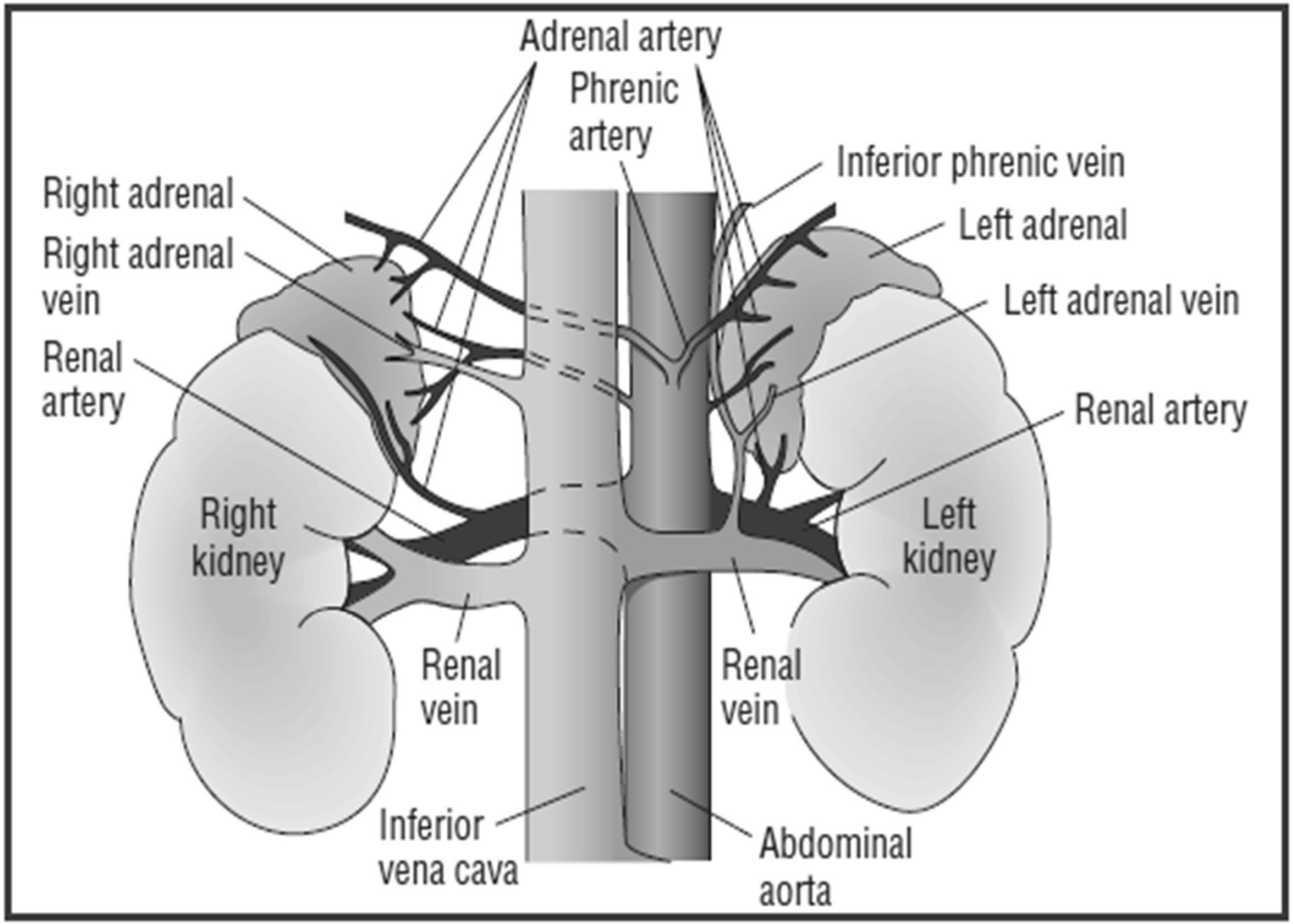
# *Adrenal gland disorders*

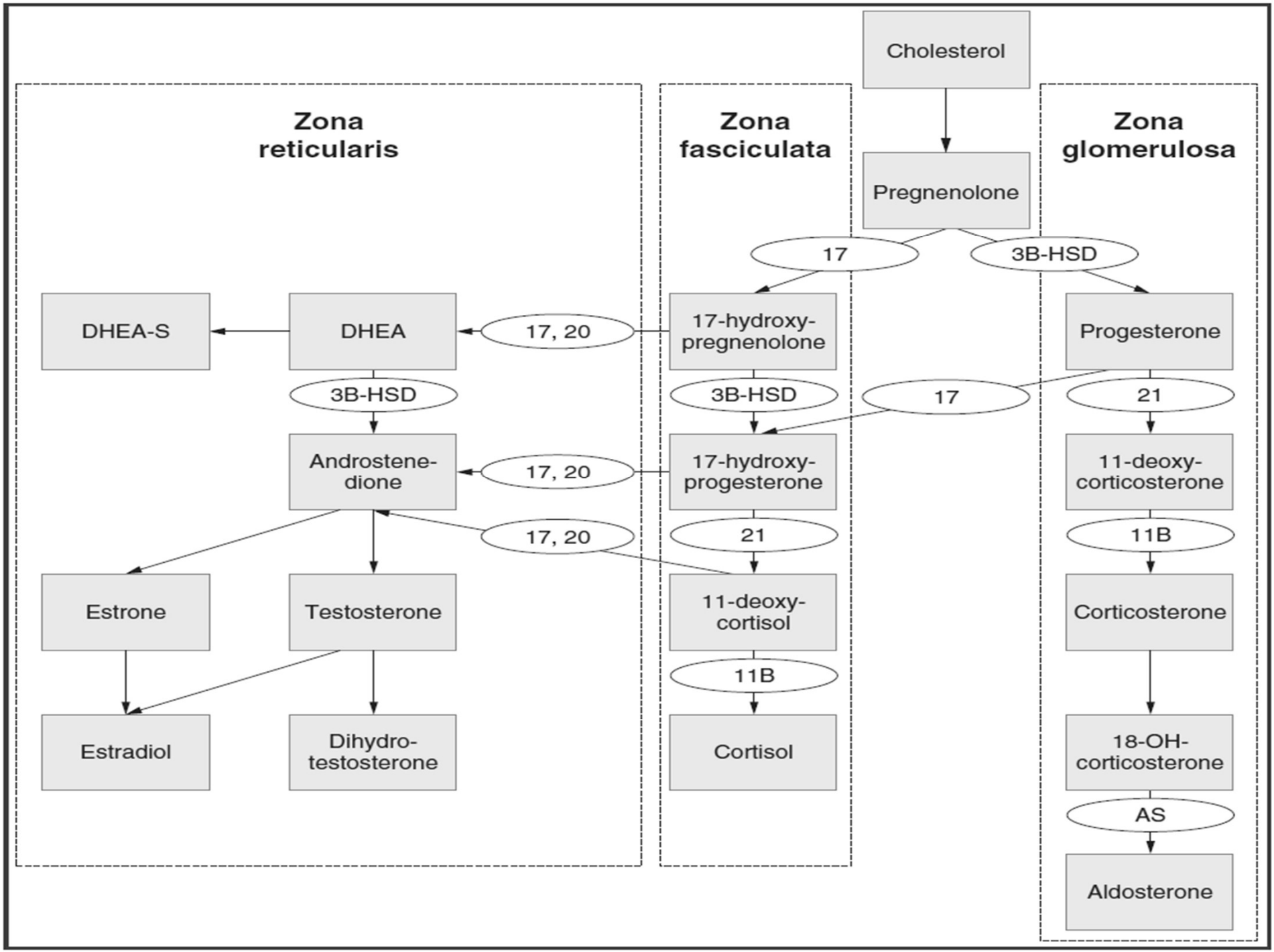
The adrenal glands are important in the synthesis and regulation of key hormones.

They play a crucial role in water and electrolyte homeostatsis, as well as regulation of blood pressure, carbohydrate and fat metabolism, physiologic response to stress, and sexual development and differentiation.

The adrenal medulla secretes the catecholamines epinephrine (also called adrenaline) and norepineprhine (also called noradrenaline), which are involved in regulation of the sympathetic nervous system.

The adrenal cortex consists of three histologically distinct zones: **zona glomerulosa**, **zona fasciculata**, and an innermost layer called the **zona reticularis**.


Adrenal artery
Phrenic artery
Inferior phrenic vein
Right adrenal
Left adrenal
Right adrenal vein
Left adrenal vein
Renal artery
Renal artery
Right kidney
Left kidney
Renal vein
Renal vein
Inferior vena cava
Abdominal aorta


Cholesterol
Pregnenolone
17
3B-HSD
Zona reticularis
Zona fasciculata
Zona glomerulosa
DHEA-S
DHEA
17, 20
17-hydroxy-pregnenolone
Progesterone
3B-HSD
3B-HSD
17
21
Androstene-dione
17, 20
17-hydroxy-progesterone
11-deoxy-corticosterone
17, 20
21
11B
Estrone
Testosterone
11-deoxy-cortisol
Corticosterone
11B
Estradiol
Dihydro-testosterone
Cortisol
18-OH-corticosterone
AS
Aldosterone

**The zona glomerulosa** is responsible for the production of the mineralocorticoids **aldosterone,** deoxycorticosterone, and 18-hydroxy-deoxycorticosterone.

**The zona fasciculata** produces the glucocorticoid hormone **cortisol.** The normal rate of cortisol production is approximately 8 to 15 mg/day.

Its production increases markedly during physiologic stress, such as during acute illness, surgery, or trauma.

Cortisol is converted in the liver to an inactive metabolite known as cortisone.

**The zona reticularis** produces the androgens **androstenedione**, **dehydroepiandrosterone** (DHEA), and the sulfated form of **dehydroepiandrosterone** (DHEA-S).

- Androstenedione and DHEA are converted in the periphery, largely to testosterone and estrogen.

- Adrenal hormone production is controlled by the hypothalamus and pituitary gland.

- When sufficient or excessive cortisol levels are reached, a **negative feedback** is exerted on the secretion of CRH and ACTH, thereby decreasing overall cortisol production.

- The control of adrenal androgen synthesis also follows a similar negativefeedback mechanism.

# *Adrenal insufficiency:*

- Adrenal insufficiency generally refers to the inability of the adrenal glands to produce adequate amounts of ***cortisol*** for normal physiologic functioning or in times of stress.

- The condition is usually classified as **primary**, **secondary**, or **tertiary** depending on the etiology.
- Chronic adrenal insufficiency is rare.

- Primary adrenal insufficiency usually is diagnosed in the third to fifth decades of life, whereas secondary adrenal insufficiency is commonly detected during the sixth decade.
- Adrenal insufficiency is more prevalent in women than in men.

## ***Pathophysiology:***

- It occurs from destruction of the adrenal cortex, usually from an autoimmune process.

- Secondary adrenal insufficiency occurs as a result of a pituitary gland dysfunction whereby decreased production and secretion of ACTH leads to a decrease in cortisol synthesis.

- Tertiary adrenal insufficiency is a disorder of the hypothalamus that results in decreased production and release of CRH, which, in turn, decreases pituitary ACTH production and release.

- Acute adrenal insufficiency (i.e., adrenal crisis) results from the body's inability to increase endogenous cortisol sufficiently during periods of excessive physiologic stress.

## ***Clinical Presentation and Diagnosis of Chronic Adrenal Insufficiency:***

The cardinal symptoms and signs are weakness and fatigue requiring rest periods, gastrointestinal symptoms, weight loss, and hypotension.

Patients with autoimmune adrenal insufficiency may have other autoimmune disorders such as **type 1 diabetes mellitus** and **autoimmune thyroiditis.**

- Dehydration, hypovolemia, and hyperkalemia (in primary adrenal insufficiency only).
- Decreased serum sodium and chloride levels.
- Increased serum blood urea nitrogen (BUN) and creatinine owing to dehydration.
- **Hyperpigmentation** of skin.
- Personality changes (irritability and restlessness)
- Loss of axillary and pubic hair in women owing to decreased androgen production.
- Blood count abnormalities.

## Laboratory Tests:

- Decreased basal and stress-induced cortisol levels.
- Decreased aldosterone level (in primary adrenal insufficiency only).
- Lack of increase in cortisol and aldosterone level after ACTH stimulation.

## Other Diagnostic Tests:

- Computed tomography (CT) or magnetic resonance imaging (MRI).
- The presence of anti-adrenal antibodies.

## Treatment and Outcome Evaluation:

## 1- Chronic Adrenal Insufficiency:

- The general goals of treatment are to manage symptoms and prevent development of adrenal crisis.

- Lifelong glucocorticoid replacement therapy *may be* necessary for patients with adrenal insufficiency, and mineralocorticoid replacement therapy usually is required for those with Addison's disease.

- ***Hydrocortisone*** often is prescribed because it most closely resembles endogenous cortisol (with its relatively high mineralocorticoid activity and short half-life) and allows the design of regimens that simulate the normal circadian cycle.

## ***2- Acute Adrenal Insufficiency:***

- During an acute adrenal crisis, the immediate treatment goals are to correct volume depletion, manage hypoglycemia, and provide glucocorticoid replacement.

- Patients who experience excessive stress should be educated regarding the need for ***additional glucocorticoid replacement*** and prompt medical attention.

- Although the dosage of glucocorticoid generally is individualized, a common recommendation is to double the maintenance dose of hydrocortisone if the patient experiences fever or undergoes invasive dental or diagnostic procedures.

## *HYPERCORTISOLISM (CUSHING'S SYNDROME):*

- Cushing's syndrome refers to the pathophysiologic changes associated with exposure to supraphysiologic cortisol concentrations (endogenous hypercortisolism) or pharmacologic doses of glucocorticoids (exogenous hypercortisolism).

- Patients receiving chronic supraphysiologic doses of glucocorticoids, such as those with rheumatologic disorders, are at high risk of developing Cushing's syndrome.

## ***Pathophysiology:***

- Cushing's syndrome can be classified as ACTH-dependent or ACTH-independent.

- ACTH-dependent Cushing's syndrome results from ACTH-secreting (or rarely, CRH-secreting) **adenomas.**

- ACTH-independent Cushing's syndrome is due either to excessive cortisol secretion by the adrenal glands (independent of ACTH stimulation) or to exogenous glucocorticoid administration.

- Patients with Cushing's syndrome owing to endogenous or exogenous glucocorticoid excess typically present with similar clinical manifestations.

The term ***Cushing's disease*** refers specifically to Cushing's syndrome from an ACTH secreting pituitary adenoma.

Circadian rhythm is lost in most patients with Cushing's syndrome. As such, detection of elevated *midnight cortisol concentrations* can be useful in the diagnosis of Cushing's syndrome.

Mortality in patients with Cushing's syndrome is mostly attributed to cardiovascular disease.

**Hypertension**, **hyperglycemia**, and **hyperlipidemia** are common findings and can be associated with cardiac hypertrophy, atherosclerosis, and hypercoagulability.

Osteopenia, osteoporosis, and increased fractures also have been reported.

## *Clinical Presentation and Diagnosis of Cushing's Syndrome*:

- Weight gain and obesity.
- A rounded and puffy face.
- Dorsocervical ("buffalo hump") and supraclavicular fat accumulation.
- Hirsutism (75%).
- Thin skin.
- Facial plethora (70%).
- Skin striae.
- Acne (35%).
- Hyperglycemia.
- Hyperlipidemia (70%).
- Polyuria (30%).
- Hypertension.
- Menstrual irregularities (amenoria) (70%).
- Erectile dysfunction (85%).
- Psychiatric changes (85%).

## *Laboratory Tests:*

**1-** 24-hour urinary free cortisol determination.

**2-**Overnight low-dose dexamethasone suppression test (DST).

**3-** Imaging studies may be used to distinguish between pituitary, ectopic, and adrenal tumors.

# *Treatment:*

- The goal of treatment in patients with Cushing's syndrome is reversal of hypercortisolism and management of the associated comorbidities, including the potential for long-term sequelae such as cardiac hypertrophy.

- Surgical resection is considered the treatment of choice for Cushing's syndrome from endogenous causes if the tumor can be localized and if there are no contraindications.

- The treatment of choice for Cushing's syndrome from exogenous causes is gradual discontinuation of the offending agent.

## *Nonpharmacologic Therapy:*

**1-** Transsphenoidal pituitary microsurgery.

**2-** Pituitary irradiation or bilateral adrenalectomy.

**3-** Bilateral adrenalectomy.

**4-** Bilateral laparoscopic adrenalectomy.

**5-** Unilateral laparoscopic adrenalectomy.

## *Pharmacologic Therapy:*

### ***Pharmacotherapy generally is reserved for patients:***

1- With ectopic ACTH-secreting tumor cannot be localized.

2- who are not surgical candidates.

3- who have failed surgery.

4- who have had a relapse after surgery.

5- in whom adjunctive therapy is required to achieve complete remission.

Pharmacological treatment of cushing syndrome includes the following classes:

1- Inhibitors of Adrenal Steroidogenesis (as **aminoglutethimide**, **Ketoconazole**, **Metyrapone**, **Etomidate**, **Adrenolytic Agent Mitotane**.

2- Central Neuromodulators of ACTH Release as Bromocriptine, Cyproheptadine, Octreotide, Ritanserin, Sodium valproate.

3- Peripheral Glucocorticoid Antagonist as *Mifepristone*.