

# Adrenocortical Insufficiency



Adrenal Glands



### **Corticosteroids**

Mineralocorticoids

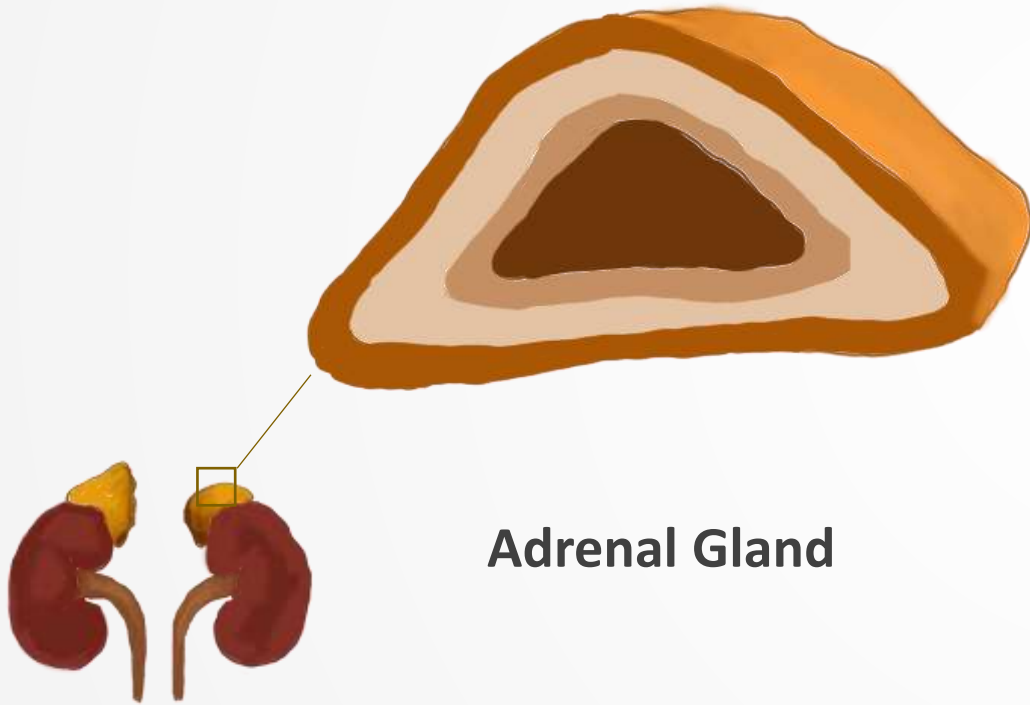
Glucocorticoids

Androgens

### **Catecholamine**

Epinephrine

Norepinephrine



**Adrenal Gland**

**Corticosteroids**

Mineralocorticoids

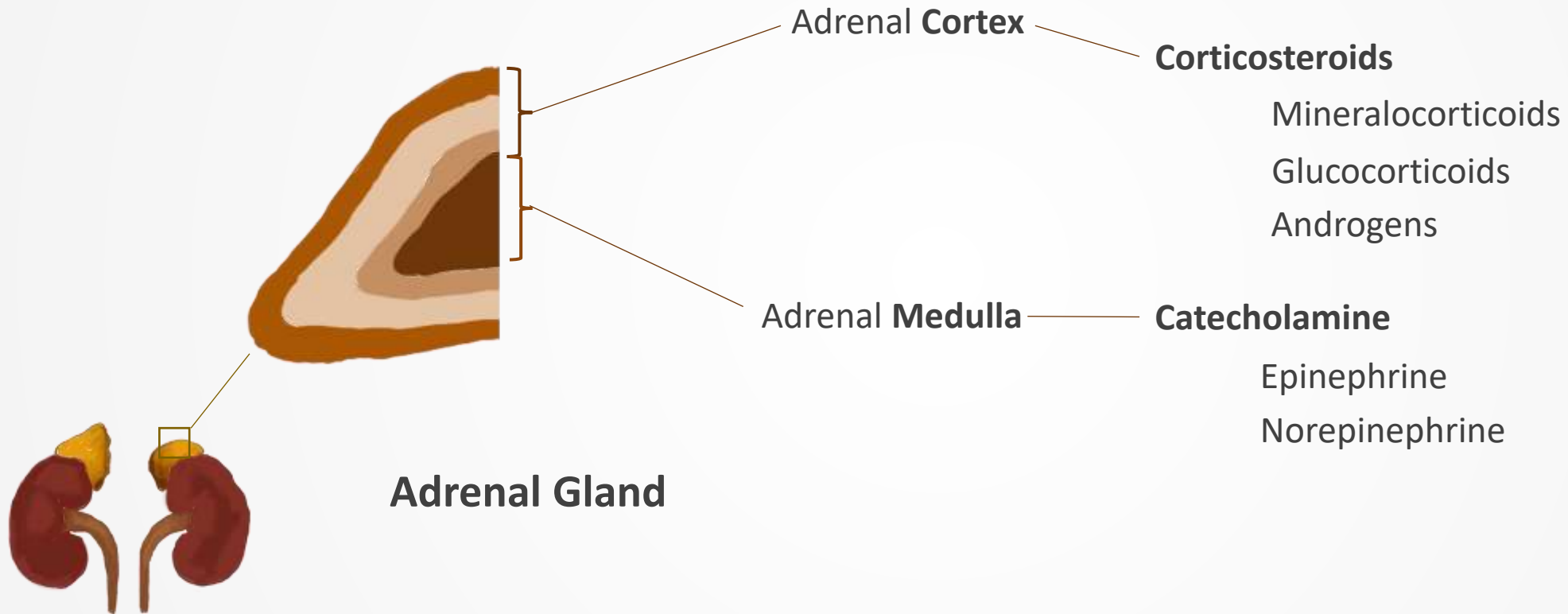
Glucocorticoids

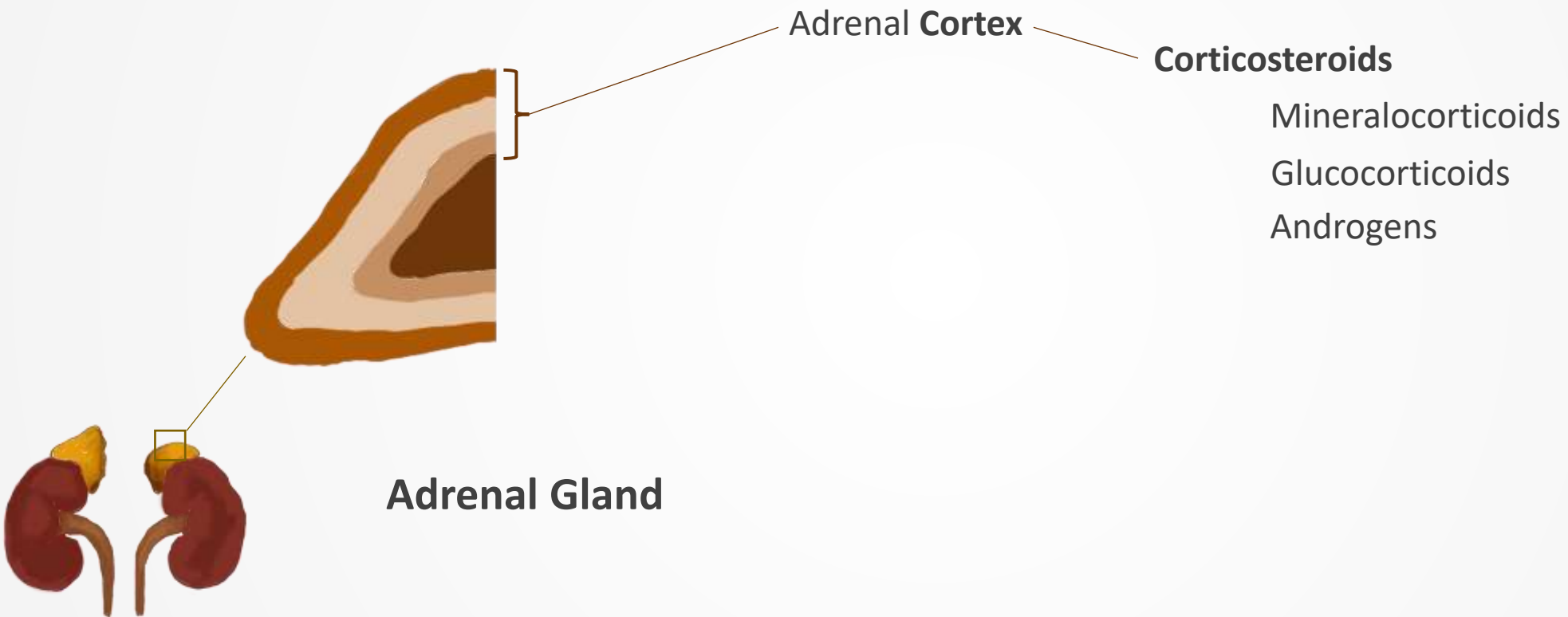
Androgens

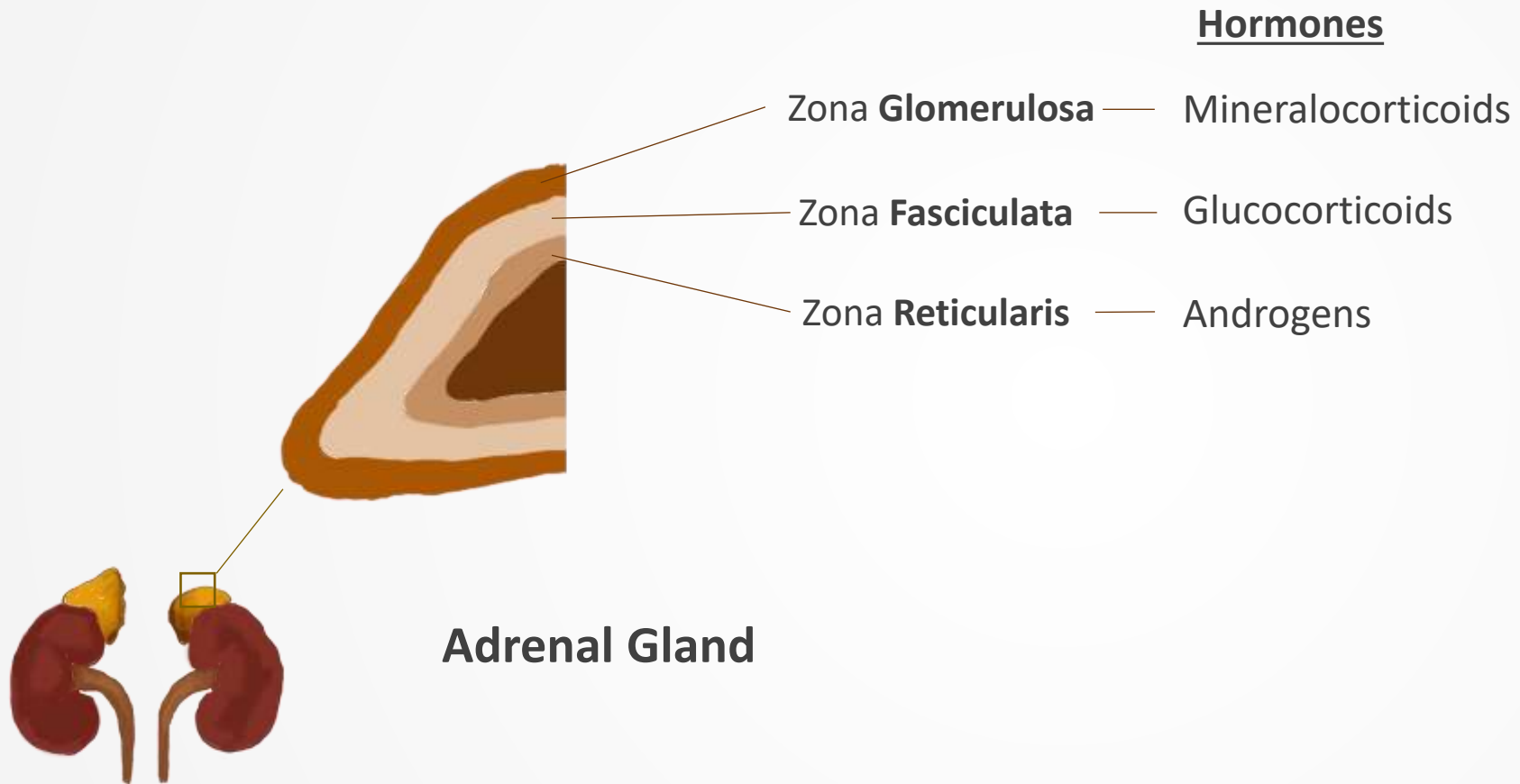
**Catecholamine**

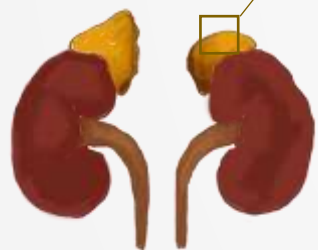
Epinephrine

Norepinephrine





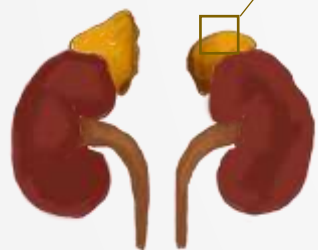




**Adrenal Gland**



<u>Hormones</u>		<u>Control Axis</u>
Zona <b>G</b> lomerulosa	Mineralocorticoids	Renin-Angiotensin-Aldosterone
Zona <b>F</b> asciculata	Glucocorticoids	Hypothalamus-Pituitary-Adrenal
Zona <b>R</b> eticularis	Androgens	



**Adrenal Gland**



Zona **Glomerulosa**

Zona **Fasciculata**

Zona **Reticularis**

### Hormones

Mineralocorticoids

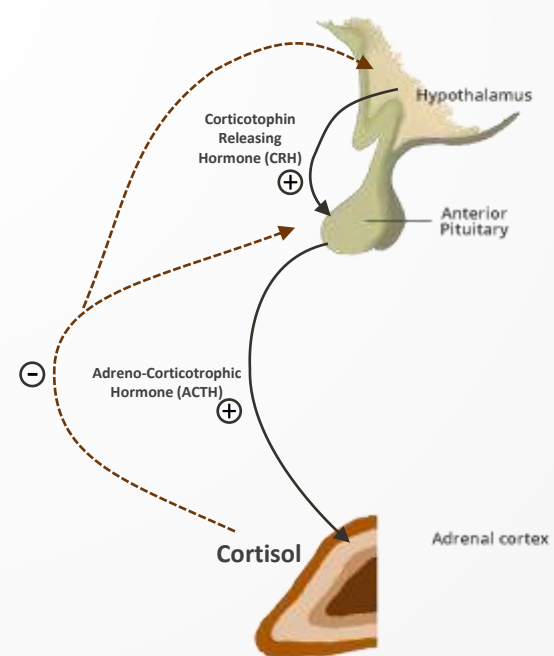
Glucocorticoids

Androgens

### Control Axis

Renin-Angiotensin-Aldosterone

Hypothalamus-Pituitary-Adrenal







Zona <b>G</b> lomerulosa	—	Mineralocorticoids	Renin-Angiotensin-Aldosterone axis
Zona <b>F</b> asciculata	—	Glucocorticoids	Hypothalamus-Pituitary-Adrenal axis
Zona <b>R</b> eticularis	—	Androgens	



Zona **Glomerulosa**

Mineralocorticoids

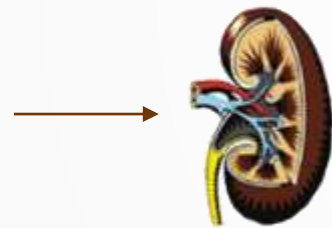
Renin-Angiotensin-Aldosterone axis

- **Aldosterone** is the most important mineralocorticoid
- Principal stimulus is angiotensin II

### Pearls

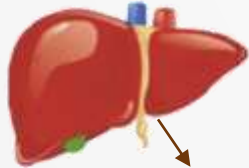
Renin activity is increased in hypovolaemia and renal artery stenosis  
Renin levels doubled when standing up from a recumbent position

↓ **perfusion pressure** in the afferent arteriole  
↓ **sodium in filtrate** at the macula densa  
↑ **sympathetic activity**

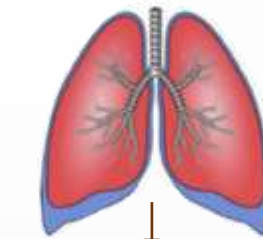


Stimulated **Juxtaglomerular (JG) Apparatus**

**Renin**



**Angiotensinogen**



**Angiotensin Converting Enzyme (ACE)**

**Angiotensin - I**

**Angiotensin - II**

- ↑ Sodium retention *with* secondary water absorption
- ↑ Potassium excretion
- ↑ Protons excretion

⊕

Binds to mineralocorticoid receptors in the kidney

**Aldosterone**

⊕





Zona <b>G</b> lomerulosa	—	Mineralocorticoids	Renin-Angiotensin-Aldosterone axis
Zona <b>F</b> asciculata	—	Glucocorticoids	Hypothalamus-Pituitary-Adrenal axis
Zona <b>R</b> eticularis	—	Androgens	



Zona Fasciculata

## Glucocorticoids

Controlled via  
Hypothalamus-Pituitary-Adrenal axis

- **Cortisol** is the major Glucocorticoid
- Has **Circadian** rhythm of secretion
  - **Highest** levels in **morning** on waking
  - **Lowest** levels in **mid-night**

### Clinical Pearl

**Replacement dose in Adrenal Insufficiency** is matched to the natural circadian rhythm of cortisol

- **Cortisol** is a **Stress** Hormone – Levels rise during any stress to:
  - Protect key metabolic functions *e.g.*, maintenance of cerebral glucose supply during starvation
  - Inhibits potentially damaging inflammatory responses to infection and injury

### Important Pearl

**Corticosteroids dose** is doubled during stress to prevent precipitation of life-threatening Acute Adrenal Crisis

- > **95%** Cortisol *bound to* **Cortisol binding globulin**
- **Cortisol binding globulin** increased with Oestrogen pills & during Pregnancy
- **Free Cortisol** is *metabolic active form*



Zona Fasciculata

Glucocorticoids

Controlled via  
Hypothalamus-Pituitary-Adrenal axis

- **Cortisol** - Bind to glucocorticoid receptors → Regulate transcription of many genes
  - Cortisol *can activate* Mineralocorticoid receptors
- BUT ...***
- Normally, **11 $\beta$ -hydroxysteroid dehydrogenase Type 2 (11 $\beta$ -HSD2)** – an enzyme in mineralocorticoid receptor containing cells → converts Cortisol to *inactive* Cortisone

### Clinical Pearl

**Inhibitors** of 11 $\beta$ -HSD2 such as **Liquorice/ Carbenoxolone** or **mutations** in the gene encoding 11 $\beta$ -HSD2 → Cortisol to act as a mineralocorticoid → Na<sup>+</sup> retention & Hypertension



Zona <b>G</b> lomerulosa	—	Mineralocorticoids	Renin-Angiotensin-Aldosterone axis
Zona <b>F</b> asciculata	—	Glucocorticoids	Hypothalamus-Pituitary-Adrenal axis
Zona <b>R</b> eticularis	—	Androgens	



Zona **Reticularis**

**Androgens**

Controlled via  
**Hypothalamus-Pituitary-Adrenal axis**

Dehydroepiandrosterone sulphate (DHEAS), Androstenedione, Testosterone, Dihydrotestosterone

- Androgens are the most abundant steroid in blood stream
- Adrenal zona reticularis is the only major source of androgens in females

### Clinical Importance

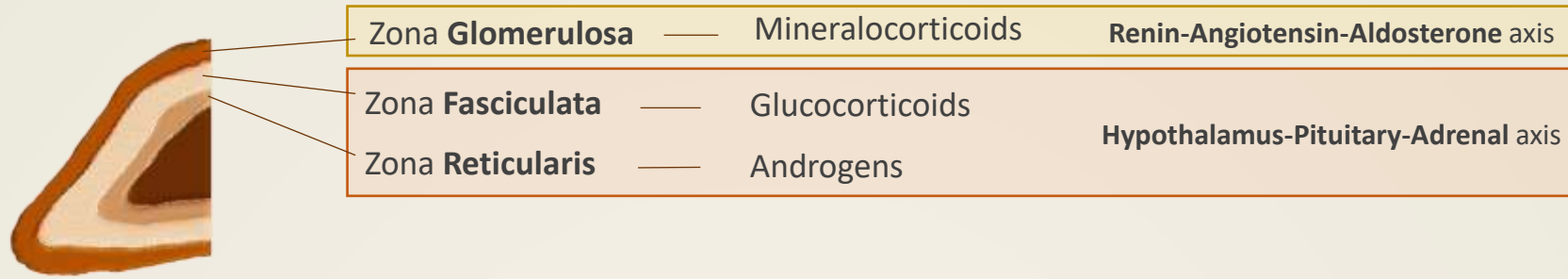
Important in initiation of puberty & in female libido



# Adrenocortical Insufficiency







- Insufficiency of secretion of Cortisol *with* or *without* deficiency of Aldosterone
- Potentially *fatal* & notoriously *variable* in its presentation
- Keep High Index of Suspicion - in patients with unexplained fatigue, Hyponatremia or Hypotension

### Primary Adrenocortical Insufficiency

(Defect lies primarily in Adrenals)

#### • Structural Damage to Adrenals (Addison's Disease)

##### Common causes

- Autoimmune
- Tuberculosis
- HIV infection
- Metastatic Ca
- Bilateral Adrenalectomy

##### Rare causes

- Lymphoma
- Adrenal hemorrhage  
(Waterhouse-Friderichsen Syndrome)
- Amyloidosis
- Hemochromatosis

#### • Issues with Corticosteroid Biosynthetic Enzymes

- Congenital Adrenal Hyperplasias
- Drugs – Metyrapone, Ketoconazole, Etimodate

### Secondary Adrenocortical Insufficiency

(Lack of **ACTH** - Adrenals Normal)

#### • Suppressive Glucocorticoid therapy withdrawal

Exogenous Steroids → Suppress ACTH secretion → Low adrenal secretion

Sudden withdrawal of exogenous steroids → Not enough time to pituitary recovery from suppressed state → Low ACTH → Adrenal insufficiency

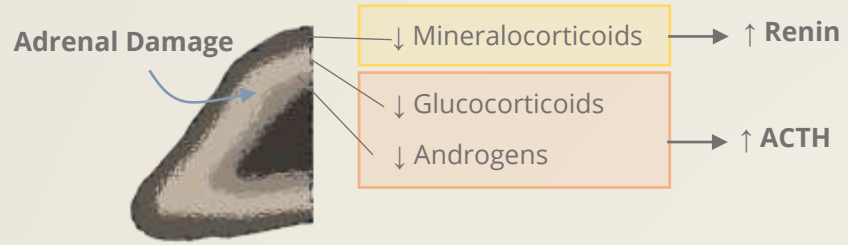
#### • Hypothalamic or Pituitary Diseases

### Clinical Pearls

- **Mineralocorticoids** secretion remains intact in Secondary Adrenal Insufficiency
- As ACTH is Low, No Hyperpigmentation in Secondary Adrenal Insufficiency

# **Addison's Disease**

(Primary Adrenocortical Insufficiency)



# Addison's Disease

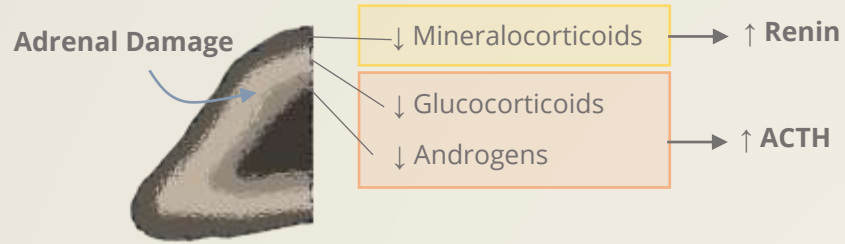
Either Glucocorticoid or Mineralocorticoid deficiency may come first, but eventually all patients fail to secrete both classes of corticosteroid

## Chronic Features

Mimic & misdiagnosed as  
Chronic fatigue syndrome or  
Depression

## Acute Adrenal Crisis

- Severe hypotension
- Hyponatremia
- Hyperkalemia
- Hypoglycemia
- Hypercalcemia



# Addison's Disease

## Clinical Features

### Glucocorticoid deficiency

- Weight loss
- Anorexia
- Malaise
- Nausea / Vomiting
- Diarrhea / Constipation
- Postural hypotension / Shock
- Hypoglycemia
- Dilutional Hyponatremia
- Hypercalcemia

### Mineralocorticoid deficiency

- Postural hypotension
- Shock
- Hyponatremia
- Hyperkalemia

### Androgens deficiency

- Hair loss
- Loss of Libido – particularly in females

Vitiligo occurs in 10 – 20 % of patients with **Autoimmune** Addison's disease

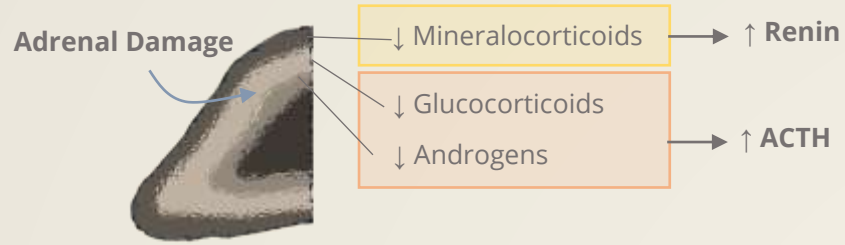
### ACTH excess

↑ ACTH → Cross react with Melanin Receptors → Hyperpigmentation

- Sun-exposed areas
- Pressure areas e.g. elbows, knees
- Palmar creases
- knuckles
- Mucous membranes
- Conjunctivae
- Recent scars



High Index of Suspicion in unexplained fatigue, weight-loss, abdominal pain, vomiting *or* Hyponatremia even without symptoms



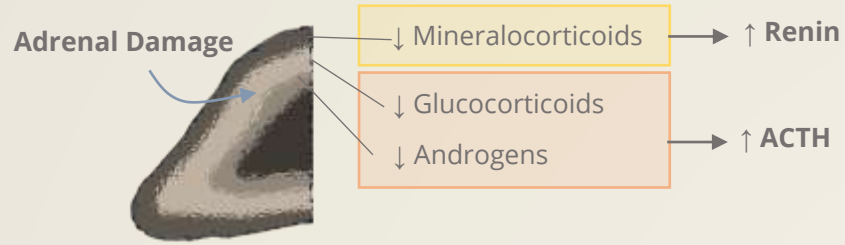
# Addison's Disease

## Investigations

- Treatment should not be delayed to wait for results in patients with suspected acute adrenal crisis
  - Random blood sample should be stored for subsequent measurement of serum cortisol and plasma ACTH
  - If clinical condition permits, do **Short ACTH stimulation test** before administering hydrocortisone

But delays must be avoided if there is circulatory compromise

- Investigations should be performed in **chronic** adrenal insufficiency, *before the treatment is given*
- Investigations can be categorized into:
  - **Assessment of Glucocorticoid** deficiency
  - **Assessment of Mineralocorticoid** deficiency
  - **Assessment of Androgen** deficiency
  - **Investigations for cause** of Addison's disease



# Addison's Disease

## Investigations

### Glucocorticoid assessment

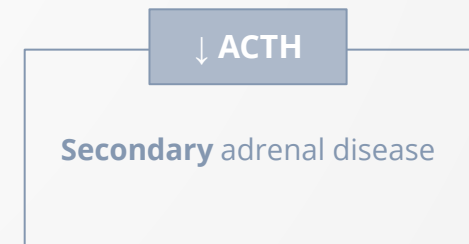
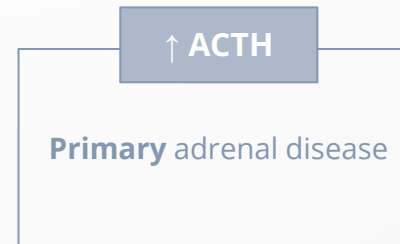
1. Random **Cortisol levels**
  - Usually low *but* can be in low normal reference range
  - *Raised* **Cortisol binding globulin** levels may give falsely normal cortisol levels
  - Value above 500 nmol/L , however, effectively exclude Addison's disease

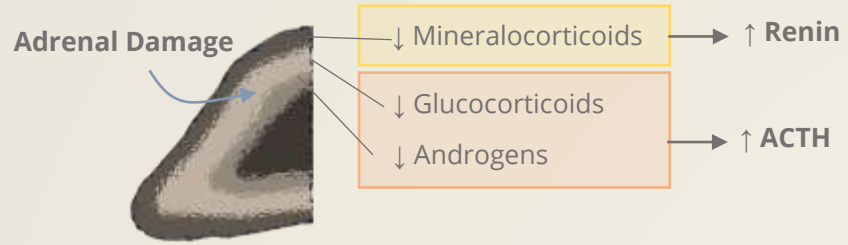
2. Short **ACTH Stimulation** test  
(Tetracosactrin / Short Synacthen test)

Synthetic ACTH 250 µg IM → Cortisol & ACTH sample at baseline  
& Cortisol sample at 30 min

### Interpretation

- **Cortisol fail to increase** at 30 min → **Primary / Secondary** Adrenal Insufficiency **present**
- **Cortisol > 550 nmol/L** → **Excludes** Addison's disease





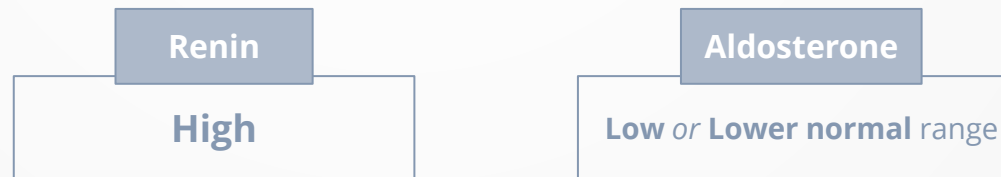
# Addison's Disease

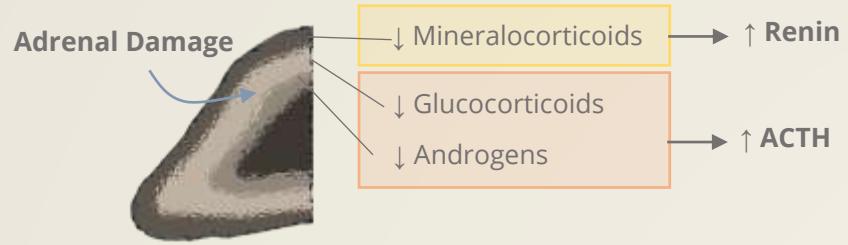
## Investigations

### Mineralocorticoid assessment

- Electrolytes measurement cannot be solely relied upon
  - ↓ Na<sup>+</sup> occur in both Cortisol & Aldosterone deficiency
  - ↑ K<sup>+</sup> common but not universally present
- Plasma **Renin & Aldosterone** level measurement
  - Sample taken in *Supine* position

### Interpretation





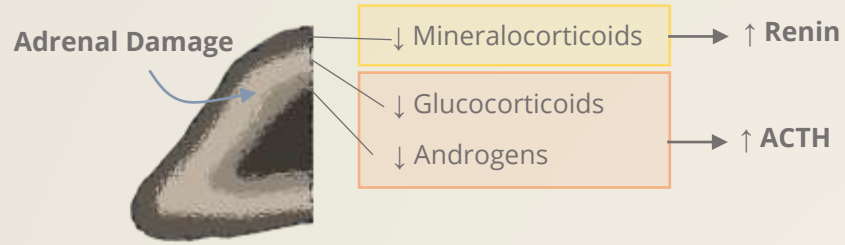
# Addison's Disease

## Investigations

### Androgens assessment

- Not necessary in male patients
- In female patients, **Dehydroepiandrosterone sulphate (DHEAS)** & **Androstenedione** measured in a random specimen of blood





# Addison's Disease

## Investigations

### Investigations for the Cause

#### 1. Adrenal Autoantibodies

- **21-Hydroxylase adrenal autoantibodies** are positive in > 80% cases
- If positive, screen for other autoimmune disorders

#### 2. CT / MRI scan of Adrenals

- To look for Tuberculosis (TB), Histoplasma or Metastatic Ca
- Adrenal hemorrhage

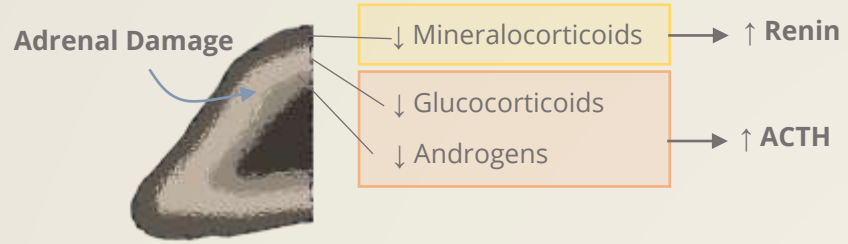
#### 3. CXR / AXR

- To look for evidence of old TB
- **Apical lung fibrosis** on CXR
- **Adrenal calcification** on AXR

#### 4. HIV testing

- If risk factors present

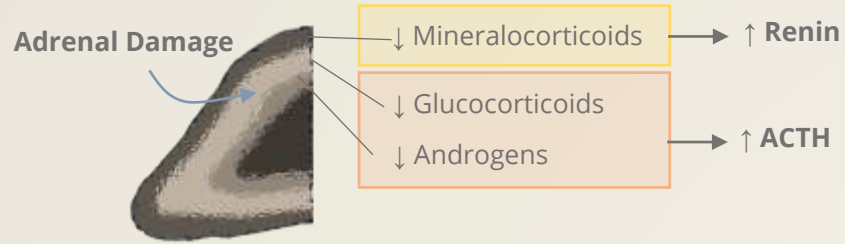




# Addison's Disease

## Management

- Patients with adrenocortical insufficiency always need **glucocorticoid** & usually, but not always, **mineralocorticoid replacement**
- Adrenal **androgen replacement** may also be beneficial in women
- Treatment of **underlying cause**



# Addison's Disease

## Management

### Glucocorticoid Replacement

- Oral **Hydrocortisone** – 15 – 25 mg in divided doses
  - 10 mg morning, 5 mg around 3 PM
- Late dose may cause insomnia
- Dose adjustments done on clinical grounds
  - Weight gain means **over-replacement**
  - Persistent lethargy or Hyperpigmentation due to **inadequate dose or lack of absorption**

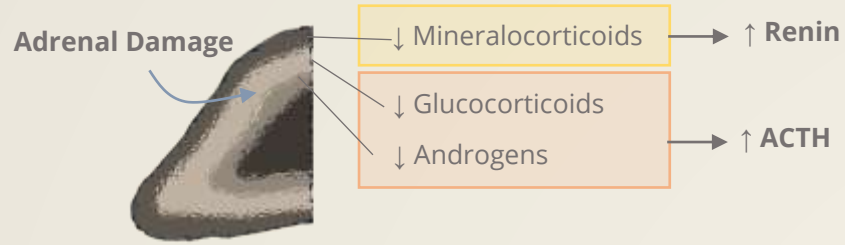
### Mineralocorticoid Replacement

- **Fludrocortisone** – 50 – 200 µg daily
- Replacement assessed by *BP, plasma electrolytes & Renin measurement*

### Androgens Replacement

- **DHEAS** – 50 mg daily in females with symptoms of reduced libido & fatigue

**Treatment of the cause, if any**



# Addison's Disease

## Advice to Patients on Glucocorticoids

- Increase Steroid dose during **Intercurrent stress**. Double the dose of Hydrocortisone
- Add 5–10mg hydrocortisone to daily intake before **strenuous activity/exercise**
- **Surgery**
  - **Minor Operation:** Hydrocortisone 100 mg IM given with pre-medication
  - **Major operation:** Hydrocortisone 100 mg 4 times daily for 24 hrs is given IV, then 50 mg IM 4 times daily until the patient is ready to take tablets
- **Vomiting:** Patients must have *parenteral* Hydrocortisone if unable to take it by mouth due to vomiting
- **Steroid card:** Patient should have and carry a steroid card at all times with information regarding diagnosis, steroid, dose and doctor
- **Bracelet:** Patients should be encouraged to buy a bracelet and have it engraved with the diagnosis, current treatment and a reference number for a central database
- **Emergency pack:** Patients should be given a hydrocortisone emergency pack and trained in the self-administration of hydrocortisone 100 mg IM. They should be advised to take the pack on holidays and trips abroad.

# Acute Adrenal Crisis

## Management

- Circulatory shock with severe hypotension,  $\downarrow$   $\text{Na}^+$ ,  $\uparrow$   $\text{K}^+$ , Hypoglycemia & Hypercalcemia
- Muscle cramps, nausea, vomiting, diarrhea and unexplained fever may be present
- Precipitated by intercurrent disease, surgery, infection *or* missing dose(s) of steroids

### Correct Volume depletion

- IV 0.9% Saline is given *as required*, to normalise BP & Pulse
- If severe hyponatremia with  $\text{Na}^+$  level  $< 125$  mmol/L, avoid increases of plasma  $\text{Na} > 10$  mmol/L/day to prevent pontine demyelination
- Fludrocortisone is not required to correct volume depletion during the acute phase of treatment

### Replace Glucocorticoids

- Hydrocortisone succinate
- 100 mg IV stat, and then 100 mg Q6Hrs for first 12 – 24 hours
- Continue 50 – 100 mg IM Q6Hrs till patient able to take oral treatment

### Correct other Metabolic abnormalities

- Acute Hypoglycemia – 10% Dextrose
- Hyperkalemia – Usually respond to volume replacement but occasionally may need specific treatment

### Identify & Treat Underlying cause

- Look for & treat acute precipitant
- Look for primary or secondary pathology of adrenal insufficiency, after the patient is stabilized

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