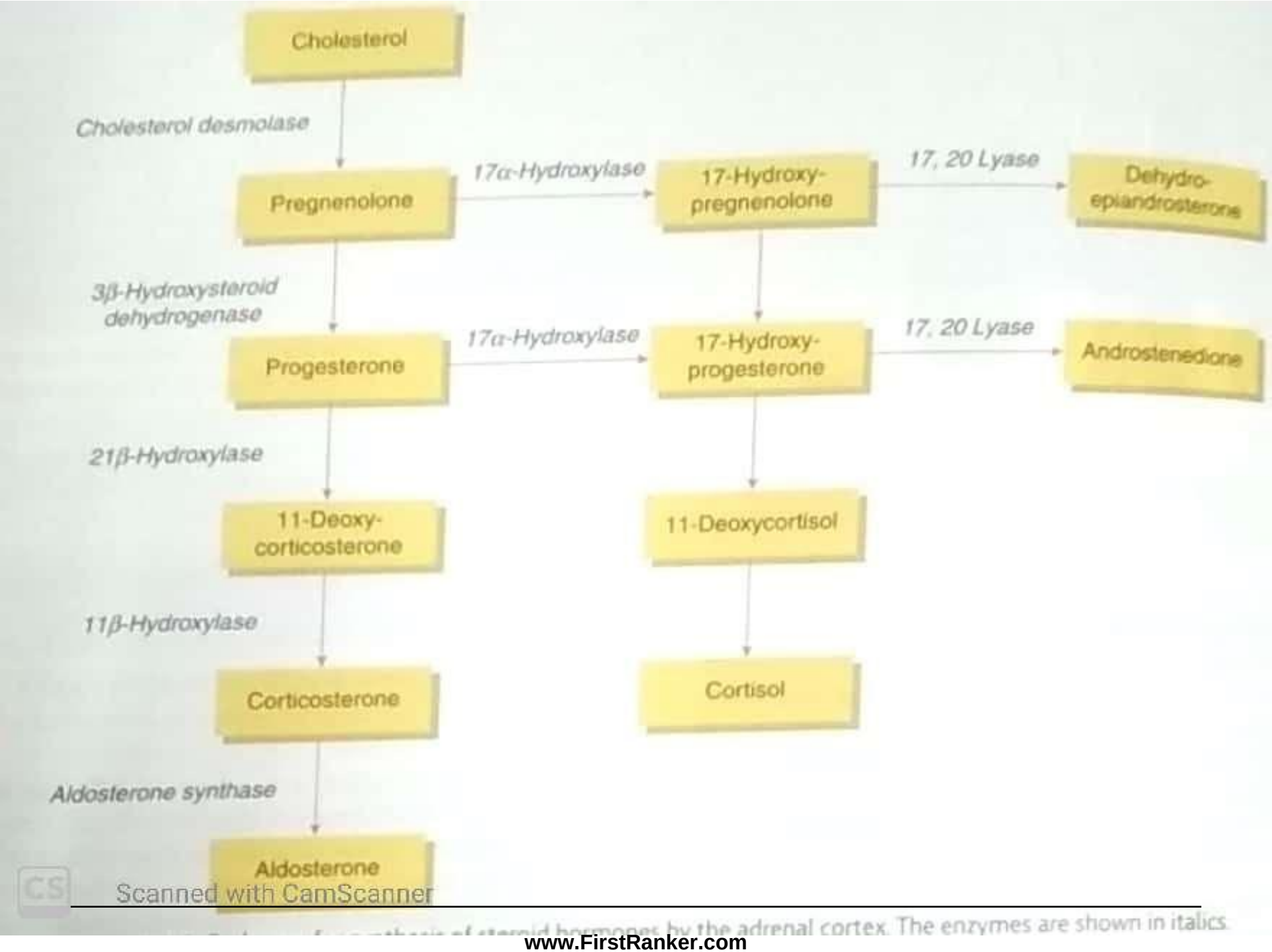
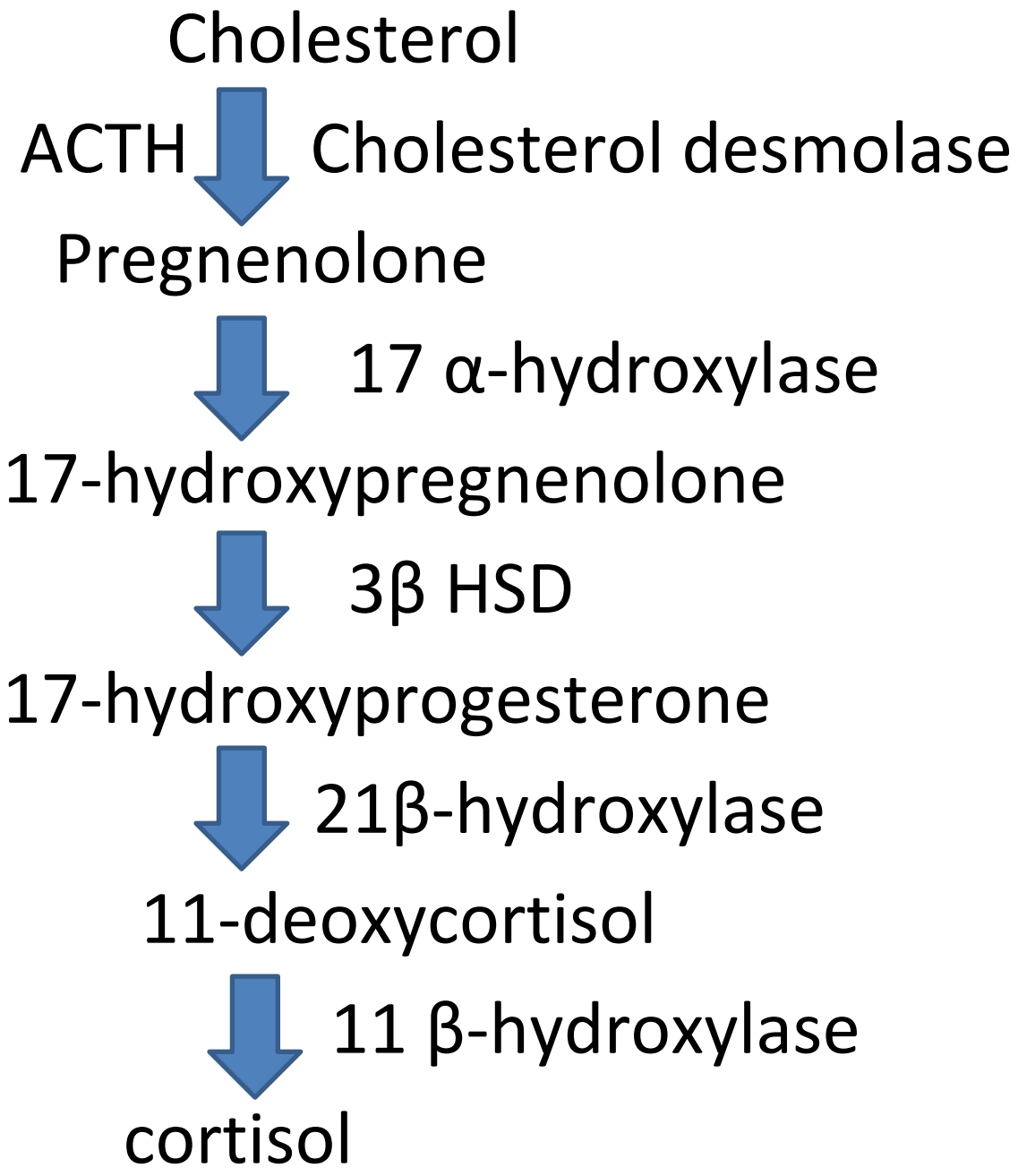
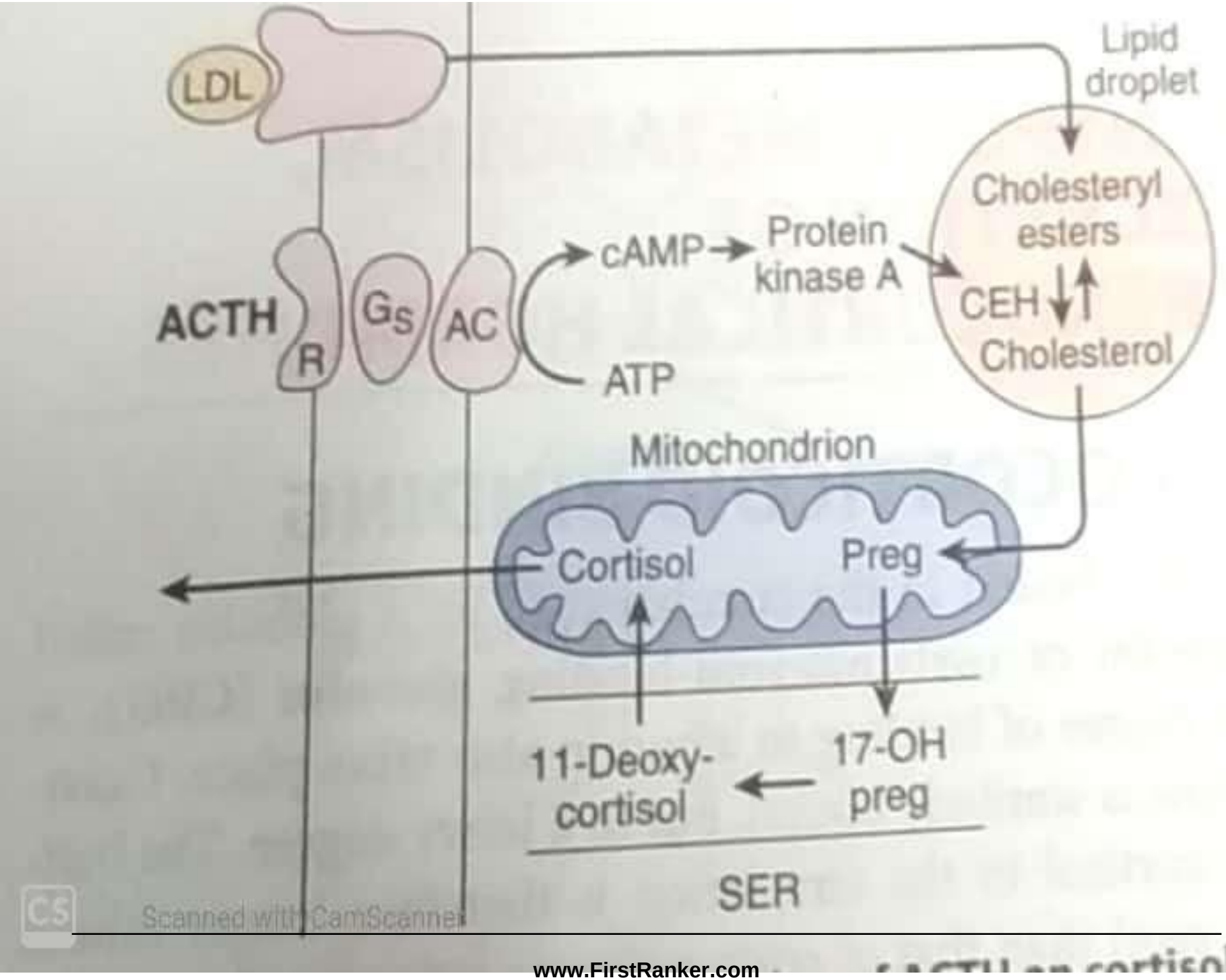
Glucocorticoids

1. Cortisol accounts for 95% of all glucocorticoid activity, very potent.
2. Corticosterone about 4% , less potent .
3. Cortisone almost as potent as cortisol
4. Prednisone (synthetic, 4 times as potent as cortisol)
5. Methylprednisone (synthetic, 5 times as potent as cortisol)
6. Dexamethasone (synthetic, 30 times as potent as cortisol)



the adrenal cortex. The enzymes are shown in italics





Transport of Glucocorticoids

- Cortisol is bound in the circulation to an α globulin called **transcortin/CBG, minor degree to albumin.**
- Half life is 30-60 min that of corticosterone is 50min
- Bound steroids are physiologically inactive.
- CBG is synthesized in liver ,**production ↑ed by estrogen** ,&↓es in cirrhosis and nephrosis .

Interrelationship of free & bound form

- **Why pregnant women have high plasma cortisol level without symptoms of glucocorticoid excess**?
- Why some patients of nephrosis have low total plasma cortisol without symptoms of glucocorticoid deficiency ?

Metabolism & Excretion of Glucocorticoids

- Principal site of glucocorticoid catabolism is **liver.**
- They are **conjugated to glucuronic acid** and lesser extent to sulfates.
- About 25% of these conjugates are excreted in the bile and then in the feces and remaining excreted in the urine.

Degradation of cortisol

Cortisol

Dihydrocortisol

Tetrahydrocortisol

Tetrahydrocortisol glucuronide

Excretion in urine

Mechanism of cortisol action

- Glucocorticoids bind with receptor to form hormone receptor complex which activate DNA to form mRNA.
- mRNA causes synthesis of proteins which alter cell function.

Physiological effects of Glucocorticoids

- **95% of glucocorticoid activity** of the adrenocortical secretion results from **secretion of cortisol/hydrocortisone.**

Effects of Cortisol on Carbohydrate Metabolism

Stimulation of Gluconeognesis

- ↑es enzymes for gluconeogenesis .
- Mobilisation of amino acids from extrahepatic tissue.
- ↑ed hepatic giycogenesis.
- ↓ed glucose utilization by cells.
- ↑ in blood glucose level.

WHAT IS ADRENAL DIABETES ?

Effects Of Cortisol On Protein & Fat Metabolism

- Reduction in Cellular Protein.
- ↑es Liver and Plasma proteins.
- ↑es blood amino acid levels by mobilising amino acid from non-hepatic tissue.

1. ↑Mobilisation of fatty acids.
2. Typical obesity of excess cortisol

Effect of cortisol on fat metabolism

- Mobilisation of fatty acid : from adipose tissue
  - ↑es the conc. of frs in starvation ee fatty acidsin the plasma
  - Enhances the oxidation fatty acids in cell.

➢ Above two mechanism utilizes fatty acid during starvation or other stresses

On Food Intake and Fat Distribution

- Cortisol ↑es appetite by stimulating neuropeptide Y secretion from hypothalamus.
- It stimulates lipogenesis by activating lipoprotein lipase and G-6-PD activity of adipocytes in some parts of body.
- So cortisol excess leads to maldistribution pf fat.
- Cortisol also ↑es leptin synthesis.

➢ Why cortisol excess leads to truncal obesity, moon face &buffalo hump

Effects on musculoskeletal system

- Cortisol increases performance of cardiac & skeletal muscle.
- The inotropic effect is due to synthesis of Ach at neuromuscular junction .
- However, excess cortisol promotes proteolysis , therefore it decreases muscle mass & strength.

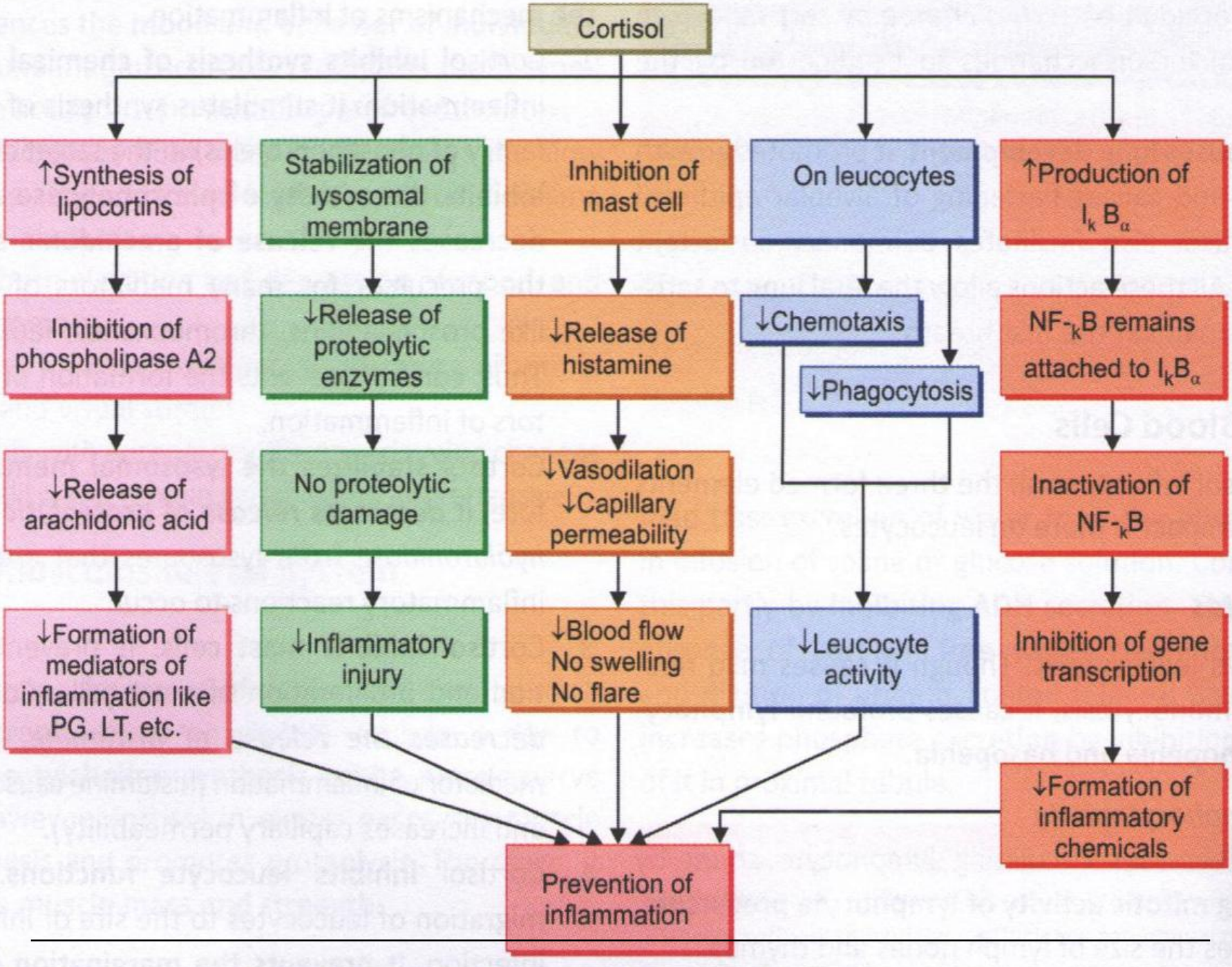
Anti-Inflammatory & Anti- Allergic Effects(On pharmacological dose)

Blocks early stages of Inflammation BY:

- Stabilising Lysosomal Membrane.
- ↓es Permeability of Capillaries.
- ↓es Migration of wbc into inflammed site.
- Suppress immune system :↓T cells
- Attenuates fever by ↓ing IL-1.

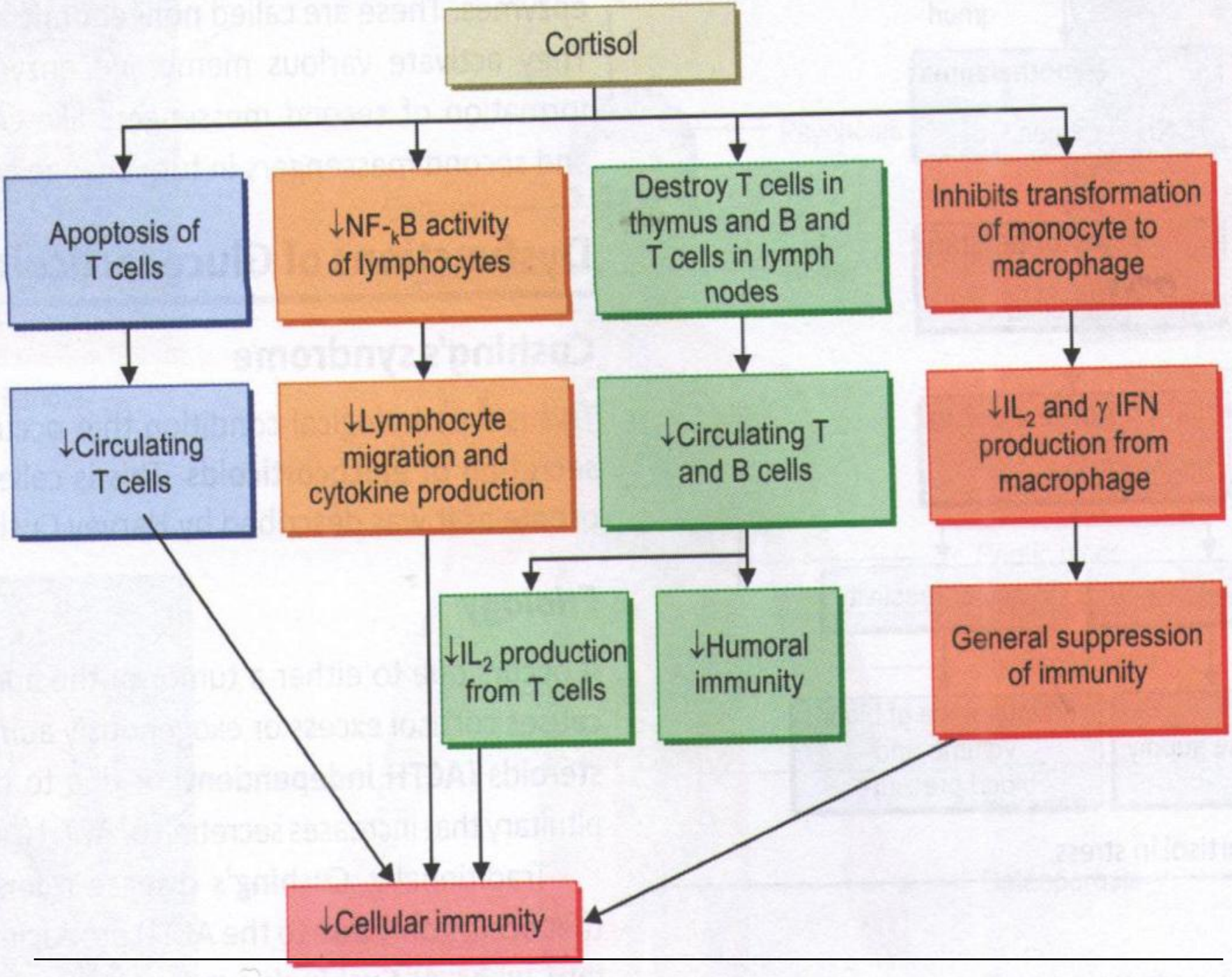
Suppress Allergic Manifestations By ↓ing Release of Histamine by Mast cells & Basophils.

- What is the role of cortisol in shock and anaphylaxis ?
- Why cortisol should be given with antibiotics ?



Effects on blood cells & lymphatic organs

- Glucocorticoid ↓**es** the no. of circulating **eosinophils** by increasing their sequestration in the spleen and lungs
- **Also** lowers no. of **basophils.**
- ↑es no. of neutrophils,platlets and rbcs.
- ↓**es circulating lymphocyte** by inhibiting their mitotic activity and size of lymph node.
- ↓es secretion of cytokines like IL-2.



On bone

- Glucocorticoid **stimulate bone resorbtion** (by stimulating osteoclasts) .
- **Inhibits bone formation** by ↓ing collagen synthesis and **inhibits** conversion of osteoprogenitor cells to osteoblast.
- It ↓es absorbtion of calcium & ↓es synthesis of active vit.D

- So **prolonged use of glucocorticoids** will lead to **osteoporosis**

Effect on nervous system

- Glucocorticoids are essential for normal functioning of nervous system.
- Insufficiency will lead to personality changes like irritability, and lack of concentration.
- Sensitivity to olfaction and taste stimuli increases in adrenal insufficiency.

Effect on Kidney & Water metabolism

- Cortisol ↑**es GFR** so essential for **rapid clearance of water load.**
- It achieves this partly **by inhibiting ADH secretion.**

➢ **Why water intoxication occur when glucose solution is infused in cortisol defcit patients ?**

➢ What is glucose fever ?

On Vascular Response

- Presence of glucocorticoids is essential for constrictor action of adrenaline and nor adrenaline.
- So vascular collapse occurs in adrenal insufficiency.

Other Effects

- Large dose of glucocorticoids inhibits growth ↓es GH secretion, ↓es TSH secretion.
- During fetal life glucocorticoids acclerates maturation of surfactant in the lungs.

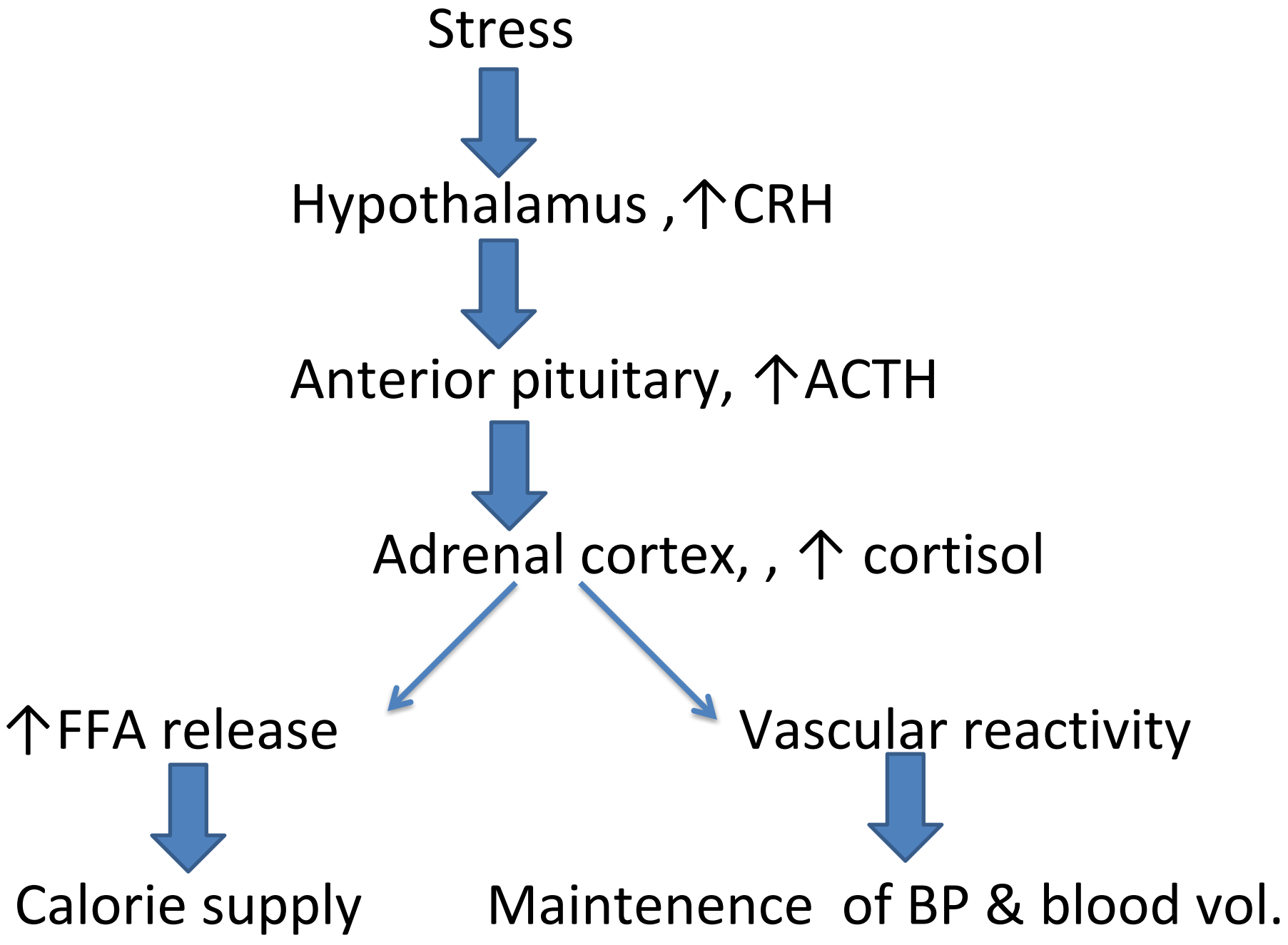
Permissive Action

Requirement of Glucocorticoids For Action Of Other Hormones e.g

- Catecholamines :Lipolytic Effect
  Pressure Response
  Bronchodilatation
- Glucagon & Thyroid hormone-Calorigenic effect

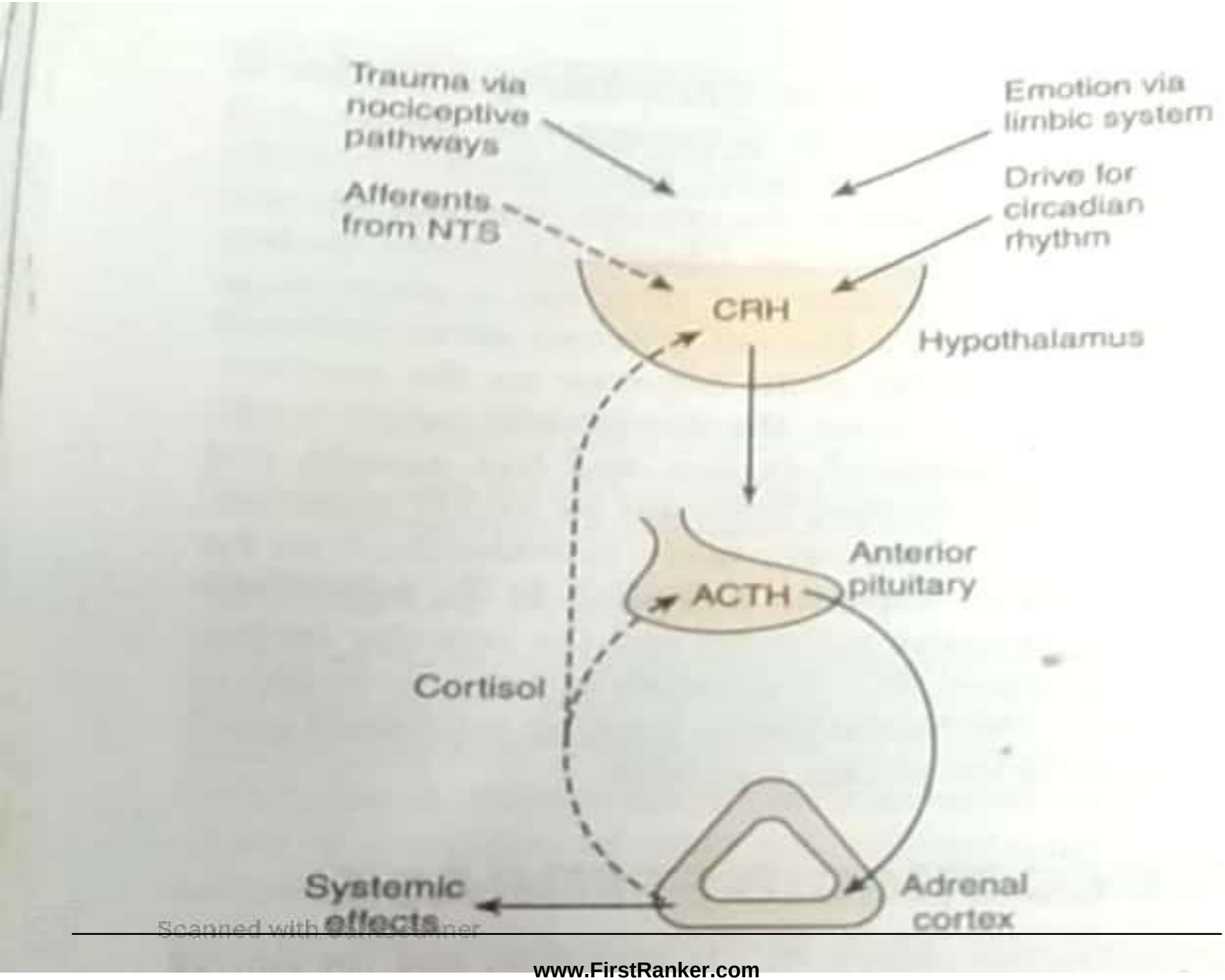
Resistance to stress

- The most important function of of cortisol is to protect the body against stress.
- Stress is defined as any change in the environment that changes an existing optimal steady state.
- Stress activates processes at the molecular, cellular or systemic level that tends to maintain homeostasis.



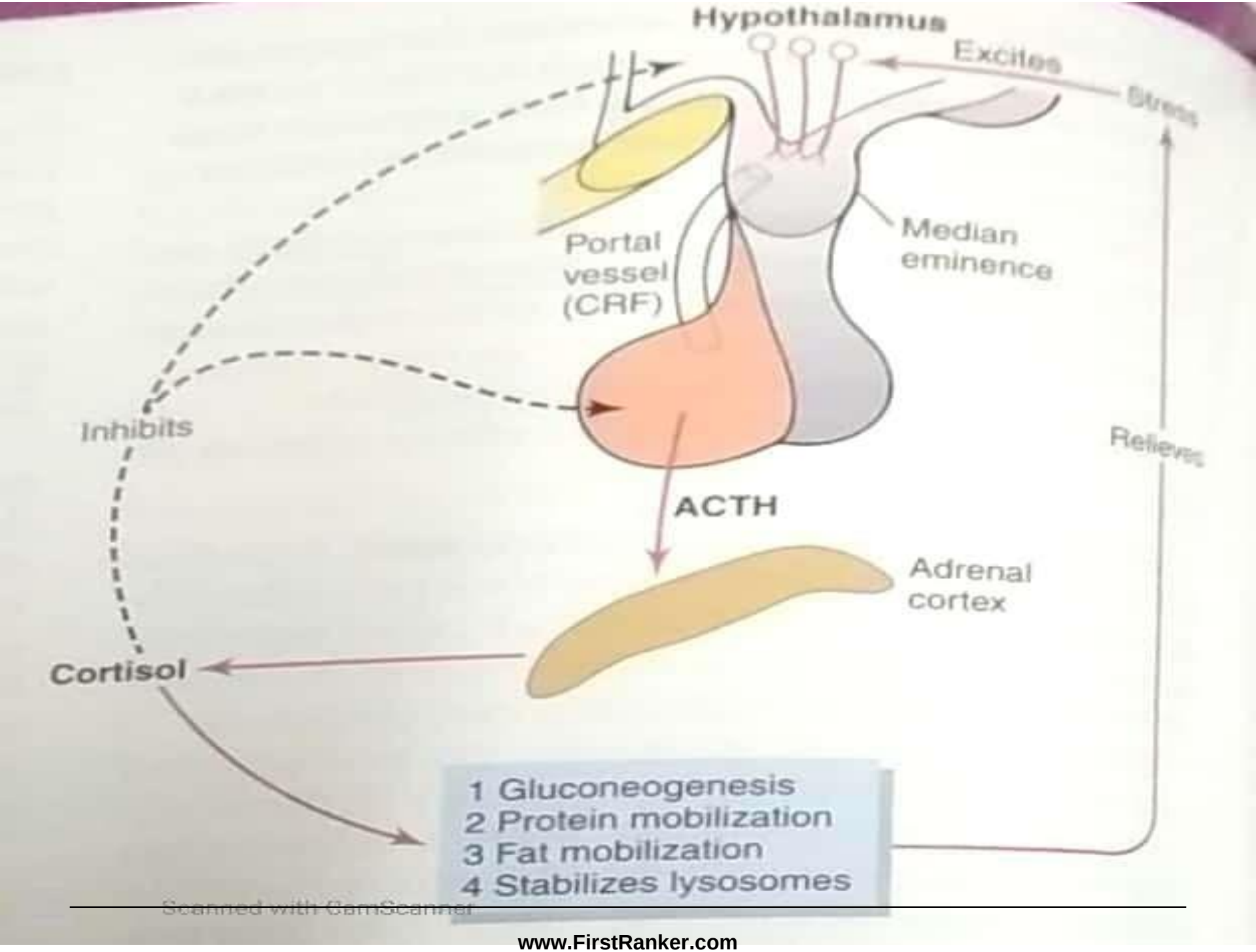
Regulation Of Cortisol Secretion

- ACTH stimulates cortisol secretion by ↑ing cAMP
- ACTH not only produces prompt increase in glucocorticoids but also ↑es the sensitivity of adrenal to subsequent dose of ACTH.



Regulation Of Cortisol by ACTH Hormone From Pituitary Gland

- ACTH stimulates cortisol secretion.
- ACTH activates Adrenocortical cells to produce steroids by ↑ing cAMP.
- Inhibitory effect of cortisol on the Hypothalamus and on the Anterior Pituitary to ↓es ACTH secretion.



ACTH

- ACTH is a single chain polypeptide containing 39 amino acids.
- **It origin** from **proopiomelanocortin (POMC**) in the pitutary.
- **Both basal secretion** of glucocorticoids and **↑ed** secretion provoked by stress **are dependent on ACTH.**
- ACTH is secreted in irregular bursts throughout the day and plasma cortisol tends to rise and fall in response to these bursts.

- In humans ,the **bursts are frequent in early morning,** & 75% between 4a.m and 10a.m.
- Bursts are **least** frequent **in evening**.
- The diurnal ACTH rhythm is located in **suprachiasmatic nuclei** of the hypothalamus.
- Free glucocorticoids inhibits ACTH seretion.
- In chronic adrenal insufficiency the rate of ACTH synthesis is markedly increased.
- Hence steroid therapy should not be abruptly stopped.