium-restricted diet (< 100 mEq of sodium per day), maintenance of ideal body weight, tobacco avoidance, and regular aerobic exercise contribute significantly to the success of pharmacologic treatment.

- Spironolactone, has been the drug of choice to treat primary aldosteronism.
  - The initial dosage is 12.5 to 25 mg/d and is increased to 400 mg/d if necessary to achieve a high-normal serum potassium concentration without the aid of oral potassium chloride supplementation. Hypokalemia responds promptly, but hypertension may take as long as 4 to 8 weeks to correct. After several months of therapy, this dosage often can be decreased to as little as 25 to 50 mg/d; dosage titration is based on a goal serum potassium level in the high-normal range.
  - Spironolactone is not selective for the mineralocorticoid receptor. For example, antagonism at the testosterone receptor may result in painful gynecomastia, erectile dysfunction, and decreased libido in men; agonist activity at the progesterone receptor results in menstrual irregularity in women.

Pharmacological treatment

- **Eplerenone** is a steroid-based antimineralocorticoid that acts as a competitive and selective mineralocorticoid receptor antagonist.

- Eplerenone is available as 25- and 50-mg tablets.

- For primary aldosteronism, it is reasonable to start with a dose of 25 mg twice daily (twice daily because of the shorter half-life of eplerenone compared to spironolactone) and titrated upward for a target high-normal serum potassium concentration without the aid of potassium supplements.

Adrenal insufficiency

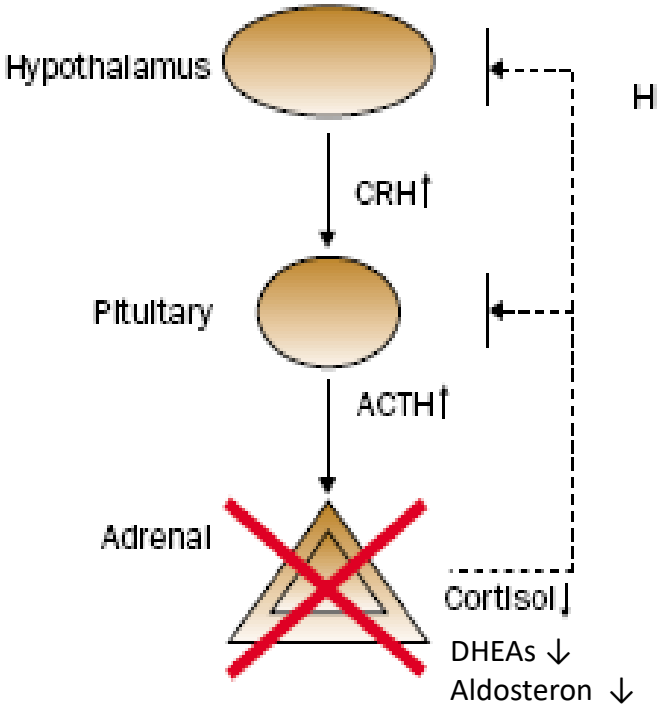
is the **clinical manifestation** of **deficient production or action of glucocorticoids**, with or without deficiency also in **mineralocorticoids and adrenal androgens**.

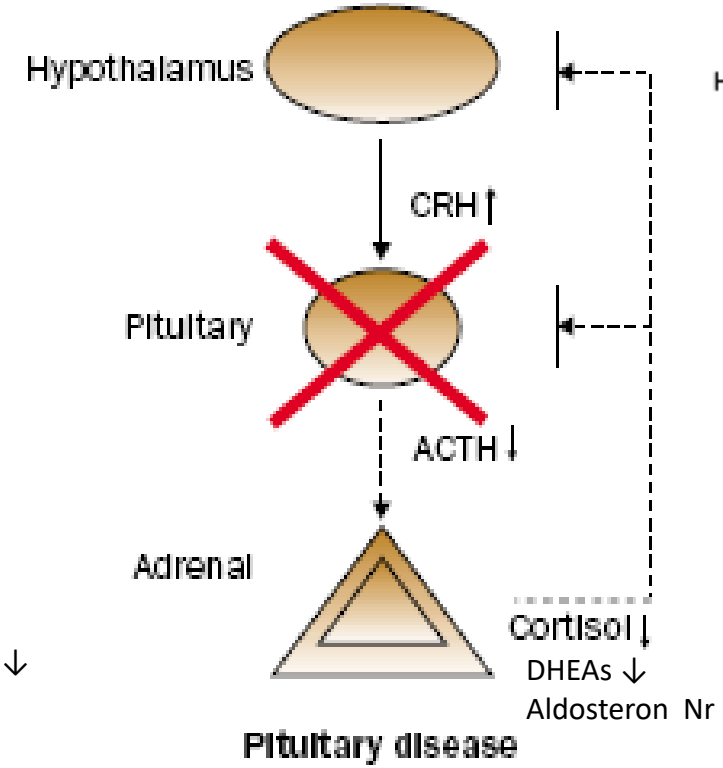
According to the underlying mechanism, adrenal insufficiency is classed as:

- **Primary** - results from disease intrinsic to the adrenal cortex;

- **Secondary** - results from pituitary disease that hampers the release of corticotropin or from a lack of responsiveness of the adrenal glands to this hormone;

- **Tertiary** - results from the impaired synthesis or action of corticotropin-releasing hormone, arginine vasopressin, or both, from the hypothalamus, which in turn inhibits secretion of corticotropin.


Hypothalamus
CRH↑
Pituitary
ACTH↑
Adrenal
Cortisol↓
DHEAs ↓
Aldosteron ↓


Hypothalamus
CRH↑
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Adrenal
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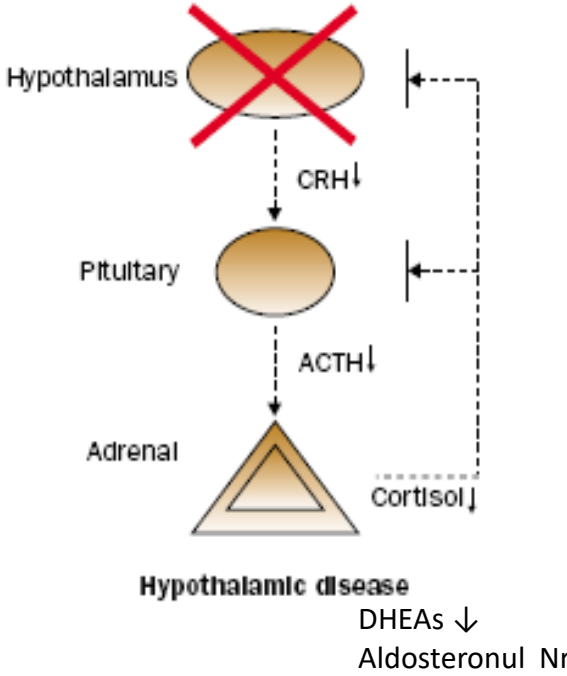
Pituitary disease


Hypothalamus
CRH↓
Pituitary
ACTH↓
Adrenal
Cortisol↓
Hypothalamic disease
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Aldosteronul Nr

Primary adrenal insufficiency

Addison's disease

The cardinal clinical symptoms of adrenocortical insufficiency, as first described by **Thomas Addison** in 1855, include *weakness, fatigue, anorexia, abdominal pain, weight loss, orthostatic hypotension, and salt craving*; characteristic ***hyperpigmentation*** of the skin occurs with primary adrenal failure.

Whatever the cause, adrenal insufficiency was invariably fatal until 1949, when cortisone was first synthesised, and glucocorticoid replacement treatment became available.

Epidemiology

- **In Europe**, the prevalence has increased
  - from 40–70 cases per million people in the 1960s to 93–144 cases per million by the end of the 20th century,
  - an estimated incidence now of 4,4–6,0 new cases per million population per year.

- **Tuberculosis was** the most common cause of primary adrenal insufficiency during the **first half of the 20th century**, but

  lately autoimmune adrenal insufficiency has become the **most common form**.

- Primary adrenal insufficiency **occurs more frequently in women** than in men, and can present **at any age**, although most often appears **between the ages of 30 and 50 years**

The causes of primary adrenal insufficiency

- In developed countries, **80–90% of cases** - are caused by **autoimmune adrenalitis**, which can be
  - **isolated** (40%) or
  - part of an **autoimmune polyendocrinopathy syndrome** (60%).

- Autoimmune Addison's disease is **characterised** by **destruction of the adrenal cortex by cell-mediated immune mechanisms**.

- **Antibodies against steroid 21-hydroxylase** are detected in about **85%** of patients with idiopathic primary adrenal insufficiency.
- In addition, other autoantigens, including steroid 17α-hydroxylase and the cholesterol side-chain cleavage enzyme, have been identified in patients with autoimmune Addison's disease, as well as patients with primary ovarian failure.

Incidence of other autoimmune diseases in 365 patients with autoimmune adrenal insufficiency

Disease	Incidence (percent)
Thyroid disease	
Hypothyroidism	8
Nontoxic goiter	7
Hyperthyroidism	7
Gonadal failure	
Ovarian	20
Testicular	2
Type 1 diabetes mellitus	11
Hypoparathyroidism	10
Pernicious anemia	5
None	53

	Pathogenetic mechanisms	Clinical manifestations in addition to adrenal insufficiency
Autoimmune adrenalitis		
Isolated	Associations with HLA-DR3-DQ2, HLA-DR4-DQ8, MICA, CTLA-4, PTPN22, CIITA, CLEC16A, vitamin D receptor	None
APS type 1 (APECED)	*AIRE* gene mutations	Chronic mucocutaneous candidosis, hypoparathyroidism, other autoimmune diseases
APS type 2	Associations with HLA-DR3, HLA-DR4, CTLA-4	Thyroid autoimmune disease, type 1 diabetes, other autoimmune diseases
APS type 4	Associations with HLA-DR3, CTLA-4	Other autoimmune diseases (autoimmune gastritis, vitiligo, coeliac disease, alopecia), excluding thyroid disease and type 1 diabetes
Infectious adrenalitis		
Tuberculous adrenalitis	Tuberculosis	Tuberculosis-associated manifestations in other organs
AIDS	HIV-1	Other AIDS-associated diseases
Fungal adrenalitis	Histoplasmosis, cryptococcosis, coccidioidomycosis	Opportunistic infections
Syphilis	*Treponema pallidum*	Other syphilis-associated organ involvement
African trypanosomiasis[27]	*Trypanosoma brucei*	Other trypanosomiasis-associated organ involvement
Bilateral adrenal haemorrhage	Meningococcal sepsis (Waterhouse-Friderichsen syndrome), primary antiphospholipid syndrome	Symptoms and signs of underlying disease
Bilateral adrenal metastases	Mainly cancers of the lung, stomach, breast, and colon	Disease-associated clinical manifestations
Bilateral adrenal infiltration	Primary adrenal lymphoma, amyloidosis, haemochromatosis	Disease-associated clinical manifestations
Bilateral adrenalectomy	Unresolved Cushing's syndrome, bilateral adrenal masses, bilateral phaeochromocytoma	Symptoms and signs of underlying disease
Drug-induced adrenal insufficiency		
Anticoagulants (heparin, warfarin), tyrosine-kinase inhibitors (sunitinib)	Haemorrhage	None, unless related to drug
Aminoglutethimide	Inhibition of P450 aromatase (CYP19A1)	None, unless related to drug
Trilostane	Inhibition of 3β-hydroxysteroid dehydrogenase type 2	None, unless related to drug
Ketoconazole, fluconazole, etomidate	Inhibition of mitochondrial cytochrome P450-dependent enzymes (eg, CYP11A1, CYP11B1)	None, unless related to drug
Phenobarbital	Induction of P450-cytochrome enzymes (CYP2B1, CYP2B2), which increase cortisol metabolism	None, unless related to drug
Phenytoin, rifampicin, troglitazone	Induction of P450-cytochrome enzymes (mainly CYP3A4), which increase cortisol metabolism	None, unless related to drug

	Pathogenetic mechanisms	Clinical manifestations in addition to adrenal insufficiency
(Continued from previous page)		
Genetic disorders		
Adrenoleukodystrophy or adrenomyeloneuropathy	*ABCD1* and *ABCD2* gene mutations	Weakness, spasticity, dementia, blindness, quadriparesis. Adrenomyeloneuropathy is a milder variant of adrenoleukodystrophy with slower progression
Congenital adrenal hyperplasia		
21-hydroxylase deficiency	*CYP21A2* gene mutations	Hyperandrogenism
11β-hydroxylase deficiency	*CYP11B1* gene mutations	Hyperandrogenism, hypertension
3β-hydroxysteroid dehydrogenase type 2 deficiency	Mutations in 3β-*HSD2* gene	Ambiguous genitalia in boys, postnatal virilisation in girls
17α-hydroxylase deficiency	*CYP17A1* gene mutations	Pubertal delay in both sexes, hypertension
P450 oxidoreductase deficiency	Mutations in gene for P450 oxidoreductase	Skeletal malformation (Antley-Bixler syndrome), abnormal genitalia
P450 side-chain cleavage deficiency	*CYP11A1* gene mutations	XY sex reversal
Congenital lipoid adrenal hyperplasia	*StAR* gene mutations	XY sex reversal
Smith-Lemli-Opitz syndrome	*DHCR7* gene mutations	Craniofacial malformations, mental retardation, growth failure, hyponatraemia, hyperkalaemia, cholesterol deficiency
Adrenal hypoplasia congenita		
X-linked	*NR0B1* gene mutations	Hypogonadotropic hypogonadism in boys
Xp21 contiguous gene syndrome	Deletion of genes for Duchenne muscular dystrophy, glycerol kinase, and *NR0B1*	Duchenne muscular dystrophy, glycerol kinase deficiency, psychomotor retardation
SF-1 linked	*NR5A1* gene mutations	XY sex reversal
IMAGe syndrome	*CDKN1C* gene mutations	Intrauterine growth retardation, metaphyseal dysplasia, adrenal hypoplasia congenita and genital abnormalities
Kearns-Sayre syndrome	Mitochondrial DNA deletions	External ophthalmoplegia, retinal degeneration, cardiac conduction defects, other endocrine disorders
Wolman's disease	*LIPA* gene mutations	Bilateral adrenal calcification, hepatosplenomegaly
Sitosterolaemia (also known as phytosterolaemia)	*ABCG5* and *ABCG8* gene mutations	Xanthomata, arthritis, premature coronary artery disease, short stature, gonadal and adrenal failure
Familial glucocorticoid deficiency or corticotropin insensitivity syndromes		
Type 1	*MC2R* gene mutations	Hyperpigmentation, tall stature, characteristic facial features, such as hypertelorism and frontal bossing, lethargy and muscle weakness but normal blood pressure
Type 2	*MRAP* gene mutations	Hyperpigmentation, normal height, hypoglycaemia, lethargy, and muscle weakness, but normal blood pressure
Variant of familial glucocorticoid deficiency	*MCM4* gene mutations	Growth failure, increased chromosomal breakage, natural killer cell deficiency
Primary generalised glucocorticoid resistance or Chrousos syndrome[28-31]	Generalised, partial, target-tissue insensitivity to glucocorticoids	Fatigue, hypoglycaemia, hypertension, hyperandrogenism
Triple A syndrome (Allgrove's syndrome)	*AAAS* gene mutations	Achalasia, alacrima, deafness, mental retardation, hyperkeratosis

APS=autoimmune polyendocrinopathy syndrome. CTLA-4=cytotoxic T-lymphocyte antigen 4. ABCD=ATP-binding cassette, subfamily D. StAR=steroidogenic acute regulatory protein. DHCR7=7-dehydrocholesterol reductase. ABCG5=ATP-binding cassette, subfamily G, member 5. ABCG8=ATP-binding cassette, subfamily G, member 8. MC2R=melanocortin 2 receptor. MRAP=melanocortin 2 receptor accessory protein. MCM4=minichromosome maintenance complex component 4. AAAS=achalasia, adrenocortical insufficiency, alacrima syndrome.

Etiology of Secondary AI

Major causes of hypopituitarism

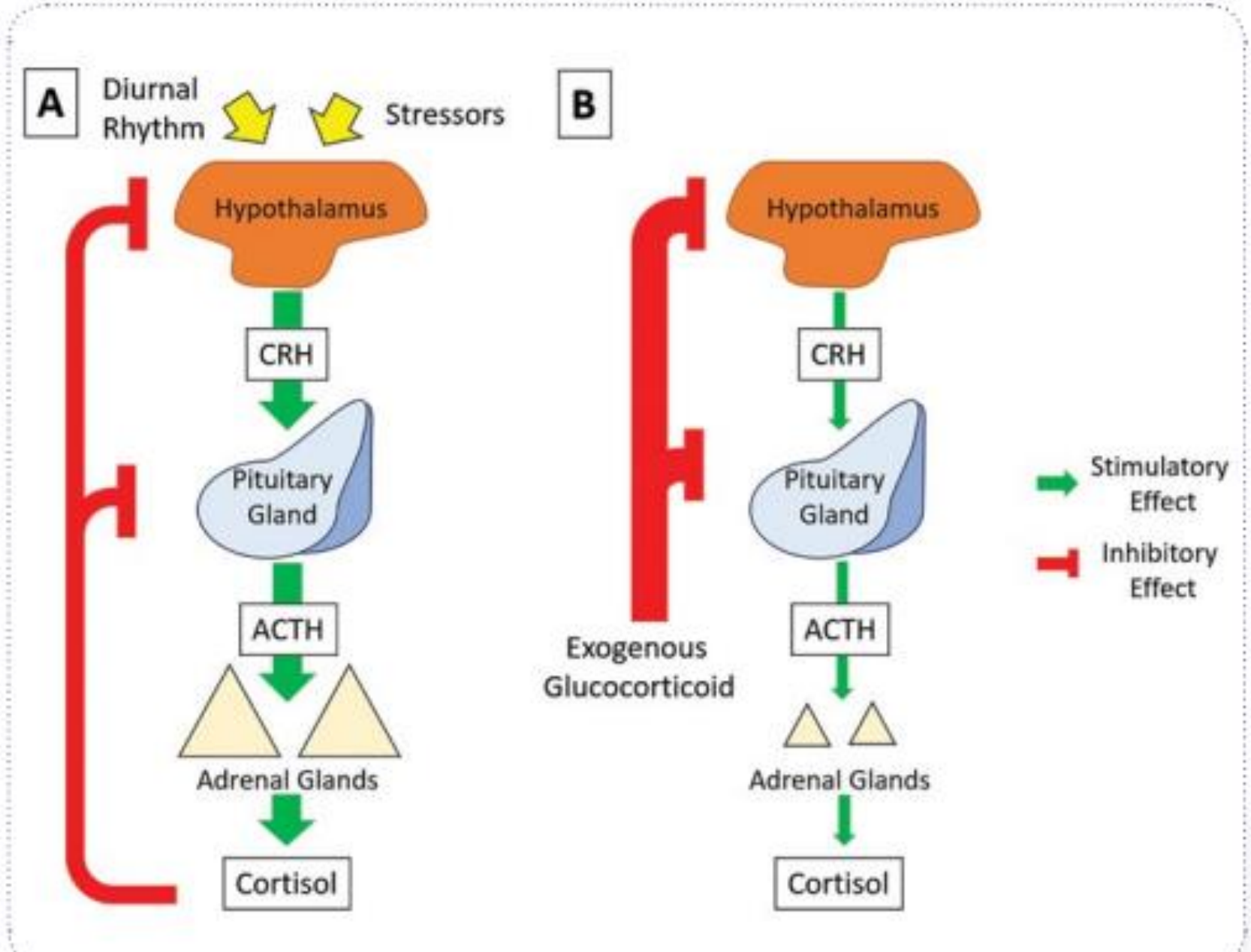
Hypothalamic diseases
Mass lesions – Benign (craniopharyngiomas) and malignant tumors (metastatic from lung, breast, etc)
Radiation – For CNS and nasopharyngeal malignancies
Infiltrative lesions – Sarcoidosis, Langerhans cell histiocytosis
Infections – Tuberculous meningitis
Other – Traumatic brain injury, stroke
Pituitary diseases
Mass lesions – Pituitary adenomas, other benign tumors, cysts
Pituitary surgery
Pituitary radiation
Infiltrative lesions – Hypophysitis, hemochromatosis
Infection/abscess
Infarction – Sheehan syndrome
Apoplexy
Genetic mutations
Empty sella

Causes of secondary and tertiary adrenal insufficiency in adults

Author: Lynnette K Nieman, MD
Section Editor: André Lacroix, MD
Deputy Editor: Kathryn A Martin, MD

All topics are updated as new evidence becomes available and our peer review process is complete.
Literature review current through: Oct 2021. | **This topic last updated:** Feb 25, 2021.

Etiology of tertiary AI



The clinical manifestations

- result **from deficiency of all adrenocortical hormones**:
  - aldosterone,
  - cortisol,
  - androgens;
- they can **also include signs of other concurrent autoimmune** conditions.

- **Most of the symptoms are non-specific and can delay diagnosis and treatment of the condition.**

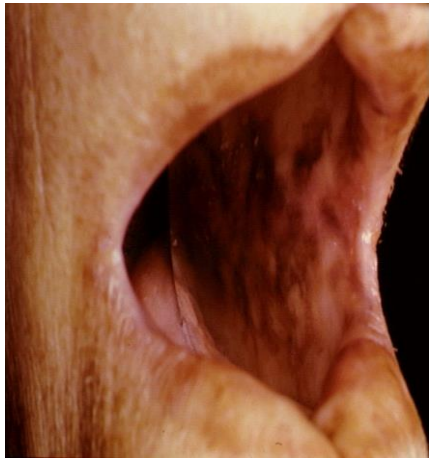
Symptoms

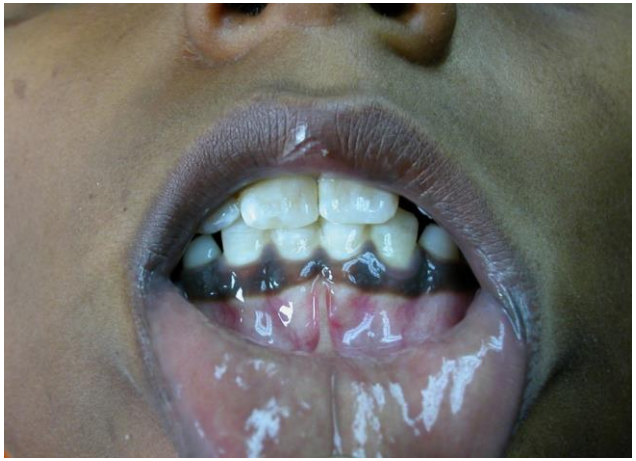
Fatigue, lack of energy or stamina, reduced strength	Glucocorticoid deficiency, adrenal androgen deficiency	100
Anorexia, weight loss (in children failure to thrive)	Glucocorticoid deficiency	100
Gastric pain, nausea, vomiting (most common in primary adrenal insufficiency)	Glucocorticoid deficiency, mineralocorticoid deficiency	92
Myalgia, joint pain	Glucocorticoid deficiency	6–13
Dizziness	Mineralocorticoid deficiency, glucocorticoid deficiency	12
Salt craving (primary adrenal insufficiency only)	Mineralocorticoid deficiency	16
Dry and itchy skin (in women)	Adrenal androgen deficiency	..
Loss or impairment of libido (in women)	Adrenal androgen deficiency	..

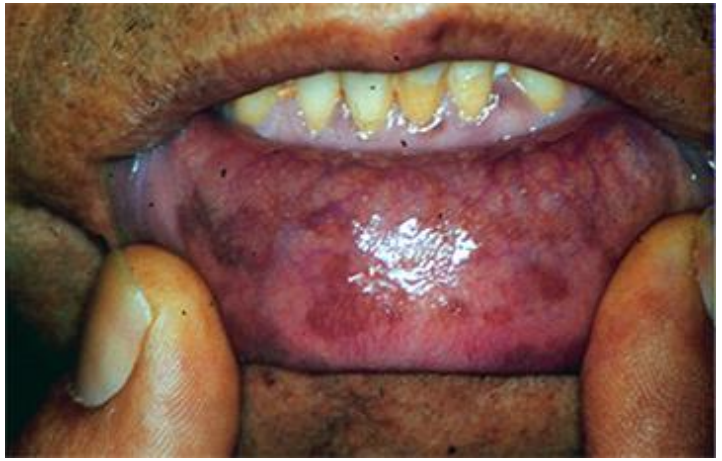
Signs

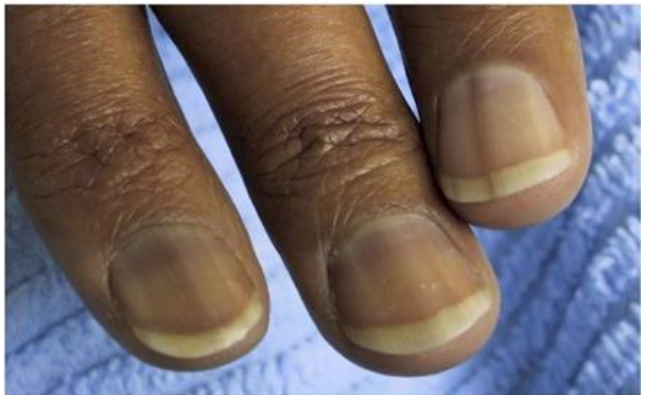
Skin hyperpigmentation (primary adrenal insufficiency only)	Excess of pro-opiomelanocortin-derived peptides	94
Alabaster-coloured pale skin (secondary adrenal insufficiency only)	Deficiency of pro-opiomelanocortin-derived peptides	..
Fever	Glucocorticoid deficiency	..
Low blood pressure, postural hypotension, dehydration (pronounced in primary adrenal insufficiency)	Mineralocorticoid deficiency, glucocorticoid deficiency	88–94
Loss of axillary or pubic hair (in women), absence of adrenarche or pubarche in children	Adrenal androgen deficiency	..

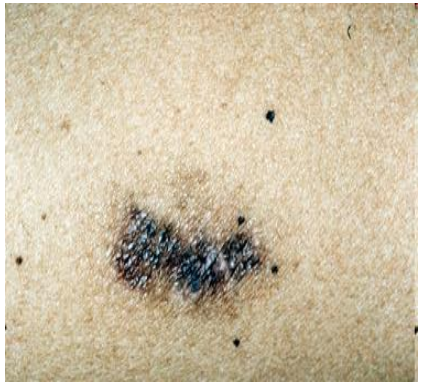
Biochemical findings		
Raised serum creatinine (primary adrenal insufficiency only)	Mineralocorticoid deficiency	..
Hyponatraemia	Mineralocorticoid deficiency, glucocorticoid deficiency (leading to SIADH)	88
Hyperkalaemia (primary adrenal insufficiency only)	Mineralocorticoid deficiency	64
Anaemia, lymphocytosis, eosinophilia	Glucocorticoid deficiency	..
Increased thyrotropin (primary adrenal insufficiency only)	Glucocorticoid deficiency (or autoimmune thyroid failure)	..
Hypercalcaemia (primary adrenal insufficiency only)	Glucocorticoid deficiency (mostly concurrent hyperthyroidism)	6
Hypoglycaemia	Glucocorticoid deficiency	..

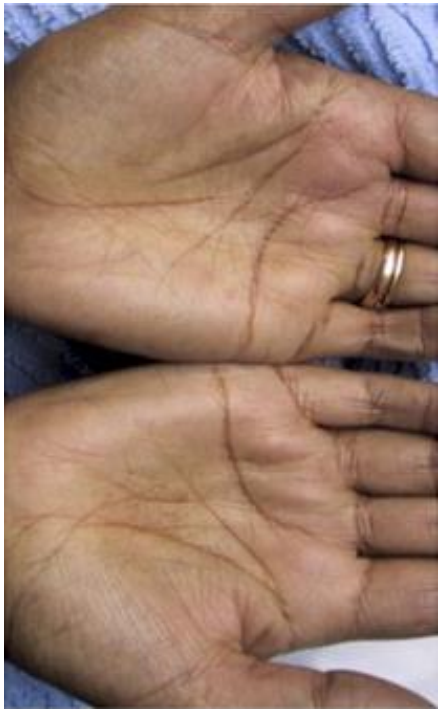


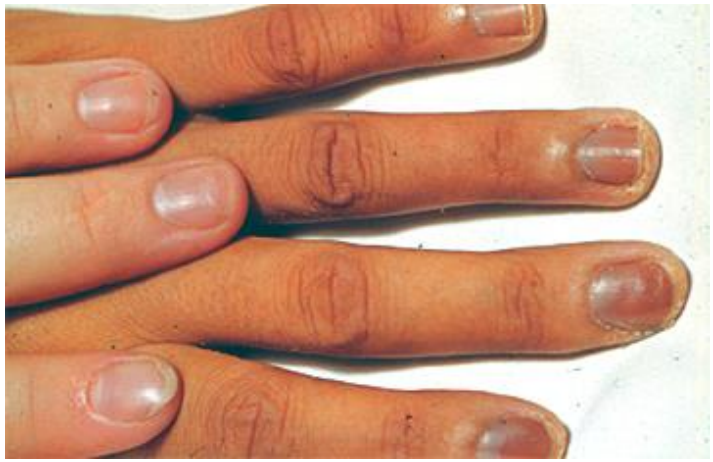


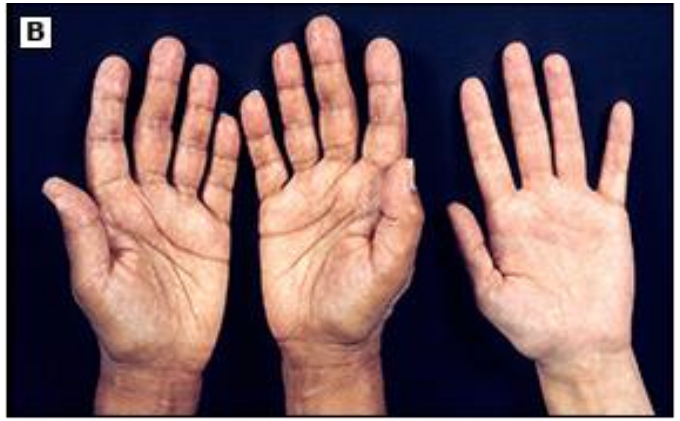











B

Diagnosis of adrenal insufficiency

There are three main aims in the diagnosis of adrenal insufficiency:

- **to confirm** inappropriately low cortisol secretion;
- **to find out whether** the adrenal insufficiency is primary or central;
- **to delineate** the underlying pathological process.

- Whatever the cause, the diagnosis of adrenal insufficiency depends entirely on the demonstration that **cortisol secretion is inappropriately low.**

Diagnosis of adrenal insufficiency

- Whatever the cause, the diagnosis of adrenal insufficiency depends entirely on the demonstration that **cortisol secretion is inappropriately low.**

	Normal range*	Interpretation
Primary adrenal insufficiency		
0800 h basal serum cortisol	165–680 nmol/L	Serum cortisol <165 nmol/L, definite adrenal insufficiency; serum cortisol <300 nmol/L, adrenal insufficiency not excluded; serum cortisol >550 nmol/L generally excludes primary adrenal insufficiency
0800 h basal plasma corticotropin	4·5–12 pmol/L	Plasma corticotropin >22 pmol/L, definite adrenal insufficiency; plasma corticotropin >45 pmol/L in most cases
24 h urinary free cortisol	11–84 µg/24 h (men); 10–34 µg/24 h (women)	Not helpful in the diagnosis of adrenal insufficiency
Standard-dose corticotropin test	Peak cortisol >550 nmol/L (sensitivity 90%, specificity 100%)	Peak cortisol <500 nmol/L, definite adrenal insufficiency; in most cases there is no cortisol increase because endogenous corticotropin stimulation is already at peak
Secondary and tertiary adrenal insufficiency		
0800 h basal serum cortisol	165–680 nmol/L	Serum cortisol <100 nmol/L, definite adrenal insufficiency; serum cortisol 100–500 nmol/L, adrenal insufficiency not excluded; serum cortisol >500 nmol/L excludes secondary adrenal insufficiency
0800 h basal plasma corticotropin	4·5–12 pmol/L	Plasma corticotropin <12 pmol/L, adrenal insufficiency not excluded
Standard-dose corticotropin test	Peak cortisol >500 nmol/L (sensitivity 90%, specificity 100%)	Peak cortisol <500 nmol/L, definite adrenal insufficiency; peak cortisol <600 nmol/L, adrenal insufficiency not excluded; peak cortisol <400 nmol/L suggests central adrenal insufficiency
Low-dose corticotropin test	Peak cortisol >500 nmol/L (sensitivity 90%, specificity 90%)	Peak cortisol <500 nmol/L, definite adrenal insufficiency; peak cortisol <600 nmol/L, adrenal insufficiency not excluded; peak cortisol <400 nmol/L suggests central adrenal insufficiency
Prolonged corticotropin test	Peak cortisol >500 nmol/L	Peak cortisol <500 nmol/L, definite adrenal insufficiency
Insulin tolerance test	Peak cortisol >500 nmol/L	Peak cortisol <500 nmol/L, definite adrenal insufficiency; peak cortisol <550 nmol/L, adrenal insufficiency not excluded
Congenital adrenal hyperplasia due to 21-hydroxylase deficiency		
Standard-dose corticotropin test	Cortisol at 30 min >500 nmol/L; peak 17-hydroxyprogesterone <50 nmol/L	Peak 17-hydroxyprogesterone >300 nmol/L, classic disease; peak 17-hydroxyprogesterone 31–300 nmol/L, non-classic disease; peak 17-hydroxyprogesterone <50 nmol/L, likely unaffected or heterozygote

CAH=congenital adrenal hyperplasia. *For serum cortisol concentrations, multiply by 0·363 to convert nmol/L to µg/L. For plasma corticotropin concentrations, multiply by 4·5 to convert pmol/L to ng/L. For serum 17-hydroxyprogesterone concentrations, multiply by 0·331 to convert pmol/L to ng/dL. Sensitivity and specificity for the standard-dose and low-dose corticotropin tests are given in comparison with the insulin-induced hypoglycaemia test, which is regarded as the gold-standard.[71]

ACTH STIMULATION TESTING

- **High-dose ACTH stimulation test** - The rapid ACTH stimulation test measures the acute adrenal response to ACTH and is used to diagnose both primary and secondary adrenal insufficiency.

- A synthetic human 1-24-ACTH called tetracosactin or cosyntropin is used.

- Fasting is not required, and the test may be performed at any time of the day.

- A baseline cortisol sample is obtained; cosyntropin is administered in a dose of 250 g intramuscularly or intravenously; and additional samples for plasma cortisol are obtained at 30 or 60 minutes following the injection.

- **Low-dose ACTH stimulation test.** Since the standard or high-dose test may be normal in patients with partial secondary adrenal insufficiency, a low-dose (1 g) ACTH stimulation test was developed.

Plasma ACTH

- **In adrenal insufficiency** due
  - to **primary adrenal disease**, plasma **ACTH levels are elevated**.
  - in **pituitary ACTH deficiency** (secondary hypoadrenalism), **ACTH levels are inappropriately normal or less than 10 pg/mL** (2.2 pmol/L).

- In primary adrenal insufficiency, the 08.00 h **plasma corticotropin concentration is high,** and is associated with
  - high plasma renin concentration or activity,
  - low aldosterone concentrations,
  - hyponatraemia, and hyperkalaemia.

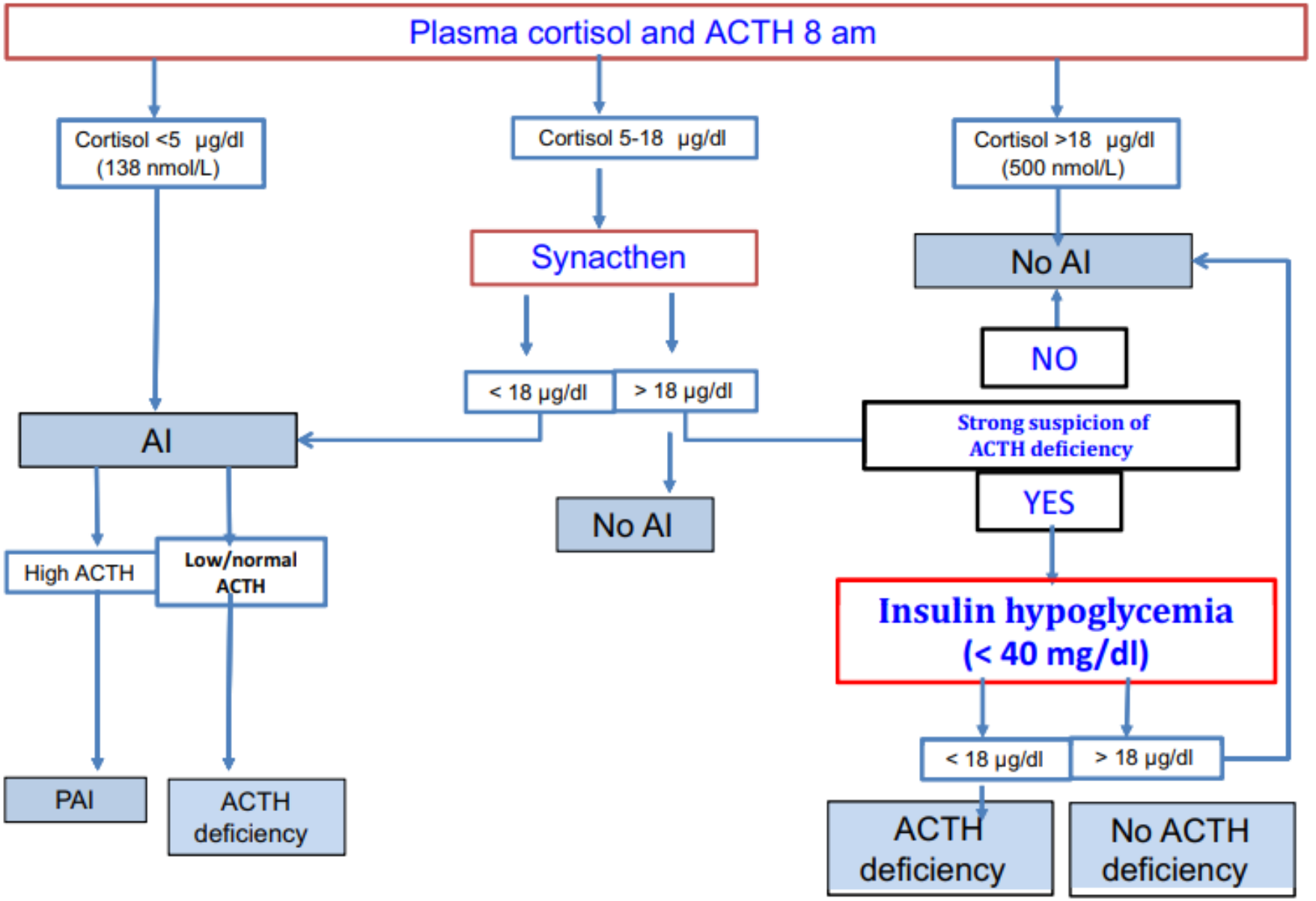
METYRAPONE TESTING

- Metyrapone testing has been used to diagnose adrenal insufficiency and to assess pituitary-adrenal reserve. Metyrapone blocks cortisol synthesis by inhibiting the 11 -hydroxylase enzyme that converts 11-deoxycortisol to cortisol. This stimulates ACTH secretion, which in turn increases the secretion and plasma levels of 11-deoxycortisol. The overnight metyrapone test is most commonly used and is best suited to patients with suspected pituitary ACTH deficiency; patients with suspected primary adrenal failure are usually evaluated with the rapid ACTH stimulation test as described earlier and discussed in the section on diagnosis of adrenocortical insufficiency.

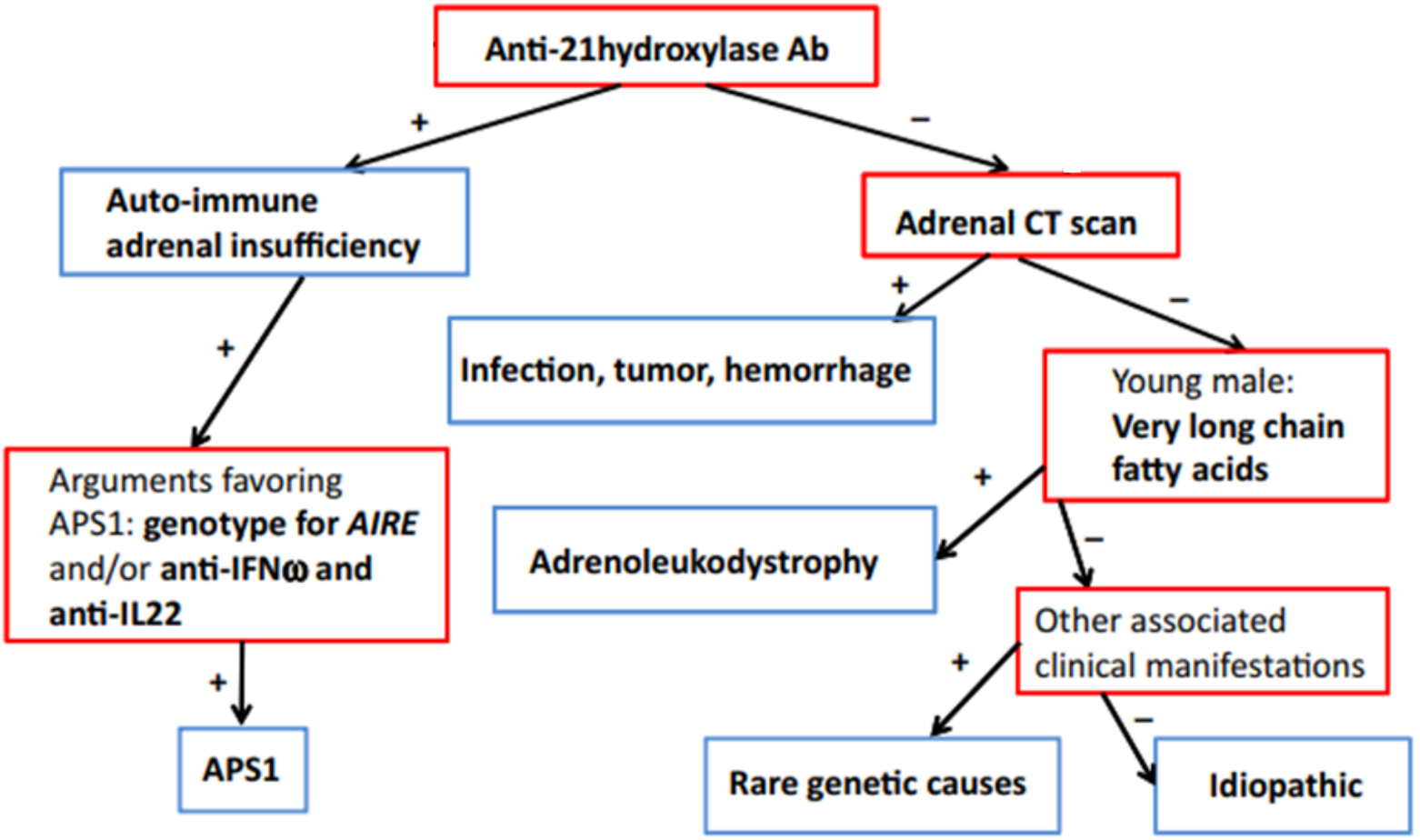
INSULIN-INDUCED HYPOGLYCEMIA TESTING

- Hypoglycemia induces a central nervous system stress response, increases CRH release, and in this way increases ACTH and cortisol secretion. It therefore measures the integrity of the axis and its ability to respond to stress.

Suspected adrenal insufficiency (not acute)



Decision tree for diagnosing etiology of primary adrenal insufficiency in the adult.



Treatment

- **Adrenal insufficiency** is potentially **life-threatening**.

- **Treatment should be initiated as soon as the diagnosis is confirmed**, or sooner if the patient presents in adrenal crisis.

- A very **important part** of the management of chronic adrenal insufficiency is **education of the patient and his or her family.**

- **They need to understand** the importance of life-long replacement therapy, the need to increase the usual glucocorticoid dose during stress, and the need to notify medical staff if the patients are to undergo any surgical procedure.

- In addition, they must always have supplies of hydrocortisone injections and should be taught how and when to administer them.

Treatment – cortizol replacement

- Patients with adrenal insufficiency **should be treated with hydrocortisone** (or cortisone acetate if hydrocortisone is not available), **which is the most physiological option for glucocorticoid replacement.**

- The **recommended daily hydrocortisone dose** is **10–12 mg/m2**;

- it can be given in two to three doses, with administration **of half to twothirds of the total daily dose in the morning.**

- **During minor illness or surgical procedures**, the dose of glucocorticoid can be **increased to up to three times the usual maintenance dose.**

- **During major illness or surgery**, doses of glucocorticoid **up to ten times the daily** production rate might be needed to avoid an adrenal crisis.

Chronic adrenal insufficiency

Glucocorticoid replacement

- Primary adrenal insufficiency—start on 20–25 mg hydrocortisone per 24 h
- Secondary adrenal insufficiency—15–20 mg hydrocortisone per 24 h; if cortisol concentrations are borderline low in response to the corticotropin test, consider 10 mg hydrocortisone daily or stress dose hydrocortisone cover only and monitor closely
- Hydrocortisone should be given in three doses with two-thirds or half of the total daily dose given early in the morning
- Educate patient and family about stress dose hydrocortisone cover
- Monitoring should include assessment of the patient for signs of glucocorticoid under-replacement (weight loss, fatigue, nausea, myalgia, lack of energy) or over-replacement (weight gain, central obesity, stretch marks, osteopenia and osteoporosis, impaired glucose tolerance, hypertension)

Treatment – mineralocorticoid replacement

- In primary adrenal insufficiency, **mineralocorticoid replacement therapy** is necessary **to prevent sodium loss, intravascular volume depletion, and hyperkalaemia**.

- It is given in the form of **fludrocortisone** (9-α-fl uorohydrocortisone) in a dose of **0.05–0.20 mg daily**, in the **morning**.

- The dose of fludrocortisone **is titrated individually** on **the basis of blood pressure, serum sodium and potassium concentrations, and plasma renin activity concentrations**.

- The mineralocorticoid dose might have to be increased in the summer, especially if patients are exposed to temperatures higher than 29°C.

Mineralocorticoid replacement

- Needed only in primary adrenal insufficiency
- Not needed if the daily hydrocortisone dose exceeds 50 mg
- Start with 100 µg fludrocortisone (50–250 µg per day) as a single dose early in the morning along with the hydrocortisone
- Monitoring should include assessment of the patient for signs of mineralocorticoid under-replacement (postural drop in arterial blood pressure >20 mm Hg, weight loss, dehydration, hyponatraemia, increased plasma renin activity) or over-replacement (weight gain, increased arterial blood pressure, hypernatraemia, suppressed plasma renin activity)

Adrenal androgen replacement

- Should be considered in patients with impaired wellbeing and mood despite optimum replacement therapy with glucocorticoids and mineralocorticoids, or in women with symptoms and signs suggesting adrenal androgen insufficiency
- Start with dehydroepiandrosterone 25–50 mg as a single morning dose
- Monitoring during treatment in women should include measurement of serum testosterone and sex-hormone binding globulin (to calculate free androgen index) concentrations; in both sexes, serum dehydroepiandrosterone sulphate and androstenedione concentrations should be monitored (24 h after the last preceding dose of dehydroepiandrosterone)

Acute adrenal insufficiency

Glucocorticoid replacement

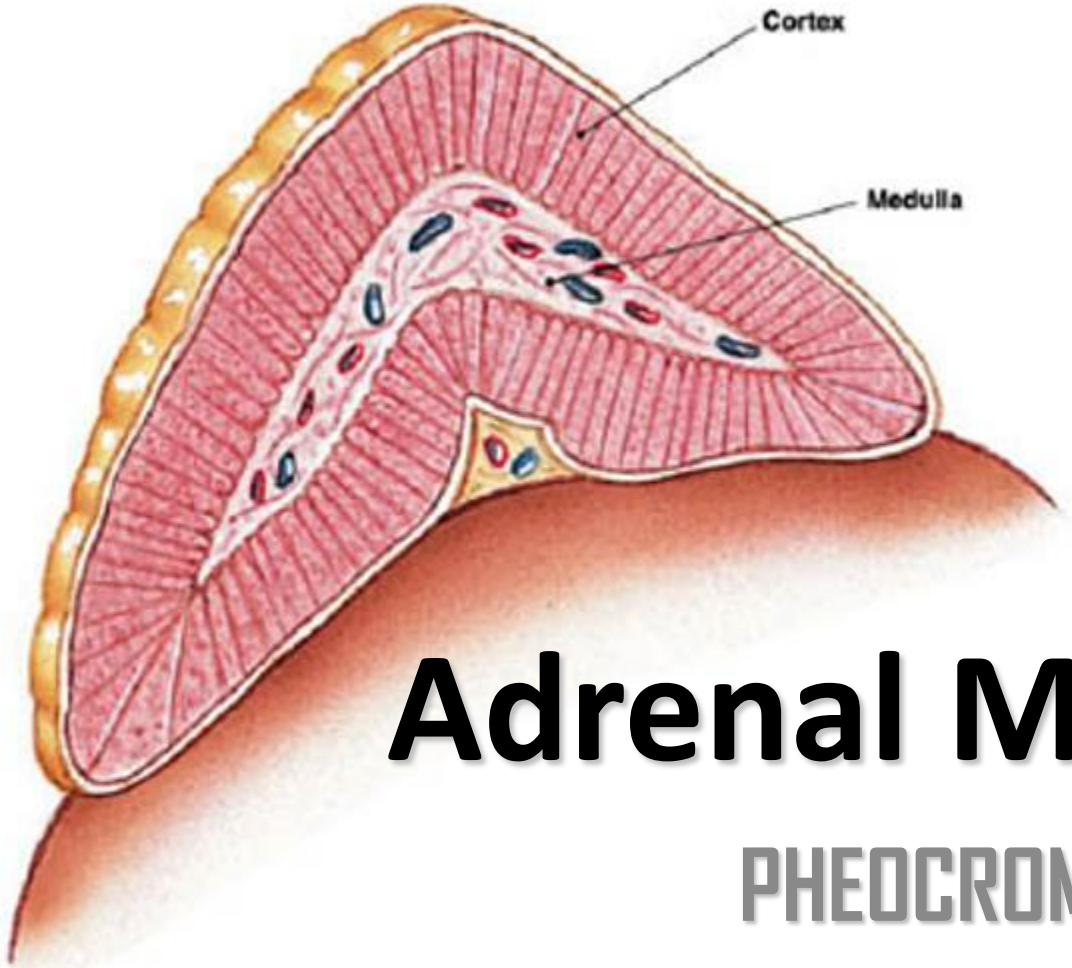
- Rapid rehydration with physiological saline infusions under continuous cardiac monitoring; inject 100 mg hydrocortisone intravenously, followed by 100–200 mg hydrocortisone in glucose 5% by continuous intravenous infusion (or, hydrocortisone intramuscularly every 6 h at a dose of 50–100 mg depending on age and body surface area)

Mineralocorticoid replacement

- Needed only in primary adrenal insufficiency
- Not needed if hydrocortisone dose >50 mg per 24 h

Adrenal androgen replacement

- Not required



Adrenal Medulla

PHEOCROMACITOMA

Physiologic Effects of Catecholamines

Cardiovascular effects

- generally increases heart rate and cardiac output and causes peripheral vasoconstriction, leading to an increase in blood pressure.

Physiologic Effects of Catecholamines

Effects on extravascular smooth muscle

- These effects include contraction (α1) and relaxation (β2) of uterine myometrium, relaxation of intestinal and bladder smooth muscle (β2), contraction of the smooth muscle in the bladder (α1) and intestinal sphincters, relaxation of tracheal smooth muscle (β2), and pupillary dilation.

Physiologic Effects of Catecholamines

Metabolic effects

- increase oxygen consumption and heat production
- regulate glucose and fat mobilization from storage depots
- leads to lipolysis and the release of free fatty acids and glycerol into the circulation
- causes the release of glucose into the circulation

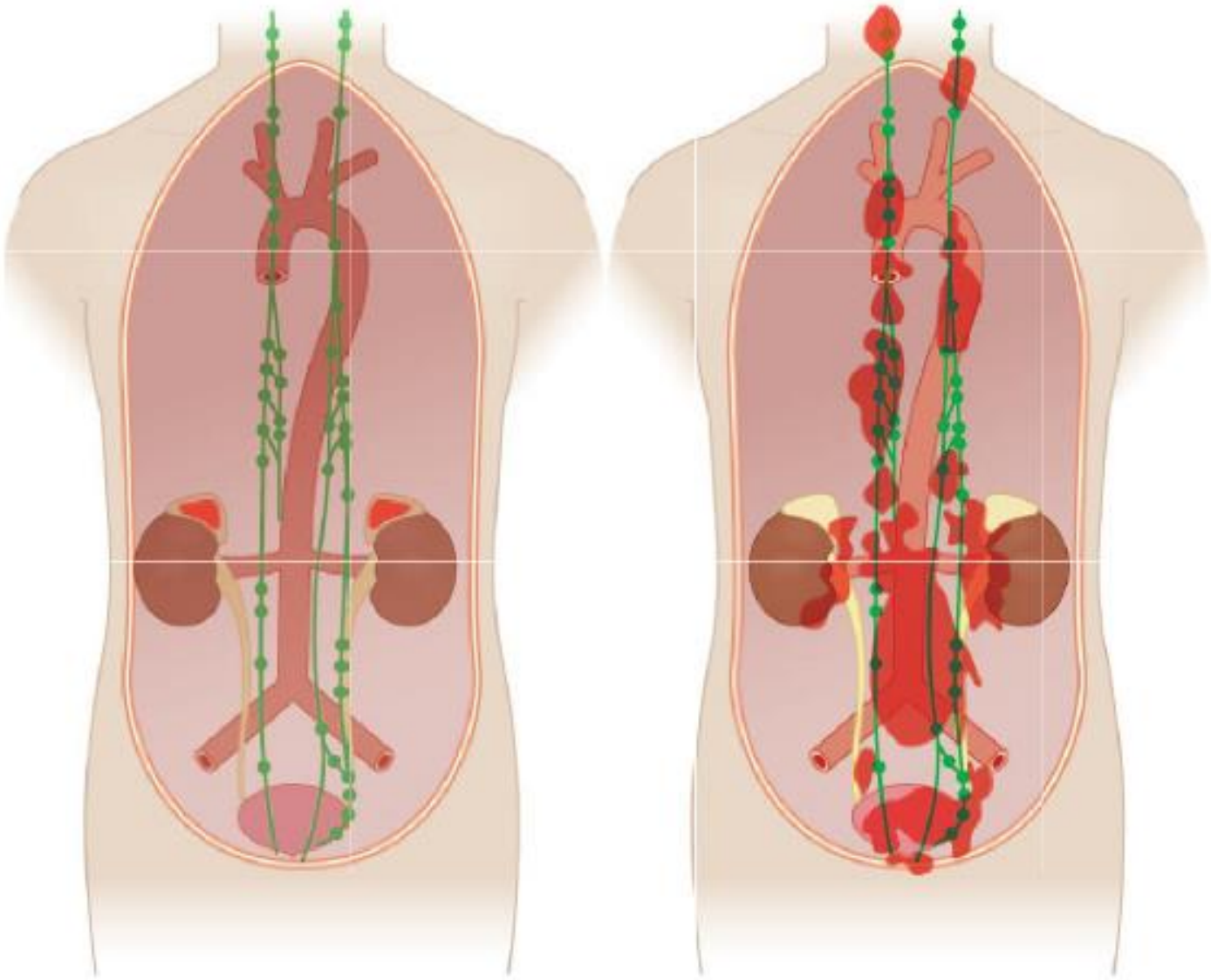
Catecholamine receptors: location and clinical effects following receptor activation.

Catecholamine Receptor	Tissue Location	Clinical Effects Following Receptor Activation
$Alpha_1$	Vascular smooth muscle	Increases vasoconstriction (increases blood pressure)
	Liver	Increases glycogenolysis and gluconeogenesis
	Eye	Increases ciliary muscle contraction (pupil dilation)
	Skin	Increases pilomotor smooth muscle contraction (erects hairs)
	Prostate	Increases contraction and ejaculation
	Uterus	Increases gravid uterus contraction
	Intestines	Increases sphincter tone and relaxes smooth muscle
	Spleen capsule	Contracts spleen volume, expelling blood
$Alpha_2$	Preganglionic nerves	Decreases release of neurotransmitter
	Vascular smooth muscle	Increases vasoconstriction (increases blood pressure)
	Pancreatic islet cells	Decreases release of insulin and glucagon
	Blood platelets	Increases platelet aggregation
	Adipose cells	Decreases lipolysis
	Brain	Decreases norepinephrine release
$Beta_1$	Myocardium	Increases force and rate of contraction
	Kidney (juxtaglomerular apparatus)	Increases secretion of renin
	Adipose cells	Increases lipolysis
	Most tissues	Increases calorigenesis
	Nerves	Increases conduction velocity
$Beta_2$	Vascular smooth muscle	Decreases vasoconstriction (increases blood flow)
	Bronchiolar smooth muscle	Decreases contraction (bronchial dilation)
	Liver	Increases glycogenolysis and gluconeogenesis
	Intestinal smooth muscle	Decreases intestinal motility; increases sphincter tone
	Pancreatic islet cells	Increases release of insulin and glucagon
	Adipose tissue	Increases lipolysis
	Muscles	Increases muscle contraction speed and glycogenolysis
	Liver and kidney	Increases peripheral conversion of T_4 to T_3
	Uterus smooth muscle	Decreases nongravid uterine contraction (uterine relaxation)
$Beta_3$	Adipose cells	Increases lipolysis
	Intestinal smooth muscle	Increases intestinal motility
$Dopamine_1$	Vascular smooth muscle	Decreases vasoconstriction (vasodilation)
	Renal tubule	Enhances natriuresis
$Dopamine_2$	Sympathetic nerves	Inhibits synaptic release of norepinephrine
	Pituitary lactotrophs	Inhibits prolactin release
	Gastrointestinal tract	Paracrine functions
	Brain	Neurotransmitter

- Pheochromocytomas are chromaffin tumors that arise from the adrenal medulla, whereas non–head-neck paragangliomas arise from extra-adrenal sympathetic ganglia.

- Pheochromocytomas can secrete excessive amounts of both epinephrine and norepinephrine, whereas most paragangliomas secrete only norepinephrine.

- Metastases from adrenal pheochromocytomas usually secrete only norepinephrine.



A Adrenal pheochromocytoma

B Extra-adrenal pheochromocytoma

- Adrenal pheochromocytomas are usually unilateral (90%).
- Unilateral pheochromocytomas occur more frequently in the right (65%) versus the left adrenal (35%).
- Adrenal pheochromocytomas are bilateral in about 10% of adults and 35% of children.
- Bilateral pheochromocytomas are particularly common (24% overall) in patients with familial pheochromocytoma syndromes caused by certain germline mutations.
- Catecholamine-secreting tumors occur with equal frequency in men and women, primarily in the third, fourth, and fifth decades.
- These tumors are rare in children.

Patients to be screened for pheochromocytoma and paraganglioma.

- Hypertension in youth
- Hypertensive crisis or shock related to:
  - Anesthesia induction
  - Drugs: decongestants, glucocorticoids, MAO inhibitors
  - Invasive procedures
  - Parturition
  - Surgery
- Hypertensive patients with:
  - Symptoms listed in Table 11–14
  - Cardiomyopathy
  - Cyanotic congenital heart disease
  - Erythrocytosis
  - Family history of PHEO/PGL or medullary thyroid carcinoma
  - Gastrointestinal stromal tumors (GIST)
  - Hemangioblastoma
  - Hyperglycemia
  - Hypertension that is uncontrolled, severe, or markedly labile
  - Medullary thyroid carcinoma
  - Mucosal neuromas
  - Neurofibromatosis and other neurocutaneous syndromes
  - Orthostatic hypotension
  - Personal history of prior PHEO/PGL
  - Pituitary adenoma
  - Renal cell carcinoma
  - Seizures
  - Shock (unexplained)
  - Weight loss
- Patients harboring germline mutations associated with PHEO or PGL
- Radiologic evidence of an adrenal mass
- Radiologic evidence of a mass in area of paraganglia

Clinical Presentation

- The symptoms, are caused by the pharmacologic effects of excess concentrations of circulating catecholamines.
- Adult patients have paroxysmal symptoms, which may last minutes or hours; symptoms usually begin abruptly and subside slowly.

Manifestations and their approximate incidence include:

- hypertension (90%),
- headaches (80%),
- diaphoresis (70%)
- palpitations or tachycardia (60%)
- episodic anxiety (60%),
- tremor (40%),
- abdominal or chest pain (35%),
- pallor (30%),
- nausea or vomiting (30%).
- Hyperglycemia (30%) but is usually asymptomatic
- fatigue (25%),
- flushing (18%)
- dyspnea (15%).
- visual changes (12%)

Triggers for paroxysms:

- Episodic paroxysms may not recur for months or may recur many times daily.
- Each patient tends to have a different pattern of symptoms, with the frequency or severity of episodes usually increasing over time.
- Attacks can occur spontaneously or may occur with bladder catheterization, anesthesia, or surgery.
- Acute attacks may also be triggered by eating foods containing tyramine: aged cheeses, meats, fish, beer, wine, chocolate, or bananas.
- Hypertensive crises can also be triggered by certain drugs.
- Paroxysms can be induced by seemingly benign activities such as bending, rolling over in bed, exertion, abdominal palpation, or micturition

- Hypertensive crisis is the quintessential manifestation of pheochromocytomas.

- Blood pressure that exceeds 200/120 mm Hg is an immediate threat to life, being associated with encephalopathy or stroke, cardiac ischemia or infarction, pulmonary edema, aortic dissection, rhabdomyolysis, lactic acidosis, and renal insufficiency.

- Hypertension is present in 90% of patients in whom a pheochromocytomas is diagnosed.

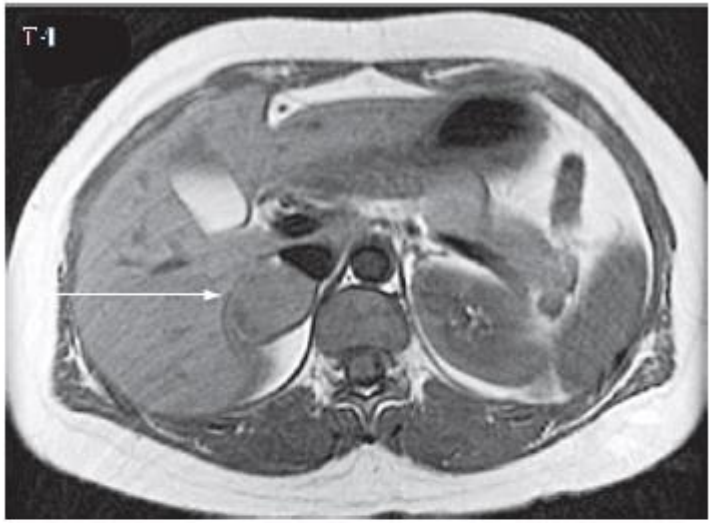
- Paroxysms of severe hypertension occur in about 50% of adults.
- Hypertension can be mild or severe and resistant to treatment.
- Vasoconstriction is responsible for the pallor and mottled cyanosis that can occur with paroxysms of hypertension.
- Palpitations are one of the most frequent complaints.
- Headache is a common manifestation during an acute paroxysm.
- Patients frequently complain of paresthesia, numbness, or dizziness.

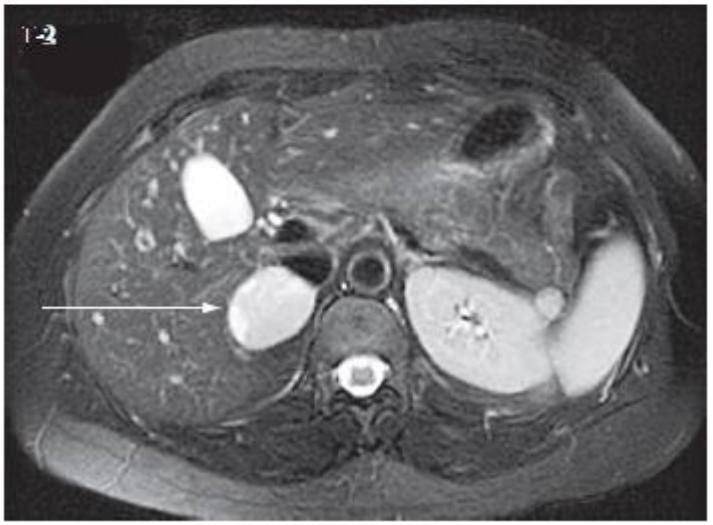
Clinical manifestations of pheochromocytoma and paraganglioma.

Blood pressure	Hypertension: severe or mild, paroxysmal or sustained; orthostasis; hypotension/shock; normotension
Vasospasm	Cyanosis, Raynaud syndrome, gangrene; severe radial artery vasospasm with thready pulse; falsely low blood pressure by radial artery transducer
Multisystem crisis	Severe hypertension/hypotension, fever, encephalopathy, ARDS, renal failure, hepatic failure, death
Cardiovascular	Palpitations, dysrhythmias, chest pain, acute coronary syndrome, cardiomyopathy, heart failure, cardiac paragangliomas
Gastrointestinal	Abdominal pain, nausea, vomiting, weight loss, intestinal ischemia; pancreatitis, cholecystitis, jaundice; rupture of abdominal aneurysm; constipation, toxic megacolon
Metabolic	Hyperglycemia/diabetes; lactic acidosis; fevers
Neurologic	Headache, paresthesias, numbness, dizziness, CVA, TIA, hemiplegia, hemianopsia, seizures, hemorrhagic stroke; skull metastases may impinge on brain structures, optic nerve, or other cranial nerves; spinal metastases may impinge on cord or nerve roots
Pulmonary	Dyspnea; hypoxia from ARDS
Psychiatric	Anxiety (attacks or constant); depression; chronic fatigue; psychosis
Renal	Renal insufficiency, nephrotic syndrome, malignant nephrosclerosis; large tumors often involve the kidneys and renal vessels
Skin	Apocrine sweating during paroxysms, drenching sweats as attack subsides; eczema; mottled cyanosis during paroxysm
Ectopic hormone production	ACTH (Cushing syndrome); VIP (Verner-Morrison syndrome); PTHrP (hypercalcemia)
Children	More commonly have sustained hypertension, diaphoresis, visual changes, polyuria/polydipsia, seizures, edematous or cyanotic hands; more commonly harbor germline mutations, multiple tumors, and paragangliomas
Women	More symptomatic than men: more frequent headache, weight loss, numbness, dizziness, tremor, anxiety, and fatigue
Pregnancy	Hypertension mimicking eclampsia; hypertensive multisystem crisis during vaginal delivery; postpartum shock or fever; high mortality
General laboratory	Leukocytosis, erythrocytosis, eosinophilia
Associated tumors	Renal cell carcinoma, hemangioblastoma, gastric sarcoma, pulmonary chondroma, pituitary adenoma, papillary thyroid cancer

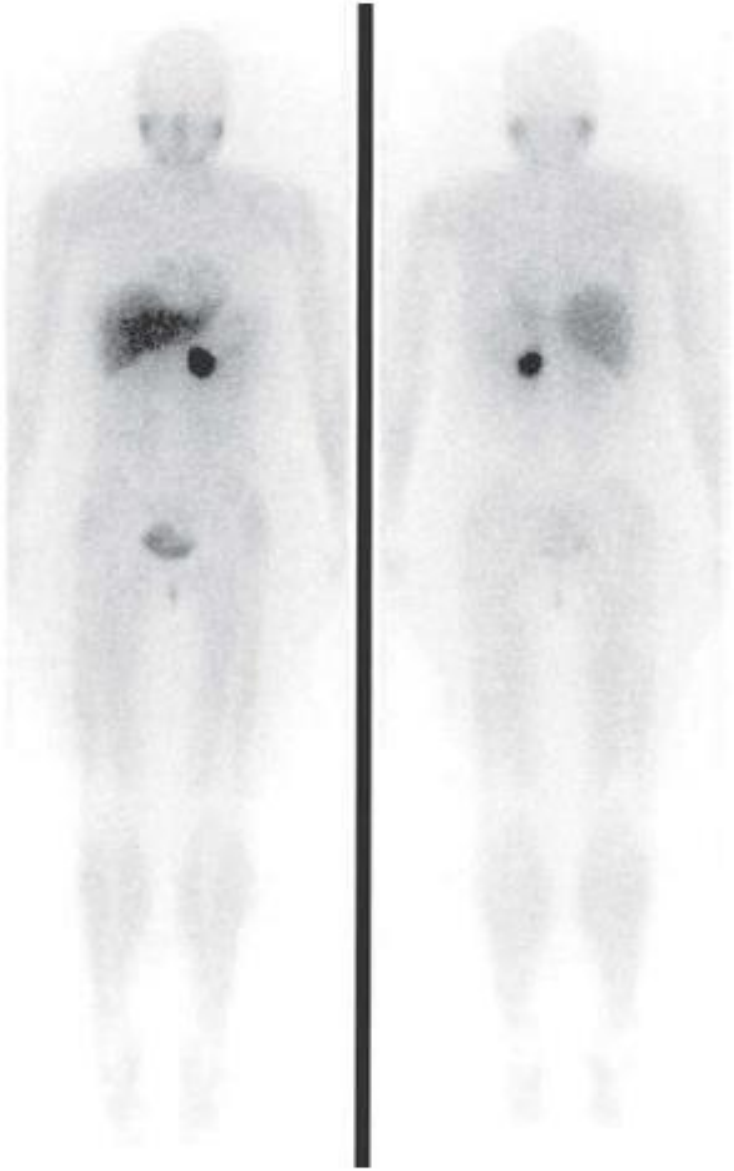
Diagnostic Investigation

- The diagnosis must be confirmed biochemically by the presence of increased concentrations of fractionated metanephrines and catecholamines in urine or plasma.
- Localization studies should not be initiated until biochemical studies have confirmed the diagnosis of a catecholamine-secreting tumor.
- CT or MRI of the abdomen and pelvis should be the first localization test.
- In patients with a biochemically confirmed catecholamine-secreting tumor where the results of abdominal and pelvic imaging are negative, additional localization studies are indicated with either 68Ga-DOTATATE PET/CT or scintigraphy with 123I-MIBG.



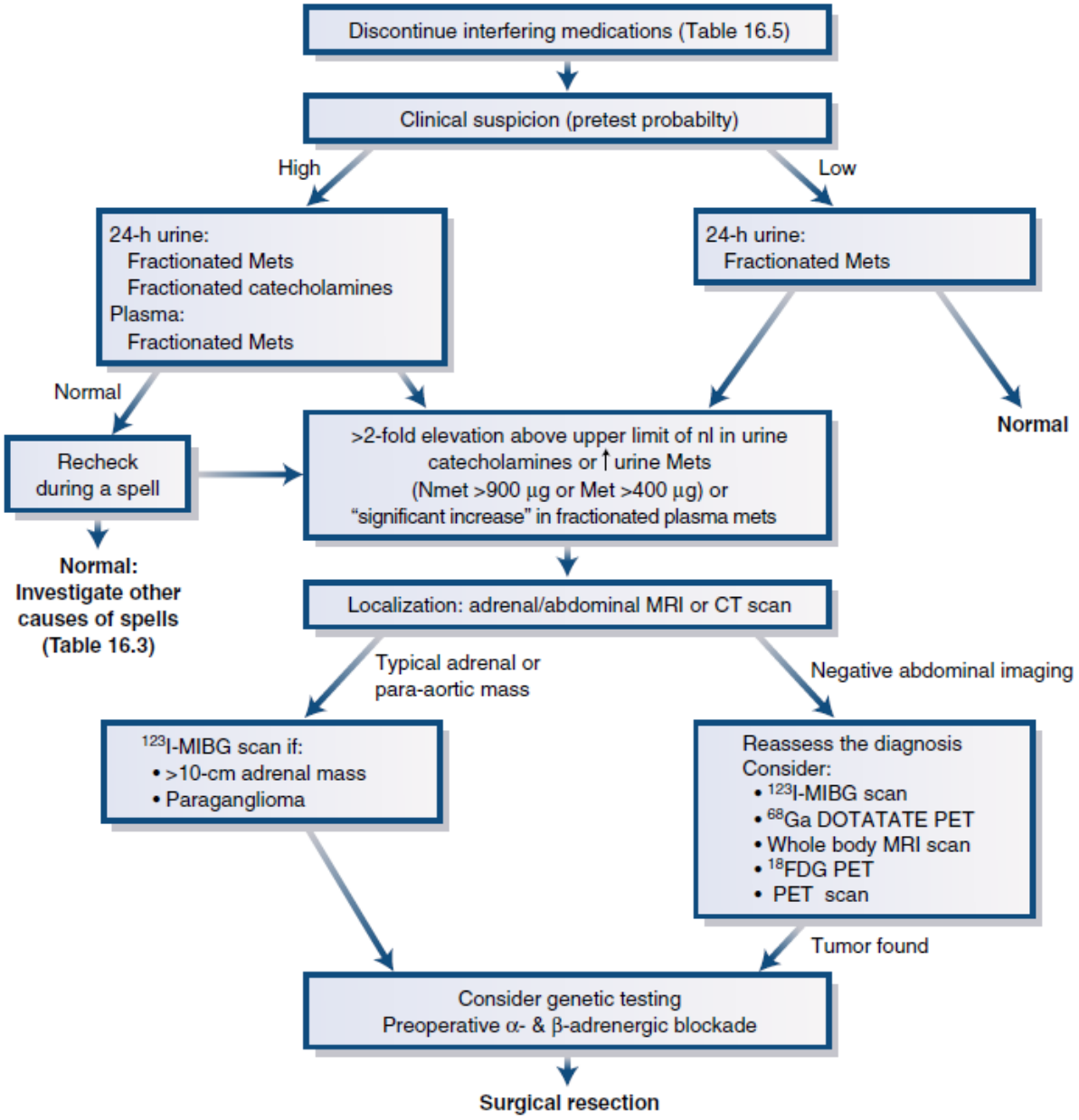


The images show a slightly heterogeneous, right adrenal mass (3.3 × 3.5 × 4.5 cm) consistent with pheochromocytoma *(arrows)* that has increased signal intensity on T2-weighted images *(lower panel)*.



^{123}I-metaiodobenzylguanidine (^{123}I-MIBG) scan of a woman with a large left PHEO. Normal ^{123}I-MIBG uptake is seen in the liver, salivary glands, and heart. ^{123}I-MIBG is renally excreted and is visible in the bladder.

Evaluation and treatment of catecholamine-secreting tumors



Causes of death in patients with unsuspected pheochromocytomas.

Myocardial infarction
Cerebrovascular accident
Cardiac dysrhythmias
Irreversible shock
Renal failure
Dissecting aortic aneurysm
Acute respiratory distress syndrome

Treatment

- The treatment of choice for pheochromocytoma is complete surgical resection.
- The most common complications are intraoperative blood pressure lability and postoperative hypotension. Careful preoperative pharmacologic preparation is crucial for successful treatment.
- Most catecholaminesecreting tumors are benign and can be totally excised. Tumor excision usually cures hypertension.

Treatment

- Patients need to be treated with oral antihypertensives and stabilized hemodynamically prior to surgery.
- Combined α-adrenergic and β-adrenergic blockade is one approach to control blood pressure and prevent intraoperative hypertensive crises.
- Phenoxybenzamine is the preferred drug for preoperative preparation to control blood pressure and arrhythmia.
- The β-adrenergic antagonist should be administered only after α-adrenergic blockade is effective.
- Calcium channel blockers, which block norepinephrine-mediated calcium transport into vascular smooth muscle, have been used successfully to preoperatively prepare patients with pheochromocytoma.