# ADRENAL INSUFFICIENCY / ADDISON'S DISEASE

## Background

In 1855, Thomas Addison first described adrenal insufficiency, which was subsequently named after him. The basis of Addison disease has dramatically changed since its initial description. Originally, the disease usually resulted from an infection of the adrenal gland; the most common infection was tuberculosis, which is still the predominant cause of Addison disease in developing countries. Currently, in developed countries, Addison disease most commonly results from nonspecific autoimmune destruction of the adrenal gland.

## Pathophysiology

Adrenal insufficiency can manifest as a defect anywhere in the hypothalamic-pituitary-adrenal axis. Primary adrenal insufficiency is a result of destruction of the adrenal cortex. The zona glomerulosa, the outer layer of the adrenal gland, produces Aldosterone. Cortisol is produced in both the zona fasciculata and the zona reticularis, the middle and innermost layers of the adrenal gland, respectively. Dehydroepiandrosterone is produced in the zona reticularis. Clinical findings are noted after 90% of the adrenal cortex has been destroyed.

## Causes of Adrenal Insufficiency

***Lab features: Cortisol Low, ACTH High***

1. **Addison's Disease**

- Primary adrenal failure of adrenal glands

2. **Idiopathic adrenal hypoplasia or destruction**

- Granulomatous disease (e.g. Tuberculosis, Fungus)
- Amyloidosis
- Haemochromatosis
- Tumour
- Autoimmune process

3. **Medication mediated cortisol inhibition**

- Etomidate
- Ketoconazole

## Causes of HPA Dysfunction

***Lab features: Cortisol Low, ACTH Low***

- Severe illness
- Exogenous Corticosteroid (suppression lasts months)

Prednisone >7.5 mg/day for >3 weeks

Dexamethasone >0.75 mg/day for >3 weeks

- Pituitary Infarction
- CNS Infection or tumor invasion
- Head Injury
- HIV Infection

**Symptoms**

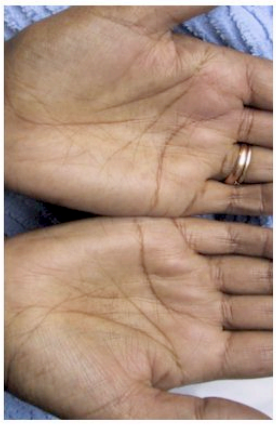
These are often nonspecific and include fatigue, weakness, anorexia, nausea, abdominal pain, gastroenteritis, diarrhoea, and mood lability.

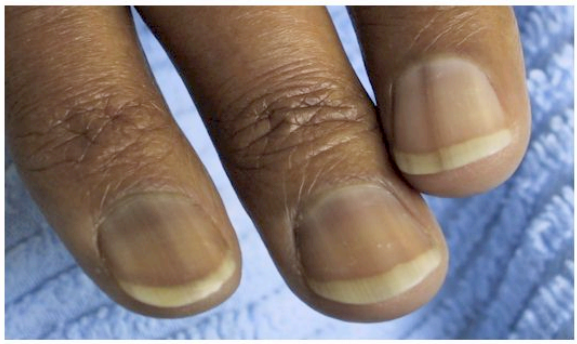
- Weakness and weight loss of 1-15 kg are universal features of Addison disease in the adults.
- Nausea, vomiting, and diffuse abdominal pain are present in approximately 90% of patients and usually represent an impending Addisonian crisis.
- Diarrhoea is less common than nausea, vomiting, and abdominal pain and occurs in approximately 20% of patients.
- If diarrhoea is present, it complicates the patient's already poor hydration status.
- Mood disturbances include depression, irritability, and decreased concentration. Diagnosis may be delayed because of comorbid depression or other psychiatric illness.
- Salt craving
- Altered Level of Consciousness (e.g. Delirium)

**Signs**

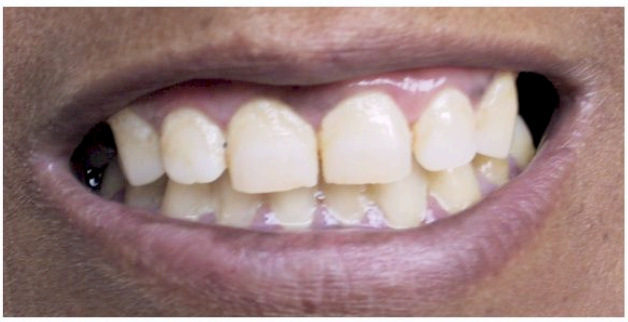
Physical findings include hyperpigmentation of the skin and mucous membranes, decreased pubic and axillary hair in women, vitiligo, dehydration, and hypotension.

- Hyperpigmentation of the skin is considered a hallmark of Addison disease and is present in 95% of patients with chronic primary adrenal insufficiency. However, hyperpigmentation is not a universal sign of adrenal insufficiency.
- The presence of normal-appearing skin does not exclude the diagnosis.
- The skin may appear normal, or vitiligo may be present.
- Increased pigmentation is prominent in areas of the skin that are subject to increased pressure, such as over the knuckles or the skin creases.
- Hyperpigmentation is also prominent on the nipples, axillae, perineum, and buccal mucosa
- Women may have loss of androgen-stimulated hair, such as pubic and axillary hair, because androgens are produced in the adrenal cortex.
- Men do not have hair loss because androgens in males are produced primarily in the testes.
- Usually, systolic and diastolic blood pressures are reduced; the systolic blood pressure is lower than 110 mm Hg.





**Addison's disease:**



- Note the generalised skin pigmentation (in a Caucasion patient) but especially the deposition in the palmer skin creases, nails and gums.

- She was treated many years ago for pulmonary TB. What are the other causes of this condition?

**Investigations**

**Haematology-** Normochromic Normocytic anaemia, Eosinophilia
**Biochemistry –** Hyponatraemia, Hypochloraemia, Hyperkalaemia, Hypoglycaemia
**Urine –** 17-Ketosteroids low, Urine 17-Hydroxysteroids low

**Diagnosis**

Corticotrophin Stimulation Test (Synacthen Tests)
Failed adrenal response

**Management**

**1. Acute** - IV Cortisol
**2. Chronic Replacement** - Hydrocortisone (glucocorticoid) AND Mineralocorticoid (9-alpha-fluorocortisol)
**3. Stress Dose Steroid**
**-** Indication: Acute severe illness
Serum Cortisol <15 to 34 mcg/dl

Cortisol <9 after Corticotropin Stimulation Test

- Management

Hydrocortisone 50 mg IV or IM qds

Consider adding fludrocortisone 50 mcg qds

**Addisonian Crisis**

*NB NOT THE ONLY CAUSE OF ADRENAL CRISIS*

**Examination**

- Unexplained shock, usually refractory to fluid and pressor resuscitation
- Nausea, vomiting, abdominal or flank pain
- Hyperthermia or hypothermia

**Treatment**

- Administration of glucocorticoids in supraphysiological or stress doses is the only definitive therapy.
- Dexamethasone does not interfere with serum cortisol assay and, thus, may be the initial drug of choice. However, because dexamethasone has little mineralocorticoid activity, fluid and electrolyte replacement is essential.
- A short ACTH stimulation test may be performed during resuscitation. Once complete, hydrocortisone 100 mg IV every 6 hours is the preferred treatment to provide mineralocorticoid support.
- *Delaying glucocorticoid replacement therapy while awaiting the results of the ACTH stimulation test is inappropriate and dangerous.*
- In addition to corticosteroid replacement, aggressive fluid replacement with 5 or 10% intravenous dextrose and saline solutions and treatment of hyperkalemia is mandatory.
- Fludrocortisone, a mineralocorticoid, may also be given.
- A thorough search for a precipitating cause and administration of empiric antibiotics is indicated. Reversal of coagulopathy should be attempted with fresh frozen plasma.
- Pressors (e.g., dopamine, norepinephrine) may be necessary to combat hypotension.