Endocrinology

The endocrine system is made up of a complex group of glands that secrete hormones. These hormones control reproduction, metabolism, growth and development. The hormones also control situational response to our environment.

The glands that make up the endocrine system include the thyroid, parathyroid, pancreas, ovaries, testes, adrenal, pituitary and hypothalamus. Other organs and tissues such as the kidney (renin) and the GI tract (GLP-1) also release hormones.

Here we look at some of the more common endocrine disorders and tests you might see.

A. Adrenal Disorders

B. Thyroid Disorders

C. Pancreatic Disorders
A. Adrenal Disorders

The adrenal glands are attached to the kidneys. Their function is to receive either hormonal or nerve input and to release hormones that either control or modulate many processes. The two adrenal glands are asymmetric with respect to the blood supply and are of slightly different shapes. There are two distinct regions of the adrenal glands.

1. **Adrenal Medula**: Manufactures and secretes the catecholamines (epinephrine and norepinephrine: roughly 9:1 ratio) for direct release into the blood principally for energy regulation and responses to various kinds of stress (fight or flight). The catecholamines act by binding to cell surface receptors on organs and tissues and exert their effects via second messenger systems. Circulating catecholamines can be released within seconds of stimulatory input by the sympathetic nervous system. The catecholamines have very short half-lives in the blood (20 to 120 seconds).
2. **Adrenal Cortex**: The adrenal cortex is subdivided into 3 zones

a. **Zona reticularis**: Here the sex steroid precursor DHEA and some androgens are manufactured and released. DHEA circulates at the highest concentration in the blood of the steroids and serves as a precursor to androgens and estrogens manufactured in other tissues. DHEA is not a precursor to the mineralocorticoids or the glucocorticoids. We won’t look at this.

![DHEA molecule](image)

b. **Zona fasciculata**: Synthesizes and releases the glucocorticoid steroids (*cortisol and cortisone*). The glucocorticoids exert strong effects on energy metabolism and prolonged stress response in most cells in the body. Importantly, the glucocorticoids also act to suppress the immune response. The glucocorticoids bind to glucocorticoid receptors (GR) in the cytosol of targeted cells. The glucocorticoid-receptor complexes enter the nucleus and control gene transcription.

c. **Zona glomerulosa**: Synthesize and release the mineralocorticoid *aldosterone* which controls electrolyte and volume via it's effects on the kidney. Aldosterone binds to mineralocorticoid receptors (MR) in the cytosol. The aldosterone-receptor complex enters the nucleus and controls gene transcription.

3. **Control over hormone synthesis and release**

a. **The pituitary gland releases** adrenocorticoid stimulating hormone (ACTH) which is a peptide hormone. It controls the synthesis of the steroid hormones and precursors. It is released from the hypothalamus/pituitary glands. ACTH controls glucocorticoid levels. It also partially controls mineralocorticoid levels. There is a feedback loop whereby the circulating adrenal hormones can inhibit the the release of the stimulating hormones from the hypothalamus/pituitary axis (HPA axis).

![HPA Axis diagram](image)
b. Renin angiotensin system. Aldosterone levels are also controlled by the renin angiotensin system. Specifically angiotensin II stimulates aldosterone release.

4. Disorders and their classifications

We are primarily concerned with disorders related to the adrenals. These disorders are classified to aid in diagnosis and treatment.

a. Primary disorder: A disorder in the operation of the adrenals themselves that leads to an over or under production of one or more of the hormones. A primary disorder can also occur due to renal transplants. This can include the effects of adrenal tumors.

b. Secondary disorder: A disorder of the pituitary that causes over or underproduction of ACTH secretion which control adrenal hormone release. These disorders can be caused by tumors and surgery.

c. Tertiary disorder: A disorder of the hypothalamus that leads to under or over production of CRH is a tertiary disorder.
5. The two major classes of corticoids

a. Glucocorticoids: *Cortisol (hydrocortisone)* Cortisol levels in the blood are subject to diurnal variation. Cortisol is the major glucocorticoid that is released from the adrenal zona fasciculata in response to ACTH. Cortisol levels vary throughout the day so the time of blood sampling is important. Cortisone is much less active however it can be converted via metabolism to the more active cortisol. Cortisone and cortisol are both used as drugs. As you know there are a number of synthetic glucocorticoids agonists and antagonists.

b. Mineralocorticoids: *Aldosterone* Aldosterone is the major mineralocorticoid that is released from the zona glomerulosa in response to ACTH levels. As stated earlier, aldosterone release is also controlled by the renin-angiotension system as well as serum potassium. In the kidney aldosterone promotes Na (and water) reabsorption and K secretion into the distal tubule. Aldosterone also acts along the intestinal epithelium to promote Na and water absorption and K secretion.

6. Cortisol: Cortisol is highly protein bound in plasma to its own binding protein (96%). It is cleared renal excretion and by metabolism. Cortisol levels are measured in serum, saliva and urine. Serum cortisol levels undergo significant diurnal variation. Thus the reference ranges are time dependent. Cortisol is measured by a competitive ELISA or by LCMS/MS when symptoms don’t match with the ELISA results.

Reference ranges: [8am; 5-25 µg/dL]; [6 pm; 3-15 µg/dL]; [rule of thumb; 8pm =50% of 8am] [24 hr urine; 10-100 µg]

a. Hypercortisolism (Cushing’s Syndrome) is marked by high plasma cortisol and high total cortisol in a 24 hr urine (cortisol >200 µg/day in urine). Cushing’s Syndrome can be caused by endogenous or exogenous factors such as drugs. Relatively rare.

Chronic Cushing’s Syndrome is marked by the redistribution of body fat and water (moon face/buffalo hump), thinning of the epidermis, hypertension as well as a whole host of other symptoms (see below). Note that Cushing’s Disease is only one cause of Cushing’s Syndrome.
Endogenous hypercortisolism: (1) Cushing's Disease. The major cause (70%) is the overproduction of ACTH (adrenal corticotrophic hormone) by the pituitary gland that is caused by a benign tumor. This disease is then classified as a secondary hypercortisolism. (2) The next major cause of endogenous hypercortisolism is an adrenal tumor. This condition is classified a primary hypercortisolism.

Diagnosis tests and procedures: A number of tests are available to help diagnose hypercortisolism. Below are some major ones.

(a) Serum Cortisol: Reference ranges: [8am; 5-25 µg/dL] [6 pm; 3-15 µg/dL] [rule of thumb; 8pm =50% of 8am] Mayo site: Acute stress (including hospitalization and surgery), alcoholism, depression, and many drugs (eg, exogenous cortisones, anti-convulsants) can obliterate normal diurnal variation, affect response to suppression/stimulation tests, and cause elevated baseline levels.

(b) Urine Cortisol (UFC): A 24 hour urine free cortisol test (UFC), reference range [24 hr urine; 10-100 µg] where total cortisol greater than 200 µg indicated hypercortisolism. This is a preferred test.

(c) DST Dexamethasone suppression test (DST). Dexamethasone (a synthetic glucocorticoid agonist) inhibits the release of ACTH from the pituitary. There are two tests here. The more common low dose test is dexamethasone (1 mg; 11 pm) followed by an 8am serum cortisol. If serum cortisol levels are not suppressed (cortisol> 5 µg/dL), Cushing’s disease is suspected.
(d) *Radioimmunoassay (RIA)* or *ELISA Chemiluminescence assay* for ACTH in the blood (10-60 pg/mL [a.m. draws]). This test directly detects hyper-secretion of ACTH (pituitary secondary Cushings Syndrome; Cushings disease). There is also a test for CRH hypersecretion by the pituitary to differentiate between secondary and tertiary Cushings Syndrome).

(e) *Abdominal CT* scans and pituitary MRI.

Treatment for hypercortisolism depends on the cause. It may include tumor removal usually adrenalectomy followed-on by temporary or permanent administration of supplemental glucocorticoid steroids (hydrocortisone, prednisolone). Note that some drugs (most frequently mitotane, ketoconazole, metyrapone) can be used to inhibit cortisol synthesis in the adrenal with some success.

**Exogenous (iatrogenic) hypercortisolism** is caused by treatment with natural corticosteroids. In addition there are a number of synthetic corticosteroids used in inflammatory disease and for immunosuppression that produce effects like hypercortisolism. These drugs may appear to augment the effects of the normal glucocorticoids but can cause concurrent adrenosuppression due to inhibition of ACTH release. They also may have undesirable have mineralocorticoid effects.

**b. Hypocortisolism** is marked by low plasma cortisol and low urine cortisol. Hypocortisolism is much more common. Often other hormones produced by the-7

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**ADDISON’S DISEASE**

- **Addison’s Crisis:**
  - Profound Tachycardia
  - Dehydration
  - Vascular Collapse (BP fall)
  - Renal Shut Down
  - Seizures
  - Coma

**Addison’s Signs:**

- **Skin Changes:**
  - Pallor
  - Hypertension
  - Changes in Distribution of Body Fat

- **Body Changes:**
  - Weight Loss
  - Weakness

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**b. Hypocortisolism** is marked by low plasma cortisol and low urine cortisol. Hypocortisolism is much more common. Often other hormones produced by the adrenals such as aldosterone (see below mineralocorticoid) and DHEA (sex steroid precursor), are low as well.
a. Primary Adrenocortical Insufficiency (Addison’s disease) can be caused by genetic mutations, destruction of the adrenal cortex by cancer, tuberculosis, AIDS, autoimmune disease. It is also observed upon sudden steroid withdrawal due to atrophy of the cortex caused by prolonged use of corticosteroids. Symptoms include fatigue, low blood pressure, salt craving, weight loss and darkening of skin. Stress can precipitate an acute adrenal crisis that is marked by hypovolemic shock, hypotension and hypoglycemia and must be treated immediately with fluids and iv hydrocortisone.

(a) Blood tests include cortisol (low to low normal), early morning ACTH (elevated), aldosterone (low) and urine cortisol (low).

(b) Cosyntropin Challenge: Patients are given a test dose of synthetic ACTH (1-24 ACTH; short corticotropin; cosyntropin) and plasma cortisol levels are monitored. The normal rise in cortisol levels (to 20 µg/dL increase after 30 minutes) is not observed in Addison’s disease. This test can also be used to diagnose hypoaldosteronism (see below) where aldosterone levels are also measured in the test.

b. Secondary Adrenocortical Insufficiency is most often caused by chronic steroid use with drugs that also inhibit the release of ACTH. Adenoma of the pituitary is another cause. Note: While the cosyntropin test should reveal a normal response (normal rise in serum cortisol) this is not always observed as the adrenal gland function may decline with chronic steroid use and pituitary adenoma.

c. Treatment for chronic hypocortisolism consists of oral administration of prednisone, cortisone or cortisone acetate bid or tid. Longer acting steroids are not indicated.

7. Aldosterone: Aldosterone levels are measure in serum and urine by LC/MS (liquid chromatography mass spectrometry). It is subject to diurnal variation and varies with age. In addition levels are 50% higher when samples are taken in the upright vs supine position. Units for this direct test are given as ng/dL.

a. Hyperaldosteronism Hypersecretion of aldosterone can accompany hypercortisolism due to high ACTH however the renin angiotensin system is of primary importance. Aldosterone has minimal feedback effects of ACTH release.

(a) Primary hyperaldosteronism leads to hypertension, hypernatremia and hypokalemia. As for primary hypercortisolism, the principal cause is adenomas of the adrenal gland that secrete aldosterone even when renin is suppressed.

(b) Secondary hyperaldosteronism has two major causes: (1) High ACTH caused by a pituitary tumor, high ACTH and can be further diagnosed with a dexamethasone test as above. (2) However a very likely case is elevated angiotensin II however this is not measure directly. A differential diagnosis between (1) and (2) involves a comparison of the plasma renin activity (PRA) and the plasma aldosterone concentration (PAC). PRA is measured in the patient’s plasma by determining the rate of formation of Angiotensin 1 from renin. The units
here are ng/mL/hr. The ratio of PAC (ng/dL) to PAR (ng/mL/hr) is also used in the analysis.

(c) Spironolactone, a potassium-sparing diurectic and aldosterone antagonist, is used to treat hyperaldosteronism.

b. Hypoaldosteronism: Low aldosterone levels are often observed in primary and secondary hypocortisolism. There is a syndrome called Salt Wasting Syndrome that is associated with a deficiency in one of the enzymes of the aldosterone synthesis pathway (a 21-hydroxylase). Treatment of hypoaldosteronism is with a synthetic mineralocorticoid (fludrocortisone acetate). Fludrocortisone does have some glucocorticoid effect as well. This treatment can be chronic.