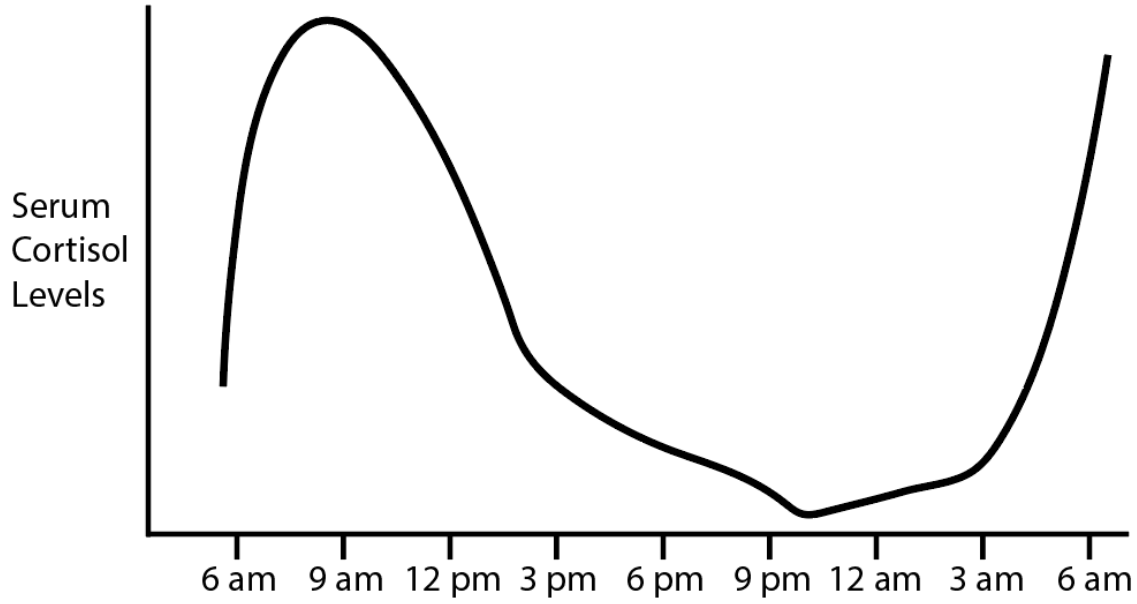
5.2.3

Cortisol (Glucocorticoids)

The zona fasciculata is responsible for the production of the glucocorticoids like cortisol. Just like the other hormones that we have discussed, there is a feedback system that regulates cortisol levels called the **hypothalamic-pituitary-adrenal (HPA) feedback system**. Stimuli like stress, trauma, infection, hemorrhage, pain, sleep, and hypoglycemia all increase the release of CRH from the hypothalamus. CRH causes the anterior pituitary to release ACTH which in turn causes the release of cortisol. Levels of CRH, ACTH, and cortisol are the highest in the early morning (see image below).



Serum Cortisol Levels in 24 Hour Period *Image BYU-I W20*

The effects of cortisol on tissues are as follows:

- Increases breakdown of protein.
- Raises blood sugar by stimulating gluconeogenesis, glycogenolysis, and increased insulin resistance.
- Redistribution of fat to be stored centrally more than peripherally. This leads to increased visceral fat and fat gain in and around the abdomen and trunk.
- Inhibition of prostaglandin and leukotriene production (remember that cortisol inhibits PLA2).
- Suppression of the immune system because cortisol is capable of downregulating many signals that function to activate the immune system.

Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia is caused by a deficiency from birth in any of the enzymes necessary for the synthesis of cortisol. As a result, cortisol levels and often aldosterone levels are low, but ACTH levels are high because of the lack of negative feedback control from cortisol. Consistently high ACTH results in hyperplasia (enlargement due to increased cell division) of the adrenal gland. Because of specific enzyme deficiencies within the adrenal cortex, steroid synthesis is shunted towards androgen production. The resulting increased levels of androgens can cause virilization in females, which is the development of male-patterned hair growth and other male characteristics. If the congenital mutation involves deficiency of the aldosterone synthesizing enzymes, then it is called the **salt-losing form**. This form results in symptoms of hypoaldosteronism including hyponatremia, hyperkalemia, dehydration, and hypovolemic shock.

Fludrocortisone is useful for the treatment of those with the salt-losing form of congenital adrenal hyperplasia. Fludrocortisone is a strong mineralocorticoid receptor agonist that has some glucocorticoid receptor activity as well.

Primary Adrenocortical Insufficiency (Addison's Disease)

Primary adrenocortical insufficiency or **Addison's disease** is characterized by a decrease in mineralocorticoids, glucocorticoids, and androgens. This decrease is commonly due to autoimmune destruction of the cells of the adrenal cortex. Destruction of the adrenal cortex can also result from metastasizing cancer cells, infections like tuberculosis and HIV, genetics, or even surgery. Addison's disease is more common in women.

An individual with Addison's disease will present with lowered cortical hormones, low blood glucose levels, high ACTH, high serum WBC count, high serum potassium levels, and will likely be in acidosis. Because corticosteroids also stimulate appetite, many Addison's disease patients experience weight loss due to decreased hunger as well. Addison's patients also experience hyperpigmentation because an increase in ACTH is associated with an increase in **melanocyte stimulating hormone (MSH)**. MSH is a bi-product of ACTH synthesis. The production of ACTH occurs by the post translational cleavage of a large protein called **proopiomelanocortin (POMC)** which is cut to give rise to multiple peptide hormones. Therefore, whenever the cells of the pituitary are stimulated to synthesize ACTH, MSH (along with other peptides not mentioned here) will also be manufactured. The increased release of MSH can stimulate melanocytes and cause symptoms of hyperpigmentation.

Hydrocortisone (glucocorticoid with mineralocorticoid activity) and **fludrocortisone** (mineralocorticoid with glucocorticoid activity) are used as hormone replacement therapy (HRT) to treat Addison's disease.

Secondary Adrenal Cortical Insufficiency

Secondary adrenocortical insufficiency is caused by anything that decreases ACTH. The most common cause of secondary hypocortisolism is called **iatrogenic hypocortisolism**, which means that a medical treatment caused the hypocortisolism. Iatrogenic hypocortisolism is most commonly caused by prolonged administration of glucocorticoids followed by a cessation of the medication. The exogenous glucocorticoids can sometimes cause hypercortisolism such that when the treatment is removed, there is often a rebound effect where endogenous hormone production is very low. This occurs because the exogenous medication caused a downregulation of endogenous cortisol production and may even have caused glandular atrophy (shrinkage). The atrophy occurs because the administration of glucocorticoids suppresses the secretion of ACTH, which normally stimulates maintenance and growth of the adrenal gland. The low endogenous hormone production combined with possible glandular atrophy leads to the hypocortisolism.

Other causes of secondary adrenal cortical insufficiency are a pituitary infarction, a pituitary tumor like a PRL or GH secreting adenoma that compresses ACTH secreting cells, or surgical removal of the pituitary gland to treat tumors (hypophysectomy). Again, the lack of ACTH causes a decreased production of endogenous glucocorticoids.

Because ACTH is primarily a stimulator of the cells in the zona fasciculata, the other layers of the adrenal cortex are not as affected by a decrease in ACTH. This means that other cortical hormones like aldosterone and androgens tend to be normal. This difference helps distinguish secondary from primary hypocortisolism. Another distinguishing factor is that

in secondary adrenal cortical insufficiency, patients do not present with hyperpigmentation like they do with Addison's disease.

Hypercortisolism (Cushing's)

Hypercortisolism is the secretion of too much cortisol by the adrenal cortex. It can be broken into two categories: Cushing's disease and Cushing's syndrome. **Cushing's disease** is defined as a pituitary adenoma that causes increased levels of ACTH. **Cushing's syndrome** is an umbrella term that refers to anything else that causes excessive cortisol and associated symptoms. For example: a cortisol secreting tumor in the adrenal cortex can cause excessive release of cortisol and result in Cushing's syndrome. Cushing's syndrome can also be caused iatrogenically in patients that must take cortisone or other cortisol derivatives as part of their treatment. Sometimes, tumors in other areas of the body besides the pituitary can secrete ACTH. Tumors in the lung have often been found to secrete ACTH. This excess ACTH will raise cortisol levels and be a type of Cushing's syndrome as well.

ACTH levels will be elevated in ACTH-dependent Cushing's syndrome or in Cushing's disease (pituitary tumor). ACTH levels will be low in ACTH-independent Cushing's syndrome because of negative feedback from cortisol. Excessive levels of ACTH can have a crossover effect on androgen secreting cells of the adrenal cortex. Because of this, it may be possible to see hirsutism and other virilizing effects in female patients with high levels of ACTH.

Some other the manifestations of hypercortisolism are thin skin, protein wasting, stretch marks because of weight gain combined with collagen and protein breakdown, osteoporosis because of decreased protein in bones, moon face due to weight gain specific to the face, a buffalo hump from fat deposit around the suprascapular region, and muscle weakness due to excess protein catabolism. Cortisol causes glucose levels to rise, so high blood sugar can often be observed. There is also an increased risk for development of gastric ulcers because cortisol decreases gastric prostaglandin production. Prostaglandin is important to signal increased mucus secretion. Cortisol affects every cell in the immune system and reduces the secretion of proinflammatory and vasoactive substances because it blocks phospholipase A2. Hypercortisolism may also cause psychiatric and neurocognitive disorders like insomnia, mood and anxiety disorders, cognitive deficits, and even psychotic disorders. Because there is some crossover between activation of cortisol and aldosterone receptors, patients can also develop symptoms related to excessive aldosterone such as hypokalemia and hypertension.

The diagnosis of Cushing's involves measuring urinary, serum, and salivary cortisol levels over a 24 hour period (recall that highest cortisol levels are expected in the early morning). An overnight 1mg dexamethasone suppression test is also common as a diagnostic procedure. In this test, a person takes a dose of dexamethasone before bed and then has their blood cortisol levels measured in the morning. Dexamethasone is like cortisol and should have a negative feedback effect on the hypothalamus and pituitary to lower ACTH. This in turn should lower cortisol levels. If the patient has high cortisol levels the morning after taking dexamethasone, then this suggests a dysfunction in their negative feedback system.

The preferred treatment for Cushing's disease is transsphenoidal surgical removal of the tumor. Radiation therapy is a secondary treatment choice. Treatment for Cushing's syndrome depends on the cause. A unilateral or bilateral adrenalectomy is performed for Cushing's syndrome caused by an adrenal adenoma. Medications that block steroid synthesis like aminoglutethimide (Cytadren) may be used for those individuals with ectopic cortisol producing tumors and for adrenal carcinomas that can't be surgically removed. Without treatment, about 50% of those with Cushing's syndrome die within five years from onset of the disease. The cause of death is most often an overpowering infection, suicide, complications from high blood sugar, arteriosclerosis, and hypertension.