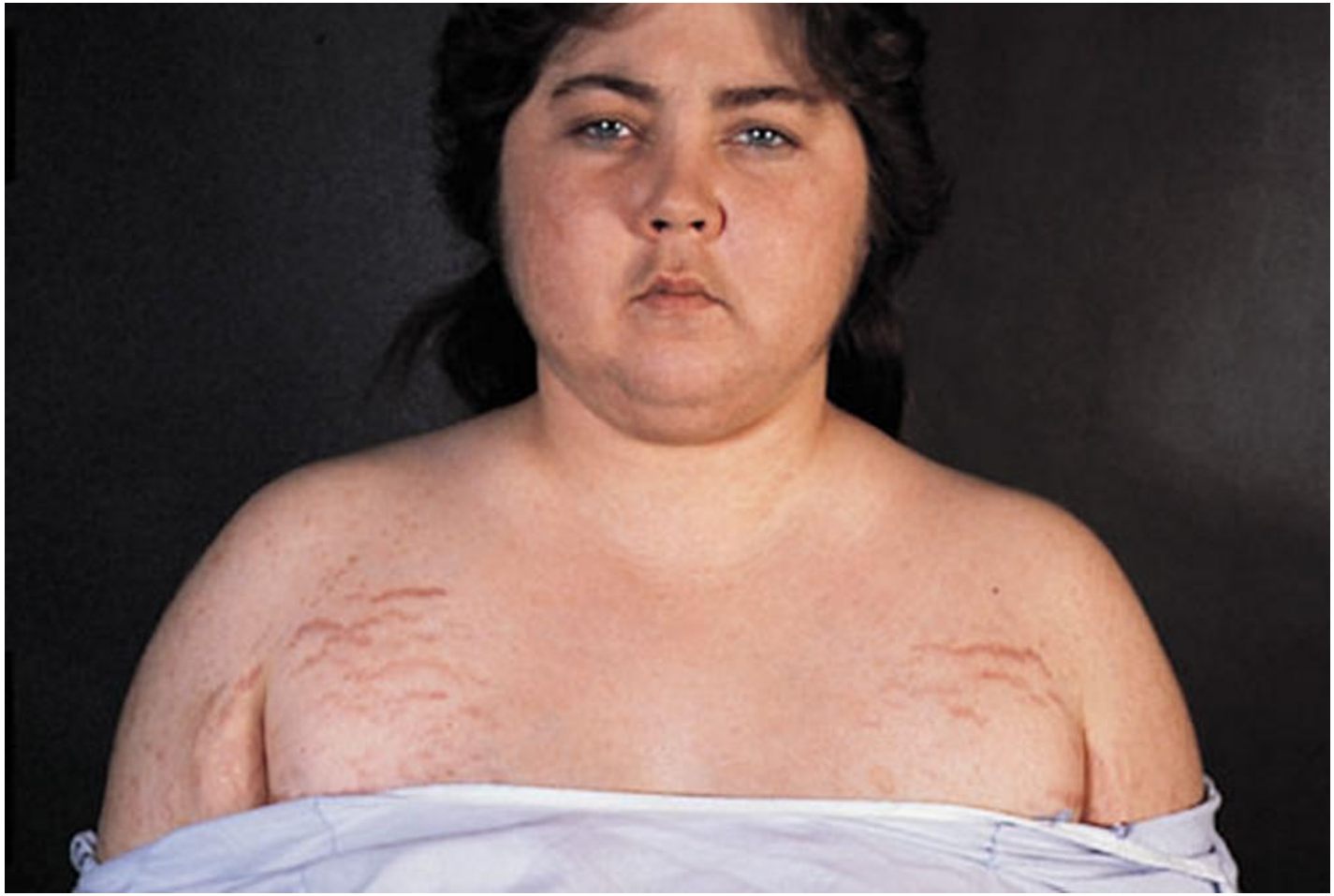
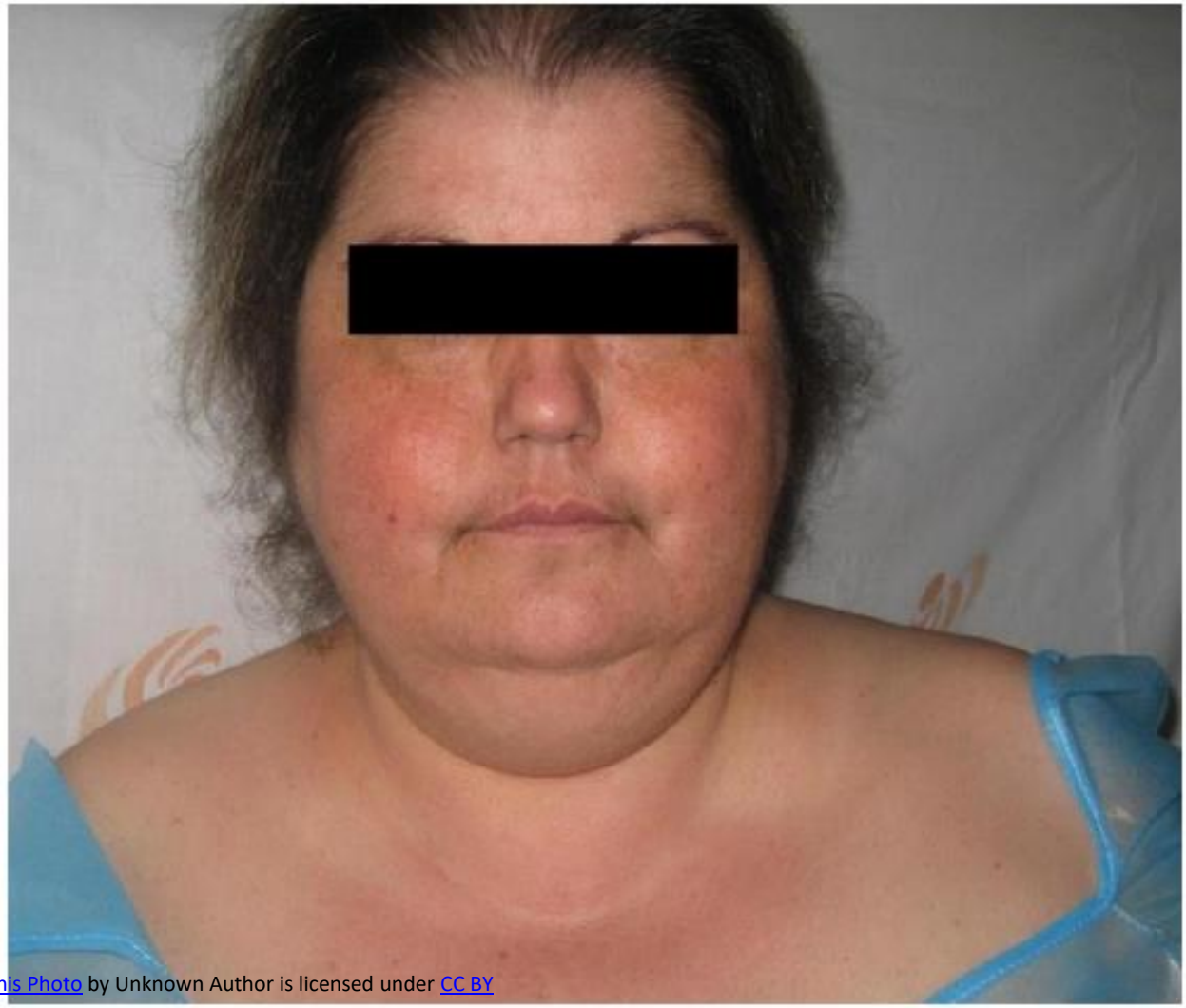
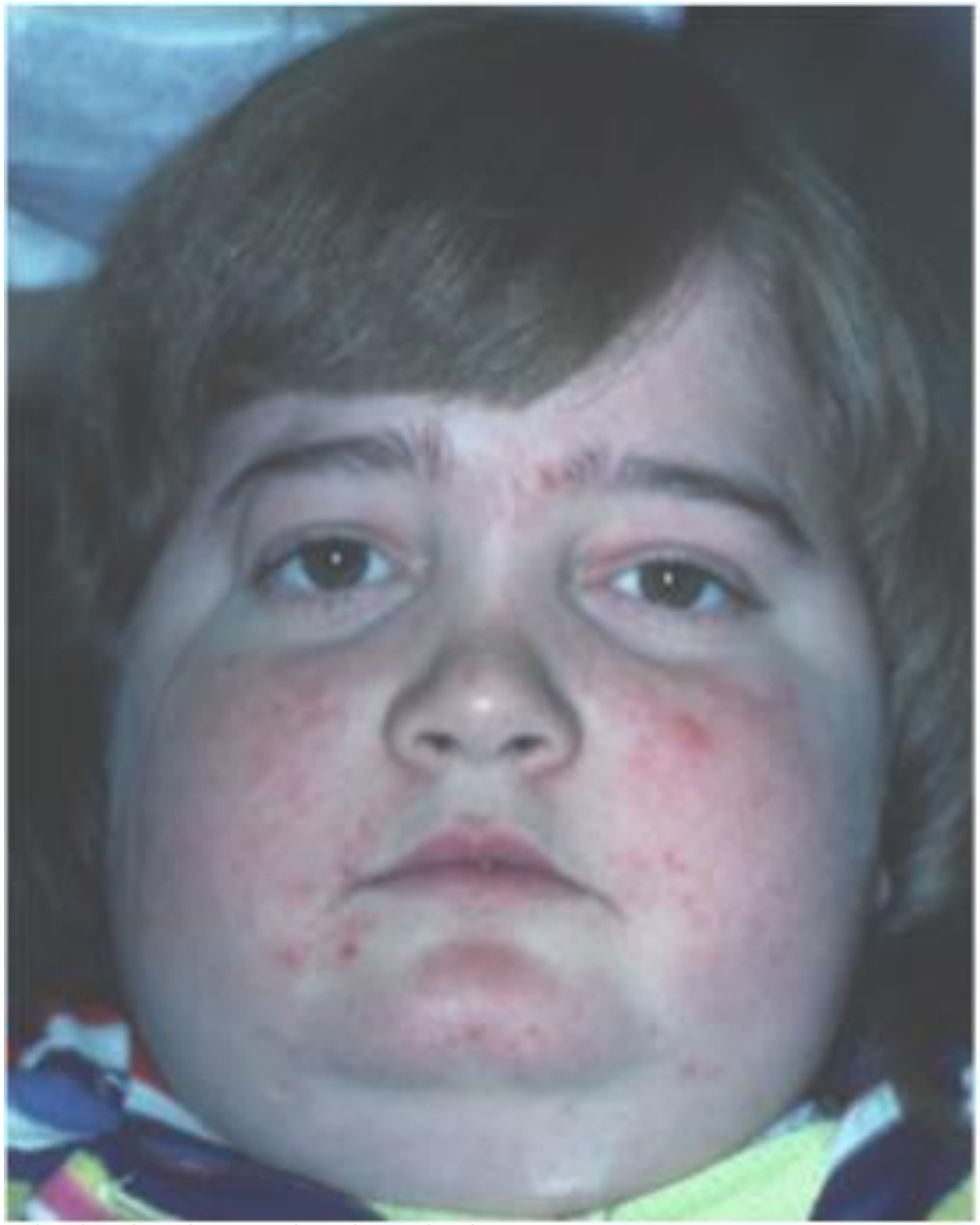
- A 40 years old lady presented to medical opd with hx of polyuria, she is also complaining of putting on more weight and having pink strie on her abdomen and thigh, her blood sugar is 300 mg /dl…..

  whats her problem?



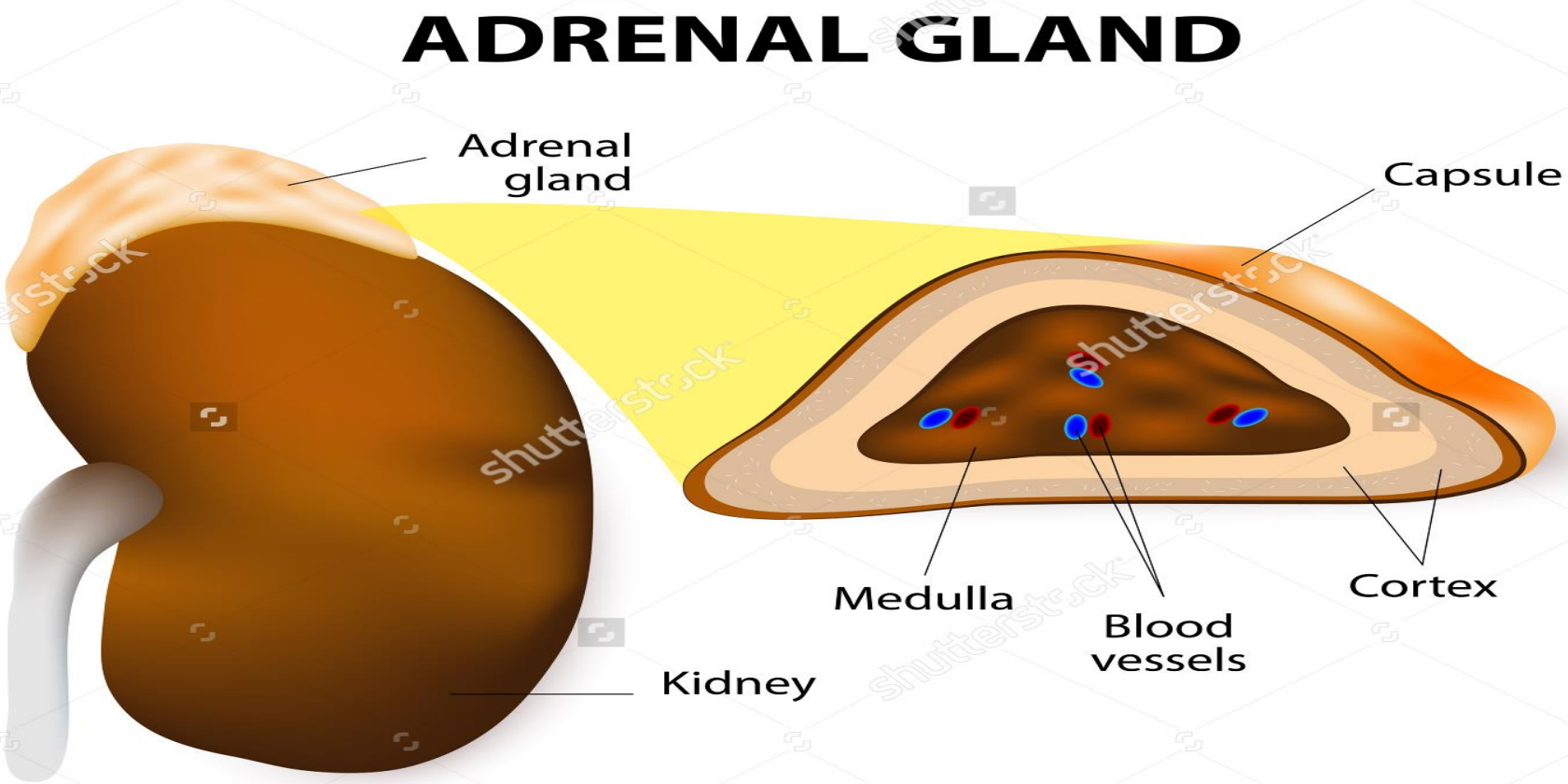




A 30 years old lady presented to ER having high grade fever and chest infection . She is dehydrated and her BP is 70/50 . She is emaciated and having pigmention on her palmar creases. She have bean diagnosed 3 years before having some hormone problem for which she was taking some pills in the morning but she missed her dose from the last one month…

Whats her problem?

FUNCTIONS OF GLUCOCORTICOIDS

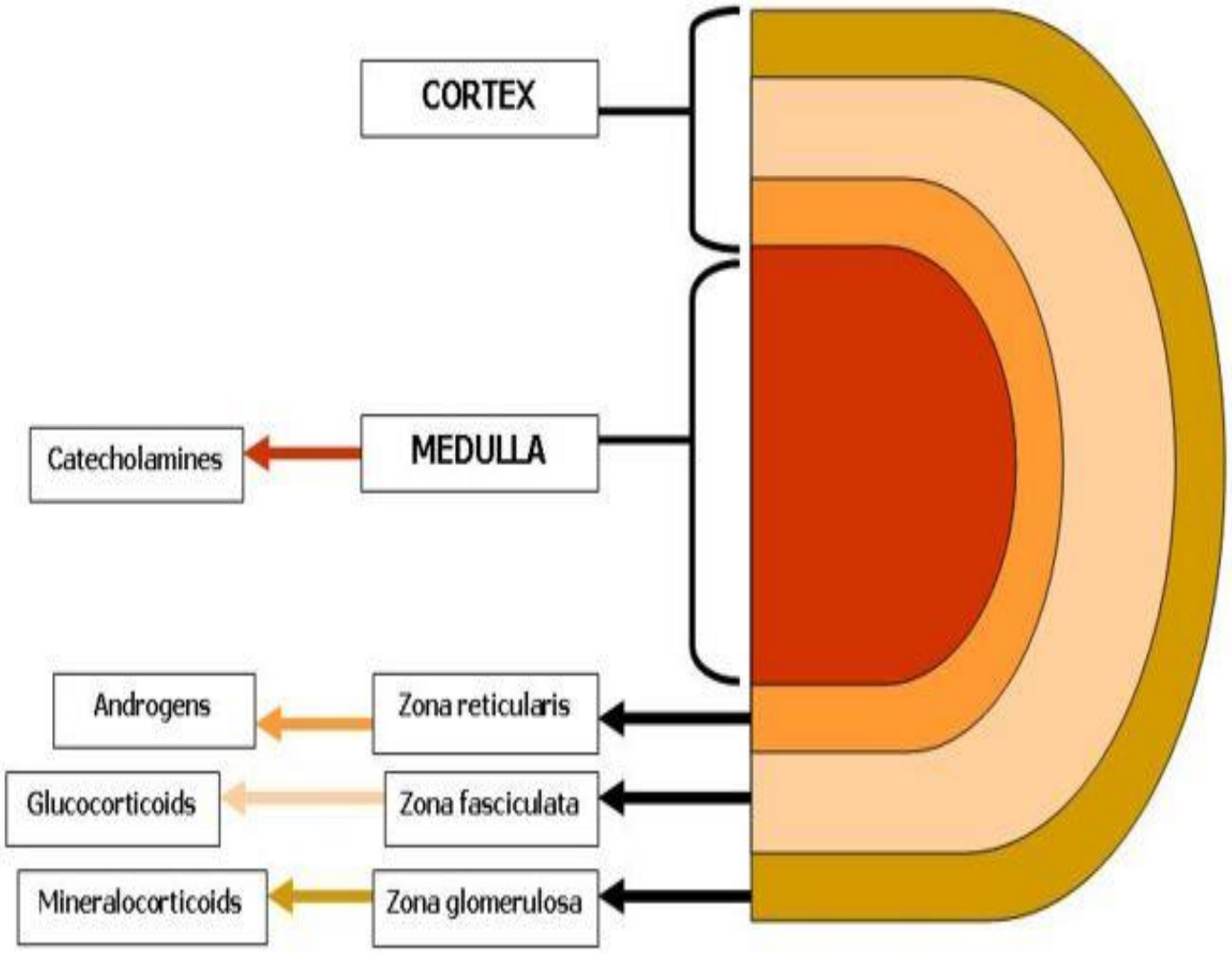


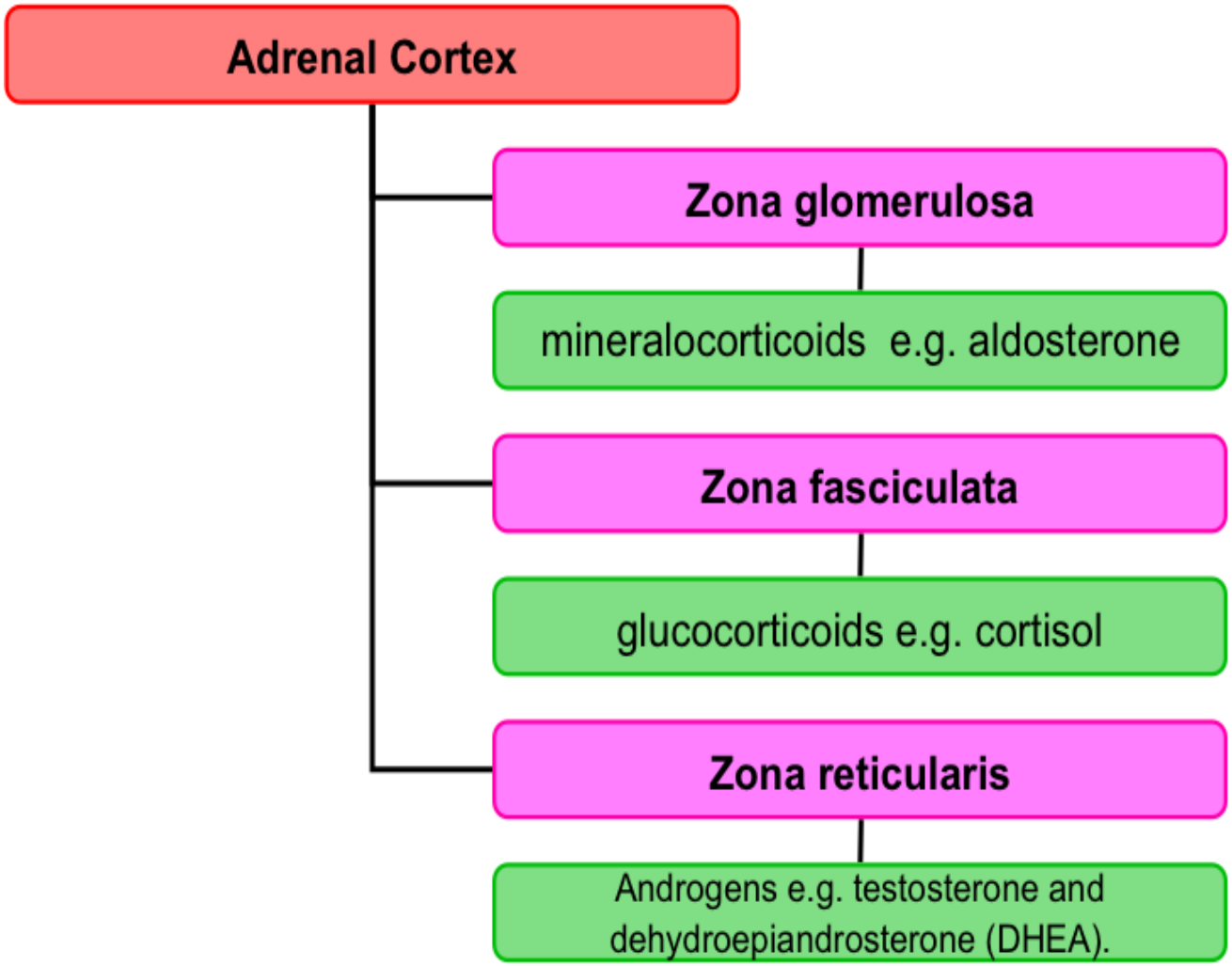
Adrenocortical hormones

- Three types:

1. **Mineralocorticoids**
2. **Glucocorticoids**
3. **Androgens**

Glucocorticoids increase blood glucose concentration


CORTEX
MEDULLA
Catecholamines
Androgens
Zona reticularis
Glucocorticoids
Zona fasciculata
Mineralocorticoids
Zona glomerulosa


Adrenal Cortex
Zona glomerulosa
mineralocorticoids e.g. aldosterone
Zona fasciculata
glucocorticoids e.g. cortisol
Zona reticularis
Androgens e.g. testosterone and dehydroepiandrosterone (DHEA).

FUNCTIONS

Functions of the Glucocorticoids

At least 95% of activity of the adrenocortical secretions results from ***cortisol*** ***corticosterone***.

CORTISOL

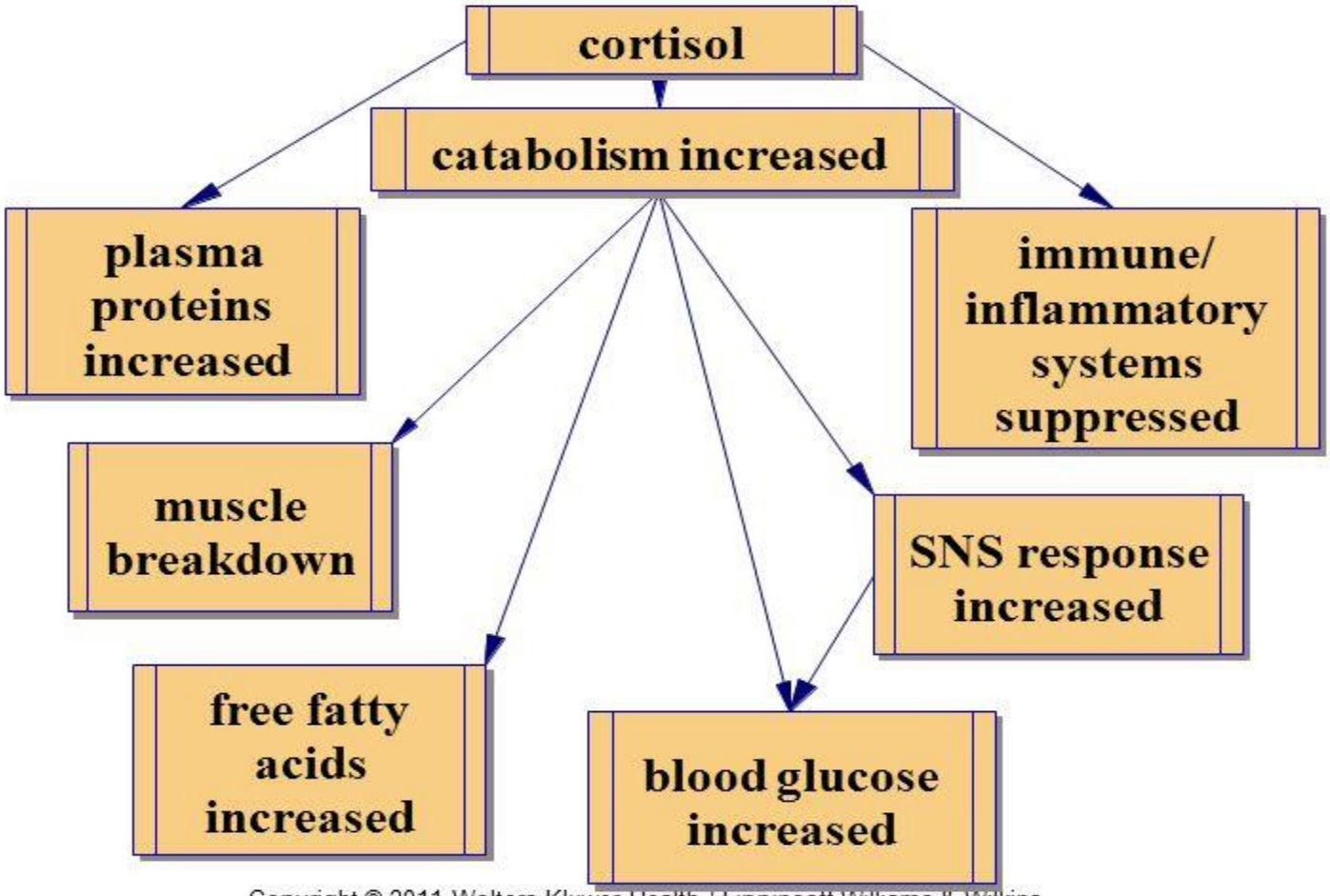
- Approximately **90--95%** of cortisol in the plasma binds to plasma proteins globulin(albumin) called ***cortisol-binding globulin or transcortin***
- Cortisol has a relatively long half- life of 60--90 min.

Functions of glucocorticoids

- Carbohydreate metabolism
- Protein metabolism
- Lipid metabolisim
- Stress hormones

- mainly
- CATABOLIC HORMONE

Actions of Cortisol



Cortisol has a small amount of mineralocorticoid activity.

Some syndromes of excess cortisol secretion can cause significant mineralocorticoid effects, along with its much more potent glucocorticoid effects.

1.Effects of Cortisol on Carbohydrate Metabolism

Stimulate **gluconeogenesis** by the liver,

(6—10 fold).

- This results mainly from 2 effects:-

1. Cortisol increases the enzymes required to convert AA into glucose in liver cells.

2. *Cortisol causes mobilization of AA from the extrahepatic tissues mainly from muscle.*

--***more AA become available in plasma for gluconeogenesis.***

CONT….

⇧ gluconeogenesis---- ⇧ glycogen storage in liver cells.

This effect of cortisol allows other glycolytic hormones (epinephrine & glucagon), to mobilize glucose in times of need, such as between meals.

Decreased Glucose Utilization by Cells.

Cortisol also causes a moderate ⇩ in the rate of glucose utilization by most cells in the body..

by

decrease glucose transporter,

insulin resistance,oxidation of NADH to NAD.

ADRENAL DIABETES

Both ⇧ gluconeogenesis & ⇩in glucose utilization by cells cause the blood glucose concentrations to ⇧.

The rise in blood glucose -- stimulates secretion of insulin.

High levels of glucocorticoid reduce the sensitivity of many tissues, to the stimulatory effects of insulin on glucose uptake & utilization.

High levels of fatty acids, caused by glucocorticoids, impair insulin's actions on the tissues.

The ⇧ in blood glucose concentration is occasionally (50 % or more above normal) --- ***adrenal diabetes.***

Administration of insulin lowers the blood glucose concentration only a moderate amount in adrenal diabetes-not nearly as much as it does in pancreatic diabetes because the tissues are resistant to the effects of insulin.

Effects of Cortisol on Protein Metabolism:

Cortisol causes reduction of the protein stores in essentially all body cells except liver.

This is caused by both ⇩ protein synthesis & ⇧ catabolism of protein already in cells.

Both these effects result from ⇩AA transport into extra-hepatic tissues.

Cortisol also ⇩ formation of RNA & subsequent protein synthesis in many extrahepatic tissues (especially in muscle & lymphoid tissue).

In the presence of great excesses of cortisol, the muscles can become so weak that the person cannot rise from the squatting position(proximal myopathy).

Cortisol ⇧ Liver & Plasma Proteins.

The liver proteins become ⇧ --- plasma proteins are also ⇧.

These increases are exceptions to the protein depletion that occurs elsewhere in the body.

This difference results from a possible effect of cortisol to ⇧ AA transport into liver cells (but not into most other cells) & to ⇧ the liver enzymes required for protein synthesis.

Catabolism of proteins in cells continues to release AA & ⇧ the plasma AA concentration.

- ⇧ transport of AA into hepatic cells cause

---- ⇧ protein synthesis in liver,

---- ⇧ formation of plasma proteins by liver

---- ⇧ conversion of AA to glucose

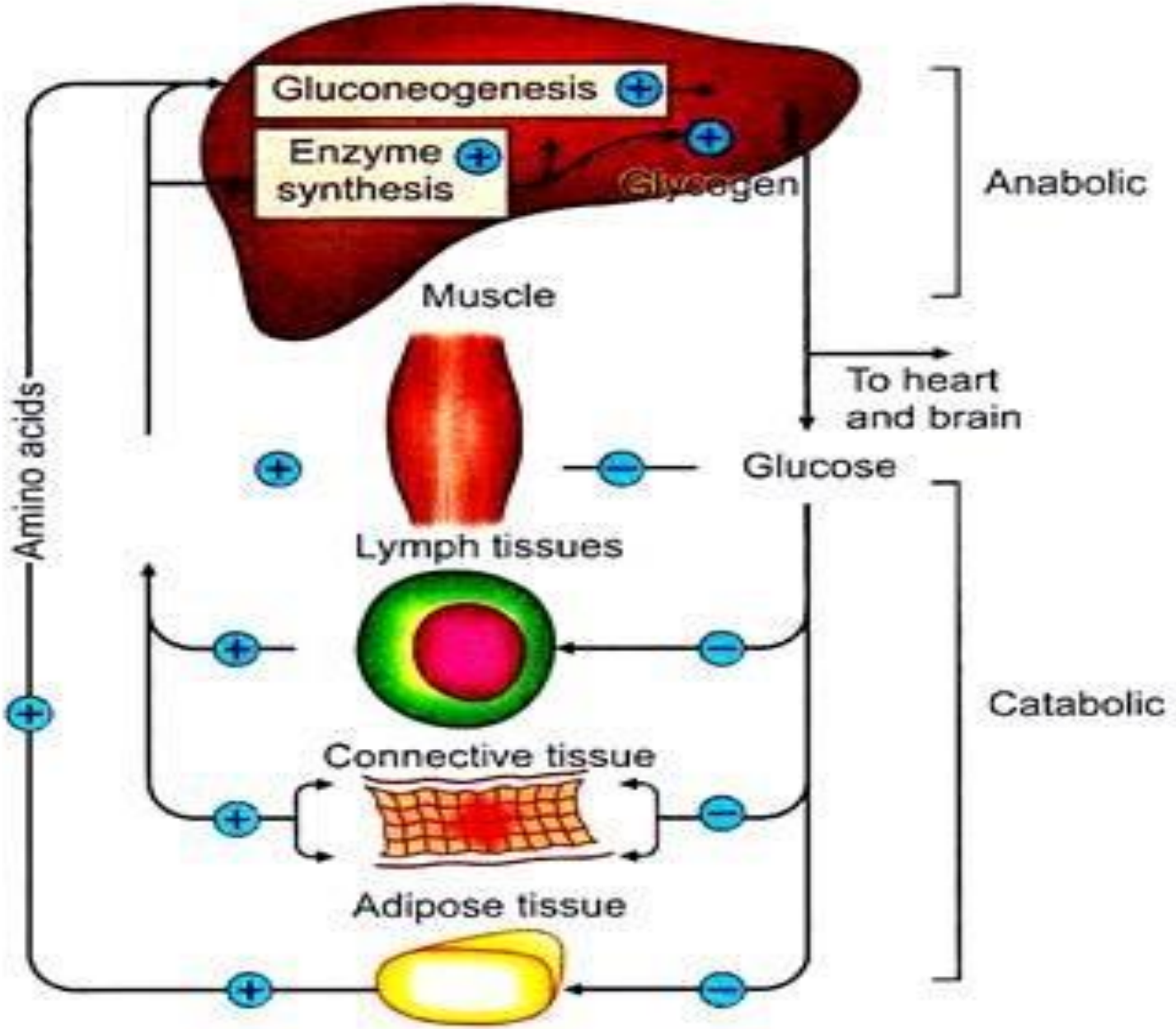


Fig. 6.21: Some of the important metabolic actions of cortisol

Effects of Cortisol on Fat Metabolism

Mobilization of Fatty Acids.

--promotes mobilization of FA from adipose tissue.

This ⇧ concentration of free FA in plasma, which also ⇧ their utilization for energy.

Cortisol have a direct effect to ⇧ oxidation of FA in cells.

This effect results from ⇩ transport of glucose into fat cells.

Glycerophosphate derived from glucose, is required for deposition of triglycerides in fat cells, & in its absence the fat cells begin to release FA.

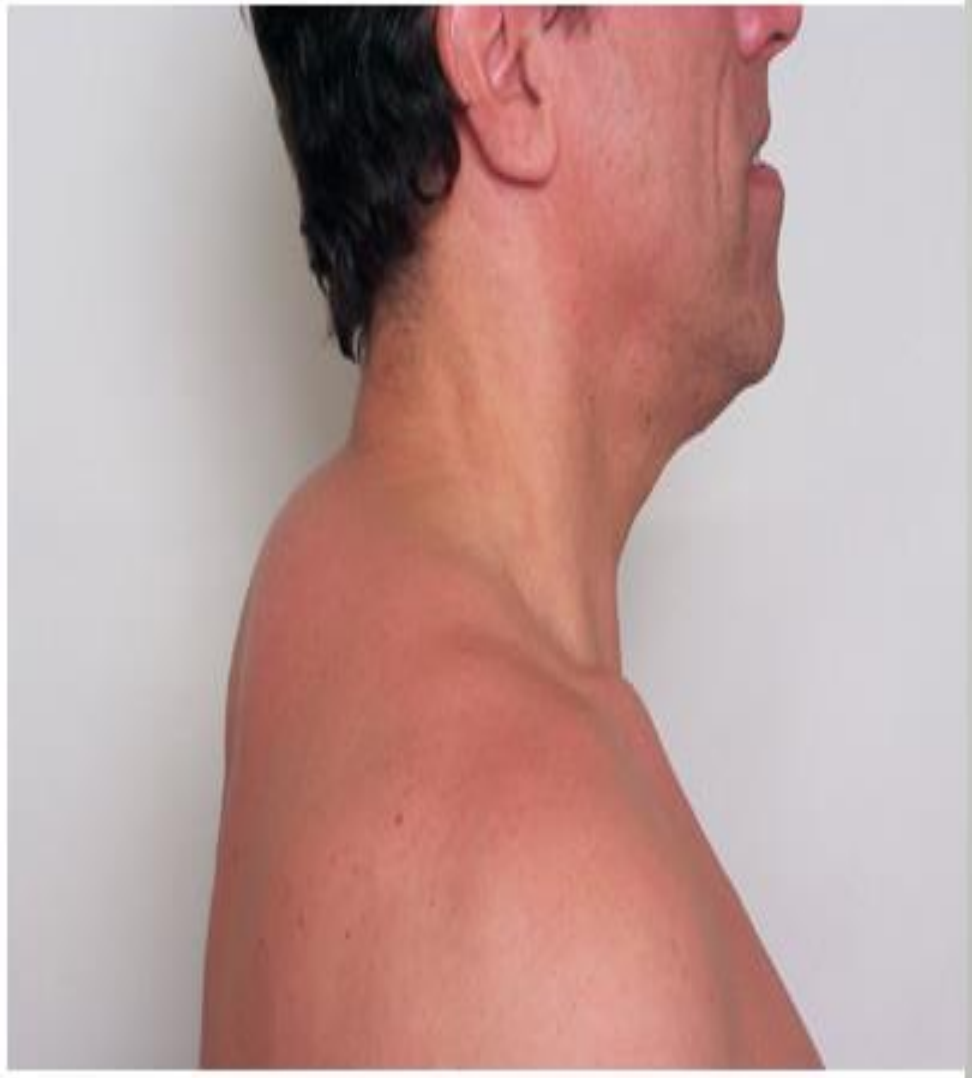
-----***helps shift the metabolic systems of cells from utilization of glucose for energy to utilization of FA in times of starvation or other stresses***.

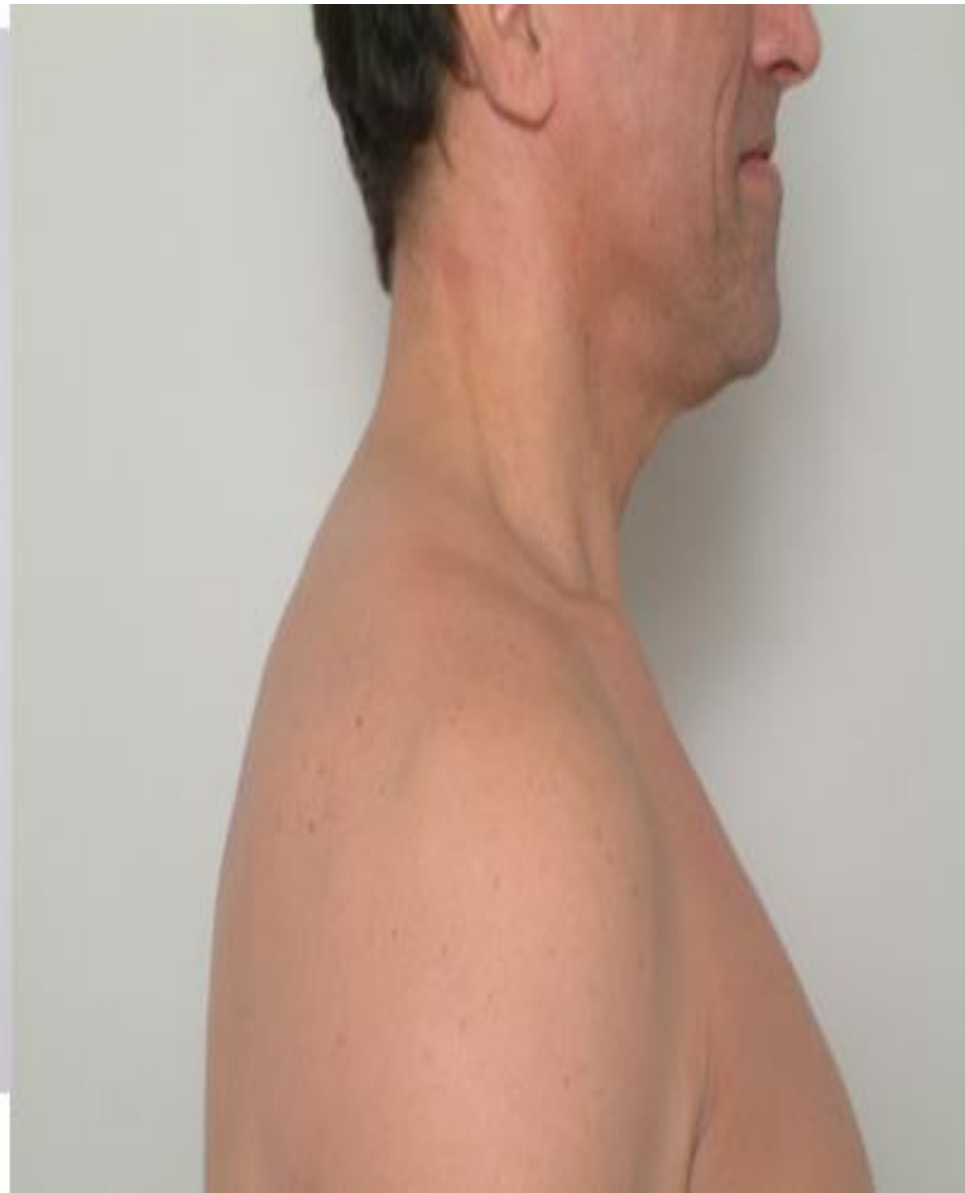
Obesity Caused by Excess Cortisol.

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

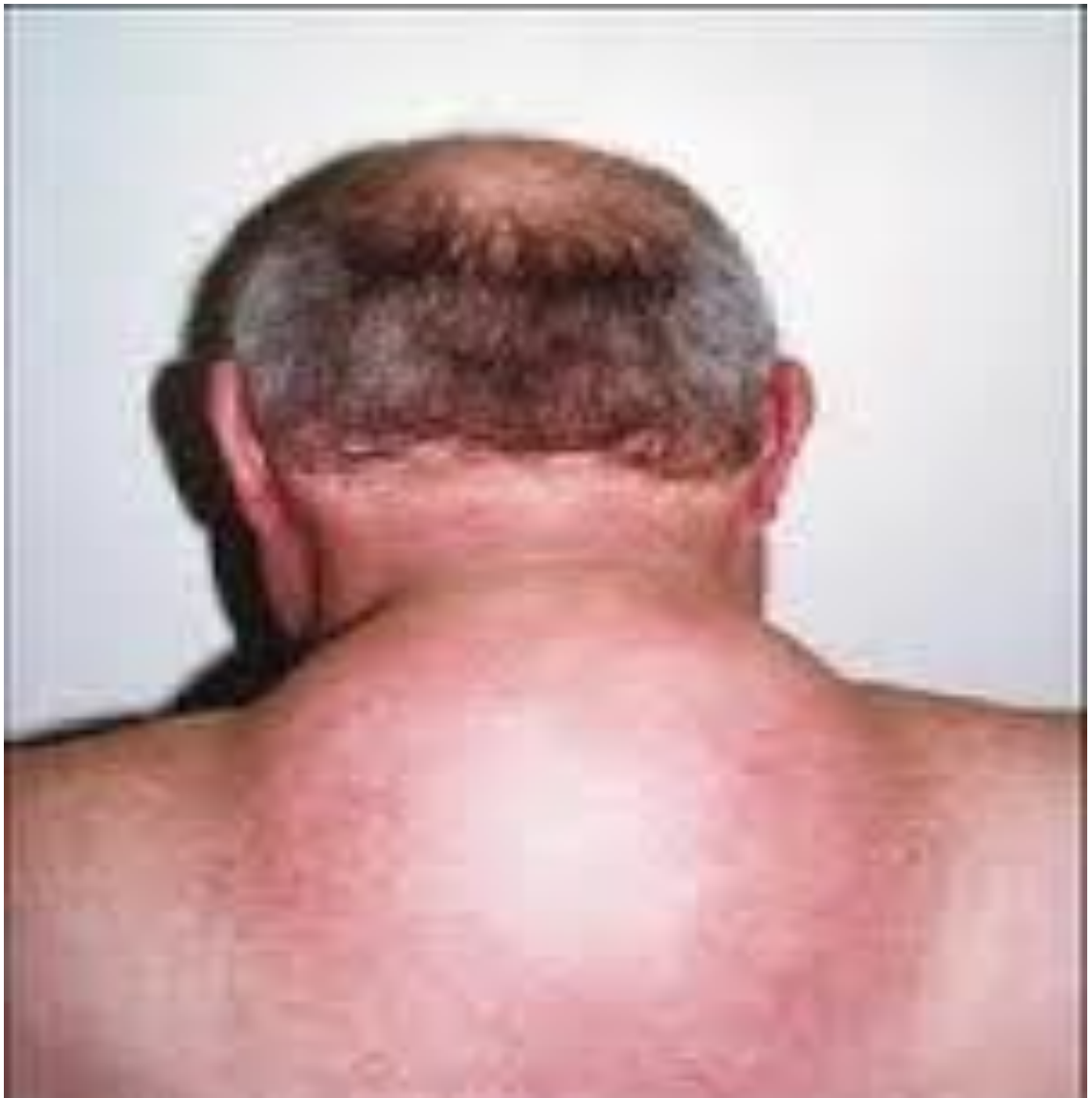
---- cause is unknown, it has been suggested that this obesity results from excess stimulation of food intake, with fat being generated in some tissues of body more rapidly than it is mobilized & oxidized.

buffalo-hump





buffalo-hump



Resisting Stress & Inflammation

Almost any type of stress, causes an immediate ⇧ in ACTH, followed within min by greatly ⇧ secretion of cortisol.

---different types of stress:

1. Trauma

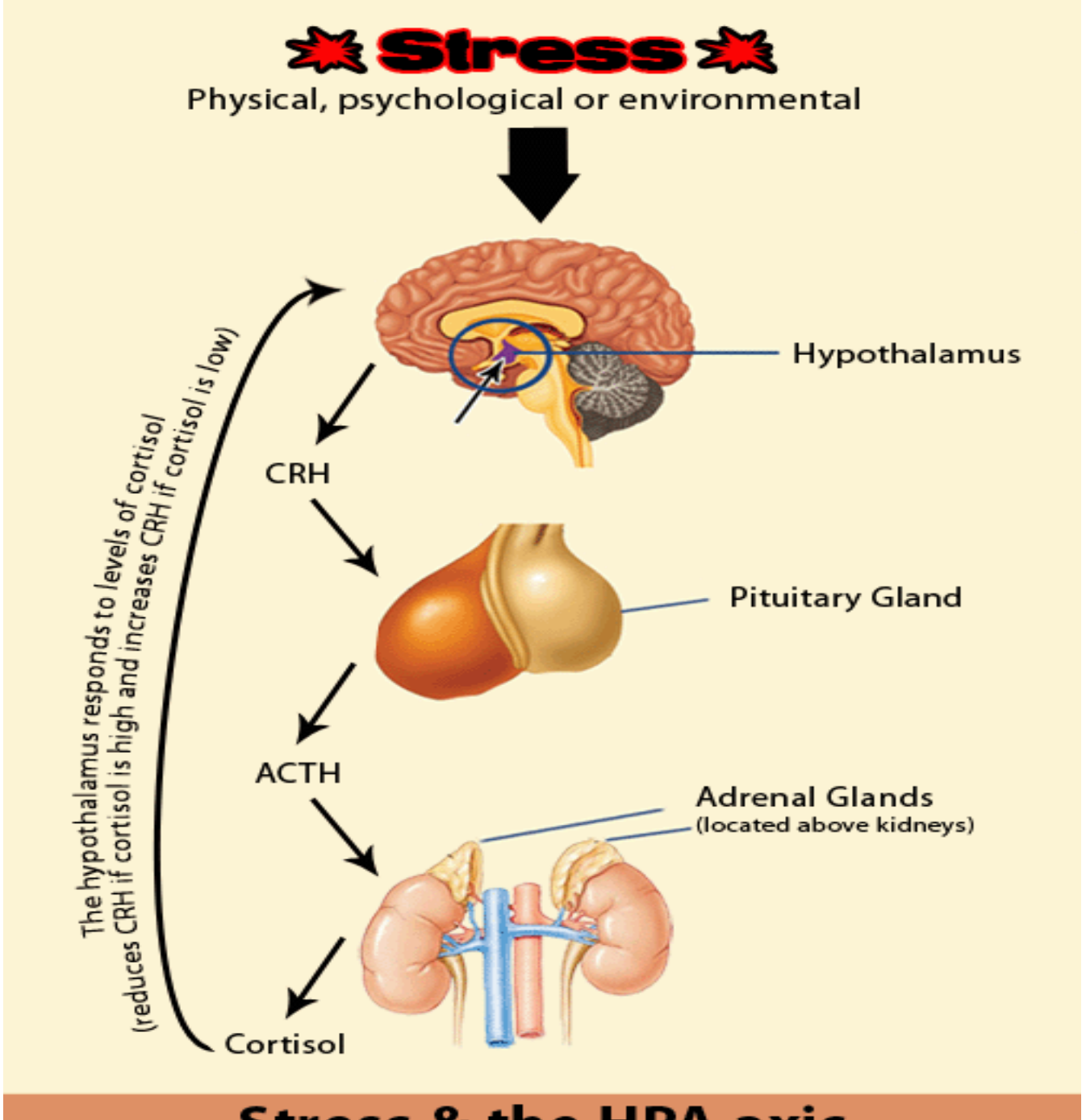
2. Infection

3. Intense heat/cold

4. Injection of norepinephrine/sympathomimetic drugs

5. Surgery

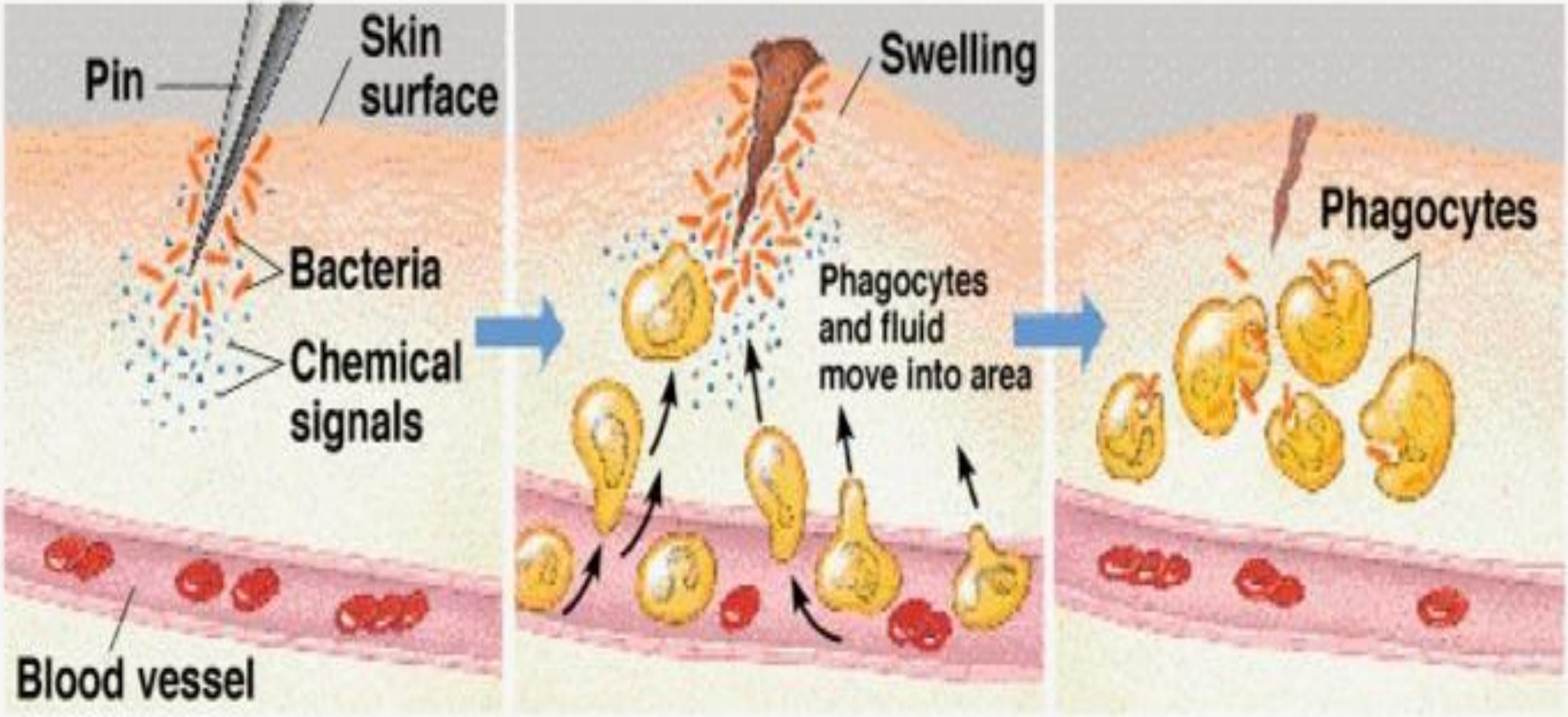
6. Restraining an animal so that it cannot move.



Stress & the HPA axis

Anti-inflammatory Effects of High Levels of Cortisol:-

- When tissues are damaged by trauma, infection, or in other ways, they almost always become “inflamed.”
- In some conditions, such as rheumatoid arthritis, the inflammation is more damaging than the trauma or disease itself.
- The administration of ⇧ amounts of ***cortisol*** can usually block this inflammation or even reverse many of its effects once it has begun.



1. Tissue injury; release of chemical signals such as histamine
2. Dilation and increased leakiness of local blood vessels; migration of phagocytes to the area
3. Phagocytes (macrophages and neutrophils) consume bacteria and cell debris; tissue heals

Cortisol has the following effects in preventing inflammation:

1. ***Cortisol stabilizes the lysosomal membranes***. Therefore, most of the proteolytic enzymes inside lysosomes, are released in greatly ⇩ quantity.

2. Cortisol ⇩ the permeability of the capillaries, *as a secondary effect of the* ⇩ release of proteolytic enzymes.

3. Cortisol ⇩ both migration of WBCs into the inflamed area & phagocytosis of the damaged cells*. These effects probably result from* ⇩ formation of prostaglandins & leukotrienes that otherwise would increase vasodilation, capillary permeability & mobility of WBCs.

4. Cortisol suppresses the immune system*.* The T- lymphocytes are especially suppressed.

⇩ amounts of T cells & Ab in the inflamed area lessen the tissue reactions.

5. Cortisol attenuates fever *mainly because it ⇩ the release of* ***interleukin-1 from the WBCs****, which is the principal excitants to the* hypothalamic temperature control system.

⇩ temp in turn ⇩ the degree of vasodilation.

- ***Thus, cortisol has an almost global effect in reducing all aspects of the inflammatory process.***

Resolution of Inflammation.

Even after inflammation has become well established, administration of cortisol can reduce it within hours to a few days.

The immediate effect is to block most of the factors that are promoting the inflammation.

In addition, the rate of healing is enhanced---this results from:

--- mobilization of AA & use of these to repair the damaged tissues;

--- ⇧glucogenesis---makes extra glucose available in critical metabolic systems;

--- ⇧ amounts of FA available for cellular energy;

--- effects of cortisol---inactivating/removing inflammatory products.

***Blocks Inflammatory Response to Allergic Reactions*.**

The basic allergic reaction between Ag & Ab is not affected by cortisol, & some of the secondary effects of the allergic reaction still occur.

Because the inflammatory response is responsible for the serious & sometimes lethal effects of allergic reactions, administration of cortisol, followed by its effect in reducing inflammation/release of inflammatory products, can be lifesaving.

--e.g. cortisol effectively prevents shock or death in anaphylaxis.


Increase
blood sugar
Suppress the
immune system
Heightened memory
and attention
Cortisol
Decrease
serotonin
Increase in
blood pressure
Decrease
sensitivity to pain

BLOOD CELLS & IMMUNITY:

Cortisol ⇩ the no. of eosinophils & lymphocytes.

cortisol causes atrophy of all the lymphoid tissue throughout the body, which in turn ⇩ the output of both T cells & Ab from lymphoid tissue.

As a result, the level of immunity is ⇩.

It makes them useful drugs in preventing immunological rejection of transplanted hearts, kidneys & other tissues.

- Circadian rhythm of glucocorticoid secretion

  ?

Synthesis/Secretion of ACTH in Association with MSH, Lipotropin & Endorphin.

When ACTH is secreted by the anterior pituitary, several other hormones that have similar chemical structures are secreted simultaneously.

Reason is that the gene that is transcribed to form the RNA molecule that causes ACTH synthesis initially causes the formation of a considerably larger preprohormone called ***proopiomelanocortin (POMC),*** *which is the precursor of ACTH as well* as several other peptides, including *MSH, b-lipotropin, b-endorphin &* a few others.

Under normal conditions, none of these hormones is secreted in enough quantity by the pituitary to have a significant effect on the human body, but when the rate of secretion of ACTH is ⇧ (Addison's disease), formation of some of the other POMC derived hormones may also be ⇧.

In *melanocytes (located between* dermis and epidermis), MSH stimulates formation of ***melanin*** *& disperses* it to the epidermis

ACTH, because it contains an MSH sequence, has about 1/30 as much melanocyte-stimulating effect as MSH.

The quantities of pure MSH secreted in the human being are extremely small, whereas those of ACTH are large, it is likely that ACTH normally is more imp than MSH in determining the amount of melanin in skin.

Abnormalities of Adrenocortical Secretion

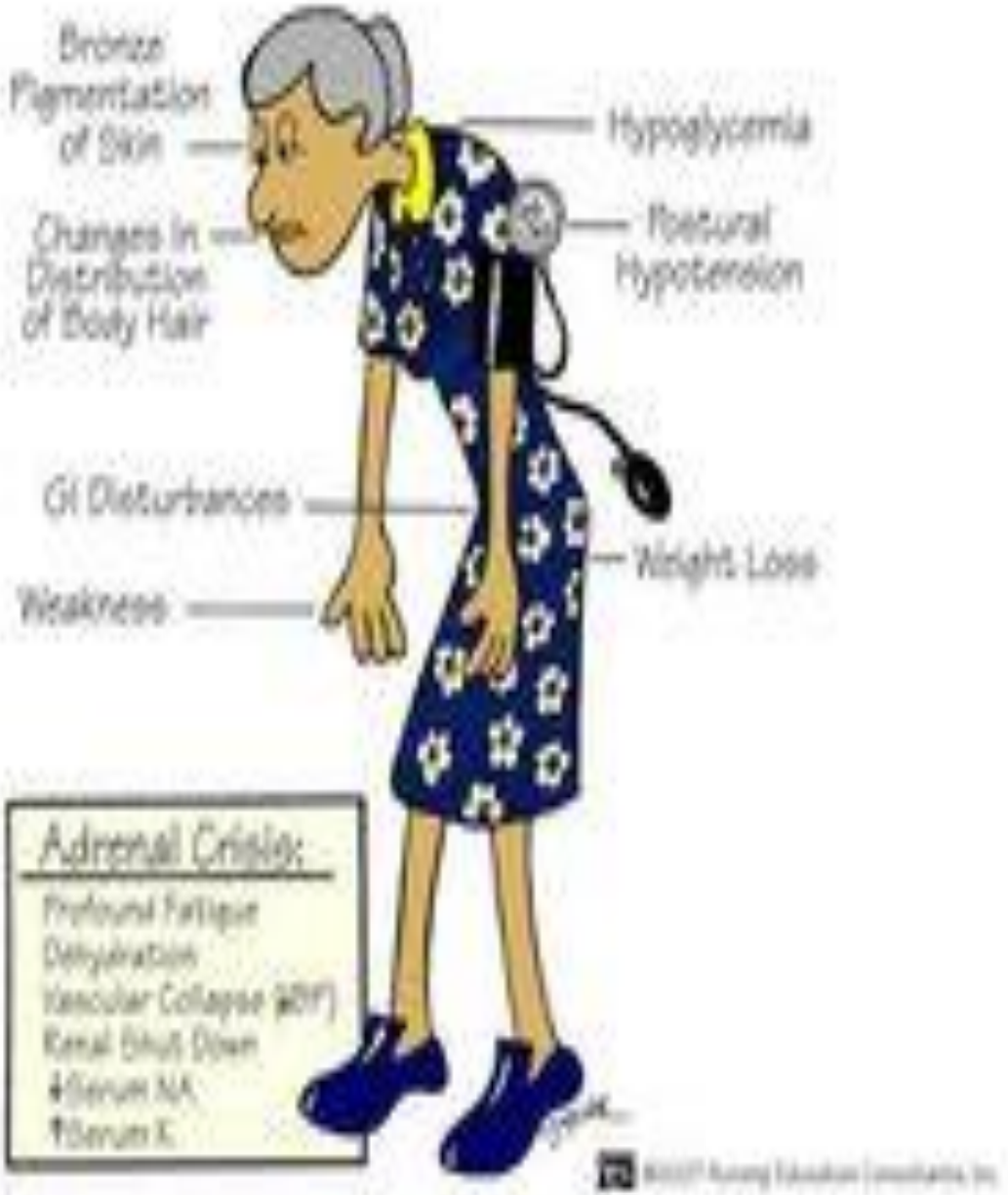
Hypoadrenalism-Addison's Disease

Addison's disease results from failure of the adrenal cortices to produce adrenocortical hormones & this in turn is most frequently caused by ***primary atrophy*** *of* the adrenal cortices.

In 80% of cases, its caused by ***autoimmunity***.

Adrenal gland hypofunction is also frequently caused by **tuberculous** destruction of the adrenal glands or invasion of the adrenal cortices by **cancer**.

ADDISON'S DISEASE



***Glucocorticoid Deficiency*.**

Loss of cortisol secretion makes it impossible for a person with Addison's disease to maintain normal blood glucose concentration between meals because he/she cannot synthesize significant quantities of glucose by gluconeogenesis.

Lack of cortisol reduces mobilization of both proteins & fats from tissues, thereby ⇩ many other metabolic functions of body.

--- muscles are weak.

--- is highly susceptible to the deteriorating effects of different types of stress, & even a mild respiratory infection can cause death.

Melanin Pigmentation

- When cortisol secretion is ⇩, the normal negative feedback to the hypothalamus & anterior pituitary gland is also ⇩,

--- rates of ACTH, as well as simultaneous MSH secretion is ⇧.

- The tremendous amounts of ACTH cause most of the pigmenting effect.

Treatment of People with Addison's Disease

---small quantities of mineralocorticoids & glucocorticoids are administered daily.

- ***Addisonian Crisis---***whenever different types of trauma, disease, or other stresses, such as surgical operations, supervene, a person is likely to have an acute need for excessive amounts of glucocorticoids & often must be given 10 or more times the normal quantities of glucocorticoids to prevent death.

This critical need for extra glucocorticoids & the associated severe debility in times of stress is called an addisonian crisis

Hyperadrenalism-Cushing's Syndrome

Hypercortisolism can occur from multiple causes, including

(1) **adenomas of anterior pituitary** that secrete large amounts of ACTH, which then causes adrenal hyperplasia & excess cortisol secretion;

(2) **abnormal function of hypothalamus** that causes high levels of CRH, which stimulates excess ACTH release;

CONT----------

(3) "**ectopic secretion**" of ACTH by a tumor elsewhere in body, such as an abdominal Ca; &

(4) **adenomas of the adrenal cortex**.

When Cushing's syndrome is secondary to excess secretion of ACTH by the anterior pituitary, this is referred to as Cushing's disease.

- Excess ACTH secretion is the most common cause of Cushing's syndrome & is characterized by high plasma levels of ACTH as well as cortisol.
- Primary overproduction of cortisol by the adrenal glands accounts for about 20 – 25% of clinical cases of Cushing's syndrome & is usually associated with reduced ACTH levels due to cortisol feedback inhibition of ACTH secretion by the anterior pituitary gland.
- Cushing's syndrome can also 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.

- A special characteristic of Cushing's syndrome is mobilization of fat from the lower part of the body, with concomitant extra deposition of fat in the thoracic & upper abdominal regions, giving rise to a ***buffalo torso***.
- The excess secretion of steroids also leads to an edematous appearance of the face ***(moon face)***, & the androgenic potency of some of the hormones sometimes causes ***acne*** & ***hirsutism***
- About 80% of patients have ***hypertension***, presumably because of the slight mineralocorticoid effects of cortisol.

CUSHING'S SYNDROME

Effects on Carbohydrate & Protein Metabolism.

The abundance of cortisol secreted in Cushing's syndrome can cause ⇧ blood glucose concentration, sometimes to values as high as 200 mg/dl after meals-as much as twice normal.

This results mainly from enhanced gluconeogenesis & ⇩ glucose utilization by the tissues.

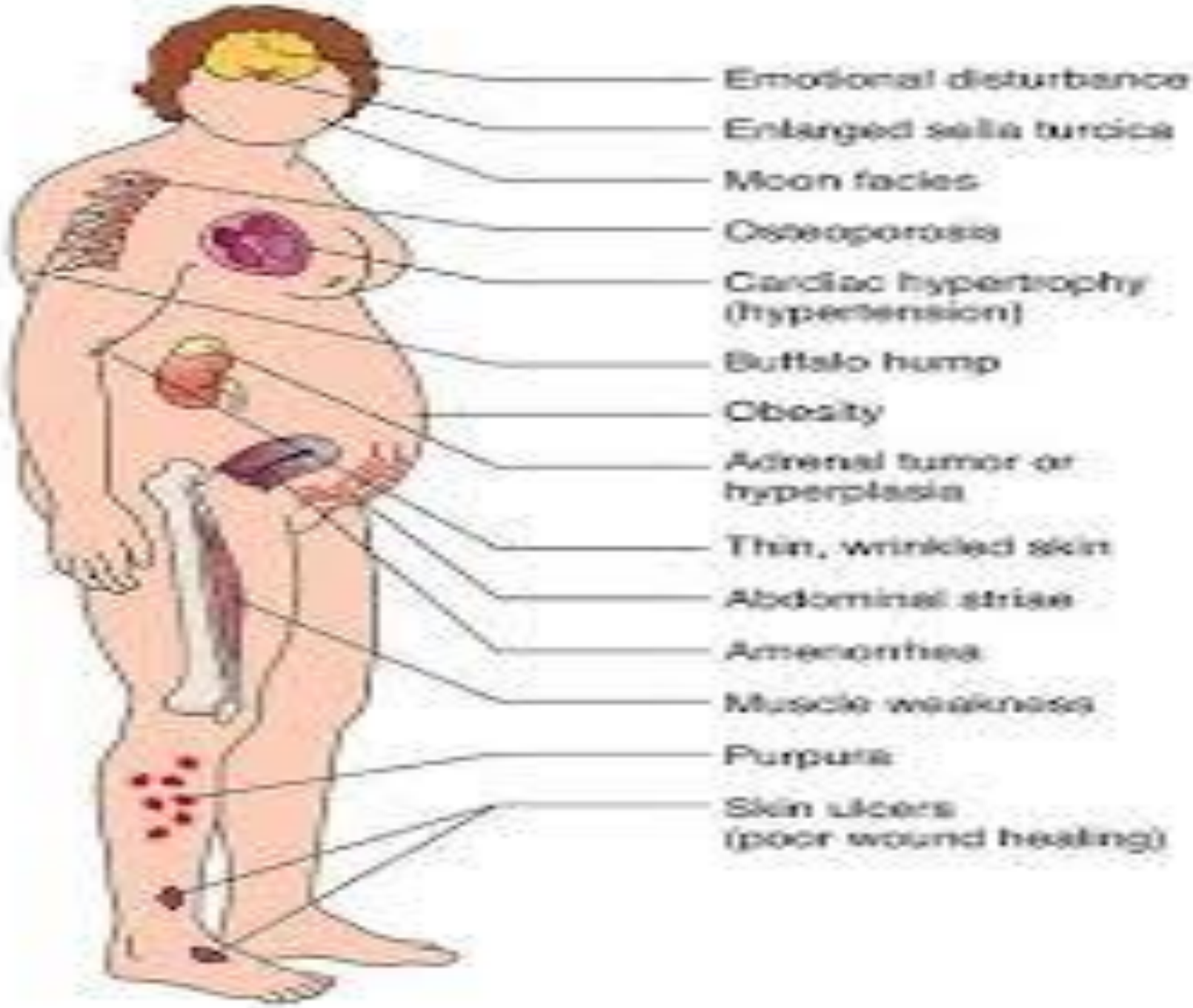
The effects of glucocorticoids on protein catabolism are often profound in Cushing's syndrome, causing greatly ⇩ tissue proteins almost everywhere in body with the exception of liver; the plasma proteins also remain unaffected.

The loss of protein from the muscles in particular causes severe weakness.

The loss of protein synthesis in the lymphoid tissues leads to a suppressed immune system, so that many of these patients die of infections.

Even the protein collagen fibers in the subcutaneous tissue are ⇩ so that the subcutaneous tissues tear easily, resulting in development of large *purplish striae where they have torn* apart.

In addition, severely ⇩ protein deposition in the bones often causes severe *osteoporosis with* consequent weakness of the bones.


Emotional disturbance
Enlarged sella turcica
Moon facies
Osteoporosis
Cardiac hypertrophy (hypertension)
Buffalo hump
Obesity
Adrenal tumor or hyperplasia
Thin, wrinkled skin
Abdominal striae
Amenorrhea
Muscle weakness
Purpura
Skin ulcers (poor wound healing)

***Treatment of Cushing's Syndrome*.**

------ consists of removing an adrenal tumor if this is the cause or decreasing the secretion of ACTH, if this is possible.

Hypertrophied pituitary glands or even small tumors in the pituitary that oversecrete ACTH can sometimes be surgically removed or destroyed by radiation.

Cont……

----Drugs that block steroidogenesis, such as *metyrapone, ketoconazole,* & *aminoglutethimide, or* that inhibit ACTH secretion, such as *serotonin antagonists* & *GABA-transaminase inhibitors, can also be* used when surgery is not feasible.

If ACTH secretion cannot easily be ⇩, the only satisfactory treatment is usually bilateral partial (or even total) adrenalectomy, followed by administration of adrenal steroids to make up for any insufficiency that develops.