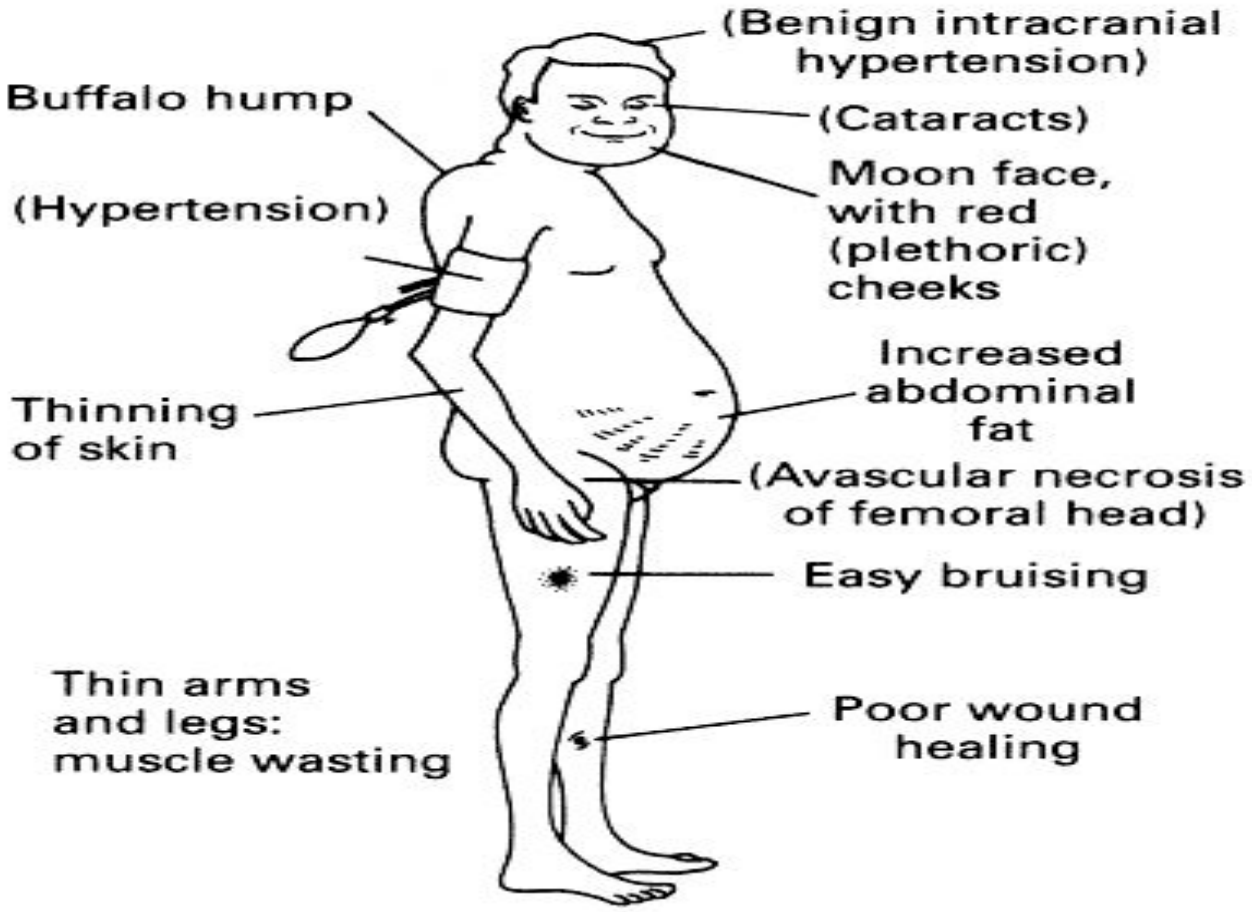
# Corticosteroids

# Steroids: the worst drugs for adverse effects

Euphoria
(though sometimes depression or psychotic symptoms, and emotional lability)




Also:

*Osteoporosis*
Tendency to hyperglycaemia
Negative nitrogen balance
Increased appetite
*Increased susceptibility to infection*
Obesity

# Corticosteroids

- History
- Synthesis
- Pharmacological Actions
- Pharmacokinetics
- Preparations
- Therapeutic principles
- Dosage schedule & Steroid withdrawal
- Uses:
  - Therapeutic
  - Diagnostic
- Adverse reactions
- Contraindications
- Precautions during therapy
- Glucocorticoid antagonists

# History

- 1855 – Addison's disease
- 1856 – Adrenal glands essential for life
- 1930 – Cortex > medulla
- 1932 – Cushing’s syndrome
- 1949 – Hench et al (Steroids in rheumatoid arthritis)
- 1952 – Aldosterone

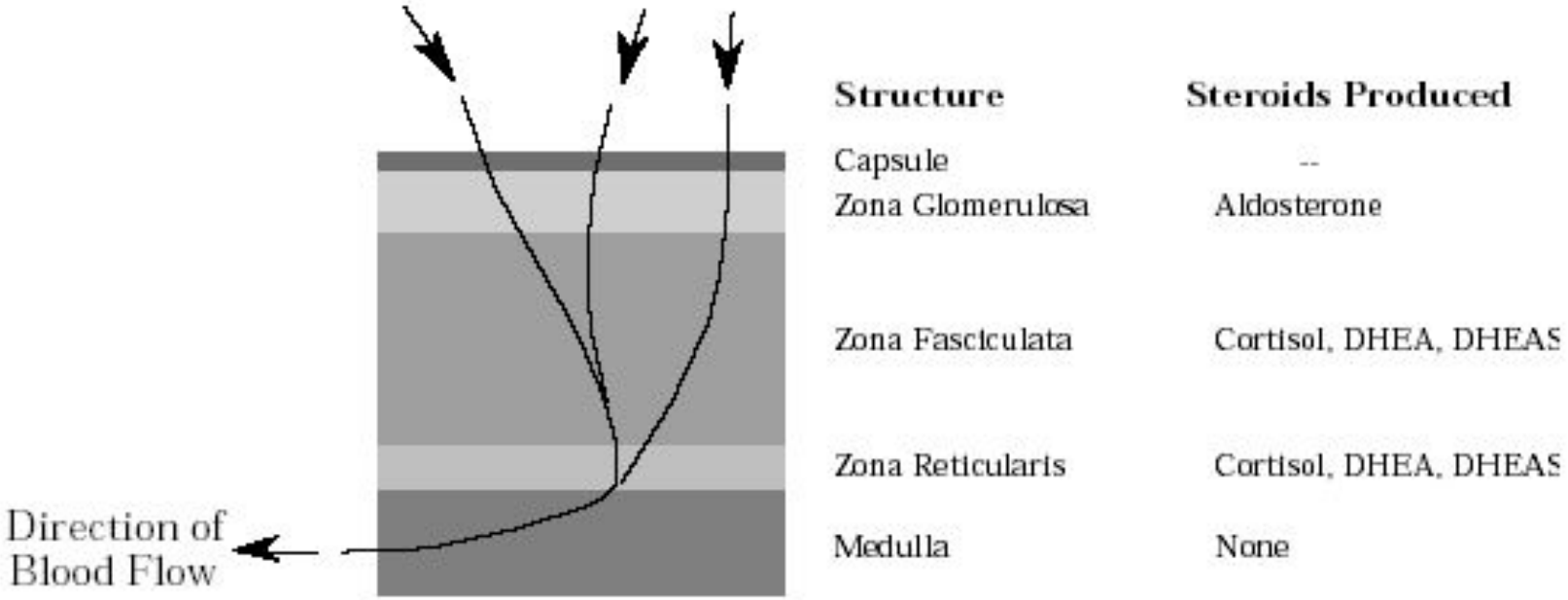
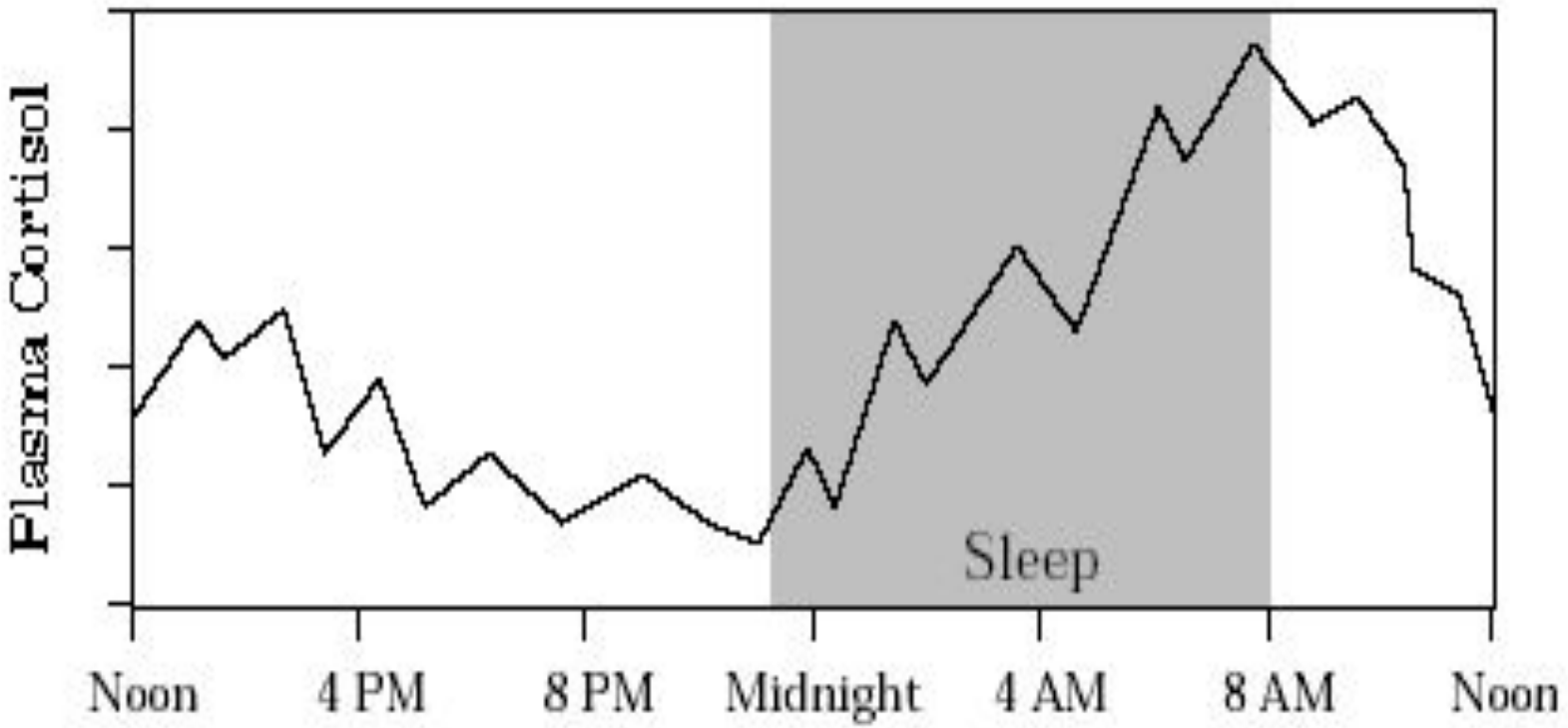
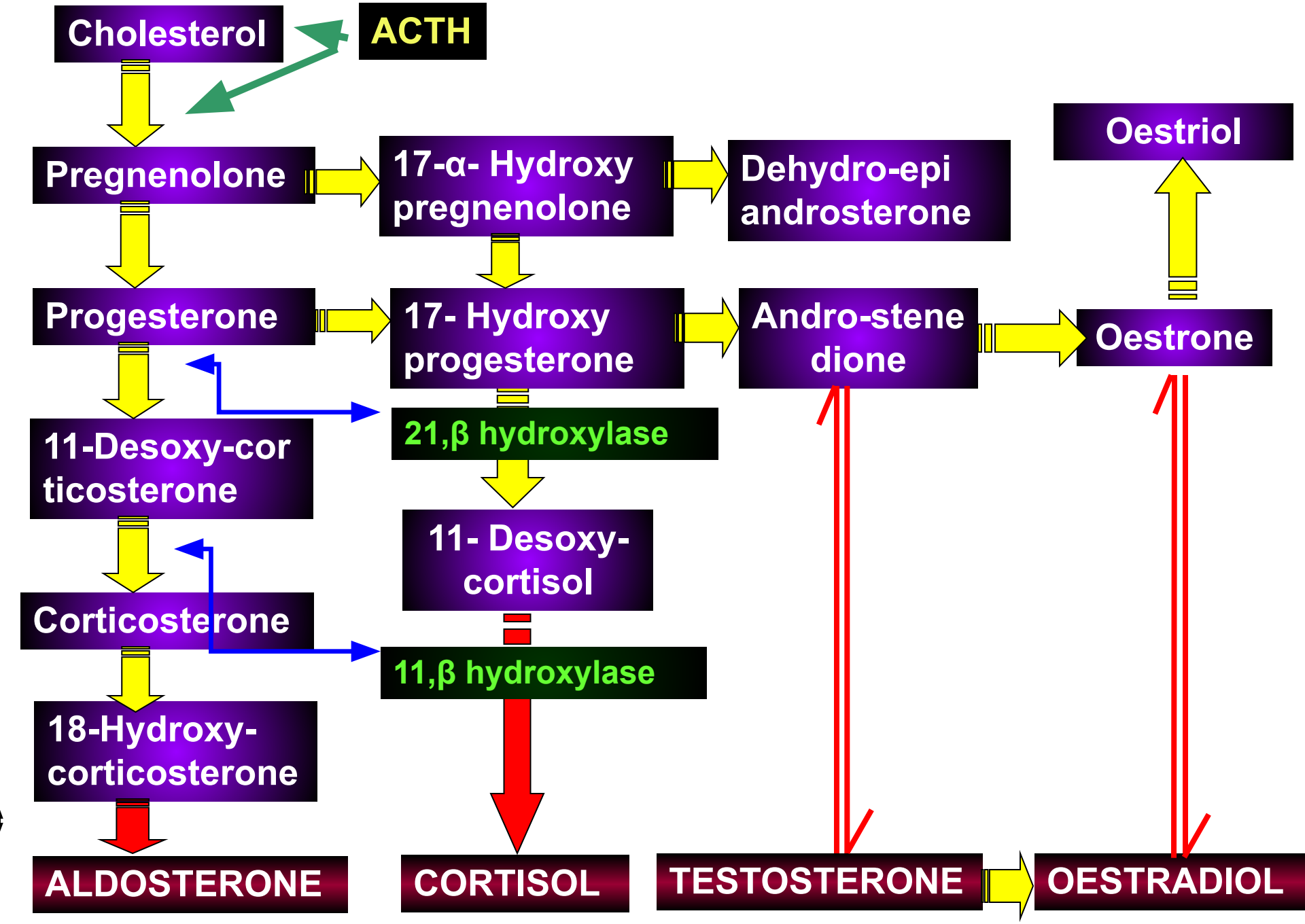



Figure 1. Cartoon of Adrenal Morphology.

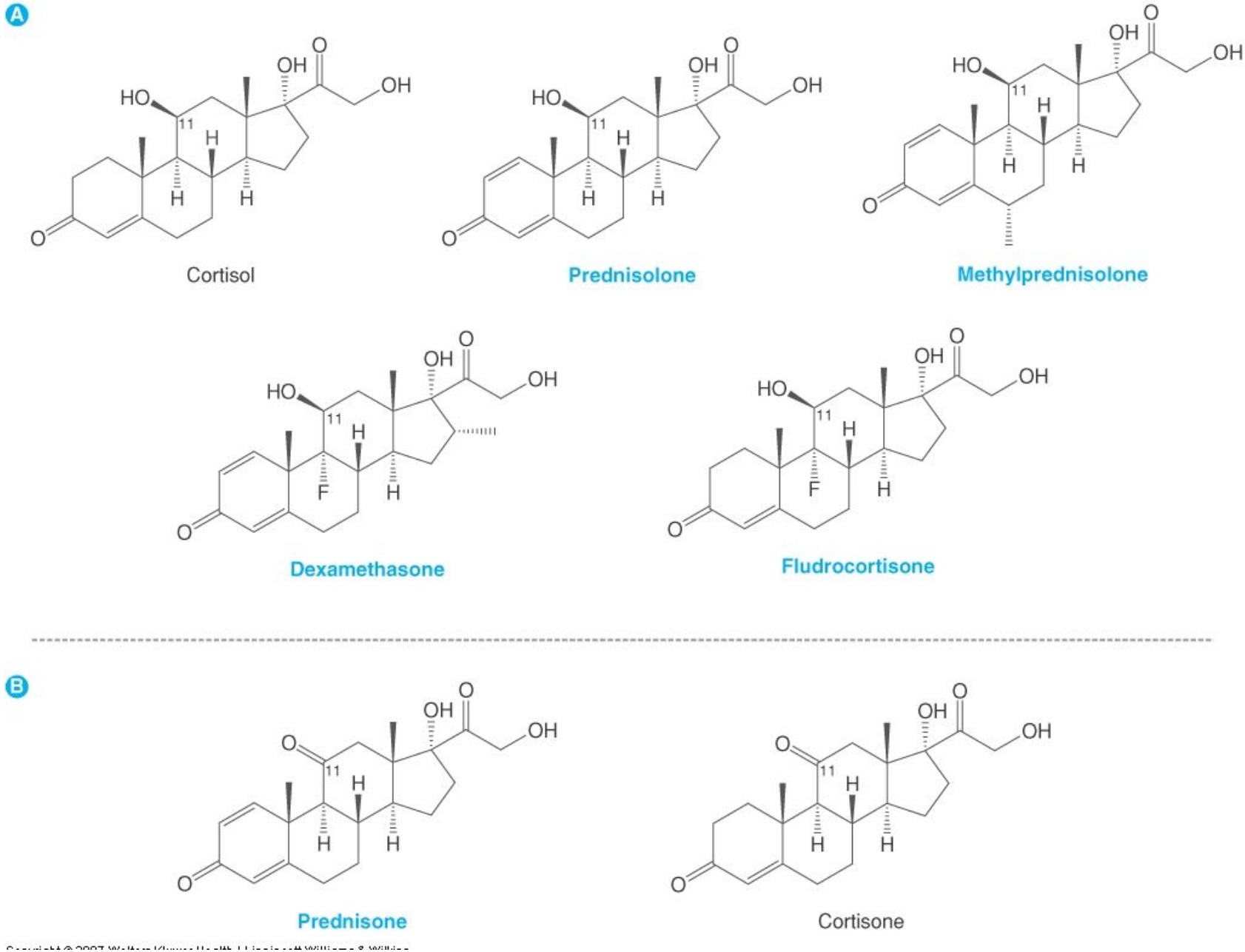

Plasma Cortisol
Sleep
Noon
4 PM
8 PM
Midnight
4 AM
8 AM
Noon

| Basal secretions | | |
|---|---|---|
| **Group** | **Hormone** | **Daily secretions** |
| **Glucocorticoids** | • Cortisol<br>• Corticosterone | 5 – 30 mg<br>2 – 5 mg |
| **Mineralocorticoids** | • Aldosterone<br>• 11- deoxycorticosterone | 5 – 150 µg<br>Trace |
| **Sex Hormones**<br>•Androgen<br>•Progestogen<br>•Oestrogen | <br>• DHEA<br>• Progesterone<br>• Oestradiol | <br>15 – 30 mg<br>0.4 – 0.8 mg<br>Trace |

*From Essential of Pharmacotherapeutics, ed. FSK Barar. P.351*


Cholesterol
ACTH
Pregnenolone
17-α- Hydroxy pregnenolone
Dehydro-epi androsterone
Oestriol
Progesterone
17- Hydroxy progesterone
Andro-stene dione
Oestrone
11-Desoxy-cor ticosterone
21,β hydroxylase
11- Desoxy- cortisol
Corticosterone
11,β hydroxylase
18-Hydroxy- corticosterone
ALDOSTERONE
CORTISOL
TESTOSTERONE
OESTRADIOL

# Glucocorticoid Analogues



# Pharmacological Actions

- Direct (Intended) Actions

  Anti-inflammatory

  Anti-allergy

  Anti-immunity

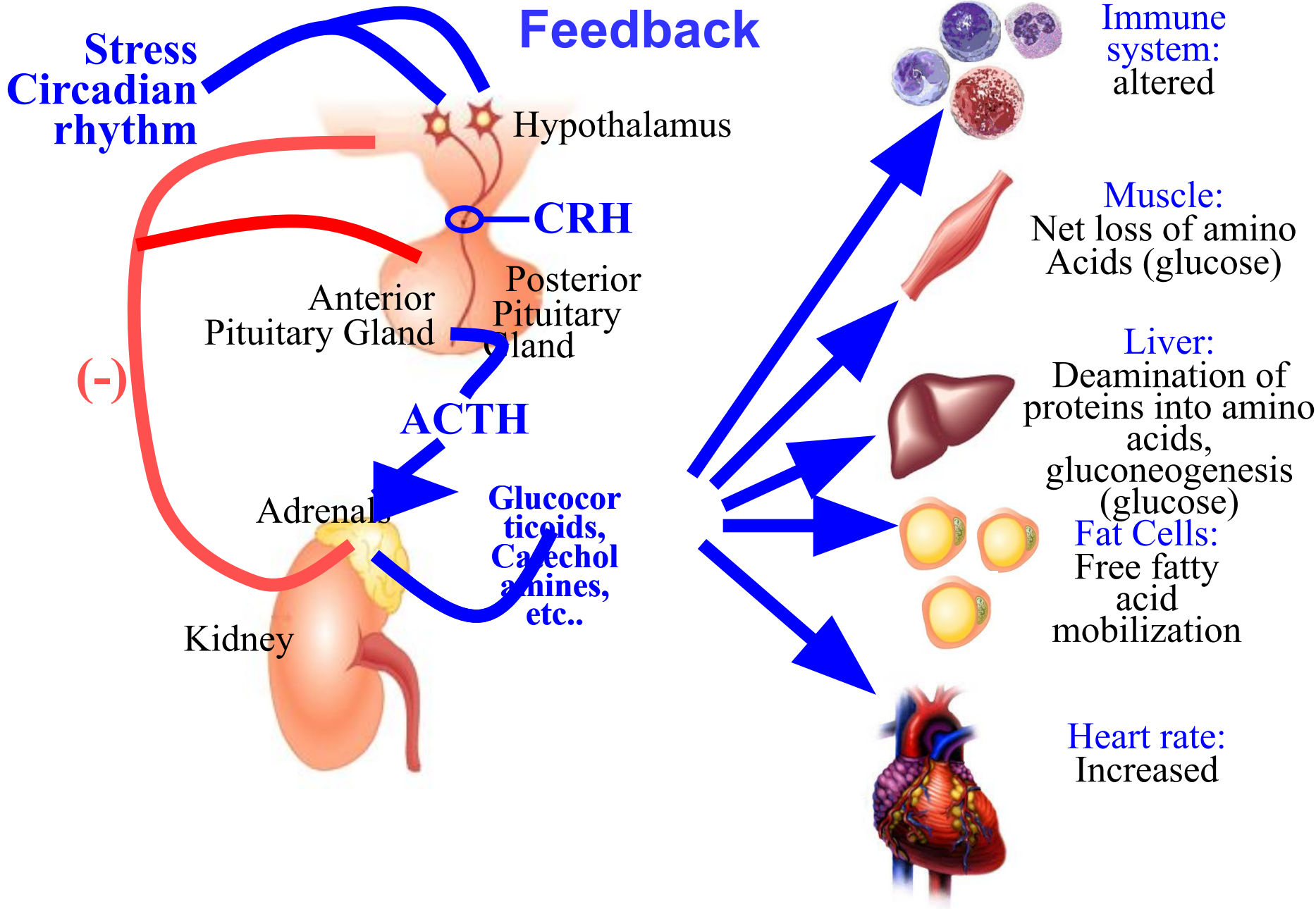
- Permissive Actions
  - Lipolytic effects
  - Effect on bp
  - Effect on bronchial muscles
  - *(e.g.,*sympathomimetic amine*)*

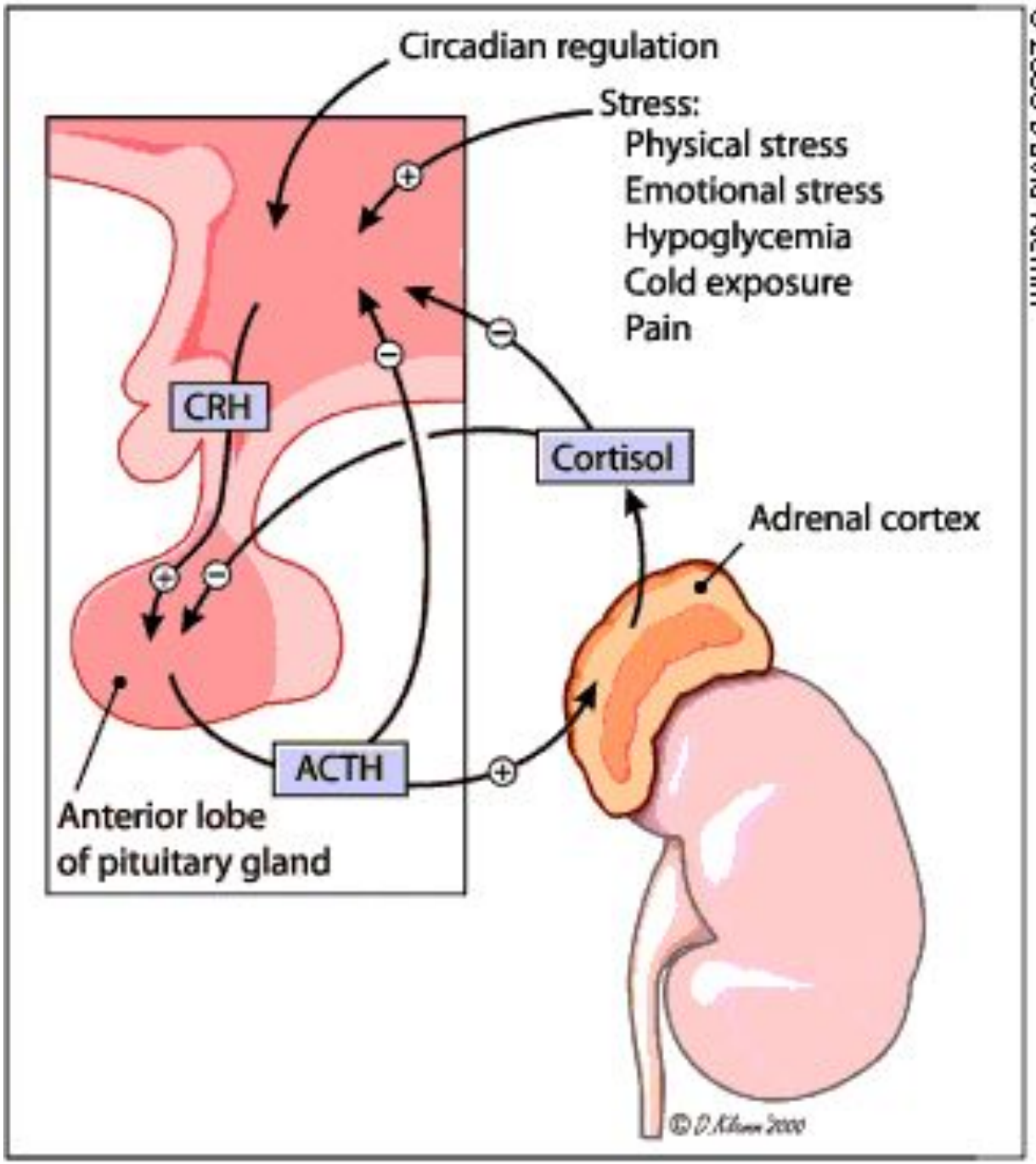
# Pharmacological Actions

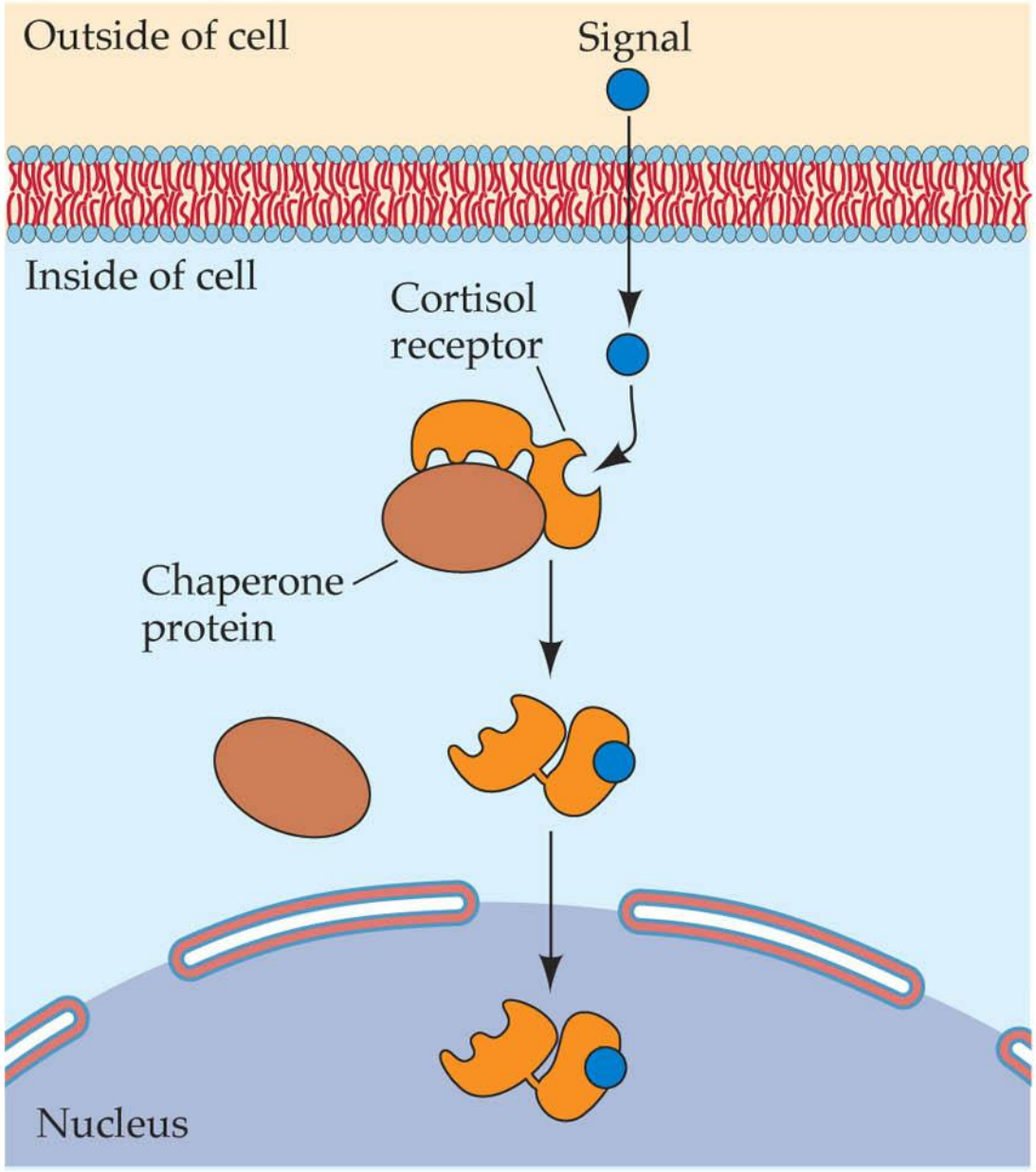
- Negative feedback mechanism.
- Steroids and drugs designed to mimic them are **directly** *gene-active*.
- Glucocorticoids (*e.g.*, prednisolone) used to suppress inflammation, allergy and immune responses.
- Anti-inflammatory therapy is used in many illnesses (*e.g.*, RA, UC, BA, eye and skin inflammations).

  -Useful in, say, tissue transplantation and lymphopoiesis (leukemias and lymphomas).
- Striking improvements can be obtained, but **severe adverse, but highly predictable, effects** are ensue.

# Hypothalamopituitary adrenal (HPA) axis: Negative Feedback

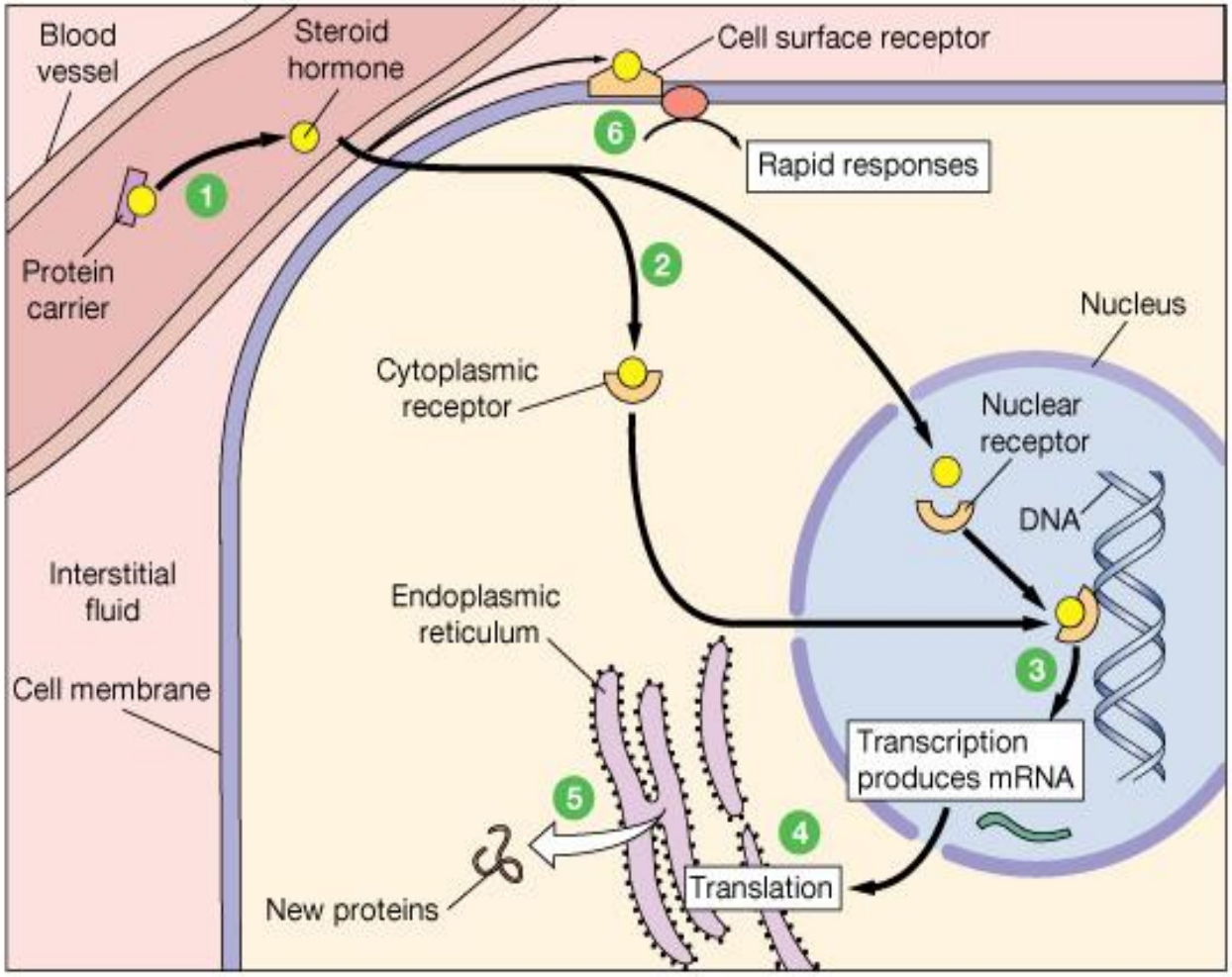







*LIFE: THE SCIENCE OF BIOLOGY, Seventh Edition,* **Figure 15.8 A Cytoplasmic Receptor**

# Corticosteroids are Gene-Active




1. Most hydrophobic steroids are bound to plasma protein carriers. Only unbound hormones can diffuse into the target cell.
2. Steroid hormone receptors are in the cytoplasm or nucleus.
3. The receptor-hormone complex binds to DNA and activates or represses one or more genes.
4. Activated genes create new mRNA that moves back to the cytoplasm.
5. Translation produces new proteins for cell processes.
6. Some steroid hormones also bind to membrane receptors that use second messenger systems to create rapid cellular responses.

# Pharmacological Actions

- For most clinical purposes, synthetic glucocorticoids are used because they have a higher affinity for the receptor, are less activated and have little or no salt-retaining properties.
- Hydrocortisone used for: orally for replacement therapy, i.v. for shock and asthma, topically for eczema (ointment) and enemas (ulcerative colitis).
- Prednisolone the most widely used drug given orally in inflammation and allergic diseases.

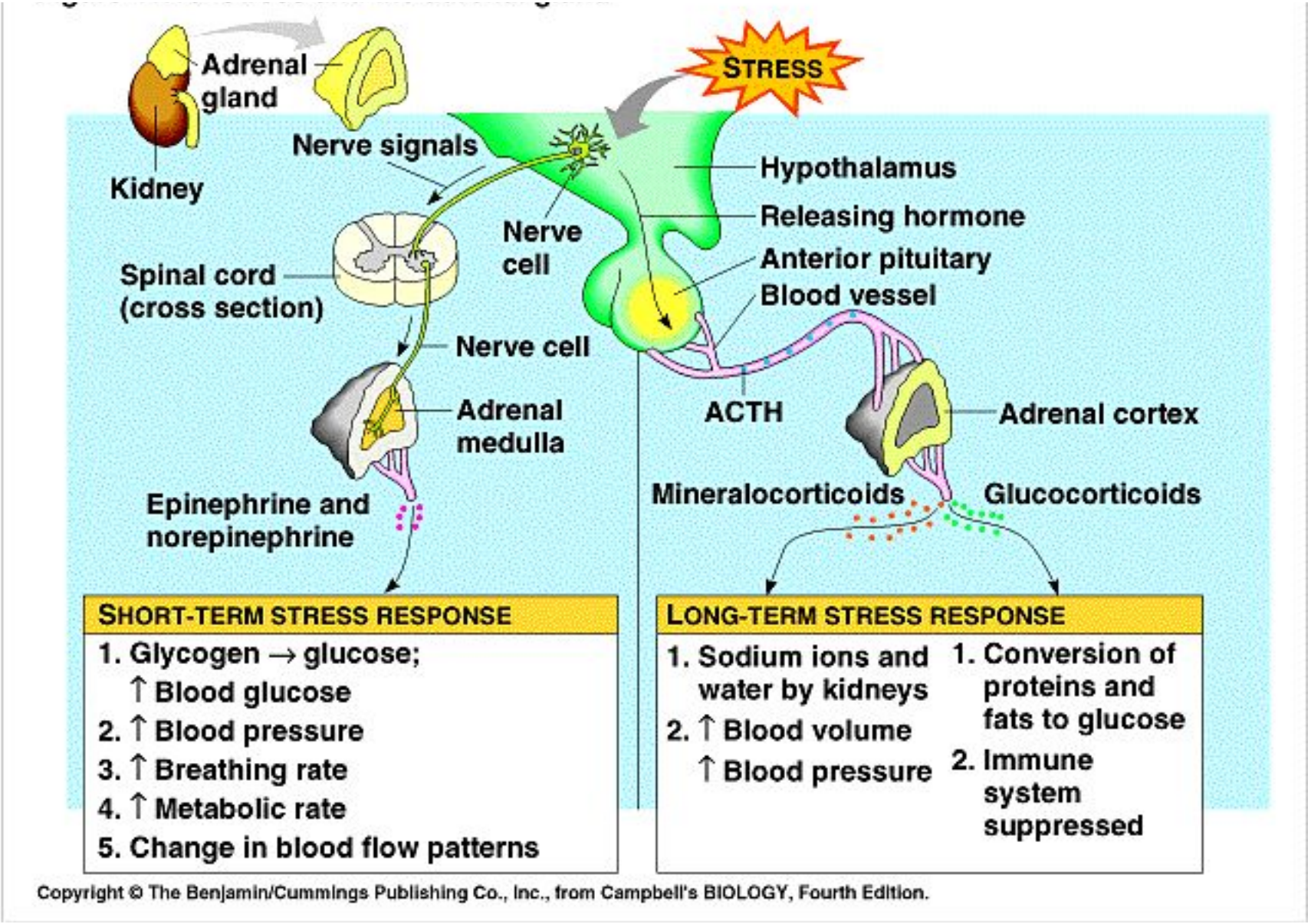
# Pharmacological Actions

- Betamethasone and dexamethasone: very potent, w/o salt-retaining properties; thus, very useful for high-dose therapies (*e.g.*, cerebral edemas).
- Beclometasone, diproprionate, budesonide: pass membranes poorly; more active when applied topically (severe eczema for local anti-inflammatory effects) than orally; used in asthma, (aerosol).
- Triamcinolone: used for severe asthma and for local joint inflammation (intra-articular inj.).

# Pharmacological Actions

1. Carbohydrate
2. Protein
3. Lipid
4. Electrolyte and $H_2O$
5. CVS
6. Skeletal Muscle
7. CNS
8. Stomach
9. Blood
10. Anti-inflammatory
11. Immunosuppressant
12. Respiratory system
13. Growth and Cell Division
14. Calcium metabolism

# Stress and The Adrenal Glands



## Actions: Carbohydrate and protein metabolism

# Negative nitrogen balance and hyperglycemia

- ↑ Gluconeogenesis
  - Peripheral actions (mobilize aas and glucose and glycogen) ↑
  - Hepatic actions
- ↓ Peripheral utilization of glucose
- ↑ Glycogen deposition in liver

  (activation of hepatic glycogen synthase)

# Actions: Lipid metabolism

- **Redistribution of Fat**
  - **Buffalo hump**
  - **Moon face**

- **Promote adipokinetic agents activity**

  ***(glucagon, growth hormone, adrenaline, thyroxine)***

# Actions: Electrolyte and water balance

- **Aldosterone is more important**
- **Act on DT and CD of kidney**
  - ↑ $Na^+$ reabsorption
  - ↑ Urinary excretion of $K^+$ and $H^+$
- **Addison's disease ??**

  - **Na+ loss**
  - **Shrinkage of ECF**
  - **Cellular hydration**
  - **Hypodynamic state of CVS**
  - **Circulatory collapse, renal failure, death**

# Actions: Cardiovascular system

- Restrict capillary permeability
- Maintain tone of arterioles
- Myocardial contractility

Mineralocorticoid induced hypertension ??

$Na^+$ sensitize blood vessels to the action of catecholamines & angiotensin

# Actions: Skeletal Muscles

**Needed for maintaining the normal function of Skeletal muscle**

Addison's disease: weakness and fatigue is due to

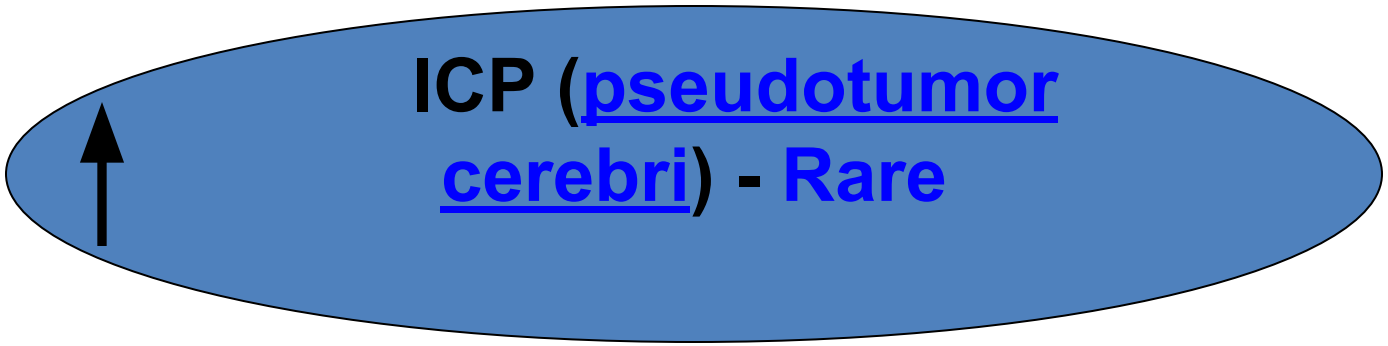
**inadequacy of circulatory system**

Prolonged use:

**Steroid myopathy**

# Actions: CNS

- Direct:
  - Mood
  - Behaviour
  - Brain excitability
- Indirect:
  - maintain glucose, circulation and electrolyte balance



# Pseudotumor cerebri

*(Intracranial hypertension)*

- Glucocorticoids
- Mineralocorticoids
- Amiodarone
- Vitamin A
- Oral contraceptives
- Tetracyclines

**From Harrison. 15th edition, volume 1, page 435**

# Actions: Stomach

**Aggravate peptic ulcer. May be due to:**

- ↑ **Acid and pepsin secretion**
- ↓ **immune response to *H.Pylori***

## Actions: Blood

**RBC:** ↑ **Hb and RBC content** ↓

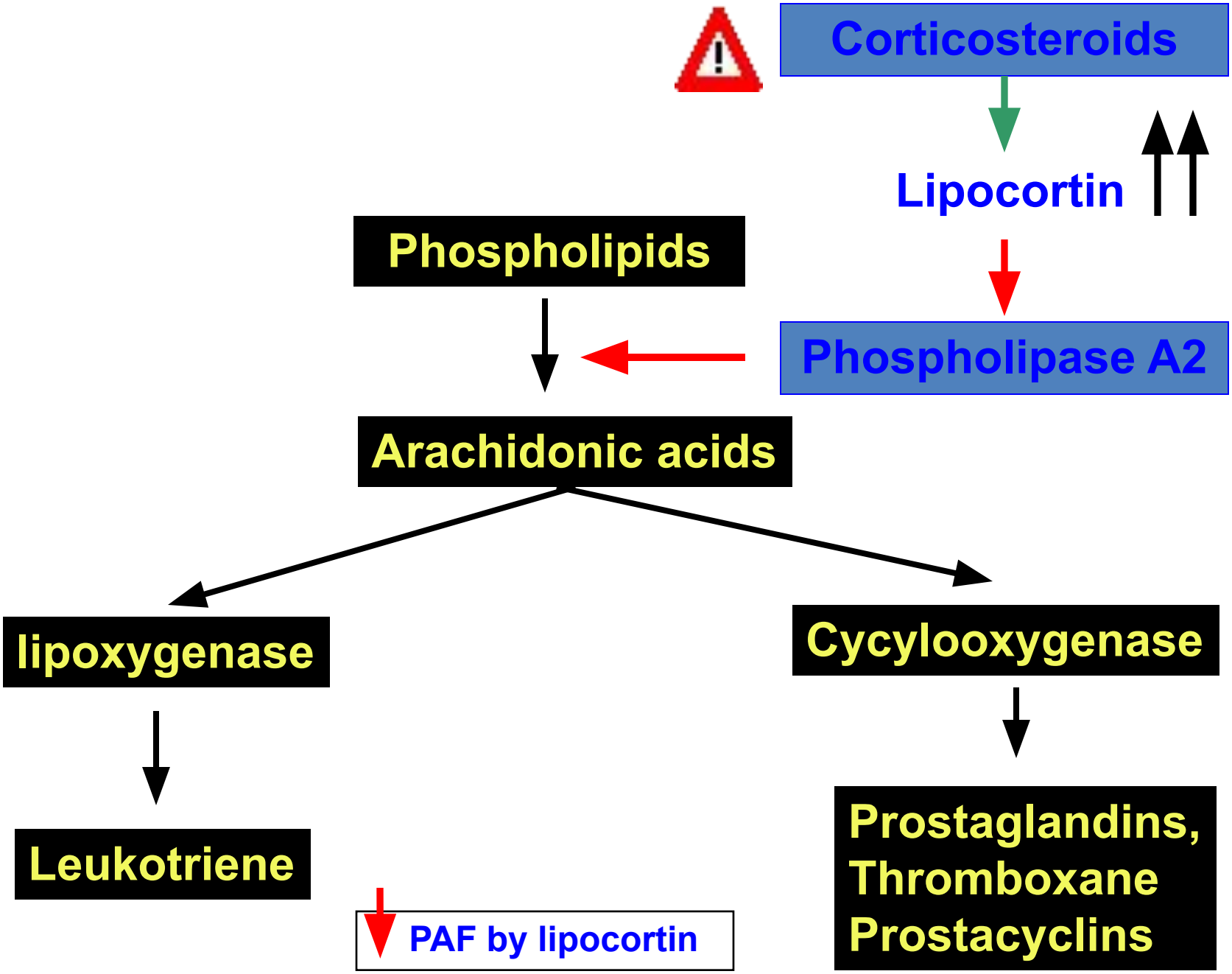
**(*erythrophagocytosis* )**

**WBC:** ↓ **Lymphocytes, eosinophils, monocytes, basophils**

↑ **Polymorphonucleocytes**

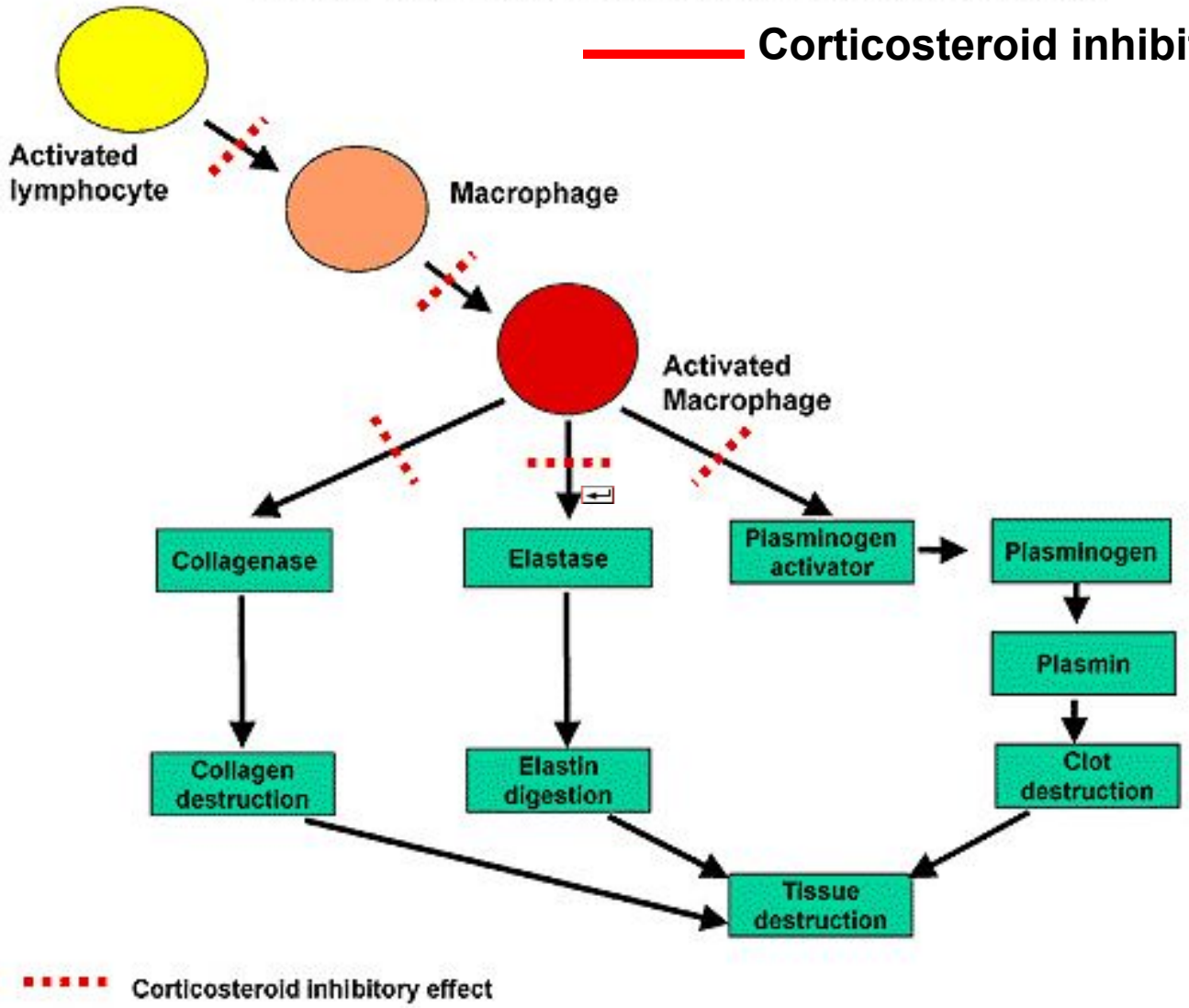
# Actions: Anti-inflammatory

- ↓↓ Recruitment of WBC and monocyte-macrophage into affected area & elaboration of chemotactic substances
- ↑ Lipocortin
- ↓ ELAM1 and ICAM-1 in endothelial cells
- ↓ TNF from phagocytic cells
- ↓ IL1 from monocyte-macrophage
- ↓ Formation of Plasminogen Activator
- ↓ Action of MIF and ↓ fibroblastic activity
- ↓ Expression of COX II


Corticosteroids
Lipocortin
Phospholipids
Phospholipase A2
Arachidonic acids
lipoxygenase
Cycylooxygenase
Leukotriene
Prostaglandins,
Thromboxane
Prostacyclins
PAF by lipocortin

# Anti-inflammatory actions of corticosteroids

Figure 1. Anti-inflammatory actions of corticosteroids.



# Immunosuppressive and anti-allergic actions

- Suppresses all types of hypersensitivity and allergic phenomenon
- **At High dose:** Interfere with all steps of immunological response
- Causes greater suppression of Cell-mediated immunity (*graft rejection and delayed hypersensitivity*)
- Transplant rejection: ↓ antigen expression from grafted tissues, delay revascularization, ↓ sensitisation of T lymphocytes *etc*.

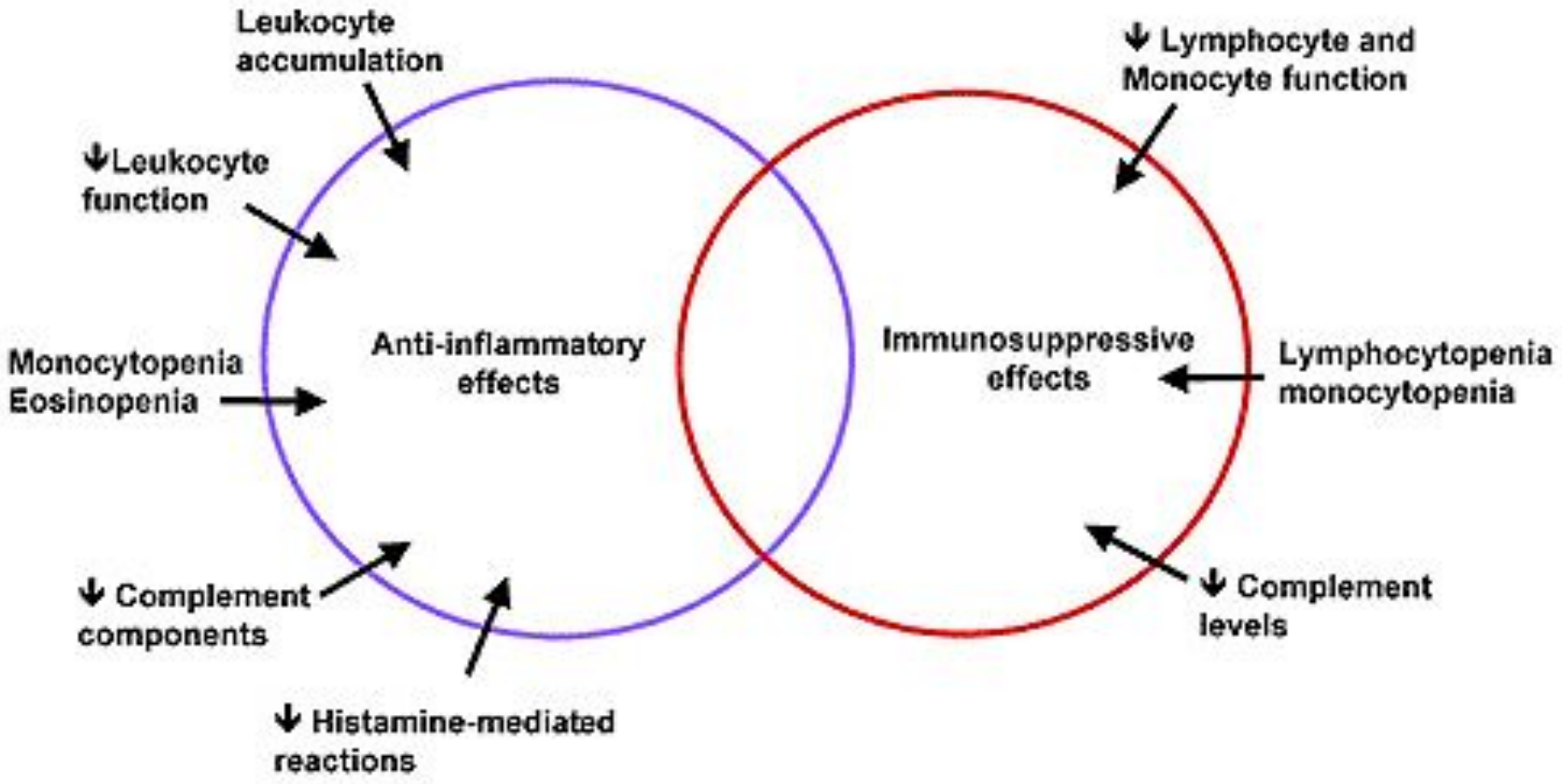



Figure 2. Anti-inflammatory and immunosuppressive effects of corticosteroids.

# Actions: Growth and Cell division

- Inhibit cell division or synthesis of DNA
- Delay the process of healing
- Retard the growth of children

# Actions: Calcium metabolism

- ↓ Intestinal absorption
- ↑ Renal excretion
- Excessive loss of calcium from spongy bones (*e.g.,* vertebrae, ribs*, etc*)

# Actions: Respiratory system

- **Not** bronchodilators
- Most potent and most effective anti-inflammatory
- Effects not seen immediately (delay 6 or more hrs)
- Inhaled corticosteroids are used for long term control

# Preparations

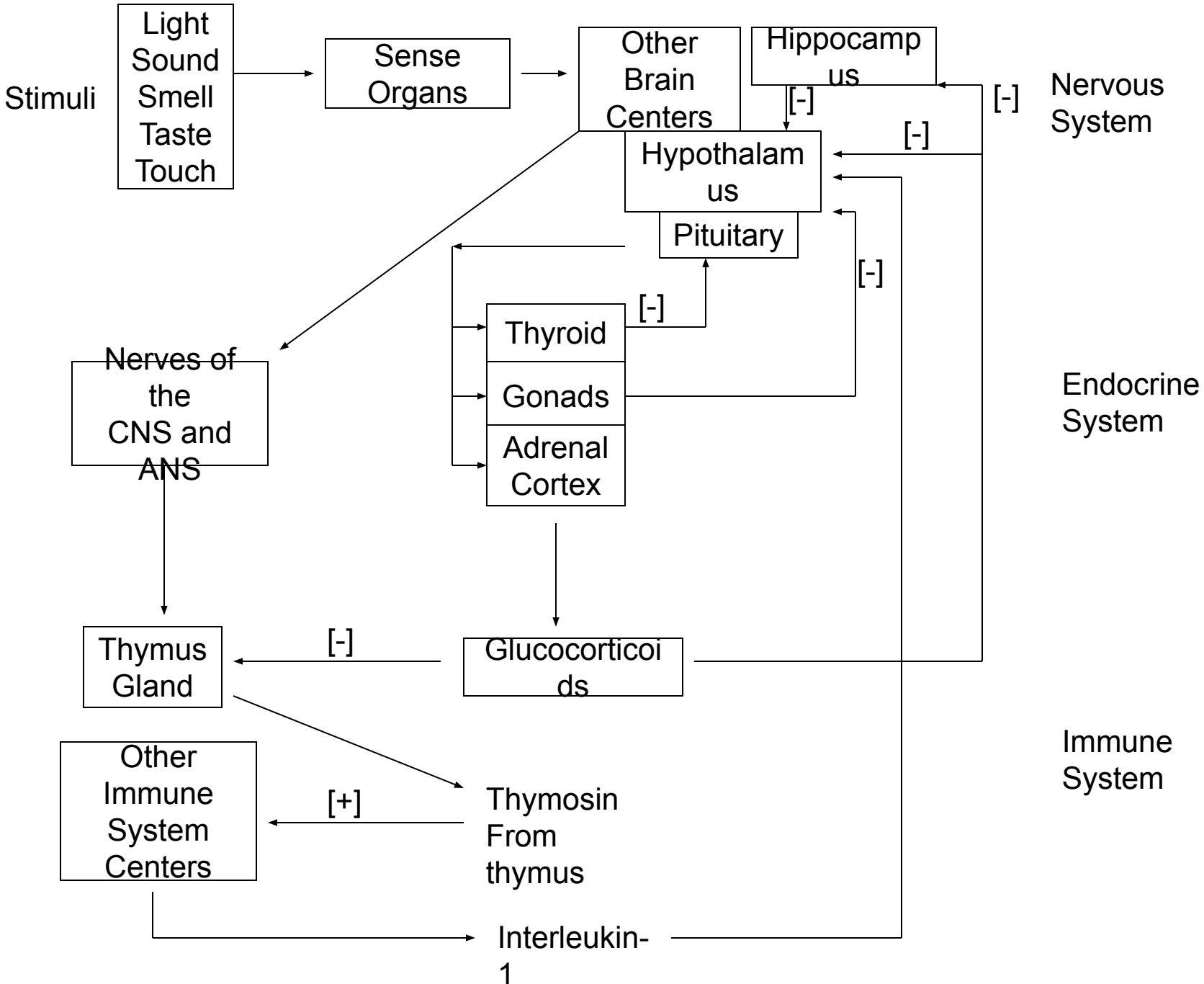
| Drug | Anti-inflam. | Salt retaining | Topical |
|---|---|---|---|
| Cortisol | 1 | 1.0 | 1 |
| Cortisone | 0.8 | 0.8 | 0 |
| Prednisone | 4 | 0.8 | 0 |
| Prednisolone | 5 | 0.3 | 4 |
| Methylpredni-solone | 5 | 0 | 5 |
| Intermediate acting | | | |
| Triamcinolone | 5 | 0 | 5 |
| Paramethasone | 10 | 0 | - |
| Fluprednisolone | 15 | 0 | 7 |

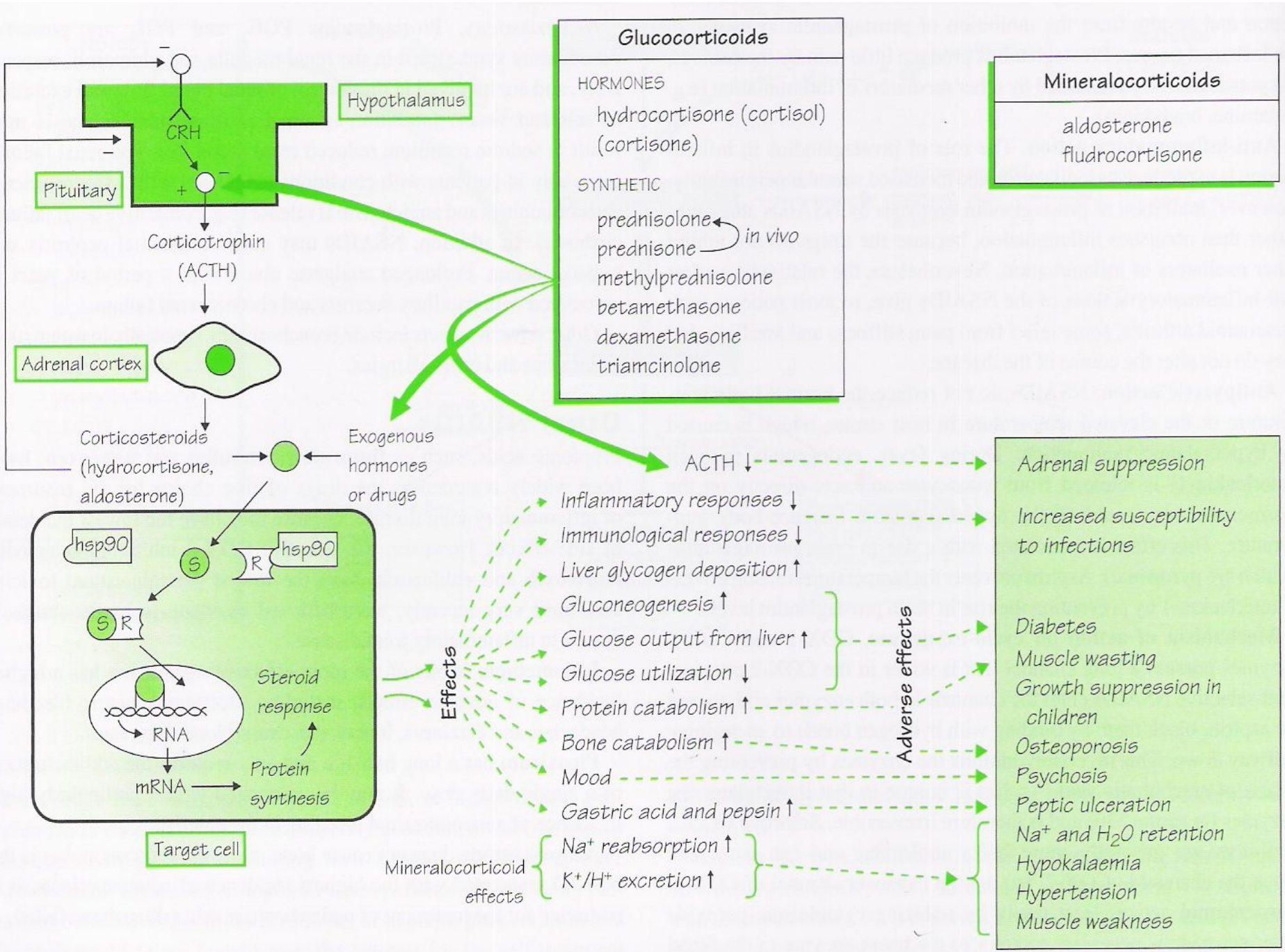
| Preparations | | | |
|---|---|---|---|
| **Drug** | **Anti-inflam.** | **Salt retaining** | **Topical** |
| Long acting | | | |
| **Betamethasone** | 25-40 | 0 | 10 |
| **Dexamethasone** | 30 | 0 | 10 |
| Mineralocorticoids | | | |
| **Fludrocortisone** | 10 | 250 | 10 |
| **DOCA** | 0 | 20 | 0 |

# Synthesis

| Stimuli | Part | Principal product |
|---|---|---|
| Angiotensin II | Zona glomerulosa | Aldosterone |
| ACTH | Zona fasiculata & reticularis | Cortisol<br>Adrenal androgens |
| Sympathetic nervous system | Medulla | Adrenaline & Nor-adrenaline |

# INTERCELLULAR COMMUNICATION – THE EFFECTS OF GLUCOCORTICOIDS




Glucocorticoids
HORMONES
hydrocortisone (cortisol)
(cortisone)
SYNTHETIC
prednisolone
prednisone
in vivo
methylprednisolone
betamethasone
dexamethasone
triamcinolone
Mineralocorticoids
aldosterone
fludrocortisone
Hypothalamus
CRH
Pituitary
Corticotrophin
(ACTH)
Adrenal cortex
Corticosteroids
(hydrocortisone,
aldosterone)
Exogenous
hormones
or drugs
hsp90
S
R
hsp90
S R
RNA
Steroid
response
mRNA
Protein
synthesis
Target cell
Effects
ACTH ↓
Inflammatory responses ↓
Immunological responses ↓
Liver glycogen deposition ↑
Gluconeogenesis ↑
Glucose output from liver ↑
Glucose utilization ↓
Protein catabolism ↑
Bone catabolism ↑
Mood
Gastric acid and pepsin ↑
Adverse effects
Mineralocorticoid
effects
Na+ reabsorption ↑
K+/H+ excretion ↑
Adrenal suppression
Increased susceptibility
to infections
Diabetes
Muscle wasting
Growth suppression in
children
Osteoporosis
Psychosis
Peptic ulceration
Na+ and H2O retention
Hypokalaemia
Hypertension
Muscle weakness