The adrenal gland is divided into two regions: cortex and medulla. The cortex is further divided into three layers: zona glomerulosa, zona fasciculata, glucocorticoids; and zona reticularis, which secretes aldosterone, glucocorticoids and androgens respectively. The medulla is composed of chromaffin cells that secrete the catecholamines epinephrine, norepinephrine and dopamine. There are many common pathologies that can present, e.g., adrenal hypo-plasia, hyperplasia and adrenal tumors specific to each region.

Adrenal Gland

The adrenal gland is located on the superior pole of the kidney and is covered by the Gerota fascia. The blood supply comes from three branches: inferior phrenic artery, renal artery and aortic branches.

Venous drainage occurs through the inferior vena cava on the right side and into the left renal vein on the left side. There are two distinct developmental origins of the adrenal
The gland that divide it into two regions: the cortex and the medulla.

The cortex is derived from the mesoderm and it consists of three layers: zona glomerulosa, zona fasciculata and zona reticularis.

The medulla is derived from the neural crest and is made of chromaffin cells.

**Physiology of the Adrenal Gland**

**Cortex**

**Zona glomerulosa**

This is the outermost layer of the cortex. It **produces and secretes the mineralocorticoid aldosterone**. It is regulated by the renin-angiotensin system (RAAS).

Aldosterone acts on the kidneys' renal collecting ducts to promote sodium reabsorption and potassium excretion. Absorption of water is followed by sodium which will lead to an increase in extracellular fluid volume.

A loss of aldosterone would result in excretion of sodium, followed by water, leading to dehydration, and due to its effects on potassium it can lead to hyperkalemia and result in cardiac toxicity. Excess aldosterone can lead to hypokalemia and result in extreme fatigue and muscle weakness. Hydrogen can also be excreted and result in metabolic alkalosis.

As a component of the RAAS system, angiotensin II induces the release of aldosterone to increase fluid retention and ultimately blood pressure.

**Zona Glomerulosa cells also respond directly to high and low levels of sodium and potassium** in the extracellular fluid to either stimulate aldosterone release in hyperkalemic states or to inhibit aldosterone release in hypernatremia.

Adrenocorticotropic hormone (ACTH) from the anterior pituitary stimulates aldosterone release.

**Zona fasciculata**

This is the middle layer of the cortex. It produces and secretes the glucocorticoid cortisol. It is **regulated by ACTH from the anterior pituitary**. For cortisol release, it is important to know that ACTH is regulated by a corticotropin-releasing hormone from the hypothalamus. There is a circadian component to cortisol regulation with the highest levels being in the morning and lowest being in the evening. Stress and other factors can influence how cortisol is regulated throughout the day.

**Note:** Cortisol acts to stimulate the liver to use proteins and free fatty acids for gluconeogenesis. This process increases liver glycogen levels and increases serum glucose.

Anti-inflammatory effects come from the prevention of lysosomal protein release through stabilization of membranes, decrease in capillary permeability and decrease in white blood cell chemotaxis. Often time with exogenous glucocorticoids you can see an increase in white cell count because of this.

Thus, cortisol play an important role in increase in glycogen store in liver, reduction in protein stores, increase in inflammatory reactions and reduction in immunity in an adverse manner.
Zona reticularis

The innermost layer of the cortex produces and secretes both male and female sex hormones. The male sex hormones are Dehydroepiandrosterone (DHEA), DHEA sulfate, androstenedione, and 11-hydroxy-androstenedione. The female sex hormones are in much smaller quantities of progesterone and estrogen.

The effect of the sex hormones mostly comes from their conversion of androgen outside of the adrenal gland into testosterone. Their effect is seen during male gonadal development and in females during puberty. ACTH stimulates its release.

For the USMLE, it will be important to remember those sex hormones are produced in this layer of the adrenal cortex and to be aware of the specific names of the hormones.

USMLE pearl: You can remember the order of the cortex with the phrase “Salty, sweet, sexy,” or “It gets sweeter the deeper you go.”

Medulla

The medulla is composed of one cell type, the chromaffin cells. The chromaffin cells are derived from the neural crest and migrate to the adrenal medulla. Chromaffin cells secrete catecholamines: epinephrine, norepinephrine, and dopamine. Medulla is responsible for release of epinephrine (80%) and norepinephrine (20%) with very little secretion of dopamine into the blood under the influence of acetylcholine.

The sympathetic nervous system stimulates the secretion of the catecholamines through acetylcholine release via preganglionic fibers originating in the thoracic spinal cord, from vertebrae T5-T11. Because it is innervated by preganglionic nerve fibers, the adrenal medulla can be considered as a specialized sympathetic ganglion. The release of catecholamines leads to increased cardiac output and increased vascular resistance.

Pathology of the Adrenal Gland
Hyperplasia

Hyperplasia manifests itself through congenital adrenal hyperplasia, which is due to an autosomal recessive disorder most commonly in the enzyme 21-hydroxylase. It is an enzyme necessary for cortisol production, which leads to ACTH oversecretion. Female patients will present at birth with ambiguous genitalia.

Hypoplasia

Hypoplasia manifests itself through a deficiency in ACTH. It is commonly diagnosed in later childhood when the patient will present with dehydration, hyponatremia, hyperkalemia, and hypotension.

The cortex has distinct pathology and expression depending upon each layer.

Zona glomerulosa

The zona glomerulosa can present with primary pathologies such as idiopathic adrenal nodular hyperplasia, adrenocortical carcinoma, and adenoma. Secondarily, it can present with renal artery stenosis and renin tumors.

Zona fasciculata

The zona fasciculata can present with Cushing syndrome. Cushing syndrome is caused by excess exogenous steroid or glucocorticoid secreting tumors. It is a very common USMLE question topic, and you should be very familiar with the material. Excess glucocorticoid production leads to the classic signs and symptoms of moon like facies, acne, obesity, hypertension, easy bruising, abdominal striae and osteoporosis. It is important to remember that there is also Cushing’s disease, which is different from Cushing’s syndrome. Cushing’s disease is usually caused by a pituitary adenoma.

Zona reticularis

The zona reticularis can present with ambiguous genitalia in females and can present in older children with pseudo precocious puberty and increased bone age. These signs are most commonly seen in congenital adrenal hyperplasia and adrenal adenomas and carcinomas.

Pheochromocytoma

The most common pathology in the medulla is pheochromocytoma. The tumors will secrete catecholamines resulting in symptoms of hypertension, headache, hyperhidrosis, palpitations, and pallor. There are several genetic conditions that can predispose to pheochromocytoma: Von Hippel-Lindau (autosomal dominant defect in repair gene on Chr. 3) and MEN2A and 2B.

Investigative tests are to check urine for vanillylmandelic acid (VMA) from the breakdown of epinephrine and norepinephrine. Treatment with α-blockers and β-blockers is for symptom relief and a safe anesthetic induction, followed by surgical resection of the tumor.

The condition follows the “10 % rule,” where 10% will be malignant, 10 % will be bilateral, 10 % outside the adrenal gland, 10 % calcify, and 10 % pediatric.
In pediatric patients, neuroblastoma is the third most common pediatric cancer (ALL being the first). Neuroblastoma accounts for 15% of all pediatric cancer deaths. It also originates from neural crest and can be found in the adrenal medulla and sympathetic chain.

Exogenous Agents

Zona glomerulosa

The zona glomerulosa secretes aldosterone. When there is a loss of aldosterone, as seen in adrenal hypoplasia, the mineralocorticoid fludrocortisone can be used to replace the aldosterone effects. This treatment is often combined with salt tablets or free restriction of salt in the patient’s diet.

Zona fasciculata

The zona fasciculata secretes glucocorticoids. They can be used in many different clinical settings, for instance, to treat asthma and decrease systemic inflammation. Direct replacement as seen in adrenal hypoplasia can be treated with long-term dexamethasone replacement.

Zona reticularis

The zona reticularis produces androgens that are converted in the periphery to testosterone. Exogenous testosterone can be used as a replacement.

Epinephrine

![Epinephrine structure](https://example.com/epinephrine.png)

Image: “Epinephrine structure” by Acdx. License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

In the medulla, the catecholamines epinephrine, norepinephrine and dopamine are released. It is secreted in response to stress, also known as adrenaline. Epinephrine acts to increase cardiac output through β1 adrenergic receptors in the heart increasing cardiac output. It also acts to increase vasoconstriction through the α-adrenergic receptors. It can be used to treat anaphylaxis, cardiac arrest, glaucoma, and hypotension.
Norepinephrine

Norepinephrine acts on both α1,2 and β1 adrenergic receptors, and it has a much greater effect on the α receptors for vasoconstriction. It is also released in medulla in response to stress, also referred as stress hormone. It is used to treat shock and hypotension.

Dopamine

Dopamine is often presented as a neurotransmitter but is commonly used in the acute setting. It acts on both α and β receptors, it has a greater effect on cardiac function. It can be used to treat shock and heart failure.

Mineralocorticoids

**Aldosterone agonists**

- Part of the RAAS
- Very strong salt-retaining activity

**Fludrocortisone (Florinef®)**

→ structurally similar to cortisol

- Moderate glucocorticoid activity
- Strong mineralocorticoid activity
  - Cerebral salt wasting syndrome
  - Addison’s disease
  - POTS (Paroxysmal Orthostatic Tachycardia Syndrome)
  - Geriatric orthostatic hypotensive syncope

**Spironolactone, eplerenone**

- Discusses in combination with diuretics
- Also used to treat hirsutism (mild anti-androgen activity)

**Glucocorticoid**

Glucocorticoid enters the cell as a free molecule.

- Binds to intracellular receptor or other proteins
- Enters nucleus
- Binds to the glucocorticoid response element (GRE) which is a portion of DNA
- GRE regulates gene expression and transcription

**Side Effects**

- **Metabolic**: gluconeogenesis, lipolysis, reduced subdermal fat
- **Morphologic**: lipid deposit in certain spots (Face, neck, shoulder)
- **Catabolic**: protein catabolism, tissue wasting, osteoporotic effects
- **Immunosuppressive**: cell-mediated immunity (i.e. lymphocyte dependent)
- **Renal**: cortisol is normally required for water excretion
- **Anti-inflammatory**: dramatic suppression multiple markers
- **Neuropsychiatric**: excess cortisol causes giddiness, euphoria

**Prednisone, active metabolite prednisolone**
- Longer half-life, better membrane penetration
- Used in acute inflammation, and steroid replacement

**Dexamethasone**
- Longer half-life, better membrane penetration
- Potent; often used in cancer therapies

**Triamcinolone**

**Beclomethasone, budesonide**
- Readily penetrate the airway mucosa; used in inhalers

**Synthesis inhibitors**

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<th>Metyrapone</th>
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<td>An antifungal drug</td>
<td>Inhibits synthesis of cortisol but not cortisol producers</td>
<td>Blocks conversion of cholesterol to pregnenolone and all....</td>
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<tr>
<td>Used in adrenal adenoma, breast cancer, prostate cancer</td>
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**References**


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