

بِسْمِ اللّٰهِ الرَّحْمٰنِ الرَّحِیْمِ



ENDOCRINOLOGY

The Adrenal Gland

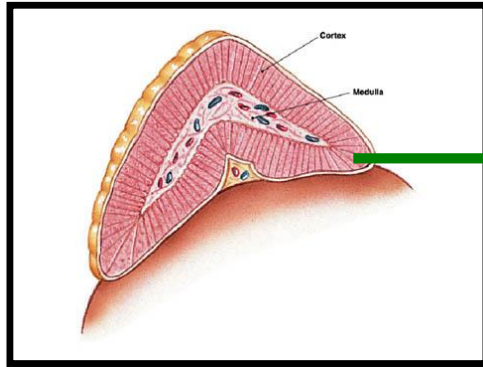
Glucocorticoids

Dr. Abeer Al-Ghumlas

Objectives

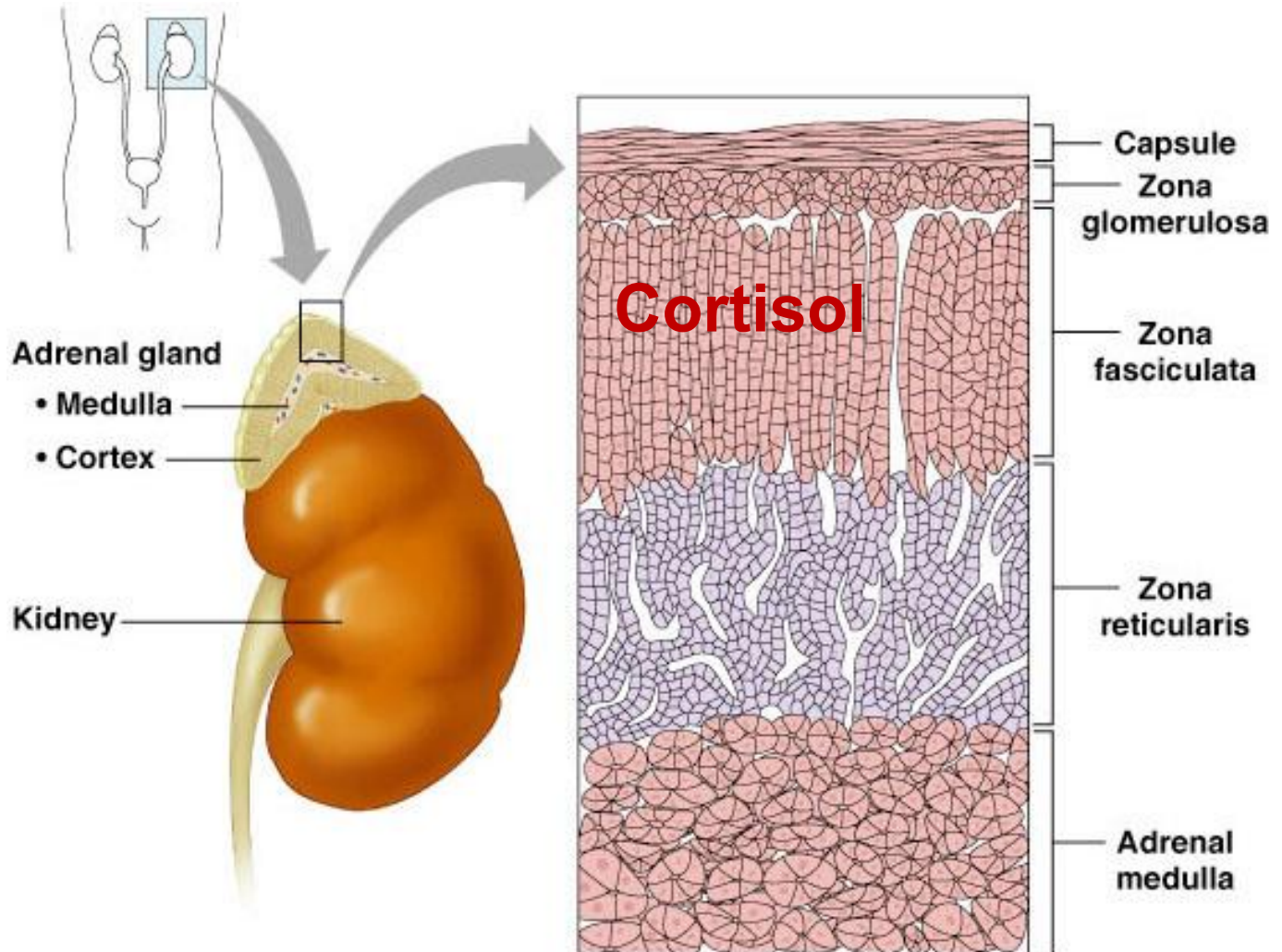
At the end of this lecture student should be able to:

- Describe the metabolism and physiological effects of glucocorticoids.
- Describe the mechanisms that regulate secretion of glucocorticoids
- Describe the main features of the diseases caused by excess or deficiency of each of the hormones of the adrenal gland.



Cortisol

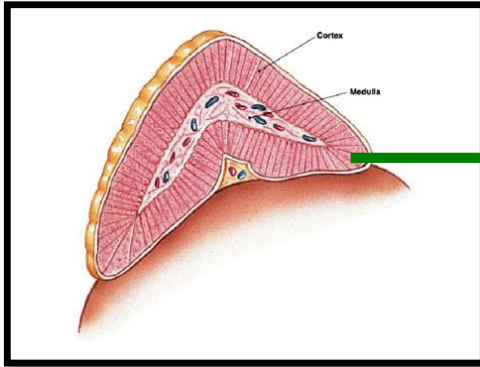
Adrenal Cortex



Glucocorticoids

Main glucocorticoids in humans:

- Cortisol:
 - very potent
 - Account for 95% of glucocorticoid activity
- Corticosterone:
 - account for about 4% of total glucocorticoid activity
 - Less potent than cortisol
- Cortisol:corticosterone produced in humans in a ratio of 10:1



Cortisol...Transport

Bound

- 90-95%
- Mostly to **transcortin**
(Cortisol Binding Globulin)
- **Albumin**

Free

- 6%
- **Active**

- Half life = 60-90 minutes
- Metabolized in liver by reductases & conjugated to glucuronides and excreted via kidney
- Free cortisol is excreted into urine.

Circadian rhythm of cortisol secretion

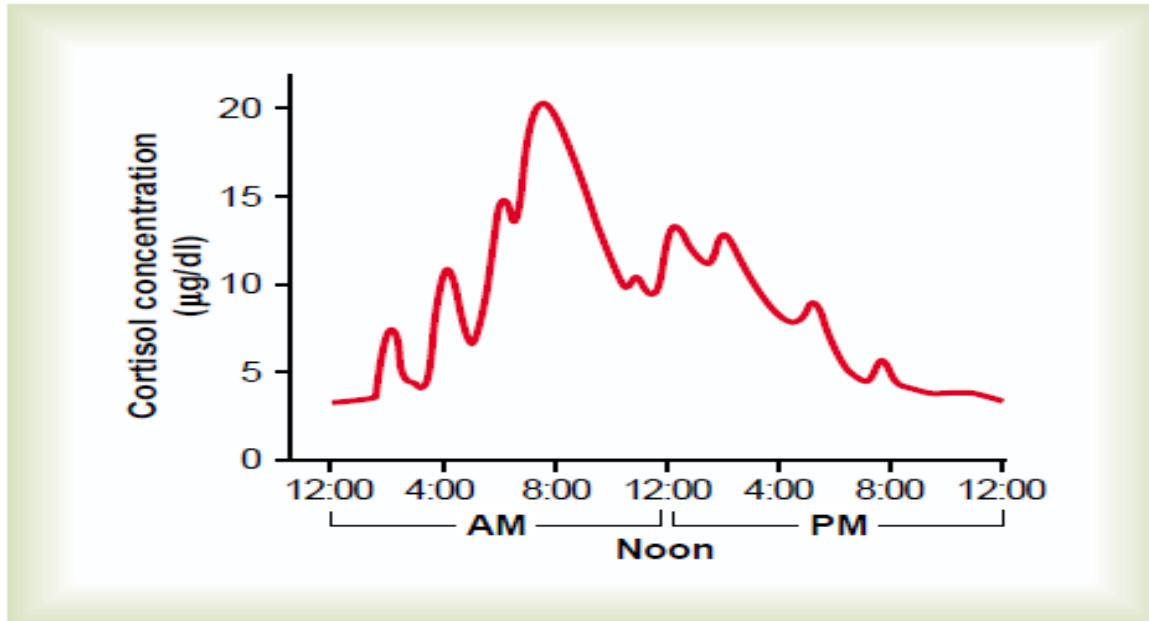


Figure 77-7

Typical pattern of cortisol concentration during the day. Note the oscillations in secretion as well as a daily secretory surge an hour or so after awakening in the morning.

Circadian rhythm of cortisol secretion

▶ The secretory rates of CRF, ACTH, and cortisol:

- high in the early morning:
the plasma cortisol level ranges between a high of about 20 $\mu\text{g}/\text{dl}$ an hour before arising in the morning
- low in the late evening:
low of about 5 $\mu\text{g}/\text{dl}$ around midnight.

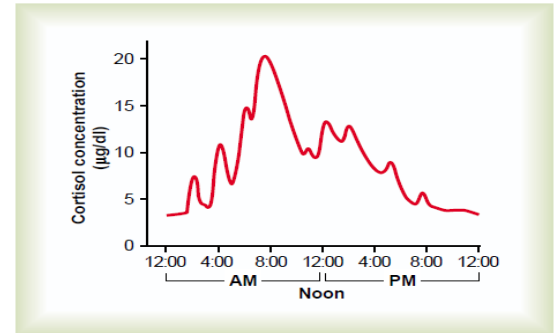


Figure 77-7

Typical pattern of cortisol concentration during the day. Note the oscillations in secretion as well as a daily secretory surge an hour or so after awaking in the morning.

▶ This effect results from a 24-hour cyclical alteration in the signals from the hypothalamus that cause cortisol secretion.

▶ When a person changes daily sleeping habits, the cycle changes correspondingly. Therefore, measurements of blood cortisol levels are meaningful only when expressed in terms of the time in the cycle at which the measurements are made.

Physiological actions of cortisol

1. On metabolism

On carbohydrate metabolism:

↑↑ Glucose level in the blood:

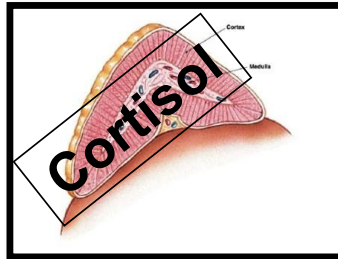
1. Liver:

- Stimulates gluconeogenesis (6-10 fold)
- Increase glycogen storage by the liver.

2. ↓↓ Glucose utilization by the cells.

3. ↓ the sensitivity of tissues to insulin.

“Adrenal Diabetes”.



On protein metabolism:

1. ↓↓ Protein stores in all body (except the liver).

(increase catabolism of protein and decrease protein synthesis)

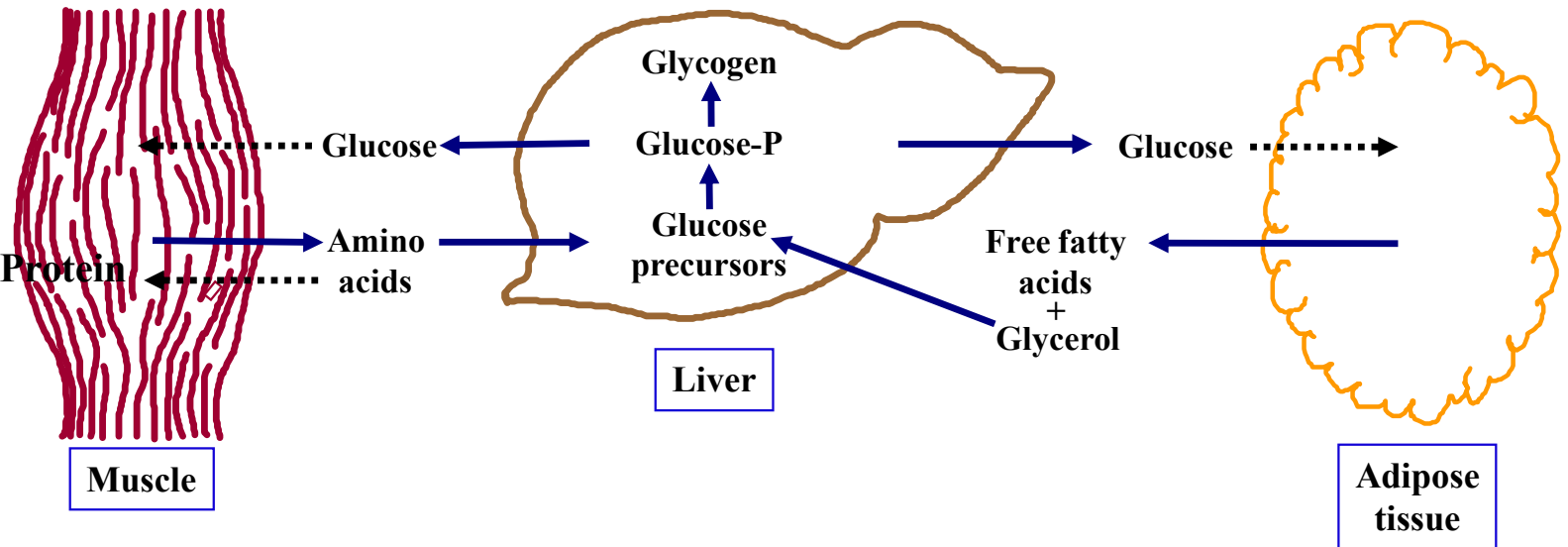
2. ↑ Liver and plasma proteins

3. a.a. - ↑↑ Amino acid level in the blood.

- ↓ a.a transport into extra hepatic cells
- ↑ a.a transport into hepatic cells

On Fat metabolism
(lipolytic):

1. Mobilization of fatty acid from adipose tissue
2. ↑↑ The concentration of free fatty acids in the blood.
3. ↑↑ Their utilization for energy.



Liver

Muscle

Adipose tissue

Plasma

—————▶ Stimulate
▶ Inhibit

↑ Glucose
 ↑ Free fatty acids
 ↑ Amino acids

2. Cortisol is important in resisting stress and inflammation.

- On Stress:

- Without GCs, the body cannot cope with even mild stressors
- Stress include (trauma, infection, surgery, any debilitating disease, increase heat or cold).
- Cortisol causes rapid mobilization of amino acids and FFA from their cellular stores, making them immediately available both for energy & synthesis of other compounds, including glucose, needed by the different tissues in the body.
- ↑ BP, ↑ glycogen, prevents stress induced reaction from becoming excessive.
- Effects on CNS

3. On inflammation

- Damage to the tissues by trauma/infection almost always leads to inflammation.

- Inflammation can be more damaging than the trauma or disease itself.

- Cortisol has anti-inflammatory effects....How?
 - Cause stabilization of the intracellular lysosomal membranes → more difficult for these membranes to rupture → less release of proteolytic enzymes that cause inflammation.

 - Reduces all aspects of the inflammatory process.

3. On inflammation:

Anti-inflammatory:

Reduces all aspects of the inflammatory process.



- (1) Block the early stages of the inflammation process before inflammation even begin
- (2) If inflammation begun: It cause rapid resolution of the inflammation and increase rapidity of healing
- (3) Resolution of inflammation

Anti-inflammatory Effect of cortisol:

- Stabilizes lysosomal membrane.
- Reduces degree of vasodilatation.
- Decreases permeability of capillaries.
- Decreases migration of white blood cells.
- Suppresses immune system.

4. Cortisol blocks the inflammatory response to Allergic reactions

Anaphylactic shock



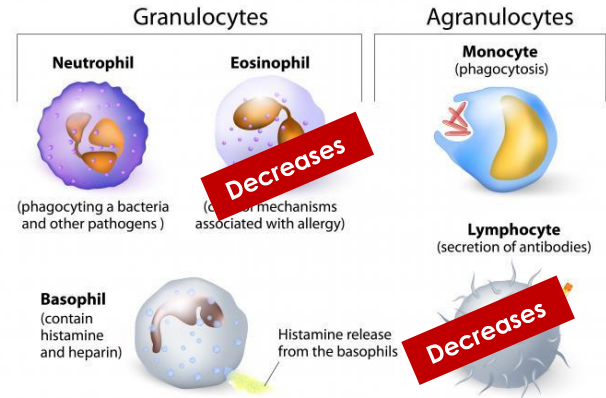
Cortisol
prevent shock
and death

5. On blood cells:

- ▶ Increases RBC production
- ▶ Decreases lymphocyte, eosinophils count
- ▶ Large doses of cortisol administration: Suppresses lymphoid tissue systemically therefore decrease T cell and antibody production decreasing immunity.
- ▶ This effect is useful in transplantation surgery in reducing organ rejection.



WHITE BLOOD CELL



Decreases

6. anti-allergic effects

(In pharmacological doses):

- It decreases fibroblastic activity and local swelling
- ↓ phospholipase A2
- Stabilizes lysosomal membrane
- Inhibits collagenase from breaking down proteins
- Inhibits histamine release (anti-allergic)



7. Effect on circulation

➤ Excrete water load:

Cortisol levels vary with water intake

➤ Mineral metabolism:

Cortisol has mineralocorticoid effect:

Na⁺ reabsorption and K⁺ secretion

Not as potent as aldosterone.

➤ Vascular Effect:

➤ Maintains body fluid volumes & vascular integrity

➤ BP regulation & cardiovascular function:

Sensitizes arterioles to action of noradrenaline (Permissive effect).

➤ Increase in GFR (vasodilatation of afferent arterioles which increases renal Blood flow)

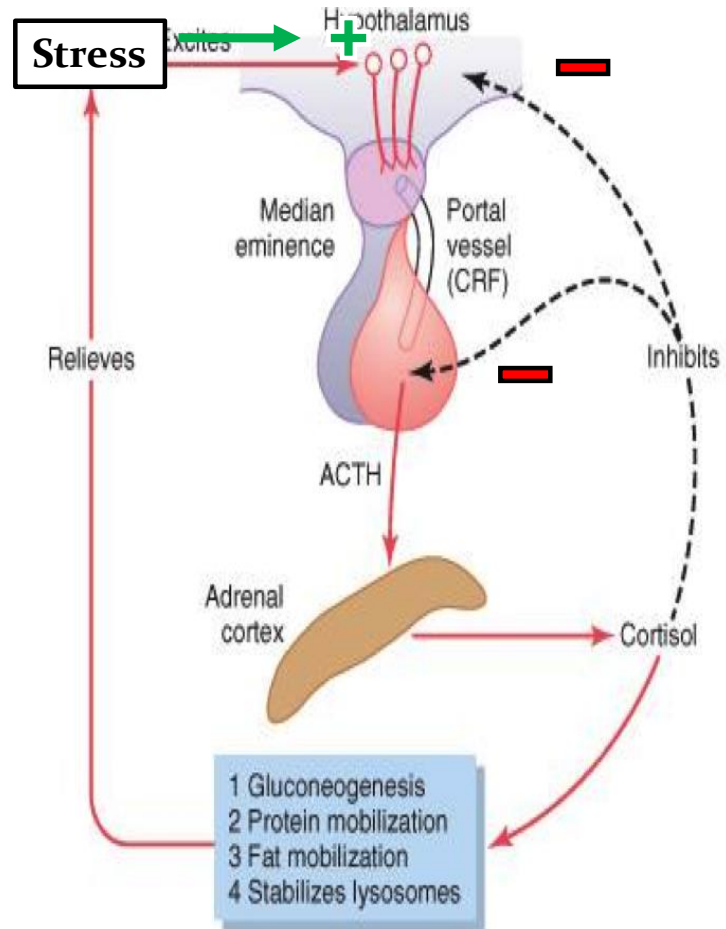
Functions - CNS

➤ 8.Effect on CNS:

- Decreases REM sleep
- Increase slow-wave sleep
- Increases awake time

Regulation of Cortisol Secretion

- Stress stimulates CRH secretion by the hypothalamus.
- Cortisol has a direct **negative feedback** effect on both the hypothalamus and ant. pituitary.



Abnormalities

(Increase secretion
of corticosteroid)



Cushing's Syndrome

(Decrease secretion
of glucocorticoids
and mineralocorticoids)



- Note the generalised skin pigmentation (in a Caucasian 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?

(Addison's disease)

Cushing's Syndrome

Cushing syndrome: (Hypercortisolism)

Causes and types:

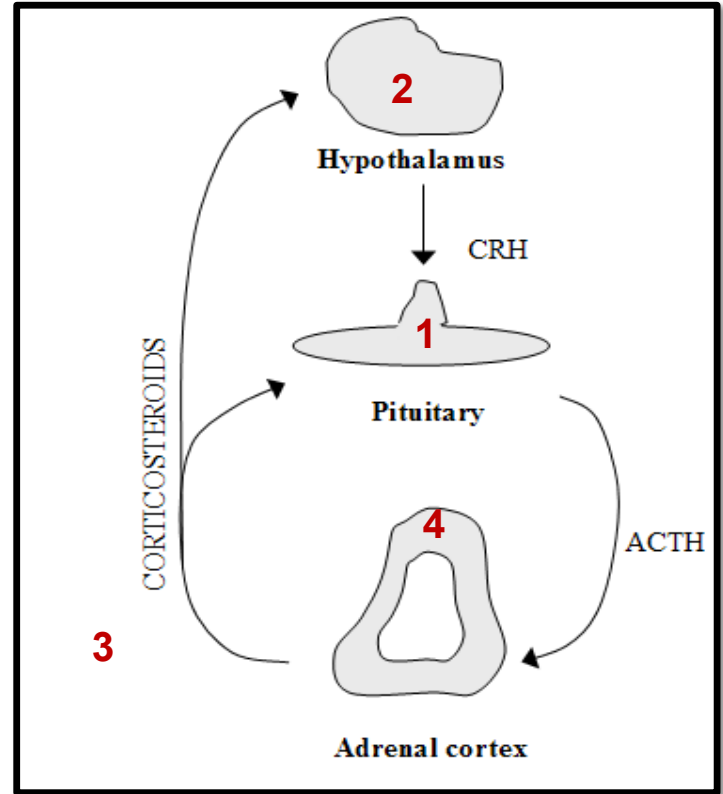
(1) adenomas of the *anterior pituitary*
→ ↑ ACTH.

(2) abnormal function of the
hypothalamus → ↑ CRH.

(3) "ectopic secretion" of ACTH by a
tumor elsewhere in the body, such as
an abdominal carcinoma.

(4) adenomas of the *adrenal cortex*.

When Cushing's syndrome is
secondary to ↑ ACTH by the anterior
pituitary = *Cushing's disease*.



(5) Cushing's syndrome may occur when large amounts of glucocorticoids are administered over prolonged periods for therapeutic purposes.

e.g. patients with chronic inflammation associated with diseases such as rheumatoid arthritis.



Cushing's Syndrome

On carbohydrate metabolism:

- ↑ blood **glucose** level
- (↑ gluconeogenesis and ↓ **glucose** utilization by the tissues).

Abnormal fat redistribution

- mobilization of **fat** from the lower part of the body, with concomitant extra deposition of fat in the thoracic and upper abdominal regions, giving rise to a buffalo torso (truncal obesity).
- The appearance of the face described as a "moon face"

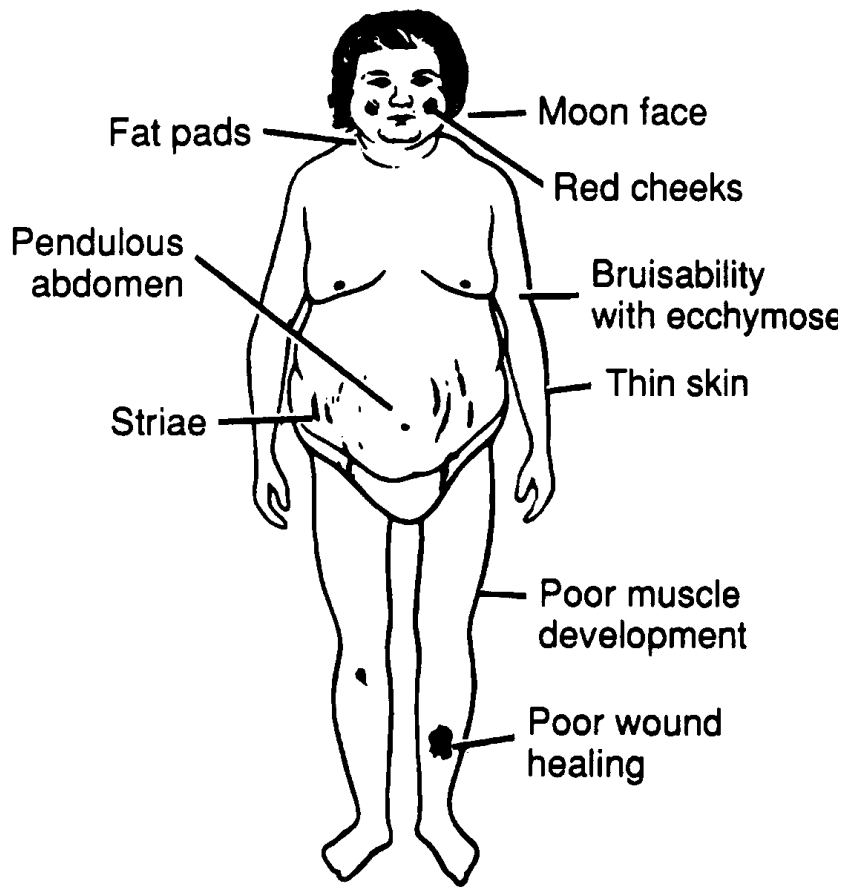
On protein metabolism:

- ↓ tissue proteins almost everywhere in the body (except liver).
- Protein loss from the muscles in particular causes severe weakness.
- protein collagen fibers in the s.c.(loss of CT)
- Thinning of the skin
- severely ↓ protein deposition in bones → severe *osteoporosis*.
- suppressed immune system.

- 80% of patients have hypertension (because of the mineralocorticoid effects of cortisol).

Cushing's Syndrome

Many people with excess cortisol secretion develop a peculiar type of obesity, with excess deposition of fat in the chest and head regions of the body, giving a buffalo-like torso and a rounded face, a "moon-face".



CUSHING'S SYNDROME



Features of Cushing's Syndrome

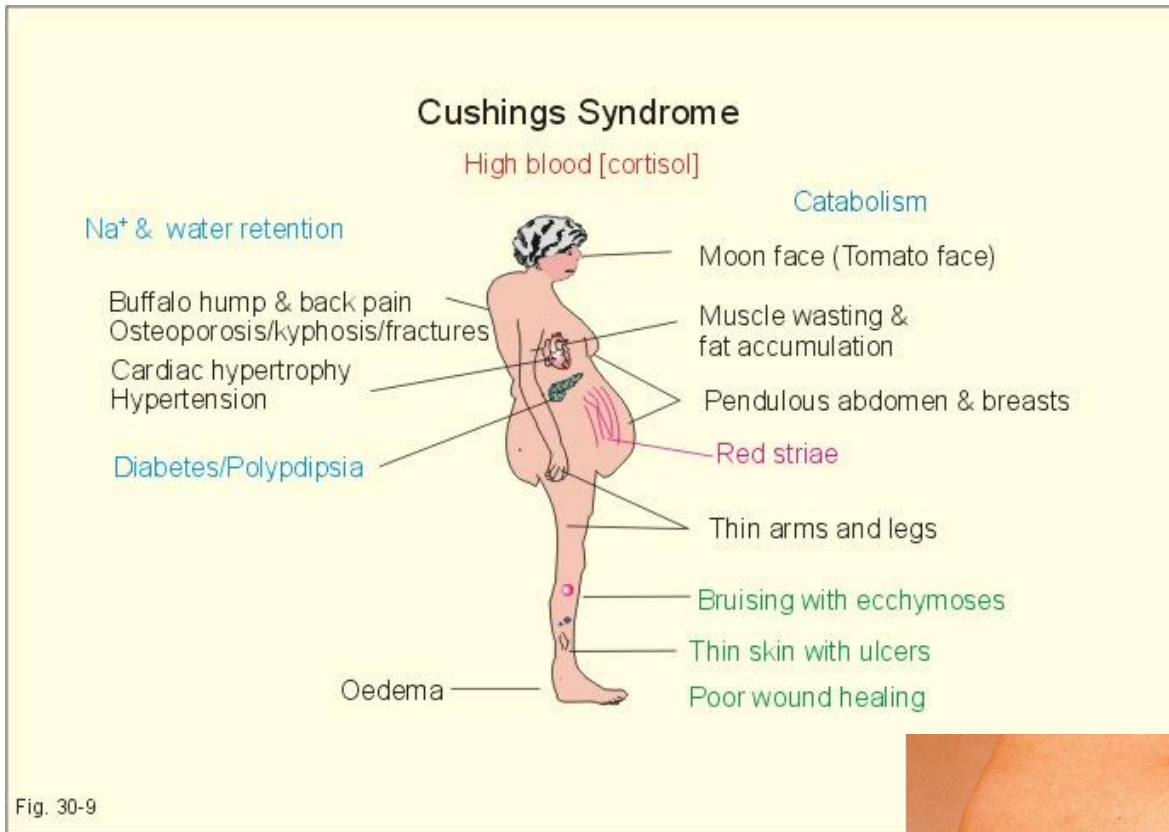
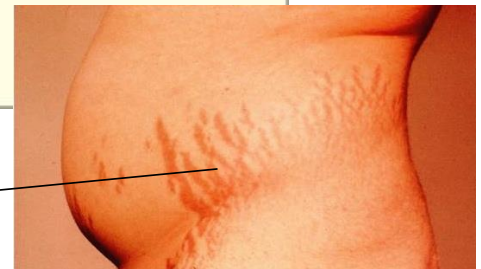


Fig. 30-9

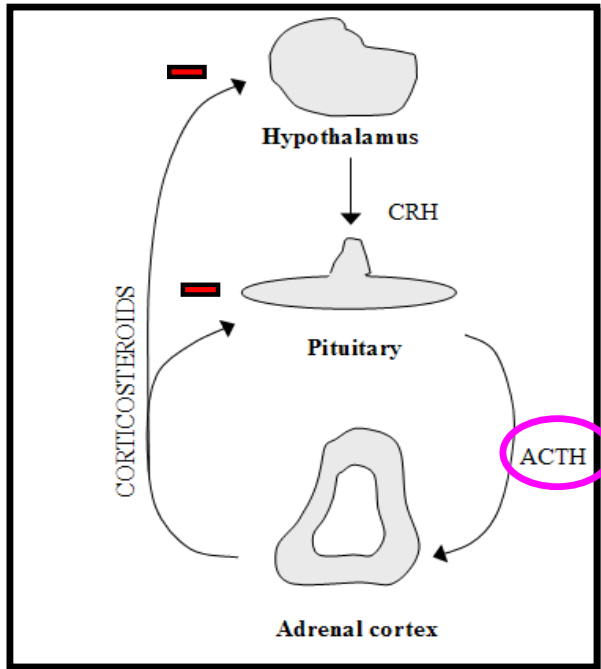
striae



How to differentiate between ACTH-dependent and ACTH-Independent Cushing's syndrome?

- By administering large doses of *cortisol (dexamethasone)*.

In patients with \uparrow ACTH \rightarrow no suppression of ACTH secretion.



patients with primary adrenal overproduction of cortisol (ACTH-independent) \rightarrow \downarrow levels of ACTH.

Abnormalities

(Increase secretion
of corticosteroid)



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of glucocorticoids
and mineralocorticoids)



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(Addison's disease)

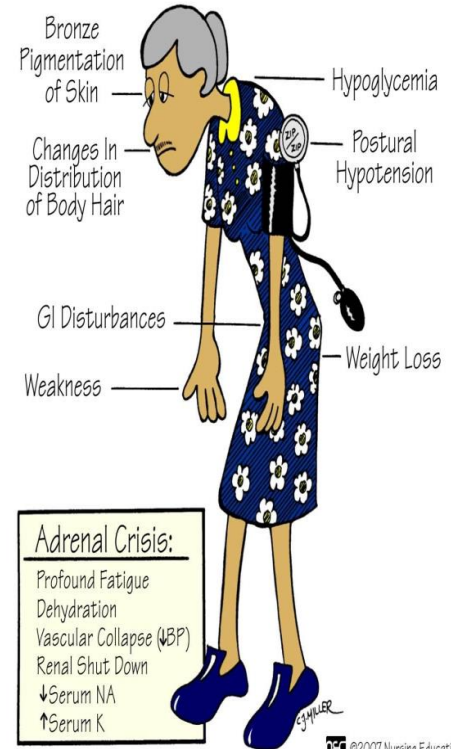
Adrenocortical insufficiency

- primary causes, ie. **Addison's disease**
 - autoimmune disease, tumors, infection, hemorrhage, metabolic failure, ketoconazole (glucocorticoid antagonist activity)
- secondary causes
 - hypopituitarism, suppression by exogenous steroids

Adrenal insufficiency: (Addison's disease)

- Increased excretion of sodium and water.
- Reduction in ECF volume.
- Tendency toward low blood pressure.
- Complete absence of aldosterone, the volume depletion may be severe.
- Hypoglycemia
- Skin pigmentation
The person is allowed to eat large amounts of salt and drink large amounts of water to balance the increased urine output of salt and water.

ADDISON'S DISEASE



CLINICAL MANIFESTATION

- General weakness and becoming easily tired.
- Darkened areas of skin ('pigmentation').
- Blood pressure is low and falls further when you stand which can make you dizzy.
- Being off your food and weight loss.
- Feeling sick and vomiting from time to time.
- Abdominal pains which may come and go.
- Diarrhoea or constipation which may come and go.
- Cramps and pains in muscles.
- Craving for salt, or salty foods and drinks.
- Menstrual periods in women may become irregular, or stop.



Addison's disease:



- Note the generalized skin pigmentation in a Caucasian patient! This is due to the deposition in the skin of melanin, melanocyte-stimulating hormone.

- For more details on this, visit our website at www.addison.org





Addison's disease:



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

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Endocrine Images: Adrenal Insufficiency



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This slide of identical twins is from Dr. Hammer's lecture and is meant to emphasize the hyperpigmentation and thin body habitus that is often seen in primary adrenal insufficiency (the woman with adrenal insufficiency is on the right). Hyperpigmentation may also be seen in the extensor surfaces of the limbs (knuckles, elbows, knees), in newly formed scars and in palmar creases and buccal mucosa. (What's the cause?)

COMMON DISORDERS OF ADRENOCORTICAL FUNCTION

<p><u>Conn's</u> <i>(Primary Hyperaldosteronism)</i></p>	<p>Aldosterone ↑</p>	<p>Hypertension, hypokalemia, alkalosis</p>
<p><u>Secondary Hyperaldosteronism</u></p>	<p>Aldosterone ↑ Renin ↑</p>	<p>Hypertension, hypokalemia, alkalosis</p>
<p><u>Cushing's</u></p>	<p>Cortisol ↑ ACTH ↑ or ↓ (depending on aetiology)</p>	<p>Altered appearance, bruising, muscle wasting, hypertension, diabetes, hypokalemia</p>
<p><u>Addison's</u></p>	<p>Cortisol ↓ Aldosterone ↓ or ↔</p>	<p>Hypoglycemia, hyponatremia, hyperkalemia and raised urea <u>Acute:</u> abdominal pain, vomiting, dehydration and hypotension <u>Chronic:</u> fatigue, pigmentation, anorexia, weight loss and postural hypotension</p>

Thank you

