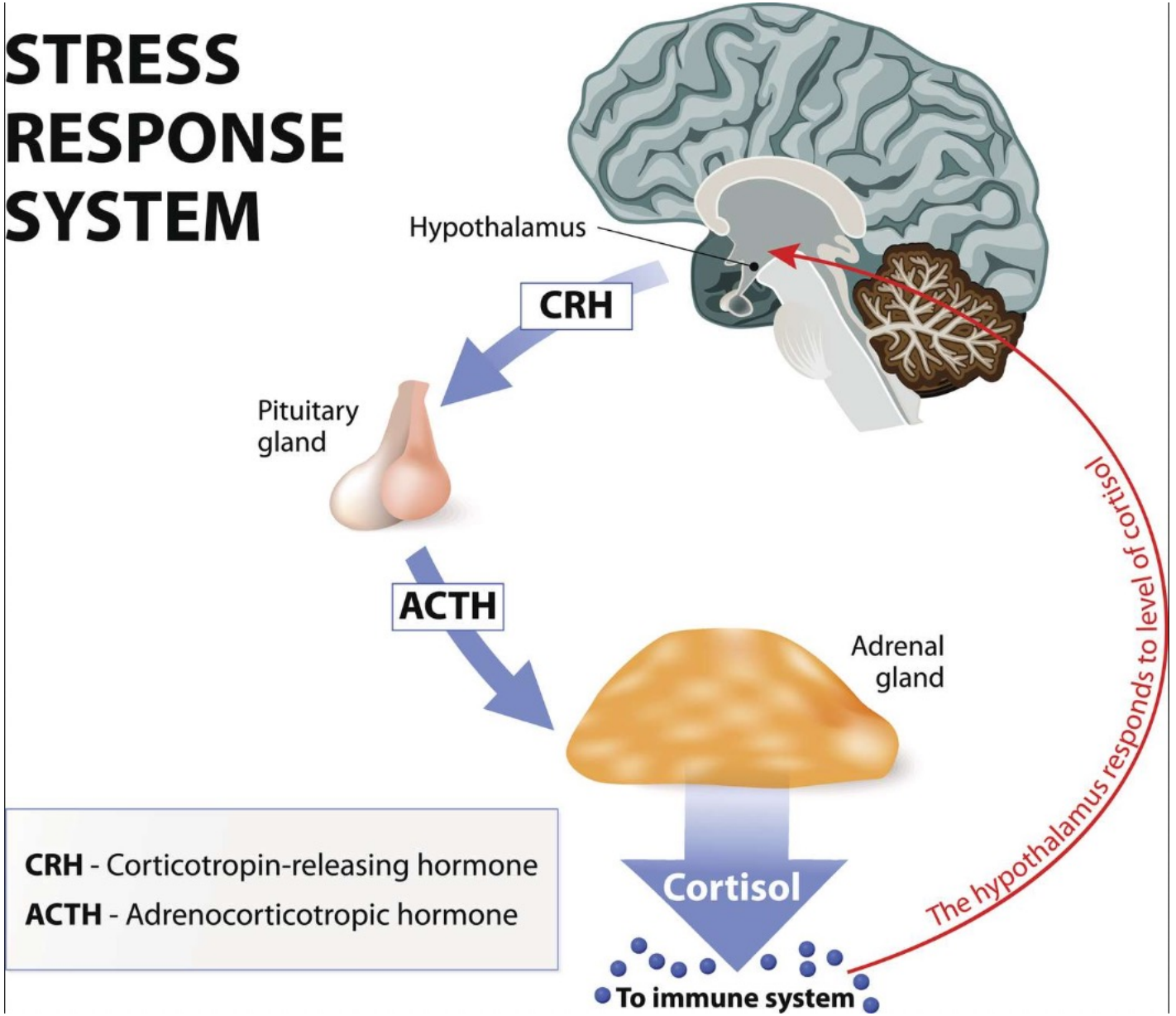
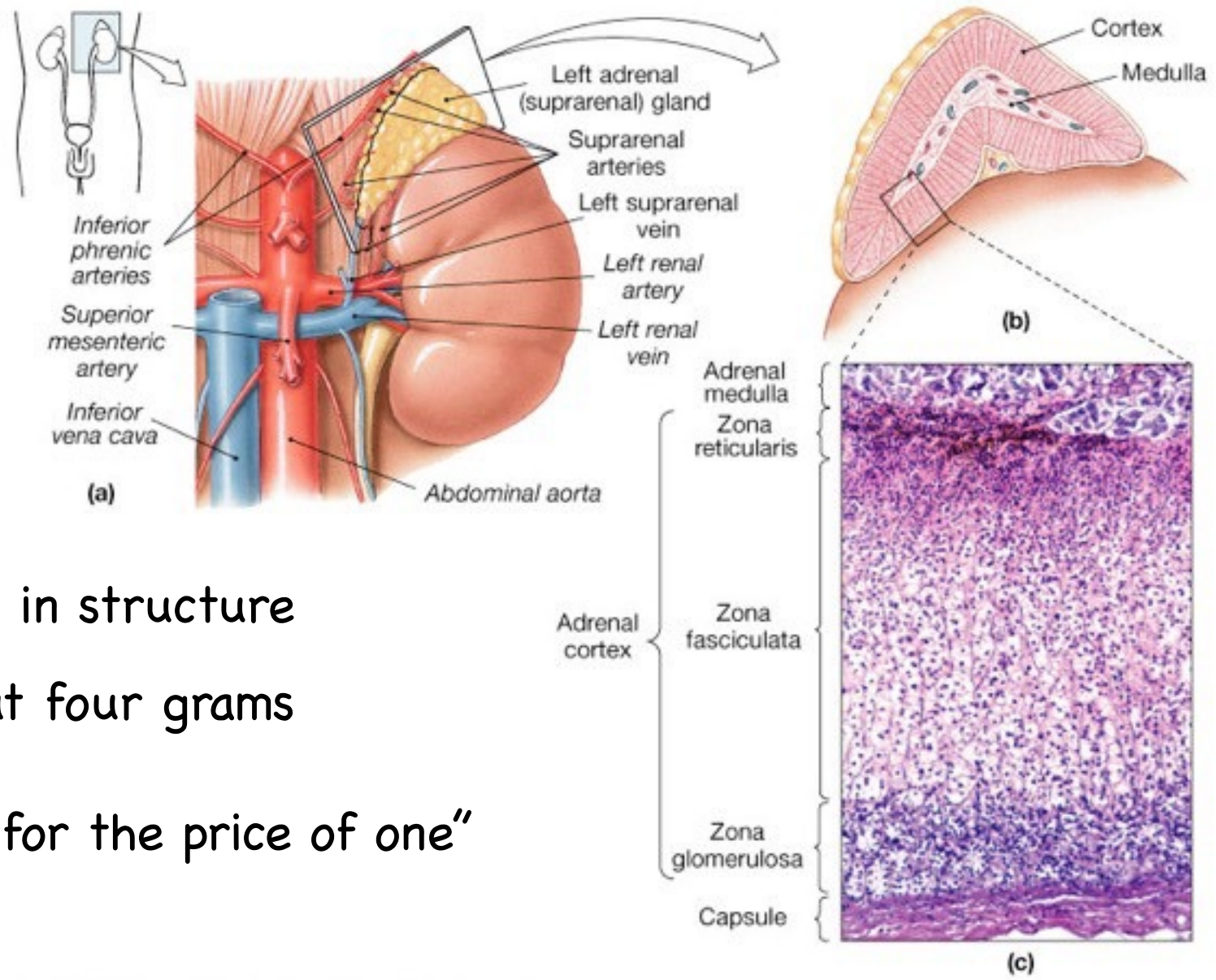
# The Adrenal Gland and Stress

**Corticotropin-releasing hormone**

**Adrenocorticotropic hormone**

**Cortisol**





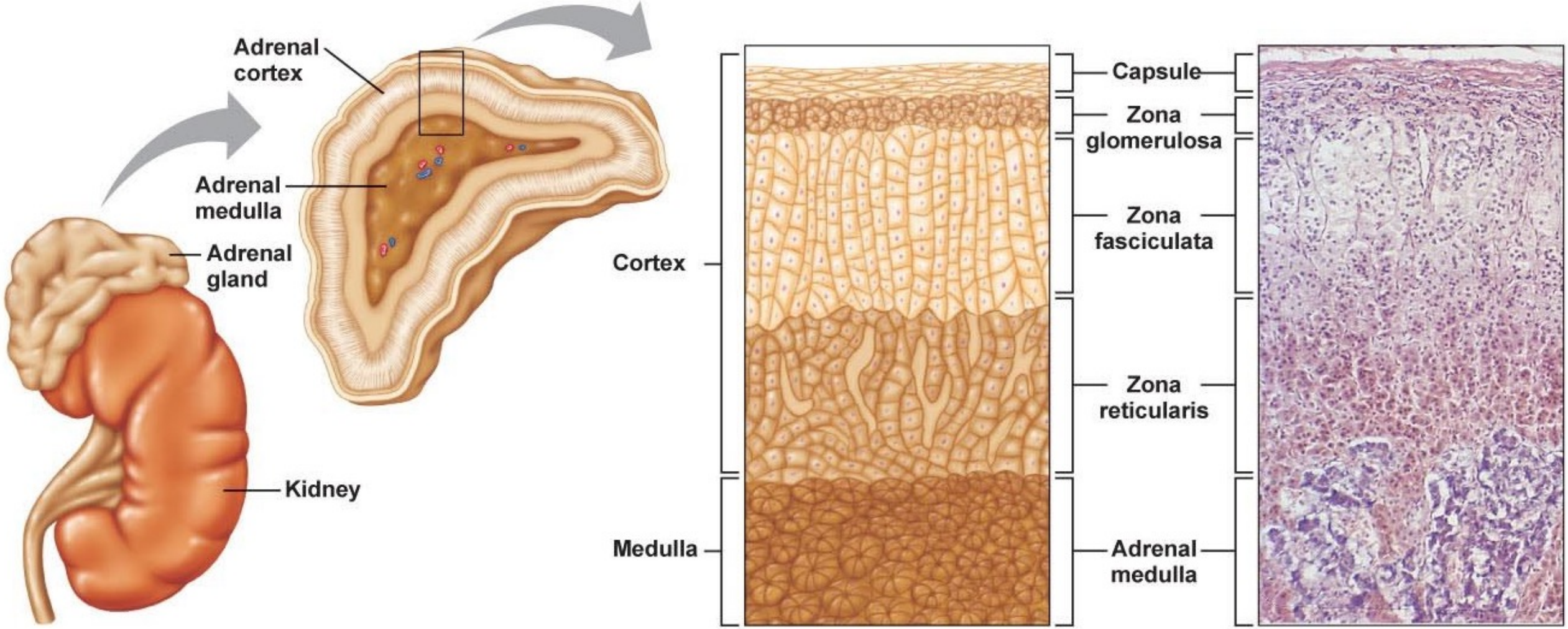

-is pyramidal in structure

-weighs about four grams

-"two glands for the price of one"

Figure 18.16

# Adrenal Gland: histology



# The Adrenal Gland

1563 Anatomy discovered by Bartolomeo Eustachi.

1855 Thomas Addison described the consequences of adrenal gland inadequacy.

Around 1900 catecholamines were identified.

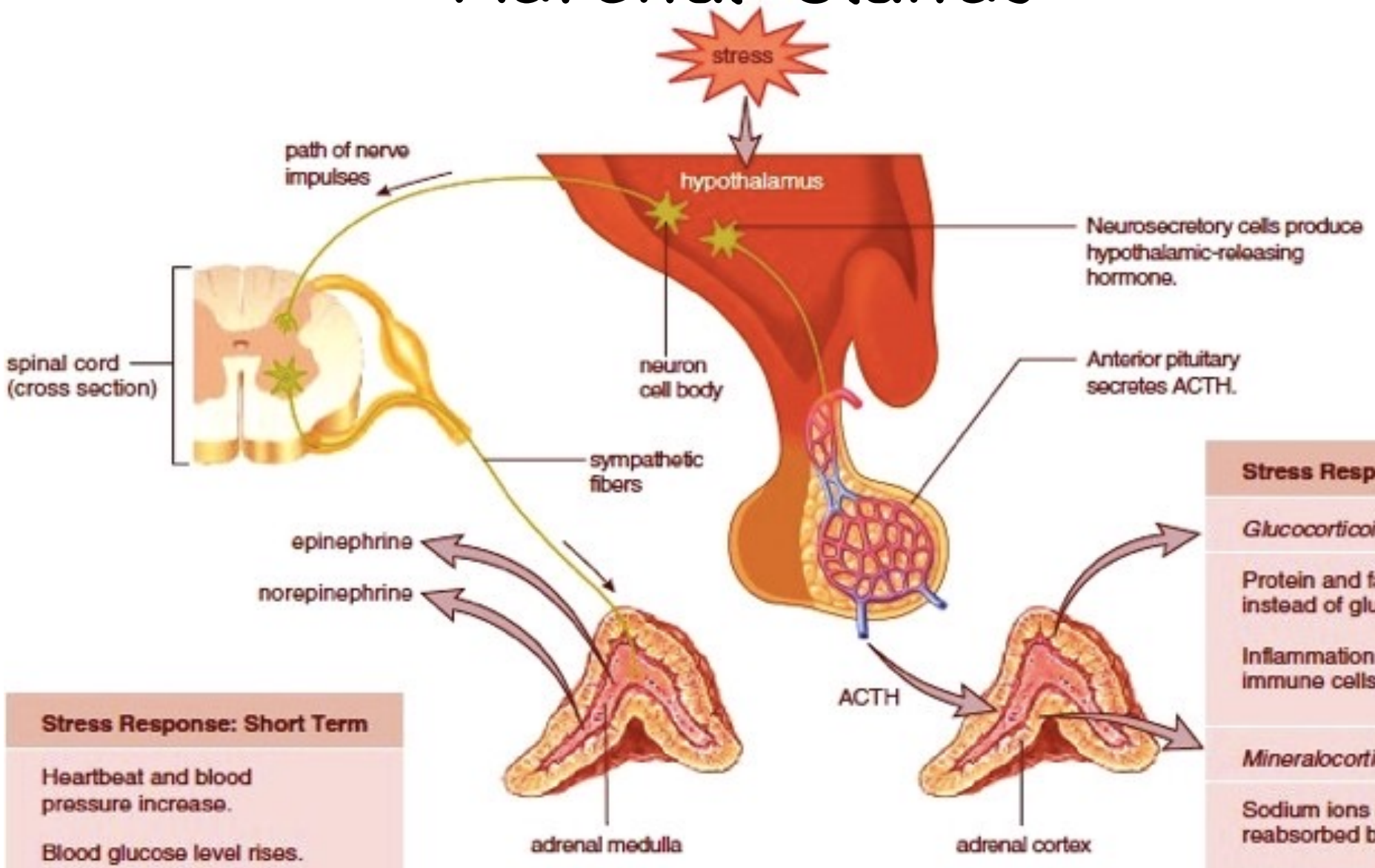
1893/4 Oliver and Schaffer discovered that these adrenomedullary substances raise blood pressure.

1904 Friedrich Stolz at Höchst identifies formula and synthesizes epinephrin (adrenalin)

1919 adrenalin enters the market as suprarenin

Activities are regulation of fluid volume and stress response.

# Adrenal Glands




**Stress Response: Short Term**

Heartbeat and blood pressure increase.

Blood glucose level rises.

Muscles become energized.

**Stress Response: Long Term**

*Glucocorticoids*

Protein and fat metabolism occur instead of glucose breakdown.

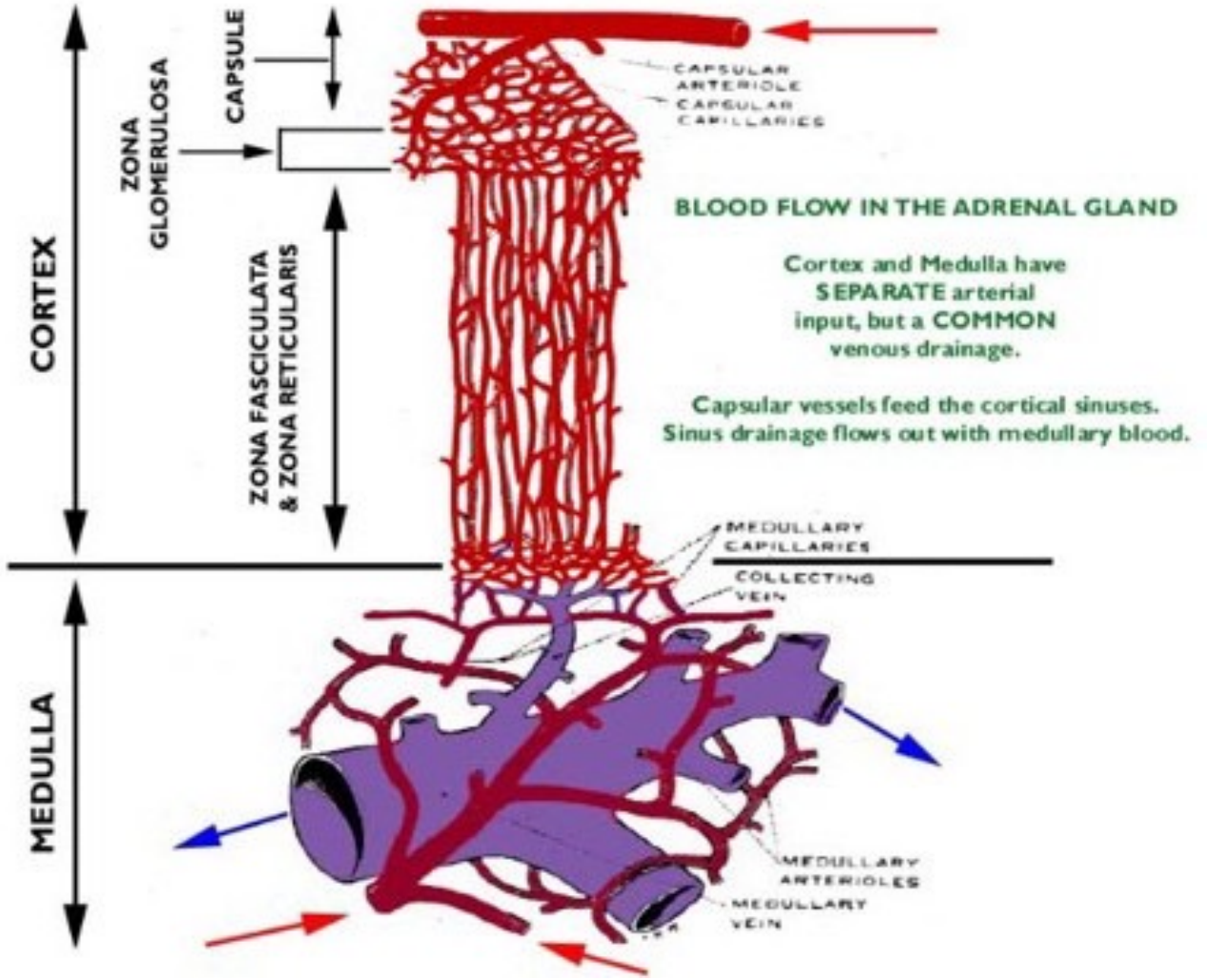
Inflammation is reduced; immune cells are suppressed.

*Mineralocorticoids*

Sodium ions and water are reabsorbed by kidney.

Blood volume and pressure increase.

# Adrenal Glands: blood flow




Venous blood flow is combined

# Negative Feedback Controls: Long & Short Loop Reflexes

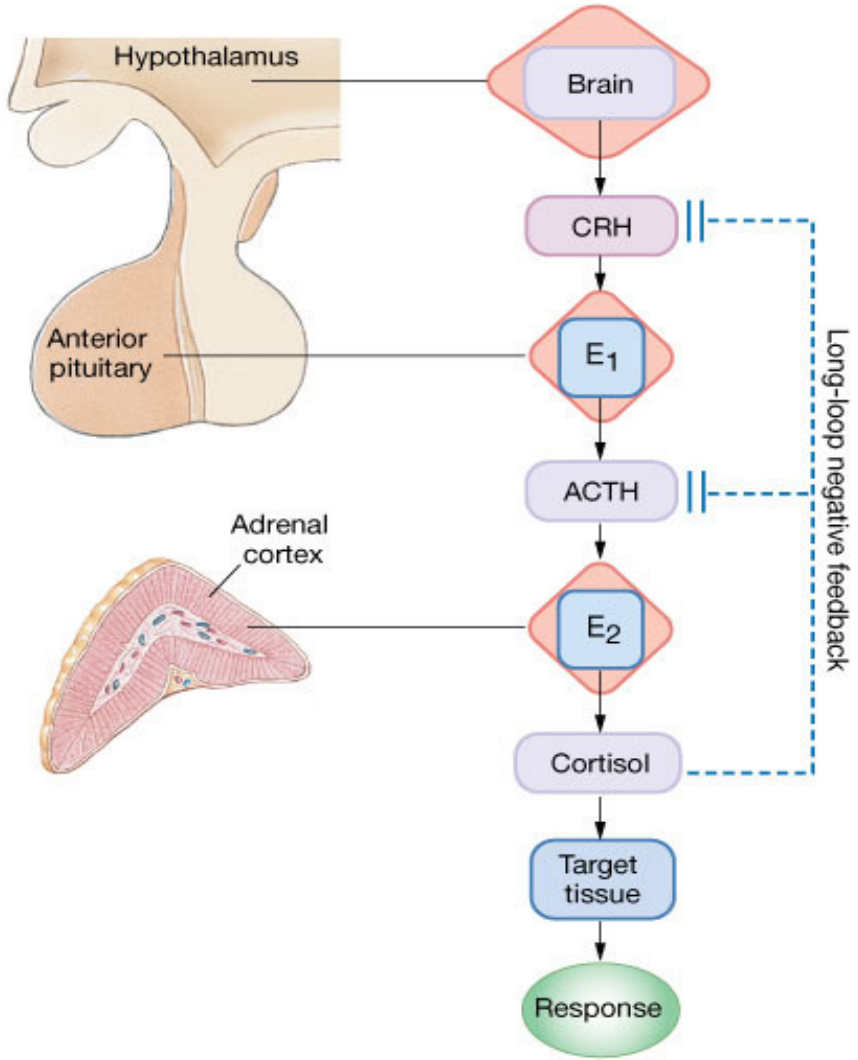
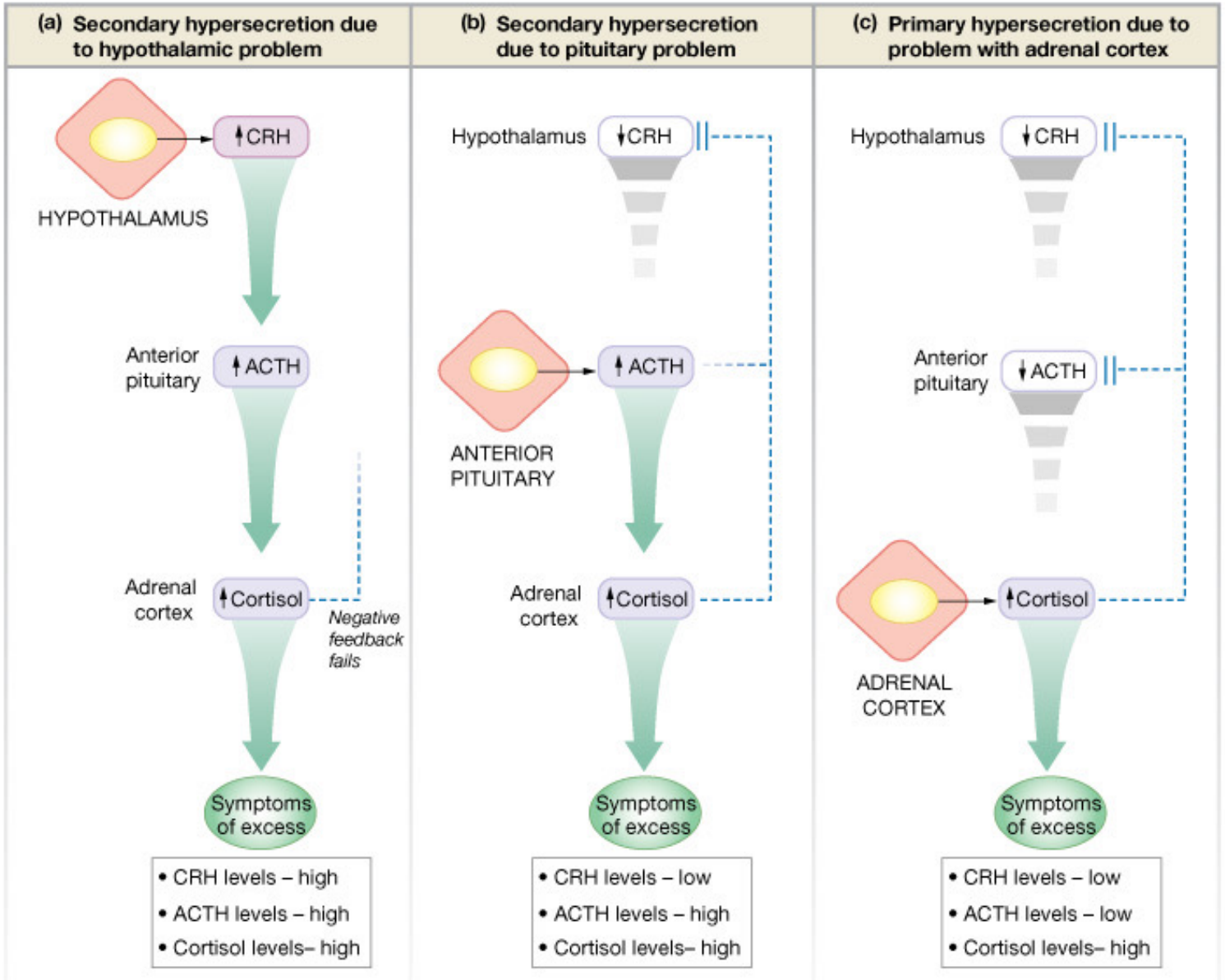
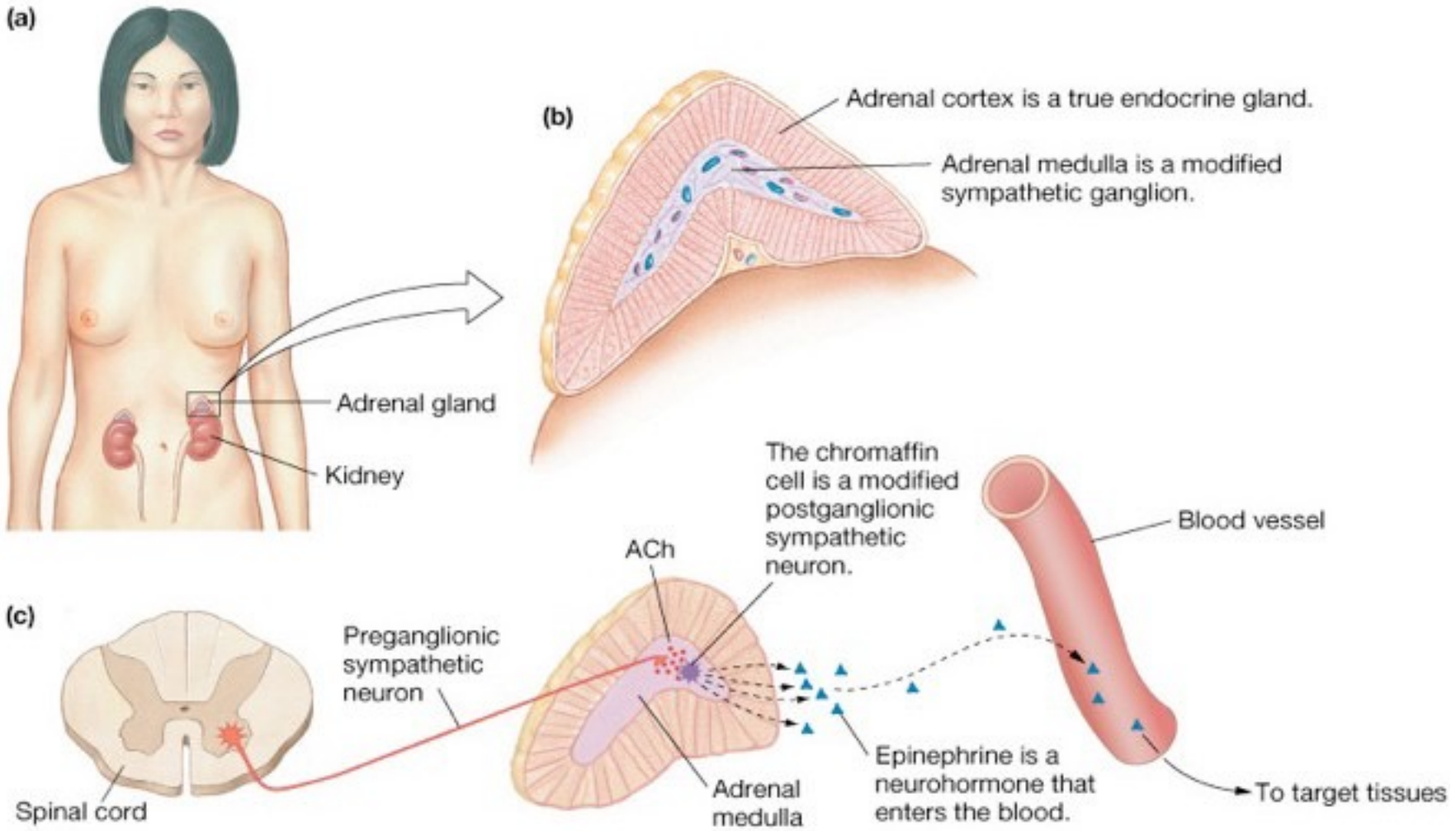



Figure 7-15: Control pathway for cortisol secretion

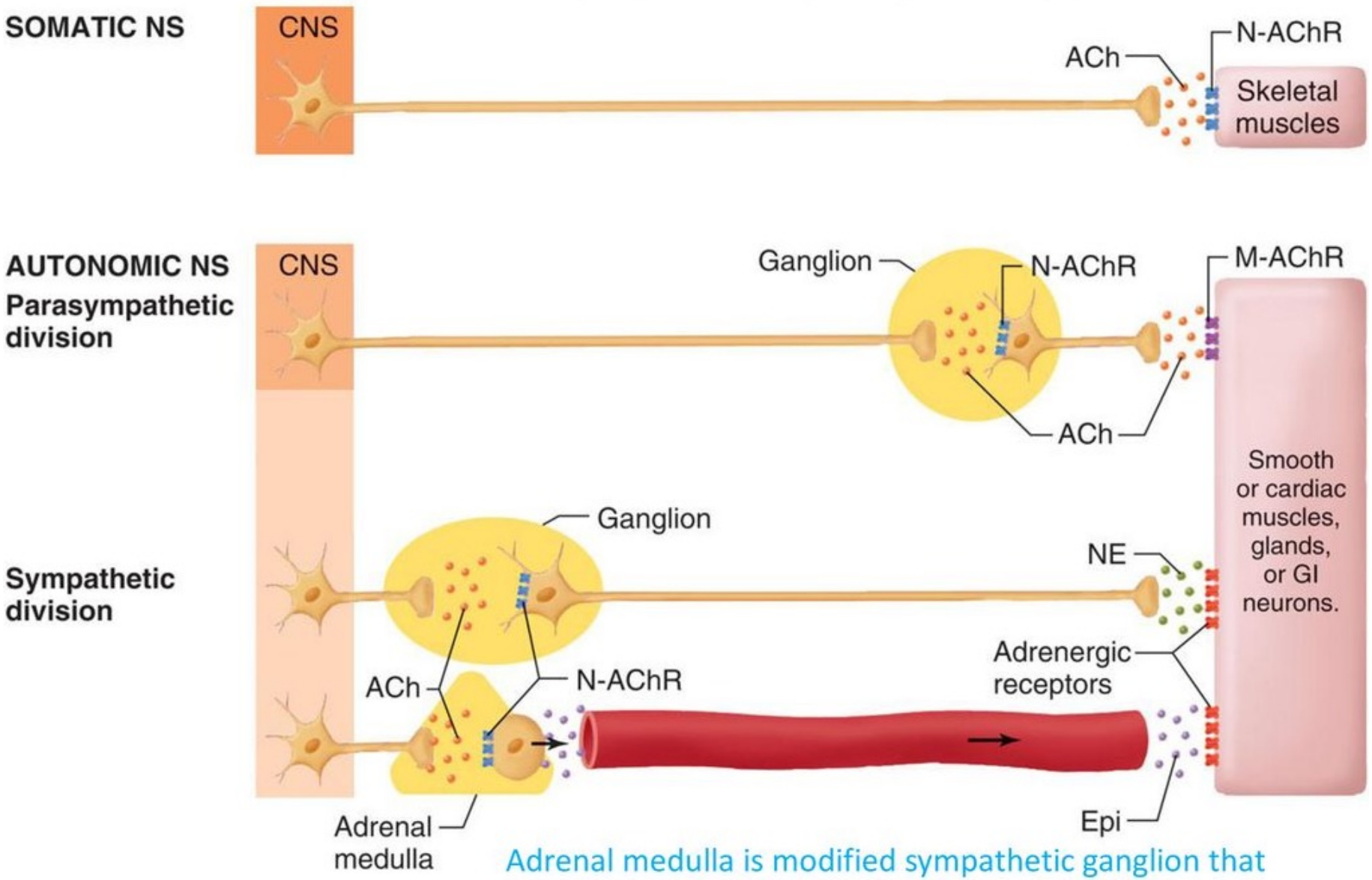
# Primary and secondary hypersecretion of cortisol



# Adrenal medulla: A modified sympathetic ganglion

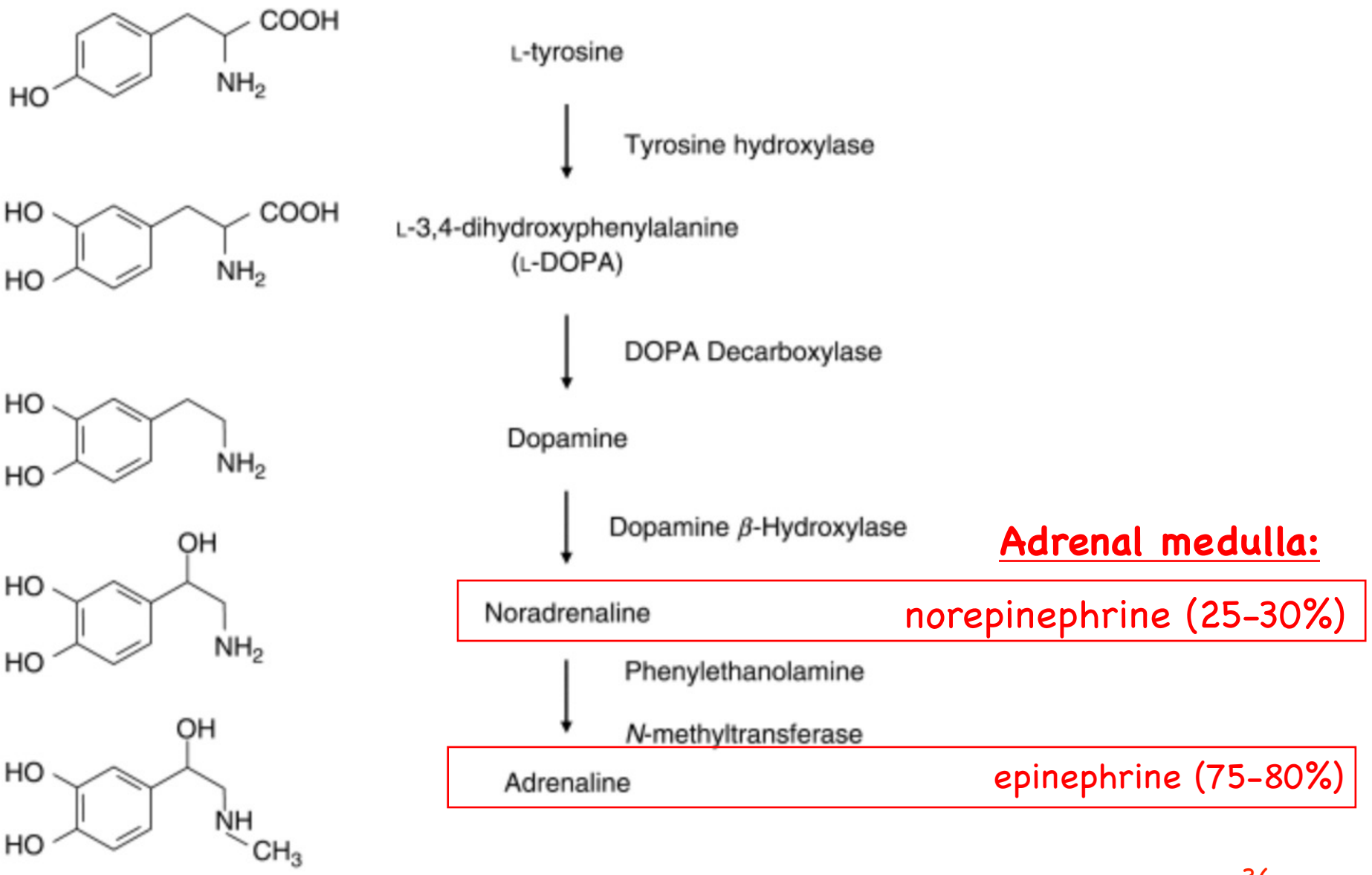


# Adrenal Medulla vs Sympathetic Nervous System




Adrenal medulla is modified sympathetic ganglion that secretes mainly EPI

# Epinephrine and Norepinephrine

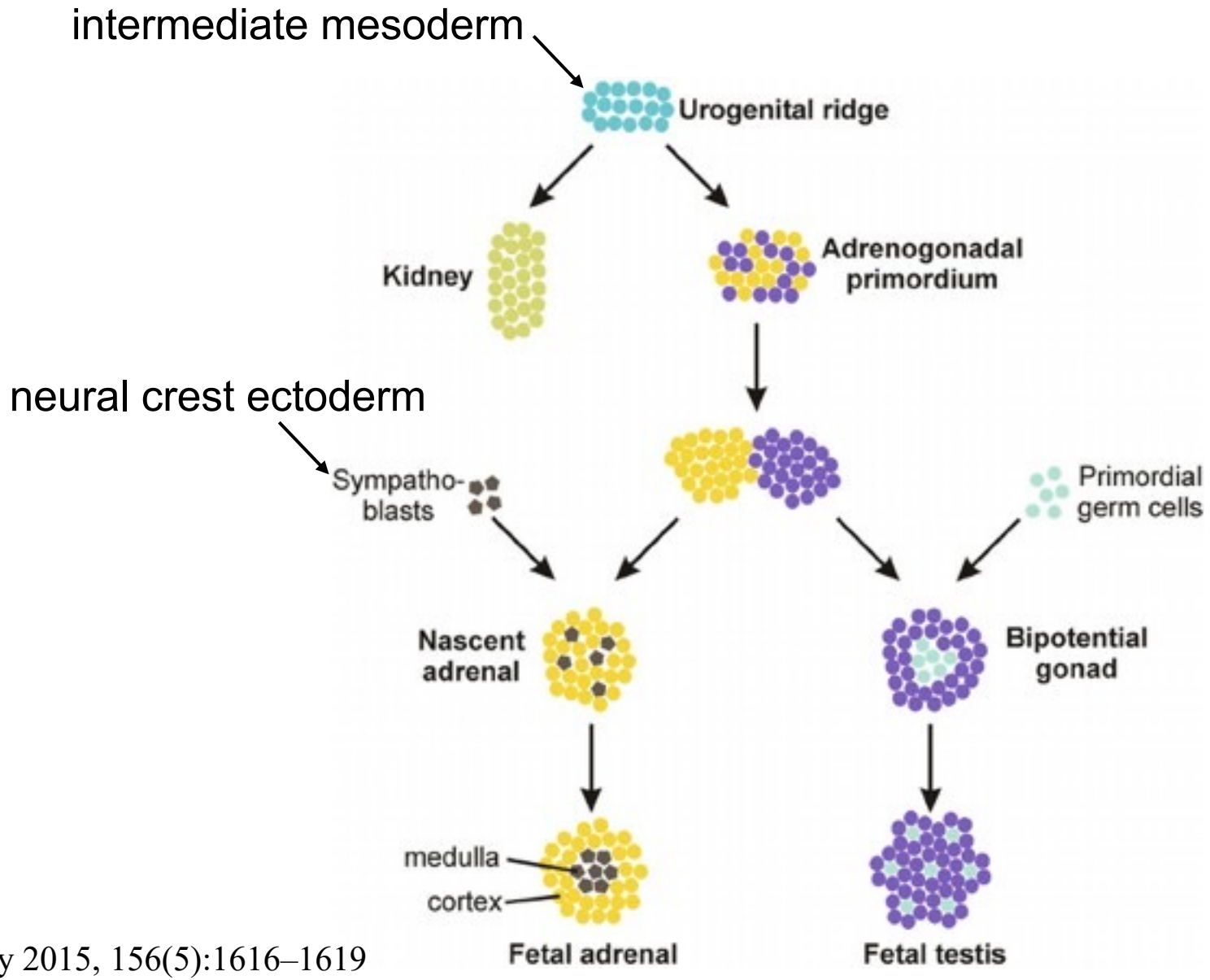



**Adrenal medulla:**

norepinephrine (25-30%)

epinephrine (75-80%)

# Development of the adrenal gland




Endocrinology, May 2015, 156(5):1616–1619

# FUNCTIONAL IMPLICATIONS

- Adrenal medulla a site of direct neuro-endocrine interaction
  - Direct stimulus to release hormones is unique
  - Different mechanism from neurohypophyseal release
- Origins and nature of medullary cells indicate they are modified neurons
  - From neural crest ectoderm
- EP and NEP are a "General Quarters" alarm to which all cells can respond
  - System bridges temporal gap between instantaneous and long-term responses

# Stress response

-rapid mobilization of energy from storage sites

-inhibition of further storage (gc block transport of nutrients into fat cells)

-increase heart rate, breathing rate, blood pressure to deliver all the glucose to muscles

-inhibit digestion

-inhibit growth

-inhibit tissue repair

-decrease sexual drive

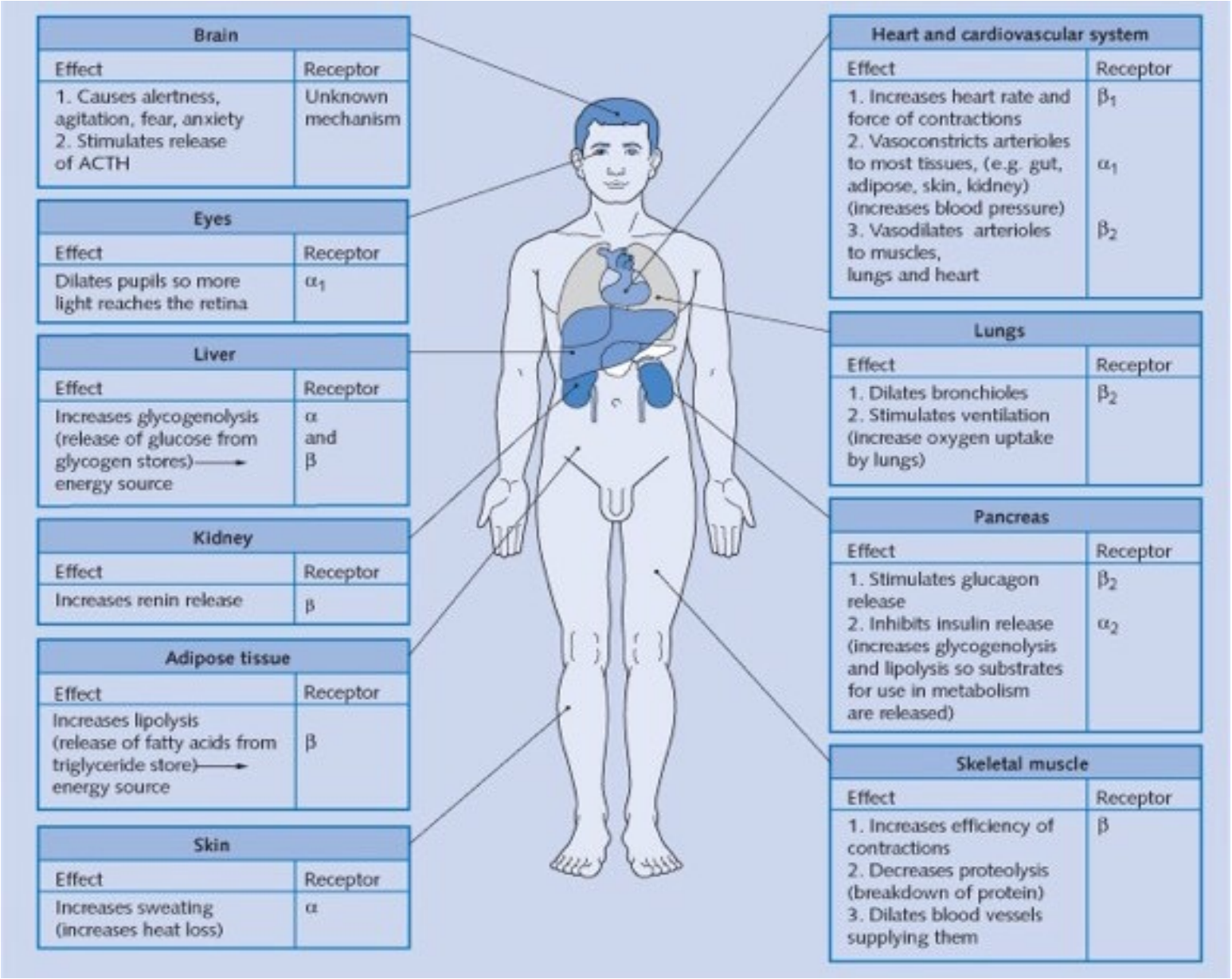
-induce analgesia

-shift in cognitive and sensory skills

- Stress-response can become more damaging than the stressor itself

Epinephrine acts within seconds, glucocorticoids back up over minutes/hours;
potentiate each other's release

# Physiological effects of epinephrine and norepinephrine



| Brain | |
|---|---|
| Effect | Receptor |
| 1. Causes alertness, agitation, fear, anxiety<br>2. Stimulates release of ACTH | Unknown mechanism |

| Eyes | |
|---|---|
| Effect | Receptor |
| Dilates pupils so more light reaches the retina | $\alpha_1$ |

| Liver | |
|---|---|
| Effect | Receptor |
| Increases glycogenolysis (release of glucose from glycogen stores) → energy source | $\alpha$ and $\beta$ |

| Kidney | |
|---|---|
| Effect | Receptor |
| Increases renin release | $\beta$ |

| Adipose tissue | |
|---|---|
| Effect | Receptor |
| Increases lipolysis (release of fatty acids from triglyceride store) → energy source | $\beta$ |

| Skin | |
|---|---|
| Effect | Receptor |
| Increases sweating (increases heat loss) | $\alpha$ |

| Heart and cardiovascular system | |
|---|---|
| Effect | Receptor |
| 1. Increases heart rate and force of contractions<br>2. Vasoconstricts arterioles to most tissues, (e.g. gut, adipose, skin, kidney) (increases blood pressure)<br>3. Vasodilates arterioles to muscles, lungs and heart | $\beta_1$<br>$\alpha_1$<br>$\beta_2$ |

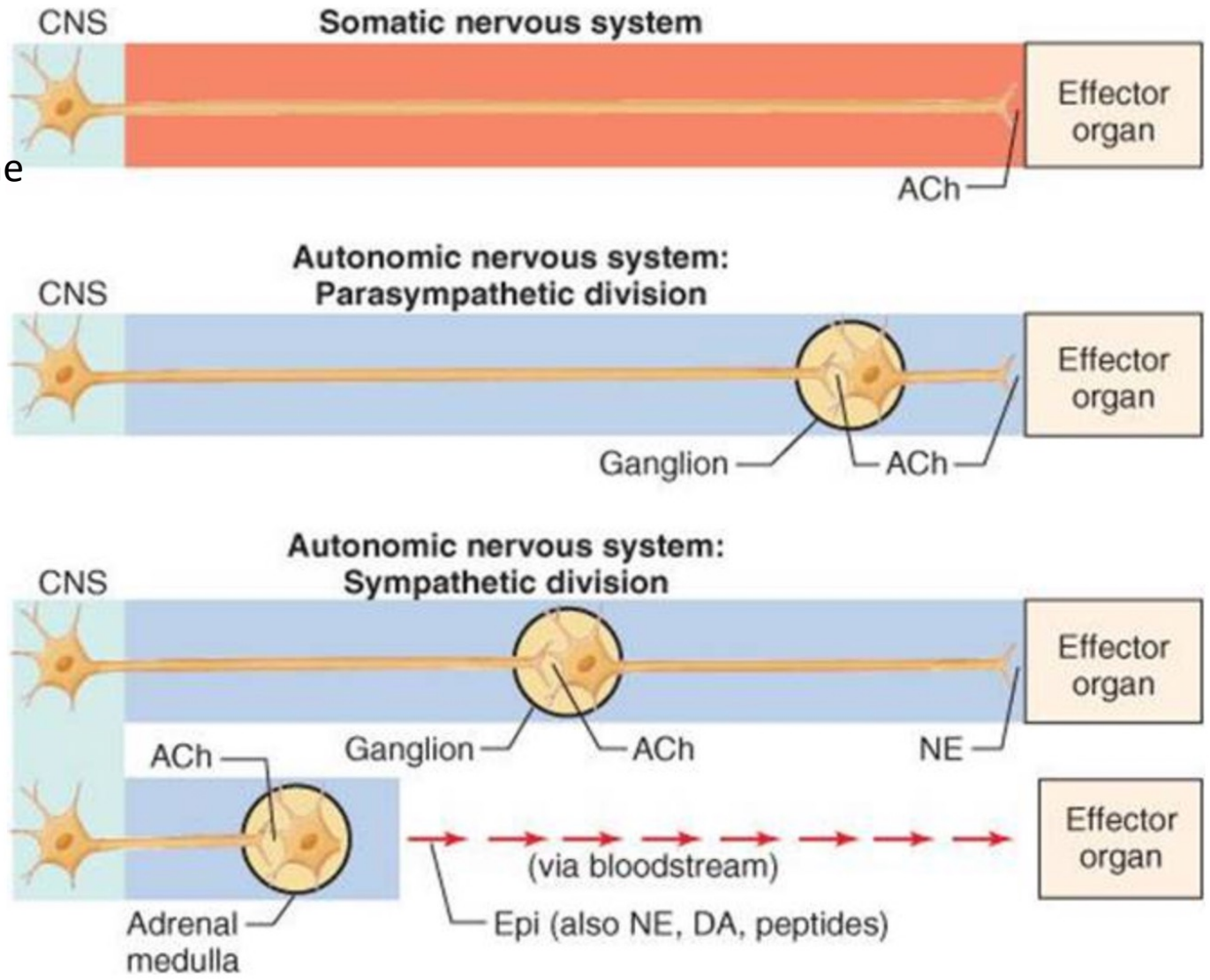
| Lungs | |
|---|---|
| Effect | Receptor |
| 1. Dilates bronchioles<br>2. Stimulates ventilation (increase oxygen uptake by lungs) | $\beta_2$ |

| Pancreas | |
|---|---|
| Effect | Receptor |
| 1. Stimulates glucagon release<br>2. Inhibits insulin release (increases glycogenolysis and lipolysis so substrates for use in metabolism are released) | $\beta_2$<br>$\alpha_2$ |

| Skeletal muscle | |
|---|---|
| Effect | Receptor |
| 1. Increases efficiency of contractions<br>2. Decreases proteolysis (breakdown of protein)<br>3. Dilates blood vessels supplying them | $\beta$ |

# Comparison of peripheral organization and transmitters released by somatomotor and autonomic nervous systems

ACh acetylcholine
DA, dopamine
Epi, epinephrine
NE, norepinephrine




Widmaier EP, Raff H, Strang KT: *Vander's Human Physiology.* McGraw-Hill, 2008.

# Hormones and stress

- Stress = any condition that threatens homeostasis
- General Adaptation Syndrome (GAS) is our bodies response to stress-causing factors
- Three phases to GAS
  - Alarm phase (immediate, fight or flight, directed by the sympathetic nervous system)
  - Resistance phase (dominated by glucocorticoids)
  - Exhaustion phase (breakdown of homeostatic regulation and failure of one or more organ systems)

# Stress response

- rapid mobilization of energy from storage sites
- Inhibition of further storage (gc block transport of nutrients into fat cells)
- Increase heart rate, breathing rate, blood pressure to deliver all the glucose to muscles
- Inhibit digestion
- Inhibit growth
- Inhibit tissue repair
- Decrease sexual drive
- Induce analgesia
- Shift in cognitive and sensory skills

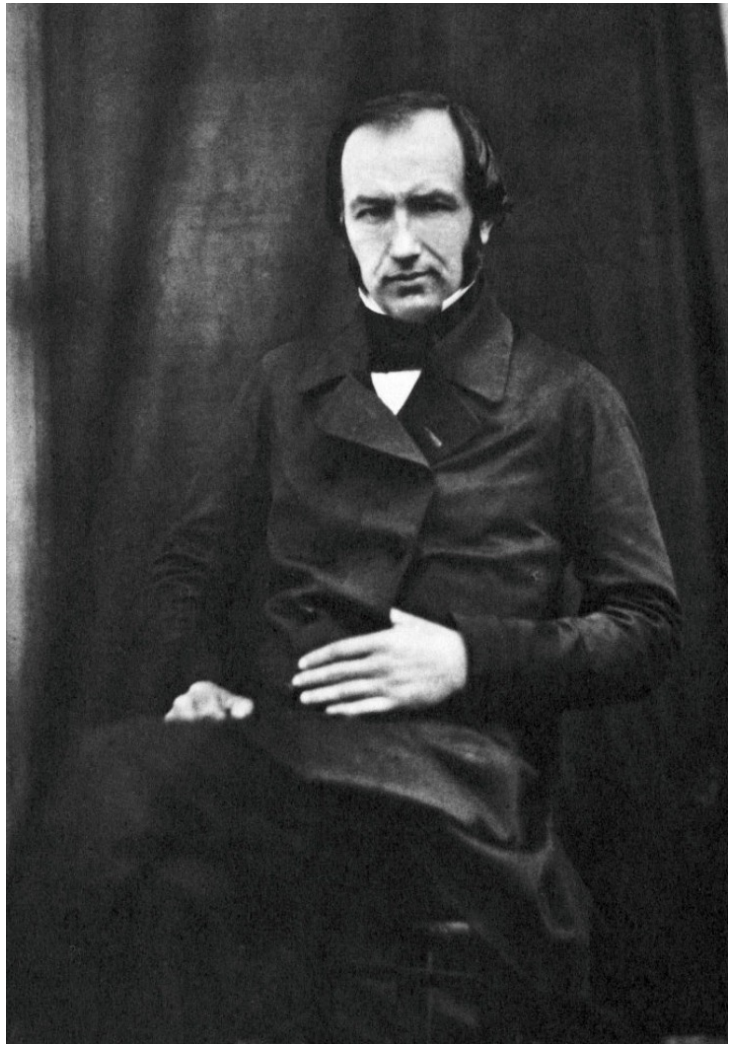
•Stress-response can become more damaging than the stressor itself

Epinephrine acts within seconds, glucocorticoids back up over minutes/hours

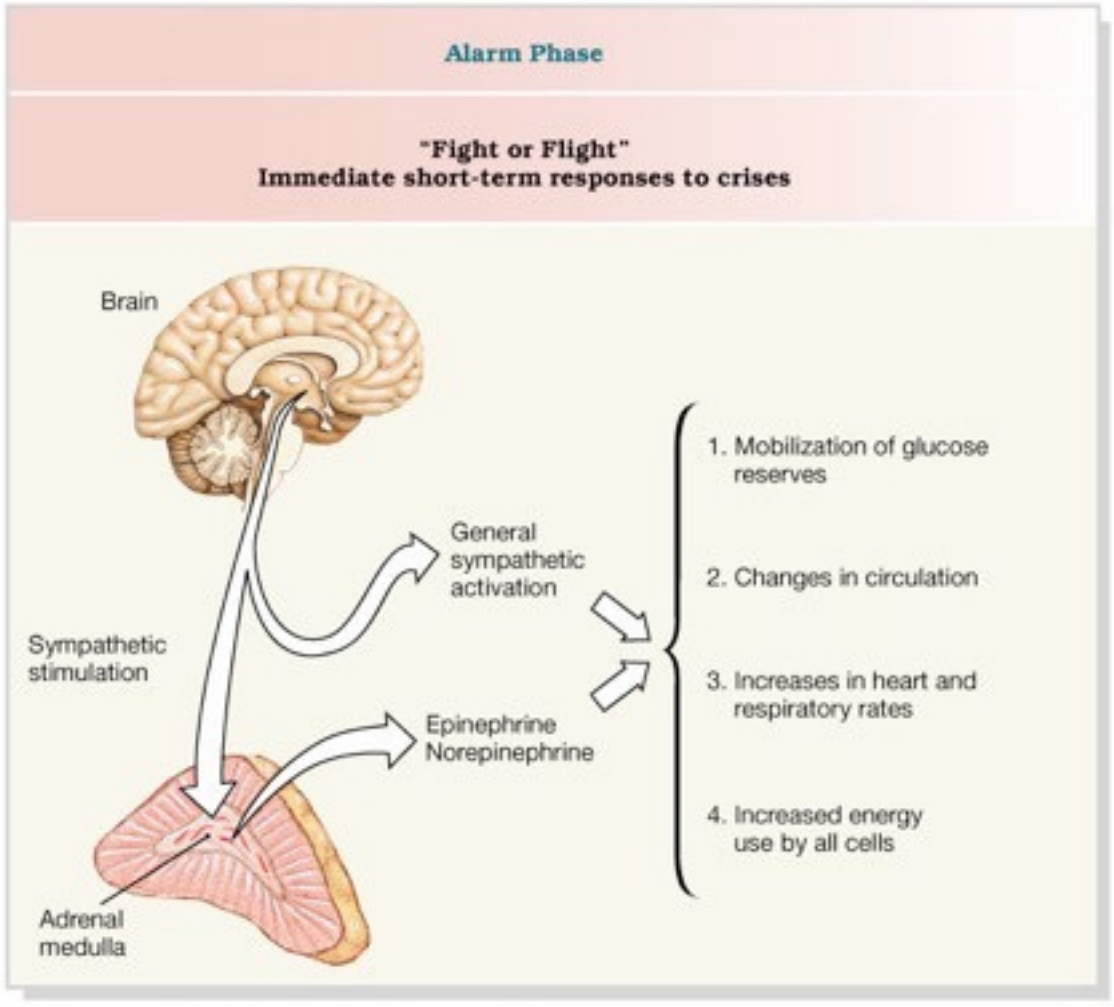
The two potentiate each other's release.

# Stress

Bernard introduced the idea of the internal environment bathing cells
—the *milieu intérieur* — maintained by continual compensatory changes of bodily functions.

# The General Adaptation Syndrome
# The body's response to stress



# "fight or flight"

## Walter Cannon
## 1871-1945

1871-1945
American Physiologist,
Harvard

Studied traumatic shock in WWI soldiers:

"Fight or flight response"

response of the body to an emergency:
epinephrine release

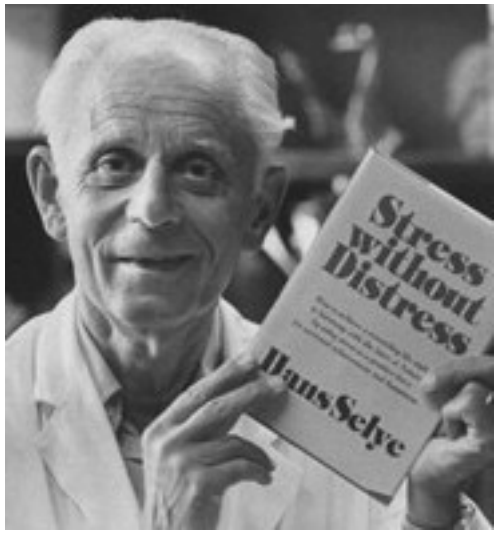
coined the word, "homeostasis," referring to a set of acceptable ranges of values for internal variables. Threats to homeostasis evoke activation of the sympathoadrenal system as a functional unit.

# General Adaptation Syndrome
# Hans Selye

defined stress as a state characterized by a uniform response pattern, regardless of the particular stressor, that could lead to long-term pathologic changes.

1930 rat experiments with ovarian extract

# 1936: The General Adaptation Syndrome




stimuli
(stressors)

cold
heat
noxious chemicals

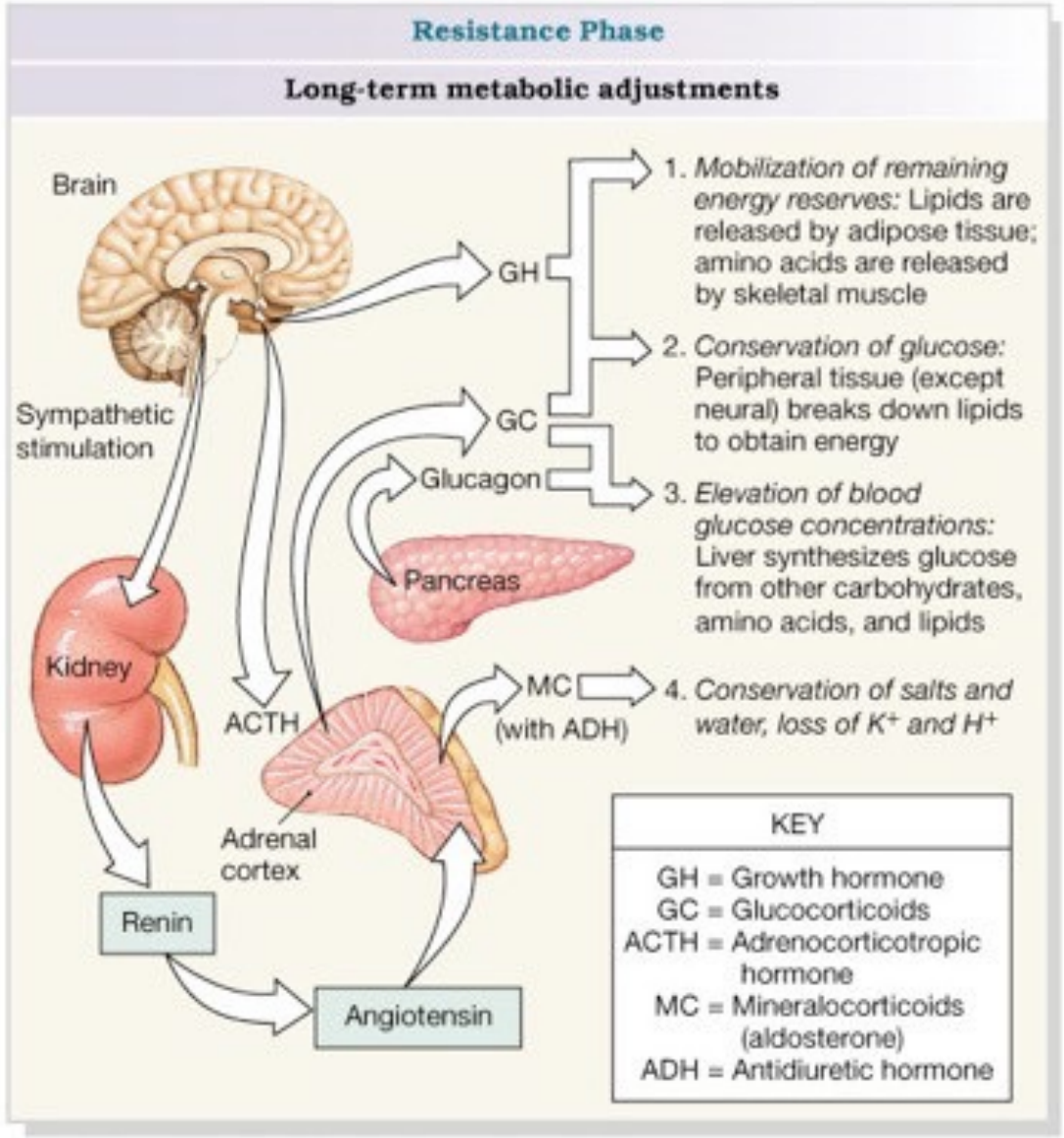
effects

gastric ulcers
enlarged adrenals

3 phases

alarm reaction
stage of resistance
stage of exhaustion

# The General Adaptation Syndrome



# The General Adaptation Syndrome

**Exhaustion Phase**

**Collapse of vital systems**

Causes may include:

- Exhaustion of lipid reserves
- Inability to produce glucocorticoids
- Failure of electrolyte balance
- Cumulative structural or functional damage to vital ‹cgans

# Allostasis:

allo: change, divergence;  stasis: stability

subtle changes an organism makes to adjust in the short term to predictable and unpredictable changes in the environment

response to perceived or actual stressor

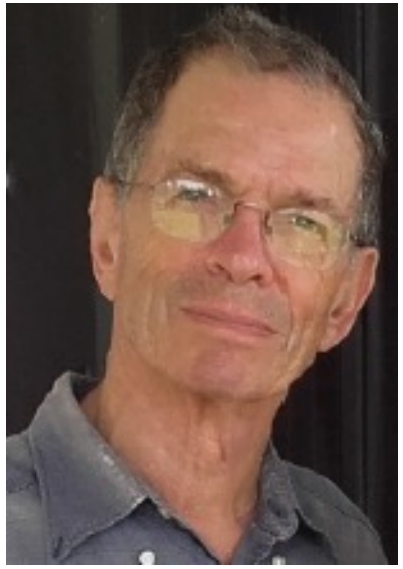
There is not one ideal blood pressure; basal conditions versus stress

Homeostasis: set point is reached through some local regulatory mechanism whereas in allostasis any given set point can be regulated in zillion different ways

- brain coordinates body-wide changes, including in behaviour

Sterling P, Eyer J. Allostasis: A new paradigm to explain arousal pathology.
In: Fisher S, Reason J, editors. Handbook of life stress, cognition, and health.
Chichester, UK: John Wiley & Sons; 1988. pp. 629–649.

# Allostasis



Peter Sterling
Philadelphia

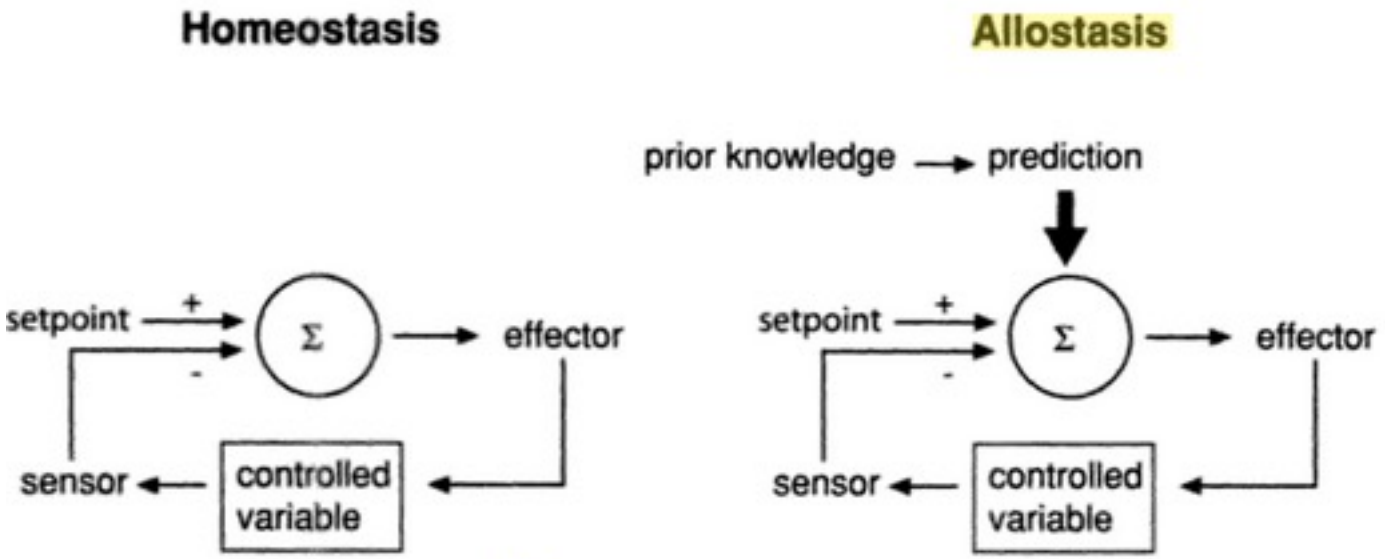



**Figure 1.1:** Alternative models of regulation. Homeostasis describes mechanisms that hold constant a controlled variable by sensing its deviation from a "setpoint" and feeding back to correct the error. Allostasis describes mechanisms that *change* the controlled variable by predicting what level will be needed and then overriding local feedback to meet anticipated demand.

# Allostasis

- -introduced as a concept in recognition that there is no single ideal set of steady-state conditions in life; instead, set points and other response criteria change continuously.

- As a result: Stress is not viewed anymore as a perturbation nor a stereotyped response pattern. It is seen as a condition characterized by a perceived discrepancy between information about a monitored variable and criteria for eliciting patterned effector responses.

- Different stressors elicit different patterns of activation of the sympathetic nervous, adrenomedullary hormonal, hypothalamic-pituitary-adrenocortical and other effectors, closing negative feedback loops. This systems concept of stress yields predictions that observation or experimentation can test and that are applicable to normal physiology and to a variety of acute and chronic disorders.

# Allostatic Load

- **= long-standing effects of continuously activated stress responses**

- can result in permanently altered brain architecture and systemic pathophysiology:
  - hypertension
  - heart disease
  - weakening of the immune system

- can be measured in physiological systems as chemical imbalances in autonomic nervous system, central nervous system, neuroendocrine, and immune system activity as well as perturbations in the diurnal rhythms, and, in some cases, plasticity changes to brain structures.

- Four conditions that lead to allostatic load are:
- 1. Repeated frequency of stress responses to multiple novel stressors
- 2. Failure to habituate to repeated stressors of the same kind
- 3. Failure to turn off each stress response in a timely manner due to delayed shut down.
- 4. Inadequate response that leads to compensatory hyperactivity of other mediators.

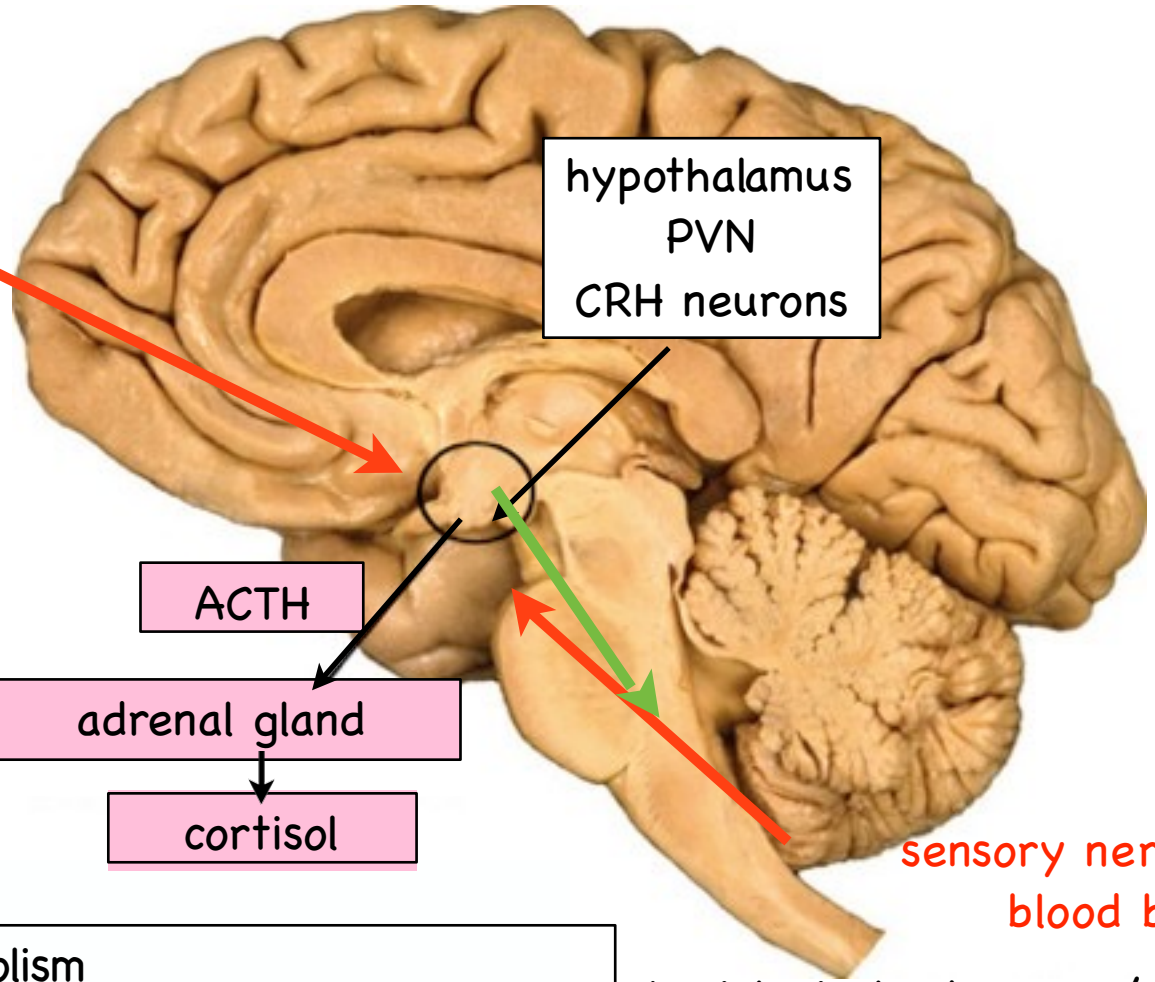
McEwen and Stellar in 1993

# Pathways in response to stressors

forebrain
limbic brain structures

anticipatory stressors

bereavement
fear restraint
unpredictability




sympathetic neurons
intermediolateral cell column

epinephrine

-glycogenolysis
-gluconeogenesis
-fat breakdown
-elevates blood glucose
-cardiovascular effects

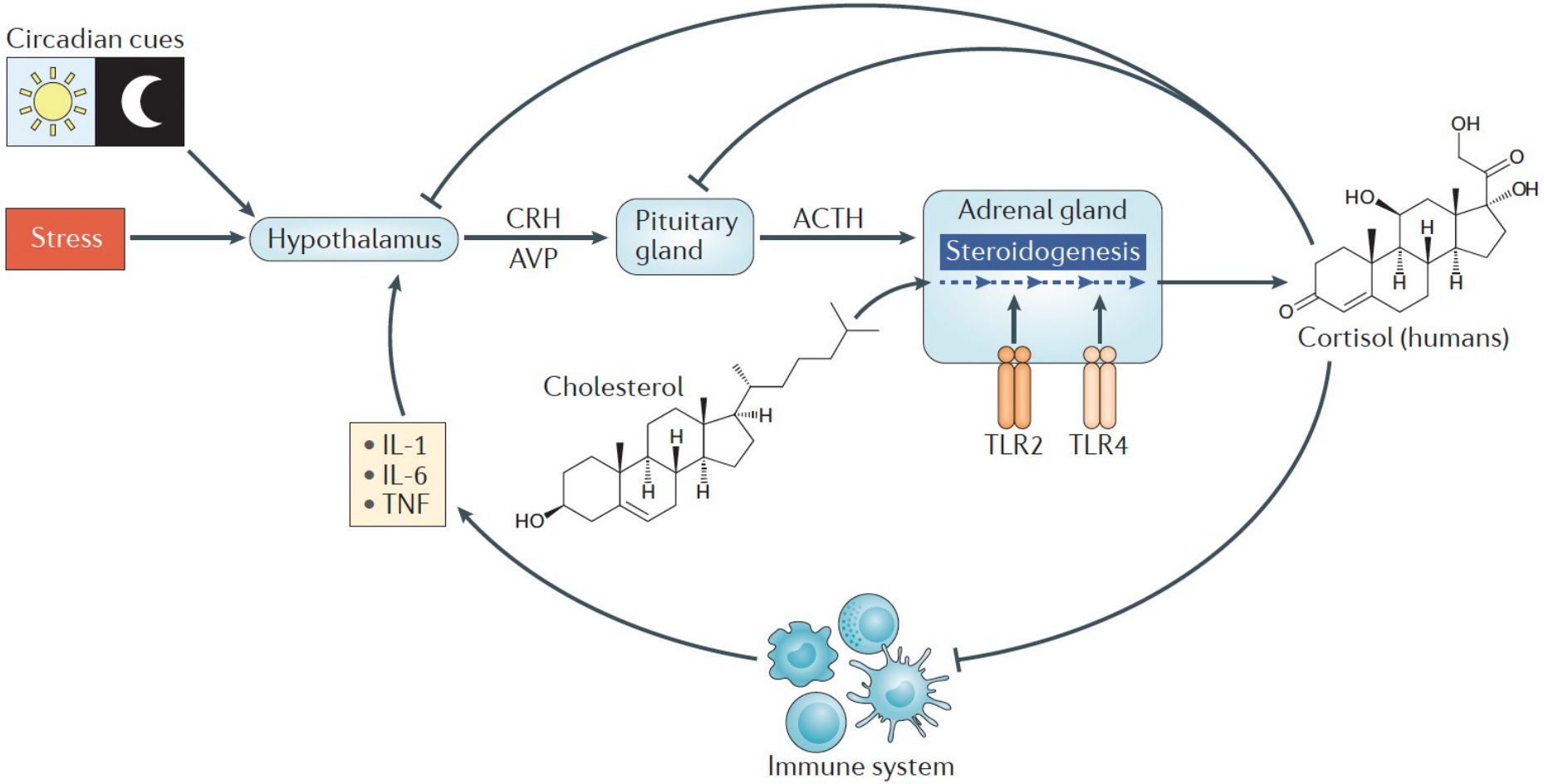
-protein catabolism
-inhibit glucose uptake by muscle - gluconeogenesis
-permissive effect on epinephrine action
-elevates blood glucose
-immune function

sensory nerves from brain stem
blood borne cytokines

physiological stressors/ reactive stimuli

inflammation
noxious chemical exposure
hemorrhage
tissue damage

# Regulation of glucocorticoid production by the HPA axis



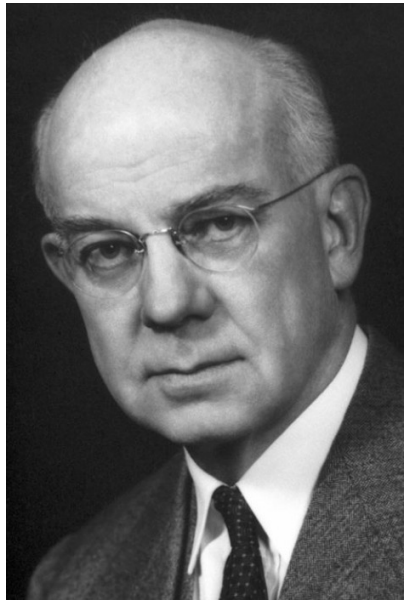

Cain, Cidlowski NRI 2017

# Immune regulation by glucocorticoids

- 1948 Mayo Clinic, Minnesota: patient with rheumatoid arthritis receives daily injections of "compound E" synthetic version of a glucocorticoid

1950 Nobel Prize in Physiology and Medicine: Philip Hench, Edward Kendall, Tadeus Reichstein for the discovery of adrenal cortical hormones

Medical doctor
1896, Pittsburgh, PA, USA
1965, Ocho Rios, Jamaica

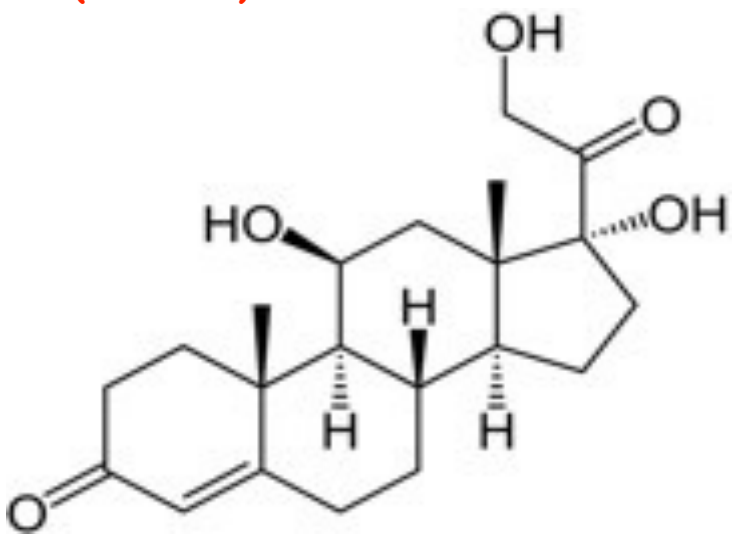


Chemist
1886 South Norwalk, CT
1972 Princeton, NJ, USA

chemist
Born 1897, at Wloclawek
Chemistry ETHZ, Basel 1996

# Cortisol (in humans)

Corticosterone (in mice)




***produced in:**

adrenal cortex
thymus,
intestine
skin

***permissive agent for other hormones:**

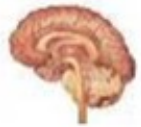
-changes in membrane permeability to important metabolites
-stimulates synthesis of enzymes and receptors to provide appropriate cellular environment, in which other hormones operate

***anti-inflammatory effects:**

-direct interactions with nuclear factor-kappaB (NF-kB) and activator protein 1 (AP1)
-inhibits immunoglobulin E secretion
-stabilizes lysosomal membranes
-inhibits cyclooxygenase enzyme (prostaglandin synthesis)
-high doses inhibit antibody synthesis

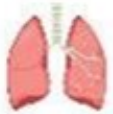
# Biological effects of cortisol

VISUAL SYSTEM
Anti-inflammatory
Anti-angiogenesis
Photoreceptor survival

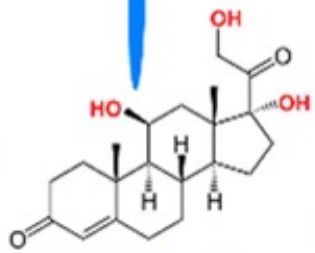


NERVOUS SYSTEM
Physiological homeostasis
Responses to stressors

CARDIOVASCULAR SYSTEM
Anti-inflammatory
Cardiomyocyte survival
Increment of blood pressure
and vascular tone
Anti-angiogenesis

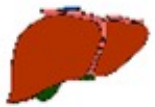


RESPIRATORY SYSTEM
Suppression of cytokines,
chemokines, and
cell adhesion molecules




Cortisol

IMMUNE SYSTEM
Suppression of pro-
inflammatory cytokines
Regulation of immune cell
maturation, migration
and apoptosis



GLUCOSE AND LIVER
METABOLISM
Glucose regulation
Lipid homeostasis

REPRODUCTIVE SYSTEM
Gonadal function
Fetal organ development
and maturation

MUSCOLOSKELETAL SYSTEM
Anti-inflammatory
Muscle catabolism and anabolism
Insulin resistance
Osteoblast apoptosis
Osteoclastogenesis

INTEGUMENTARY SYSTEM
Anti-inflammatory
Delayed wound healing
Epithelial integrity

Michael Santoro and his twin sister, Paula, who had Cushing's Syndrome.

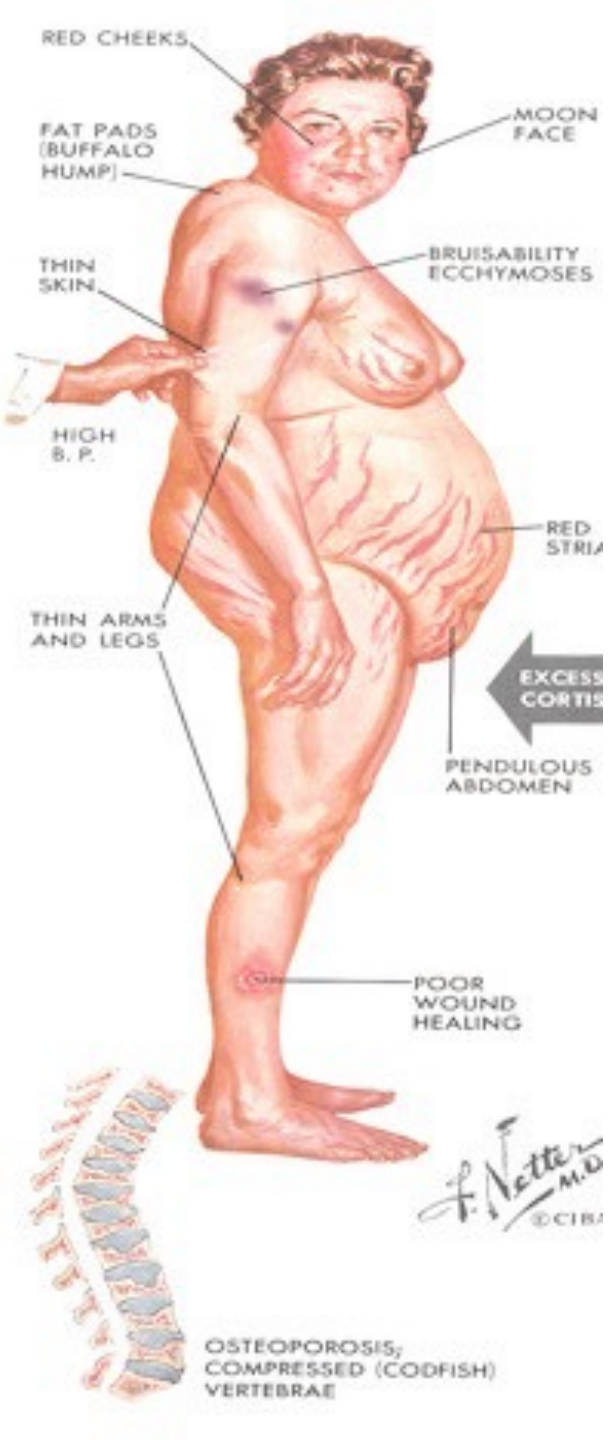
- Cushing's sydndrome

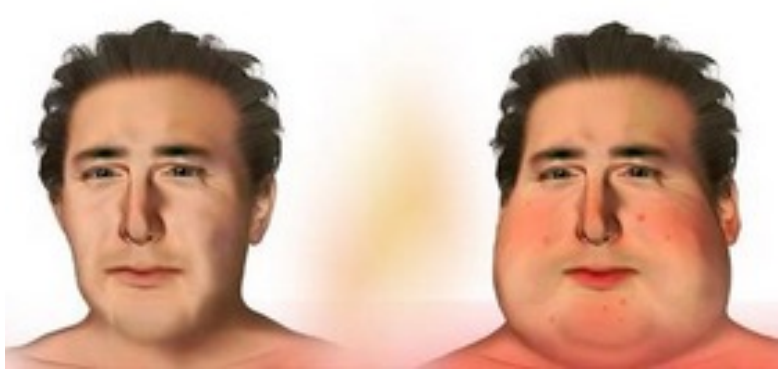
- causes
  - pharmacologic
  - pituitary adenoma
  - adrenal adenoma, carcinoma
  - ectopic ACTH

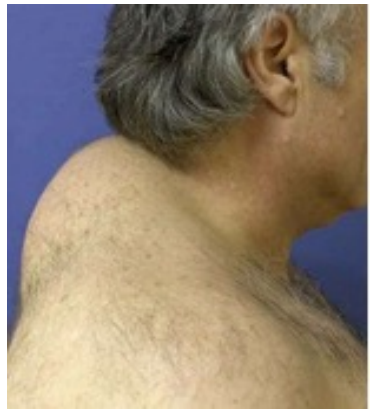
- treatment based on cause

# Cushing's syndrome

Hyperadrenocorticism





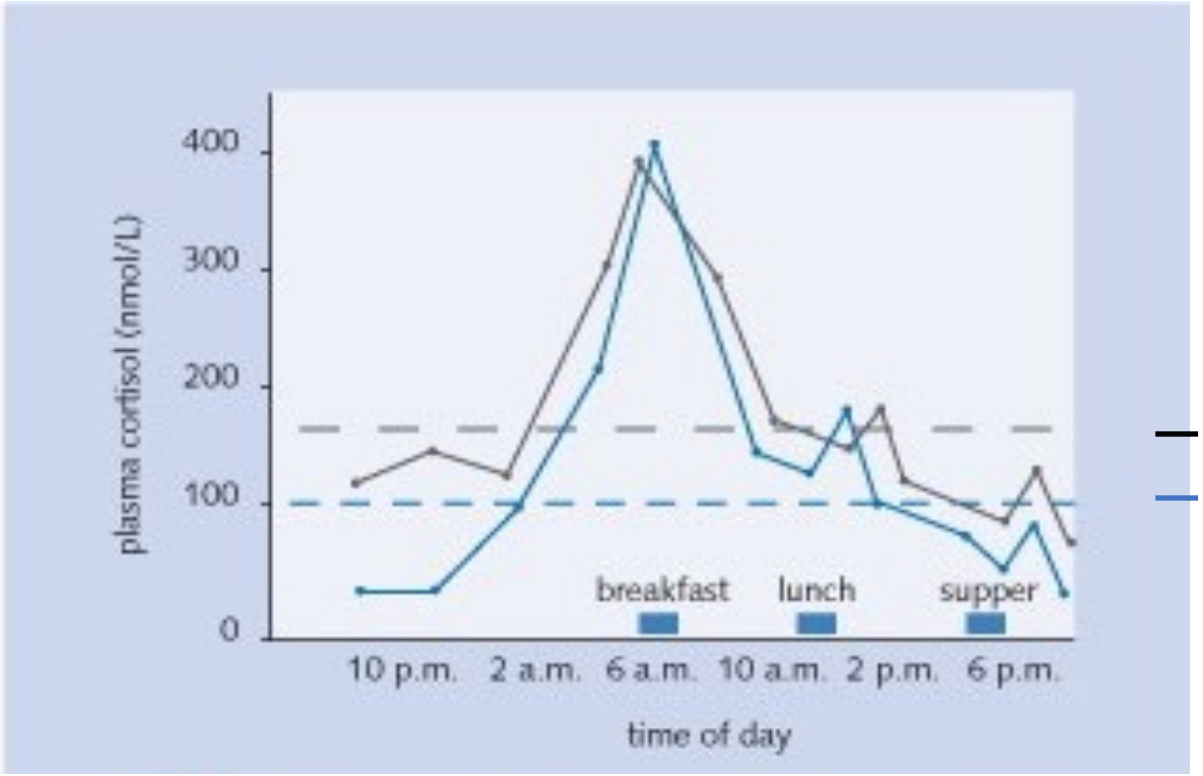
Box 1 | **Adverse effects of glucocorticoid excess: the CUSHINGOID mnemonic**

The term 'cushingoid' describes the collection of signs and symptoms that are associated with Cushing syndrome, which results from excess glucocorticoid activity (either endogenous or exogenous). The medical mnemonic below reveals the widespread roles of glucocorticoids in various physiological systems.

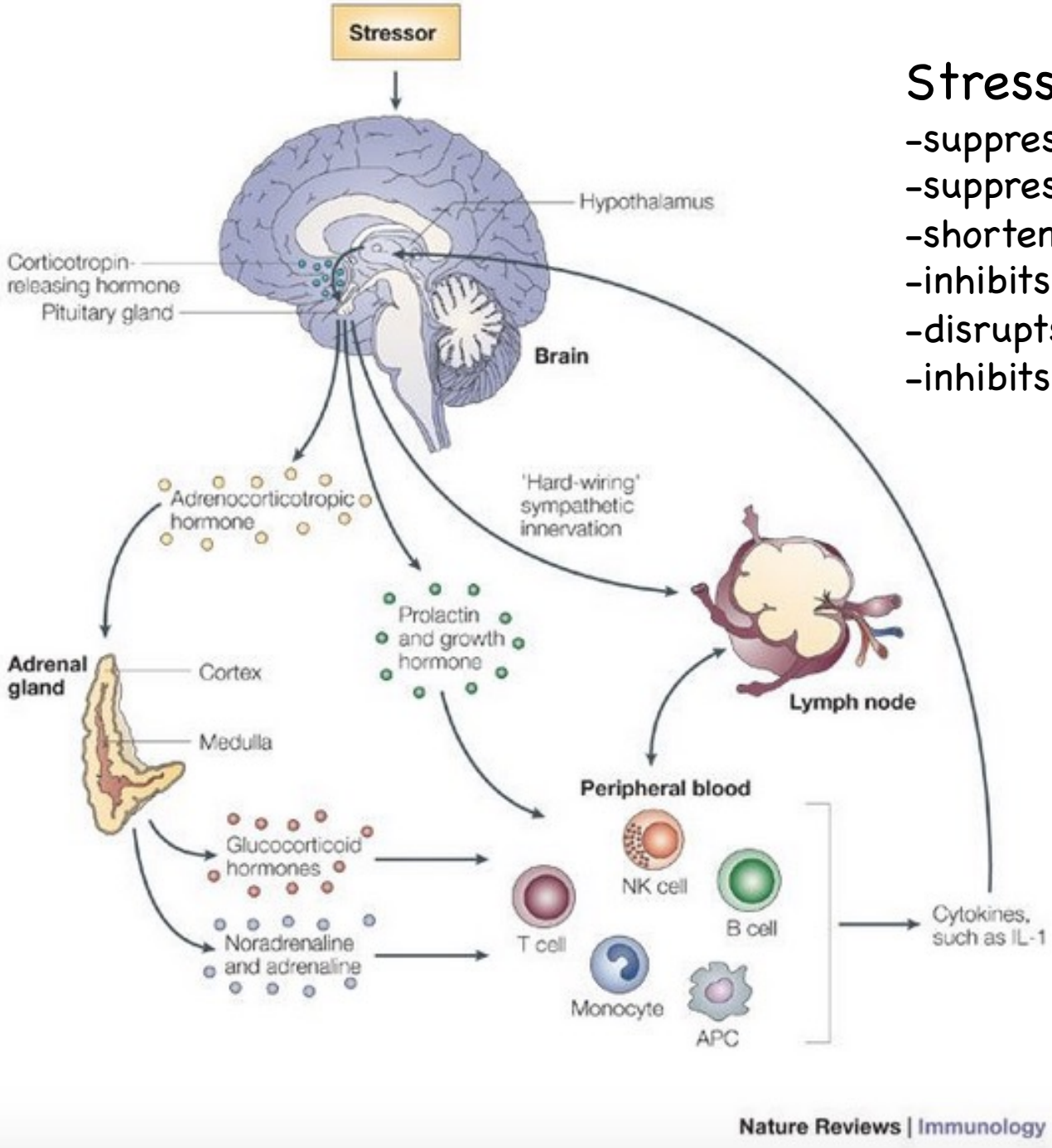
| Letter of mnemonic | Sign or symptom | Pathophysiology |
|---|---|---|
| C | Cataracts | Unknown but may involve perturbed migration of lens epithelial cells[113] |
| U | Ulcers | Disputed, but may be due to the inhibition of gastric-protective prostaglandins, mucus production and/or bicarbonate secretion[114] |
| S | Striae and skin thinning | Unclear but may involve decreased fibroblast proliferation and/or altered metabolism of the extracellular matrix[115] |
| H | Hypertension and hirsutism (in women) | Increased plasma volume, cardiac output and peripheral vascular resistance occur through both mineralocorticoid and glucocorticoid effects[116]; hirsutism occurs due to dysregulated production of adrenal testosterone |
| I | Immunosuppression and infections | Discussed in the main text |
| N | Necrosis of femoral heads | Increased bone marrow fat, decreased bone perfusion and osteocyte apoptosis[117] |
| G | Glucose elevation | Glucose intolerance and insulin insensitivity[118] |
| O | Osteoporosis and obesity | Inhibition of osteoblast function and survival, decreased bone mass (osteoporosis)[119] and redistribution of adipose tissue (obesity)[118] |
| I | Impaired wound healing | Reduced proliferation of fibroblasts and epidermal cells, inhibition of collagen synthesis and reduced angiogenesis[120] |
| D | Depression and mood changes | Psychological, cognitive and behavioural disturbances[121] |

Cain, Cidlowski NRI 2017

# Circadian variation in plasma cortisol levels in resting and chronically stressed




There is a 40% decline in the number of circulating T cells from night to morning as a result of altered tissue homing.




# Stress

-suppresses formation of new lymphocytes
-suppresses release of lymphocytes into the circulation
-shortens their stay in the circulation
-inhibits antibody synthesis
-disrupts intercellular communication
-inhibits innate immune response

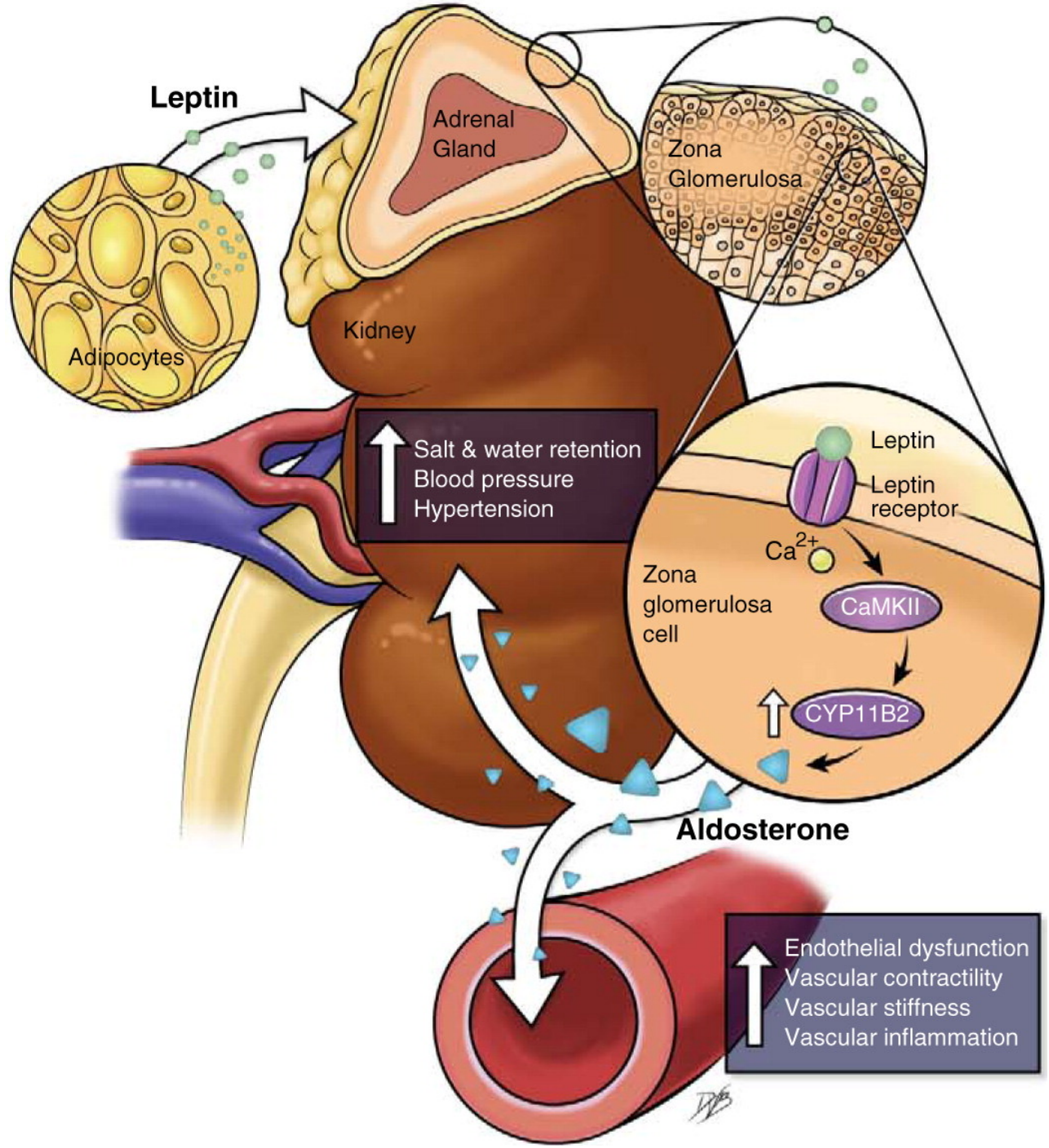
# SERPINA6 corticosteroid-binding globulin (CBG)

-primarily produced in the liver
-binds to cortisol
-when cortisol is bound to CBG, the hormone is inactive
-normally, around 80 to 90% of the body's cortisol is bound to CBG
-5-10% is unbound and active
-remaining cortisol is bound to albumin
-when cortisol is needed in the body, CBG delivers the cortisol to the appropriate tissues and releases it, causing cortisol to become active

=> CBG regulates the amount of cortisol that is available for use in the body

-cleaved by **neutrophil elastase** between a valine and a threonine residue in the reactive center loop. The single cut causes a strong decrease of the cortisol binding activity:

=> local or systemic release of high amounts of free cortisol at sites of inflammation.

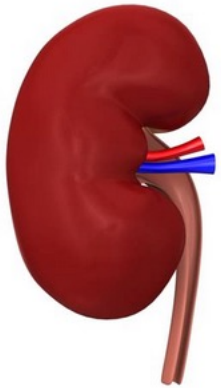

Leptin
Adrenal Gland
Zona Glomerulosa
Adipocytes
Kidney
Salt & water retention
Blood pressure
Hypertension
Leptin
Leptin receptor
$Ca^{2+}$
Zona glomerulosa cell
CaMKII
CYP11B2
Aldosterone
Endothelial dysfunction
Vascular contractility
Vascular stiffness
Vascular inflammation

# **Aldosterone:** principal mammalian "mineralocorticoid"

-maintains Na+ and K+ balance in body fluids

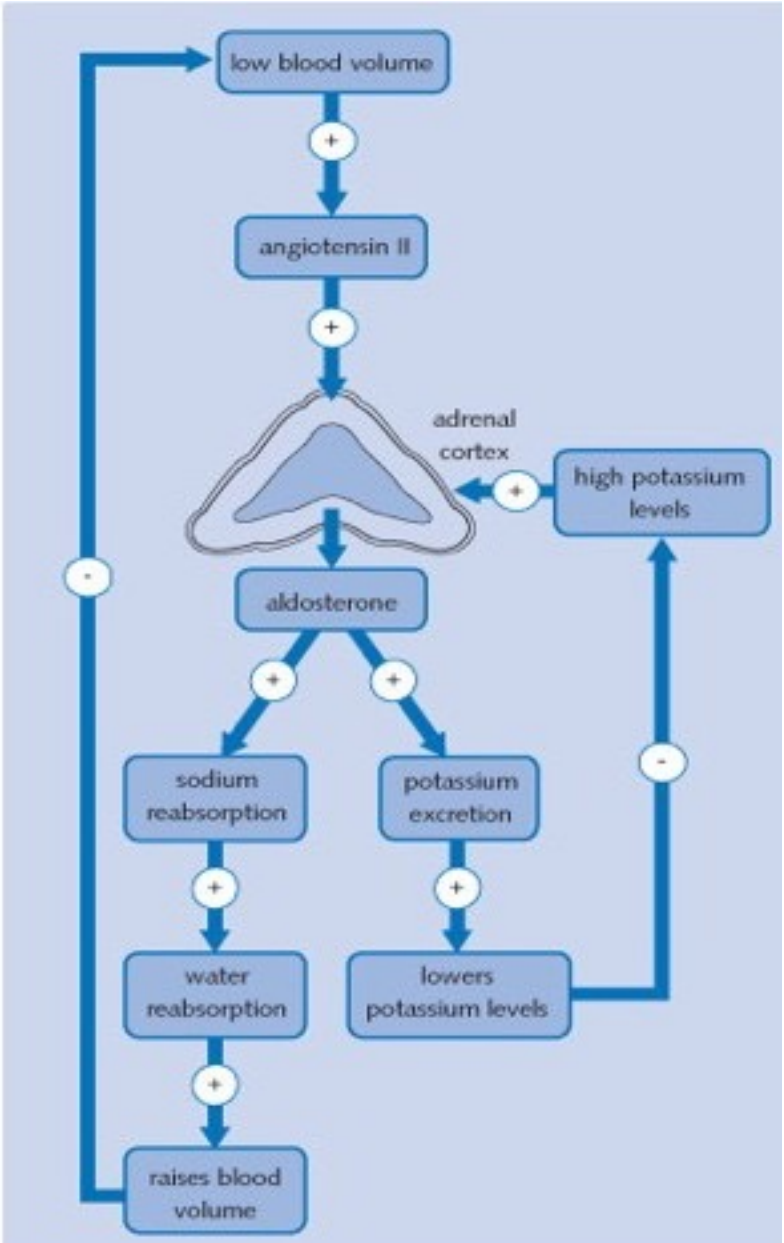
-regulates extracellular fluid volume

Increase reabsorption of Na+



Aldosterone

Decrease the loss of Na+



# Effects of proteins induced by aldosterone in the nephron

| Protein | Location | Action | Physiological response |
|---|---|---|---|
| $Na^+/K^+$ ATPase | Cell membrane on the side of the blood supply | Active pump that increases cell potassium and lowers cell sodium levels | Creates an ion gradient that drives the other proteins |
| $Na^+$ channel | Cell membrane on the side of the nephron | Reabsorbs sodium from the nephron lumen | Increases plasma sodium and water to increase blood volume |
| $K^+$ channel | Cell membrane on the side of the nephron | Excretes potassium into the nephron lumen | Decreases plasma potassium |
| $Na^+/H^+$ ion exchanger | Cell membrane on the side of the nephron | Reabsorbs sodium in exchange for hydrogen ions | Makes the plasma more alkaline |

# Hypoadrenocorticism

## Addison's disease

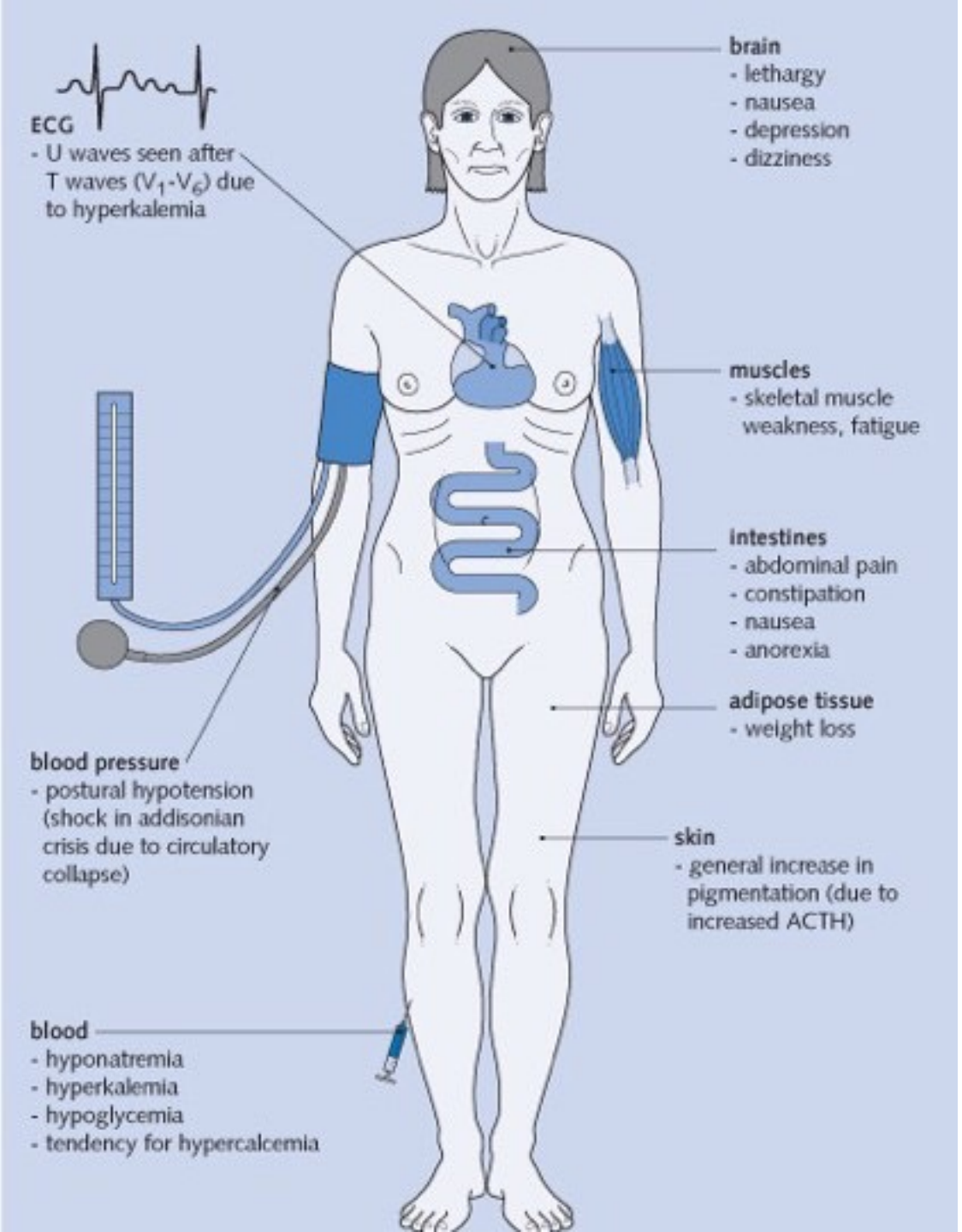
Causes:

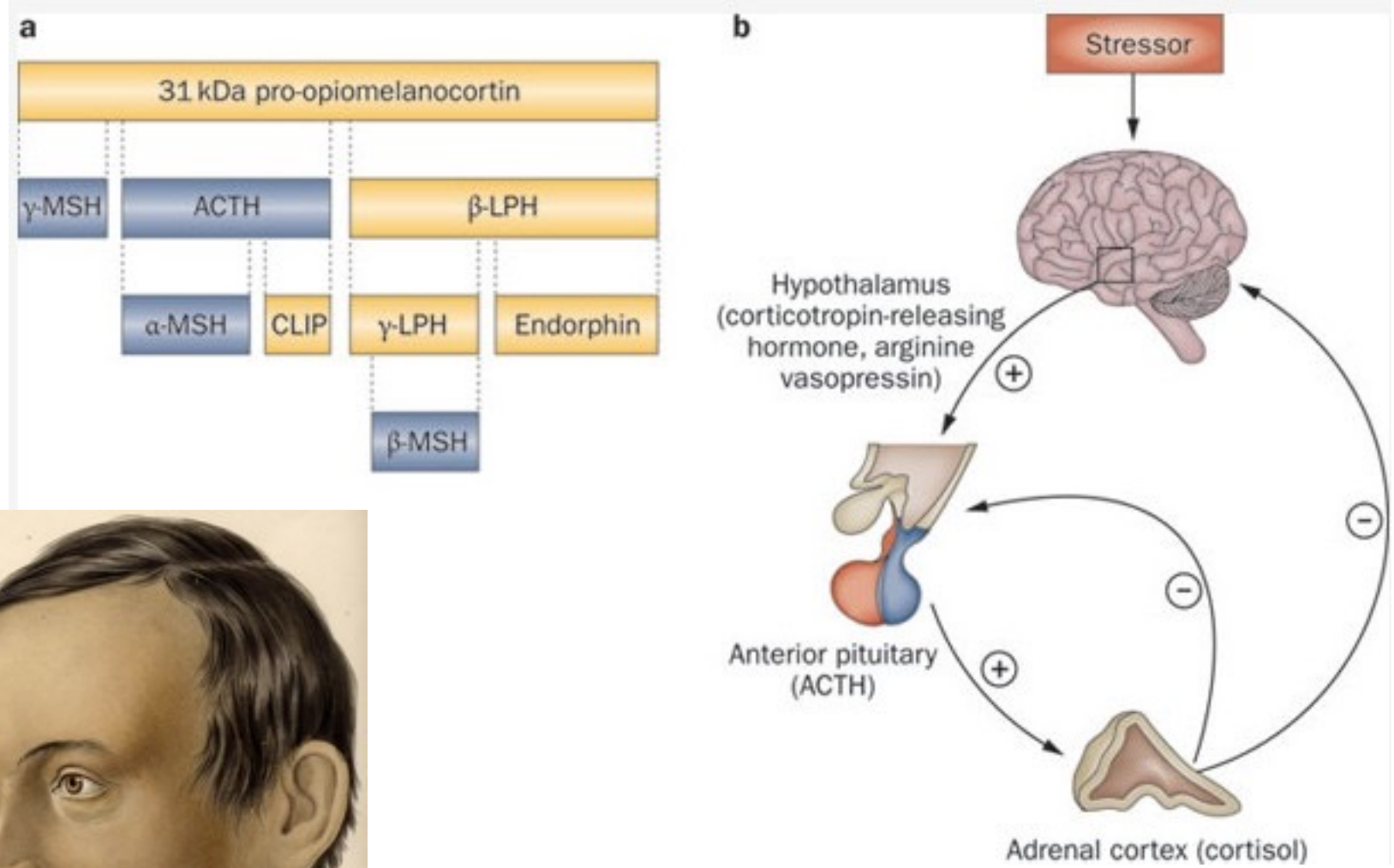
-tuberculosis

-autoimmune

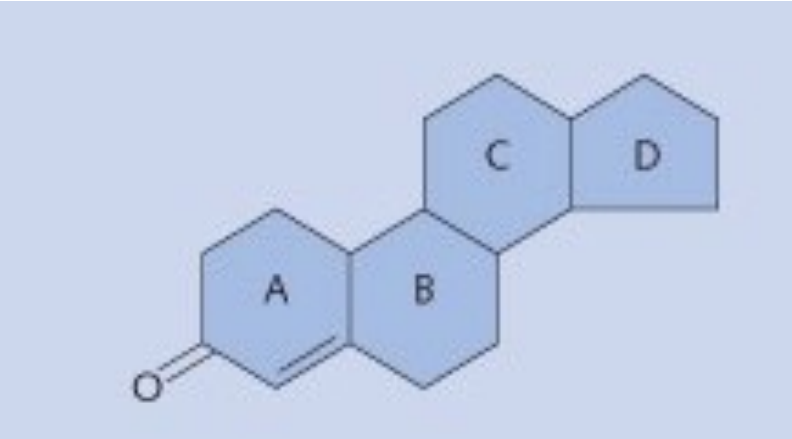
## Congenital adrenal hyperplasia (CAH)

-21 hydroxylase deficiency (P450 c21)




a
31 kDa pro-opiomelanocortin
γ-MSH
ACTH
β-LPH
α-MSH
CLIP
γ-LPH
Endorphin
β-MSH
b
Stressor
Hypothalamus
(corticotropin-releasing
hormone, arginine
vasopressin)
+
Anterior pituitary
(ACTH)
+
−
−
Adrenal cortex (cortisol)

# Steroid hormones biosynthesis



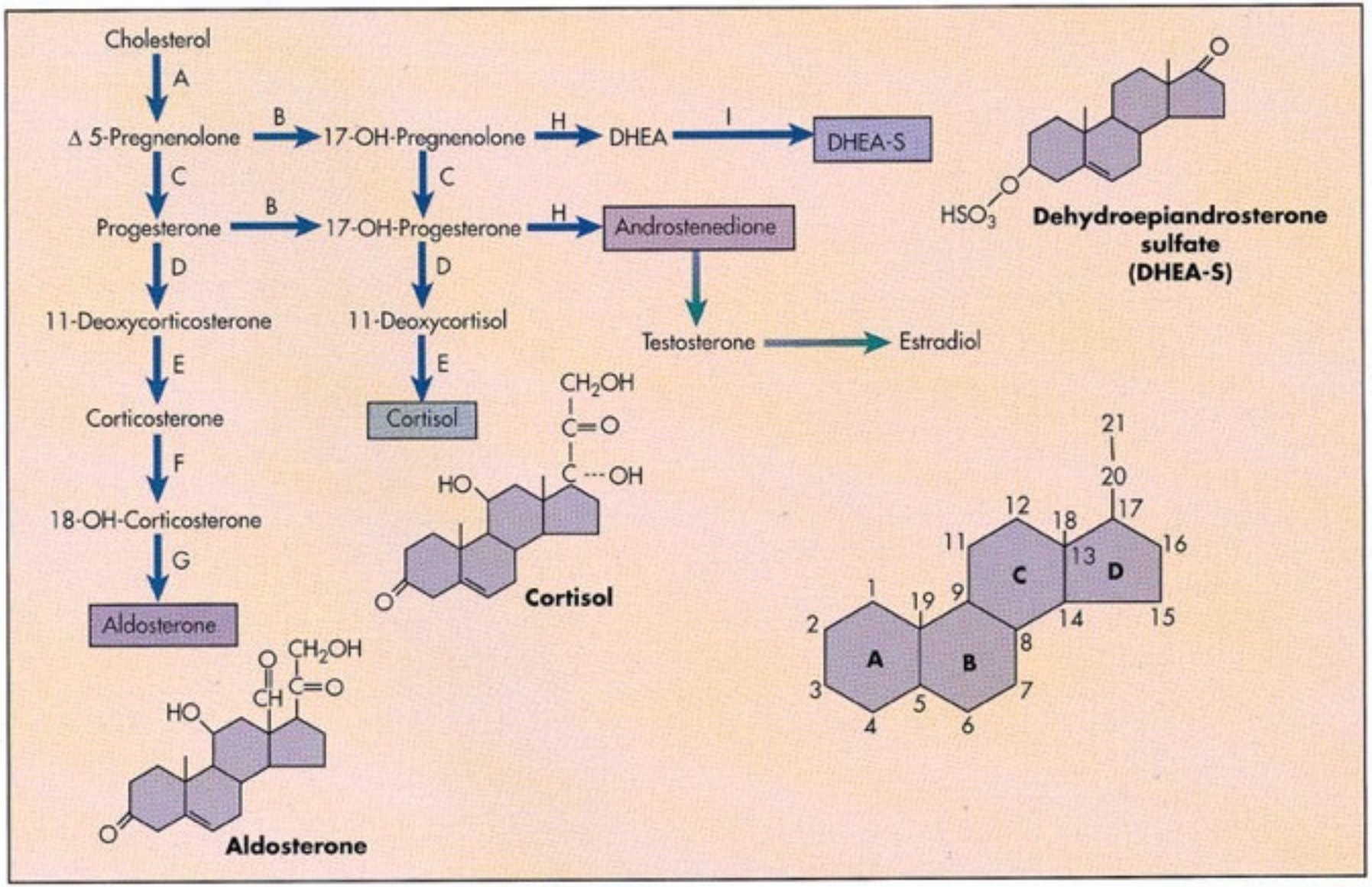

**A, B, C = 6-carbon ring**
**D = 5-carbon ring**

-small
-lipophilic
-circulate bound to plasma proteins

# Steroid Hormones

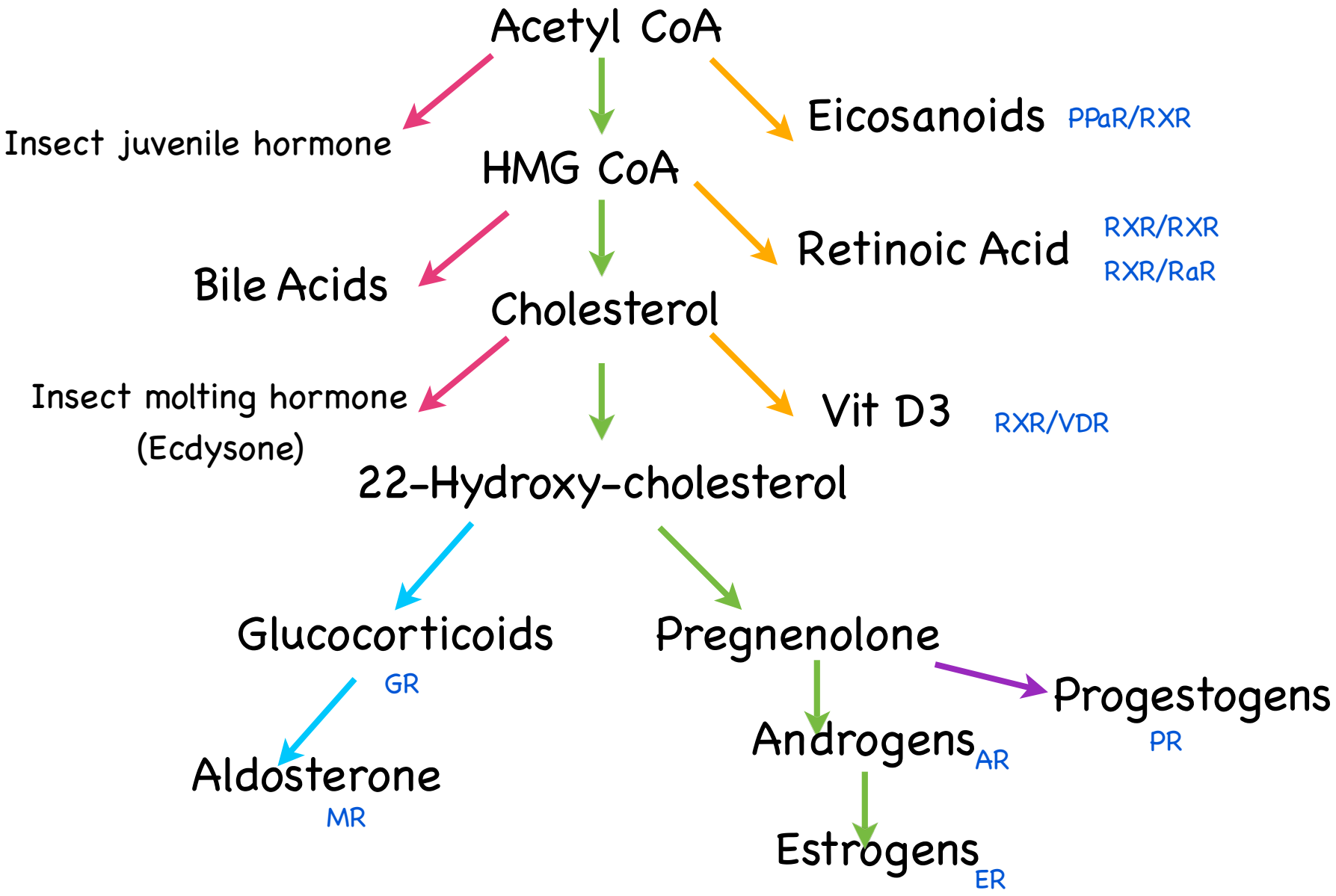
- Formed and secreted by:
  - adrenal cortex
  - testis
  - ovary
  - placenta (progesterone during pregnancy)
  - kidney: forms vitamin D3 from cholesterol precursor

- Precursor of steroid hormones
  - cortisol
  - aldosterone
  - testosterone
  - estrogen
  - progesterone

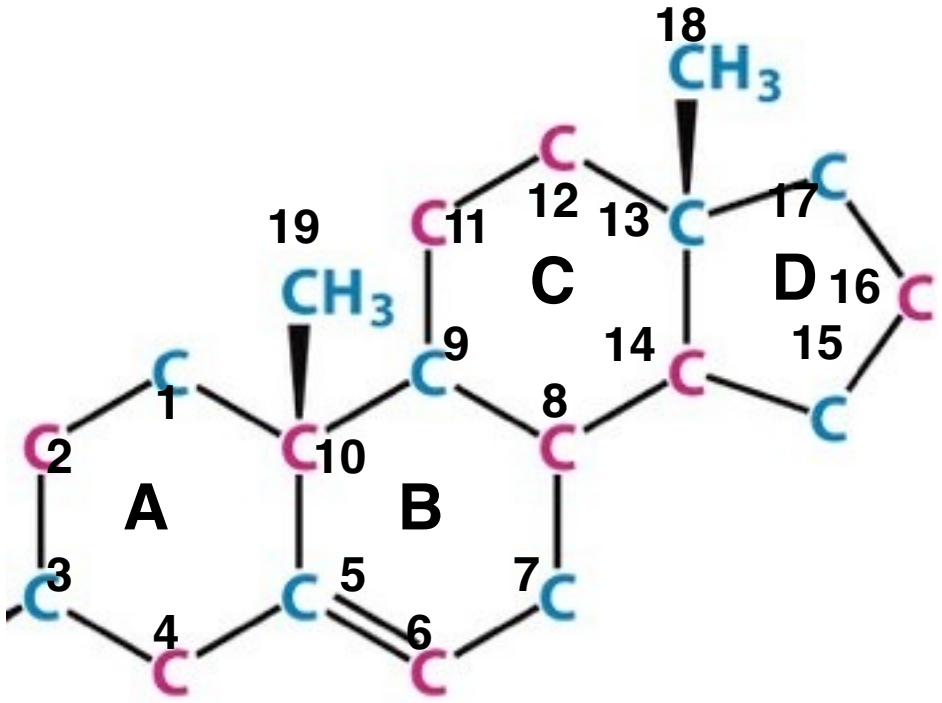

Cholesterol
A
Δ 5-Pregnenolone
B
17-OH-Pregnenolone
H
DHEA
I
DHEA-S
C
C
Progesterone
B
17-OH-Progesterone
H
Androstenedione
D
D
11-Deoxycorticosterone
11-Deoxycortisol
Testosterone
Estradiol
E
E
Corticosterone
Cortisol
F
18-OH-Corticosterone
G
Aldosterone
Dehydroepiandrosterone sulfate (DHEA-S)
Cortisol
Aldosterone
A
B
C
D

| Class | Example | Nr of Carbons | Major Sites of Synthesis |
|---|---|---|---|
| Progestogens | Progesterone | 21 | Adrenal Cortex |
| | | | Male:testis |
| | | | Female: Ovary; adipose tissue |
| Glucocorticoid | Cortisol | 21 | Adrenal Cortex: z. fasciculata |
| | Corticosterone | 21 | Adrenal Cortex: z. fasciculata |
| Mineralocortic | Aldosterone | 21 | Adrenal C.: zona glomerulosa |
| Androgens | Testosterone | 19 | Male:testis |
| | | | Female: ovary; adrenal cortex |
| | Dihydroepiandrosterone | 19 | Adrenal Cortex: z. reticularis |
| Estrogens | Estradiol | 18 | Ovary, testis |
| Vitamin D | Cholecalciferol | 25 | Skin (UV light dependent) |
| | 25-Hydroxycholecalciferol | 25 | Liver (from cholecalciferol) |
| | 1,25-Dihydroxycholecalciferol | 25 | Kidney (from 25-hydroxycho.) |
| Cholesterol | | 27 | Liver, gonads, adrenal cortex |

# Steroids and synthetically related lipid bioregulators



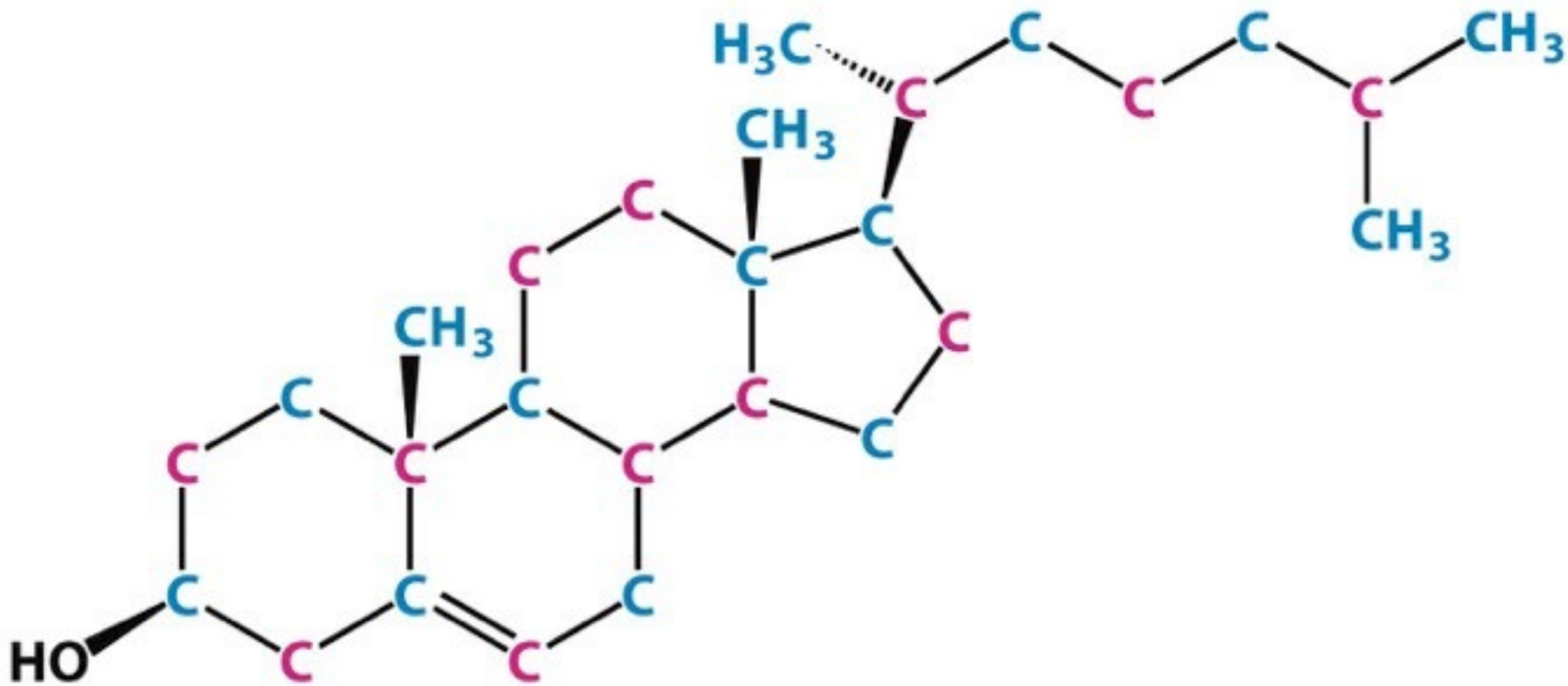
# Steroids




are lipids that contain 4 carbon rings joined to form the steroid nucleus:

cyclopentaoperhydrophenanthrene

# Cholesterol



# Cholesterol

- "13 Nobel Prizes have been awarded to scientists who devoted part of their careers to cholesterol.

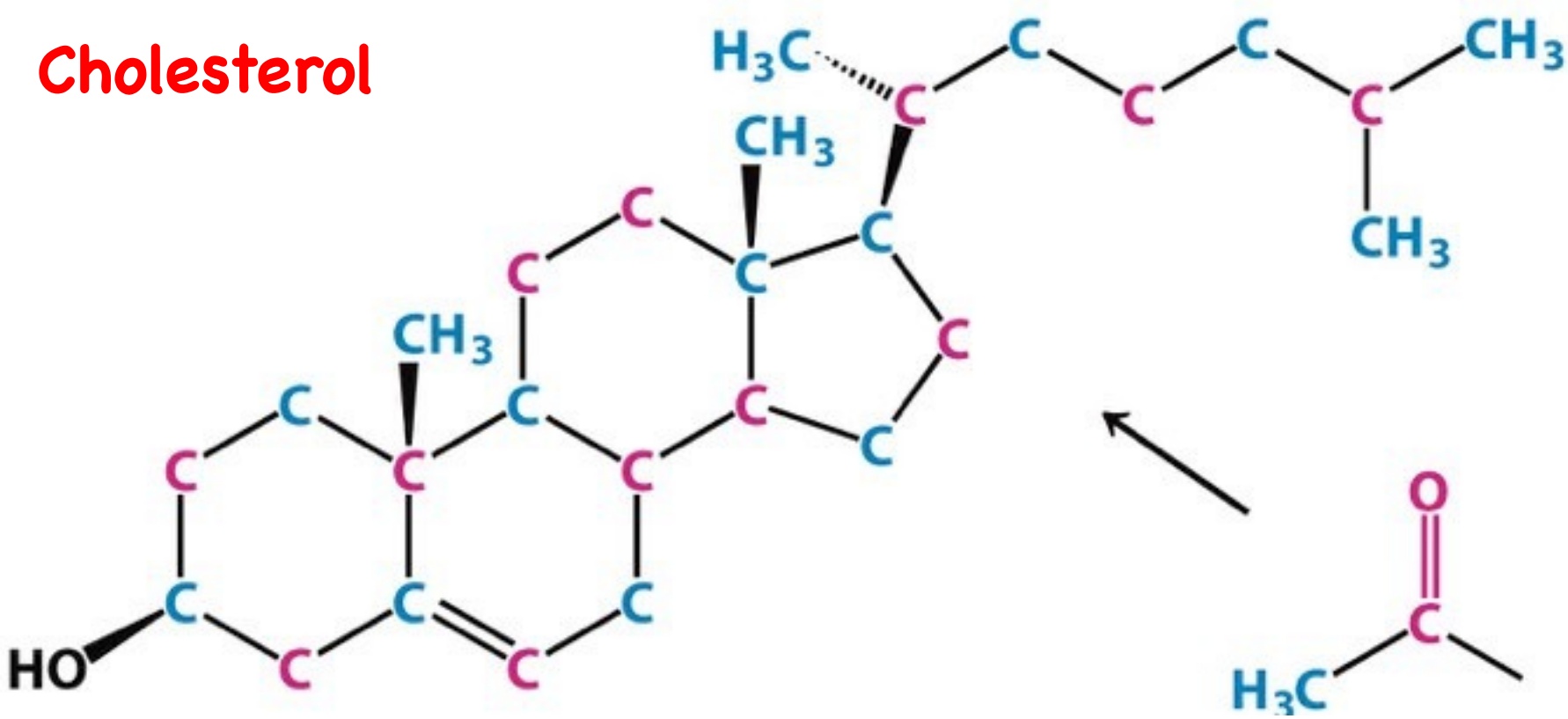
- ...is a Janus faced molecule. The very property that makes it useful in cell membranes, namely its absolute insolubility in water, also makes it lethal."

  Michael Brown and Joseph Goldstein, Nobel Lectures (1985)

- sites of cholesterol biosynthesis
  - major: liver
  - other: intestines, adrenals, gonads, skin, neural tissue, aorta

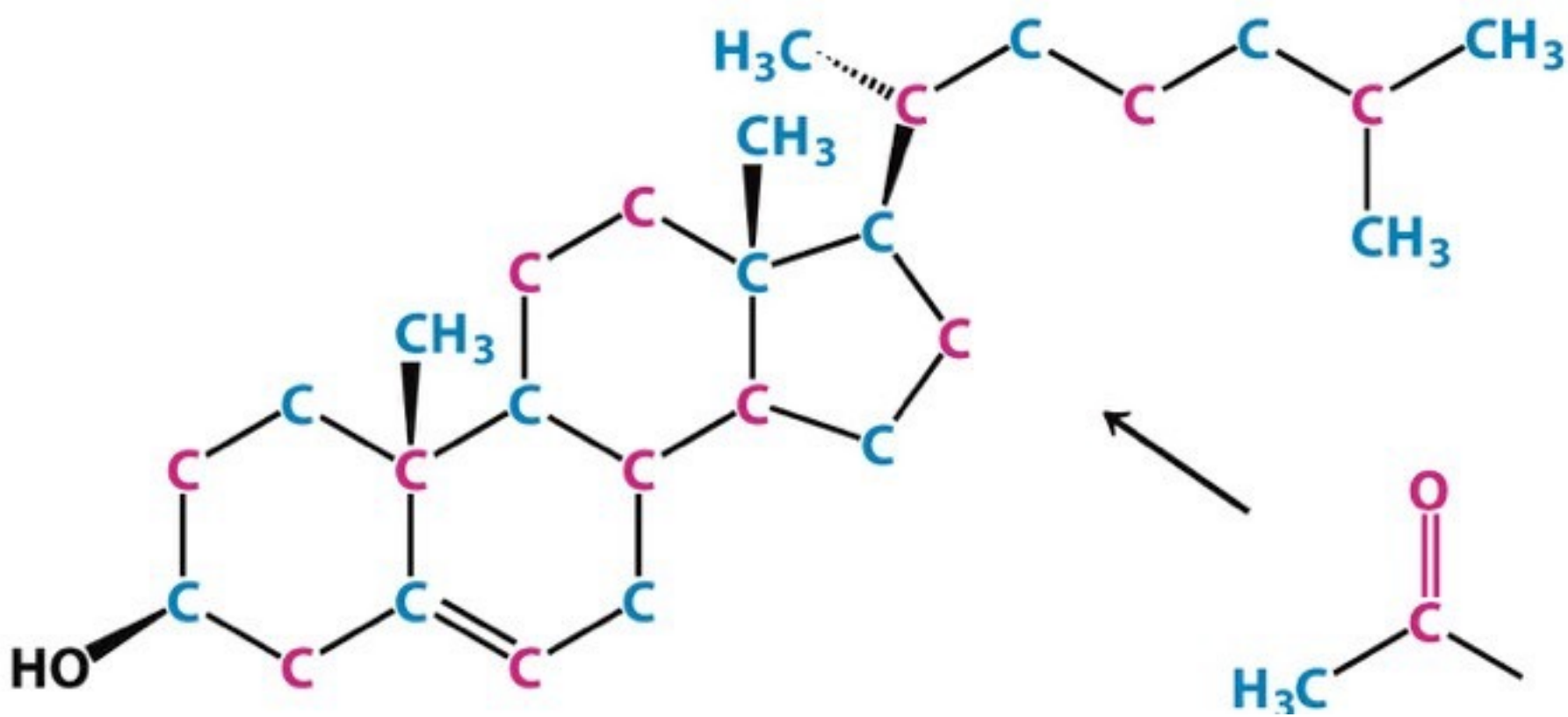
- Note: Cholesterol evolved only after the earth's atmosphere became aerobic. Cholesterol is ubiquitous in eucaryotes but absent from most procaryotes.

# Cholesterol



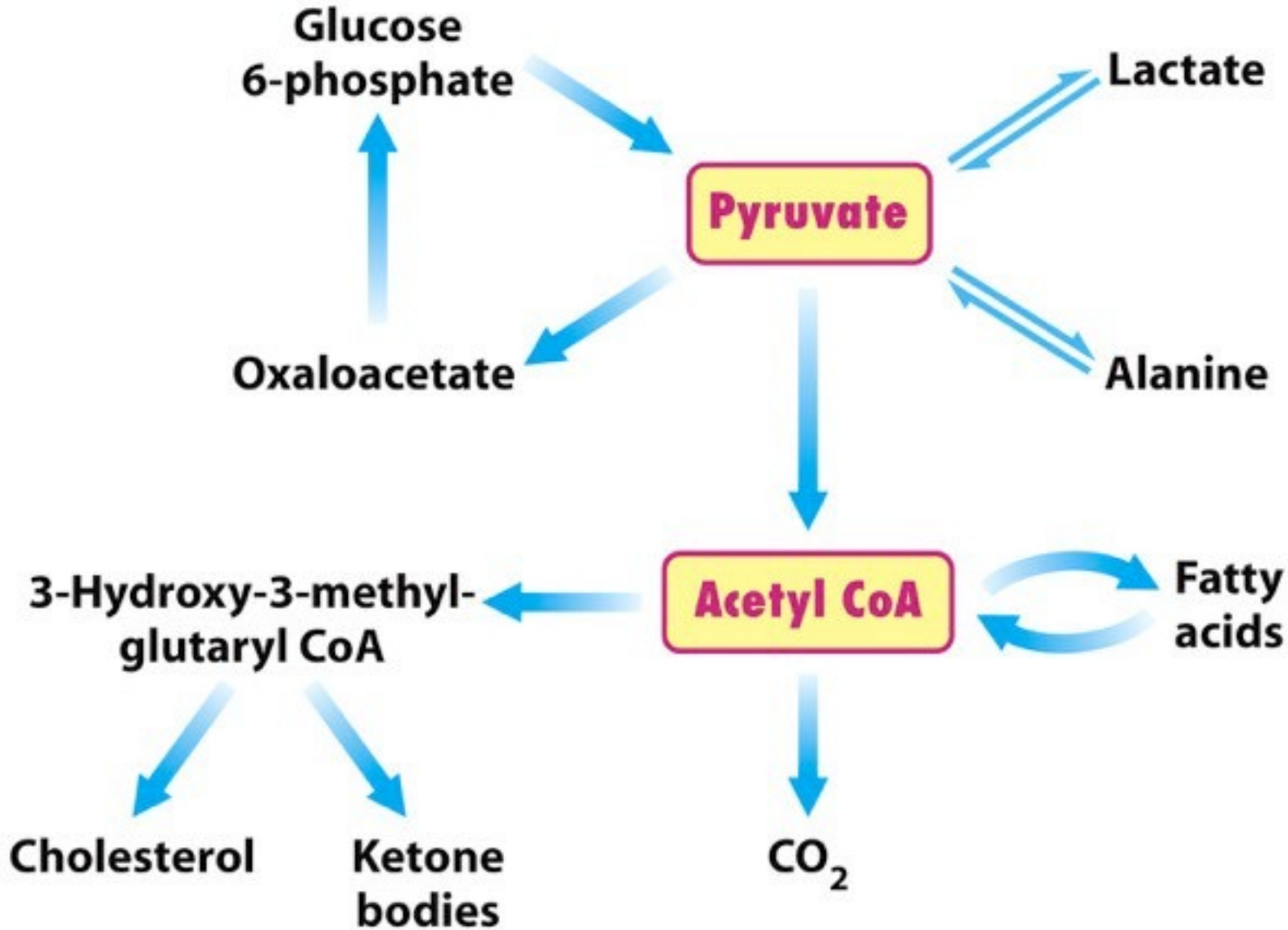

1940, Konrad Bloch (Nobel Prize 1964):
fed radioactively labeled acetate to rats: cholesterol contained radioactivity
=> acetate is a precursor of cholesterol

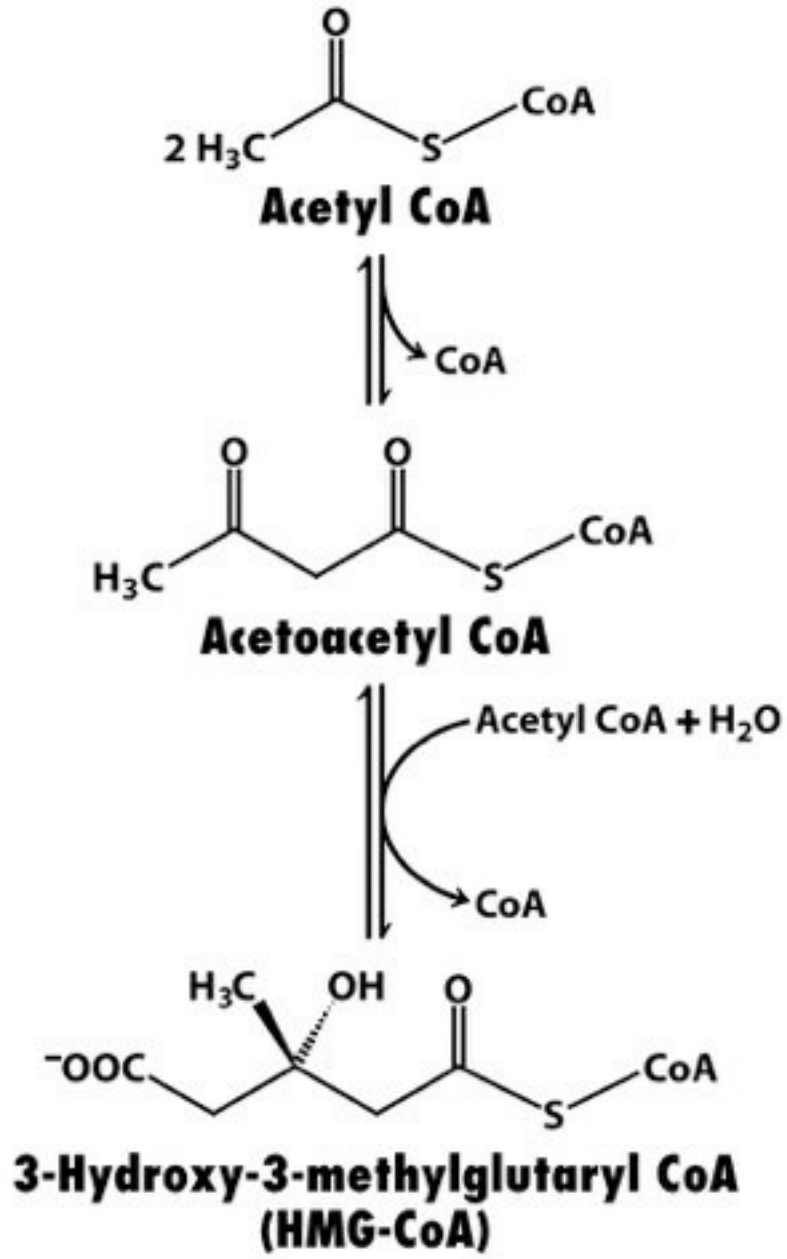
All 27 carbon atoms of cholesterol are derived from acetyl CoA.




Degradation of cholesterol synthesized from acetate labeled in either its methyl or its carboxyl carbon showed the origin of each atom.

Magenta: carboxyl carbon atom
Blue: methyl carbon atom


Glucose
6-phosphate
Lactate
Pyruvate
Oxaloacetate
Alanine
Acetyl CoA
3-Hydroxy-3-methyl-
glutaryl CoA
Fatty
acids
Cholesterol
Ketone
bodies
$CO_2$


O
2 H3C
S
CoA
Acetyl CoA
CoA
O
O
H3C
S
CoA
Acetoacetyl CoA
Acetyl CoA + H2O
CoA
H3C
OH
O
-OOC
S
CoA
3-Hydroxy-3-methylglutaryl CoA
(HMG-CoA)

STATINS

commited step

HMG-CoA reductase

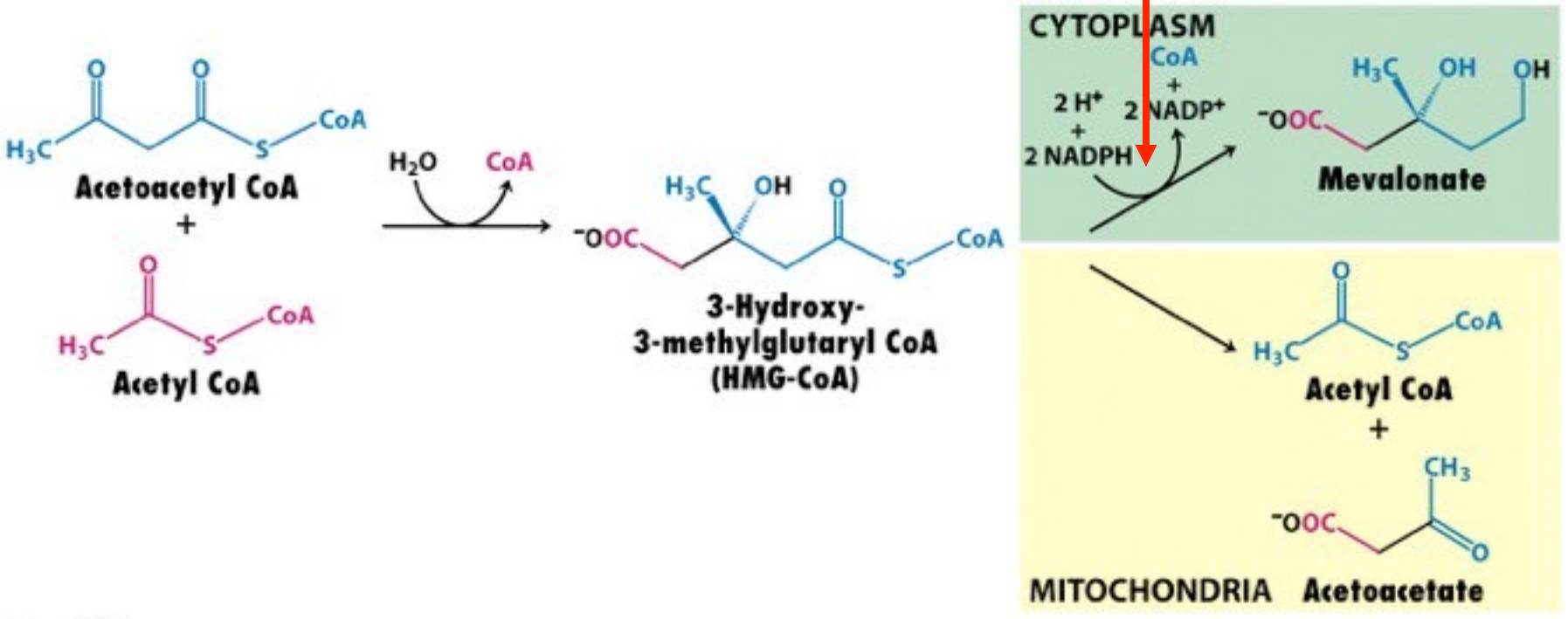
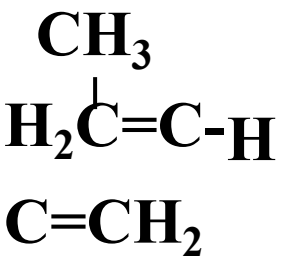
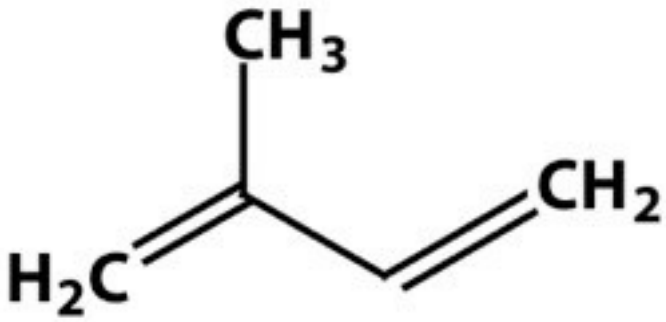


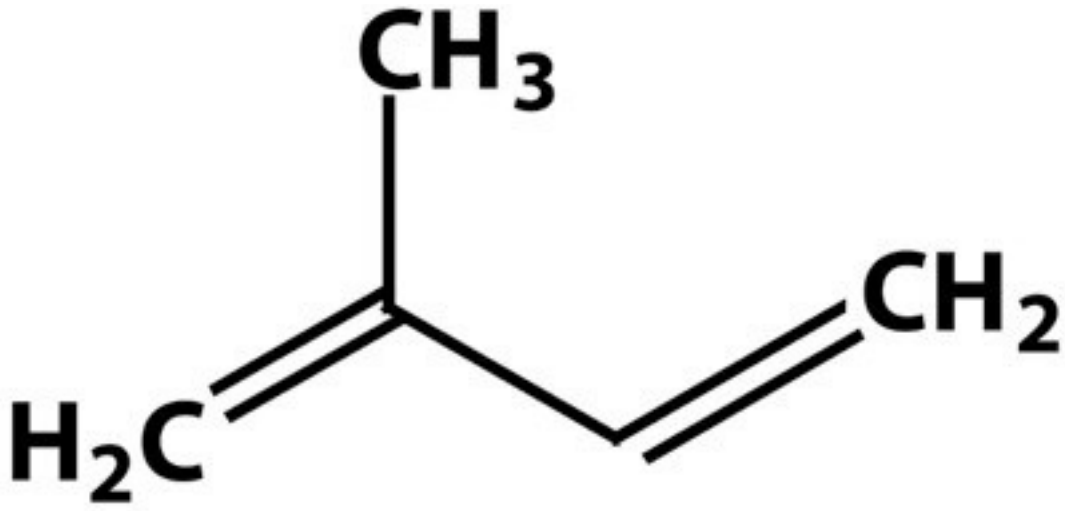

Figure 26-7
*Biochemistry, Sixth Edition*


**Mevalonate: 6 carbons**

- Next clue:
  - Squalene
    - a C30 hydrocarbon is an intermediate in the synthesis of cholesterol
    - Consists of six isoprene units






**Isoprene**

**General principle:**

5 carbon units are used to assemble extended carbon skeletons

- mevalonate C6 decarboxylates to yield C5 isoprene

- the activated isoprene intermediate proved to be isopentyl pyrophosphate, which is formed by decarboxylation of a derivative of mevalonate.

- THUS:

activated isoprene intermediate

**acetate -> mevalonate ->isopentyl pyrophosphate -> squalene -> cholesterol**
**C2 C6 C5 C30 C27**

Mevalonate is converted into 3-isopentenyl pyrophosphate by three consecutive reactions involving ATP

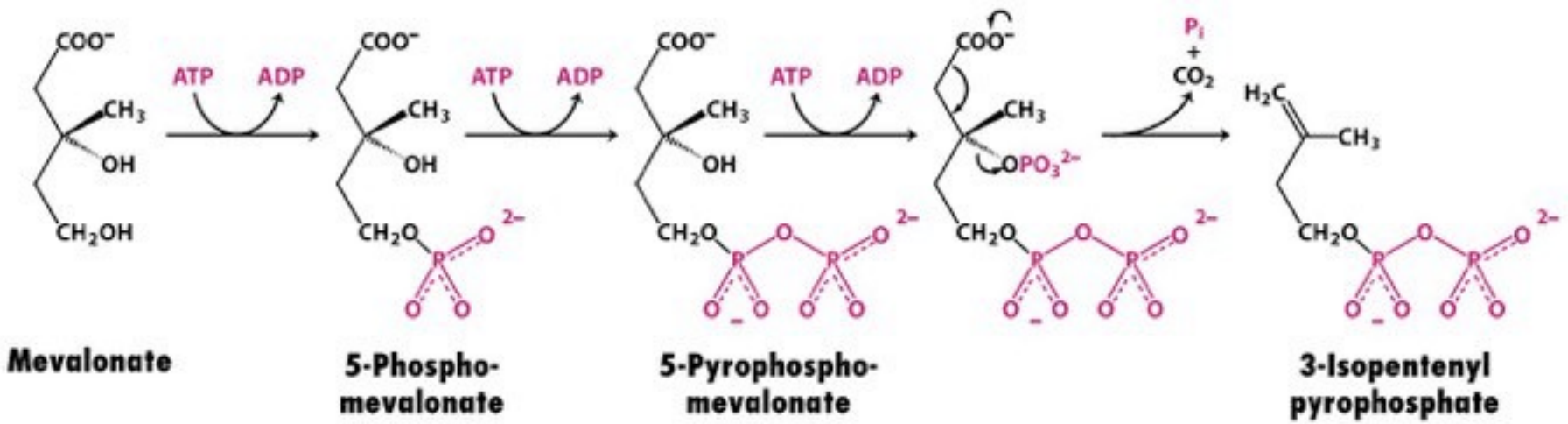
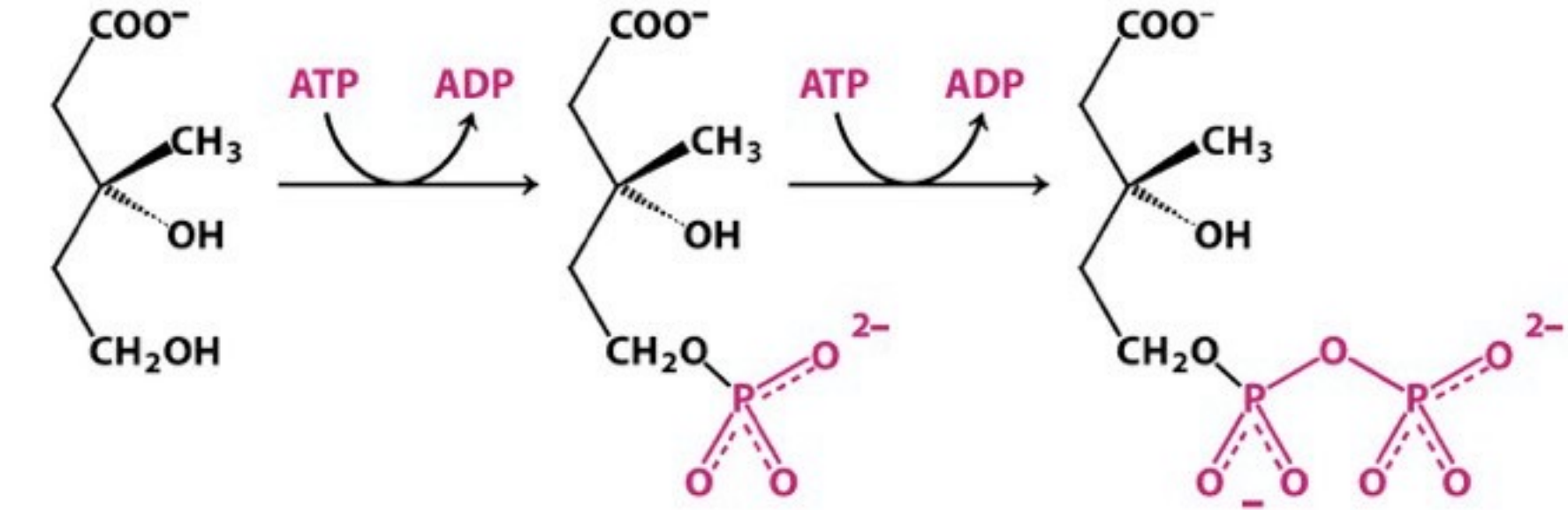



Figure 26-8
*Biochemistry, Sixth Edition*


**last step: the release of CO2 from 5-pyrophosphomevalonate occurs in concert with the hydrolysis of ATP to ADP and Pi.**




**Mevalonate** **5-Phospho-mevalonate** **5-Pyrophospho-mevalonate**

**Figure 26-8 part 1**
***Biochemistry, Sixth Edition***

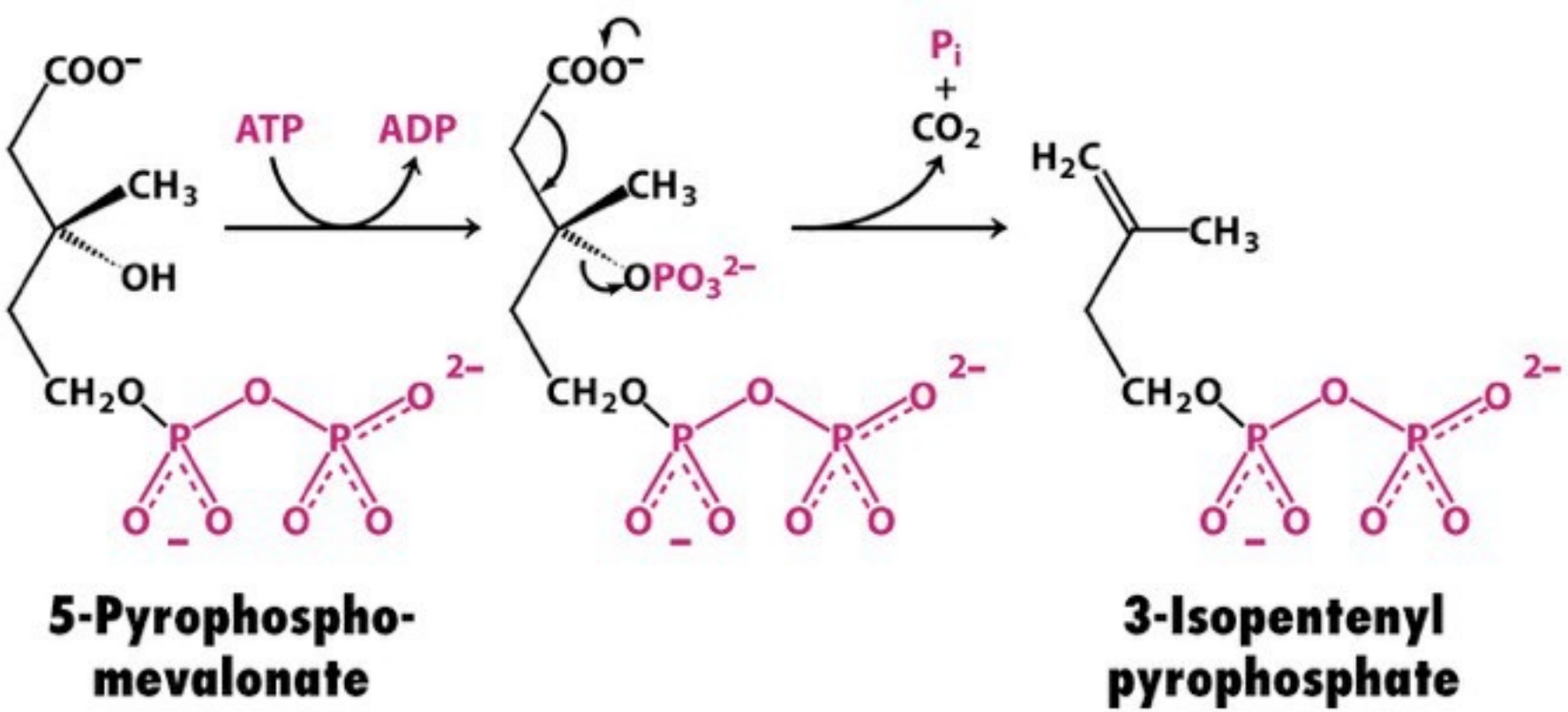



Figure 26-8 part 2
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Activated isoprene

# Synthesis of squalene from isopentenyl pyrophosphate

- squalene is synthesized from isopentenyl pyrophosphate by the reaction sequence:
- C5 -> C10 -> C15 -> C30

- 1. isopentyl pyrophosphate is isomerized to dimethylallyl pyrophosphate

- 2. the isomeric C5 units condense to form a C10 compound

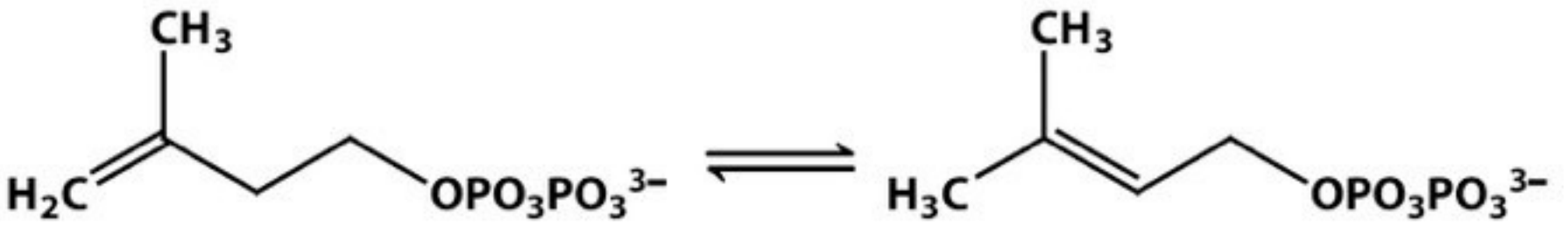
- 3. elimination: an allylic carbonium ion formed from dimethylallyl pyrophosphate is attacked by isopentyl pyrophosphate to form geranyl pyrophosphate.

- 4. the same type of reaction occurs again: geranyl pyrophosphate is converted into an allylic carbonium ion, which is attacked by isopentenyl pyrophosphate. The resulting C15 compound is called farnesyl pyrophosphate.

- last: reductive condensation:

2 Farnesyl pyrophosphate + NADPH --> squalene + 2PPi + $NADP^+$ + $H^+$ C15
C30

Isopentyl pyrophosphate is isomerized to dimethylallyl pyrophosphate




**Isopentenyl pyrophosphate** **Dimethylallyl pyrophosphate**

Unnumbered figure pg 740b
*Biochemistry, Sixth Edition*

# The isomeric C5 units condense to form a C10 compound

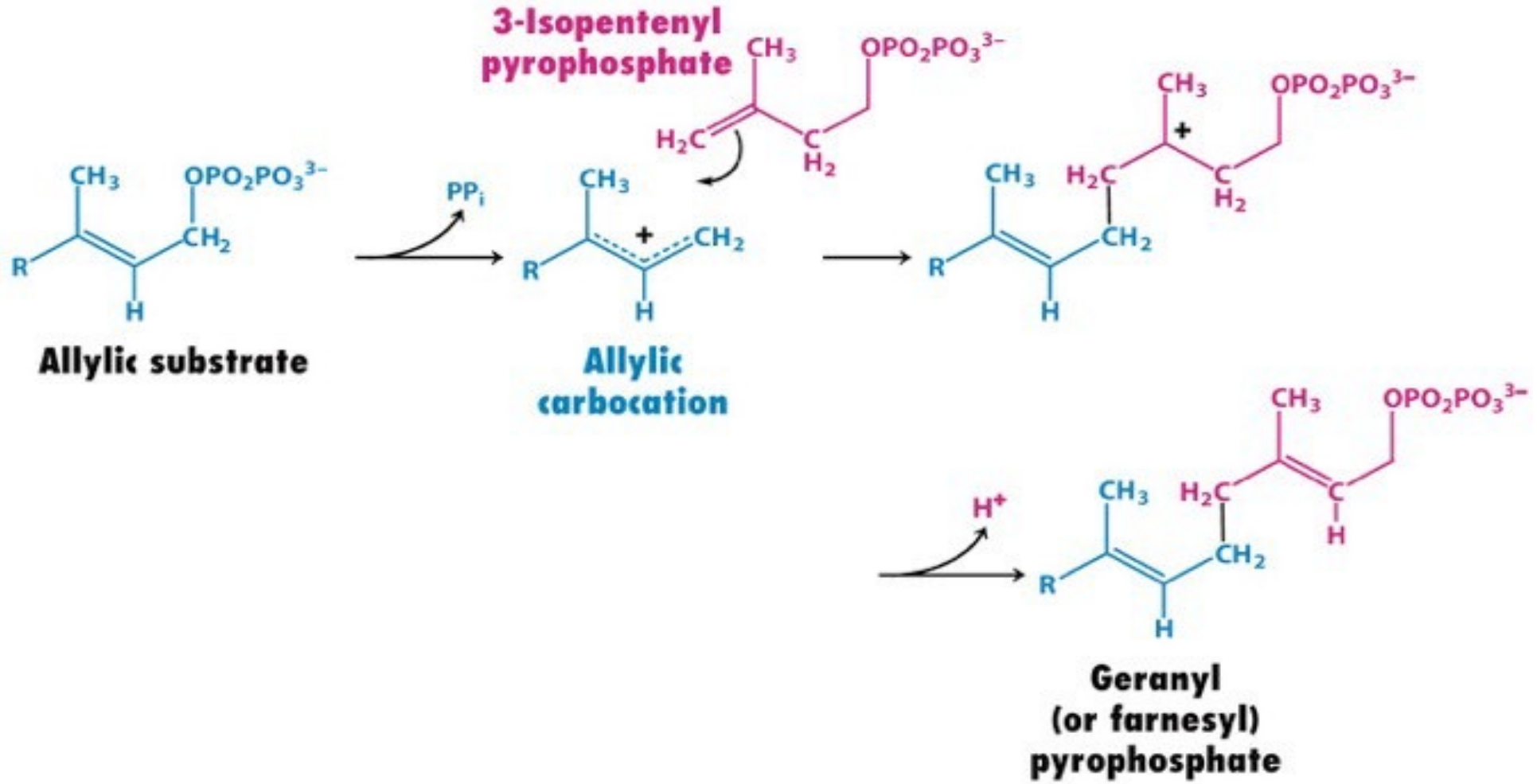



Figure 26-9
*Biochemistry, Sixth Edition*

**elimination:** an allylic carbonium ion formed from dimethylallyl pyrophosphate is attacked by isopentyl pyrophosphate to form geranyl pyrophosphate

**elimination:** the same type of reaction occurs again: geranyl pyrophosphate is converted into an allylic carbonium ion, which is attacked by isopentenyl pyrophosphate. The resulting C15 compound is called farnesyl pyrophosphate.

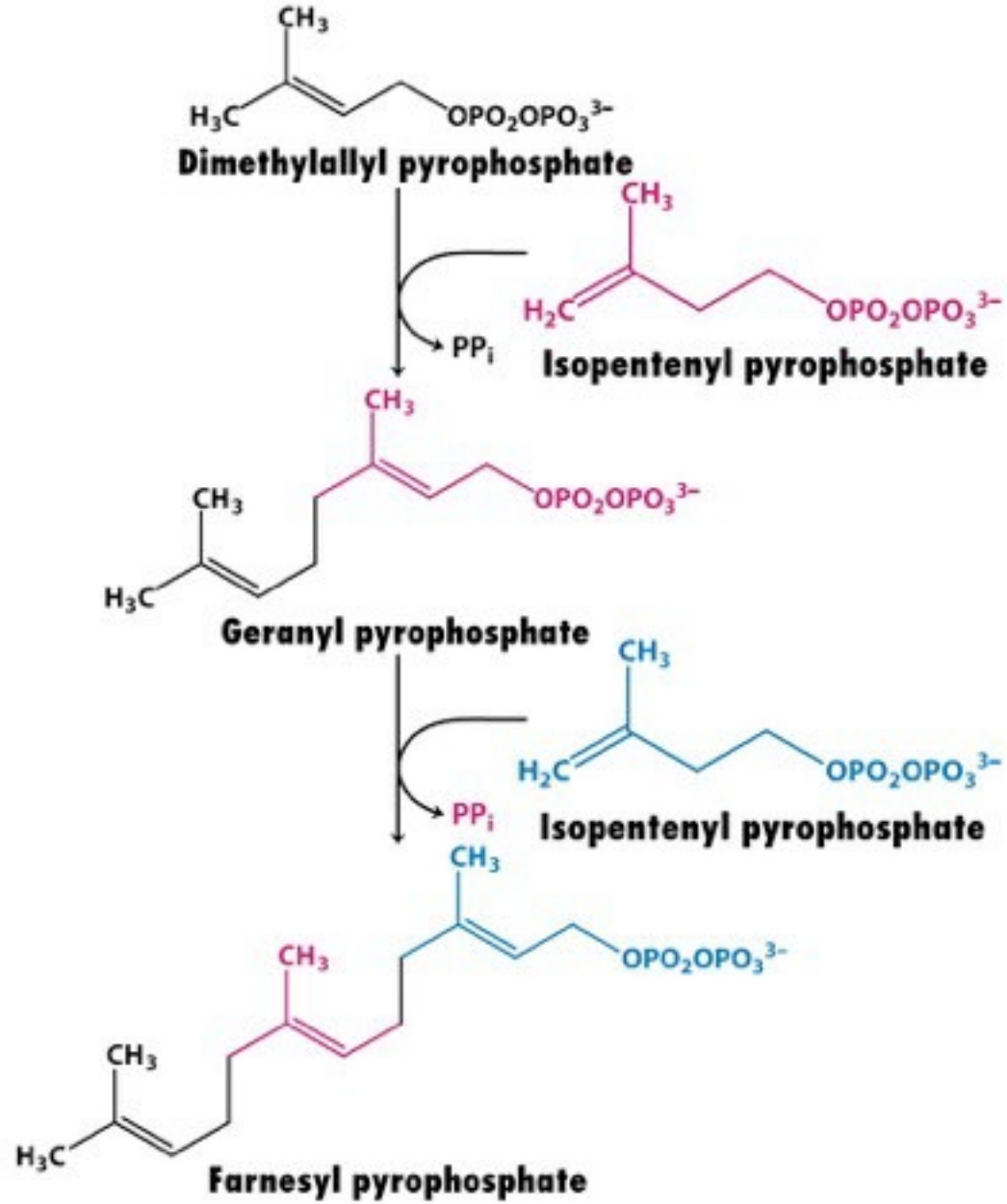
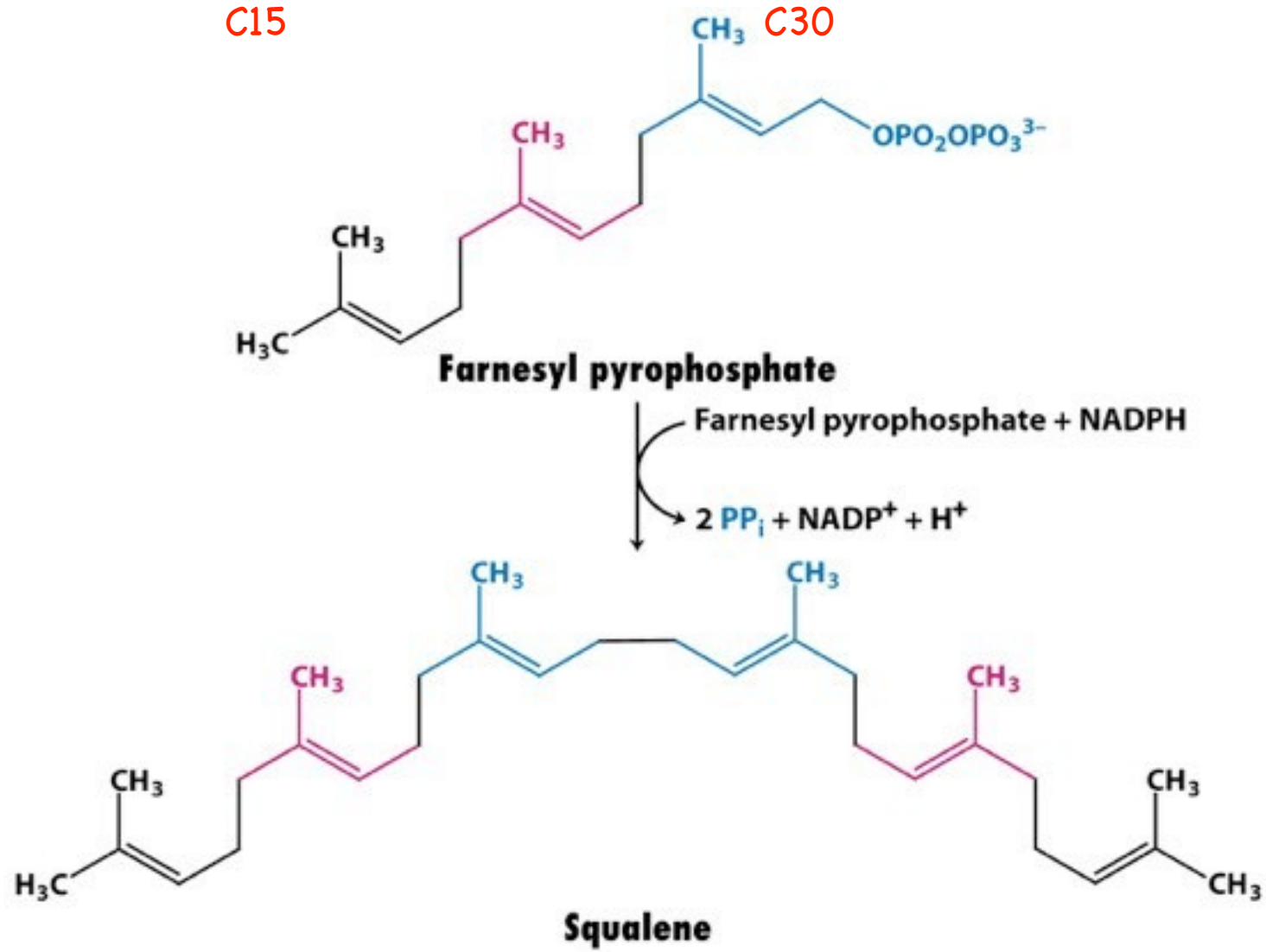



Figure 26-10 part 1
*Biochemistry, Sixth Edition*

Last: reductive condensation:

2 farnesyl pyrophosphate + NADPH --> squalene + 2PPi + $NADP^+$ + $H^+$



# Synthesis of cholesterol from squalene

- Cyclization of squalene requires molecular oxygen.

- Squalene epoxide is the reactive intermediate formed in a reaction that uses $O_2$ and NADPH.

- Squalene epoxide is then cyclized by a cyclase to lanosterol.

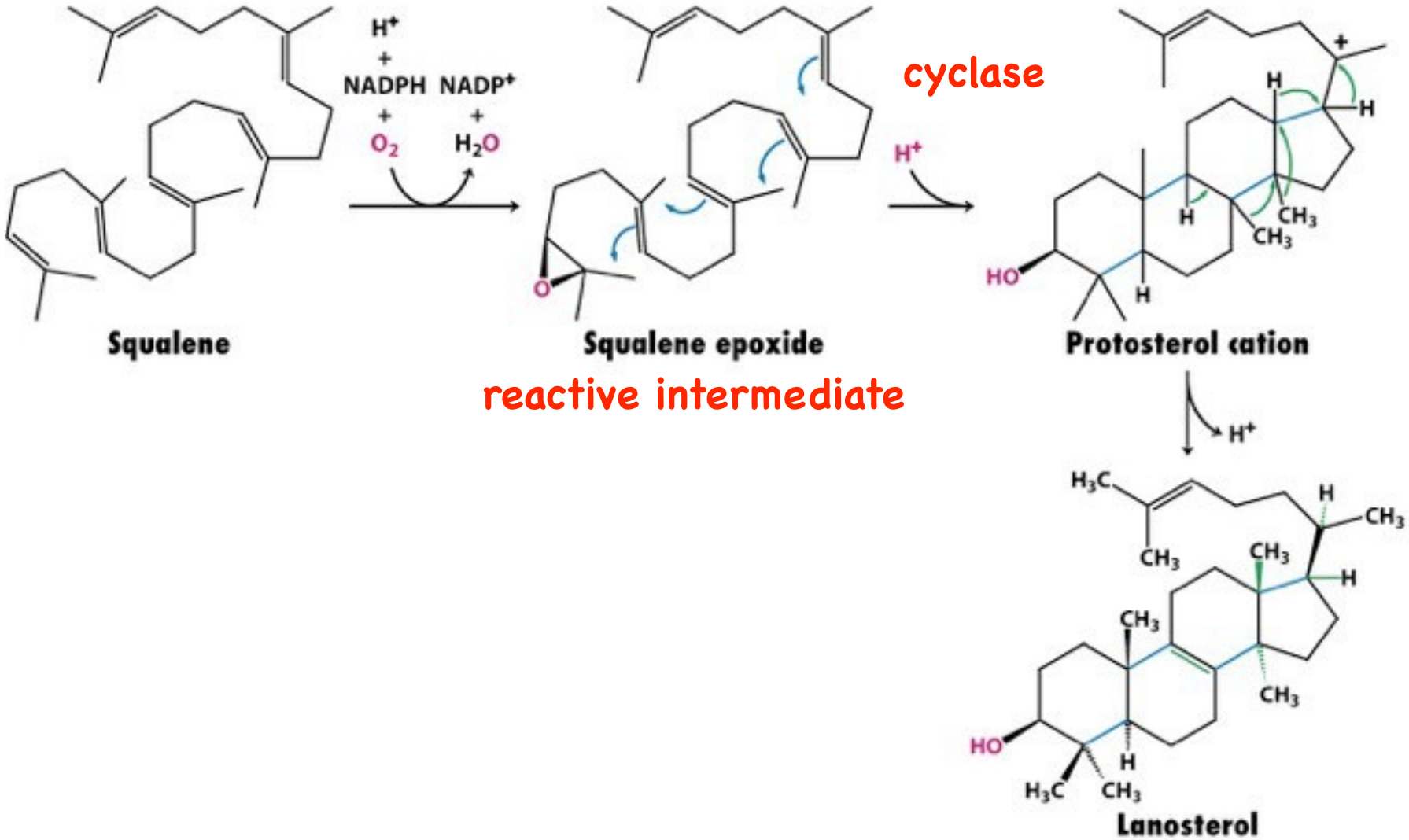
Involves:

- concerted movement of electrons through four double bonds

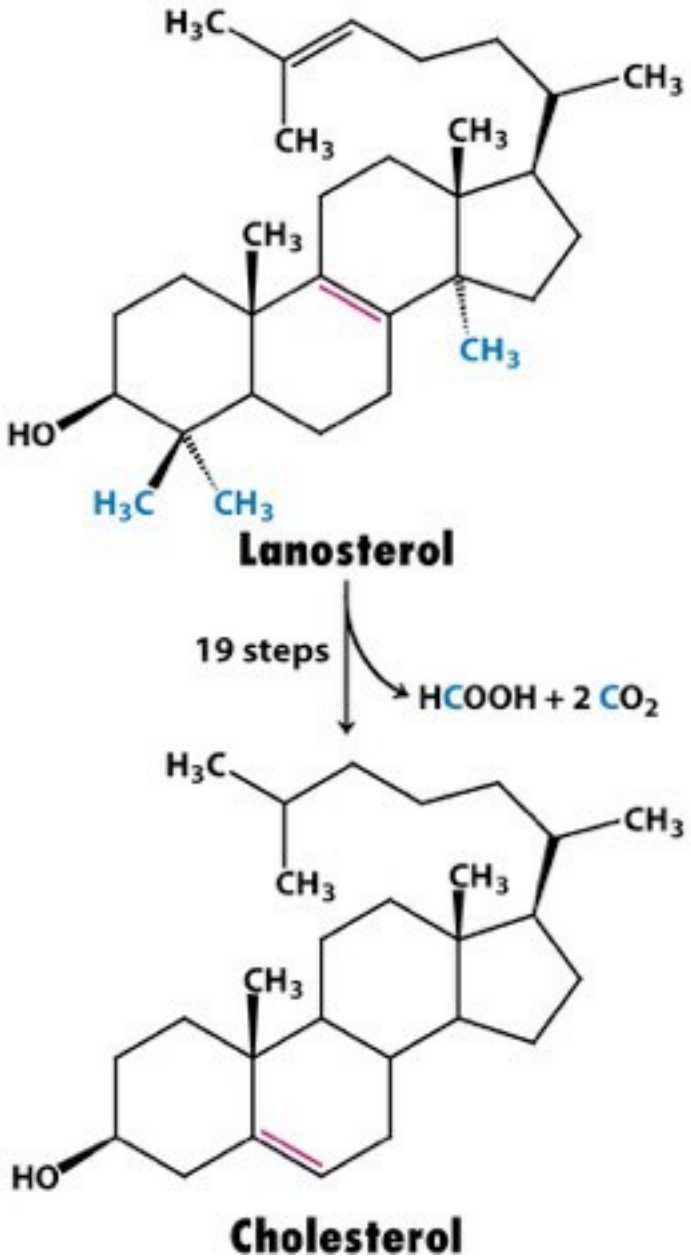
and

migration of two methyl groups

# Cyclization



# Synthesis of cholesterol from squalene - 2




- Lanosterol is converted into cholesterol by
  - removal of 3 methyl groups
  - the reduction of one double bond by NADPH
  - migration of the other double bond.

# Cholesterol

**rate limiting step: reduction of HMG-CoA by HMG-CoA reductase to form mevalonate is inhibited by dietary cholesterol as well as by endogenously synthesized**

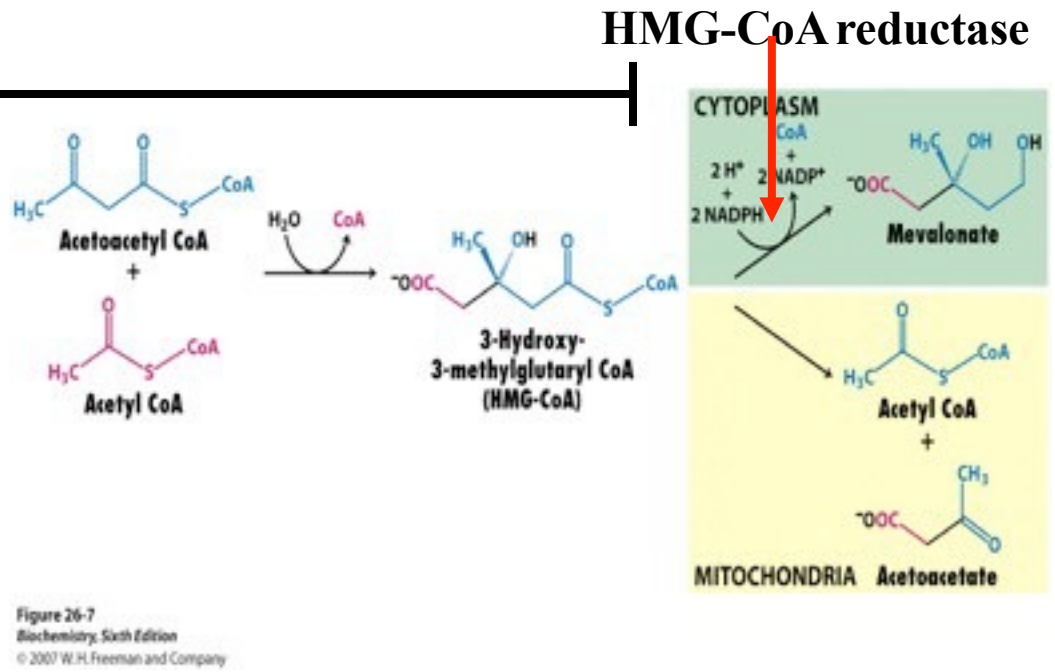



Figure 26-7
*Biochemistry, Sixth Edition*
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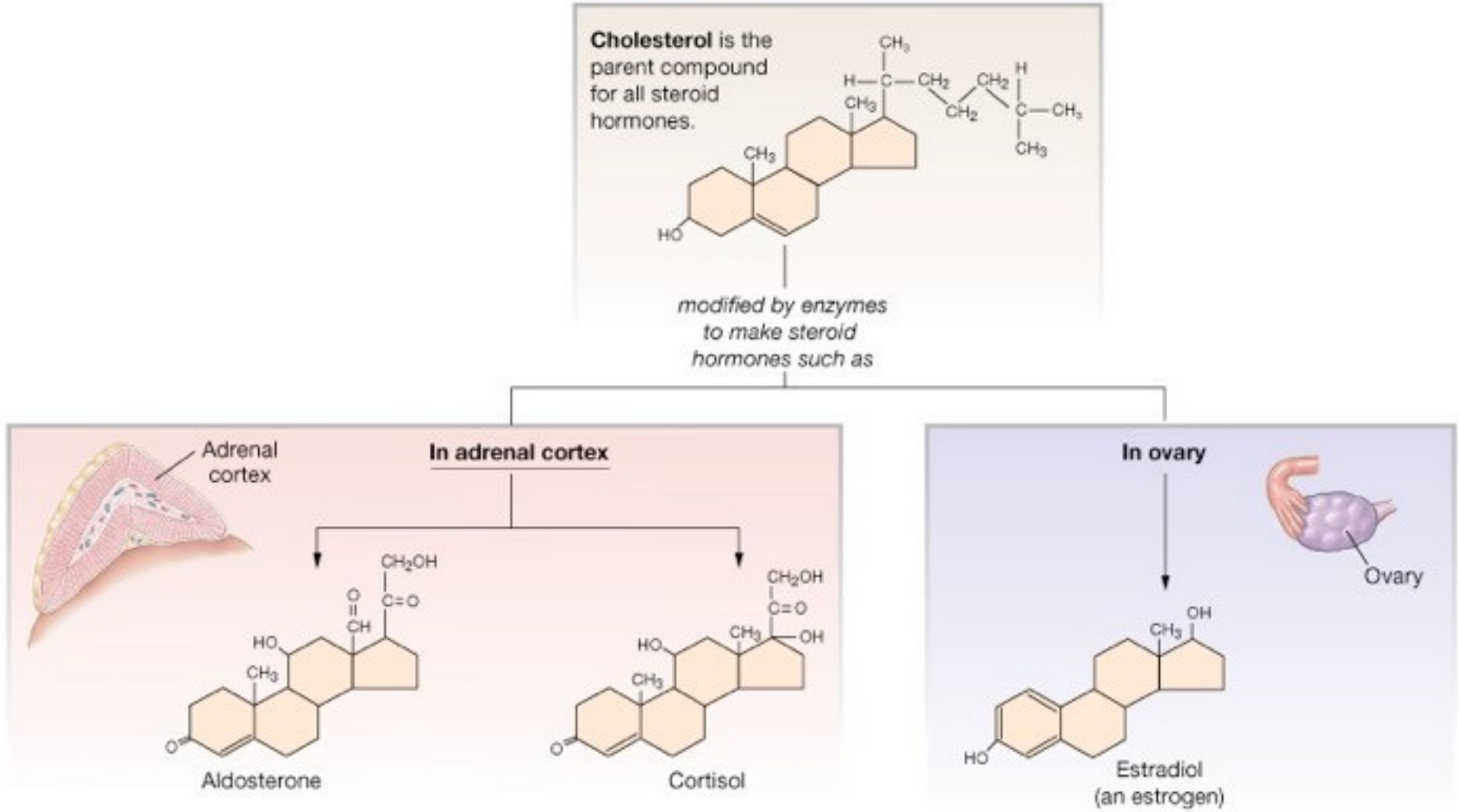
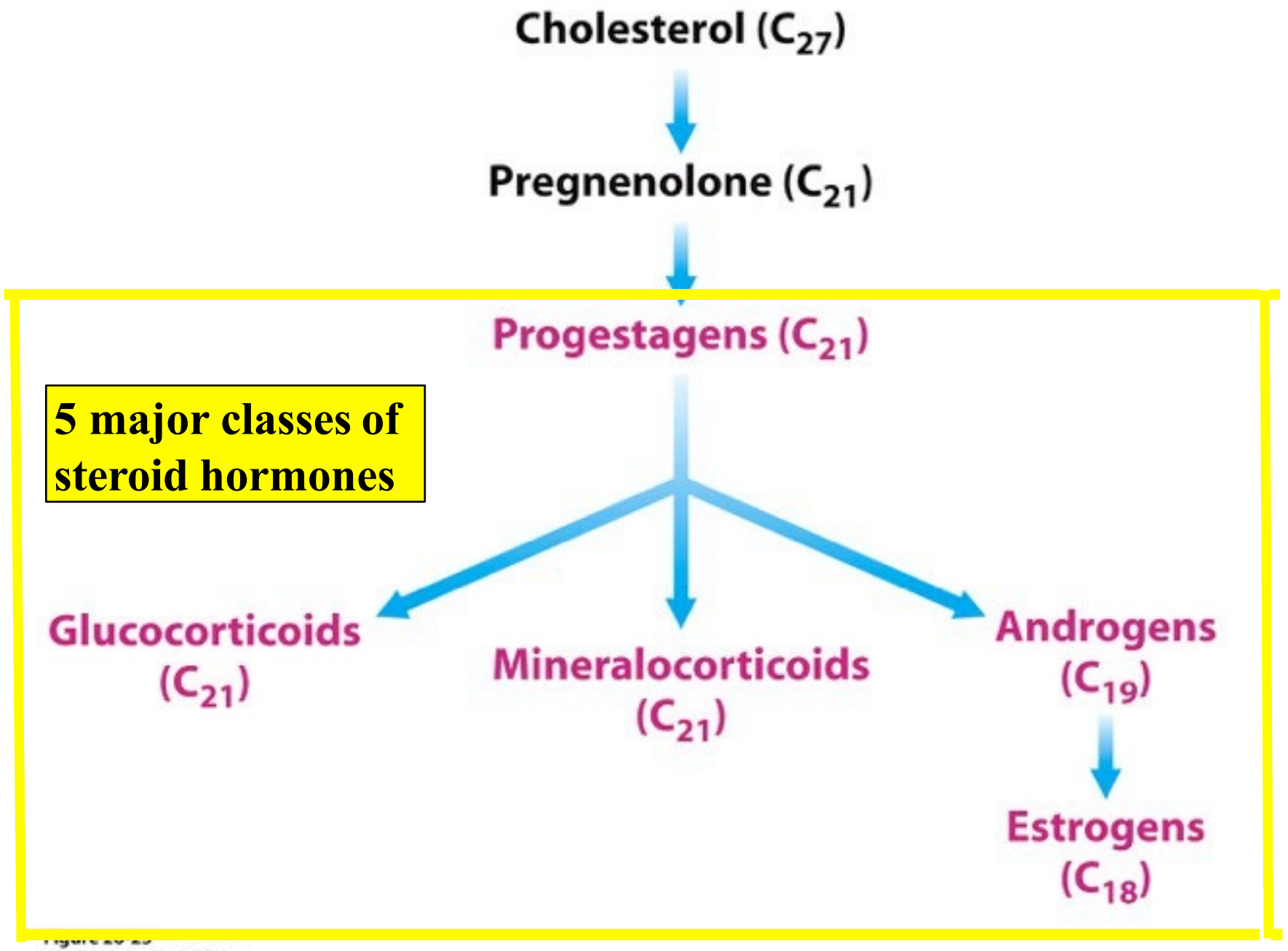
insulin stimulates HMG-CoA reductase. The hormone is required for the diurnal rhythm that occurs in cholesterol biosynthesis, a phenomenon probably related to feeding cycles and the need for bile acid synthesis. Diabetes therefore reduces HMG-CoA reductase activity and abolishes the diurnal rhythm of hepatic cholesterol biosynthesis.

glucagon if insulin in intact animals antagonizes the effect

thyroid hormone stimulates HMG-CoA reductase activity


Cholesterol is the parent compound for all steroid hormones.
modified by enzymes to make steroid hormones such as
Adrenal cortex
In adrenal cortex
Aldosterone
Cortisol
In ovary
Ovary
Estradiol (an estrogen)




*Biochemistry, Sixth Edition*

# Biosynthesis of adrenocortical hormones

cholesterol

is stored in lipid droplets, predominantly as cholesterol esters

is hydrolyzed to free cholesterol and converted to progesterone, a key intermediate in the biosynthesis of adrenal and gonadal hormones

-steroid acute regulator, StAR, transports cholesterol from the cell membrane to the mitochondria

-conversion of cholesterol to progesterone involves side-chain cleavage between C20 and C22 followed by oxidation of the 3-hydroxyl to a keto, and then isomerization of the Δ5 double bond to a Δ4 configuration

-progesterone then undergoes hydroxylations at C-17, C-21, and C-11 to form cortisol. The C-17 and C-21 hydroxylation at C-11 occurs in the mitochondria. All the hydroxylations require NADPH and molecular oxygen

-aldosterone is formed from corticosterone (11b, 17a, 21-trihydroxy-progesterone) in the zona glomerulosa

# Nomenclature of steroids

- Cholesterol contains two angular methyl groups
  - C-19 attached to C-10
  - C-18 attached to C-13

  That are above the plane "β-oriented"

  Substituent below the plane "α-oriented"

  A hydrogen atom attached to C-5 can be α-or β-oriented. If this hydrogen is α-oriented, the A and B rings are fused in trans conformation, whereas a β-orientation corresponds to a cis fusion. The absence of a symbol for the C-5 hydrogen atom implies a trans fusion. The C-5 hydrogen atom is α-oriented in all steroid hormones that contain a hydrogen atom in that position.

# Steroids are hydroxylated by monooxygenases that utilize NADPH and O2

- $RH + O_2 + NADPH + H^+ \xrightarrow{\text{monooxygenase}} ROH + H_2O + NADP^+$

- Hydroxylation requires the activation of oxygen. This is accomplished by $P_{450}$, a specialized cytochrome that absorbs light maximally at 450 nm
- cytochrome $P_{450}$ is the terminal component of an electron transport chain in adrenal mitochondria with the aim of hydroxylation.
- NADPH transfers its high-potential electrons to a flavoprotein in this chain, which are then conveyed to adrenodoxin, a non-heme iron protein.
- Adrenodoxin transfers an electron to the oxidized form of cytochrome $P_{450}$. The reduced form then activates O2.

- Steroid hormones contain 21 or fewer carbon atoms
- Removal of C6 side chain to form pregnenolone using NADPH and O2
  - A) side chain is hydroxylated at C20 and C22
  - B) bond between C20 and C22 is cleaved (desmolase)

ACTH stimulates this conversion

# Synthesis of progesterone and corticoids

- Progesterone is synthesis from pregnenolone in two steps:
  - The 3-hydroxyl group of pregnenolone is oxidized to a 3-keto group, and the Δ5 double bond is isomerized to a Δ4 double bond

- Cortisol is synthesized from progesterone by hydroxylations at C-17, C-21, and C-11.
  - C-17 must be hydroxylated before C-21, whereas hydroxylation at C-11 may occur at any stage.

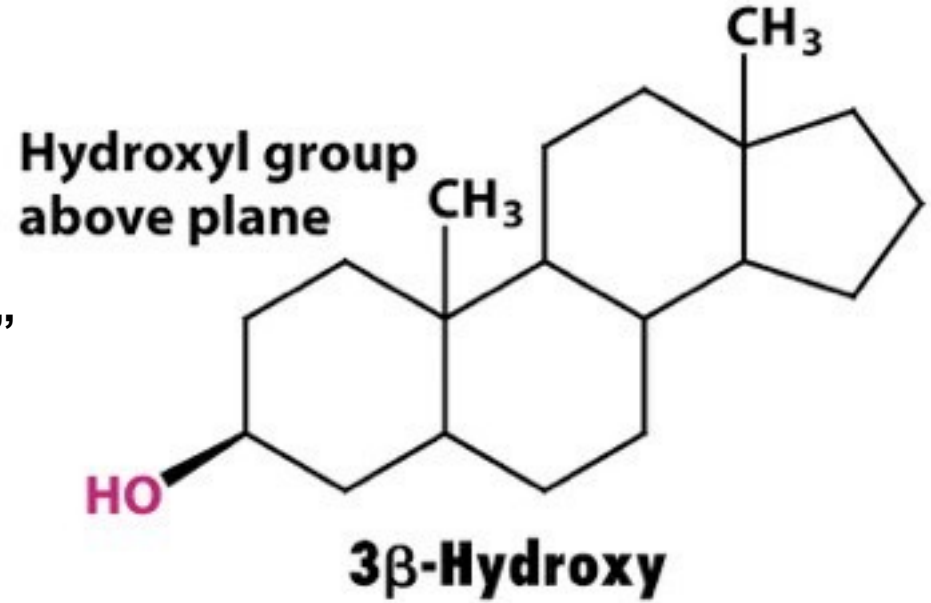
- Aldosterone is synthesized from progesterone by a first hydroxylation C-21. The resulting deoxycorticosterone is hydroxylated at C-11. The oxidation of the C-18 angular methyl group to an aldehyde then yields aldosterone.

# Synthesis of androgens and estrogens

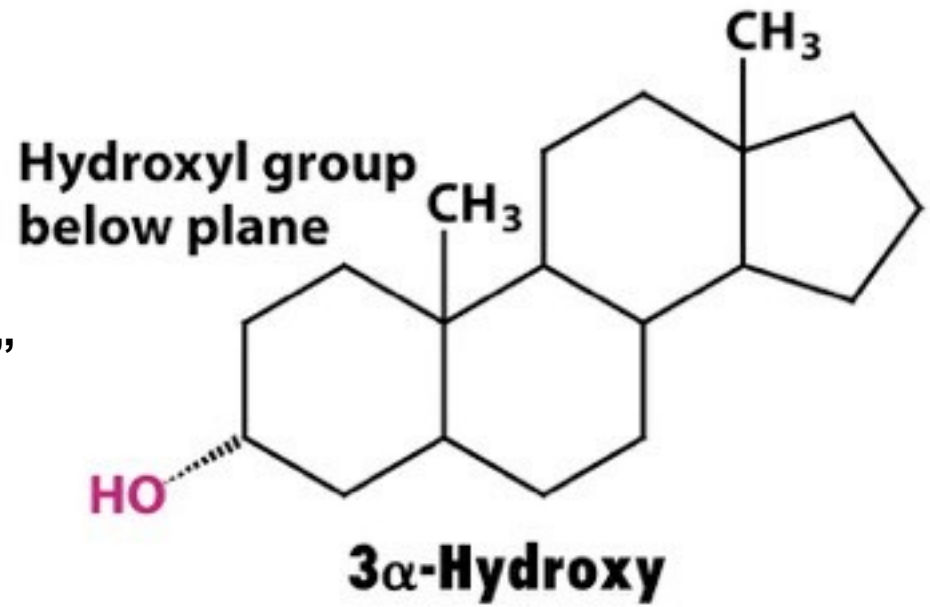
- Androgens C19
  1. hydroxylation of progesterone at C-17
  2. side chain C20 and C21 is cleaved to yield androstenedione
  3. reduction of the 17-keto group yields testosterone

- Estrogens
  - are synthesized from androgens by the loss of the C-19 angular methyl group and the formation of an aromatic A ring
  - these reactions require NADPH and O2
  - estrone is formed from androstenedione
  - estradiol is formed from testosterone

"β-oriented"




"α-oriented"

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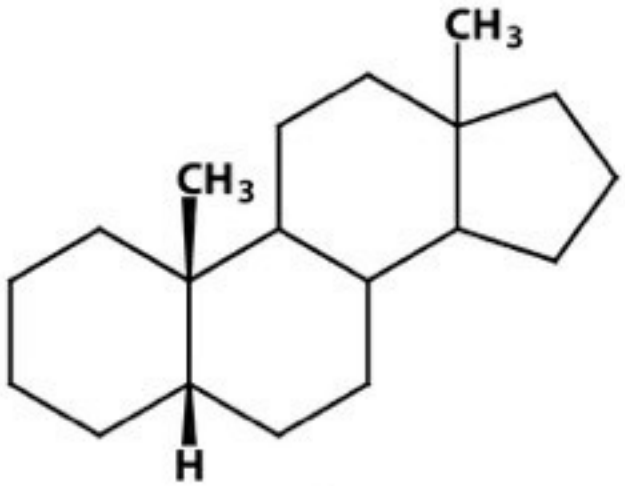
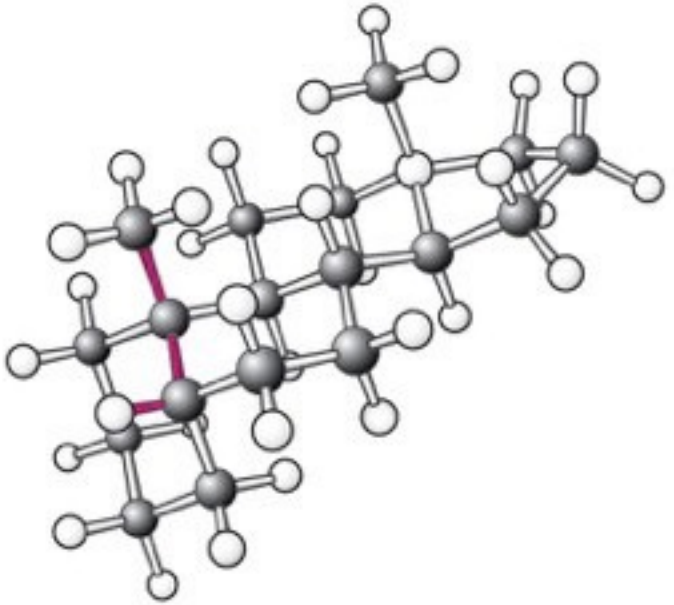
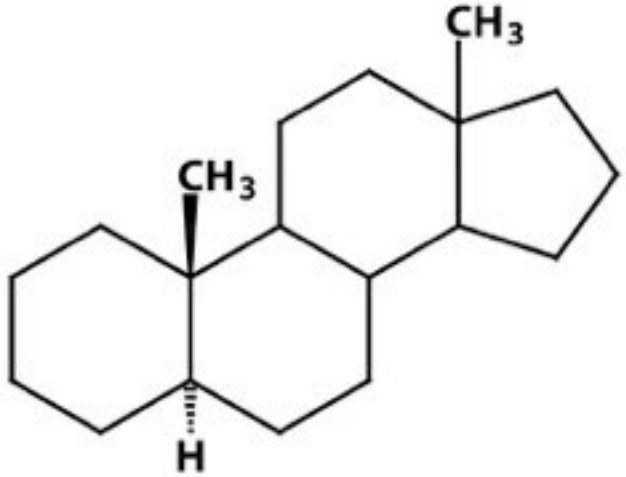
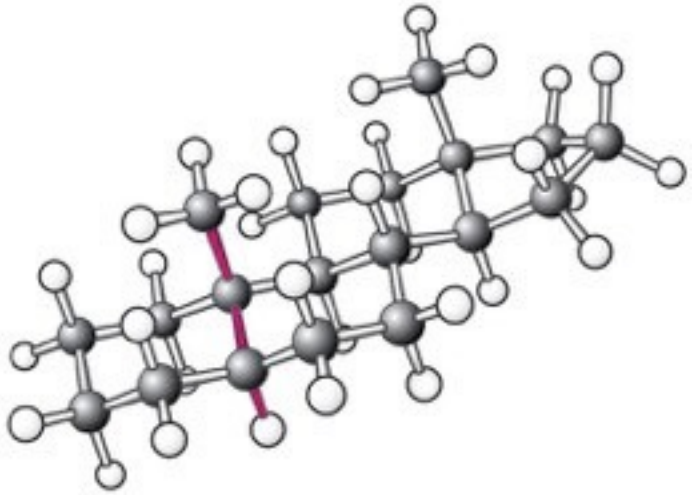



**5β-Hydrogen**
**(cis fusion)**






**5α-Hydrogen**
**(trans fusion)**



Unnumbered figure pg 750b
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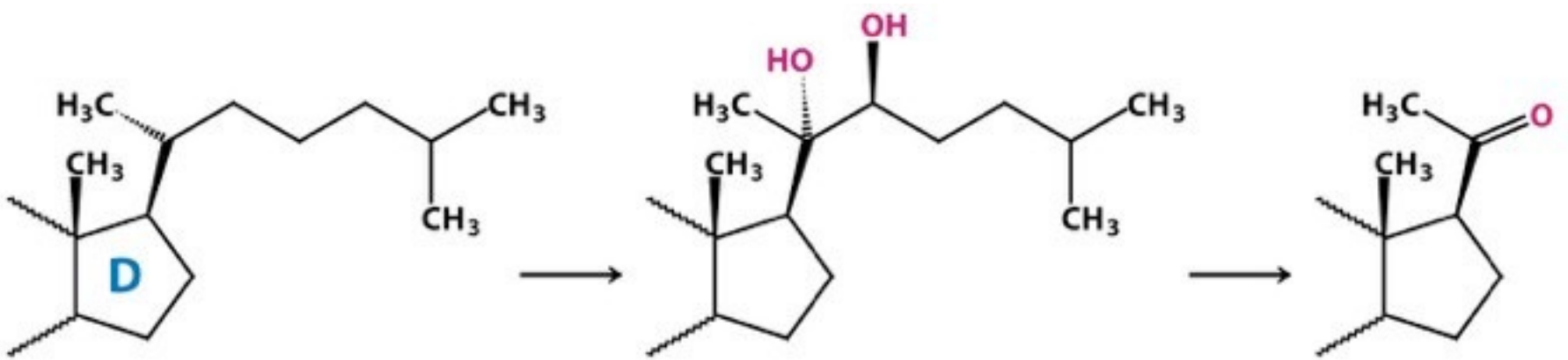


Unnumbered figure pg 752
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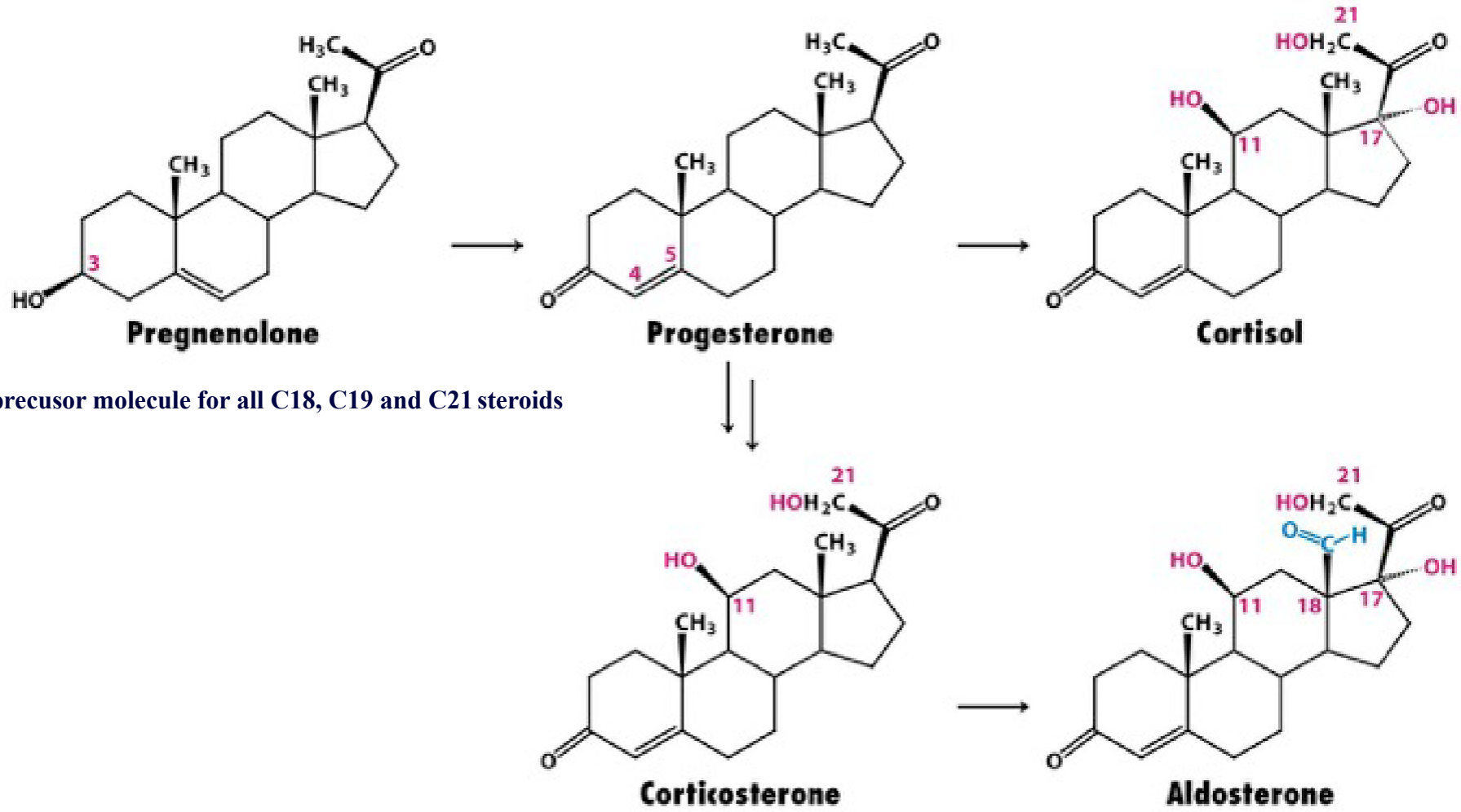
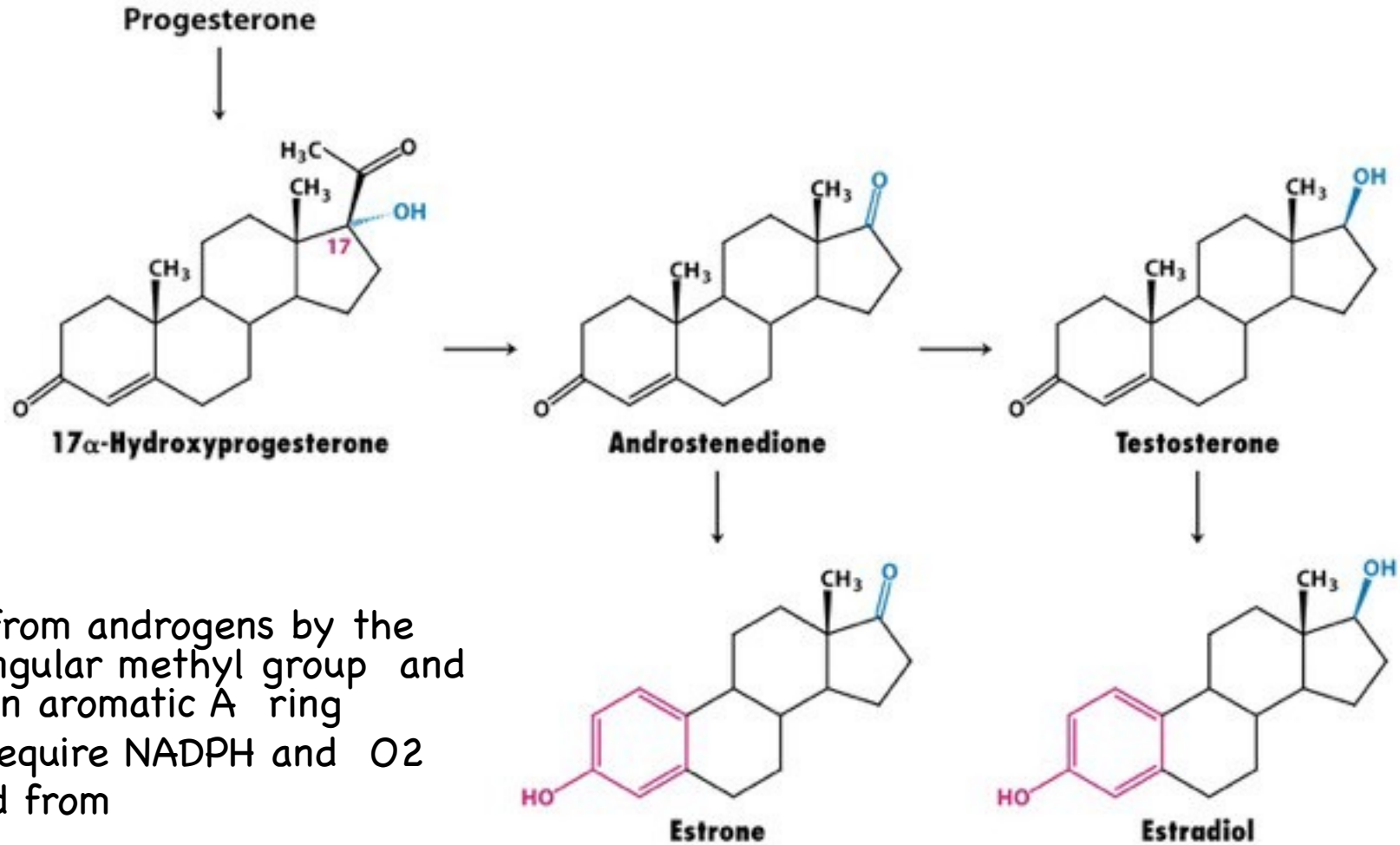



precusor molecule for all C18, C19 and C21 steroids




- Estrogens
  - -are synthesized from androgens by the loss of the C-19 angular methyl group and the formation of an aromatic A ring
  - -these reactions require NADPH and O2
  - -estrone is formed from androstenedione
  - -estradiol is formed from testosterone