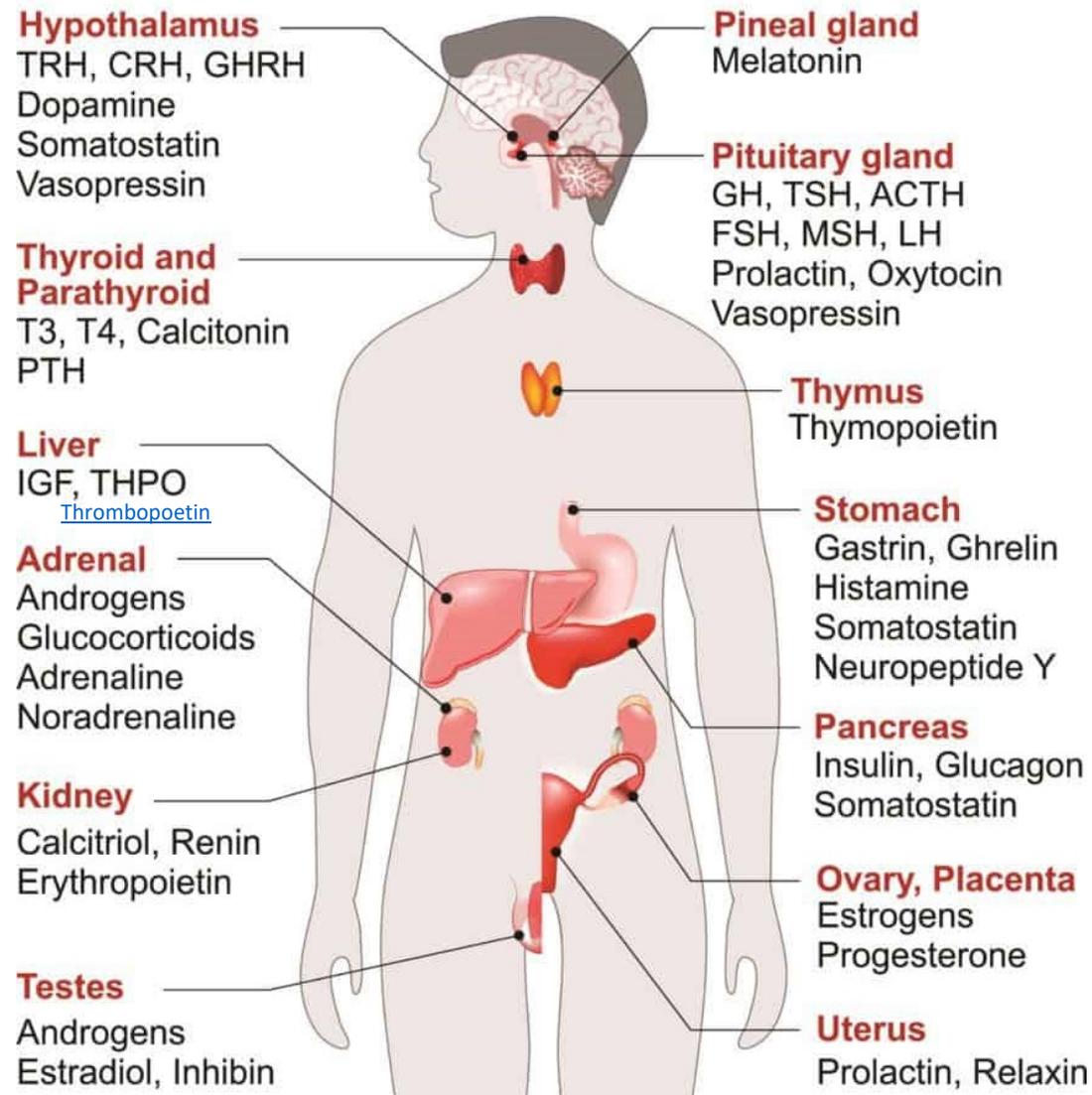


ICAK
Nutrition Course
Module 10
Hormones

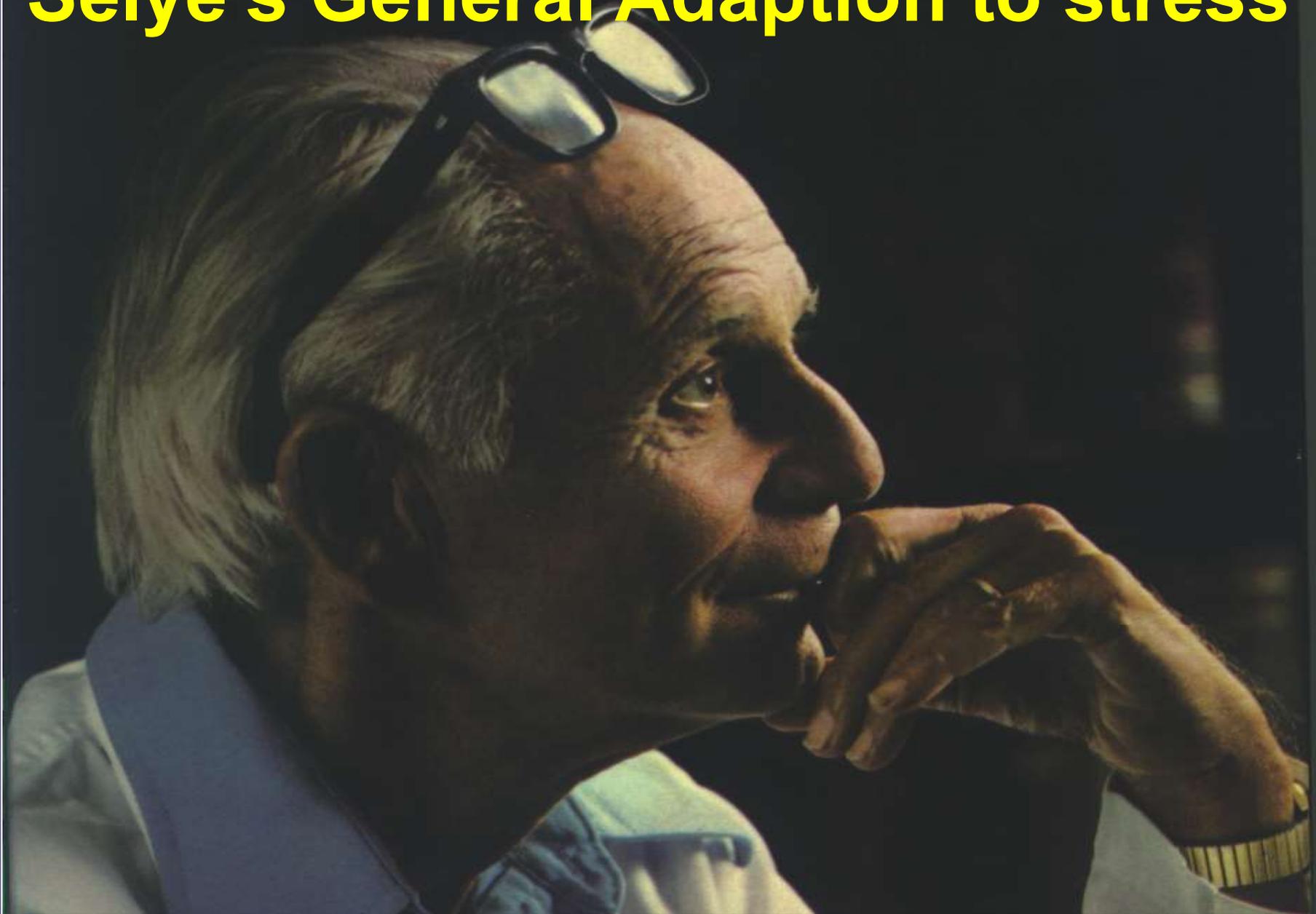
Hormones

All enzyme Co-enzymes, Co-factors, Inhibitors and Activators
verified in BRENDA Enzyme database

HORMONES



Selye's General Adaption to stress



ADAPTION

ALARM

↑ Na⁺
↓ K⁺
↑ Glucose

↓ Na⁺
↑ K⁺
↓ Glucose

EXHAUSTION

1. Atrophy of the **Thymus gland and other Lymphoid Tissues**

2. Enlarged **Adrenal Glands**

3. Gastrointestinal **ulcerations**

Indicating that the main areas that **stress** affects are

1. The Immune System

2. The Endocrine System

3. The Gastro-Intestinal System

NORMAL PHYSIOLOGY

DYSFUNCTIONING PHYSIOLOGY

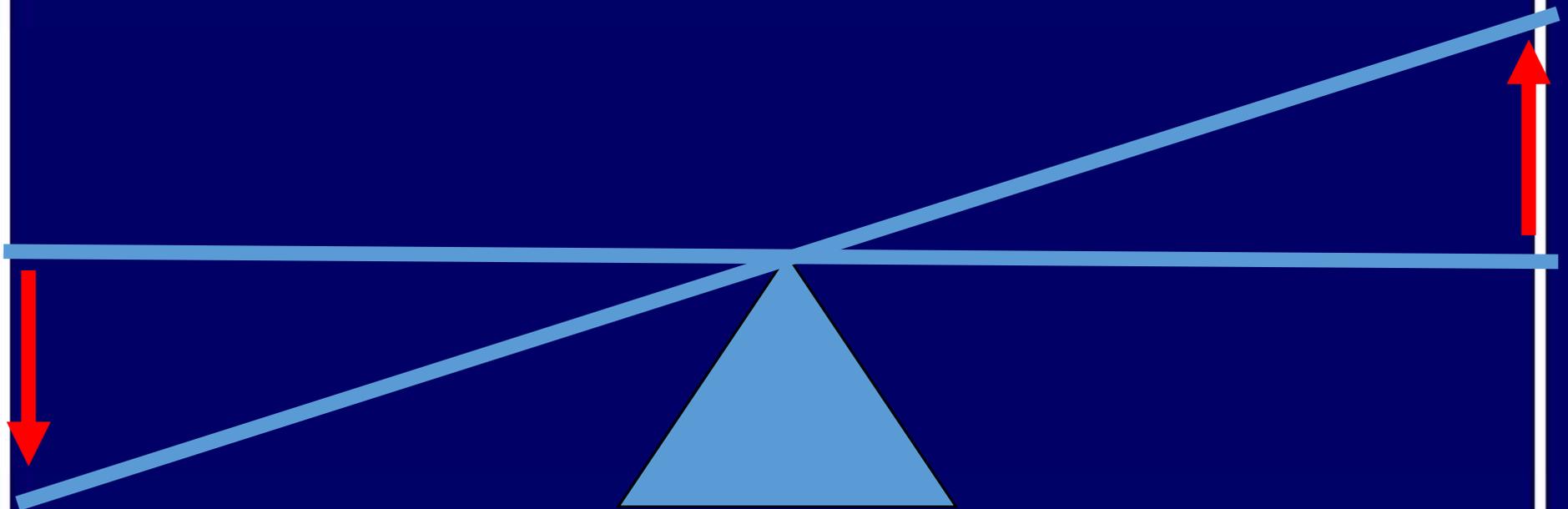
PATHOLOGY

DEATH



ADAPTION

HYPER



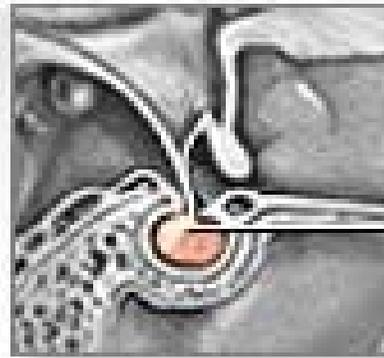
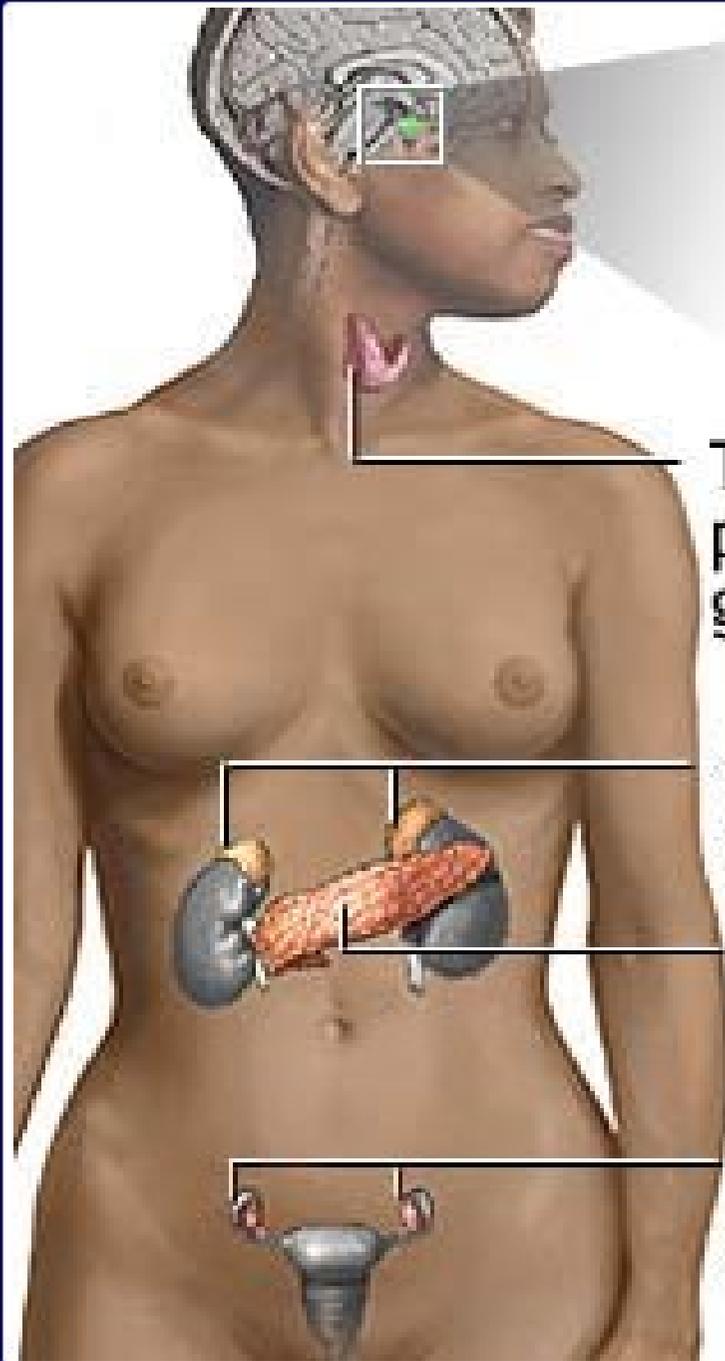
HYPO

e.g. Neurotransmitters, Hormones Neuropeptides, CVS, GU, Gut.

Adaption occurs

**Initially in the
Nervous System (Neural)**

**Secondarily in the Endocrine
System (Humoral)**



Pituitary gland

Thyroid and parathyroid glands

The endocrine glands secrete hormones which regulate various functions throughout the body

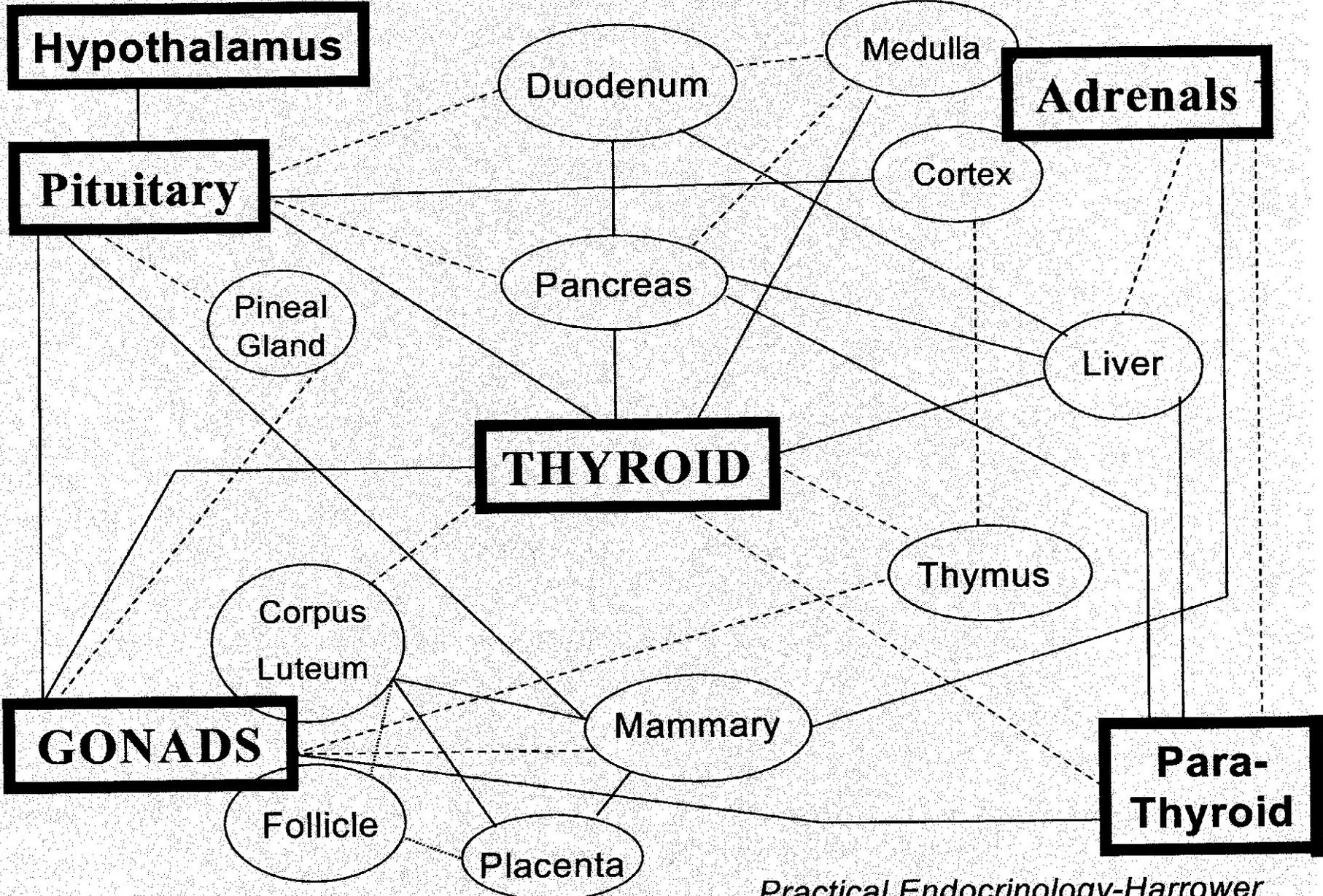
Adrenal glands

Pancreas



Testes (male)

Ovaries (female)



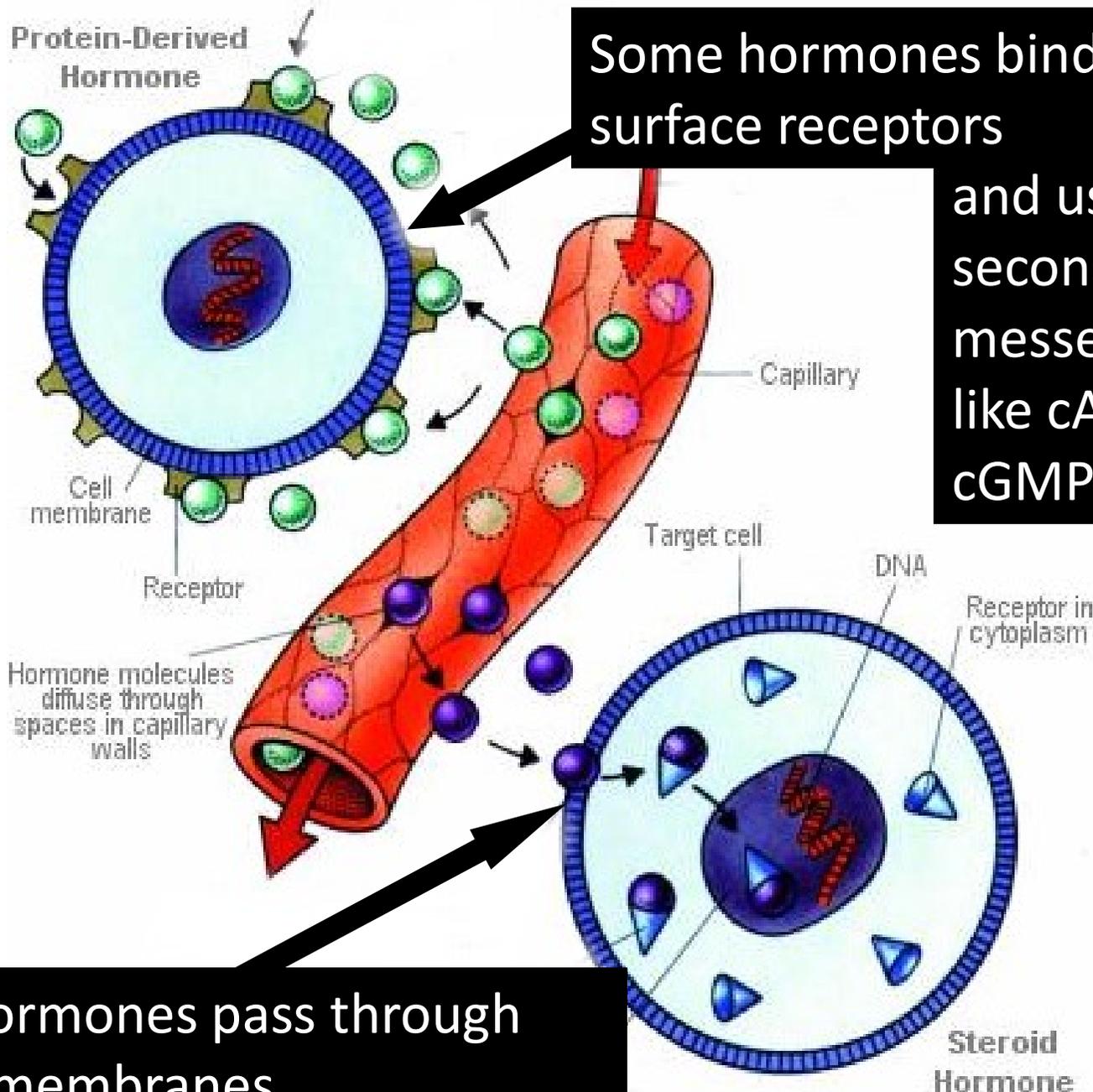
Practical Endocrinology-Harrower

The endocrine system carries out a wide variety of physiological processes through chemical messengers called "hormones."

This system is a collection of glands that produces these hormones, which are necessary for normal bodily functions.

The hormones regulate **metabolism, growth and sexual development.**

These glands release the hormones directly into the bloodstream, where they are transported to organs and tissues throughout the entire body.



Some hormones bind to cell surface receptors

and use secondary messengers like cAMP, cGMP

Other hormones pass through the cell membranes

Hormones that bind to cell surface receptors

Adrenalin

Calcitonin

LH ✨

Somatostatin

TRH ★

Glucagon

ACTH ✨

CRH ★

MSH ✨

TSH ✨

GRH ★

Insulin

ADH ✨

FSH ✨

PTH ✨

GnRH ★

PRL ★

PRIH ★

★ *hypothalamic releasing hormones pituitary*

✨ *trophic hormones*

Main hormones that bind to intracellular receptors.

- **Thyroxin and T3**
- **Mineralocorticoids (Aldosterone)**
- **Glucocorticoids (Cortisol)**
- **Androgens (DHEA, Testosterone)**
- **Progesterone**
- **Estrogens**

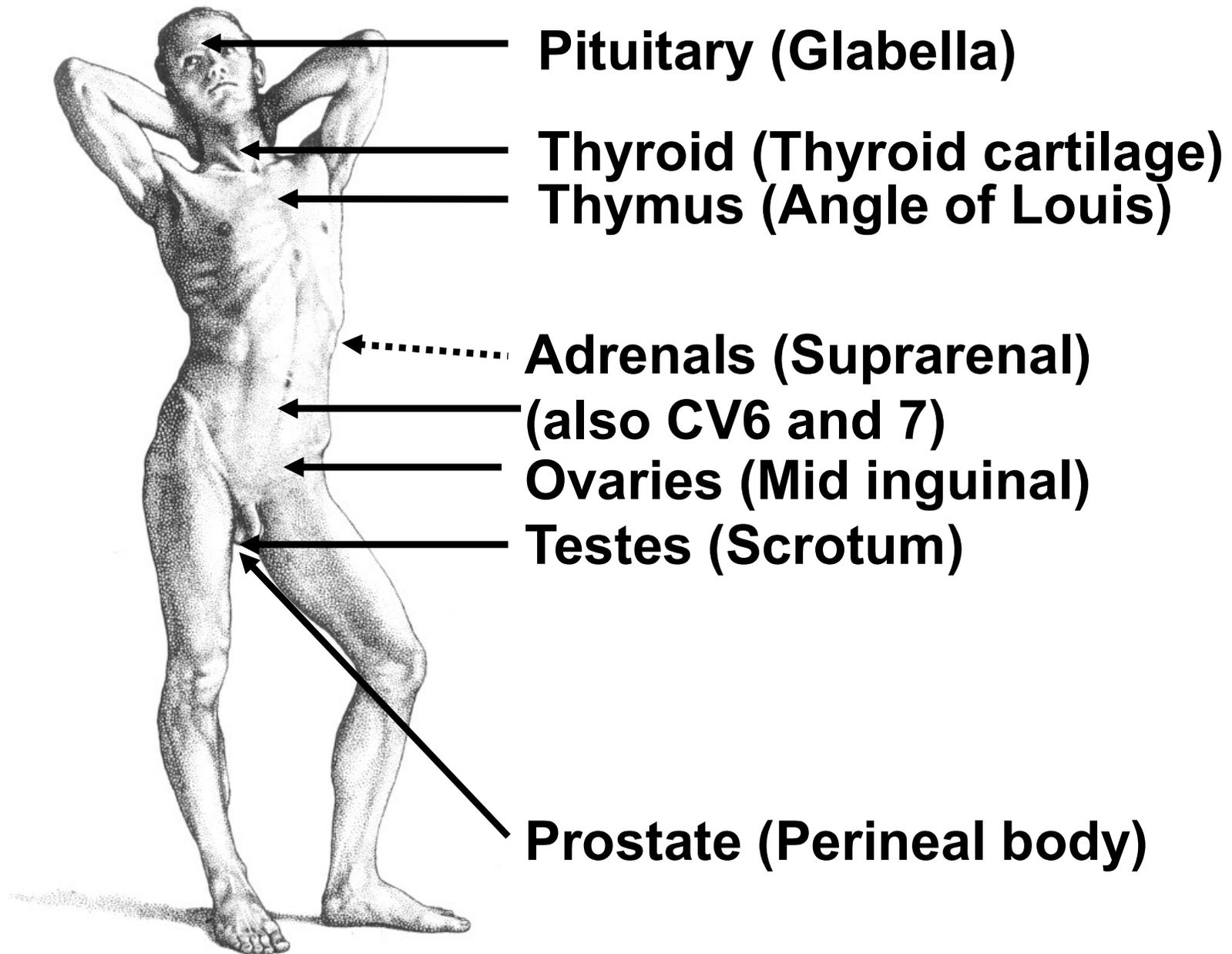
HPA axis

The **HPA axis** is a neuroendocrine system that mediates a stress response. Neurons in the hypothalamus, particularly the paraventricular nucleus, release vasopressin and corticotropin releasing hormone, which travel through the hypophysial portal vessel -

where they travel to and bind to the corticotropin-releasing hormone receptor on the anterior pituitary gland. The secretion of ACTH into systemic circulation allows it to bind to and activate Melanocortin receptor, where it stimulates the release of steroid hormones.

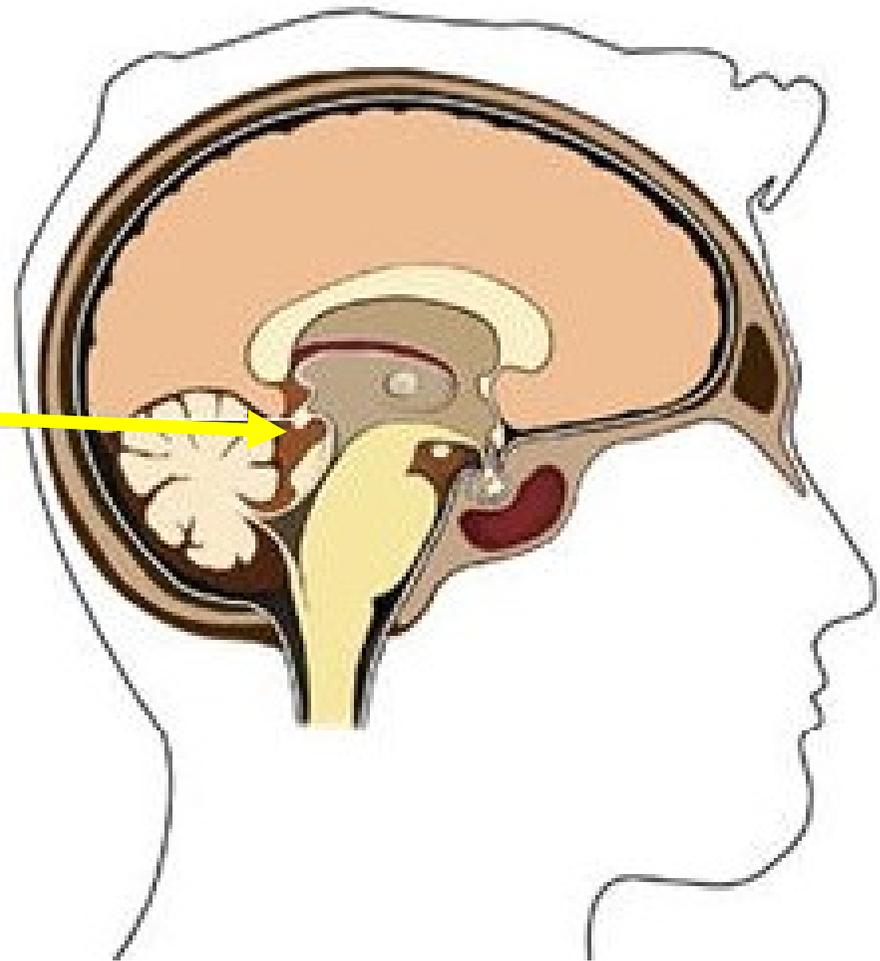
Smith, Sean M.; Vale, Wylie W. (7 February 2017). "The role of the hypothalamic-pituitary-adrenal axis in neuroendocrine responses to stress". *Dialogues in Clinical Neuroscience*. 8 (4): 383–395

ENDOCRINE THERAPY LOCALISATION POINTS



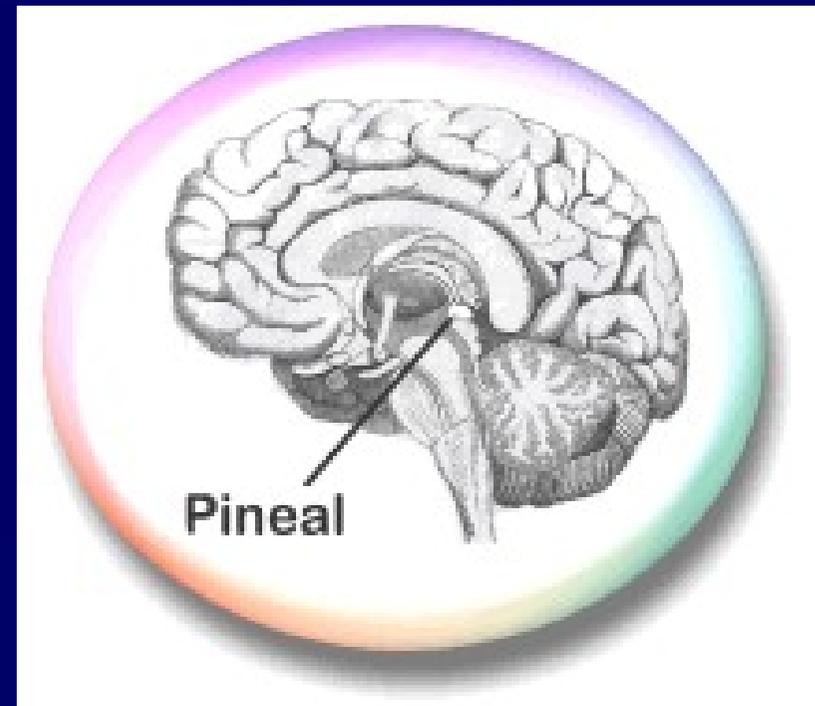
Melatonin

The Pineal Gland (epiphysis)



Located in the exact centre of the brain suspended between the **two tentorium cerebri.**

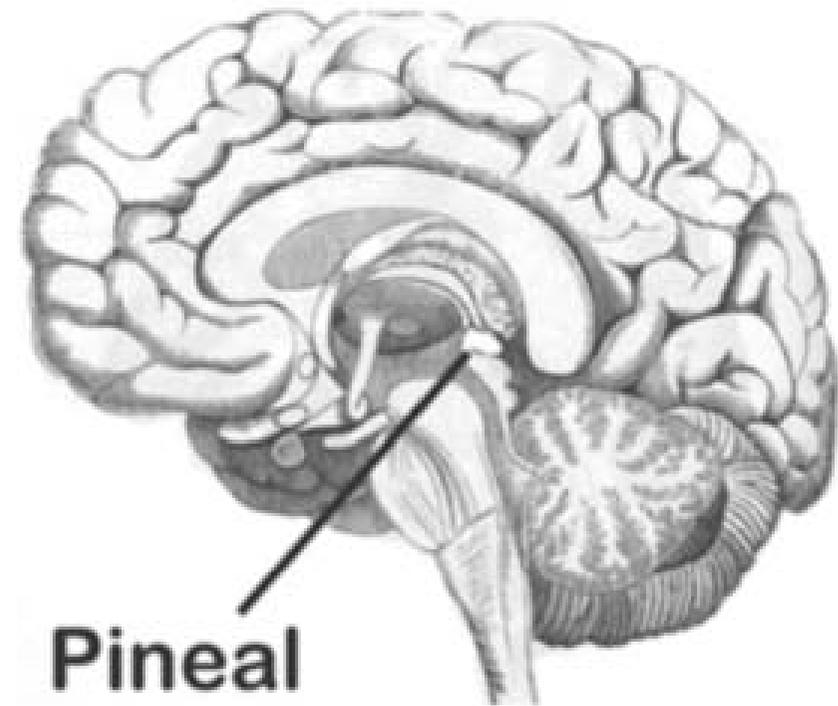
It's often prematurely **calcified.**



Bocchi G, Valdre G (February 1993). "Physical, chemical, and mineralogical characterization of carbonate-hydroxyapatite concretions of the human pineal gland". *J. Inorg. Biochem.* 49 (3): 209–20.

It secretes a **number of hormones** directly into the neuronal extra-cellular fluid.

Juszczak M, Michalska M (2006). "Wpływ melatoniny na syntezę i wydzielanie prolaktyny, hormonu luteinizującego (LH) i folikulotropowego (FSH)" [The effect of melatonin on prolactin, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) synthesis and secretion]. *Postepy Hig Med Dosw (Online)* (in Polish). 60: 431–38



The Pineal Gland secretes

Serotonin

Melatonin

Epithalamin

TRH

Vasopressin (ADH)

Prolactin

Somatostatin

Noradrenalin

Dopamine

GnRH

DMT

Pinoline

Motta, Marina; Fraschini, F.; Martini, L. (1967). "Endocrine Effects of Pineal Gland and of Melatonin". *Exp Biol Med (Maywood)*. 126 (2): 431–435

Melatonin is the pineal hormone of most biological significance.

It is synthesized from **serotonin**.

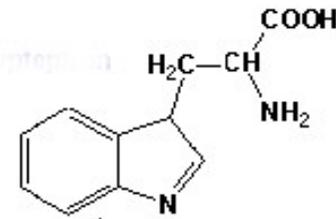
Axelrod J (1970). "The pineal gland". *Endeavour*. 29 (108): 144–8.

Tryptophan

hydroxylase

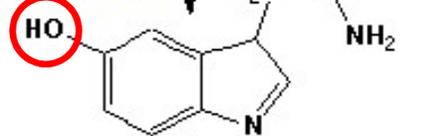


Tetrahydro-biopterin



Dihydro-biopterin

5-Hydroxytryptophan

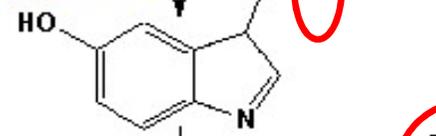


decarboxylase



CO₂

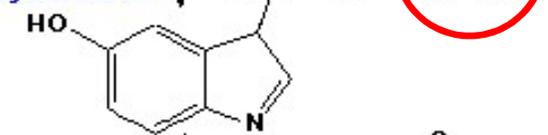
Serotonin



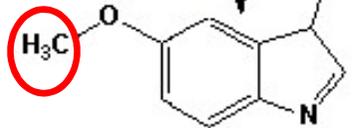
acetyltransferase



N-Acetylserotonin

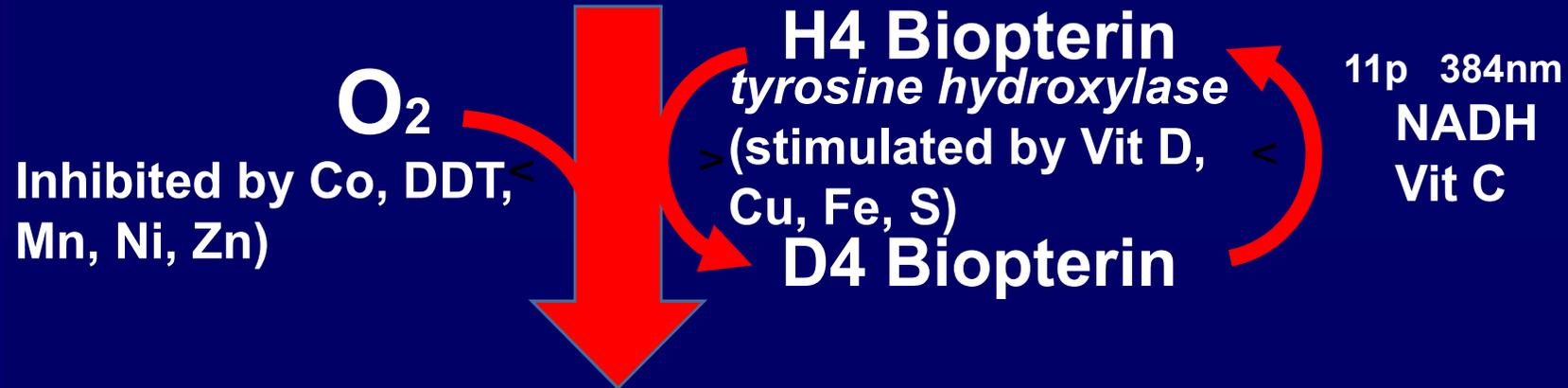


methyltransferase



Melatonin

TRYPTOPHAN



5-Hydroxytryptophan



SEROTONIN

Inhibited by

Acetoaminophen

Curcumin

Folic acid

H₂O₂

Ibuprofen

Quercetin

Silymarin

Vit C

Serotonin

Acetyl CoA

n.acetyltransferase

17q 392nm

CoA

N-Acetylserotonin

SAM

O-methyltransferase

(Mg, Zn, P5P,
Methylcobalamin
Methyl H4 folate,
Vit A)

23X 400nm

MELATONIN

MELATONIN

Fe⁺⁺⁺

NADPH + H⁺

hydroxylase

Fe⁺⁺

NADP⁺

5-Hydroxymelatonin

PAPs (Sulfur)

or

Glucuronate

sulfatase or

glucuronidase

Key Nutrients

Iron

NADPH

Sulfur or

Glucuronic

acid

Sulfate or Glucuronate conjugates

Melatonin

production is small in young children, peaks around puberty and declines after 50 years of age.

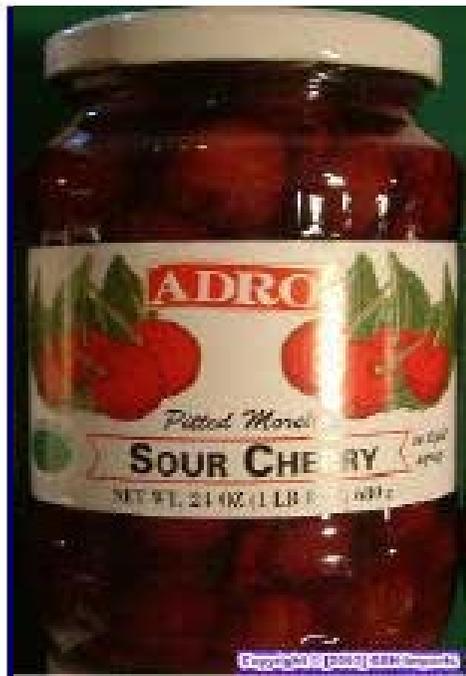
"Melatonin Production and Age". *Chronobiology*. Medichron Publications.



It is most
abundant and
active in total
darkness
peaking at **2am**
and declining to
half levels by
5am.

Axelrod J (1970). "The pineal gland". *Endeavour*. 29 (108): 144–8.

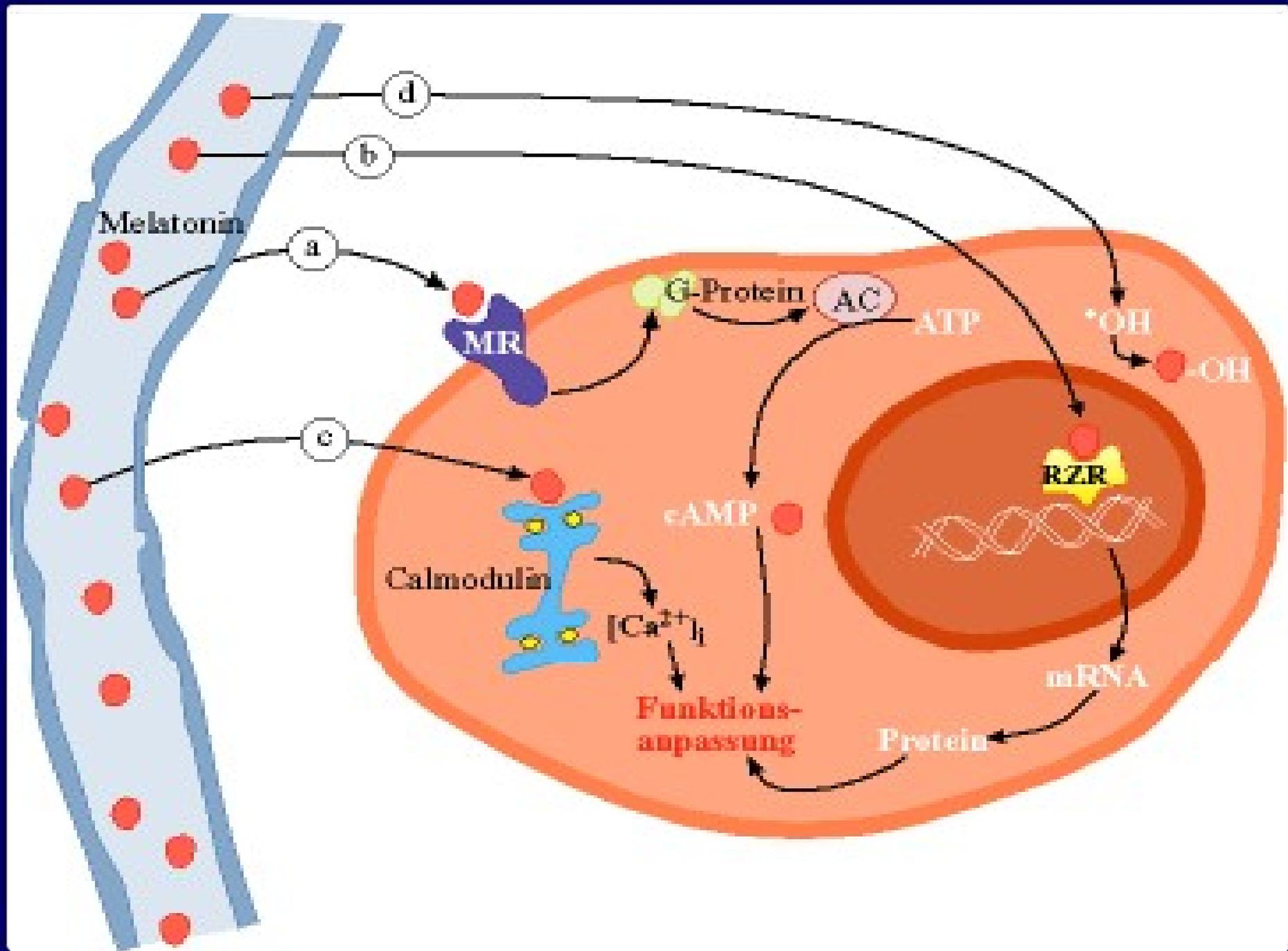




Melatonin is found naturally in Bananas, Morello cherries, Porridge oats



Sae-Teaw M, Johns J, Johns NP, Subongkot S (October 2012). "Serum melatonin levels and antioxidant capacities after consumption of pineapple, orange, or banana by healthy male volunteers". *J. Pineal Res.* 55 (1): 58–64





Clinically, it is best to **double** the night-time dose of melatonin to that required during the daytime. Or use **NOW** and **THEN** technique.

Melatonin is also secreted by the retina, the gastrointestinal tract, the liver, lungs, skin and certain lymphocytes.

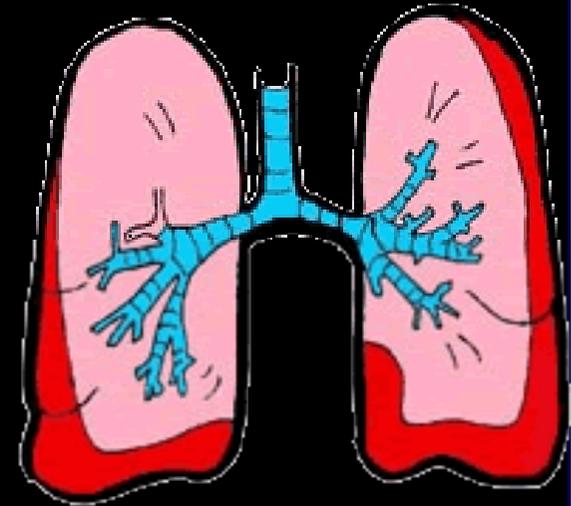
Retina



Liver



Lungs



Skin

GUT



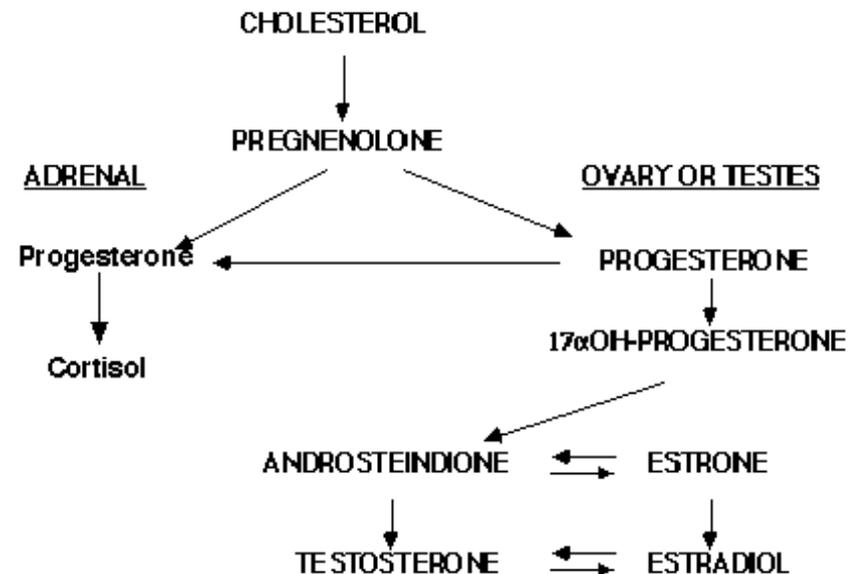
Lymphocytes

Blue light, principally around 460–480 nm, suppresses melatonin biosynthesis, proportional to the light intensity and length of exposure.*

***Brainard GC, Hanifin JP, Greeson JM, Byrne B, Glickman G, Gerner E, Rollag MD (August 2001). "Action spectrum for melatonin regulation in humans: evidence for a novel circadian photoreceptor". *J. Neurosci.* 21 (16): 6405–12. [doi:](#)**

Melatonin has a modulating effect on all the steroid hormones.

Juszczak M, Michalska M (2006). "Wpływ melatoniny na syntezę i wydzielanie prolaktyny, hormonu luteinizującego (LH) i folikulotropowego (FSH)" [The effect of melatonin on prolactin, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) synthesis and secretion]. *Postepy Hig Med Dosw (Online)* (in Polish). 60: 431–38.



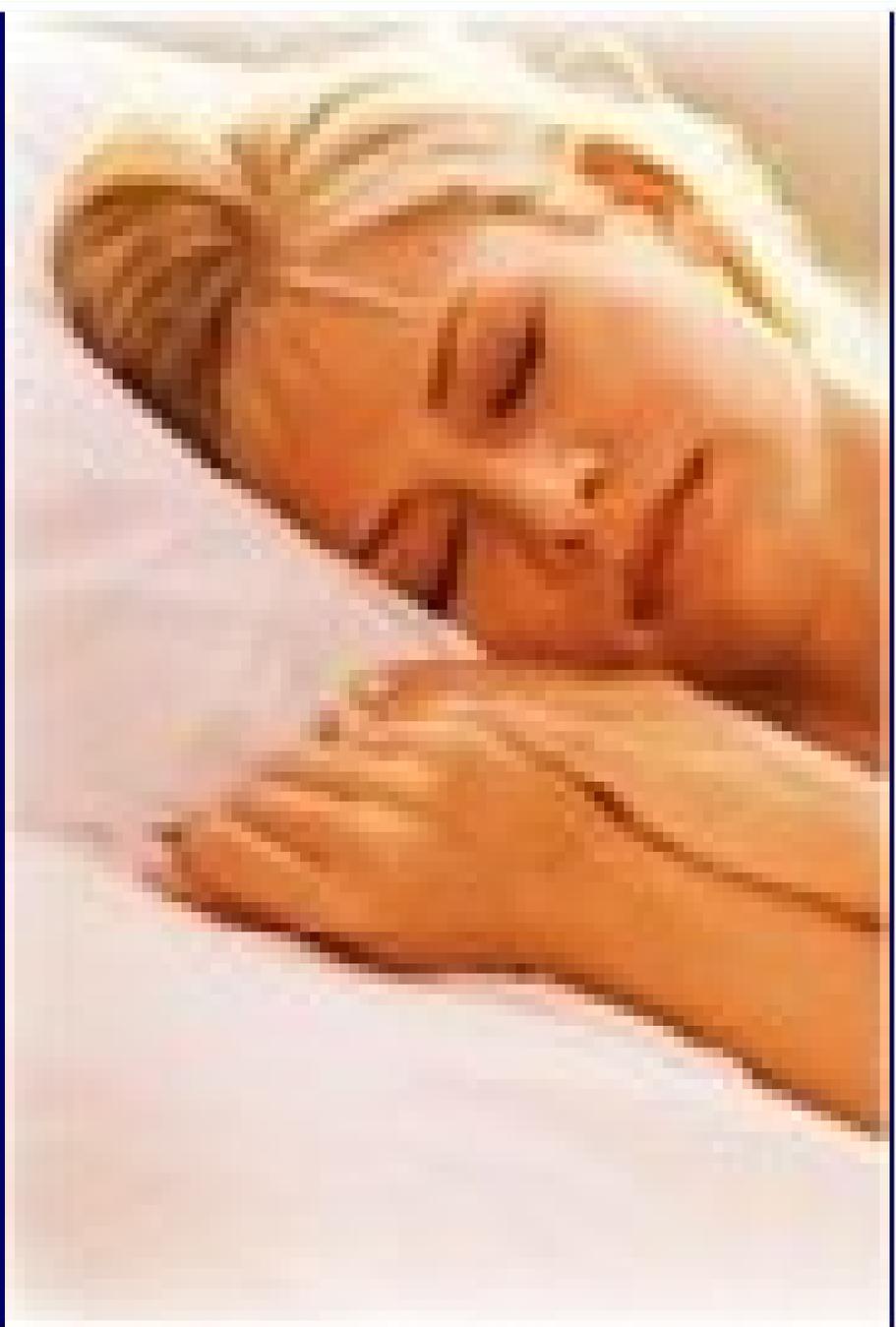
It stimulates **monoamine oxidase** thus reducing high levels of dopamine, noradrenalin, serotonin and histamine.*

This is why a good night's sleep solves most problems.

**Nesbitt AD, Leschziner GD, Peatfield RC (September 2014). "Headache, drugs and sleep". Cephalalgia (Review). 34 (10): 756–66.*

Melatonin induces a state of relaxation leading to a sleep state. It is not a sleeping medicine.

Juszczak M, Michalska M (2006). "Wpływ melatoniny na syntezę i wydzielanie prolaktyny, hormonu luteinizującego (LH) i folikulotropowego (FSH)"[The effect of melatonin on prolactin, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) synthesis and secretion]. *Postepy Hig Med Dosw (Online)* (in Polish). 60: 431–38

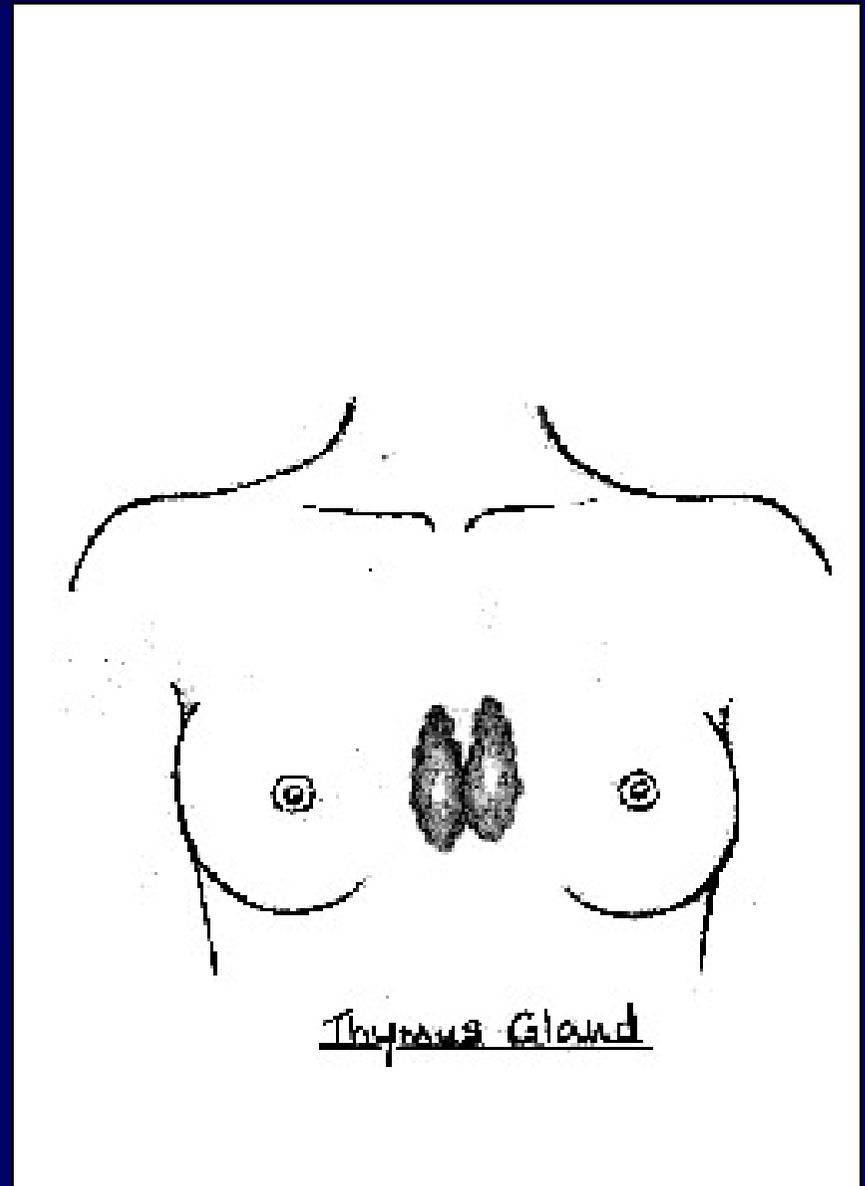


**High levels
during the night
inhibit sexual
function.**

Juszczak M, Michalska M (2006). "Wpływ melatoniny na syntezę i wydzielanie prolaktyny, hormonu luteinizującego (LH) i folikulotropowego (FSH)" [The effect of melatonin on prolactin, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) synthesis and secretion]. *Postepy Hig Med Dosw (Online)* (in Polish). 60: 431–38



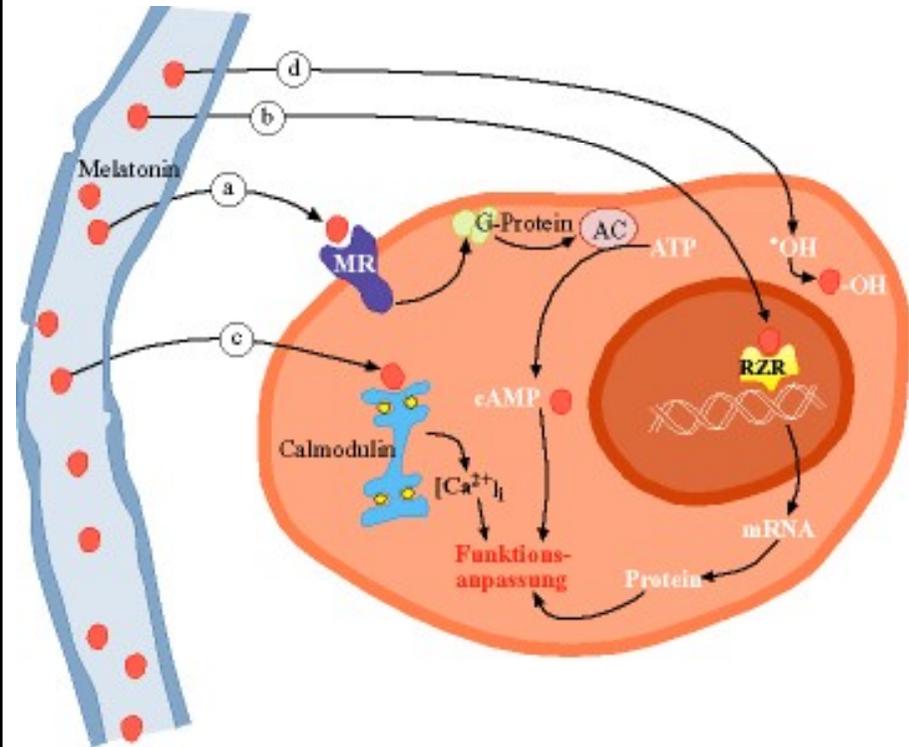
Melatonin has an **immuno-modulatory** effect on the thymus gland by differentiating undifferentiated white cells into mature T, B and NK cells.

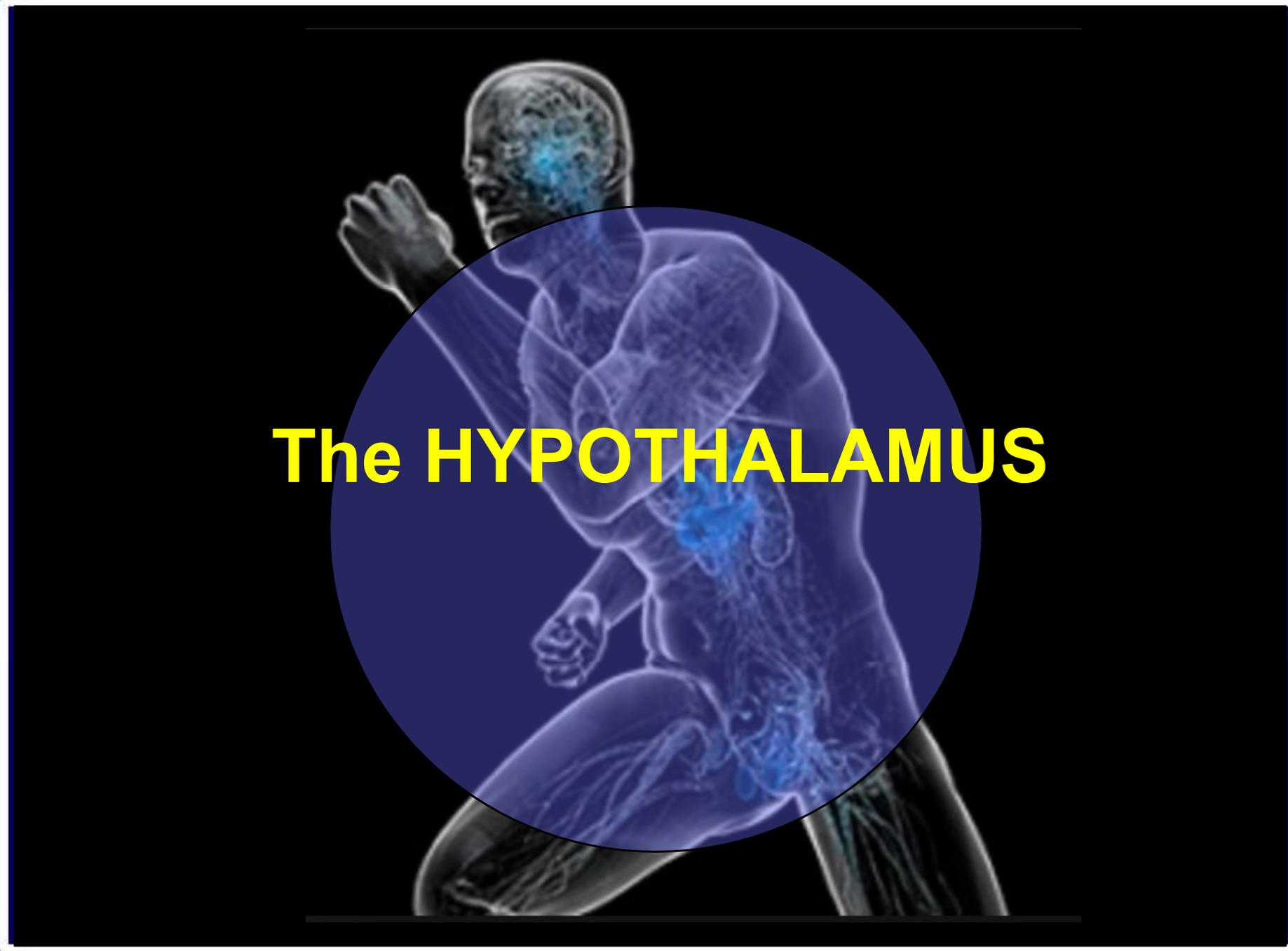


Carrillo-Vico A, Guerrero JM, Lardone PJ, Reiter RJ (July 2005). "A review of the multiple actions of melatonin on the immune system". *Endocrine*. 27 (2): 189–200.

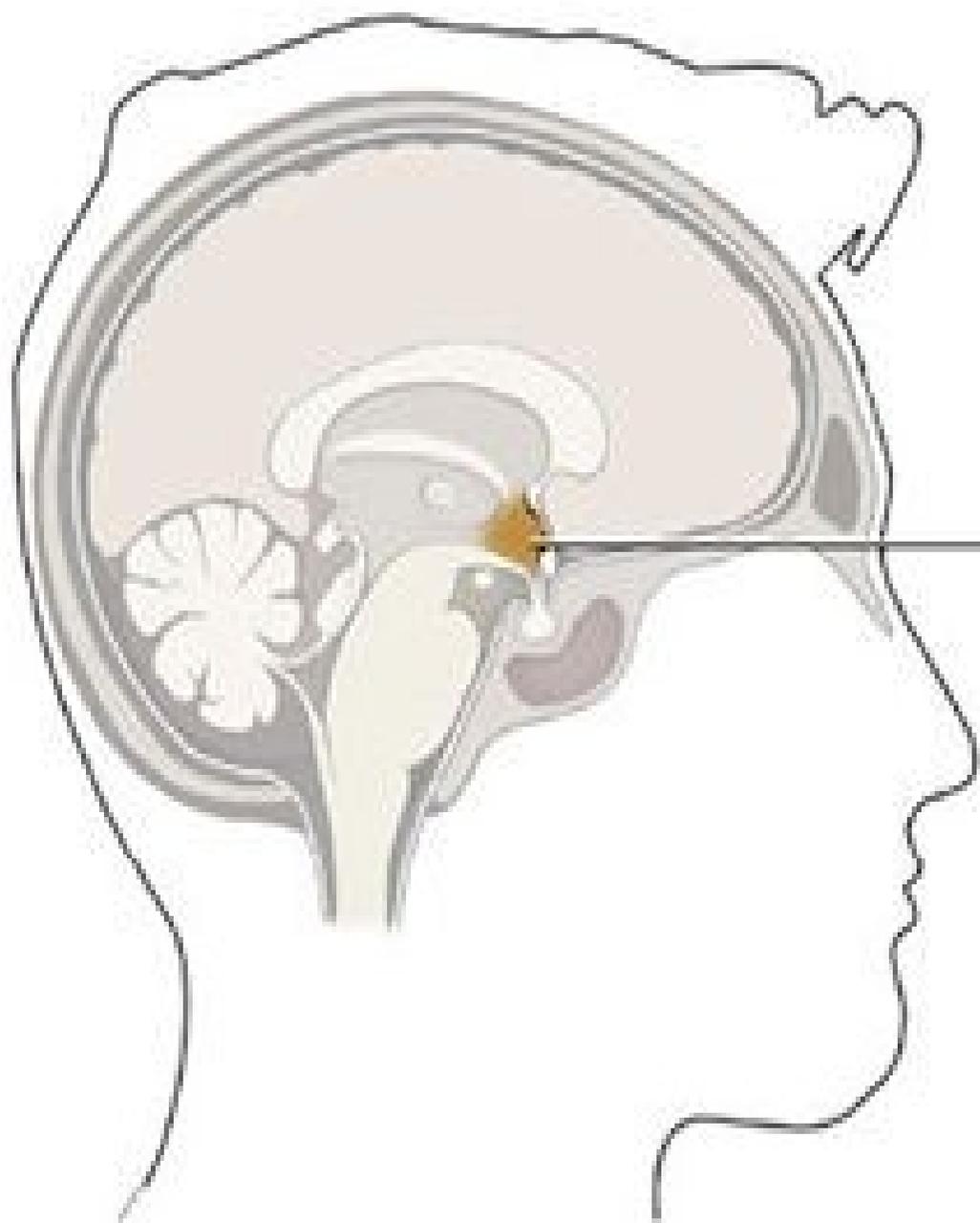
It is a powerful
antioxidant
against the
hydroxyl
radical.

Poeggeler B, Saarela S, Reiter RJ, Tan DX, Chen LD, Manchester LC, Barlow-Walden LR (November 1994). "Melatonin – a highly potent endogenous radical scavenger and electron donor: new aspects of the oxidation chemistry of this indole accessed in vitro". *Ann. N. Y. Acad. Sci.* 738 (1): 419–20.

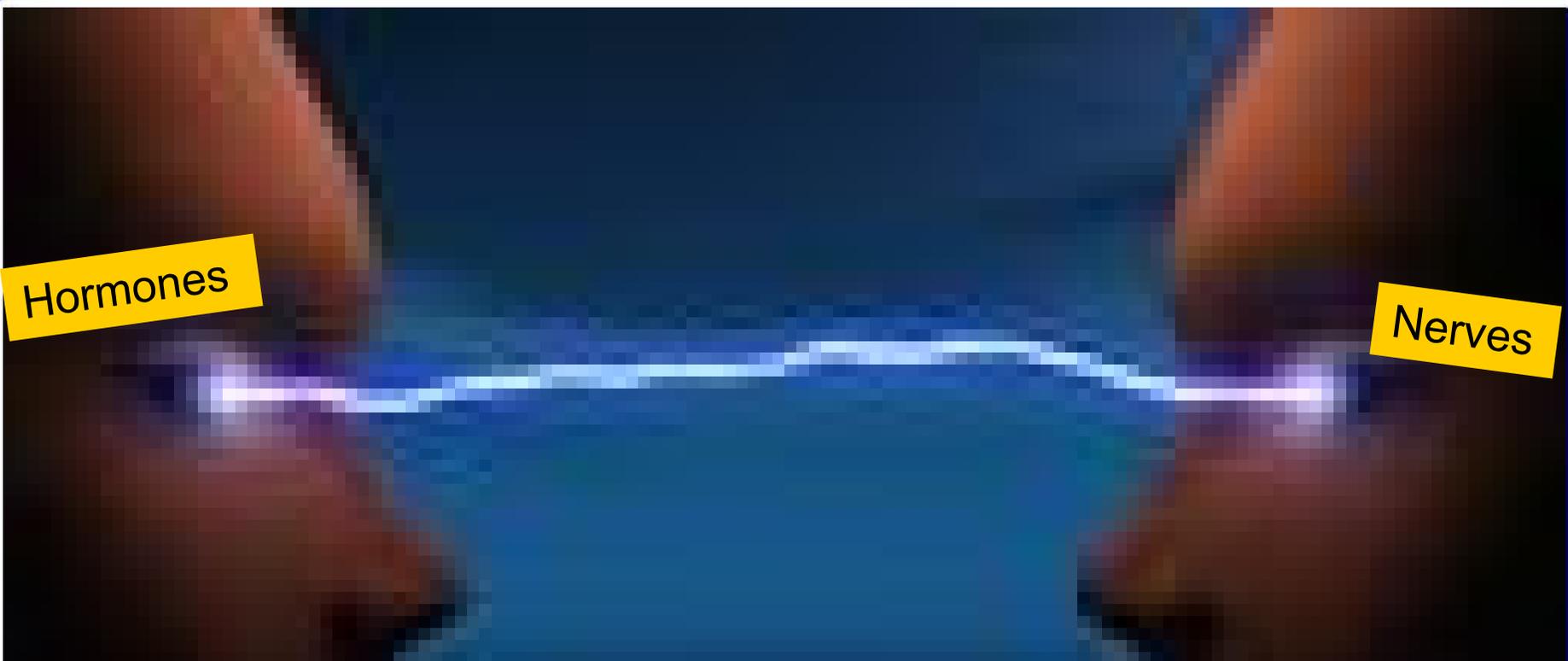




The HYPOTHALAMUS



Hypothalamus

A diagram showing a central blue brain structure, the hypothalamus, with two large, reddish-brown, cone-shaped structures on either side. A horizontal blue line passes through the center of the brain structure. A yellow label 'Hormones' is on the left, and a yellow label 'Nerves' is on the right, both pointing towards the central brain structure.

Hormones

Nerves

The **hypothalamus** is the main interface in the brain between the neurological system and the hormonal system.

The Hypothalamus regulates

- 1. Autonomic nervous system**
- 2. Biological rhythms (Clock)**
- 3. Hormones**
- 4. Heart rate**
- 5. Blood pressure**
- 6. Appetite and thirst**
- 7. Body weight**

- 8. Water balance**
- 9. Body temperature**
- 10. Sleep pattern**
- 11. Pain**
- 12. Pupillary dilation**
- 13. Ovulation**

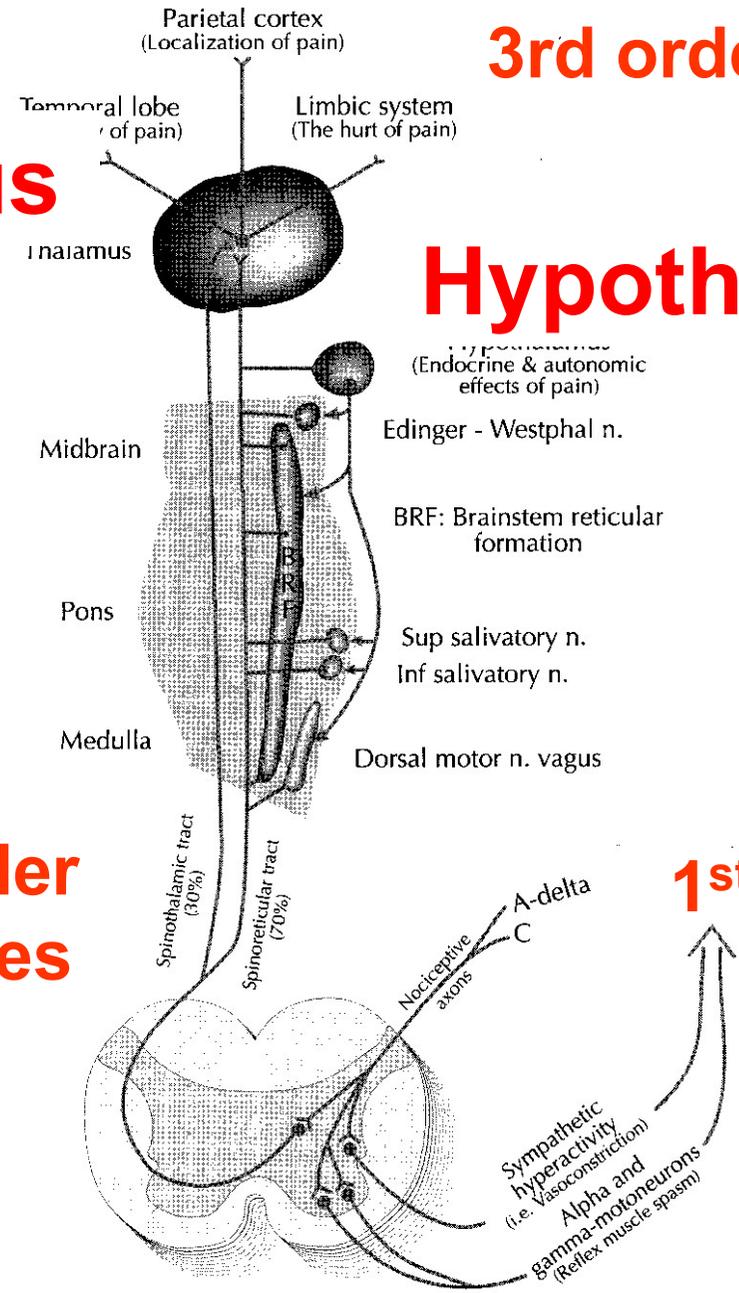
Thalamus

3rd order neurones

Hypothalamus

2nd order neurones

1st order neurones



All sensory information travels either directly or indirectly to the **thalamus** and from there third order neurons relay information to the sensory cortex for a motor response if required and to the **hypothalamus** for any autonomic and / or any hormonal response.

The Hypothalamus secretes 6 releasing hormones

CRH = Corticotrophin Releasing Hormone

TRH = Thyrotrophin Releasing Hormone

GnRH = Gonadotrophin Releasing Hormone

GRH = Growth Releasing Hormone

**Somatostatin = Growth Hormone Release –
Inhibiting Hormone**

**PRIH = Prolactin Release – Inhibiting
Hormone**

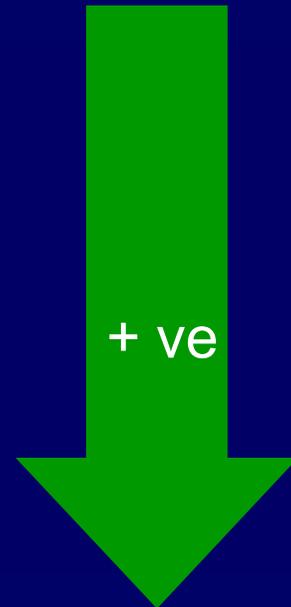
They are released in a pulsatile manner from the hypothalamic nerve fibre endings and travel through a special portal system to the anterior lobe of the pituitary gland.

Each **pituitary hormone is under tonic control of at least one hypothalamic hormone.**

Corticotrophin releasing hormone

8 381nm

(CRH)



+ ve

ACTH

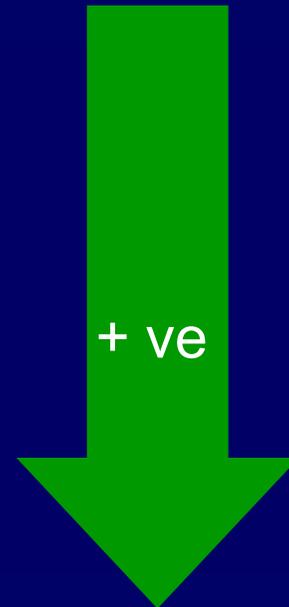
2p 372nm

Adrenocorticotrophic hormone

Thyrotrophin releasing hormone

3q 375nm

(TRH)



+ ve

TSH

6q 379nm

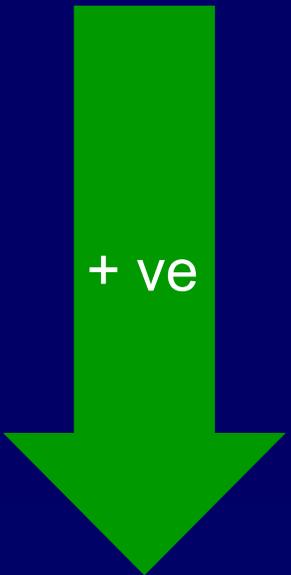
1p 370nm

Thyroid stimulating hormone

Gonadotrophin releasing hormone

8 381nm

(GnRH)



+ ve

6q 379nm
19q 395nm

LH

6q 379nm
19q 395nm

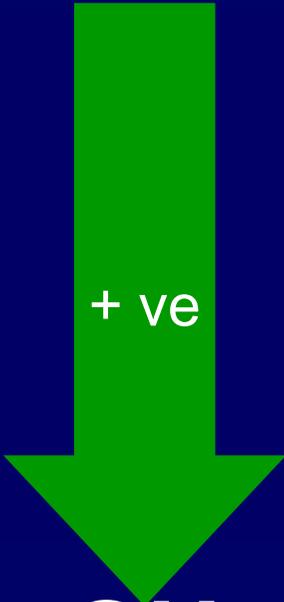
FSH

Luteinising hormone
Follicle stimulating hormone

Growth hormone releasing hormone

20p 396nm

(GRH)



+ ve

GH

17q 382nm

Growth hormone

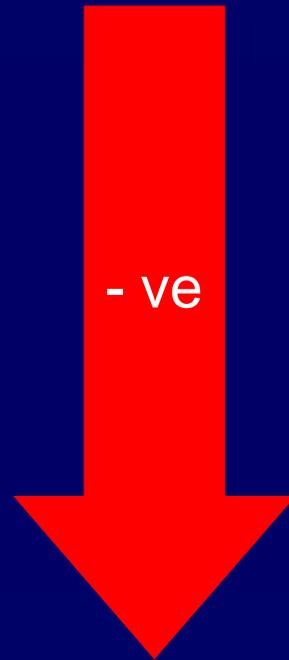
**Growth hormone release –
inhibiting hormone 3q 375nm
(Somatostatin)**



17q 392nm 6q 379nm 6q 379nm 19q 395nm 2p 372nm

**GH (TSH, FSH, ACTH)
Growth hormone**

Prolactin releasing – inhibiting hormone (Dopamine)



PRL

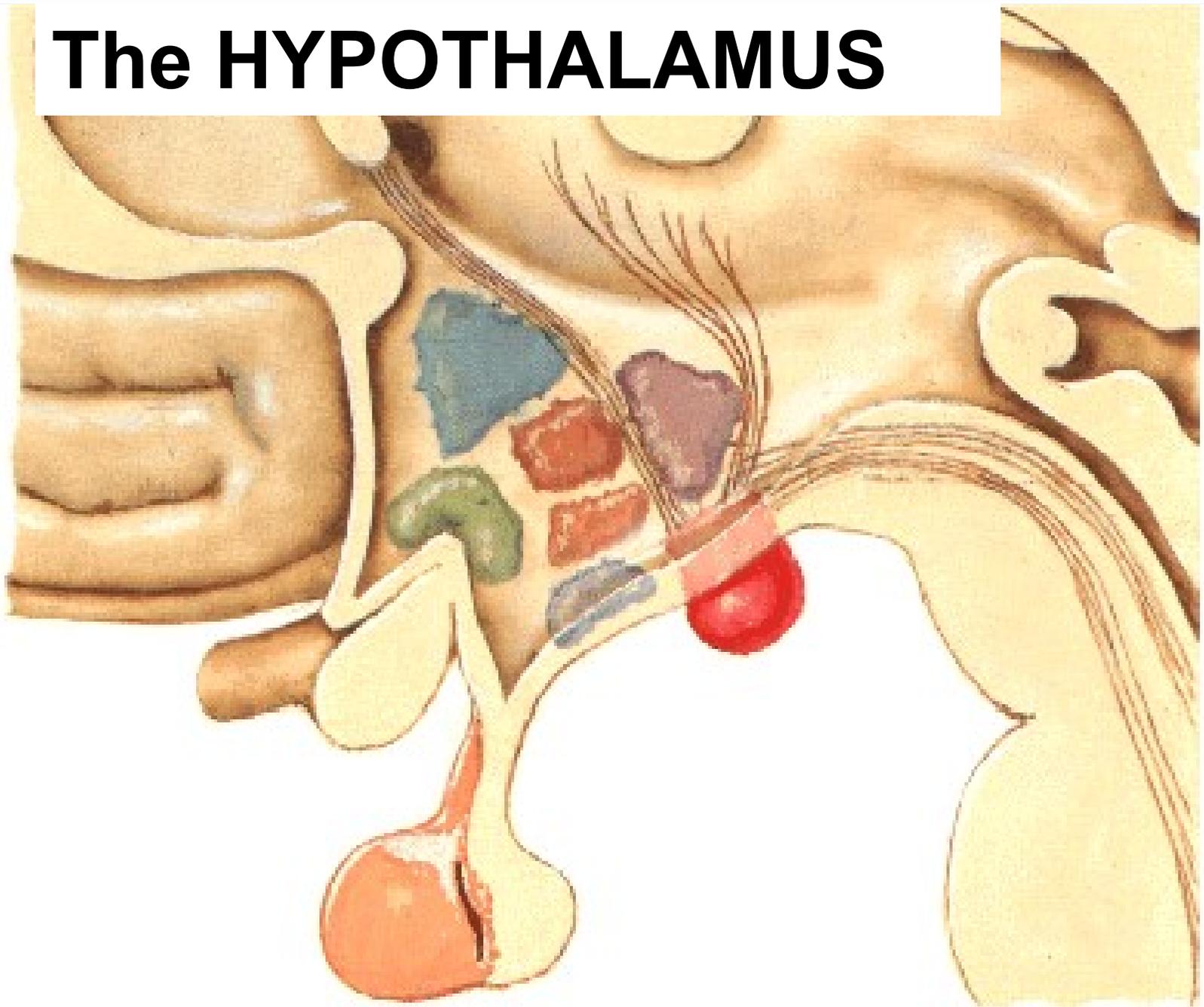
6p 378nm

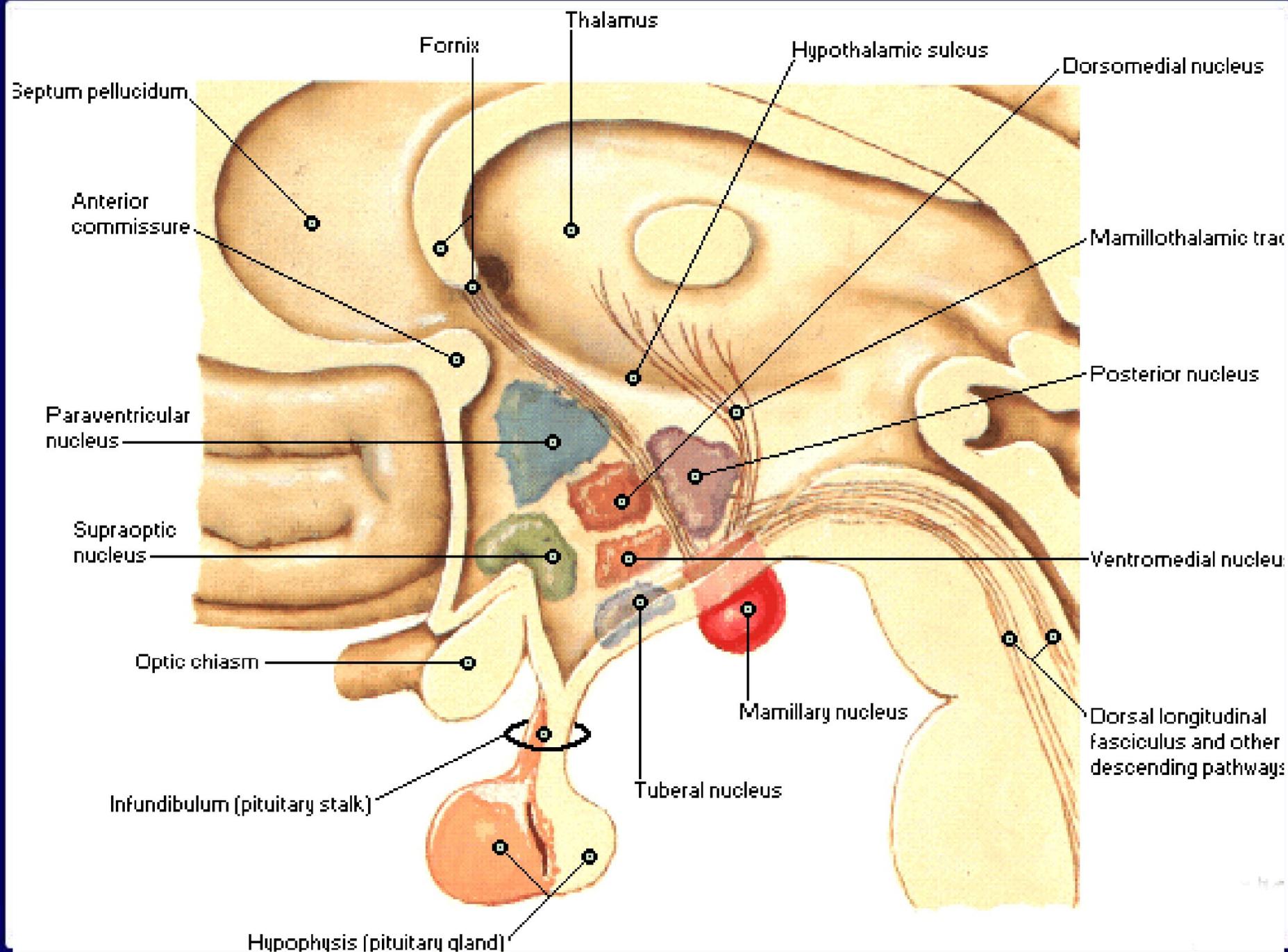
6q 379nm

Prolactin hormone (and TSH)

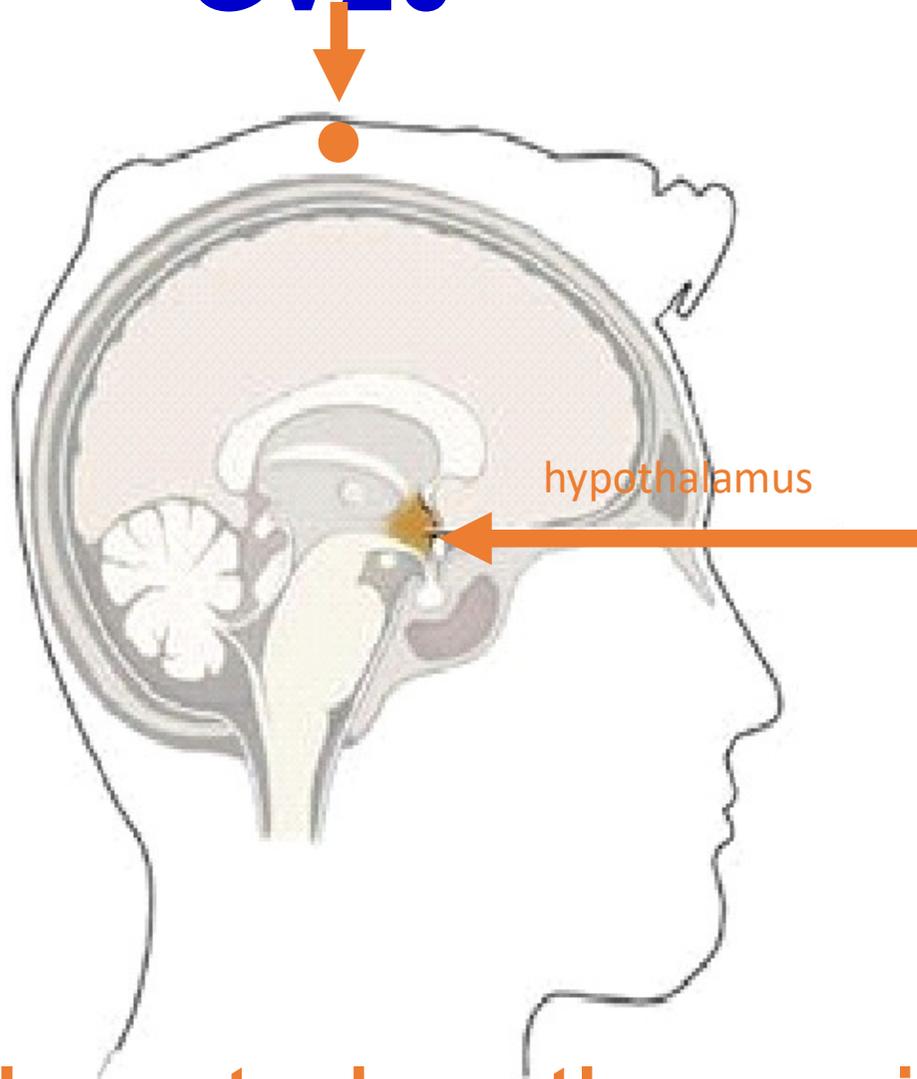
MERIDIAN	NEUROTRANS	HYPOTHALAMIC	PITUITARY	TARGET
CV	↓ Dopamine	↓ CRH	↓ ACTH (MSH)	↓ Mineralocorticoids, Glucocorticoids
GV	↑ Dopamine	↑ CRH	↑ ACTH (MSH)	↑ Mineralocorticoids, Glucocorticoids
TW	↓ Excitatory	↓ TRH	↓ TSH (PRL)	↓ T3 and T4
Cx	↑ Excitatory	↑ TRH	↑ TSH (PRL)	↑ T3 and T4
GB	↓ Acetylcholine	↓ GnRH	↓ LH, FSH	↓ Androgens, Estrogens Progestins
LIV	↑ Acetylcholine	↑ GnRH	↑ LH, FSH	↑ Androgens, Estrogens Progestins
St	↓ Histamine	↓ GHRH	↓ GH	↓ IGF1
Sp	↑ Histamine	↑ GHRH	↑ GH	↑ IGF 1
SI	↓ Noradrenalin	↓ Somatostatin	↑ GH (TSH, FSH, ACTH)	↑ IGF 1, T3 and T4
Ht	↑ Noradrenalin	↑ Somatostatin	↓ GH (TSH, FSH, ACTH)	↓ IGF 1, T3 and T4
LI	↓ Inhibitory	↓ PRIH	↑ PRL	↑ Neurohormones
Lung	↑ Inhibitory	↑ PRIH	↓ PRL	↓ Neurohormones
BI	↓ Serotonin	↓ PHL	↓	
Kid	↑ Serotonin	↑ PHL	↑	

The HYPOTHALAMUS

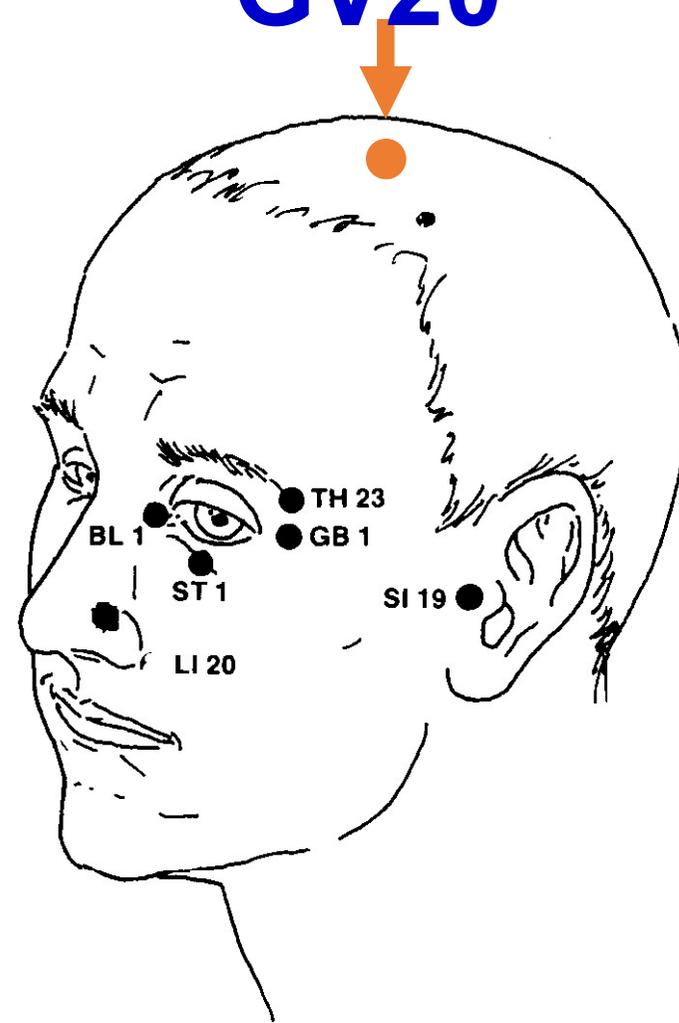




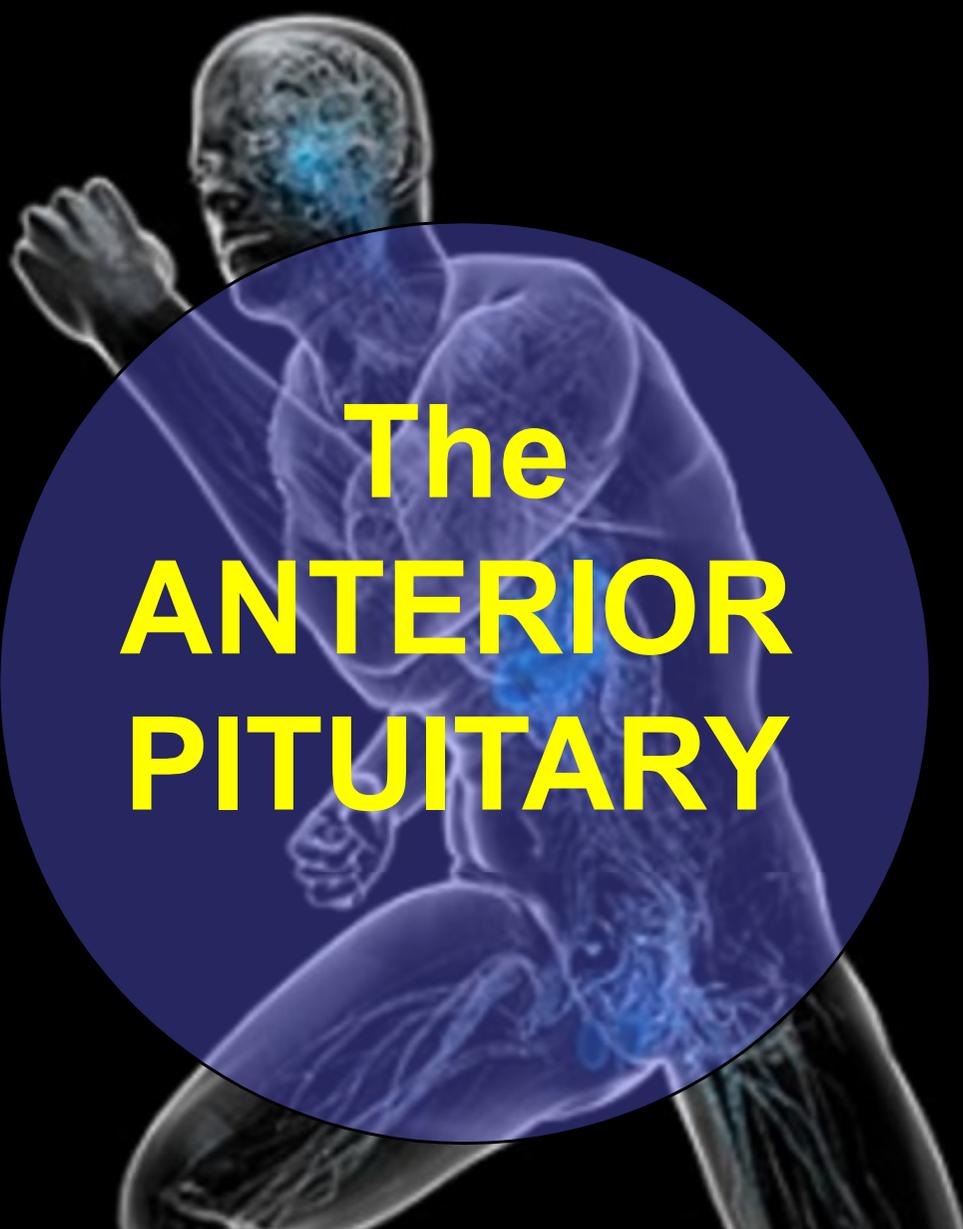
GV20



GV20



Located on the sagittal suture mid way between the ears.

An anatomical illustration of a human figure in a dynamic, forward-leaning pose. The figure is rendered in a semi-transparent, light blue color. The brain is highlighted in a darker blue, and the pituitary gland is specifically highlighted in a bright yellow. The background is black, and the entire illustration is framed by a white border.

**The
ANTERIOR
PITUITARY**

GROUP 1

17q 392nm

**1. Growth Hormone (GH) -
mediates IGF I and II**

12 385nm

11 384nm

**2. Prolactin (PRL) - 6p 378nm
mediates lactation.**



Acromegaly



GROUP 2

6q 379nm

1p 370nm

1. Thyroid stimulating hormone (TSH)– mediates Thyroxin and T3.

6q 379nmm

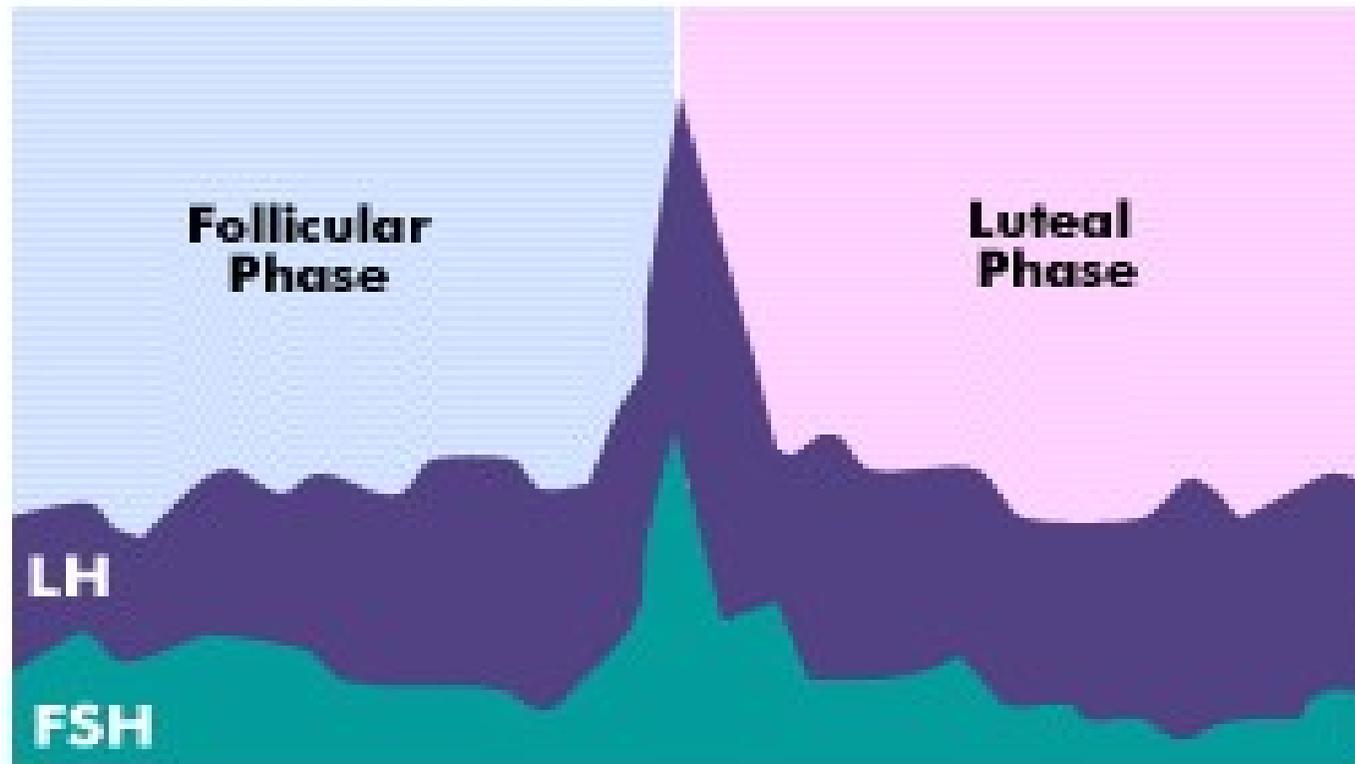
19q 395nm

2. Luteinising hormone (LH) - mediates progesterone, testosterone.

Pituitary Hormones

**Follicle-stimulating
Hormone (FSH)**

**Luteinizing Hormone
(LH)**



0

7

14

21

0

DAYS

3. Follicle stimulating hormone (FSH) - mediates the follicular cells.

6q 379nm
19q 395nm

4. Chorionic gonadotrophin (HCG) - mediates the placenta.

6q 379nm
19q 395nm

GROUP 3

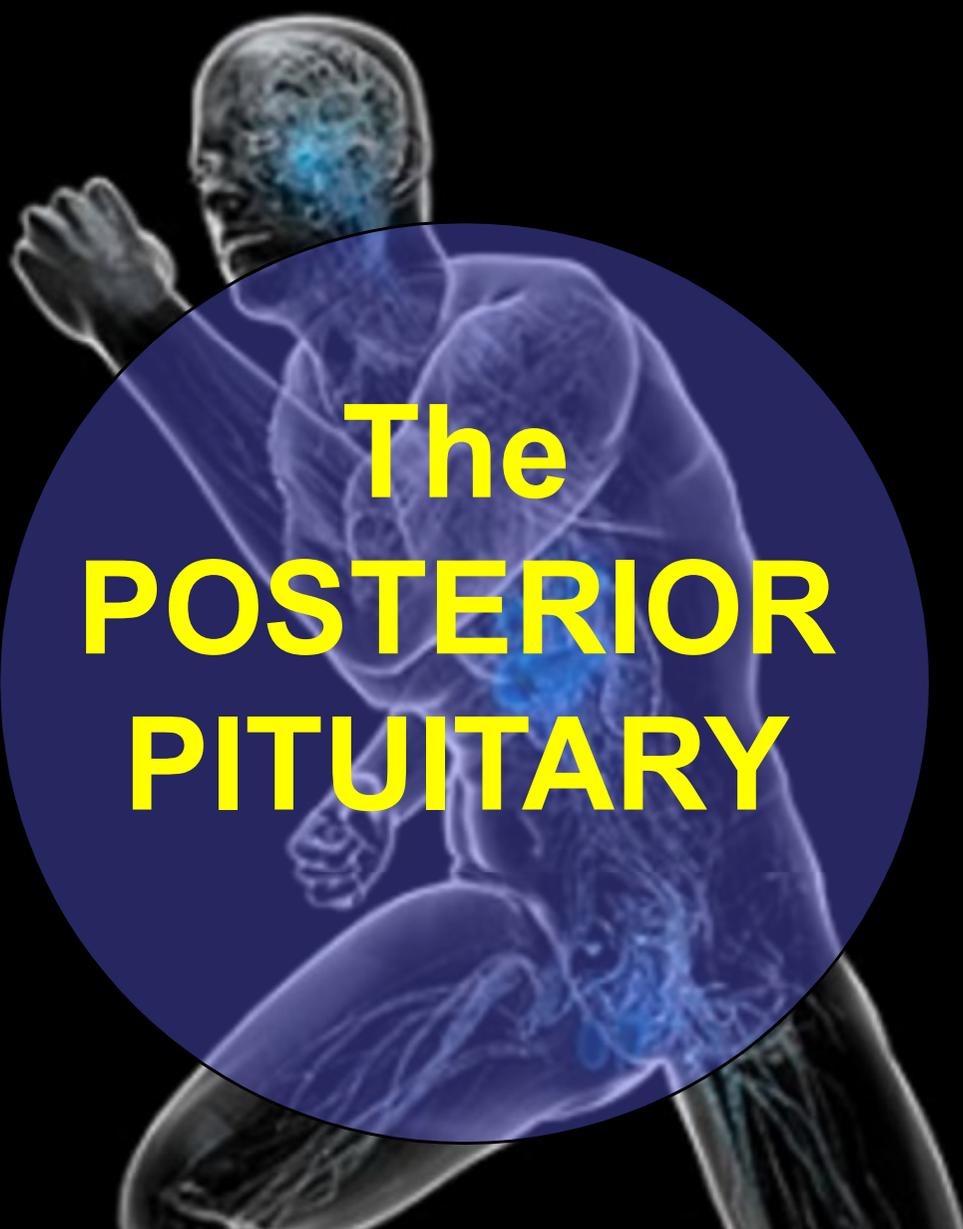
2p 372nm

1. Adrenocorticotrophic hormone (ACTH) - mediates the adrenal cortical steroids.

2. Melanocyte stimulating hormone (MSH) – mediates melanin production.

2p 372nm

2p 172nm

An anatomical illustration of a human figure in a dynamic, forward-leaning pose. The figure is rendered in a semi-transparent, light blue color. The brain is highlighted in a darker blue, and the pituitary gland is specifically highlighted in a bright yellow. The background is black, and the entire illustration is framed by a white border.

The POSTERIOR PITUITARY

The Posterior Pituitary Hormones

20p 396nm

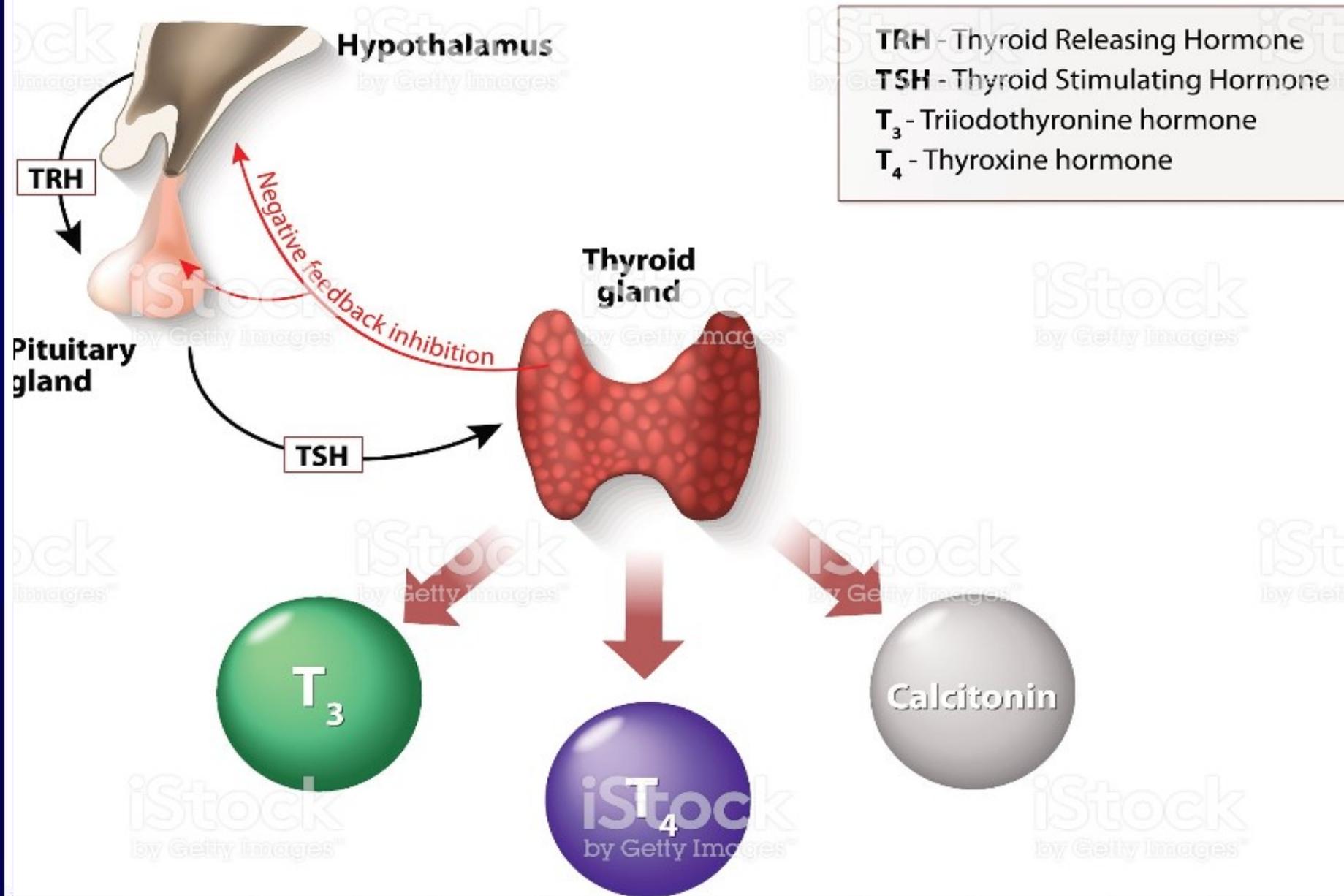
1. Vasopressin (Antidiuretic hormone) – mediates the reabsorption of water from the distal renal tubules.

20p 396nm

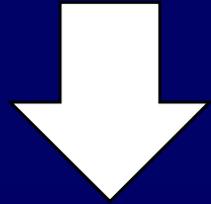
**2. Oxytocin – mediates uterine smooth muscle contraction.
The hormone of love!**

THYROXINE and T3 SYNTHESIS

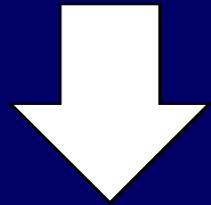
THYROID HORMONES



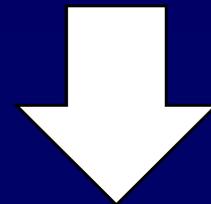
Hypothyroid



Insulin resistance

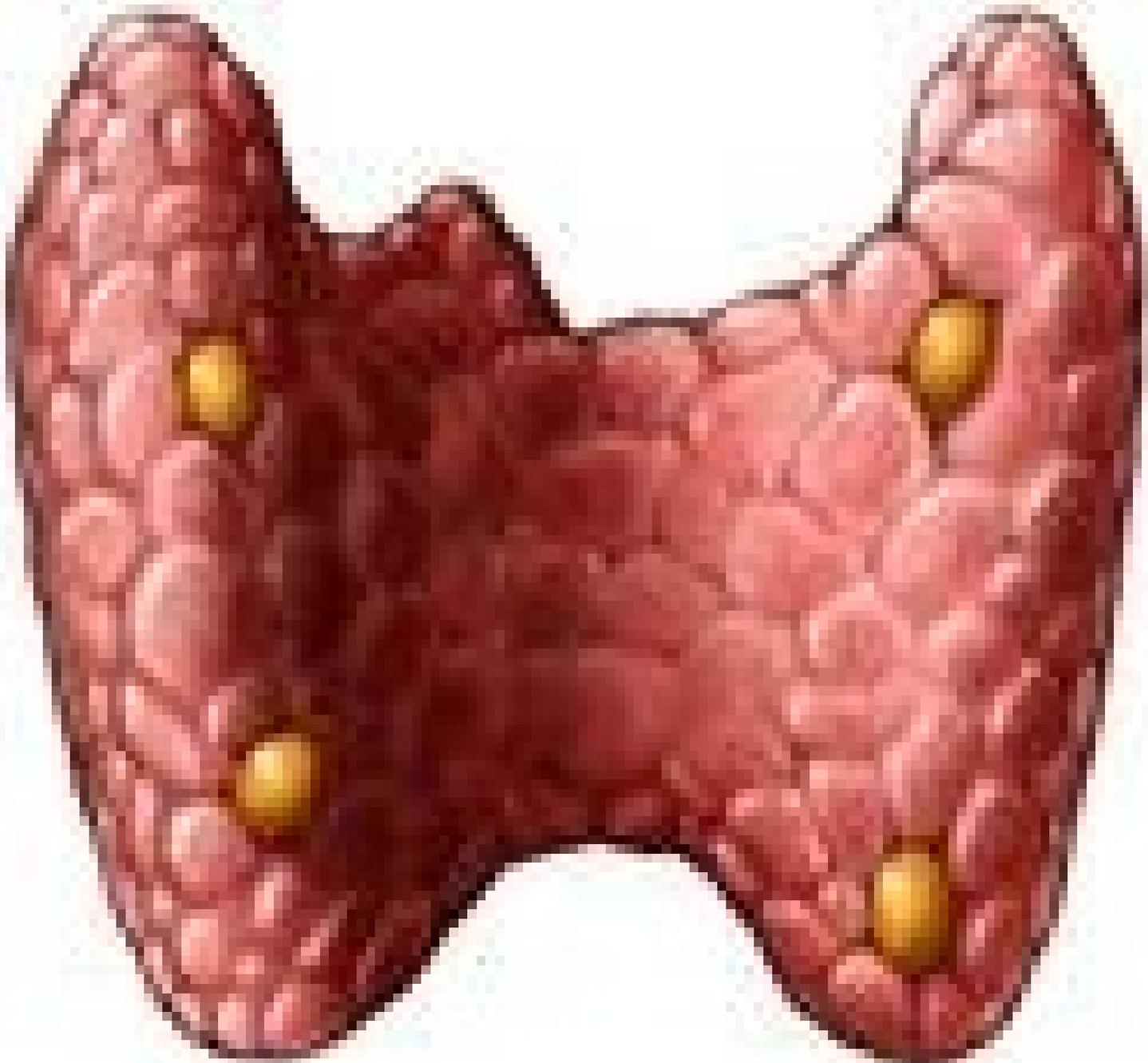


Frozen shoulder



Heart Failure



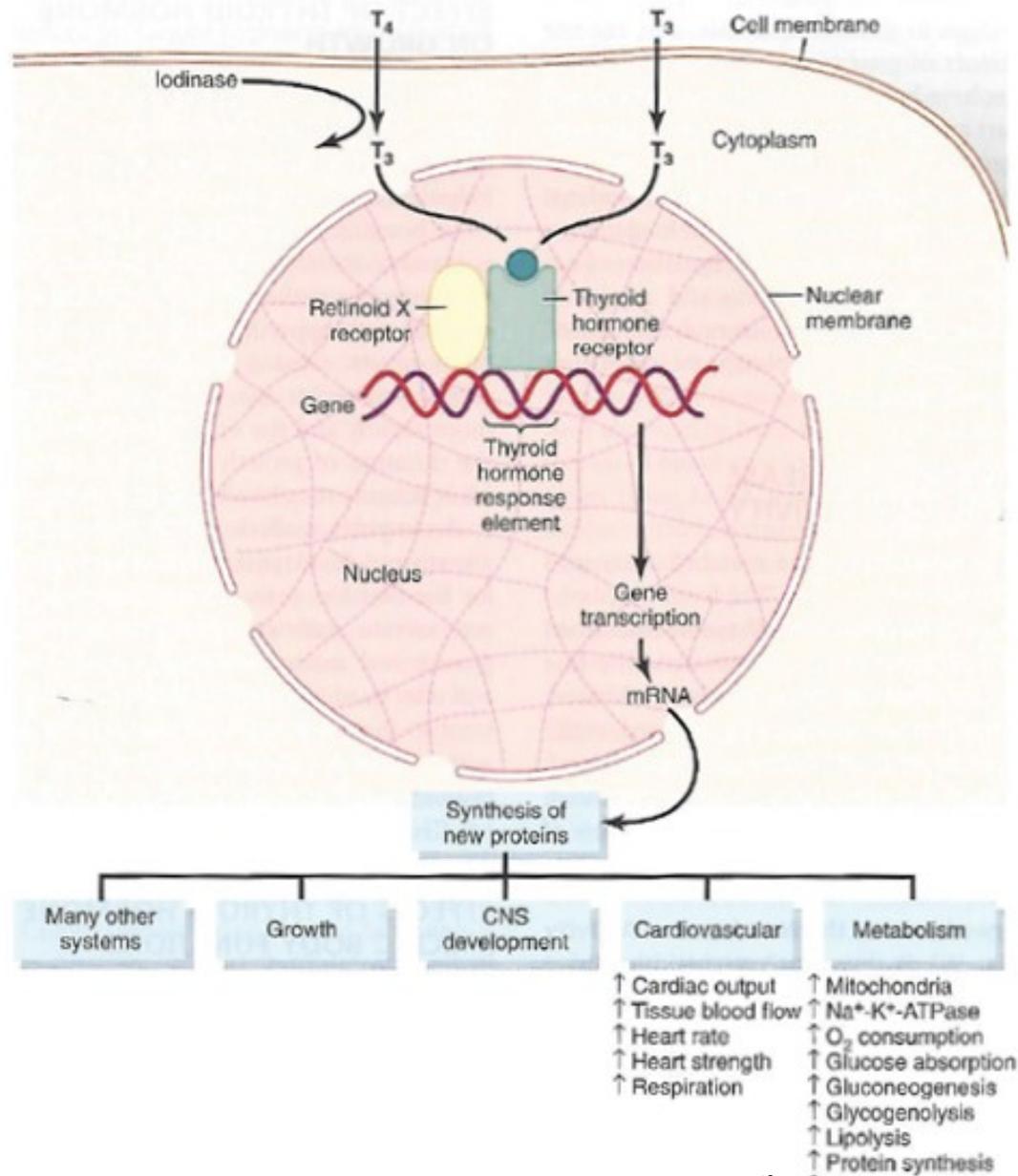


Thyroid

- **Extremely common**
- **Medication not always resolve**
- **Weight gain, tiredness, bloated, depressed**
- **Thyroid cancer rates are rising. Everyday chemicals linked to nodules and cancer**

Thyroid Hormones activity is to activate nuclear transcription of a large number of genes.

Most of the thyroxine secreted by the thyroid is converted to **Triiodothyronine (T3)**



Guyton and Hall (2011). *Textbook of Medical Physiology*. 13th Edition U.S.: Saunders Elsevier. p. 955

Thyroid Hormones have two main functions

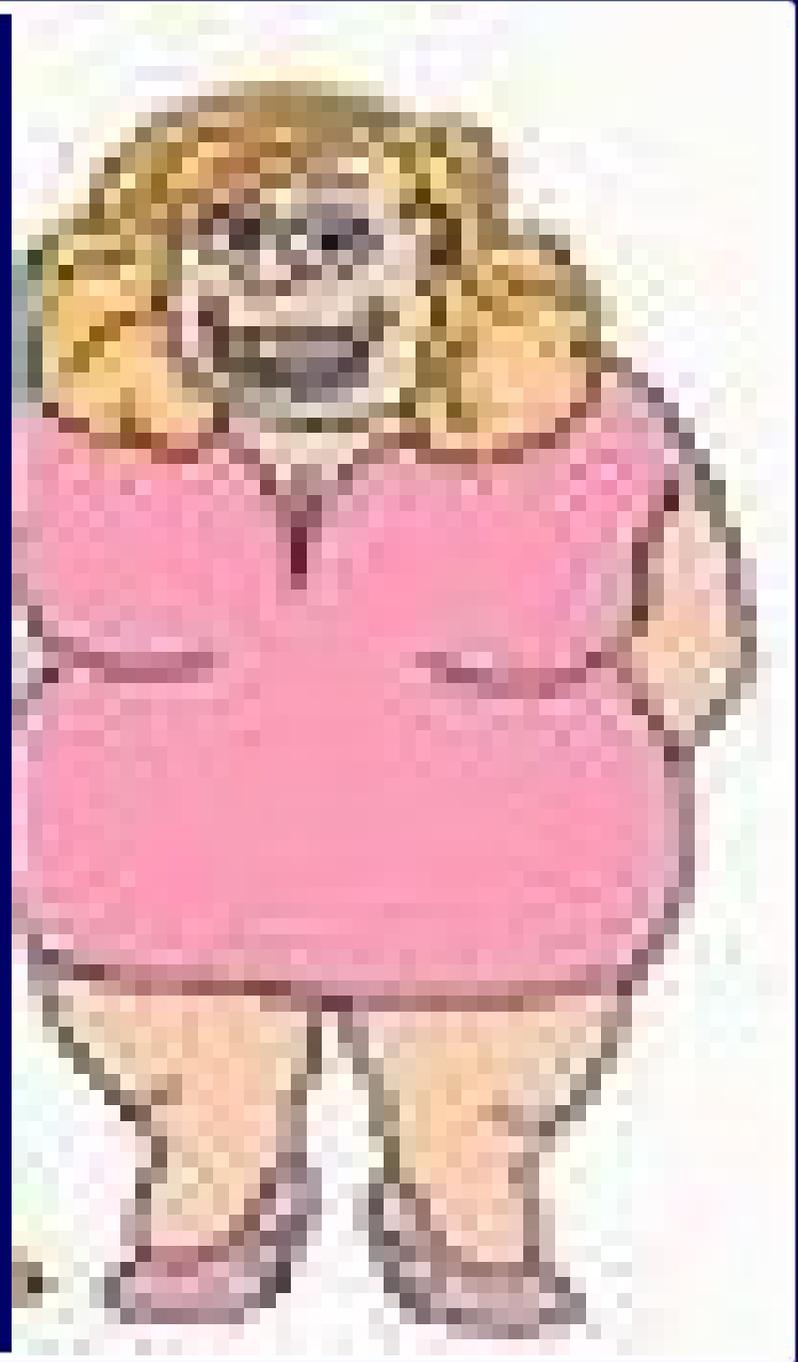
- 1. Regulation of metabolic rate**
- 2. Stimulation of growth and repair in children**

Because a fully functioning thyroid gland is required for normal development of the brain, any reduction in function (for example as a result of **iodine deficiency**) can cause mental retardation.

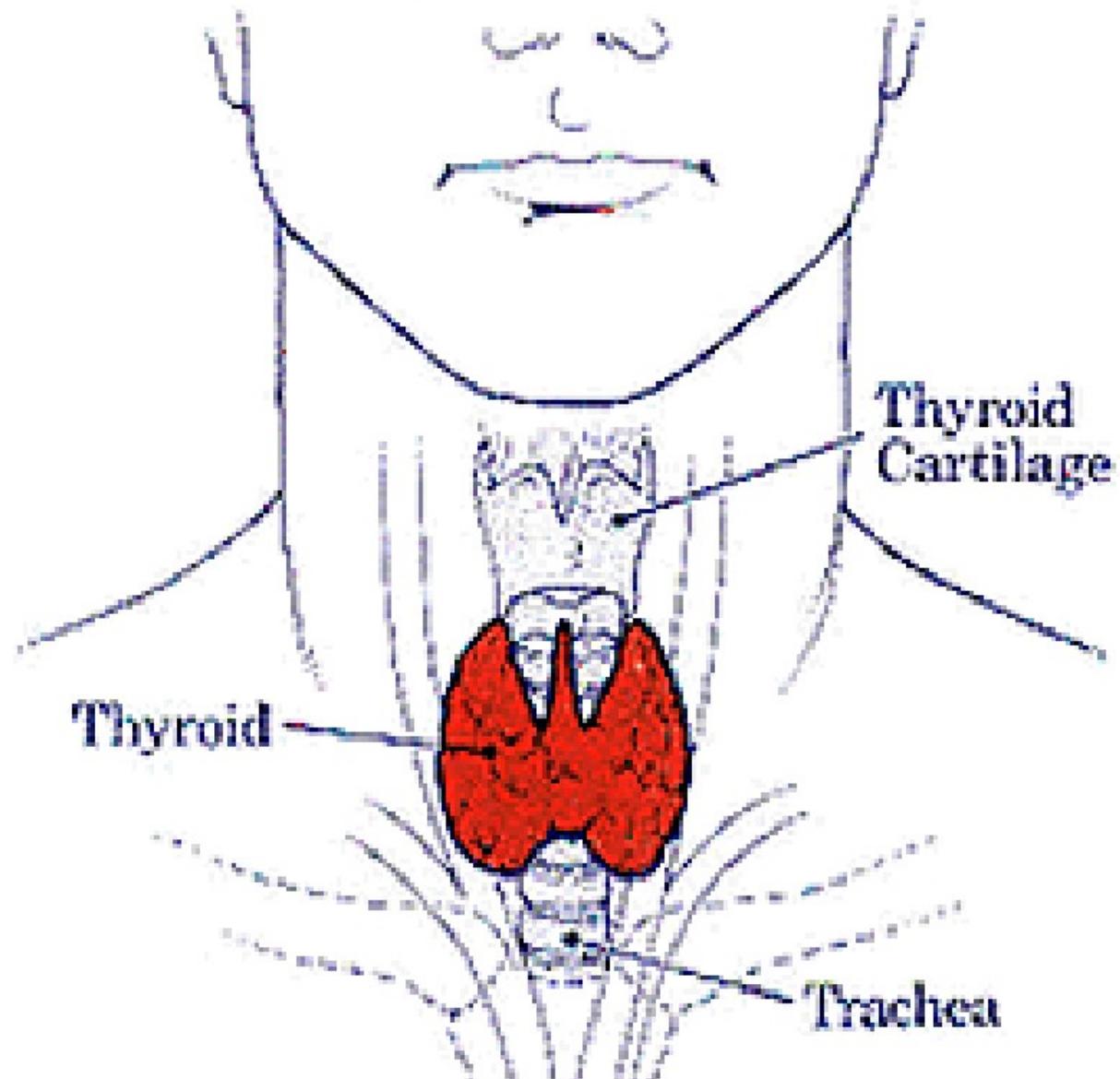


The major symptoms of low thyroid are so common today as to be considered normal –

**Low energy,
marginal health
and overweight.**



The Thyroid Gland



Thyroid Gland

- Gland is located at the front of the neck attached to the lower part of the larynx(voice box) and the upper part of the trachea(windpipe)
- It is shaped like a butterfly and composed of 2 lobes

Thyroid

- Lobes are connected in the middle by a narrow band of tissue called the isthmus
- The thyroid cartilage surrounding the gland sticks out in the neck and forms the Adam's apple

Thyroid Gland

- One of the largest endocrine glands in body – approx. 18 g in women and 25 g in men
- Contains many follicles or small spheres
- These contain a protein mixture called colloid where the protein thyroglobulin is found

Thyroid Gland

- T4 and T3 are made out of thyroglobulin
- Parafollicular cells are found between the follicles, these secrete hormone calcitonin which reduces calcium in the body fluids & drives it into bone

Thyroid Hormones

- Produces 2 main hormones
- Triiodothyronine T3 – 3 iodine
- Tetraiodothyronine T4 – 4 iodine
- Thyroglobulin (thyroid binding protein) contains numerous tyrosine molecules

Thyroid Hormones

- Produces more T4 than T3 – ratio of 80% to 20%
- T3 is approx. 10 times stronger in its action, more biologically active
- Most T3 is made out of T4 in other parts of the body besides the thyroid. Only small amounts from the thyroid

Thyroid Hormones

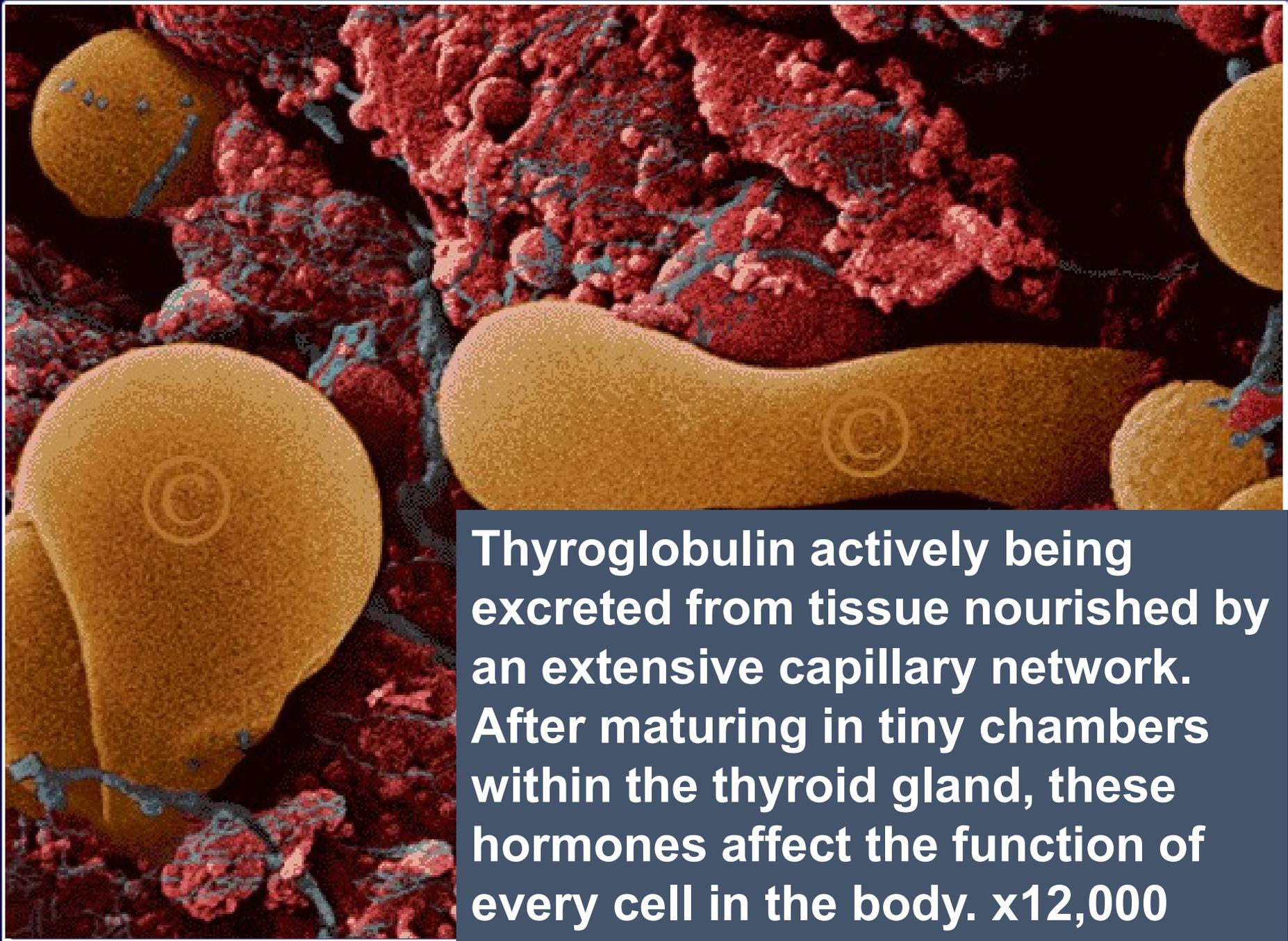
- In thyroid, tyrosine plus 1 iodine make T1. 2 molecules of iodine make T2
- In thyroid $\text{DIT} \times 2 = \text{T4}$
- In thyroid $\text{MIT} + \text{DIT} = \text{T3}$

Thyroid Hormones

- In mitochondria, liver and kidney T4 loses an iodine molecule to become T3
- Deiodinase enzyme – selenium dependant, zinc and copper co-factors

Thyroid Hormones

- If deficient in T3 then the thyroid may not be producing from T1 & T2. Or in tissues not converting T4 to T3
- If too high in T4 then too much in mitochondria and not converting
- If deficient in T1 and/or T2 then problem is in the thyroid gland



Thyroglobulin actively being excreted from tissue nourished by an extensive capillary network. After maturing in tiny chambers within the thyroid gland, these hormones affect the function of every cell in the body. x12,000

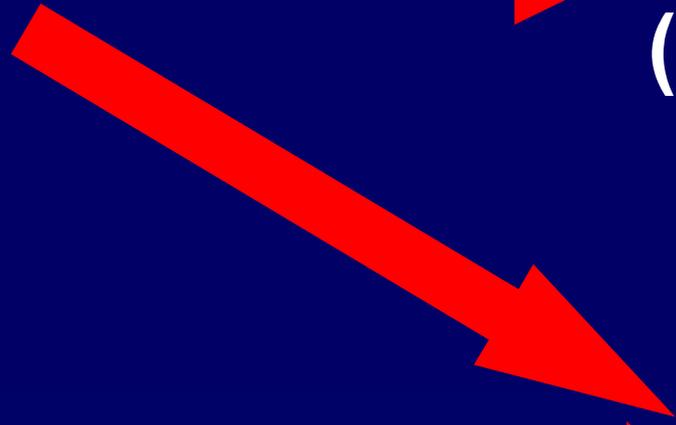
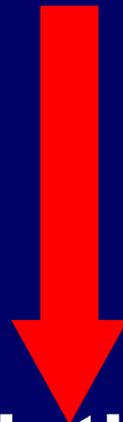
Tyrosine



**Diodotyrosine
(DIT)**



**Monoiodotyrosine
(MIT)**



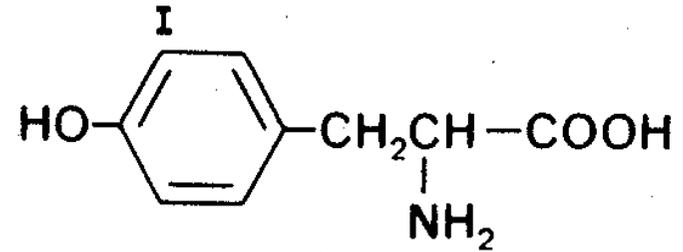
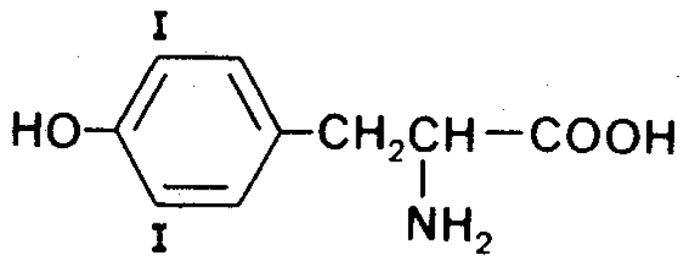
**Tetraiodothyronine
THYROXIN (T4)**



**Triiodothyronine
(T3)**

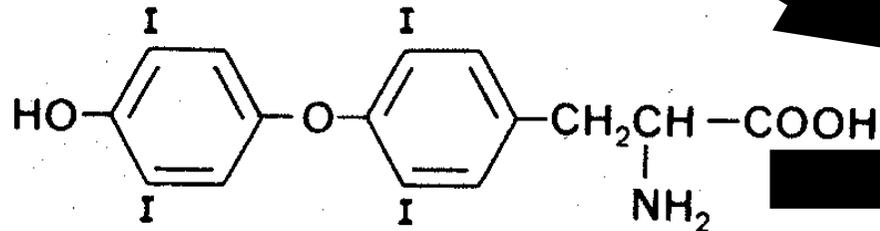
or Reverse T3

Tyrosine

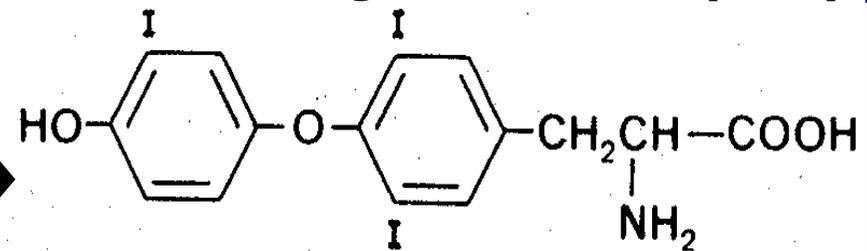


Diodotyrosine (DIT)

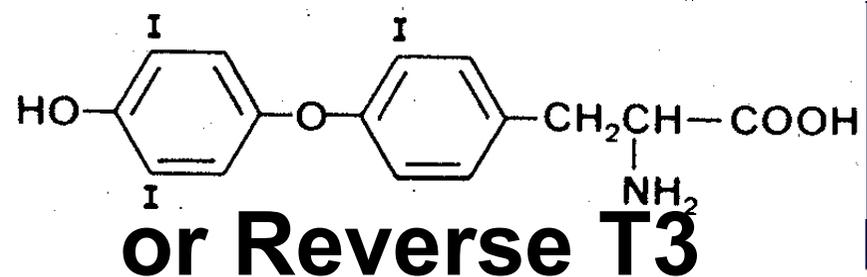
Monoiodotyrosine (MIT)



Triiodothyronine (T3)



**Tetraiodothyronine
THYROXIN (T4)**

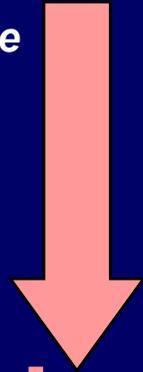


or Reverse T3

Thyroxin (T4)

Type 1&2 deiodinase

1p 370nm
9 382nm



**35% deiodination
to T3**

Type 1&3 deiodinase

1p 370nm
14 387nm



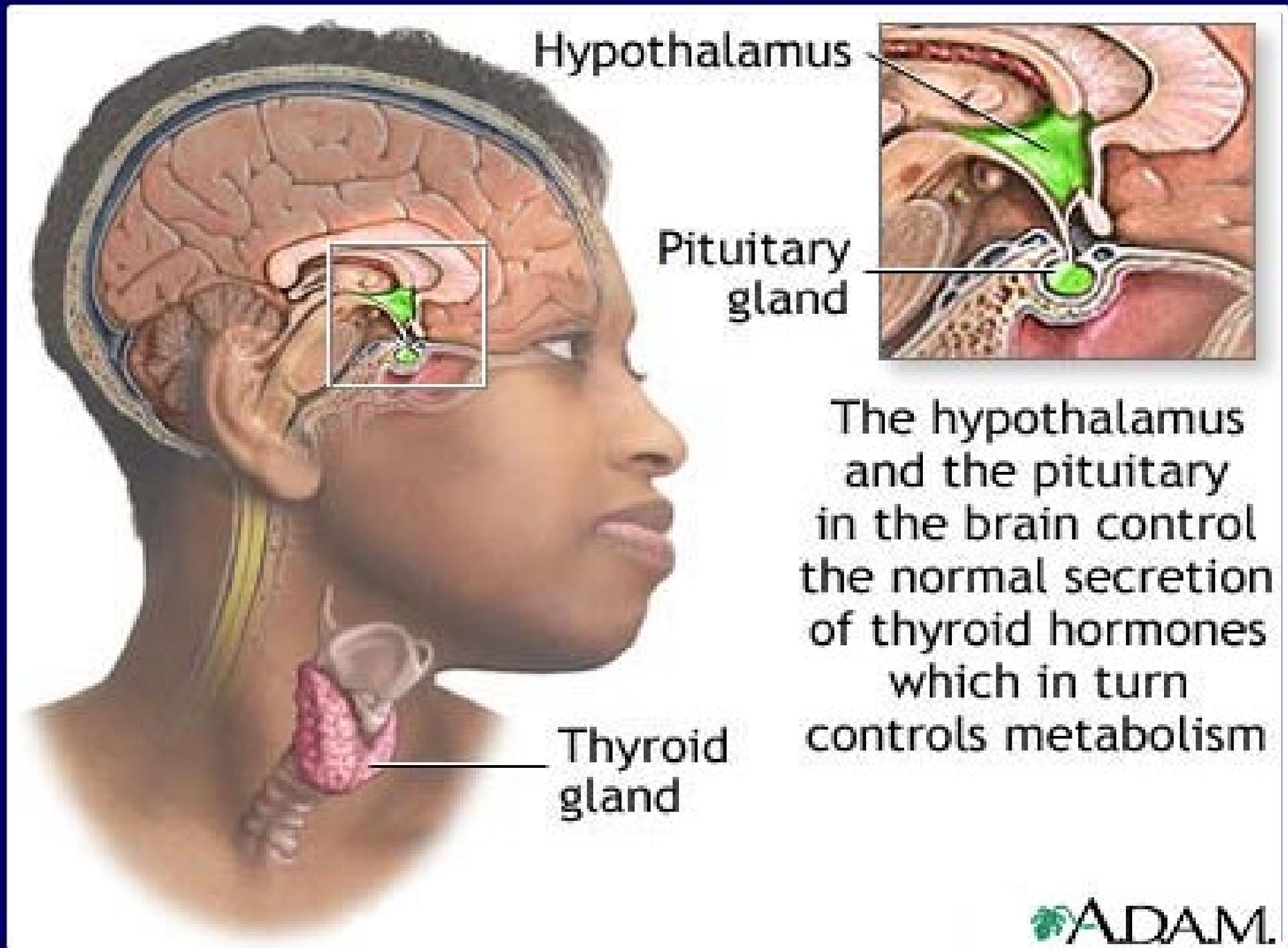
**45% deiodination to
reverse T3 and T4 to DIT**



**20% conjugation mainly with
glucuronate in the liver**

Function of the Thyroid Gland

- **Thyroid hormones control the basic activity of each cell in the body, including metabolism, growth and development**
- **If levels drop, metabolism slows and energy levels drop**
- **If too high – speeds up**

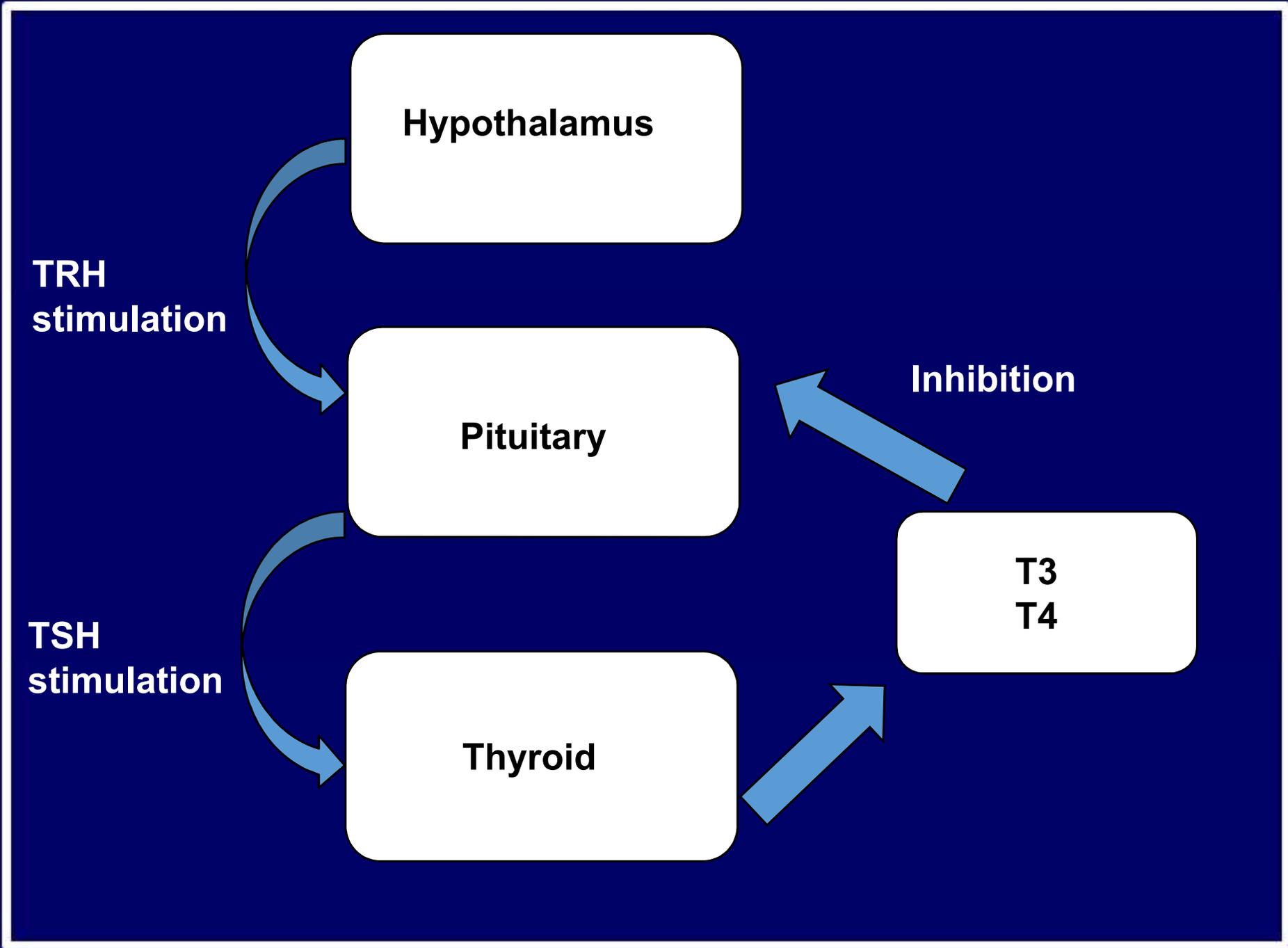


Hypothalamus

Pituitary gland

Thyroid gland

The hypothalamus and the pituitary in the brain control the normal secretion of thyroid hormones which in turn controls metabolism



Hypothalamus

**TRH
stimulation**

Pituitary

Inhibition

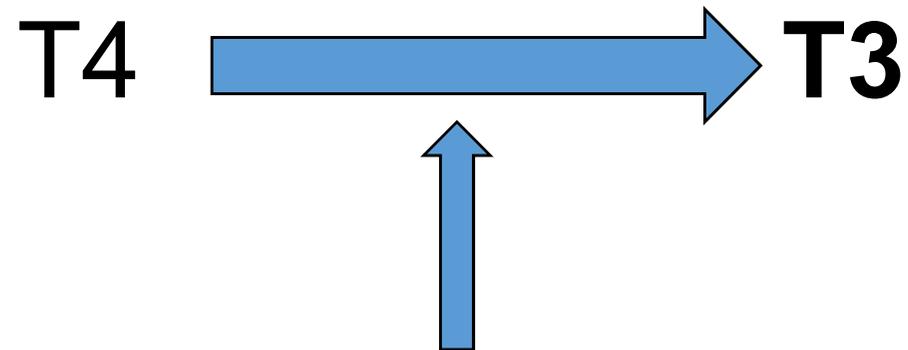
**T3
T4**

**TSH
stimulation**

Thyroid

Thyroid deiodinase

Requires selenium



Inhibited by Toxic Metals

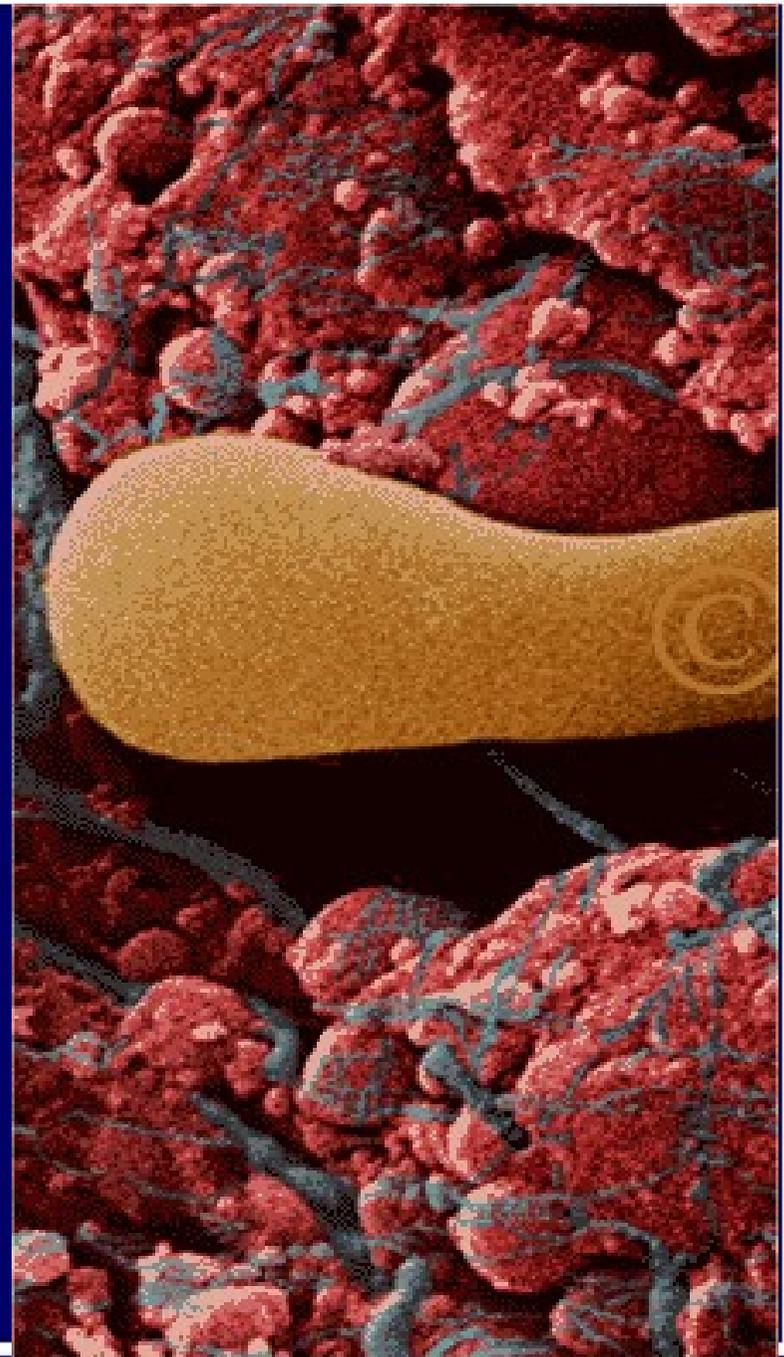
Thyroid hormones in circulation

- **T3 and T4 stored in the follicles attached to protein called thyroglobulin**
- **Proteinase enzymes split T3/T4 from the thyroglobulin and these enter the bloodstream**
- **Can store 2-3 months of T4**

Conversion of T4 to T3

- **T4 converted into T3 by 5'deiodinase**
- **Occurs mainly in liver & kidneys**
- **Enzyme is selenium dependant and also zinc**
- **T4 can be converted into Reverse T3**

Most T4 and T3 in the body is extra-thyroidal and most circulates bound to **Thyroid Binding Globulin (TBG)** or to Thyroxine Binding Pre-albumin (TBPa).



Thyroid Diseases and Disorders

- Underactive
- Overactive
- Goitre, enlarged gland
- Thyroid nodules, lumpy growths
- Thyroid cancer

Hypothyroidism

- Iodine deficiency
- Hashimoto's thyroiditis causes hypothyroidism
- Body's immune system attacks and destroys thyroid cells, causing inflammation and inability to produce thyroid hormones

Hypothyroidism

- Iatrogenic, doctor induced
- Patient treated for hyperactive thyroid and because of the treatment the gland becomes underactive
- Metabolism and all body processes slow down
- Rate of aging accelerates

Hypothyroidism Symptoms

- **Lethargy and fatigue**
- **Weight gain for no apparent reason**
- **Decreased appetite**
- **Increased sensitivity to cold**
- **Slow heart rate (bradycardia)**

Hypothyroidism Symptoms

- **Slow, weak pulse**
- **Goitre (enlarged gland)**
- **Depression**
- **Poor concentration**
- **Poor memory**
- **Mental confusion**

Hypothyroidism Symptoms

- **Loss of interest in sex**
- **Dry skin and hair**
- **Aging skin**
- **Scalp hair loss and eyebrows**
- **Constipation**
- **Deeper, hoarse voice**

Hypothyroidism Symptoms

- **Muscle weakness, arms & legs**
- **Slow reflexes**
- **Carpal tunnel syndrome**
- **Aches & pains in muscles, bones**
- **Infertility**
- **Fluid retention, myxoedema**
- **Puffiness around the eyes**

Iodine Deficiency

- **Main cause of hypothyroidism in developing world**
- **Found in oceans and soils**
- **Goitre belt, Derbyshire neck**
- **Babies can have intellectual impairment and physical development issues, cretinism**

Iodine Deficiency

- **Increased risk of attention deficit disorder, learning difficulties**
- **In pregnancy can lead to miscarriage and stillbirths**
- **Thyroid enlarges to try to become more efficient when iodine is scarce**

Goitres are benign (not cancerous) enlargements of the gland. They may occur as a result of iodine deficiency, autoimmune disease or quite normally during pregnancy.



Other swellings of the gland may be caused by **benign cysts or cancer** in the gland. The majority of thyroid enlargements are not malignant.



Adults may develop hypothyroidism from **dietary iodine deficiency**, although iodine is added to salt, breads and cereals to prevent deficiency it is usually sodium or potassium iodide.



Iodine Deficiency

- **More prone to developing radiation induced thyroid cancer if exposed to radioactive iodine**
- **More susceptible to damage by environmental pollutants, pesticides, toiletry toxins**

Iodine

- **Goitrogens, like cabbage and broccoli, can inhibit the absorption of iodine in stomach and upper SI**
- **Cooking mostly inactivates goitrogens**

Selenium

- **Essential for thyroid hormone production, activation and metabolism**
- **Thyroid contains more selenium per gram than any other tissue**
- **Required by enzyme converting T4 to T3**

Selenium

- **Deficiency associated with a greater risk of cancer, including thyroid cancer**
- **Can improve the outcome of autoimmune diseases**
- **Many parts of the world have selenium deficient soils**

Other nutrients for thyroid

- **Zinc – to convert T4 to T3**
- **Copper**
- **Tyrosine – good digestion is important for the absorption**
- **Thyroid hormones convert beta carotene to vitamin A. Riboflavin to FMN and FAD (thus maintaining speed of the Krebs's cycle)**

Other nutrients for thyroid

- **Manganese**
- **Vitamin D3**
- **Unsaturated fatty acids**

Hyperthyroidism

Hyperthyroidism Symptoms

- **Rapid pulse & heart palpitations**
- **Fast heart rate (tachycardia)**
- **Overly sensitive to heat**
- **Increased sweating**
- **Increased appetite**
- **Weight loss**

Hyperthyroidism Symptoms

- Inability to sleep
- Irritability, anxiety, nervousness
- Panic attacks
- Diarrhea or frequent bowel movements
- Hand tremors

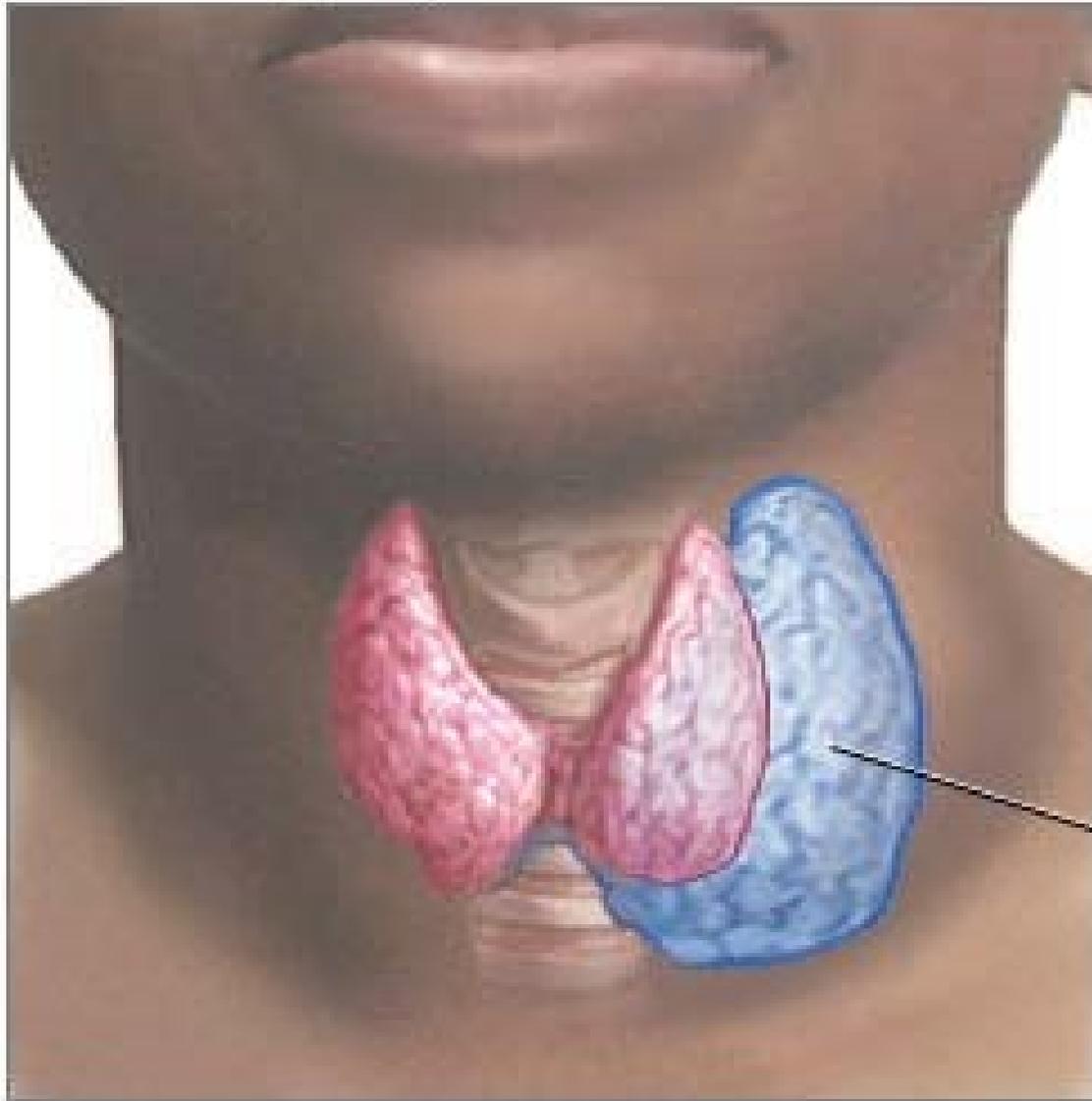
Hyperthyroidism Symptoms

- **Mood swings**
- **Goitre**
- **Raised, thickened skin over top of feet or shins**
- **Fatigue**
- **Shortness of breath**
- **Muscle weakness**

Hyperthyroidism Symptoms

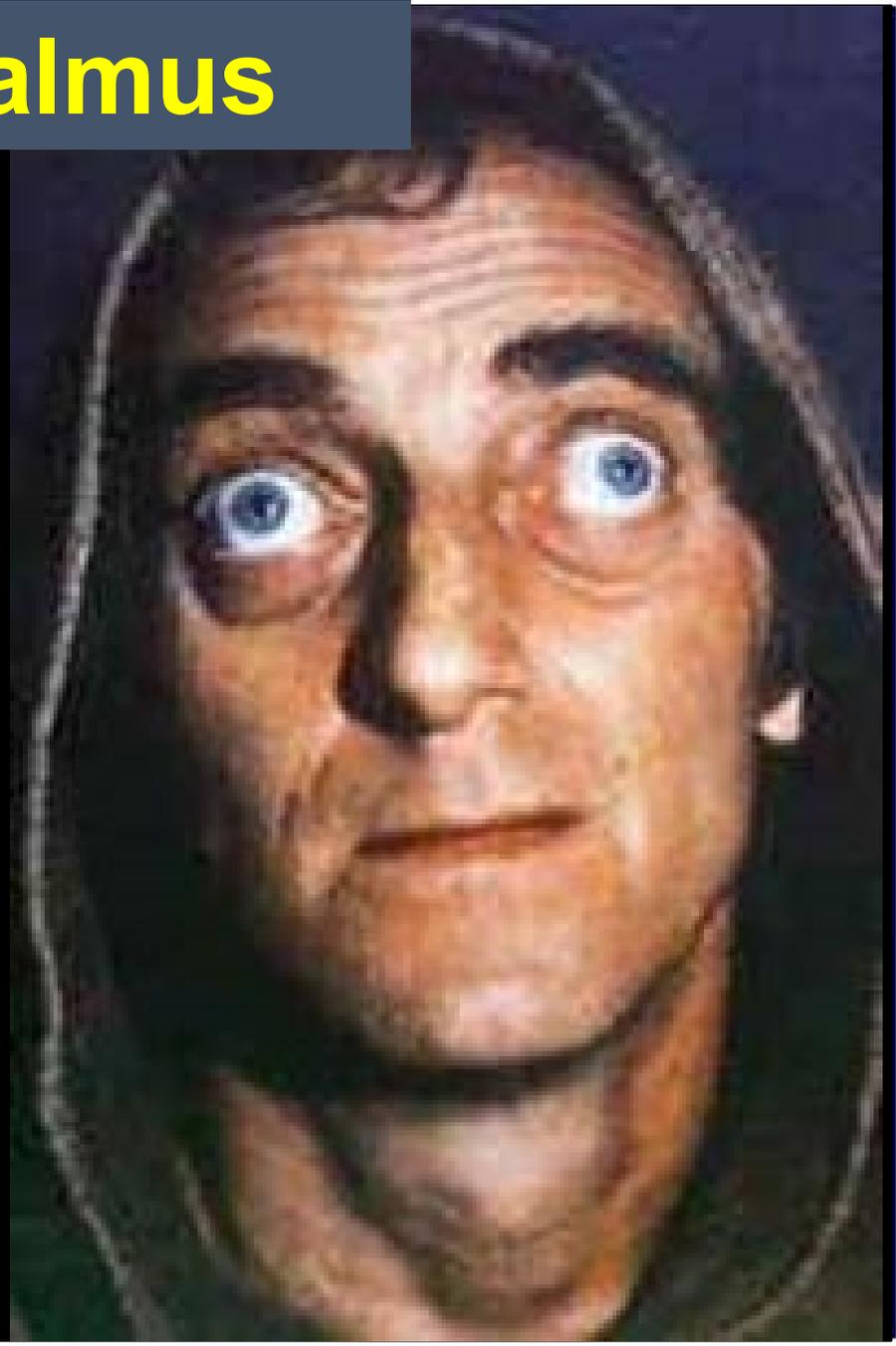
- **Thin, moist skin**
- **Periods become light or stop**
- **Joint pains**
- **Difficulty in concentrating**
- **Brittle nails**
- **Eye complaints, bulging, gritty**

Hyperthyroidism caused by thyroid adenoma



Hyperfunctioning
thyroid (goiter)

Exophthalmus



Grave's Disease



Thyroid hormone tests

- **Low TSH – overactive thyroid gland or pituitary gland not able to make TSH**
- **High TSH – under active thyroid not producing enough T4 & T3 in response to TSH stimulation**

Thyroid hormone tests

- **Low T4 – under active thyroid.
Thyroid not able to make hormones or pituitary not stimulating the thyroid**
- **High T4 – overactive thyroid.**
- **Low T3 – under active thyroid.
Not converting T4 into active T3**

Reverse T3

- **Inactive form of T3**
- **5-deiodinase converts T4 into rT3**
- **High rT3 suppress the formation and action of regular T3**
- **Binds to T3 receptors**
- **Inhibits 5'deiodinase**

Reverse T3

- **Normally T4 is converted into T3 and rT3 and the body eliminates rT3 quickly**
- **Main stimulants of rT3 are stress, low calorie intake, starvation, lack of vital nutrients, liver disease**

Thyroid Resistance

- Inability of cells and tissues to respond to thyroid hormone
- Causes symptoms of hypo
- Unhealthy cell membranes
- Deficiency of selenium, iodine, zinc
- Heavy metal toxicity

Thyroid Resistance

- Toxic chemicals
- Poor liver function
- High rT3 blocking receptors

Factors in thyroid dysfunction

- **Aging**
- **Stress causing high adrenalin and cortisol**
- **Severe injury**
- **Calorie restriction and fasting**
- **Cold exposure**
- **Chemical exposure**

Factors in thyroid dysfunction

- **Increased free radical exposure and lack of antioxidants**
- **Toxic metals, aluminium, cadmium, mercury, lead**
- **Selenium / iodine deficiency**
- **Chronic high alcohol intake**
- **Insulin dependant diabetes**

Factors in thyroid dysfunction

- **Liver or kidney disease**
- **Hemorrhagic shock**
- **Severe illness**
- **Surgery**
- **High inflammatory chemicals, cytokines, IL-6, TNFa**

Hypothyroidism & Infertility

- **Heavy painful periods or more frequent periods**
- **Can trigger early menarche**
- **Reduced ability to excrete oestrogen and androstenedione**
- **Increased risk of polycystic ovarian syndrome**

Hypothyroidism & Infertility

- **Can increase pituitary gland hormone prolactin**
- **May cause milk production**
- **High prolactin can prevent ovulation**
- **Menstrual periods irregular or stop altogether**

Hypothyroidism & Infertility

- **Failure to ovulate creates a progesterone deficiency, leading to oestrogen dominance**
- **PMS, painful heavy periods, reduced fertility, increased risk of breast and uterine cancer**
- **Suppresses the thyroid**

Hypothyroidism & Infertility

- **Women who fall pregnant with underactive thyroid have increased risk of miscarriage and stillbirth**
- **Child can be at increased risk of mental retardation , physical abnormalities and impaired IQ**

Hyperthyroidism & Infertility

- **Very light periods, irregular periods or amenorrhea**
- **May fail to ovulate so will not produce progesterone, fertility problems**
- **Teenage girls can have delayed puberty and menarche**

Hyperthyroidism & Infertility

- **If pregnant, greater risk of miscarriage, fetal growth retardation, premature labour, congenital malformations, pre-eclampsia**
- **Can have 2 to 3 times the normal level of oestrogen**

Thyroid & Cardiovascular Disease

- **Heart muscle is very sensitive to changes in thyroid hormone levels**
- **Heart contains receptors for thyroid hormones, needed for growth & function of the heart**
- **Too little or too much detrimental**

Hypothyroidism & CV Disease

- **Heart rate slows**
- **High LDL cholesterol, low HDL**
- **High triglycerides**
- **High Lipoprotein (a) thickens artery walls**
- **High blood pressure**

Hypothyroidism & CV Disease

- **High homocysteine which erodes walls of arteries and promotes blood clots**
- **High C-reactive protein. Marker of inflammation in body. The more inflammation the greater the risk of heart disease**

Hypothyroidism & CV Disease

- **Can develop thicker carotid arteries, leading to arteriosclerosis and stroke**
- **Weakens heart muscle and can encourage the accumulation of fluid in the pericardium**
- **70% more likely – hardened aorta**
- **More than twice risk of heart attack**

Hyperthyroidism & CV Disease

- **Rapid heart rate, fast pulses and palpitations**
- **Heart rate may go up faster when exercise and takes longer to get back to normal**
- **Systolic Bp can be elevated**
- **Irregular heart rhythm, atrial fibrillation**

**Compounds that
adversely affect the
thyroid**

Foods that affect the Thyroid

- **Goitrogens interfere with thyroid hormone production**
- **Can cause enlargement of the thyroid if consumed in large quantities**
- **Cooking mostly inactivates goitrogens in food**

Foods containing Goitrogens

- **Cruciferous vegetables
(cabbage, broccoli, cauliflower,
Brussel sprouts)**
- **Corn**
- **Sweet potatoes**
- **Lima beans**
- **Tapioca**

Foods containing Goitrogens

- **Swede**
- **Millet**
- **Peanuts**
- **Soy**

A common cause of thyroid malfunction

Per ton of phosphate, 1 to 1.2 percent will be fluoride. A couple of tons per field is not an unusual fix. Fluoride is a halogen and is thyrotoxic. It dominates iodine. This is the Law of Halogen Displacement.

Chemicals & Pesticides - Fluoride

- **Halogen family**
- **Chemically very similar to iodine**
- **Displaces iodine in thyroid gland**
- **Added to drinking water 1ppm**
- **Foods, medications, chemicals**
- **Accumulates in body**

Chemicals & Pesticides - Fluoride

- **Slows down the production of T3 and T4 by interfering with the enzymes**
- **Inhibits the secretion of TSH**
- **Competes with TSH for receptor sites on the thyroid gland**

Sources of Fluoride

- **Drinking water**
- **Toothpaste**
- **Tea – accumulates more fluoride than any other edible plant**
- **Fluoride pesticides**
- **Soft/carbonated drinks**
- **Medication eg SSRI**

Sources of Chlorine

- **Water purification, disinfectants and bleach**
- **Paper production, paints, plastics and solvents**

Sources of Bromine

- **Evaporates easily**
- **Flame proofing agents**
- **Water purification compounds**
- **Dyes**
- **Photographic products**
- **Brominated vegetable oil – emulsifier in soft drinks**

Sources of Bromine

- **Brominated Flame Retardants (BFR)**
- **Computer monitors and casings**
- **Interior of new cars**
- **Televisions**
- **White goods**
- **Mobile phones**

Sources of Bromine

- **Carpet**
- **Polyurethane foam in furniture and bedding**
- **Easily outgases into the environment**
- **Found in blood, liver, fat, breast milk**

Adverse effects of Pesticides

- **1998 in journal “Thyroid” 90 compounds identified with thyroid disrupting properties**
- **Chlorpyrifos – organophosphate insecticide. California State University found caused antibodies against thyroid**

Adverse effects of Pesticides

- **Amitrole – systemic herbicide**
- **Known to be an anti-thyroid agent**
- **Increases release of TSH by pituitary and so has goitrogenic effects – enlargement of thyroid**
- **In animals causes thyroid tumours**

Pyrethrins & Pyrethroids

- **Pyrethrins insecticides derived from chrysanthemum**
- **Pyrethroids – synthetic version**
- **Fly sprays, bug bombs, head lice treatment, pet flea sprays**
- **Raises TSH & suppresses T4 T3**
- **Aerial pesticide spraying**

Chemicals that disrupt thyroid

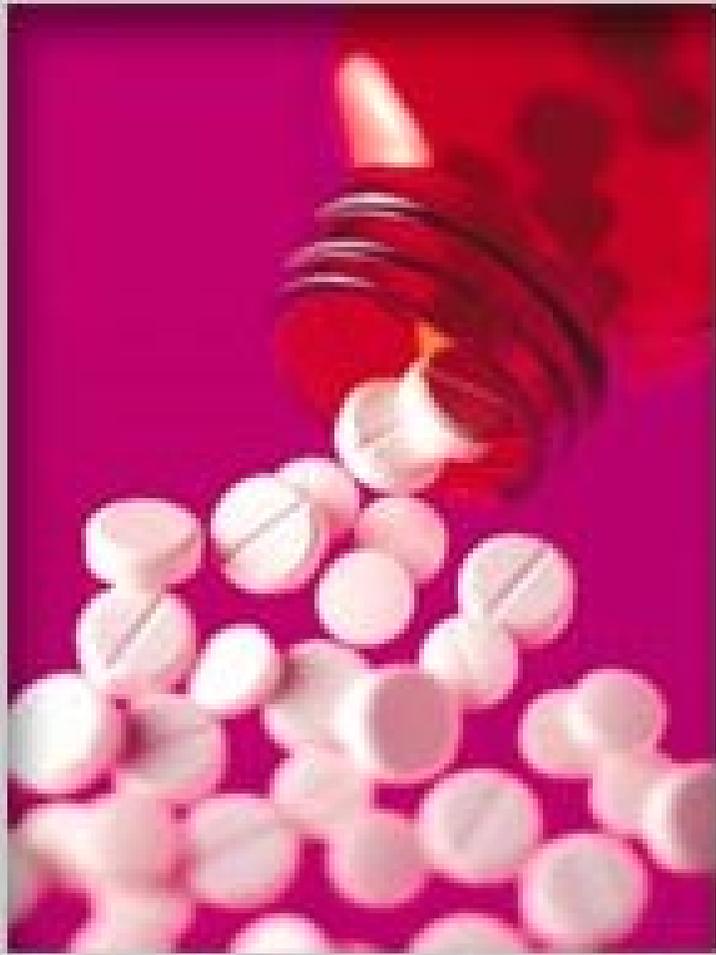
- **Dioxins and PCBs – by-products of PVC production**
- **Remain in environment for many years and accumulate in human and animal tissue**
- **Reduce levels of T4 hormone**

Chemicals that disrupt thyroid

- **EBDCs – fungicides**
- **Roots, leafy veg, fruits, cereal**
- **Inhibit iodine uptake by thyroid & can cause goitres**
- **Body breaks down into ethylenethiourea – thyroid carcinogen**

Chemicals that disrupt thyroid

- **In rats – EBDCs lower thyroid hormone levels**
- **Inhibit thyroid peroxidase – enzyme required for synthesis of T4 and T3**

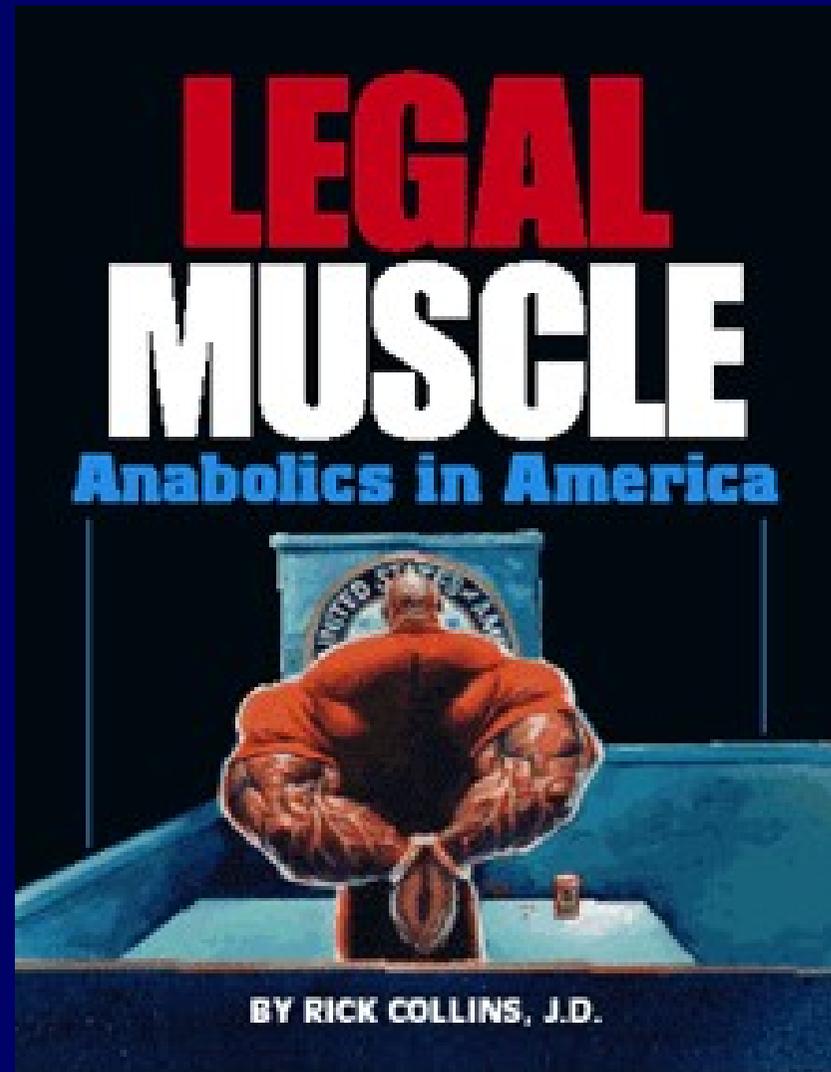


Because of the resultant change in endocrine **feedback** taking birth control pills, adrenalin, amphetamines, cortisone, can lead to thyroid dysfunction.

Taking **synthetic thyroid** hormone for an inactive thyroid gland will tend to make your thyroid rely more on exogenous thyroxin and will thus lead to further inactivity.



Decreased
production
occurs
following
androgen or
glucocorticoid
therapy



Toxic metals

Most common toxic metals are aluminium, nickel and mercury.

Thyroid is high in the amino acid cysteine.



Toxic metals disrupt the thyroid

- **Mercury – reduces production of T4 and inhibits conversion of T4 to T3**
- **Selenium antagonist and selenium is required by enzyme that converts T4 to T3**

Toxic metals disrupt the thyroid

- **Cadmium blocks the action of selenium and zinc and depletes levels in the body**
- **These are required for conversion of T4 to T3**
- **Lead suppresses conversion of T4 to T3**

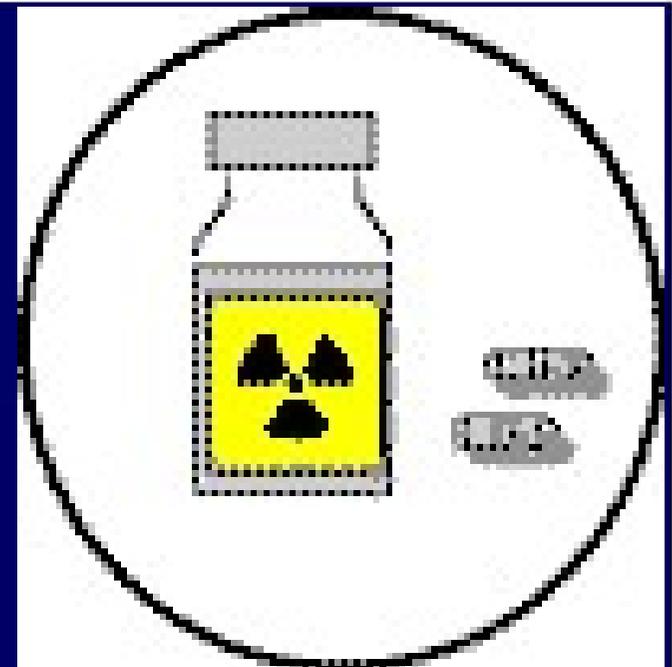
Radiation disrupts the thyroid

- **Sensitive to all types of radiation**
- **Cannot distinguish between regular iodine and radioactive iodine**
- **People who are iodine deficient are more prone to radiation induced disease**

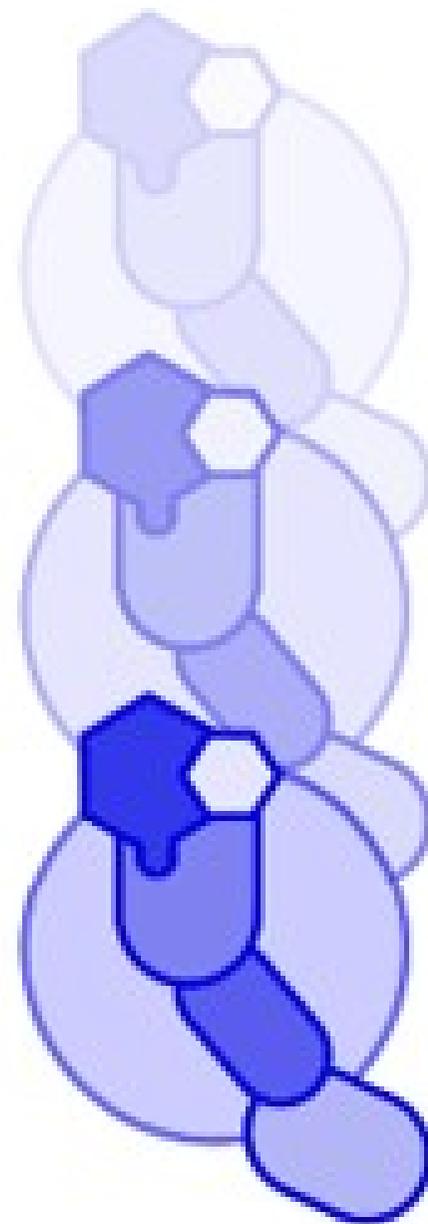
X-rays striking the thyroid (including dental x-rays) can damage the thyroid.



Since 1945 every human has been repeatedly dusted with radioactive **Iodine 131**.



An imbalance in the amount of **estrogen** in the body (be it due to pituitary, liver, ovary, or adrenal malfunction) can alter thyroid function.



Thyroid Binding Globulin is produced in the liver and its synthesis is increased by **estrogens** (pregnancy and the birth control pills).



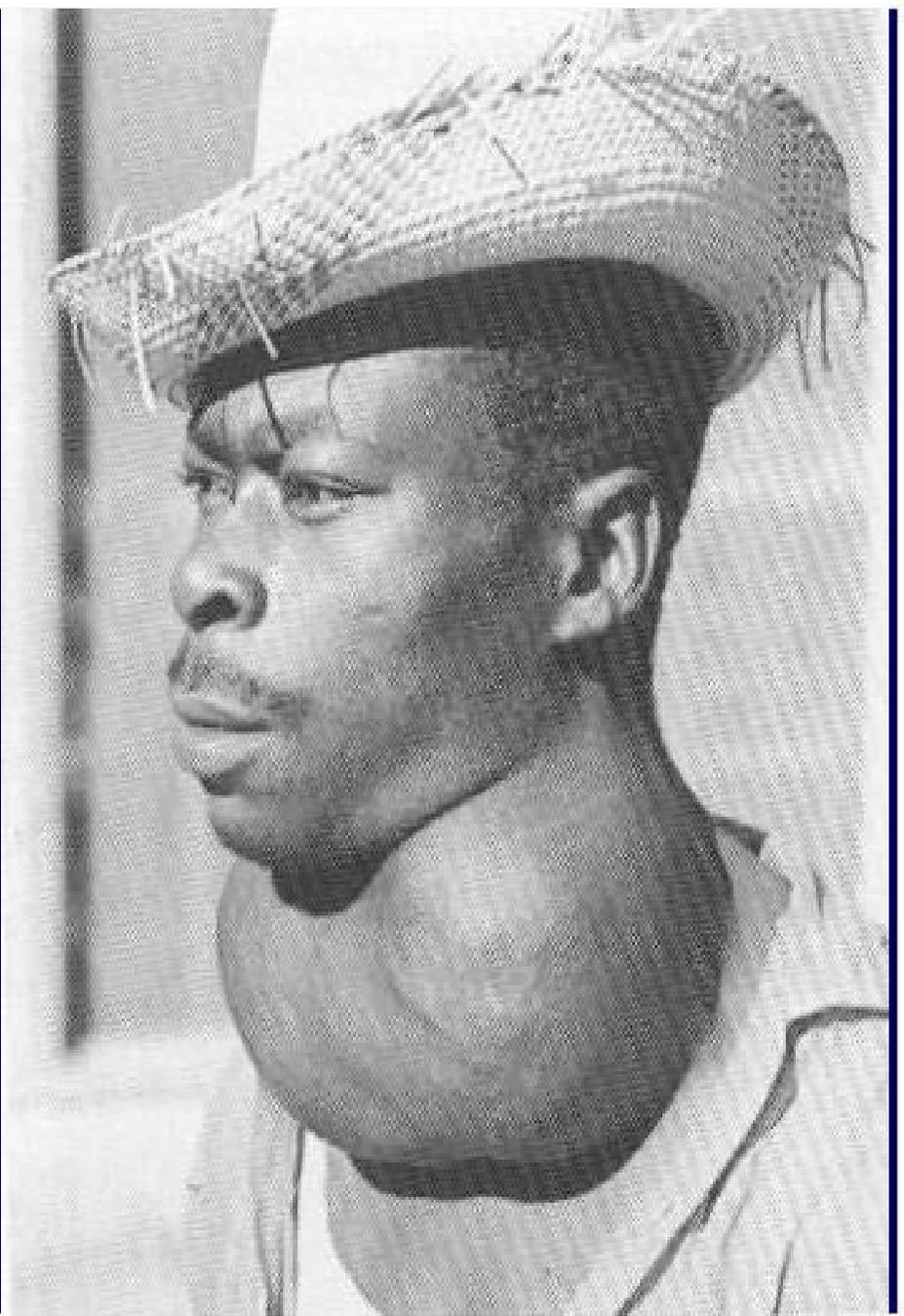
Estrogen Dominance

- **High estrogen blocks the effect of thyroid hormones**
- **Stimulates greater production of thyroid binding globulin, a protein that binds with T4 in blood and makes it inactive**
- **Lowers amounts of free T4**

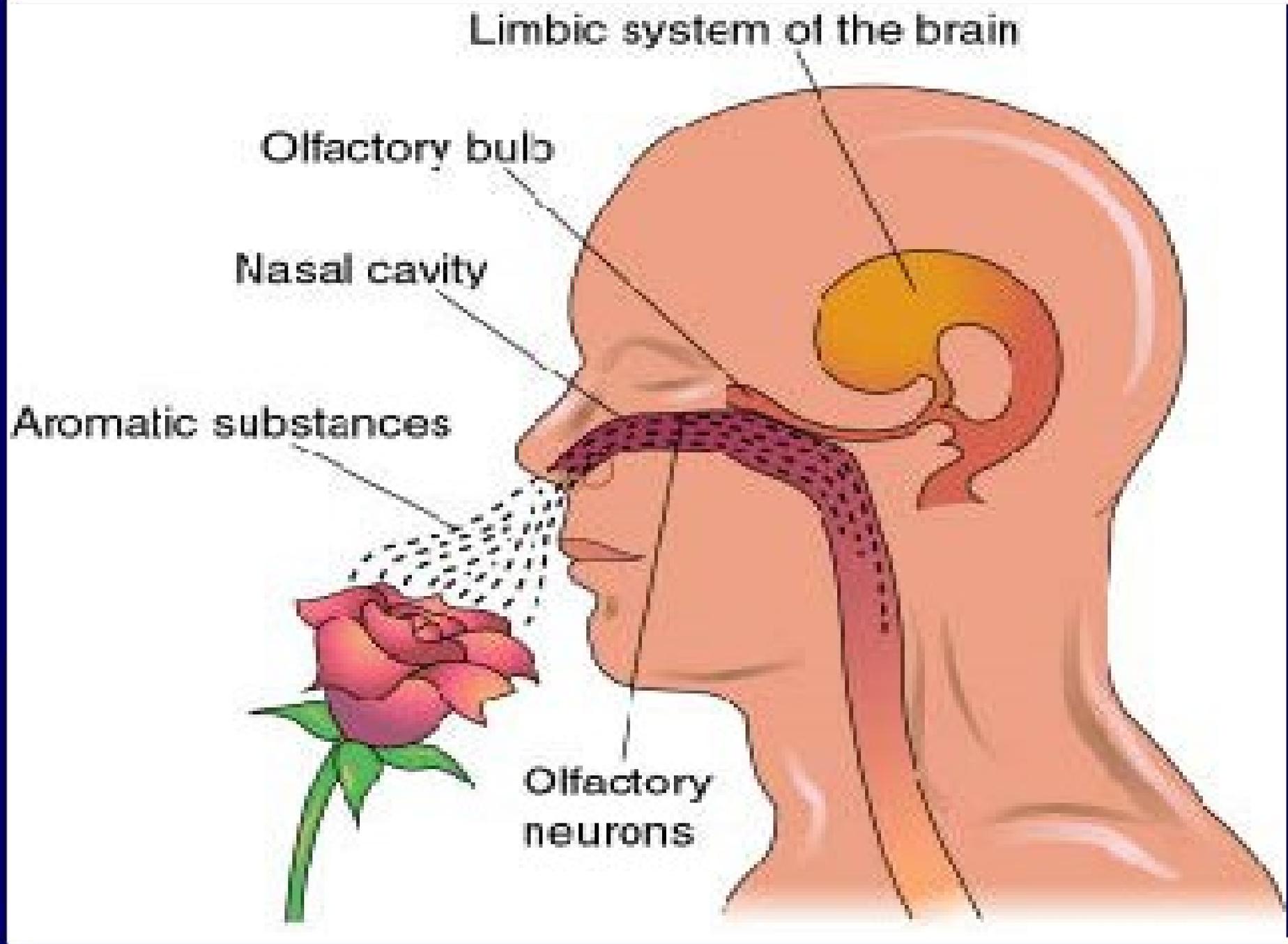
Estrogen Dominance

- **Estrogen excess stimulates body to retain copper**
- **Copper and zinc are antagonists so high oestrogen can result in zinc deficiency**
- **Zinc is needed for conversion of T4 to T3**

In **hypoadrenia**, the thyroid may become inhibited to decrease the metabolic rate and give the adrenals a chance to rest.



Various strong **emotional states can affect TSH and thus cause thyroid hormone output to change. Failure to treat an emotional state properly may result in thyroid dysfunction. Other causes of pituitary dysfunction can cause thyroid disturbances secondary to pituitary malfunction.**



Overeating, especially fats and sugars over prolonged periods will make the body produce more thyroid hormones (to increase fat burning and glucose uptake) than it can comfortably produce.

This can lead to hypothyroidism.

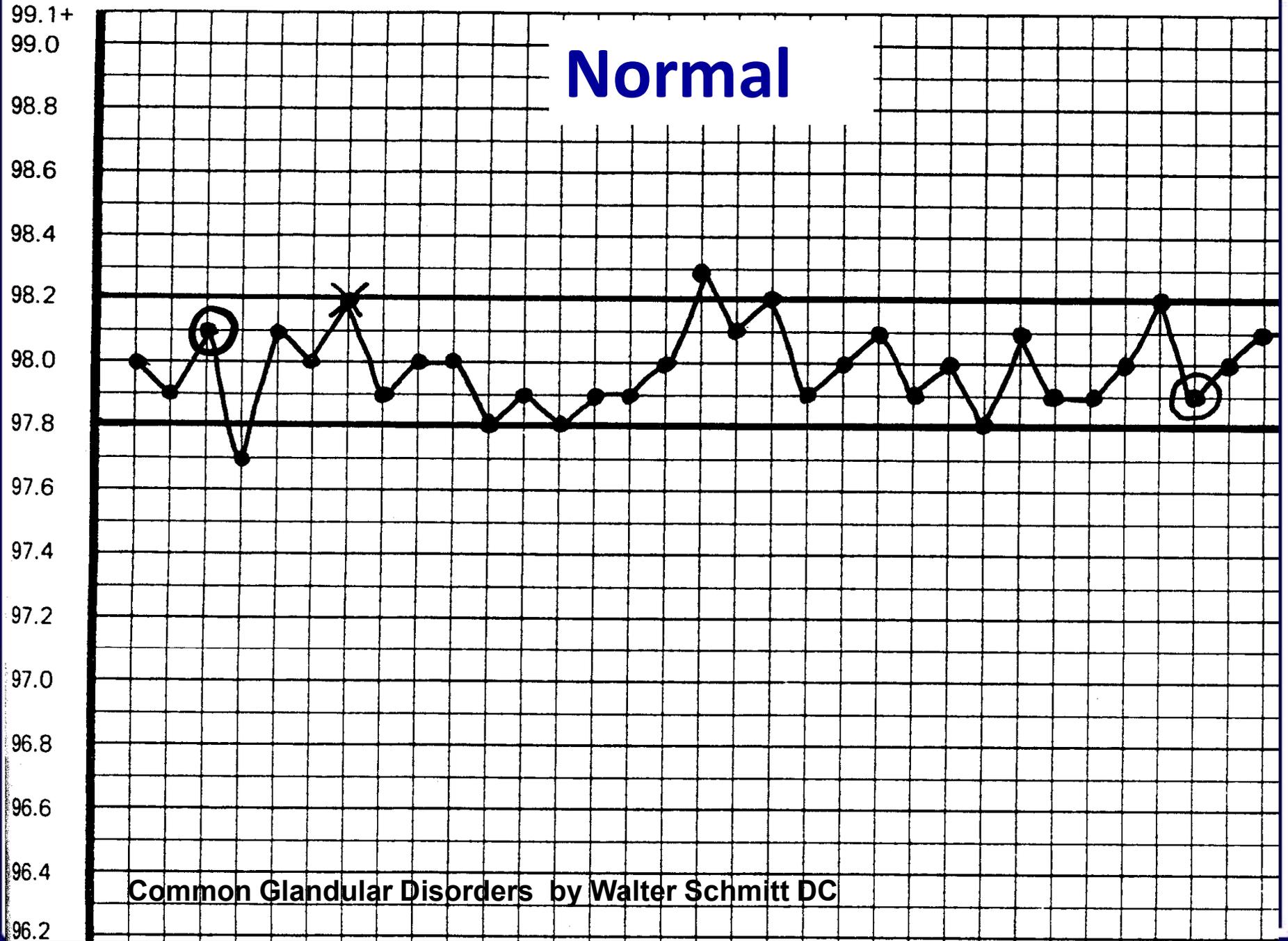
Because of the thyroid's effect on **insulin secretion**, prolonged intake of sugar can cause the over stimulation of the thyroid gland and lead to dysfunction.



Nerve pressure at the mid cervical spine can cause thyroid dysfunction. Many times patients involved in car accidents with resultant whiplash and cervical nerve dysfunction, go into a state of hypothyroidism and put on 5-12Kg (10-30 pounds) over the following 3-4 months.

BASAL AXILLARY TEMPERATURE

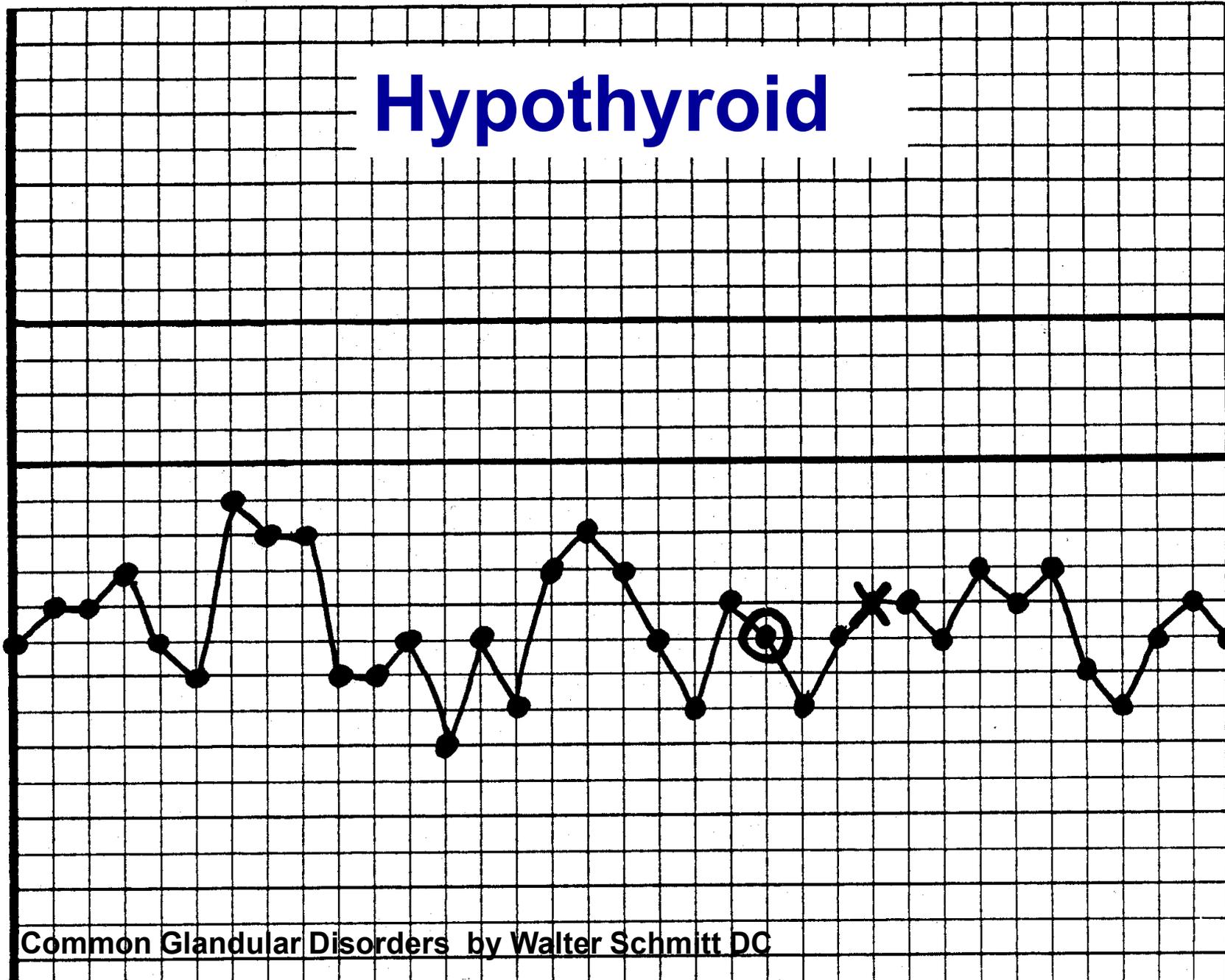
Normal



Common Glandular Disorders by Walter Schmitt DC

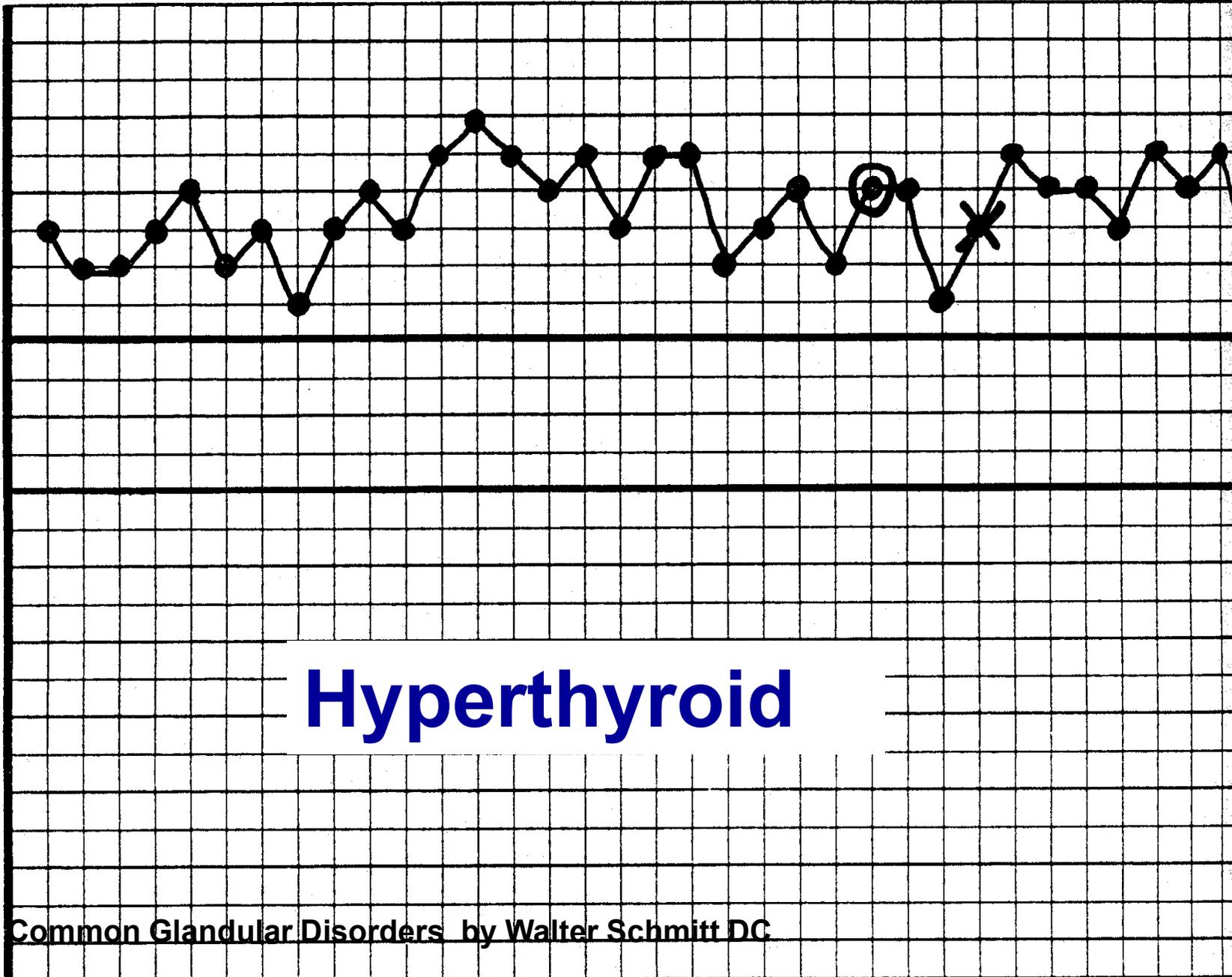
Hypothyroid

99.1+
99.0
98.8
98.6
98.4
98.2
98.0
97.8
97.6
97.4
97.2
97.0
96.8
96.6
96.4



Common Glandular Disorders by Walter Schmitt DC

99.1+
99.0
98.8
98.6
98.4
98.2
98.0
97.8
97.6
97.4
97.2
97.0
96.8
96.6



Hyperthyroid

Common Glandular Disorders by Walter Schmitt DC

THYROID PATCH TEST

Purchase a small bottle of Tincture of Iodine (Iosol) and paint a 2" x 2" patch at the crease of your elbow or behind your knee. The iodine patch should be seen for 24 hours. If the iodine patch leaves, it is a sign that your body is utilizing and/or absorbing the iodine. Keep track of the hours that the iodine is visible.

_____ hours

Iodine skin test

-1/2 hour

5 drops

1/2 - 1 hour

4 drops

1 - 2 hours

3 drops

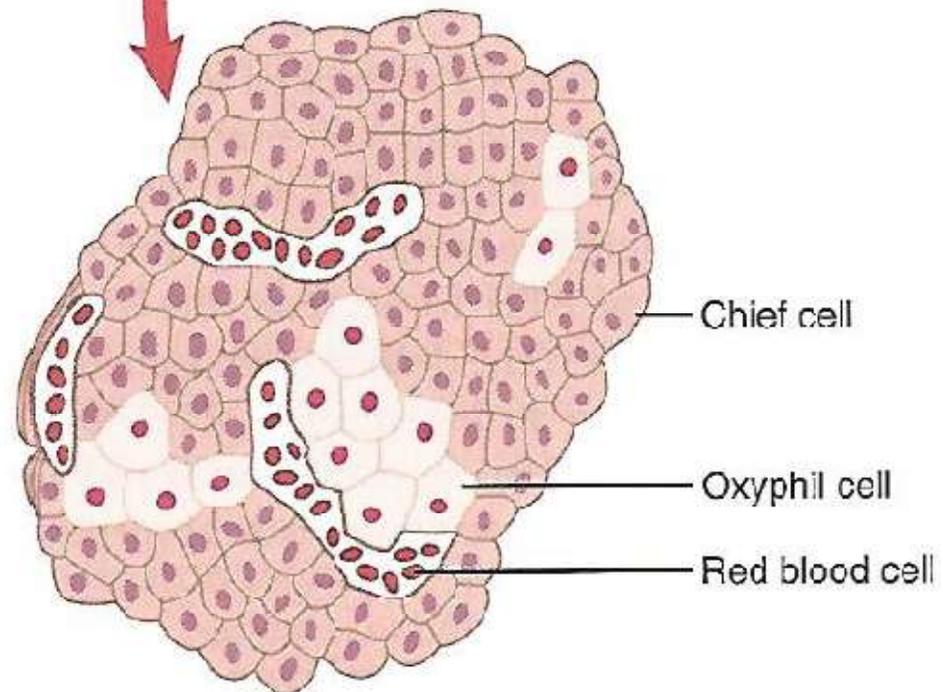
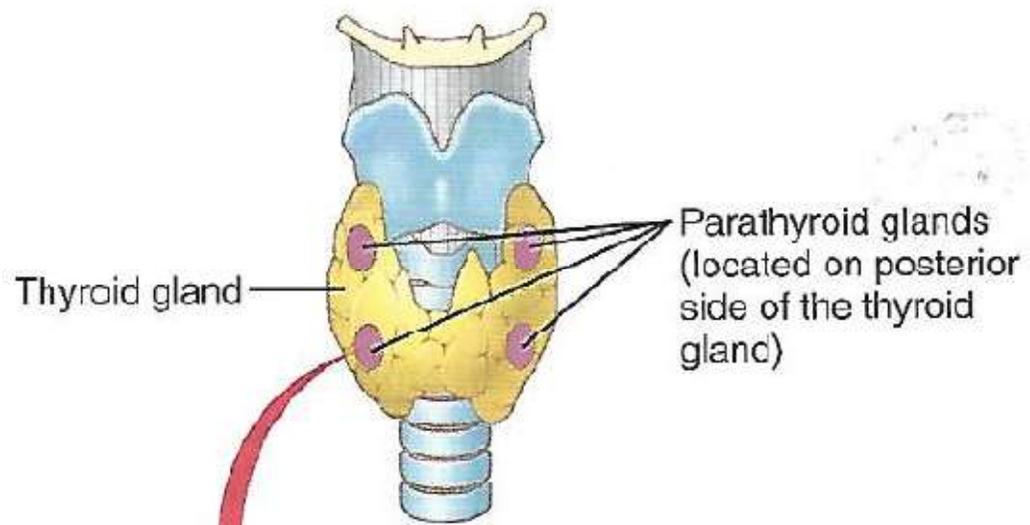
2- 4 hours

2 drops

4 + hours

1 drop

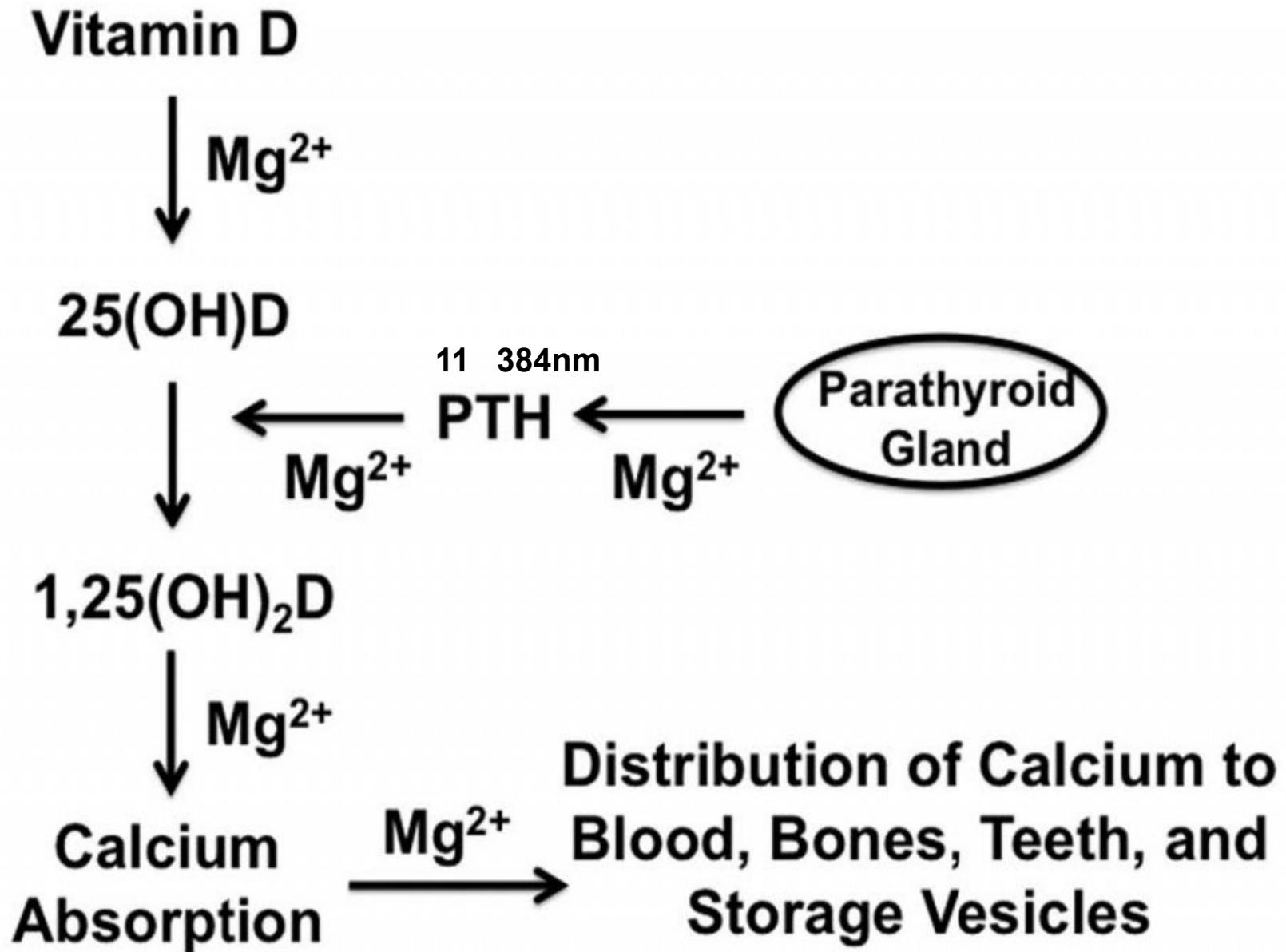
Parathyroid Glands



Parathyroid Gland

- **4 small glands – parathyroid glands are located behind the thyroid**
- **Parathyroid hormone which increases calcium in the blood by drawing it out of the bones**

The conversion of 25 OH D₃ to 1.25 OH D₃ is catalyzed by the enzyme **25-hydroxyvitamin D₃ 1-alpha-hydroxylase**, the levels of which are increased by parathyroid hormone (and additionally by low calcium or phosphate) and modulated by magnesium.



Osteoclasts reabsorb bone

Stimulated by

Vitamin A

Parathyroid hormone

1,25 OH D3

IL1 and IL6

TNF

TGF- α

Inhibited by

Calcitonin

Estrogens

TGF- β

INF α

PgE2

Osteoblasts form bone.

Stimulated by

Parathyroid hormone

1,25-OH D3

T3 and T4

hGF and IGF-1

PgE2

TGF- β

Progesterone

DHEA

Testosterone

Dihydrotestosterone in women

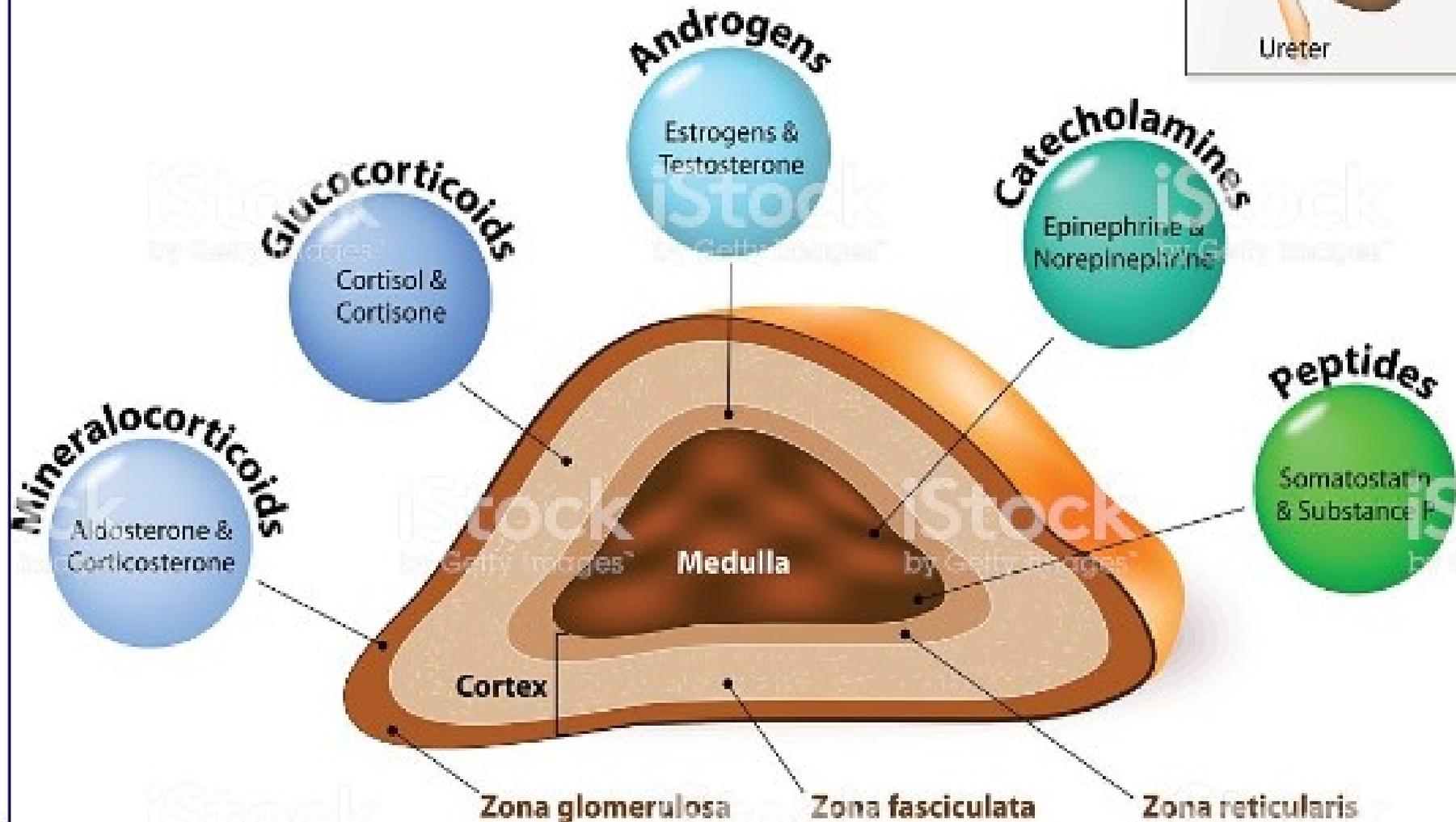
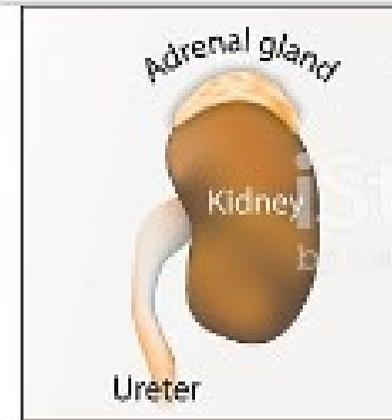
Inhibited by

Corticosteroids

The Adrenal Glands

ADRENAL GLAND

(hormones)



Adrenal Stress Syndrome

Muscle association

Sartorius

Gracilis

Soleus

Gastrocnemius

Tibialis posterior

Adrenal Stress Syndrome

- 1. Rogoff's sign Tenderness 12th rib head.**
- 2. Pupil dilation. Bright light pupil dilation.**
- 3. Louder second heart sound over the first.**

4. Ligament stretch reaction – weakness of adrenal muscles with ligament stretch.

5. Sacroiliac subluxation – Category 2.

6. Ragland sign – postural hypotension

7. Laboratory testing with ACTH. DHEA, DHEA sulfate and Cortisol salivary levels

The CATECHOLAMINES

THE CATCHOLAMINE HORMONES

80% ADRENALIN

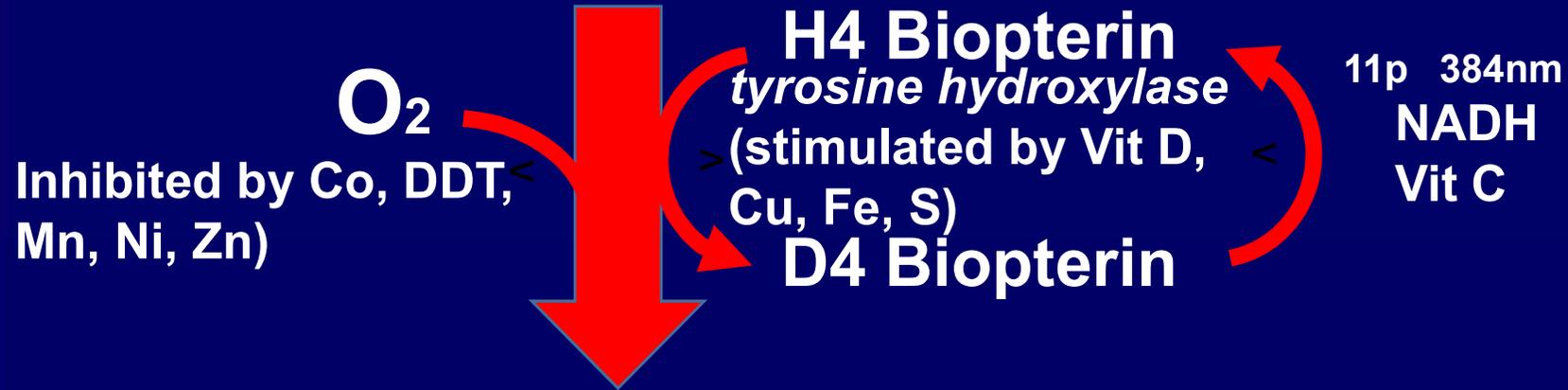
10% NORADRENALIN

10% DOPAMINE

Guyton and Hall (2011). *Textbook of Medical Physiology*. 13th Edition U.S.: Saunders Elsevier. p. 928

Dopamine

TYROSINE



L.DOPA



DOPAMINE

DOPAMINE

monoamine oxidase 14 387nm
23x 400nm

Cu⁺ FAD

Inhibited by benzoic acid,
caffeine, anthrocyandins,
eugenol, naringen, raison

O₂ + H₂O

H₂O₂

Fe⁺⁺

Fe⁺⁺⁺

·OH + OH⁺

Dihydroxyphenyl
acetic acid + NH₂

catechol-O-methyltransferase

22 399nm

Mg⁺⁺, Fe, Mn, Cysteine

Inhibited by epicatechin, 2OH and
CH₃ Estrogens, Vit C, Ca, quercetin,
SAH, SAM,

Homovanillic acid

Homovanillic acid

*Glutathione (Cysteine,
Glycine, Glutamic acid)*

NAC, Zn⁺⁺, P5P, Sel
a-Lipoic or

Sulfation (PAPs) S, MSM

Taurine or

Glucuronidation (UDP

Gucuronic acid) Glucuronate,

Vit C, or

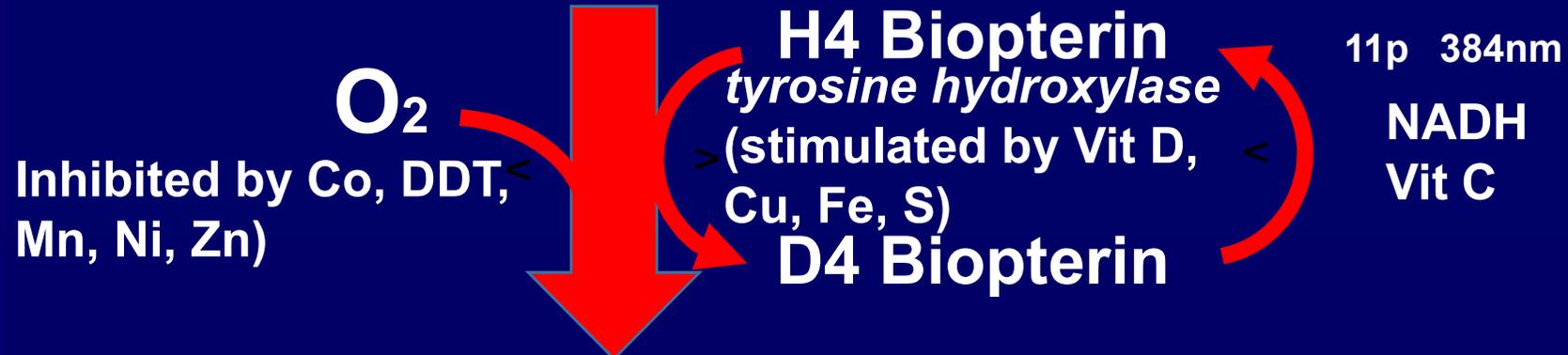
Acetylation (Acetyl CoA) B5,

Acetyl CoA

Conjugates excreted through
the bile or urine

**Noradrenalin
(Norepinephrine)**

TYROSINE



L.DOPA



DOPAMINE



NORADRENALIN

monoamine oxidase 14 387nm
23x 400nm

Cu+ FAD

Inhibited by benzoic acid,
caffeine, anthrocyandins,
eugenol, naringen, raison

O₂ + H₂O

H₂O₂

Dihydroxymandelic
acid + NH₂

catechol-O-methyltransferase

Mg⁺⁺, Fe, Mn, Cysteine 22 399nm

Inhibited by epicatechin, 2OH and
CH₃ Estrogens, Vit C, Ca, quercetin,
SAH, SAM,

Vanillylmandelic acid

Fe⁺⁺

Fe⁺⁺⁺

·OH + OH⁺

SAM

Vanillylmandelic acid

*Glutathione (Cysteine,
Glycine, Glutamic acid)*

NAC, Zn⁺⁺, P5P, Sel

a-Lipoic or

Sulfation (PAPs) S, MSM

Taurine or

Glucuronidation (UDP

Gucuronic acid) Glucuronate,

Vit C, or

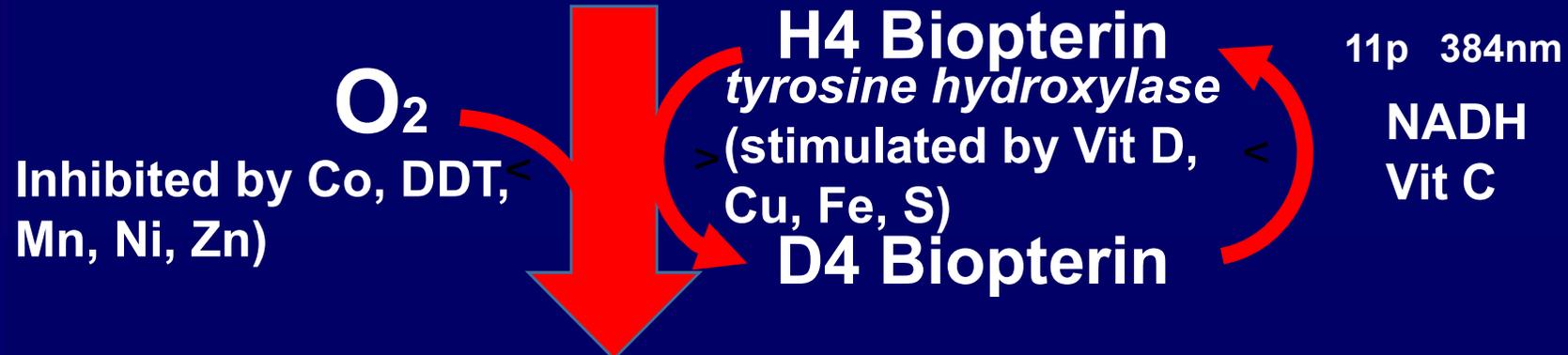
Acetylation (Acetyl CoA) B5,

Acetyl CoA

Conjugates excreted through
the bile or urine

**Adrenalin
(Epinephrine)**

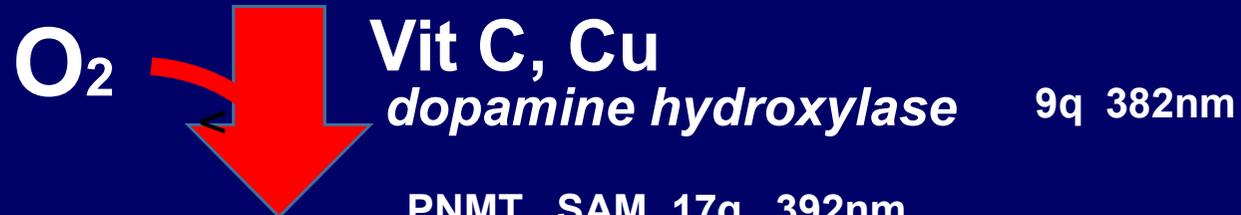
TYROSINE



L.DOPA



DOPAMINE



The adrenal medulla is an extension to the sympathetic nervous system since pre-ganglionic fibres from the splanchnic nerve terminate in the adrenal medulla.

Hormonal Catecholamines cannot cross the blood / brain barrier so have to be produced locally.

Catecholamines act through two classes of receptors:

α - Alpha

β - Beta

Adrenoreceptors

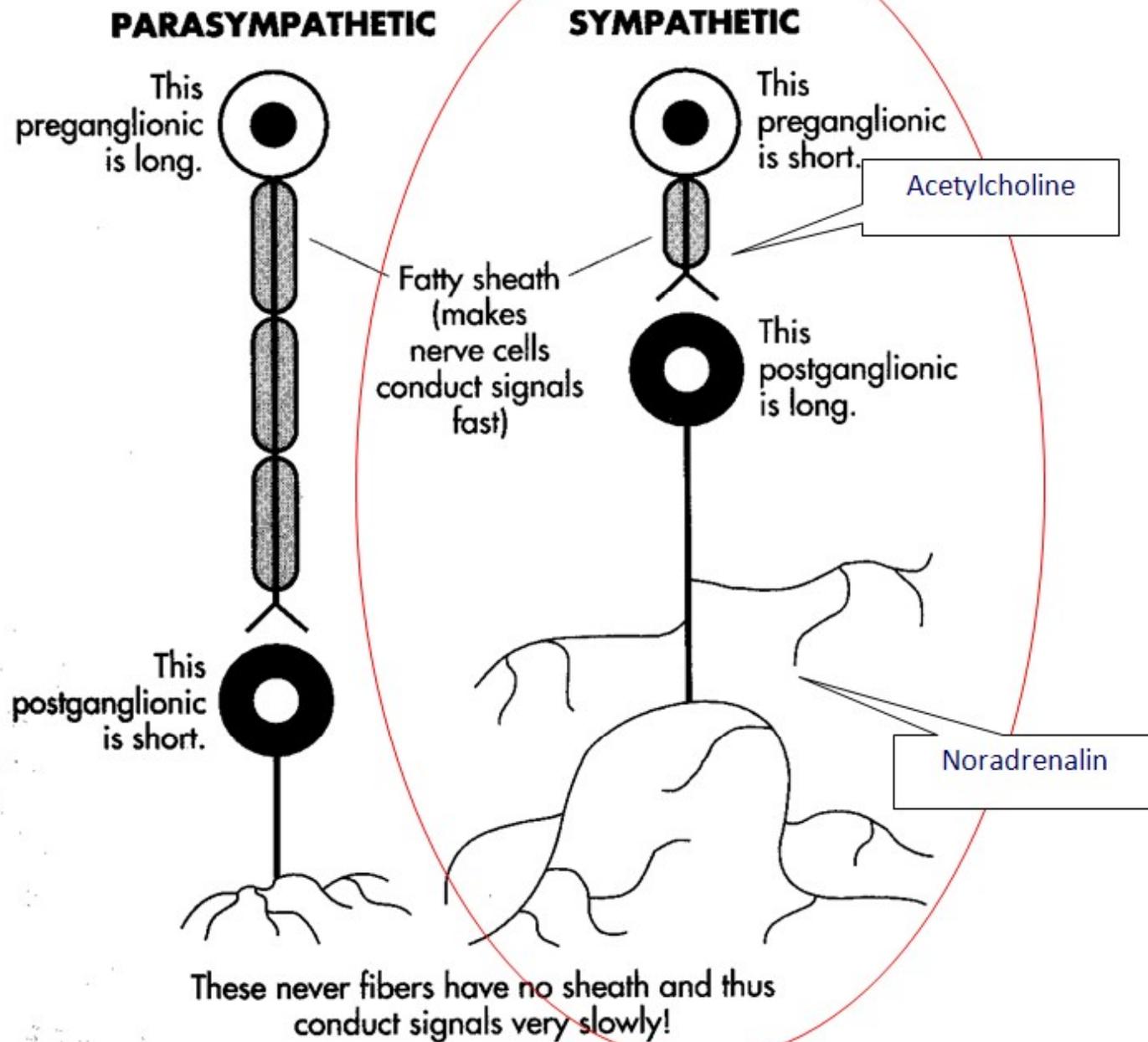
Two sub-types designated alpha and beta.

Alpha 1 receptors are found postsynaptically.

Alpha 2 receptors are found in presynaptic autoreceptors, postsynaptically and in the CNS.

Post synaptic effects

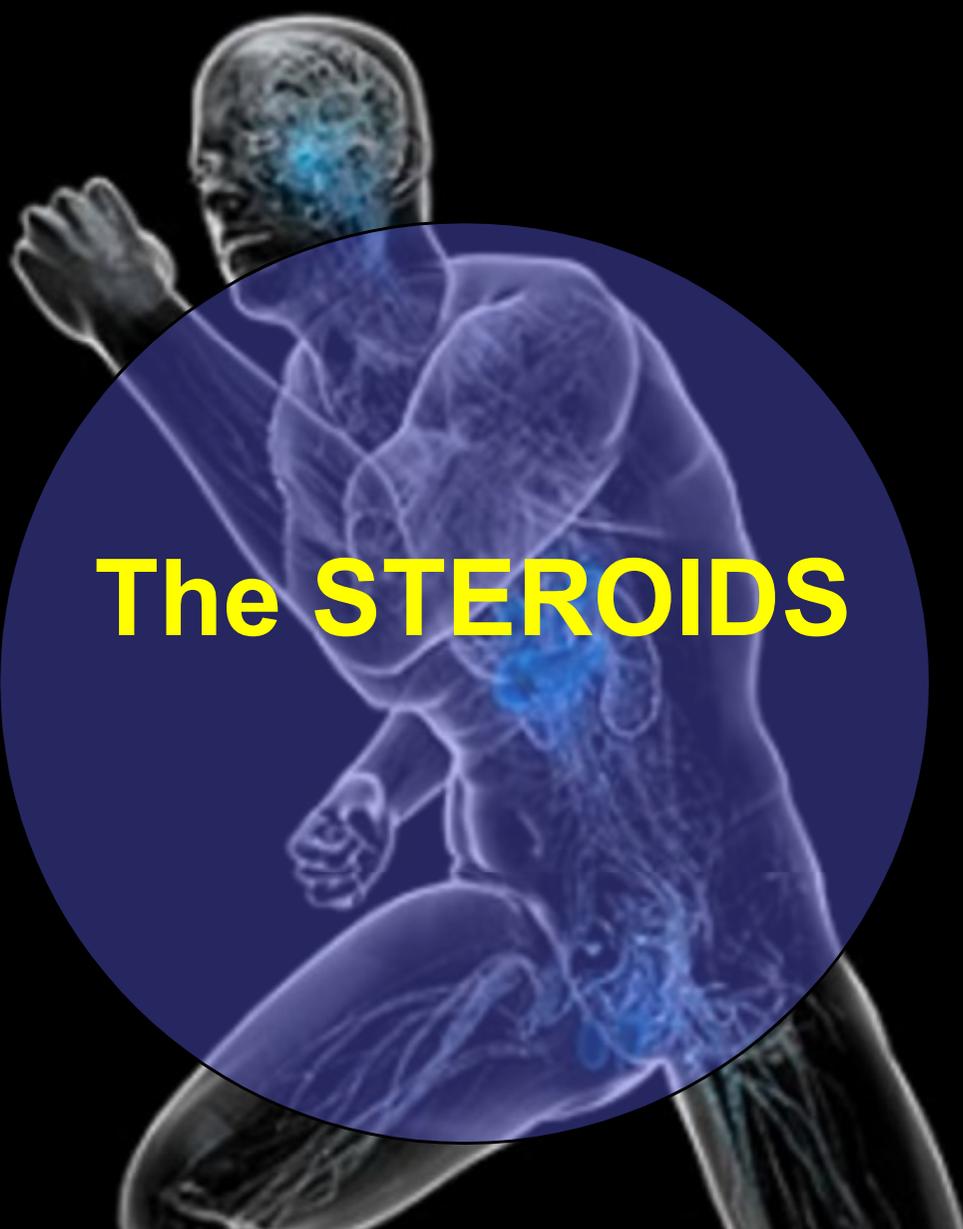
- i) Contraction of the radial muscles of the iris leading to papillary dilation. Also keeps the eyelid open.
- ii) Vasoconstriction.
- iii) GI smooth muscle relaxation but sphincter contraction.
- iv) Seminal vesicle and vas deferens contraction.
- v) Constriction of trigone and bladder sphincter



Beta 1 receptors are found in the heart and increases force and contraction.

Beta 2 receptors cause

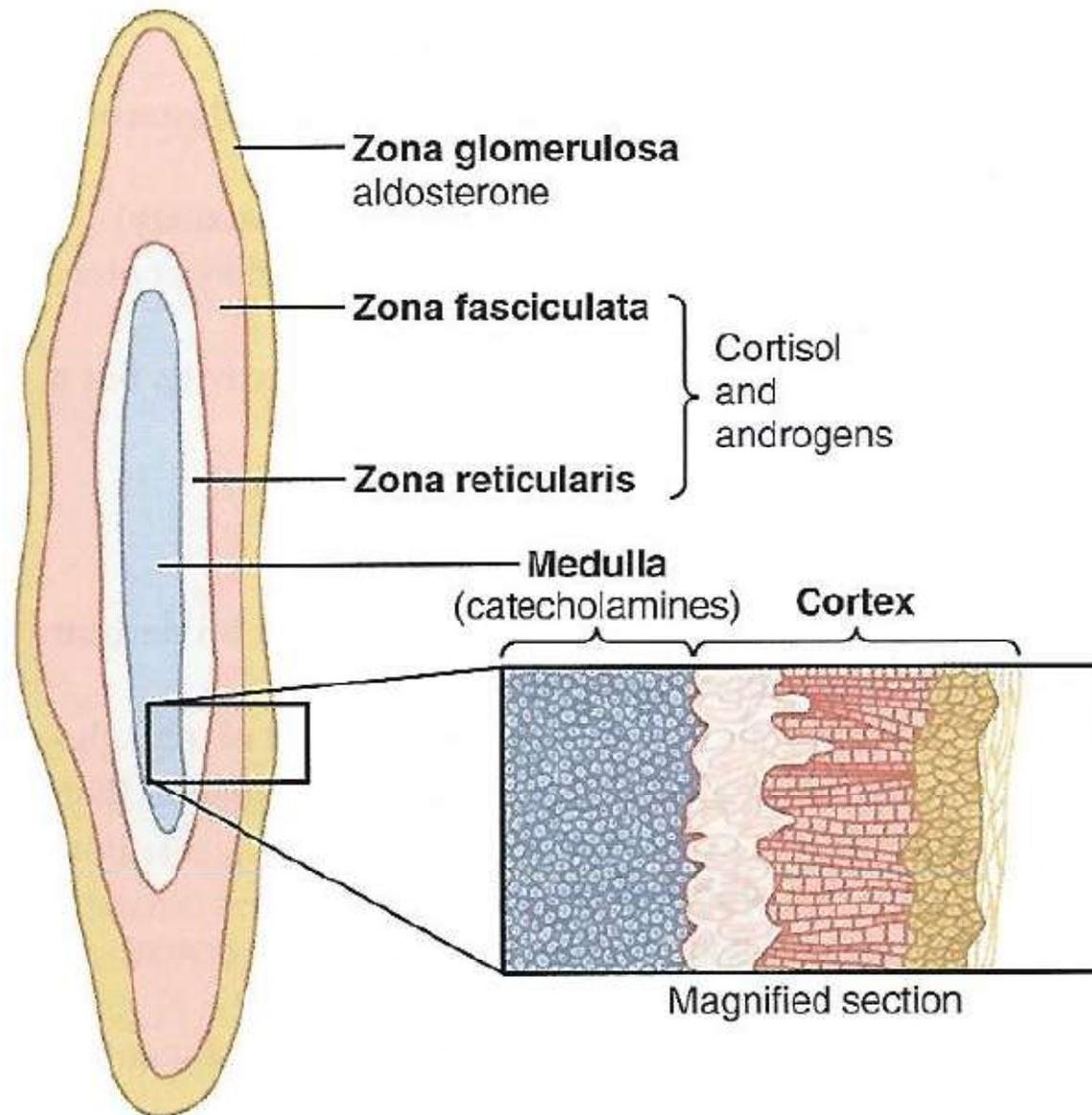
- i) Skeletal muscle and liver vasodilation
- ii) Brochodilation.
- iii) GI smooth muscle relaxation.
- iv) Relaxation of the uterus in pregnancy.
- v) Relaxation of the bladder detrusor muscles.
- vi) Release of renin causing hypertension
- vii) Stimulates glycogenolysis, lipolysis and hypoinsulinism.



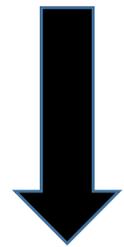
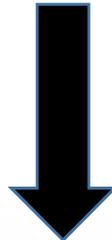
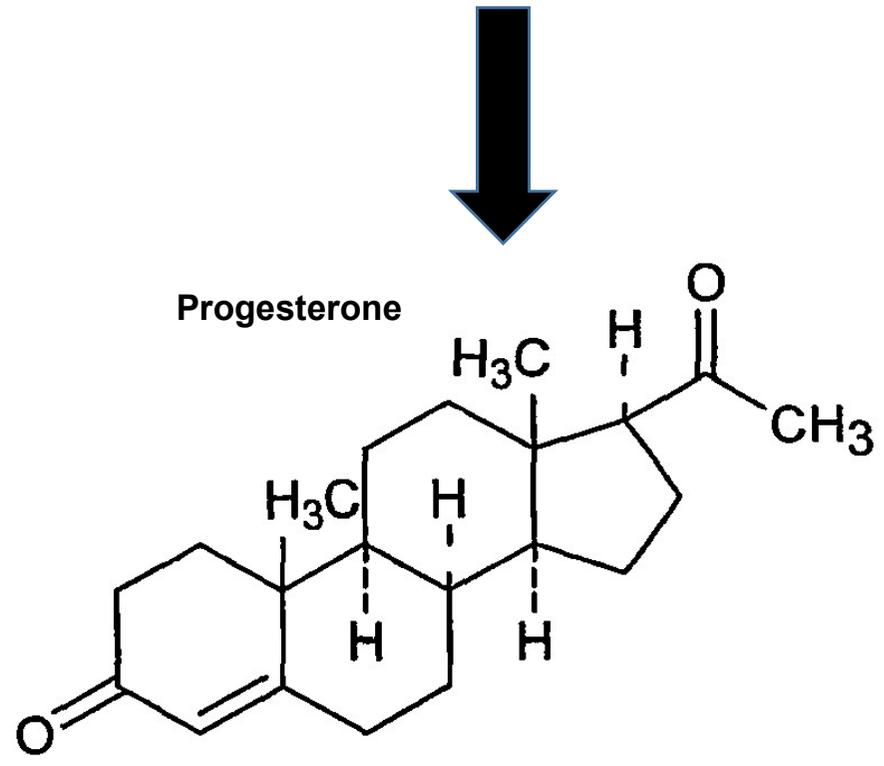
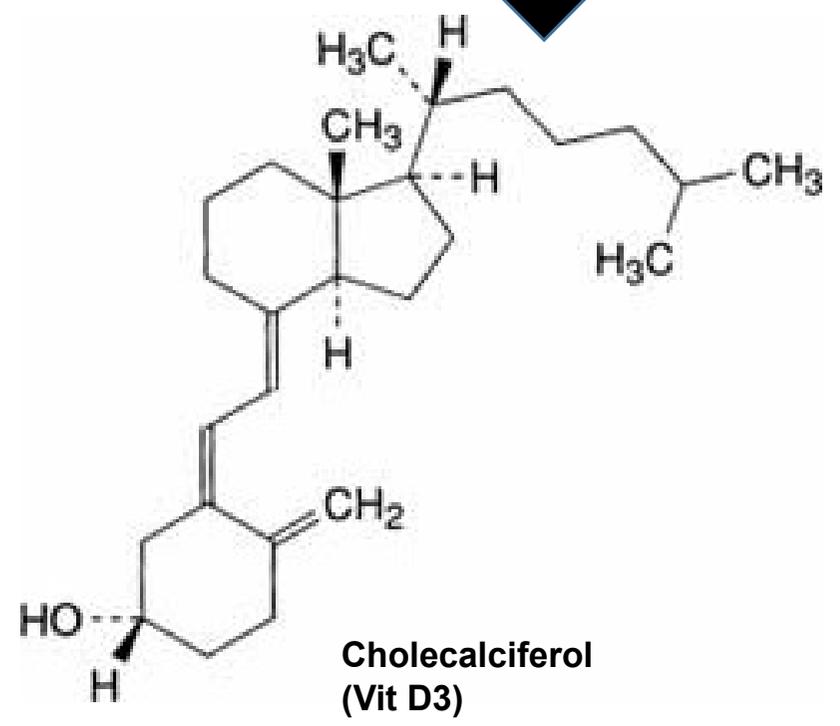
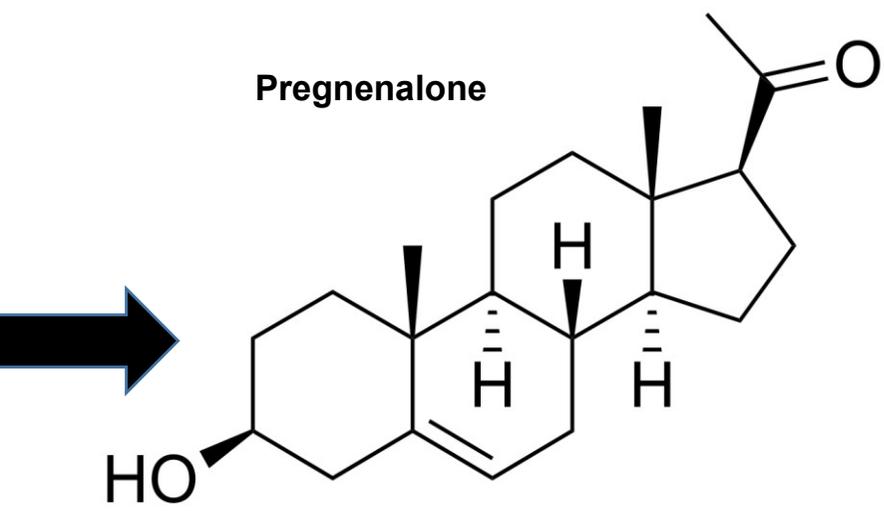
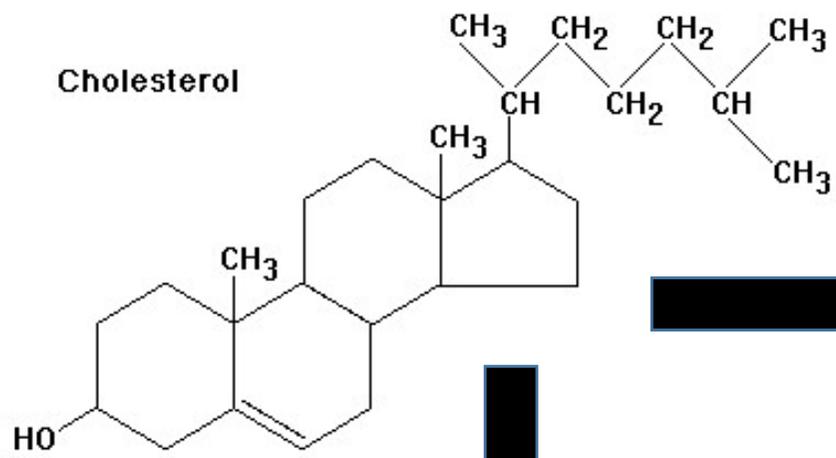
The STEROIDS

Master Steroid Ring





Guyton and Hall (2011). *Textbook of Medical Physiology*. 13th Edition U.S.: Saunders Elsevier. p. 965



Cholesterol



Pregnenalone



DHEA



Progesterone



Androstenedione



Aldosterone



Cortisol

Testosterone



Estradiol

Estrone

Estriol

Modified from Applied Kinesiology Synopsis 2nd Edition by David Walther DC page 508

Estrone (E1)

NADPH
Fe++, O2
Indole-3-carbinols
Rosemary
Watercress
Retinol

15q 388nm
cytochrome p450 CYP 1A1

cytochrome p450 CYP 1B1
2p 372nm

NADPH
Fe++, O2
Char grilling
Tobacco

Sulforaphanes

15q 388nm
cytochrome p450 CYP 1A2

NADPH,
Fe++, O2
Omega 3,
Brassicas,
Retinol,
Iodide,

2-Hydroxy-
estrone

4-Hydroxy-
estrone

16-Hydroxy-
estrone

C
O
M
T
22 399nm
SAM
(Mg, ATP, Zn)
CH3H4Folate
Methyl B12
P5P
Mumie

2-Methoxy-
estrone

Glutathione
(Cysteine,
Glycine,
Glutamic acid,
NAC, Zn++, P5P
Selenium).
Glucuronidation
(Artichoke, Vit C)
Sulfation (PAPs,
MSM, Sulfur)
Acetylation
(Acetyl CoA
Pantethine)

Conjugated
2-Methoxy-
estrone
metabolites

C
O
M
T
22 399nm
SAM
(Mg, ATP, Zn)
CH3H4Folate
Methyl B12
P5P

4-Methoxy-
estrone

Glutathione
(Cysteine,
Glycine,
Glutamic acid,
NAC, Zn++, P5P
Selenium).
Glucuronidation
(Artichoke, Vit C)
Sulfation (PAPs,
MSM, Sulfur)
Acetylation
(Acetyl CoA
Pantethine)

Conjugated
4-Methoxy-
estrone
metabolites

C
O
M
T
22 399nm
SAM
(Mg, ATP, Zn)
CH3H4Folate
Methyl B12
P5P

16-Methoxy-
estrone

Glutathione
(Cysteine,
Glycine,
Glutamic acid,
NAC, Zn++, P5P
Selenium).
Glucuronidation
(Artichoke, Vit C)
Sulfation (PAPs,
MSM, Sulfur)
Acetylation
(Acetyl CoA
Pantethine)

Conjugated
16-Methoxy-
estrone
metabolites

Estradiol (E2)

NADPH
Fe++, O2
Indole-3-carbinols
Rosemary
Watercress
Retinol

15q 388nm
cytochrome p450 CYP 1A1

cytochrome p450 CYP 1B1
2p 372nm

NADPH
Fe++, O2
Char grilling
Tobacco

Sulforaphanes

15q 388nm
cytochrome p450 CYP 1A2

NADPH,
Fe++, O2
Omega 3,
GLA
Brassicas,
Retinol,
Iodide

2-Hydroxy-
estradiol

4-Hydroxy-
estradiol

16-Hydroxy-
estradiol
(Estriol E3)

C
O
M
T
22 399nm
SAM
(Mg, ATP, Zn)
CH3H4Folate
Methyl B12
P5P
Mumie

2-Methoxy-
estradiol

Glutathione
(Cysteine,
Glycine,
Glutamic acid,
NAC, Zn++, P5P
Selenium).
Glucuronidation
(Artichoke, Vit C)
Sulfation (PAPs,
MSM, Sulfur)
Acetylation
(Acetyl CoA
Pantethine)

Conjugated
2-Methoxy-
estradiol
metabolites

C
O
M
T
22 399nm
SAM
(Mg, ATP, Zn)
CH3H4Folate
Methyl B12
P5P

4-Methoxy-
estradiol

Glutathione
(Cysteine,
Glycine,
Glutamic acid,
NAC, Zn++, P5P
Selenium).
Glucuronidation
(Artichoke, Vit C)
Sulfation (PAPs,
MSM, Sulfur)
Acetylation
(Acetyl CoA
Pantethine)

Conjugated
4-Methoxy-
estradiol
metabolites

C
O
M
T
22 399nm
SAM
(Mg, ATP, Zn)
CH3H4Folate
Methyl B12
P5P

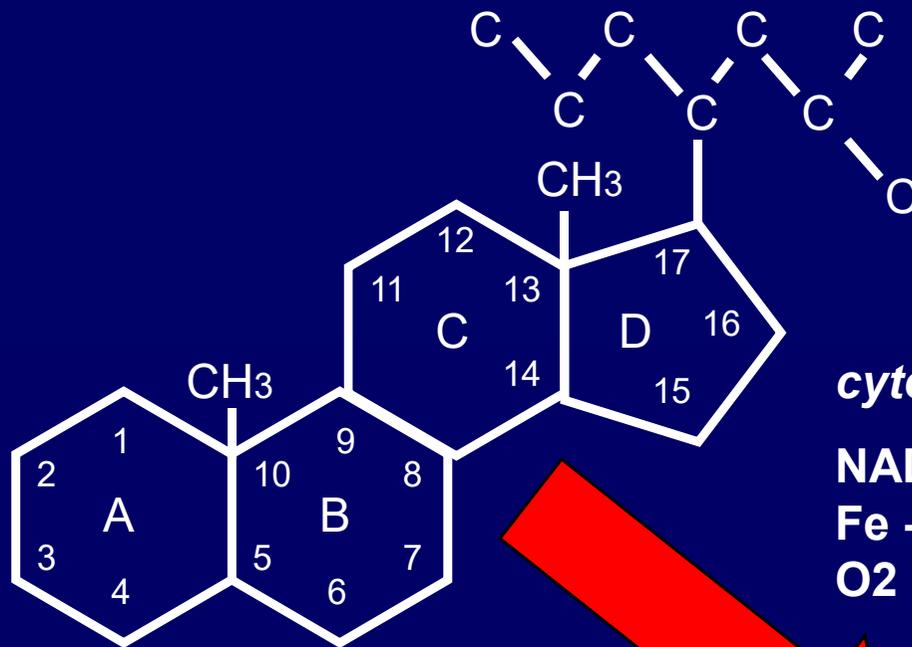
16-Methoxy-
estradiol

Glutathione
(Cysteine,
Glycine,
Glutamic acid,
NAC, Zn++, P5P
Selenium).
Glucuronidation
(Artichoke, Vit C)
Sulfation (PAPs,
MSM, Sulfur)
Acetylation
(Acetyl CoA
Pantethine)

Conjugated
16-Methoxy-
estradiol
metabolites

**The synthesis of
PREGNENALONE**

Cholesterol



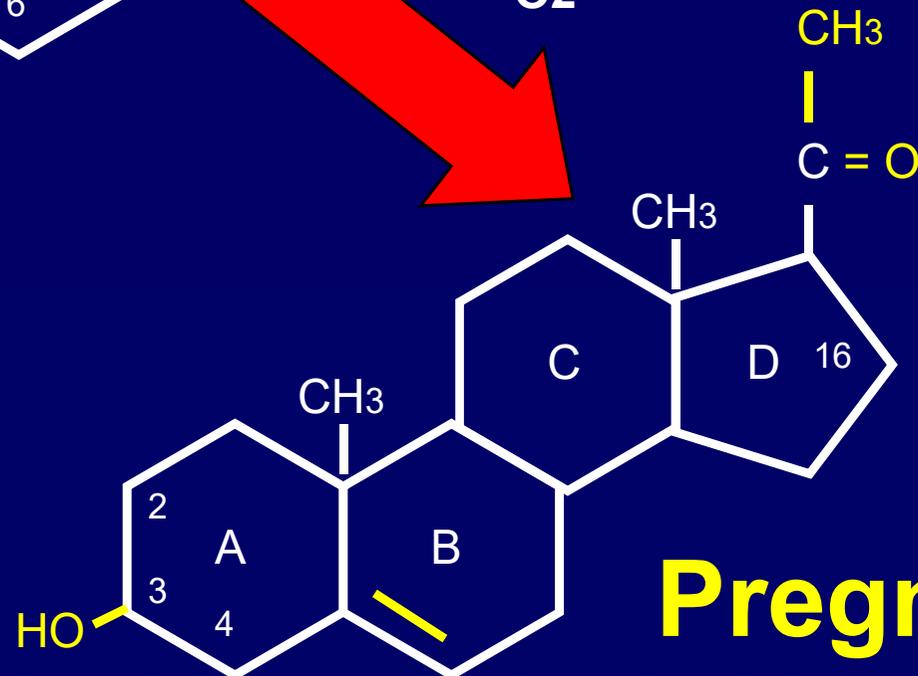
cytochrome p450

15q 388nm

NADPH

Fe - S

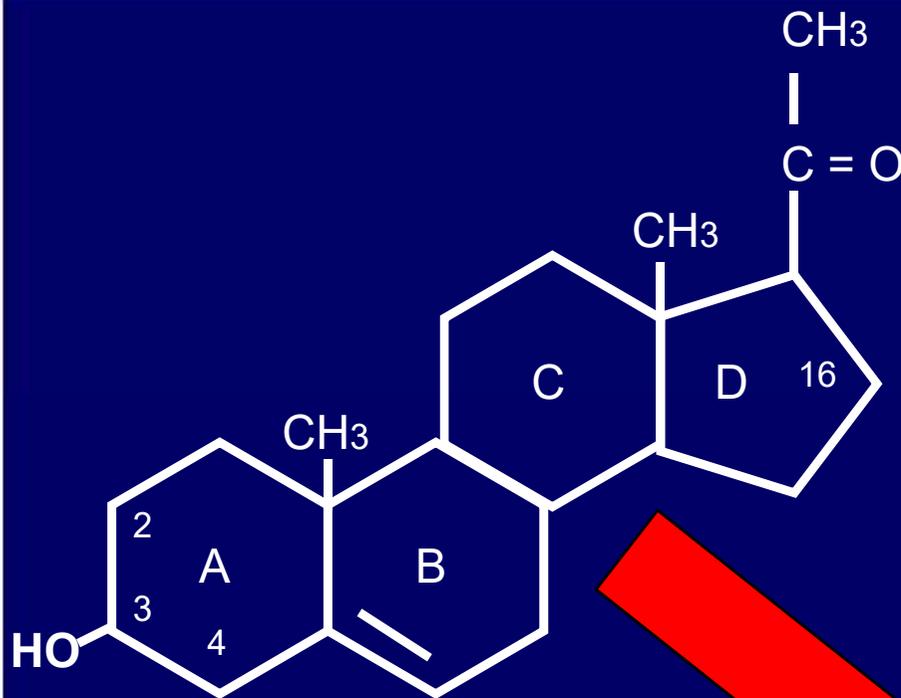
O₂



Pregnenalone

**The synthesis of
PROGESTERONE**

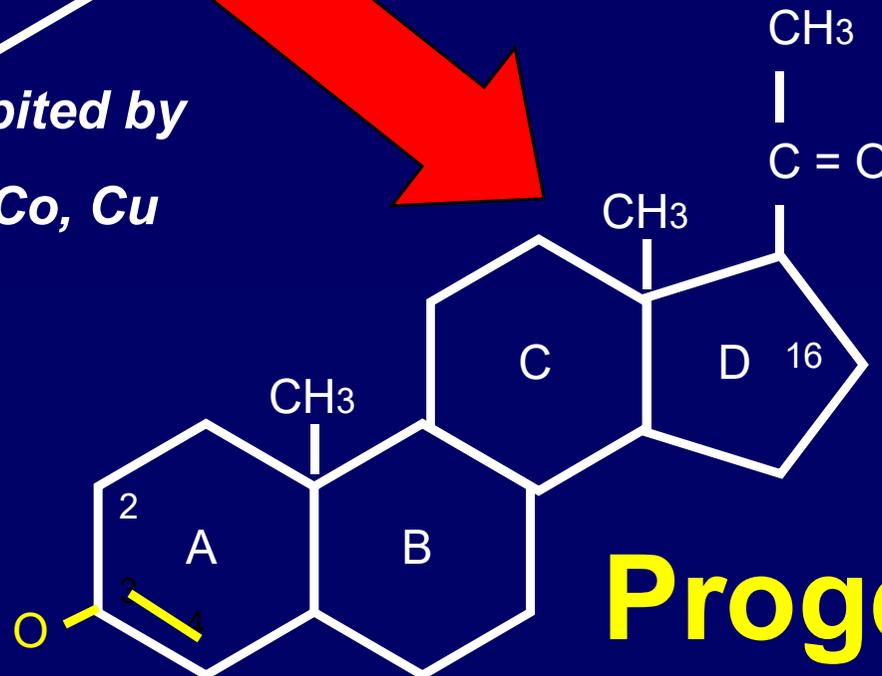
Pregnenalone



*3 β -hydroxysteroid
dehydrogenase* 1p 370nm

NAD(P)
Fe

*inhibited by
Cd, Co, Cu*



Progesterone

Progesterone reduces the proliferative activity of the estrogens on the vaginal epithelium and convert the uterine epithelium to secretetory, thus preparing the uterine epithelium for implantation of the fertilised ovum.

Guyton and Hall (2011). *Textbook of Medical Physiology*. 13th Edition U.S.: Saunders Elsevier. p. 1039

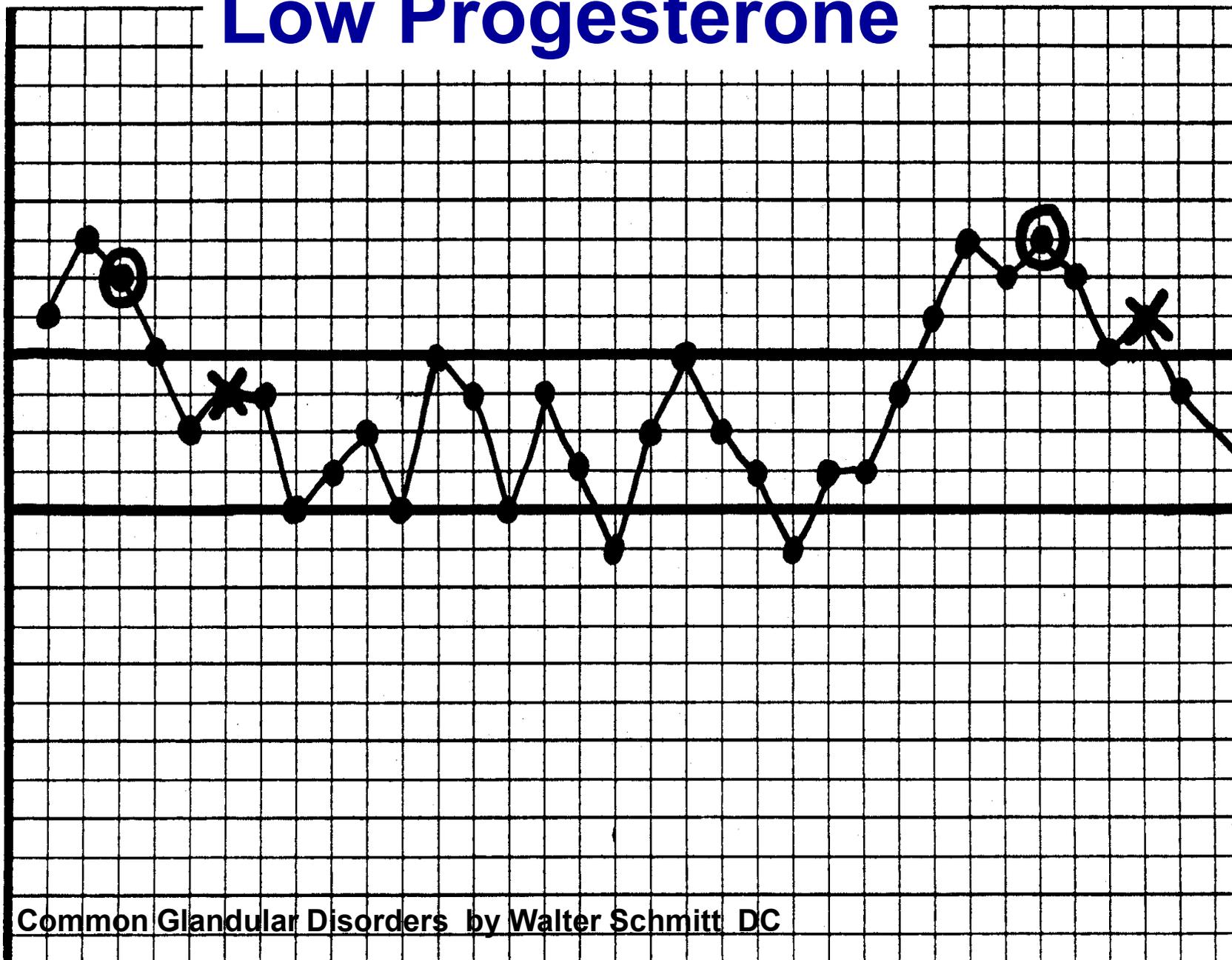
Progesterone

- 1. Enhances the acinar portions of the breasts.**
- 2. Decrease peripheral blood flow thereby decreasing heat loss during the luteal phase and in pregnancy.**
- 3. Requires estrogens to stimulate their receptor sites.**

Guyton and Hall (2011). *Textbook of Medical Physiology*. 13th Edition U.S.: Saunders Elsevier. p. 1039

Low Progesterone

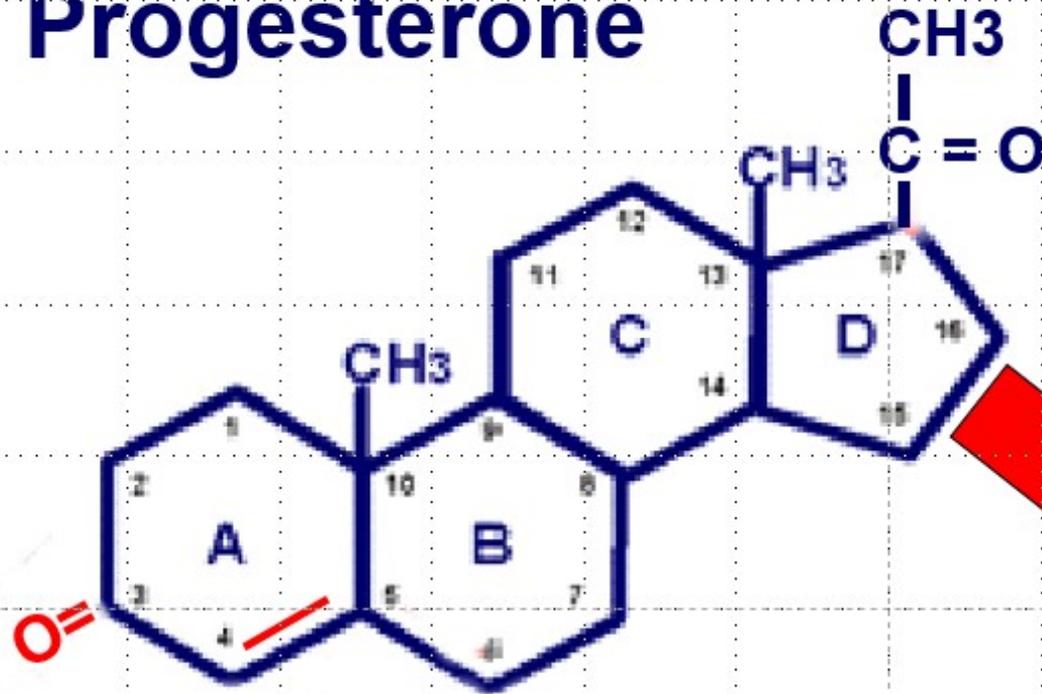
99.1+
99.0
(37.2C)
98.8
(37.1C)
98.6
(37 C)
98.4
(36.9C)
98.2
(36.8C)
98.0
(36.7C)
97.8
(36.5C)
97.6
(36.4C)
97.4
(36.3C)
97.2
(36.2C)
97.0
(36.1C)
96.8
(36 C)



Common Glandular Disorders by Walter Schmitt DC

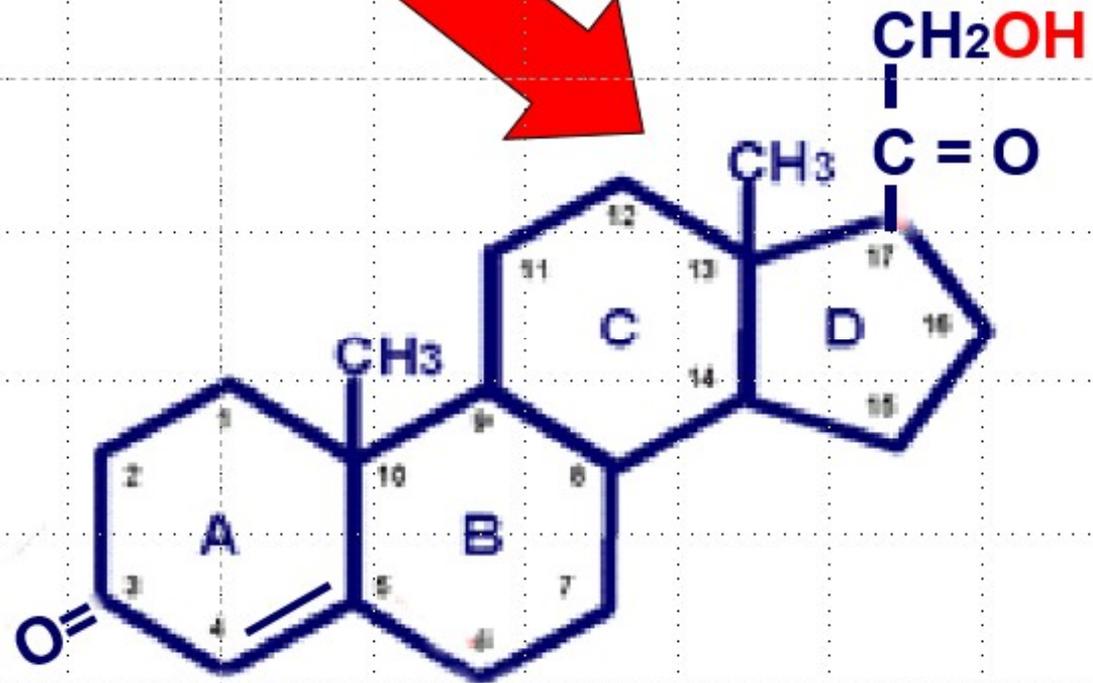
**The synthesis of
ALDOSTERONE
Glomerulosa**

Progesterone

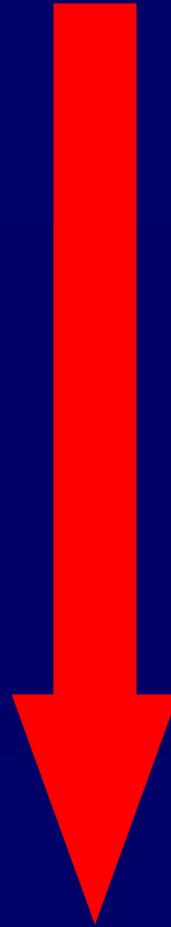


6q 379nm

11-Deoxy-corticosterone



Progesterone



21-hydroxylase 6q 379nm
(CYP21 A2)

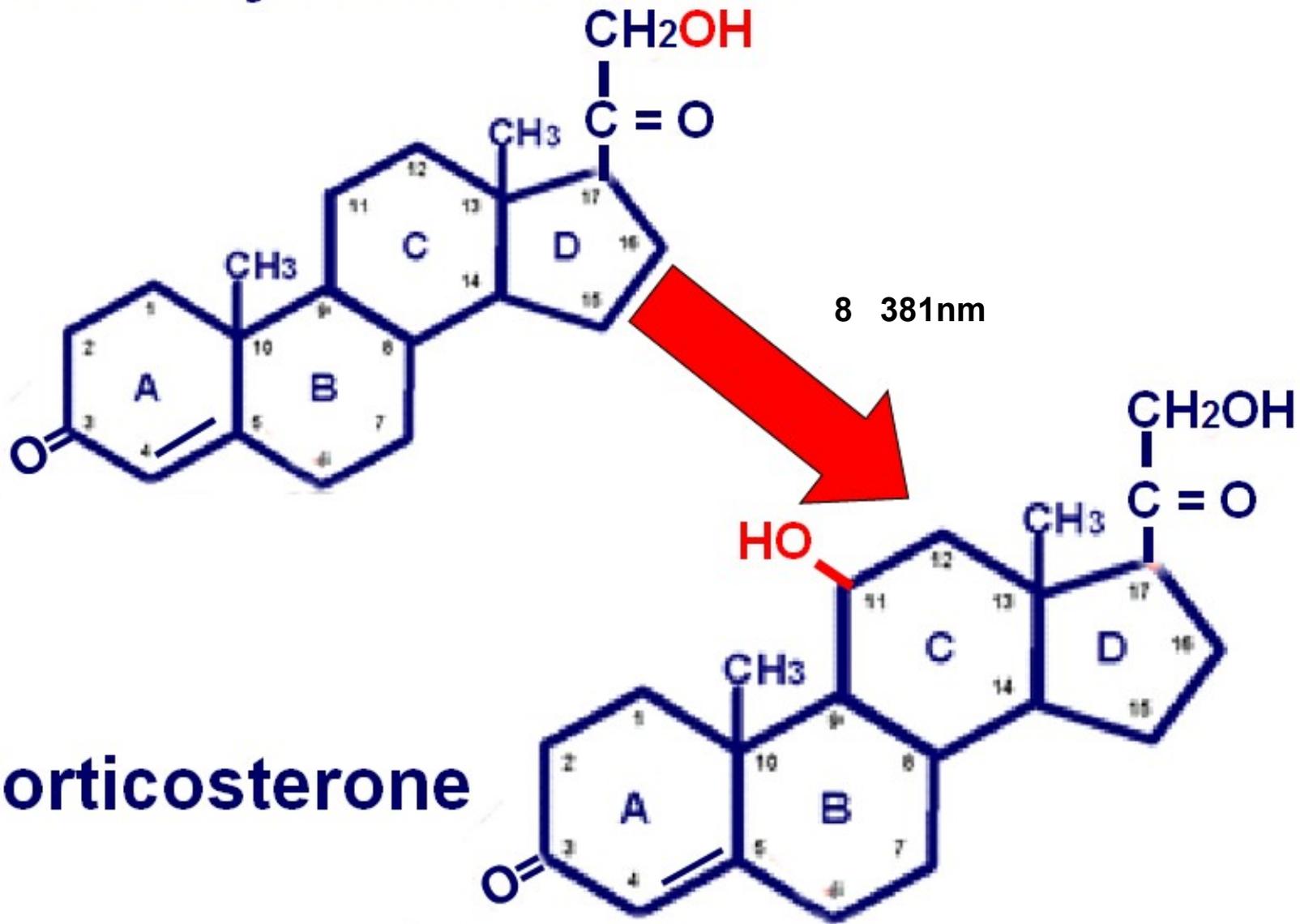
NADPH

Fe⁺⁺⁺

O₂

11-Deoxy- corticosterone

11-Deoxycorticosterone



Corticosterone

11-Deoxycorticosterone

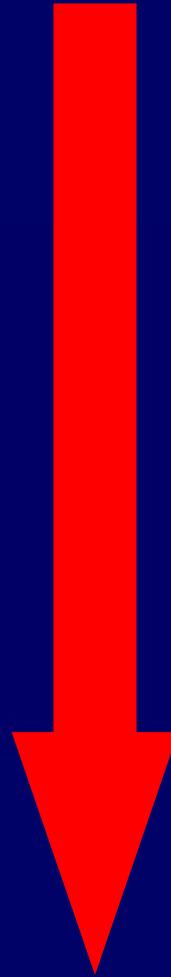
inhibited by
Testosterone

11 β -hydroxylase
(CYP 11B1)

8 381nm

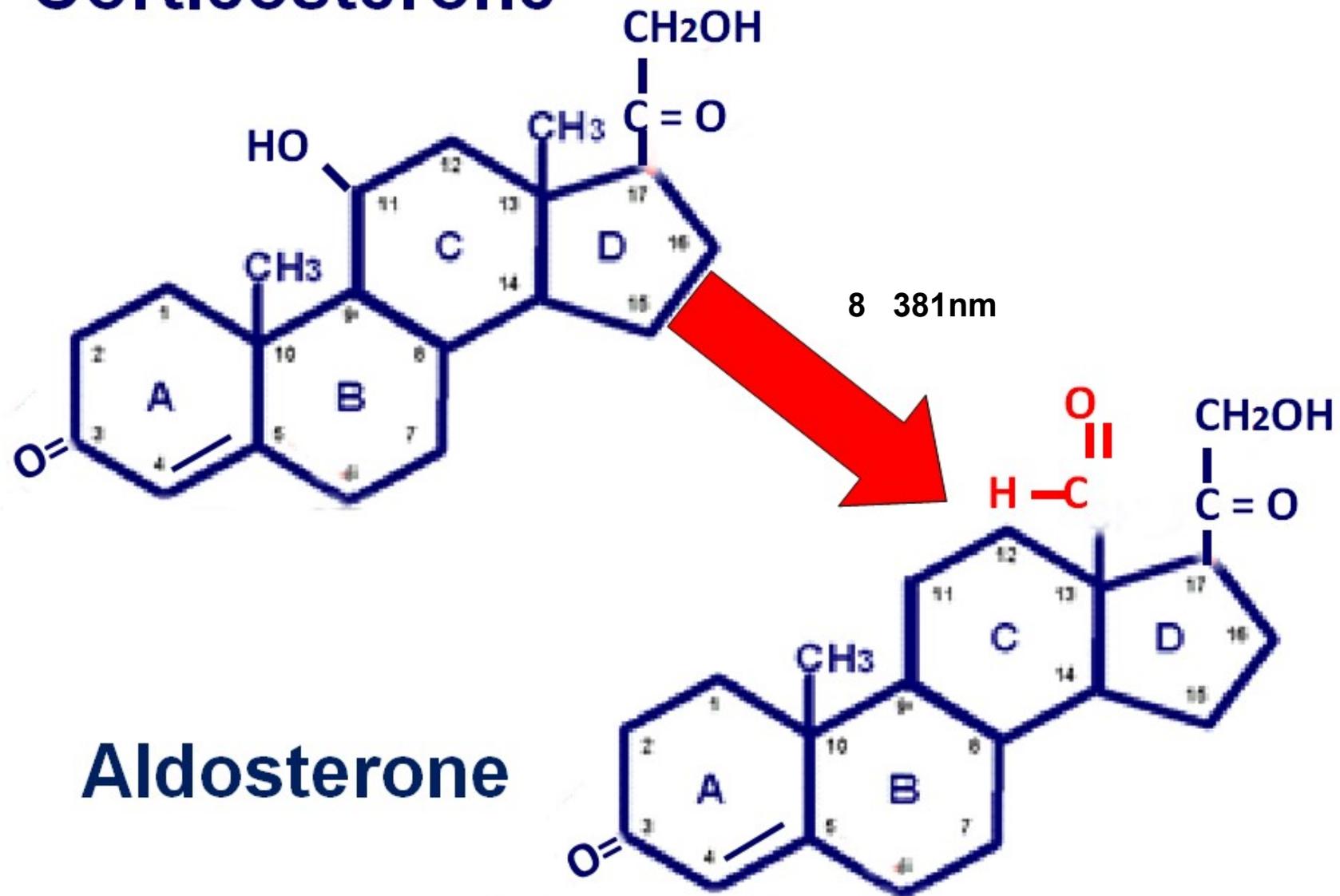
NADPH

Fe
O₂

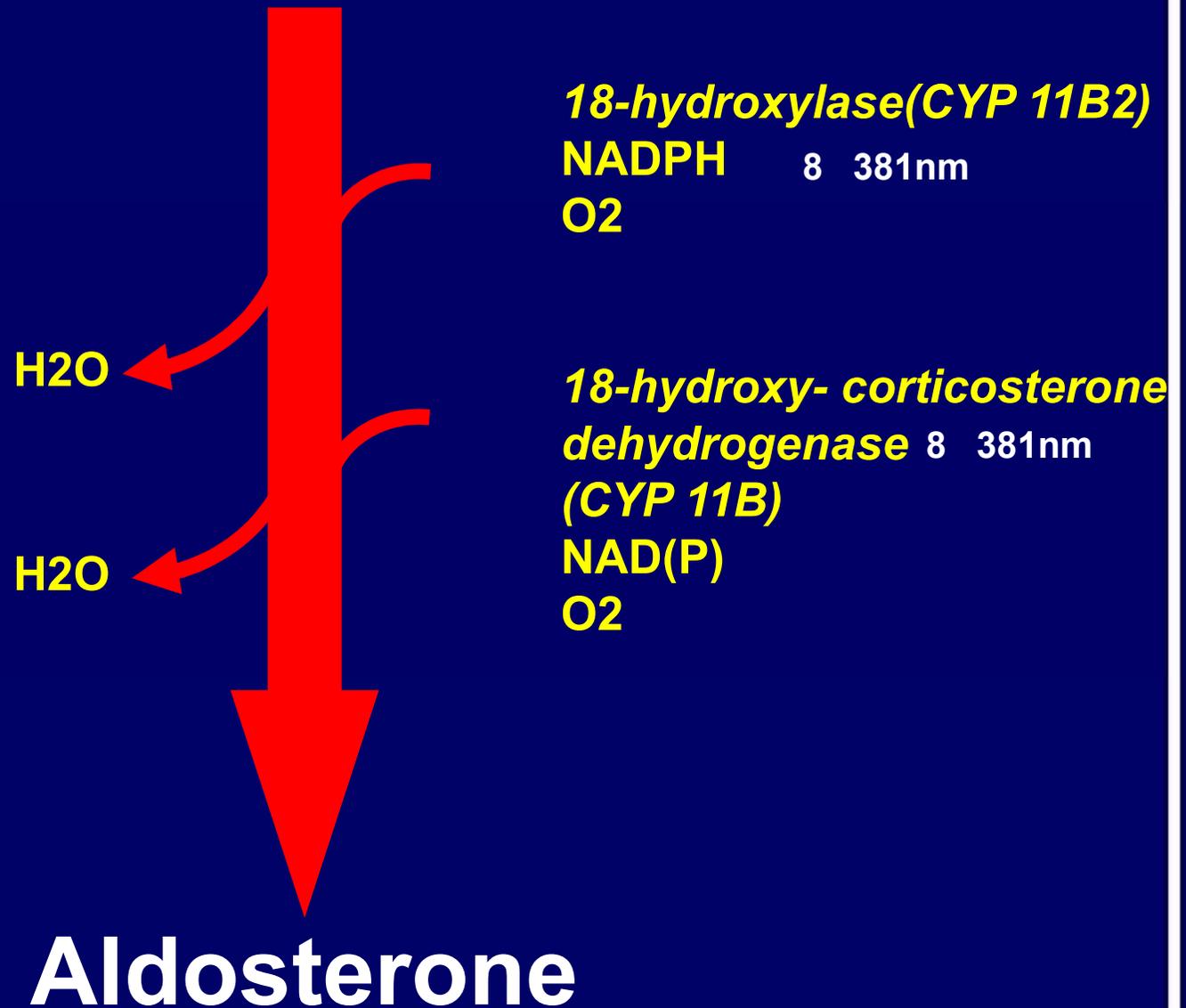


Corticosterone

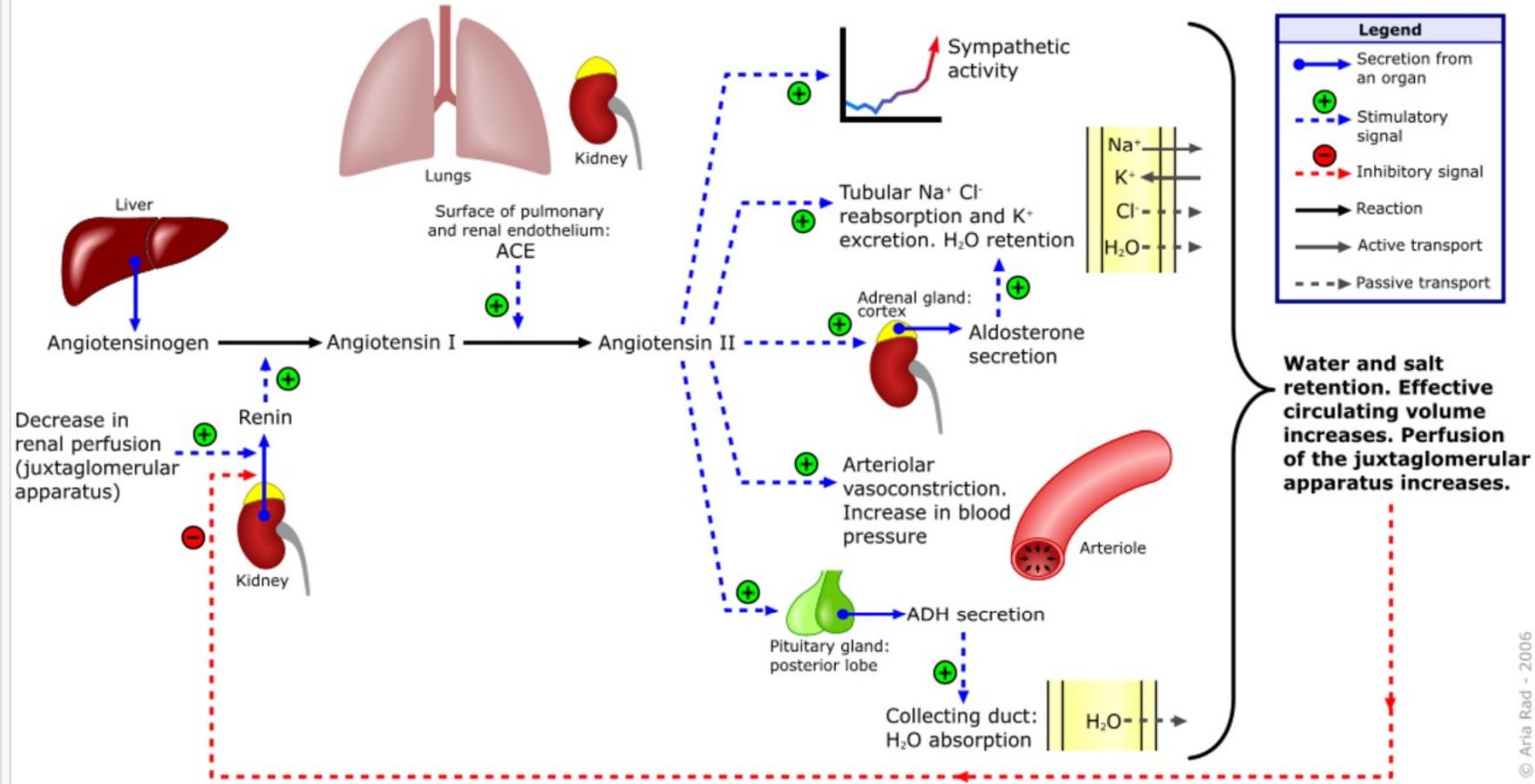
Corticosterone



Corticosterone



Renin-angiotensin-aldosterone system



Renin-angiotensin system schematic showing aldosterone activity on the right

Aldosterone and Aldosterone Metabolism

Aldosterone has effects on sweat glands, salivary glands and the colon which are essentially identical to those seen in the distal tubule of the kidney.



Guyton and Hall (2011). *Textbook of Medical Physiology*. 13th Edition U.S.: Saunders Elsevier. p. 968

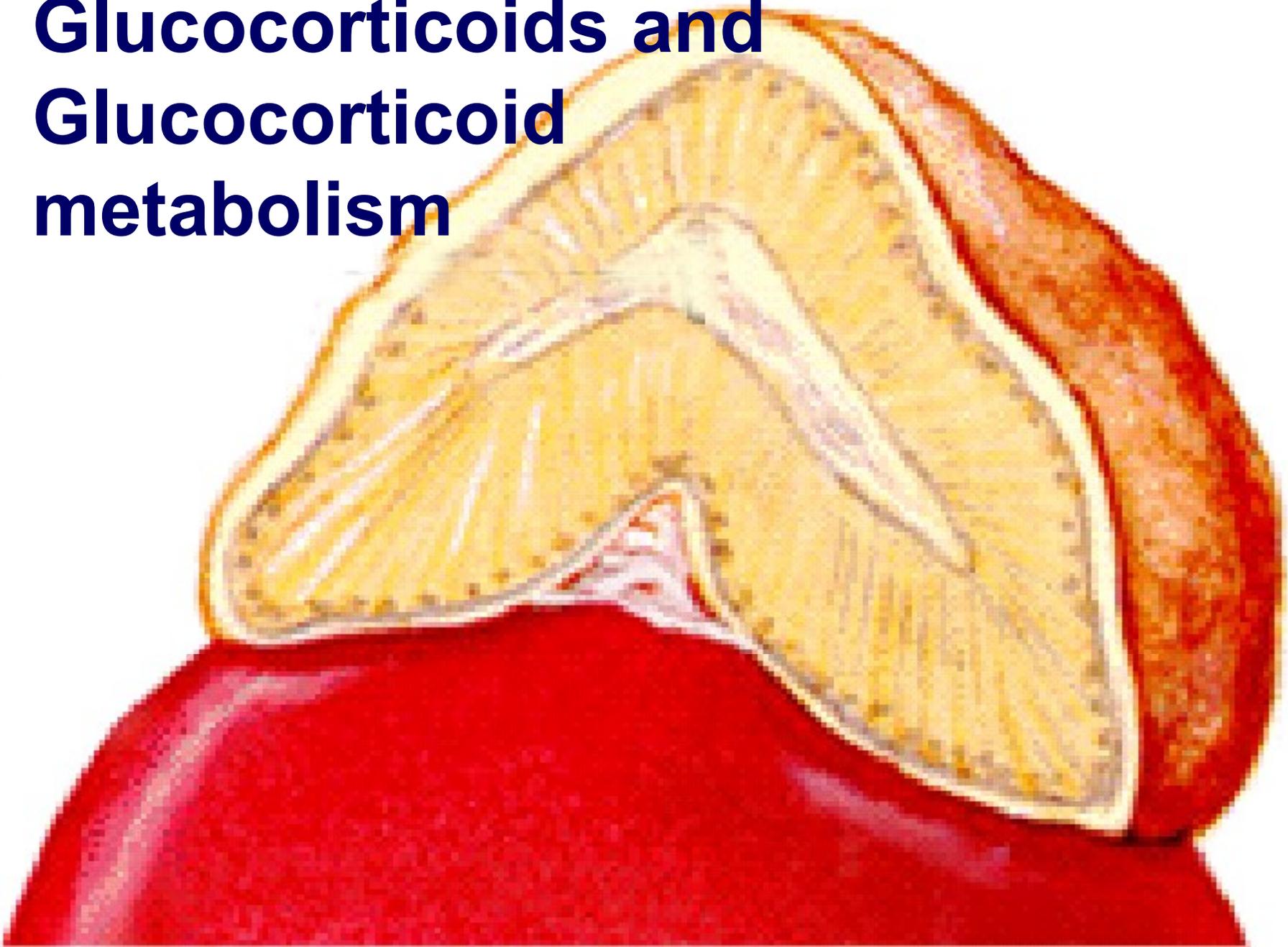
**Aldosterone is the main
mineralocorticoid and regulates
sodium and other mineral
retention.**

Guyton and Hall (2011). *Textbook of Medical Physiology*. 13th Edition U.S.: Saunders Elsevier. p. 966

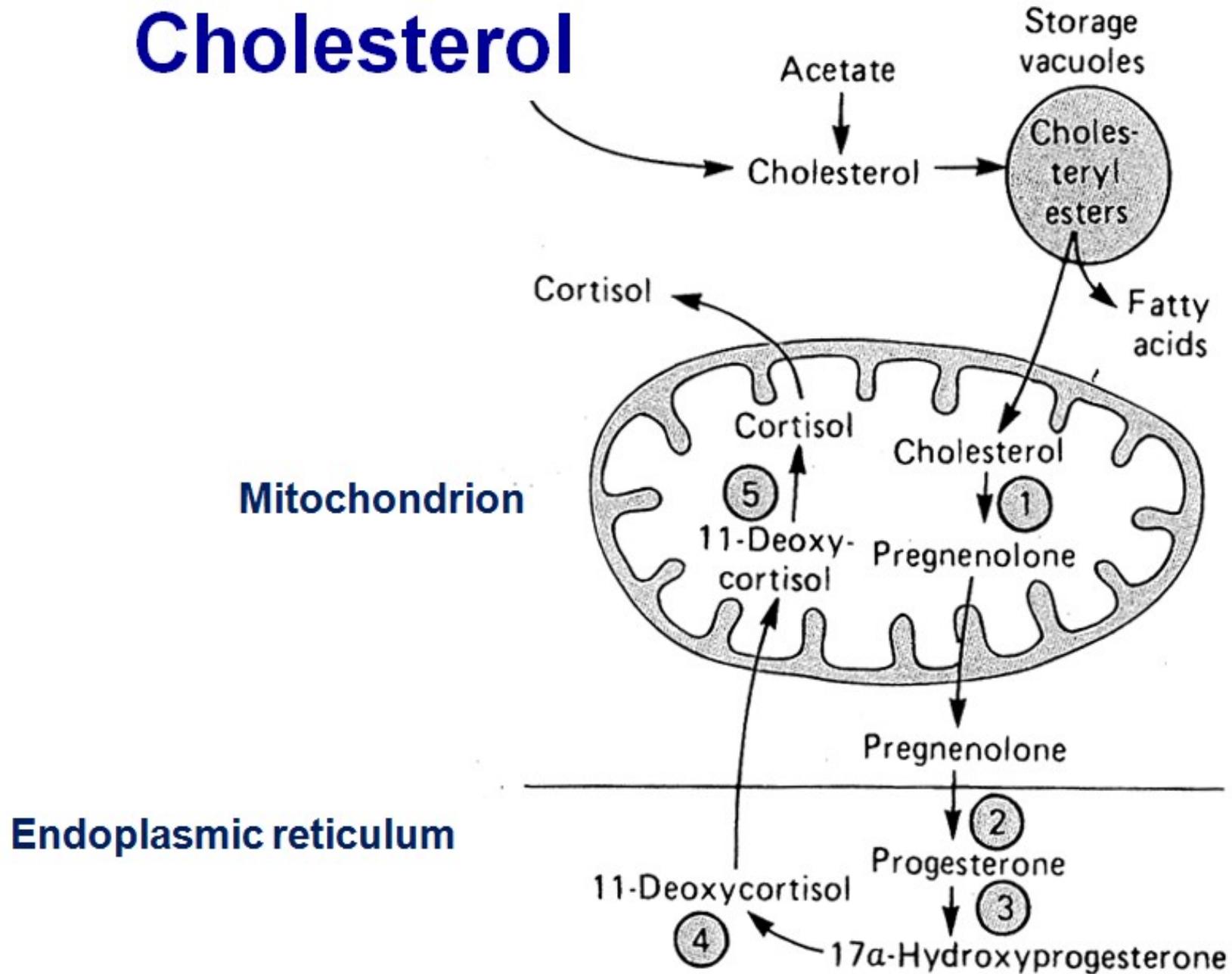
Metabolism consists of reduction of the C3 and C20 keto groups and the D4 double bond followed by conjugation with **glucuronic acid or sulfate** and secretion in the urine.

**The synthesis of the
GLUCOCORTICOIDS
(cortisol)**

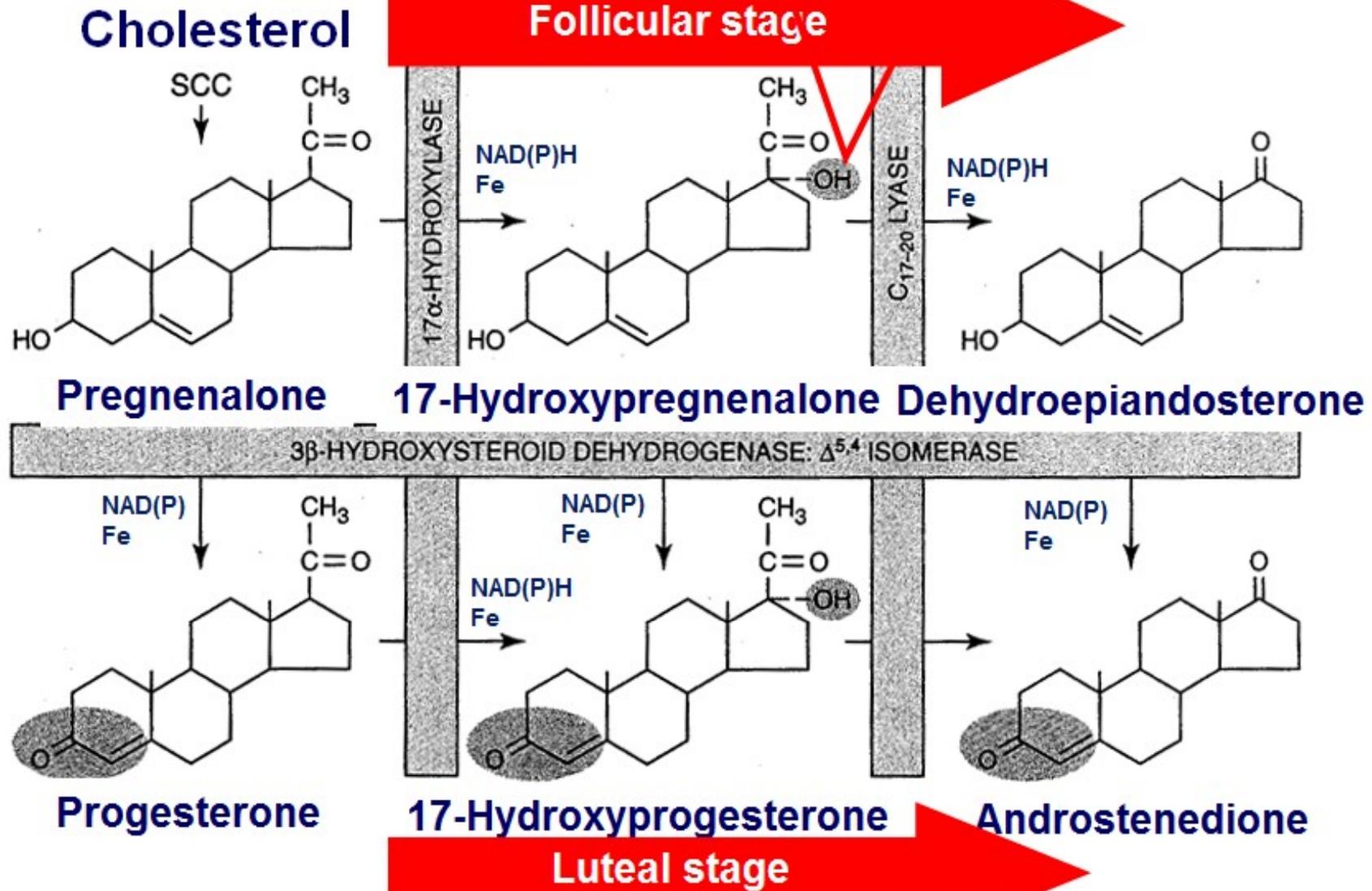
Glucocorticoids and Glucocorticoid metabolism



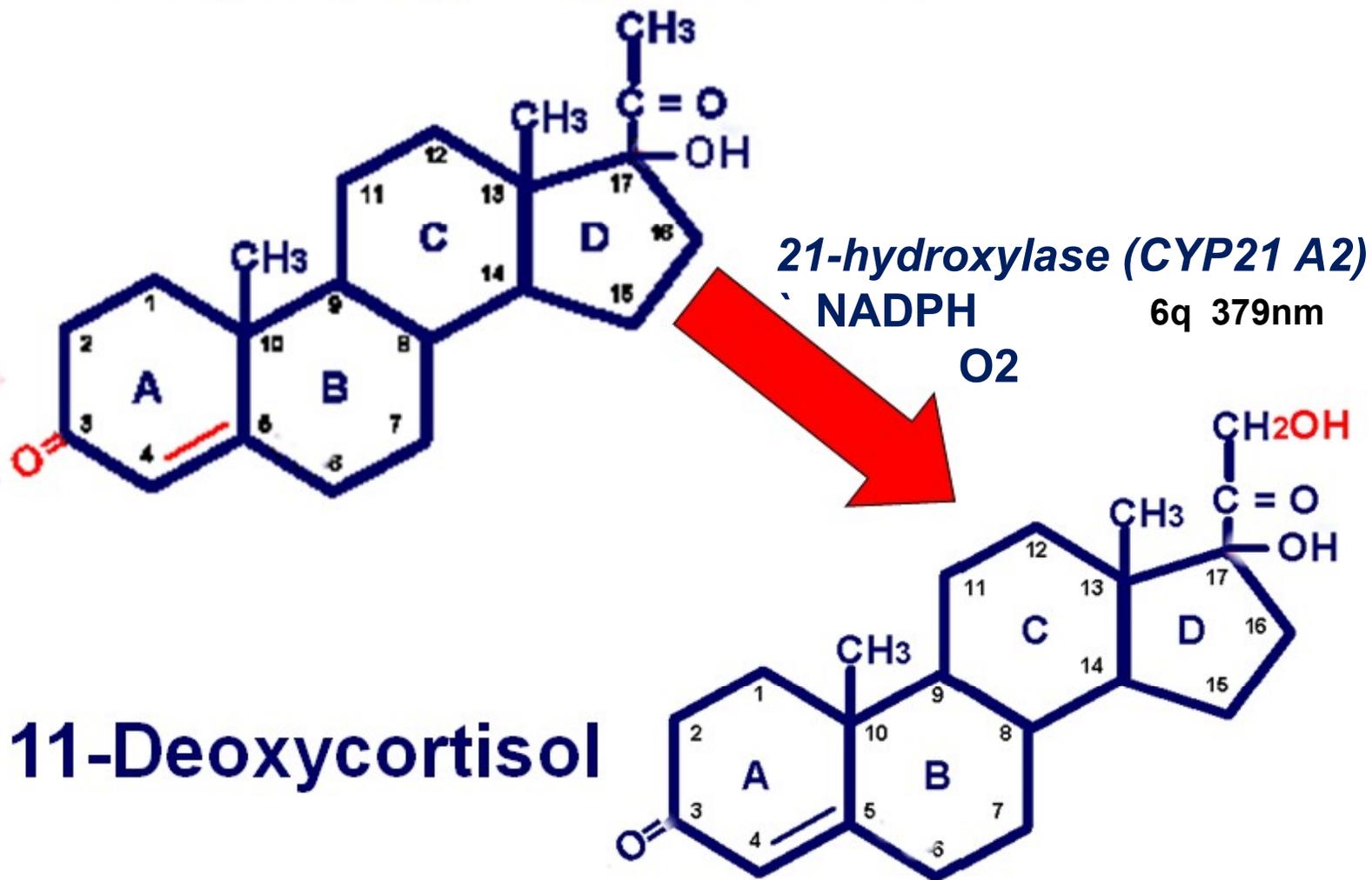
Cholesterol



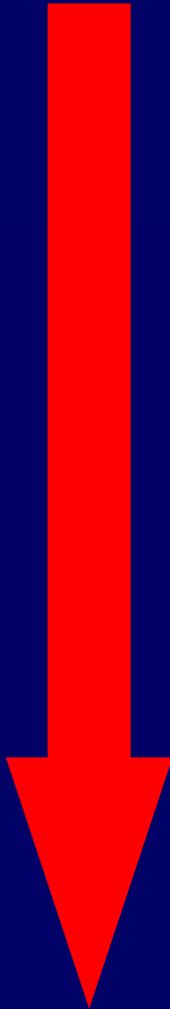
This OH group gives the glucocorticoid properties



17-Hydroxyprogesterone



17-Hydroxyprogesterone



21-hydroxylase (CYP21 A2)

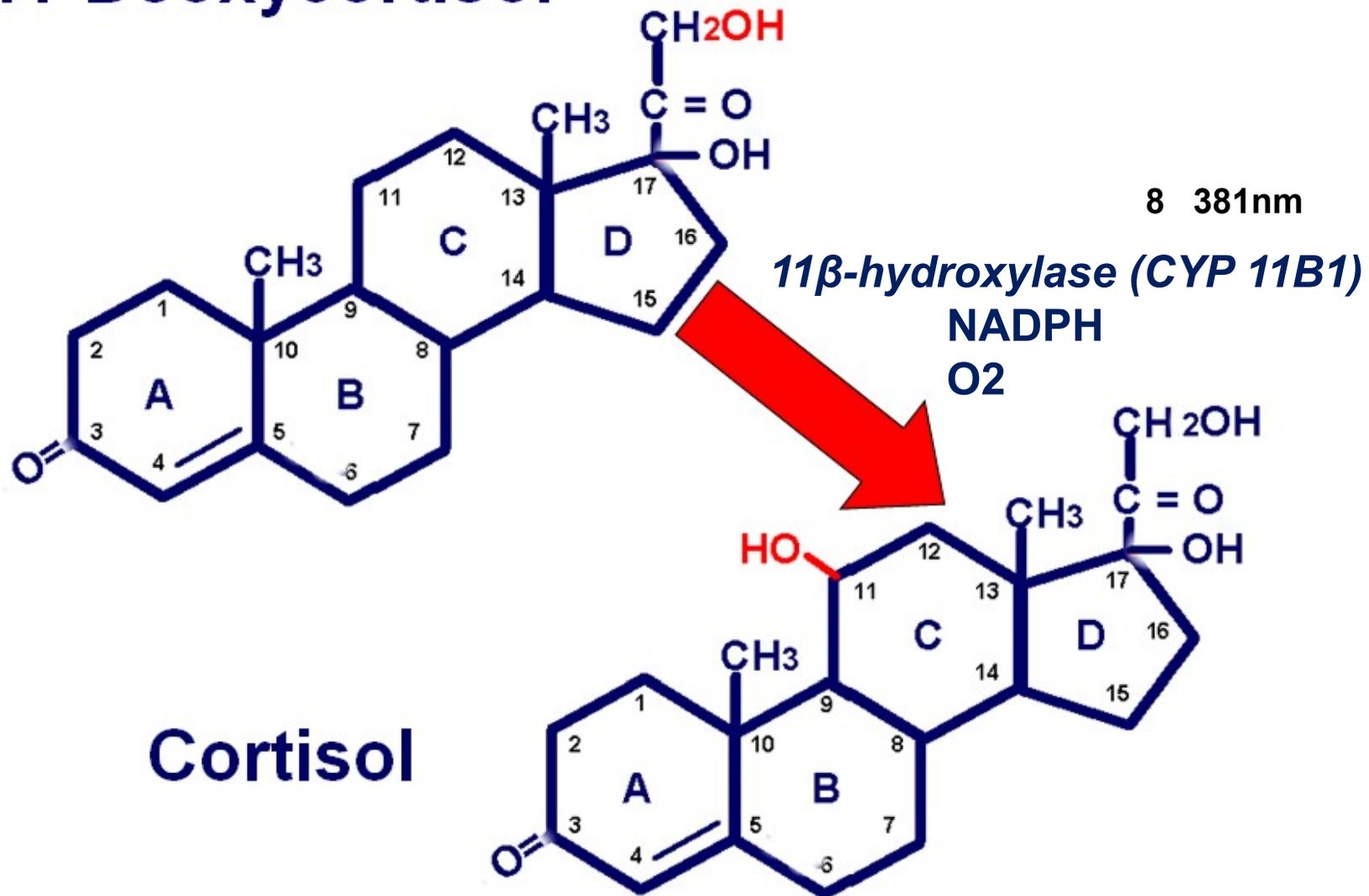
NADPH

6q 379nm

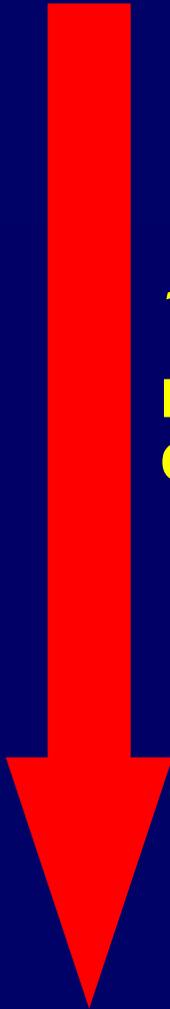
O₂

11-Deoxycortisol

11-Deoxycortisol



11-Deoxycortisol



8 381nm

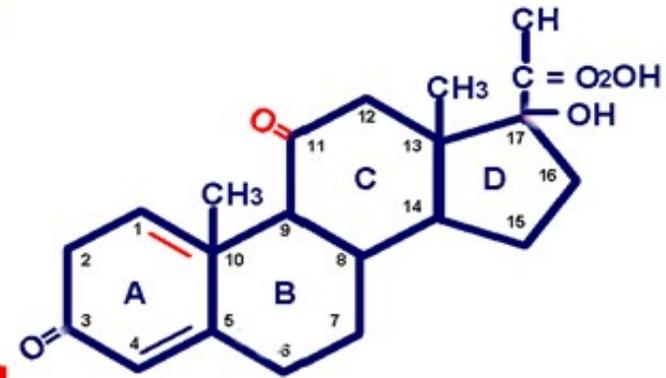
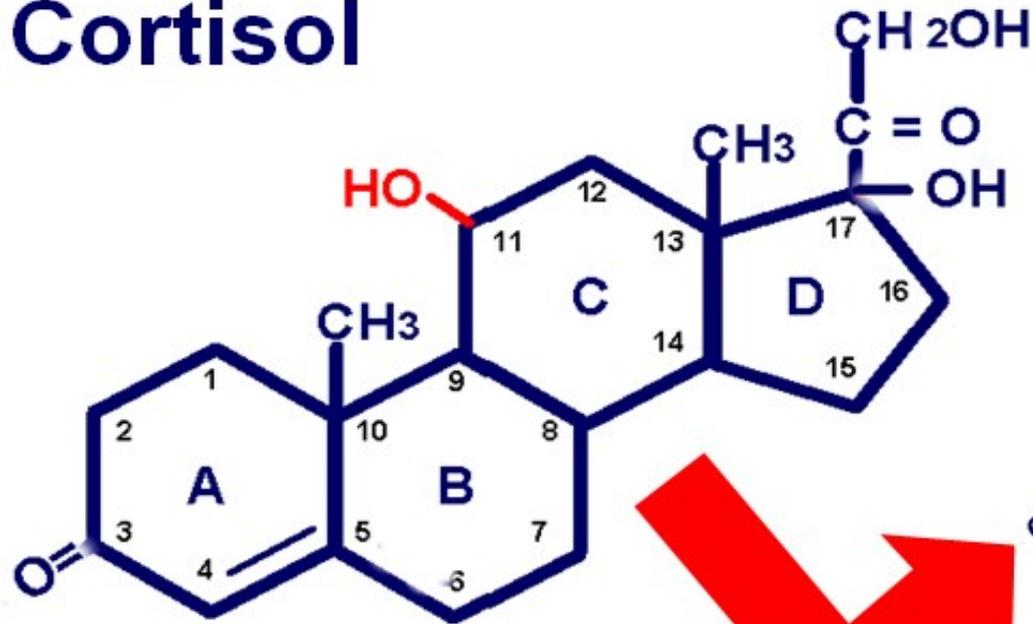
11 β -hydroxylase (CYP 11B1)

NADPH

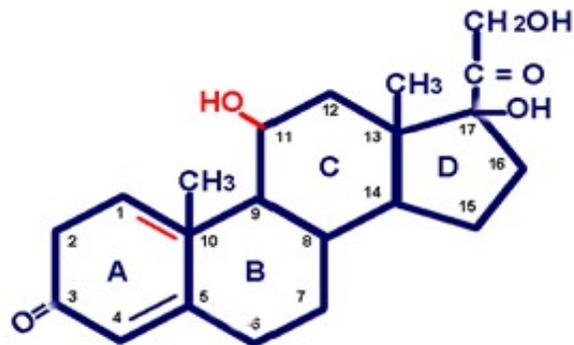
O₂

Cortisol

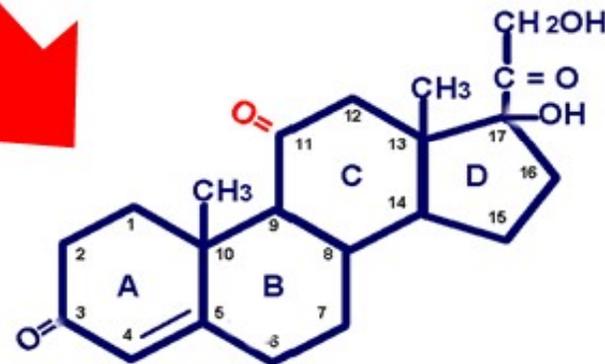
Cortisol



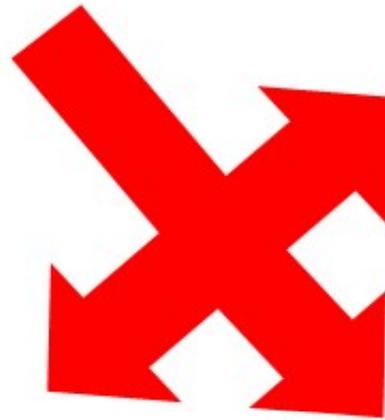
Prednisone



Prednisolone



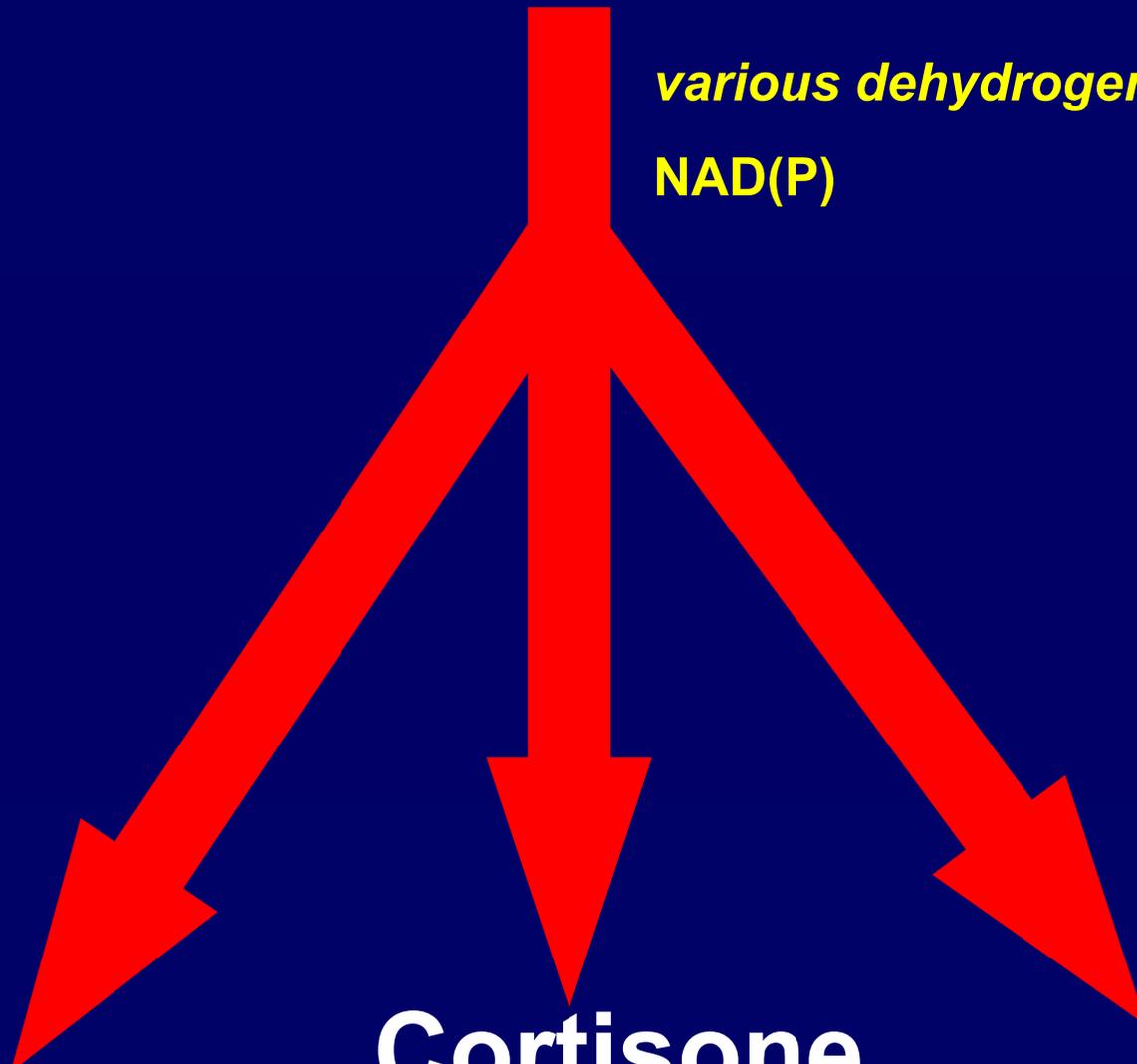
Cortisone



Cortisol

various dehydrogenases

NAD(P)

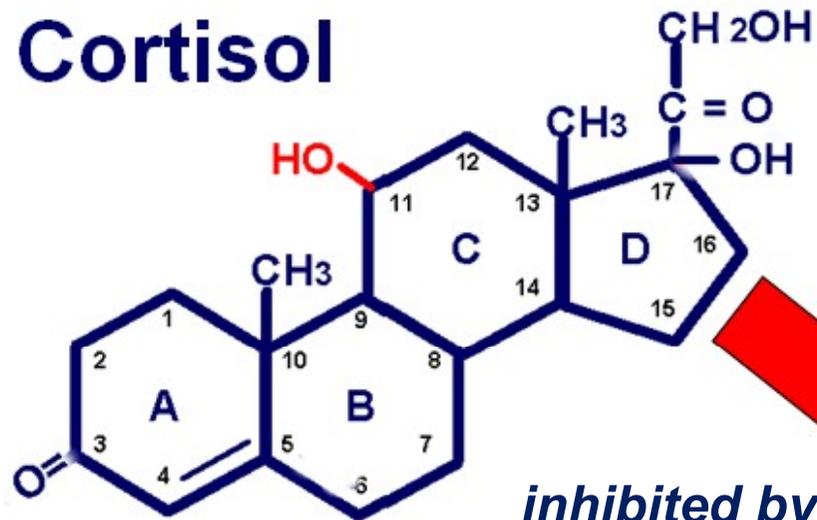


Prednisolone

Cortisone

Prednisone

Cortisol

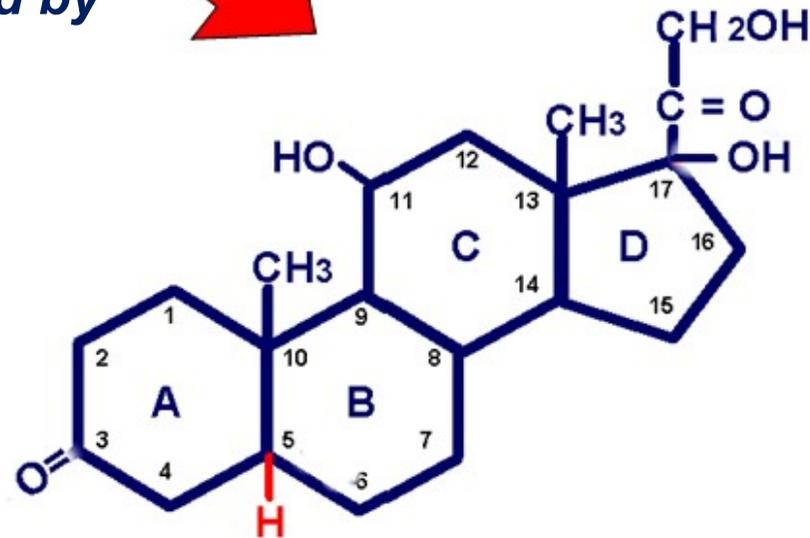


5 α -reductase

NADPH

*inhibited by
GLA*

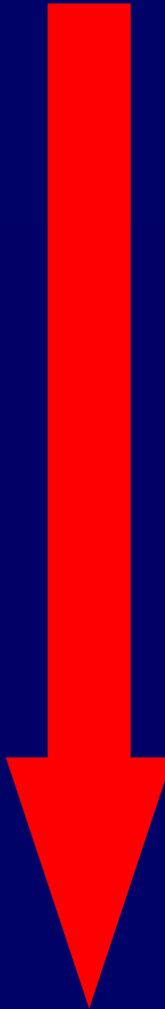
Hydrocortisol



Cortisol

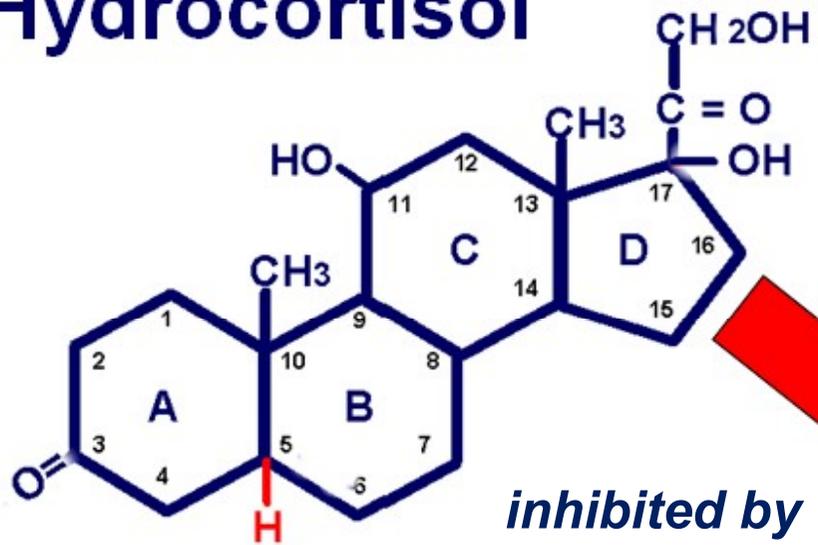
inhibited by
GLA

5 α -reductase
NADPH



Hydrocortisol

Hydrocortisol

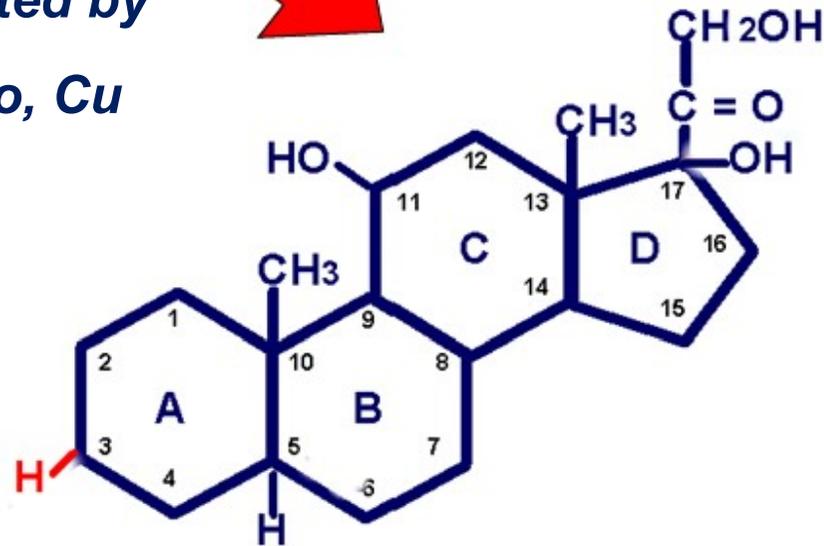


*3-β-hydroxysteroid
dehydrogenase*

NAD(P)H
Fe

*inhibited by
Cd, Co, Cu*

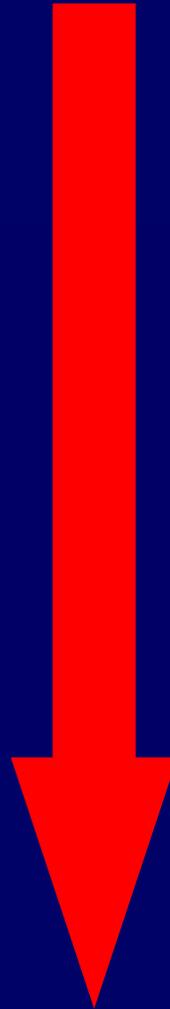
Dihydrocortisol



Hydrocortisol

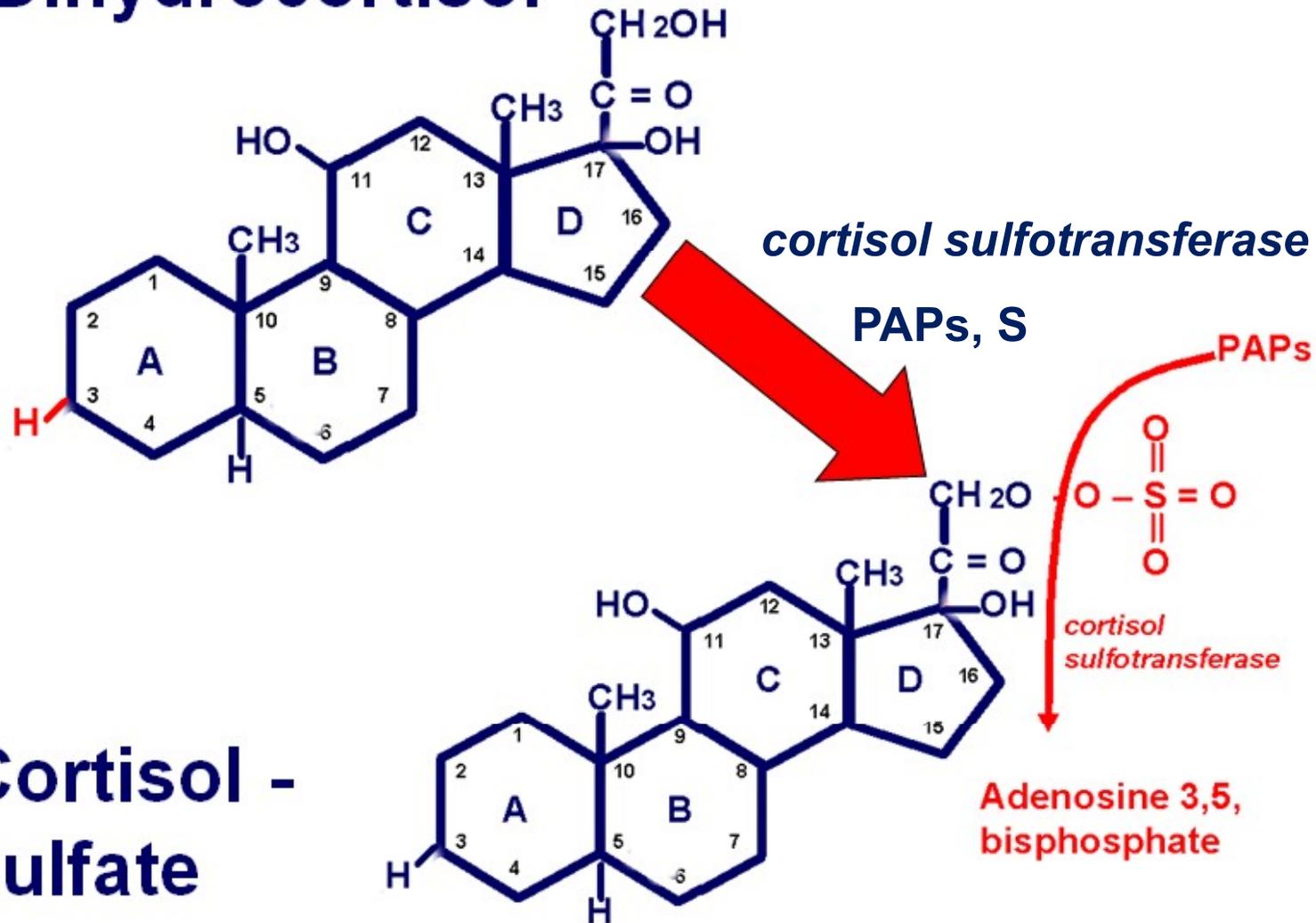
inhibited by
Cd, Co, Cu

3- β -hydroxysteroid
dehydrogenase
NAD(P)H

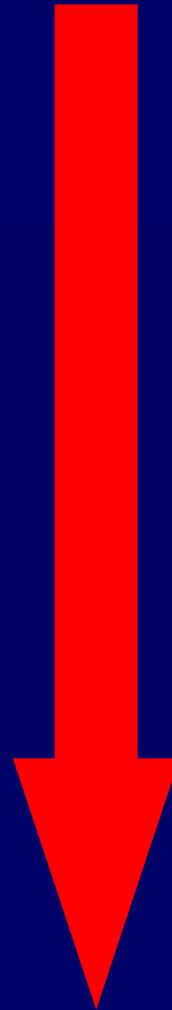


Dihydrocortisol

Dihydrocortisol



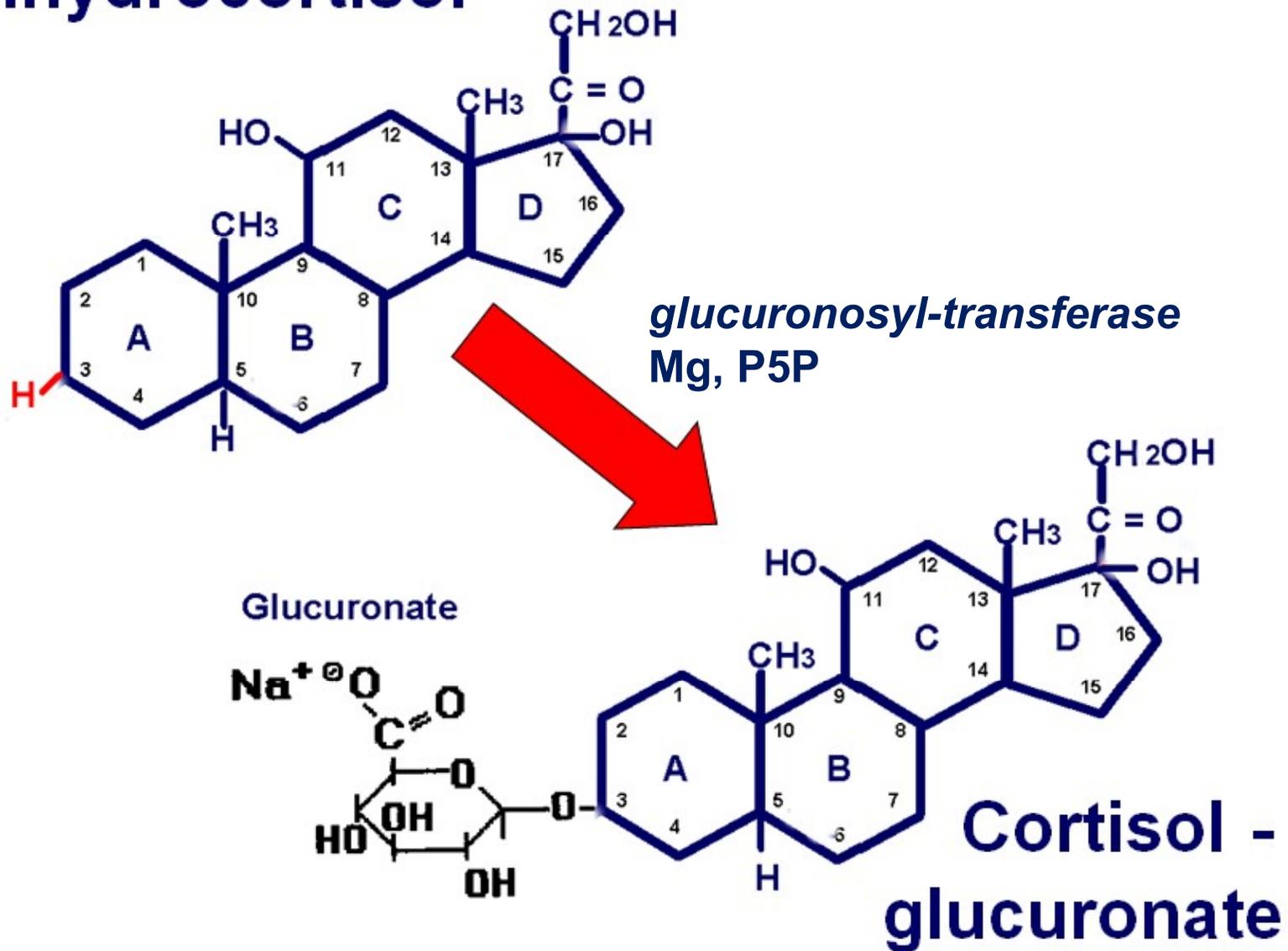
Dihydrocortisol



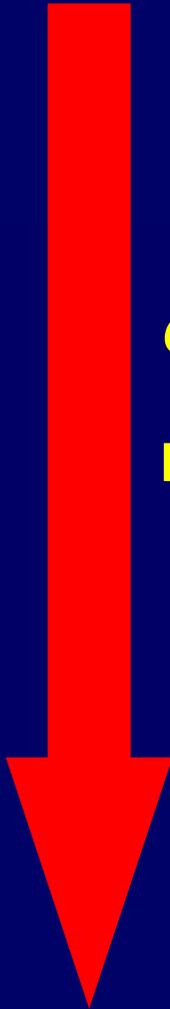
cortisol sulfotransferase
S

Cortisol - sulfate

Dihydrocortisol



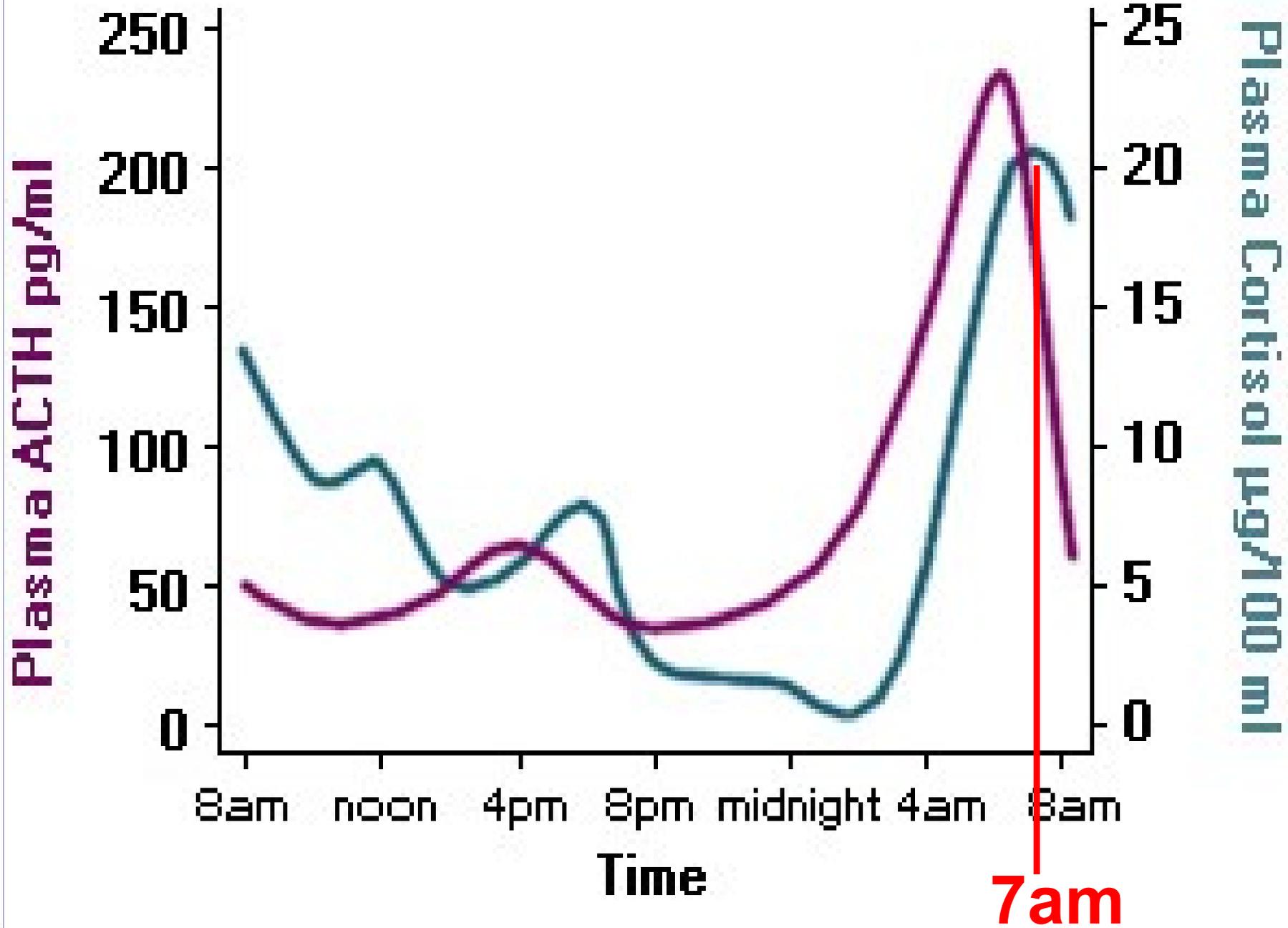
Dihydrocortisol



Glucuronosyl-transferase

Mg, P5P

Cortisol - glucuronate



Normal cortisol production follows a **diurnal cycle**. Levels peak in the early morning hours (6 am–8 am) and decline throughout the day with a second, lower peak in the late afternoon (4 pm–6 pm).

Cortisol secretion from the adrenal gland is also increased in response to stress (physical or emotional) and low endogenous glucocorticoid levels.

Guyton and Hall (2011). *Textbook of Medical Physiology*. 13th Edition U.S.: Saunders Elsevier. p. 976

The effect of thyroid hormone on cortisol metabolism.

- 1. Hypothyroid patients have slower metabolism and need less cortisol.**
- 2. Hypothyroid patients metabolize cortisol more slowly.**
- 3. Hence, hypoadrenal, hypothyroid patients are made worse by giving thyroid hormone without planning for adrenal insufficiency!**

Glucocorticoids cause protein and fat breakdown. They promote gluconeogenesis in the liver, which leads to increased blood glucose levels.

Glucocorticoids cause a decrease in circulating lymphocytes (including T cells), eosinophils, basophils, monocytes, and macrophages.

This may be due to redistribution of these cells out of the blood and into other body compartments.

Glucocorticoids conversely cause an increase in the numbers of circulating neutrophils, hemoglobin, and erythrocytes.

The anti-inflammatory effects of glucocorticoids are related to decreased production of prostaglandins and leukotrienes.

Phosphatidyl serine reduces cortisol levels.

Cortisol can inhibit growth-hormone levels by stimulating the release of somatostatin (a growth-hormone antagonist). It may also reduce IGF-1 expression (IGF-1 is one of the most anabolic agents in the body and is the substance that is responsible for most of growth hormone's positive effects because GH converts into IGF-1 in the liver).

Cortisol has other hormone-modifying effects. Cortisol can directly inhibit pituitary gonadotropin and TSH (thyroid stimulating hormone). By doing so, it can make the target tissues of sex steroids and growth factors resistant to these substances. It may also suppress an enzyme known as **5' deiodinase**, which converts the relatively inactive thyroid hormone T4 to the active T3.

Since the most serious aspect of the diarrheas is wasting potassium, cortisol has acquired the attribute of conserving potassium by moving it into the cells when cortisol declines. **Cortisol** (but not corticosterone) is reduced during a potassium deficiency, and this reduction accounts for many of the symptoms of RA.

Cortisol shuts down most of the copper enzymes when it declines so that excretion of copper is increased and *lysyl oxidase* inhibited.

These last two attributes are proposed to account for most of the mortality from aneurysms and infections during **rheumatoid arthritis**.

Cortisol

- 1. Regulates gluconeogenesis.**
- 2. Decreases glucose utilization by cells**
- 3. Suppresses host defence mechanisms.**
- 4. Suppresses the response to stress.**

The Sex Hormones

Sex hormone muscles

Gluteus maximus

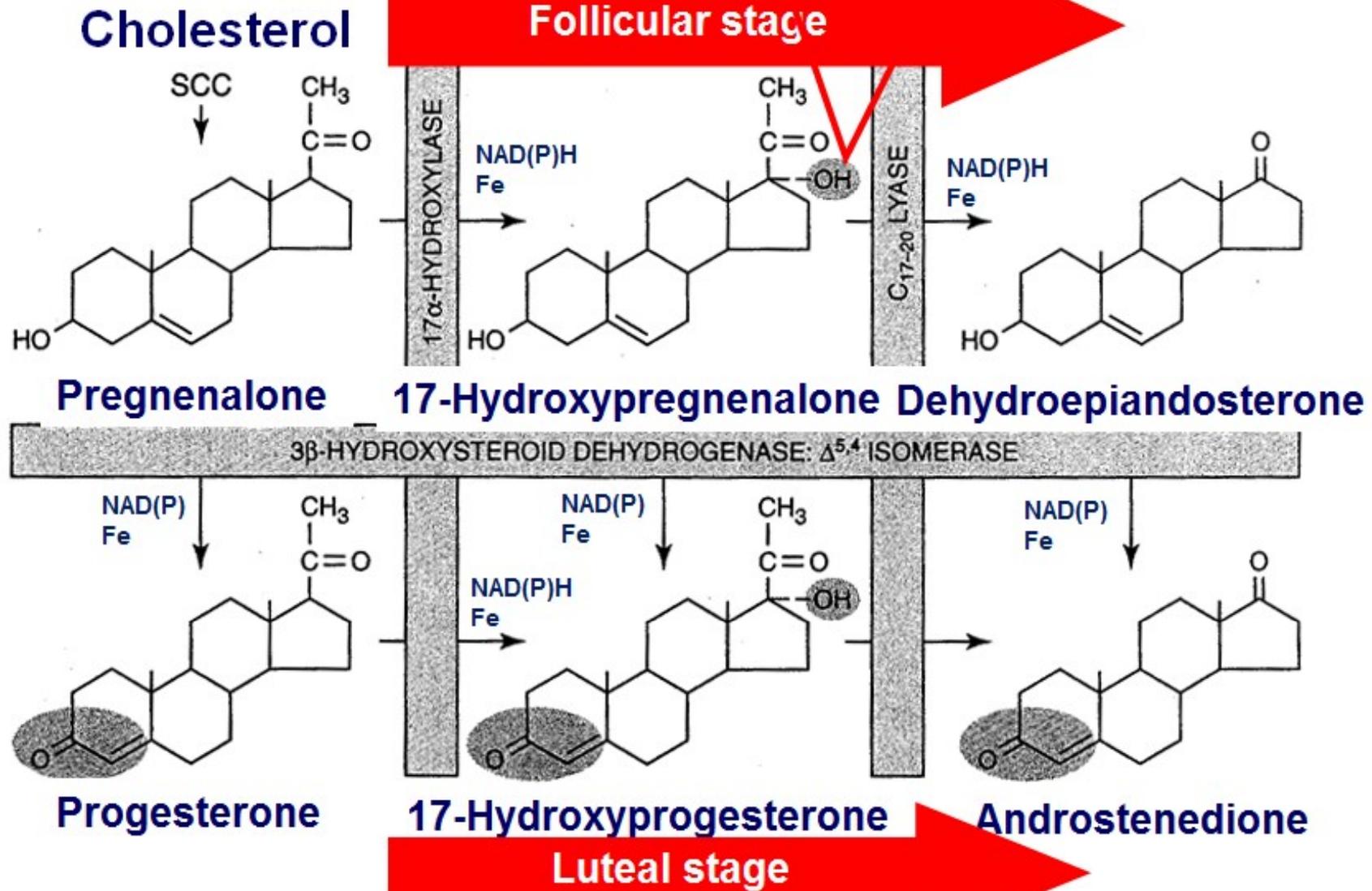
Gluteus medius and minimus

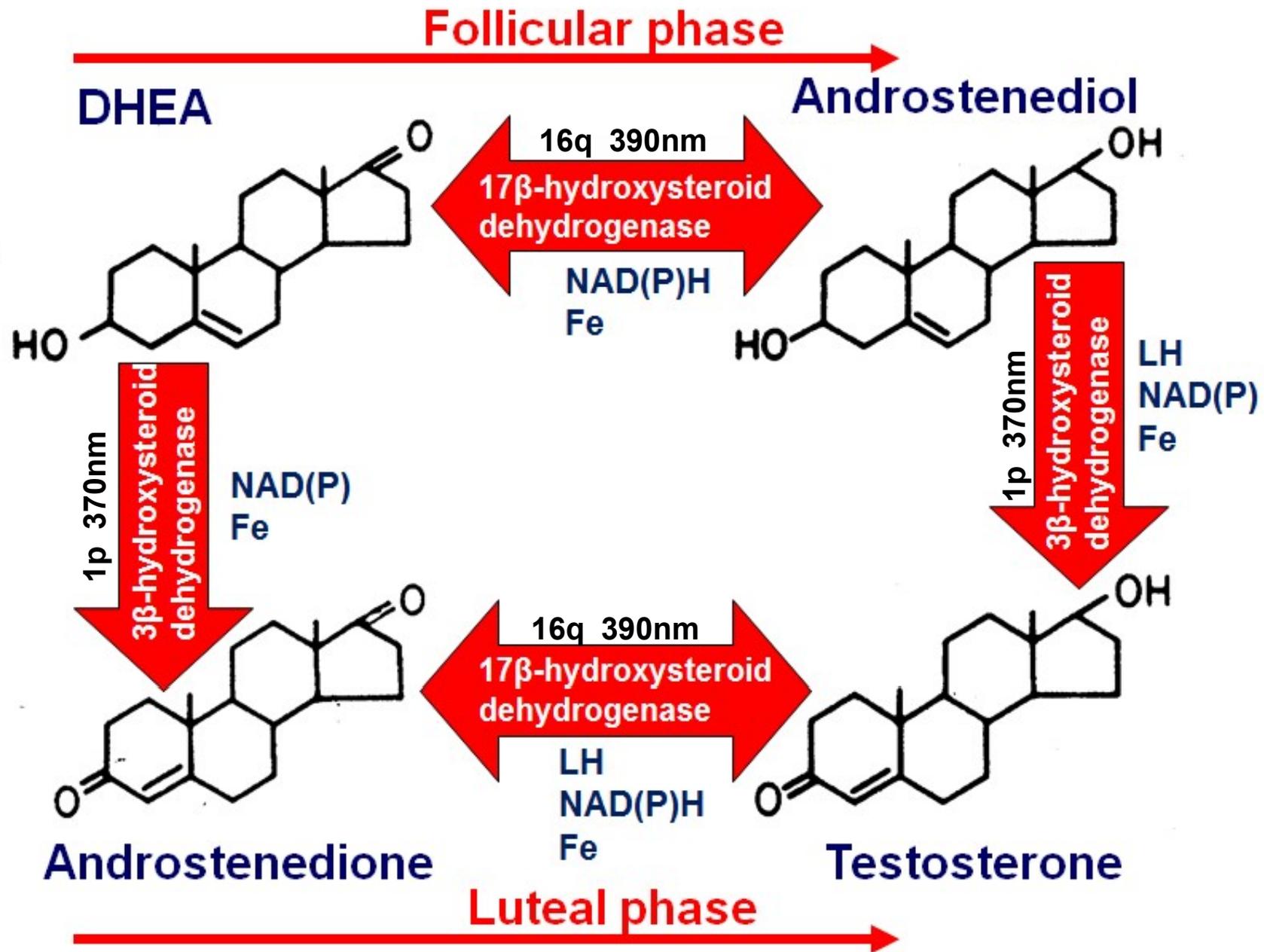
Piriformis

Adductors

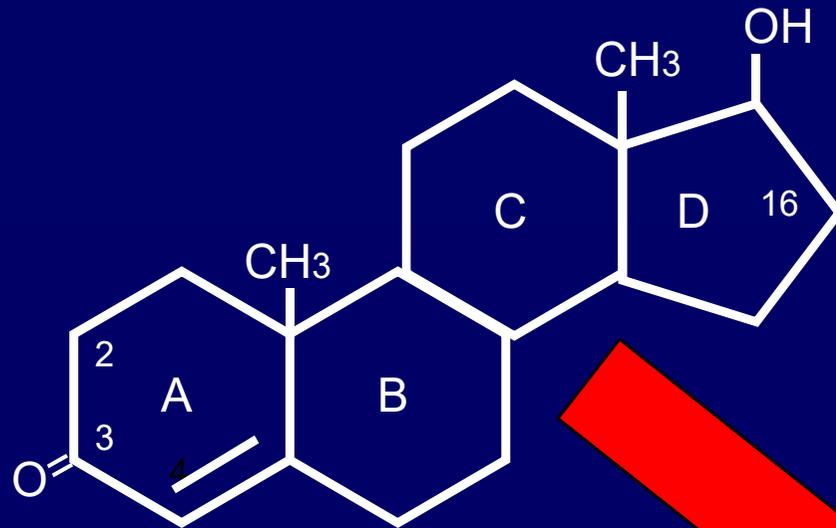
The Androgens

This OH group gives the glucocorticoid properties



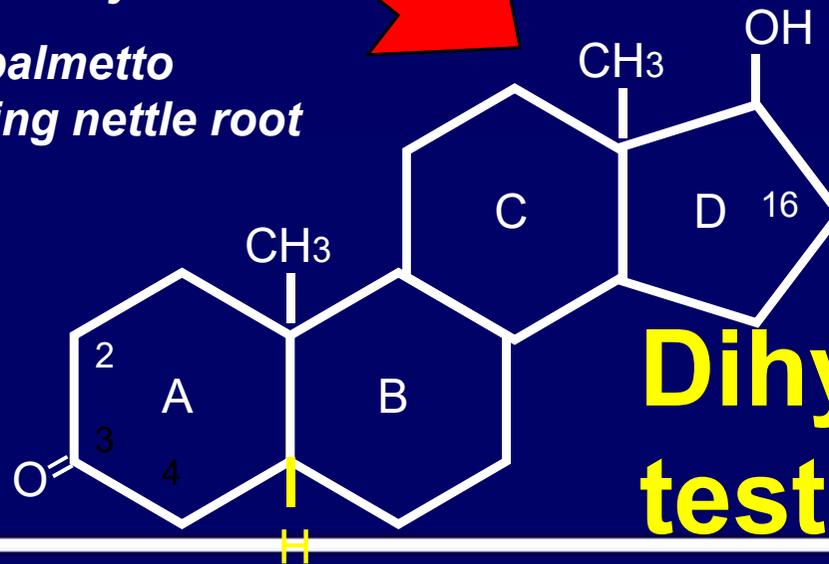


Testosterone



5 α -reductase 5q 377nm
NADPH 2p 372nm
Fe

Inhibited by
Saw palmetto
Stinging nettle root



**Dihydro-
testosterone**

DHEA

**Dehydro-
epiandrosterone
is the most
abundant
androgen in the
body.**

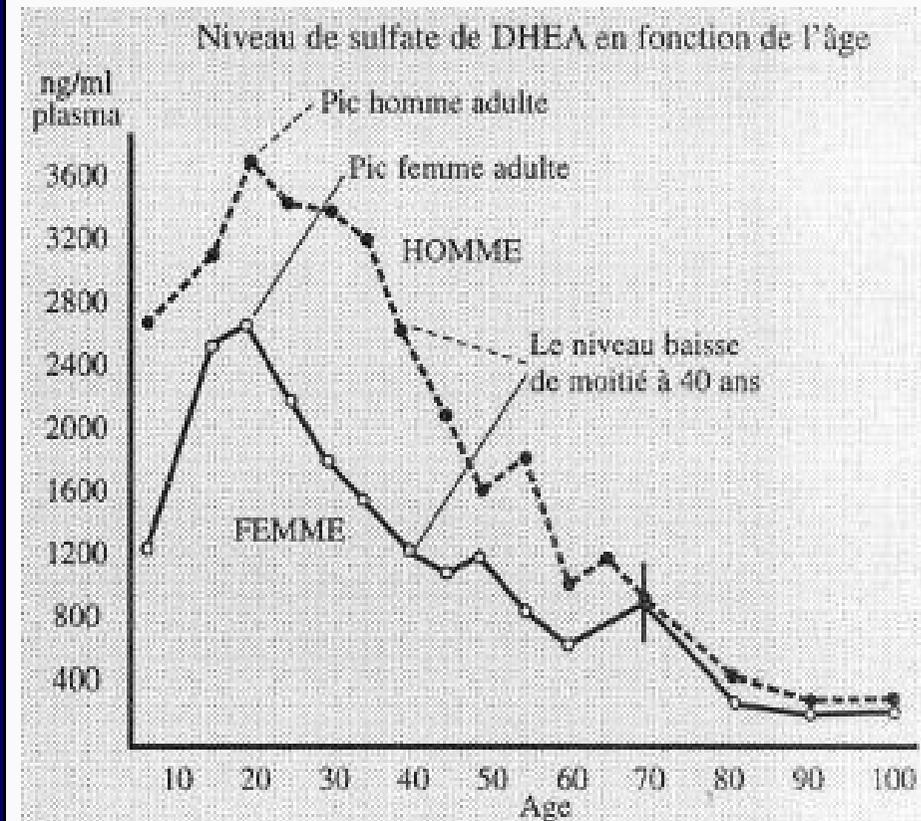
William F Ganong MD, 'Review of Medical
Physiology', 22nd Ed, McGraw Hill, 2005, p.
362.



**Females have
90% of the
levels of males.**

It peaks by **age 20** years and declines with age and chronic stress.

Prough RA, Clark BJ, Klinge CM (April 2016). "Novel mechanisms for DHEA action". *Journal of Molecular Endocrinology*. 56 (3): R139–55



DHEA stimulates sexual function.

Increases gonadal growth.

Maintains wakefulness.

Lifts depression.

Stimulates the thymus to mature and differentiate T, B and NK cells.

It is a powerful antioxidant.

Lowers cholesterol.

Salhan S (1 August 2011). Textbook of Gynecology. JP Medical Ltd. pp. 94–

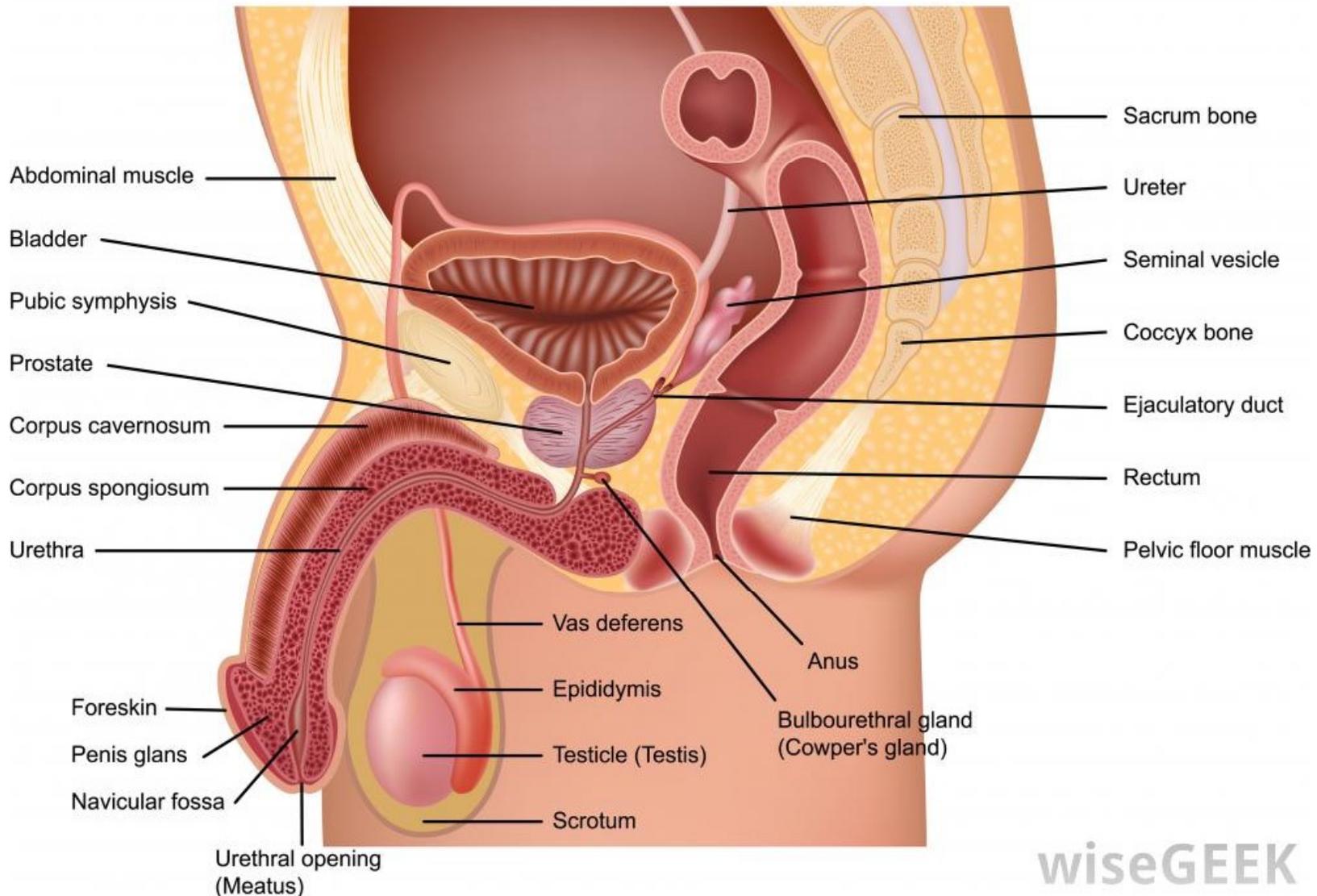
TESTOSTERONE

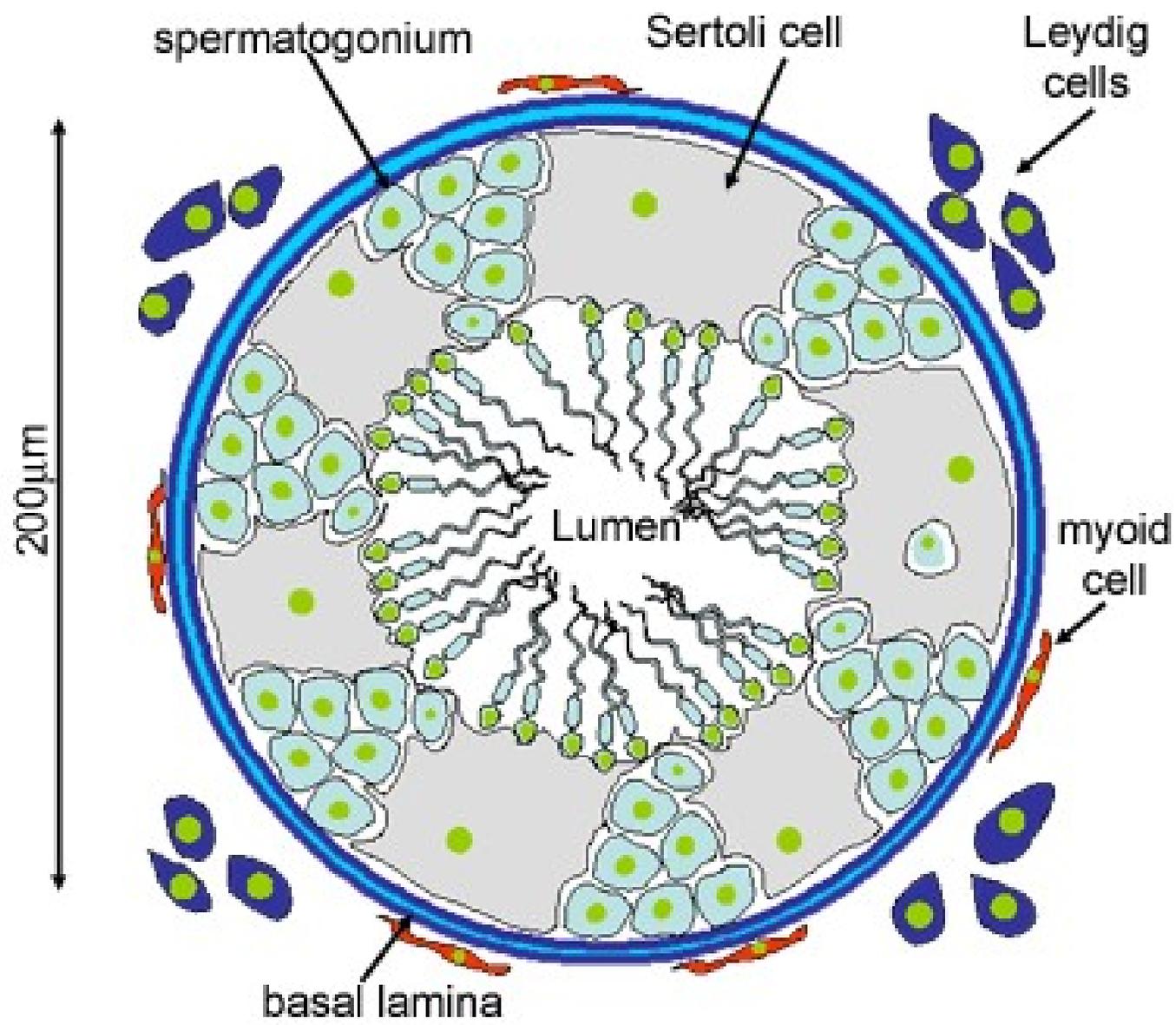
Is produced in response to LH in the Leydig cells.

(Both LH and FSH are necessary for spermatogenesis which occurs first in the seminiferous tubules and later in the Sertoli cells.)

Swerdloff RS, Wang C, Bhasin S (Apr 1992). "Developments in the control of testicular function". *Baillière's Clinical Endocrinology and Metabolism*. 6 (2): 451–83

Male Reproductive System





Testosterone
targets the
Wolffian
structures (vas
deferens),
spermatogonia,
muscles, bones,
kidney and brain.

Sheffield-Moore M (2000). "Androgens and the control of skeletal muscle protein synthesis". *Annals of Medicine*. 32 (3): 181–6.



**DIHYDRO-
TESTOSTERONE
(DHT)** is the active
form that targets the
seminal vesicles,
prostate, external
genitalia, skin and
hair.

Marks LS (2004). "5 α -reductase: history and clinical importance". *Rev Urol.* 6 Suppl 9: S11–21



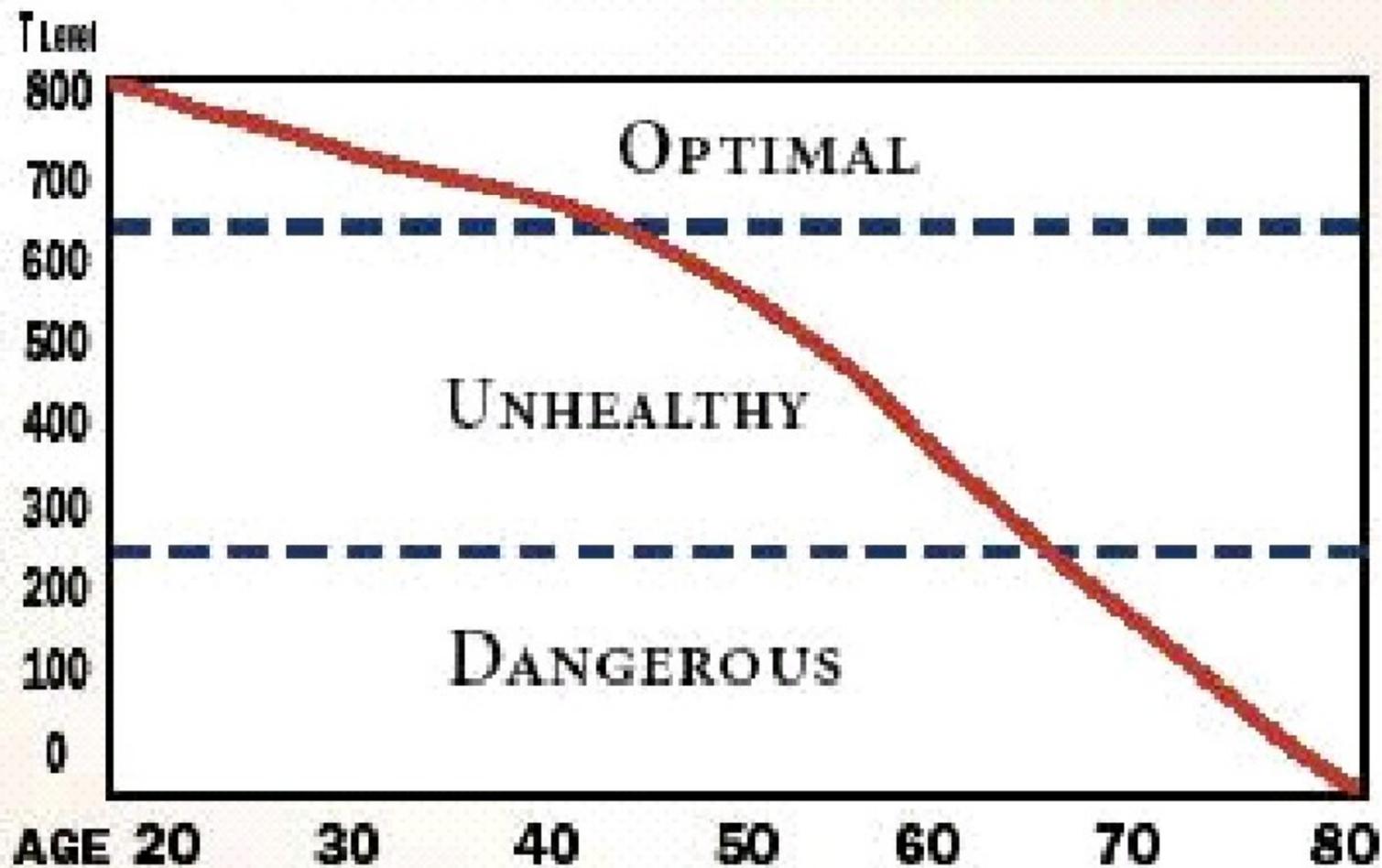
Testosterone and DHT function to

1. Sexual differentiation.
2. Spermatogenesis.
3. Secondary sexual characteristics.
4. Anabolic metabolism.
5. Gene regulation.
6. Male behaviour patterns.

Testosterone	DHT
Spermatogenesis and fertility	Prostate enlargement and prostate cancer risk
Male musculoskeletal development	Facial, axillary, pubic, and body hair growth
Voice deepening	Scalp temporal recession and pattern hair loss
Increased sebum production and acne	
Increased sex drive and erections	

Chang C (31 October 2002). *Androgens and Androgen Receptor: Mechanisms, Functions, and Clinical Applications*. Springer Science & Business Media. pp. 451–.

Blood-Testosterone Level vs. Age



Typical Testosterone Declination for U.S. Males

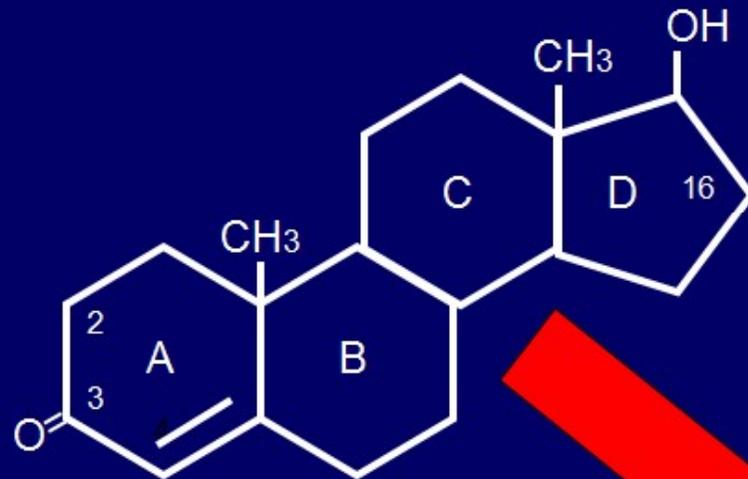
Sperm count fall

Sperm counts have dropped by almost a third in a decade, a study of 7,500 men at the Aberdeen Fertility Centre from 1989 to 2002 showed. Siladitya Bhattacharya, the lead researcher, said they could not conclude that male fertility had fallen, because factors other than sperm count played a part.

**The
Times
5/1/04**

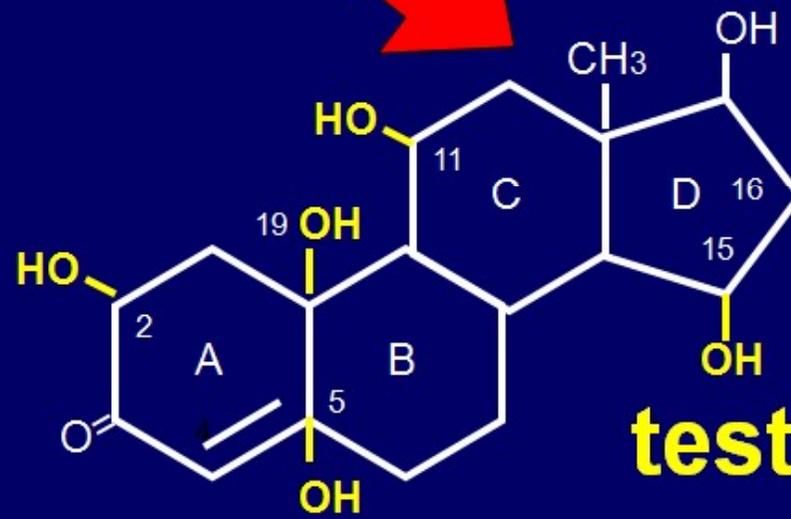
Metabolism of Testosterone

Testosterone



P450 3A4
NADPH
Fe

7 380nm



2, 5, 11, 15, 19

**Hydroxy-
testosterone**

Approximately 50% of testosterone is **metabolized** in the liver via conjugation into testosterone glucuronide and to a lesser extent testosterone sulfate by glucuronosyltransferases and sulfotransferases, respectively.*

*Melmed S, Polonsky KS, Larsen PR, Kronenberg HM (30 November 2015). *Williams Textbook of Endocrinology*. Elsevier Health Sciences. pp. 711–

Prostate-specific antigen (PSA)

is a glycoprotein enzyme encoded in humans by the *KLK3* gene (19q31.3). PSA is secreted by the epithelial cells of the prostate gland. PSA is produced for the ejaculate, where it liquefies semen in the seminal coagulum and allows sperm to swim freely.*

*Balk SP, Ko YJ, Bubley GJ (Jan 2003). "Biology of prostate-specific antigen". *Journal of Clinical Oncology*. 21 (2): 383–91.

It is also believed to be instrumental in dissolving cervical mucus, allowing the entry of sperm into the uterus.*

***Hellstrom WJG, ed. (1999). "Chapter 8: What is the prostate and what is its function?". *American Society of Andrology Handbook*. San Francisco: American Society of Andrology.**

Prostate-specific antigen test (PSA test.) The PSA test analyzes a blood sample drawn. It checks the sample for PSA, a substance the prostate gland naturally produces to help liquefy semen. A small amount of PSA naturally enters the bloodstream. If higher-than-normal levels of PSA occur (above a reading of 4), it may indicate prostate infection, inflammation (prostatitis), enlargement of the prostate gland — or cancer. Most important is the change of PSA levels.

Gomella LG, Liu XS, Trabulsi EJ, Kelly WK, Myers R, Showalter T, Dicker A, Wender R (Oct 2011). "Screening for prostate cancer: the current evidence and guidelines controversy". *The Canadian Journal of Urology*. 18 (5): 5875–83.

What Is Benign Prostatic Hyperplasia ? (B.P.H.) *

Benign Prostatic Hyperplasia, abbreviated to BPH, is when the walnut-sized prostate gland becomes enlarged, a common condition that affects more than 1 in 3 men over 40.

Once over 50 you are more likely than not to have a prostate problem, usually BPH.

Within the prostate testosterone is converted to the more potent hormone Dihydrotestosterone (DHT). It is this compound DHT along with estrogens that stimulates prostate cells to multiply, eventually causing the gland to enlarge.

The enlarged prostate presses on the bladder and also restricts the urethra, the tube carrying urine from the bladder. This leads to:

- Frequent urge to urinate (especially during the night),**
- Difficulty starting urination,**
- Weak urination,**
- Difficulty emptying the bladder completely,**
- Dribbling after the end of urination.**

***"Prostate Enlargement (Benign Prostatic Hyperplasia)". *NIDDK*. September 2014. Archived from the original on 4 October 2017. Retrieved 19 October 2017.**

Nutrients to stimulate testosterone:

Zinc

Iron

Magnesium

Selenium

Ornithine

Phosphatidyl serine

Resistance exercises

B-Complex

α -Lipoic acid

Vitamin C

Vitamin D

Vitamin E

Vitamin A deficiency may lead to sub-optimal plasma testosterone levels.* **Vitamin D** in levels of 400–1000 IU/d (10–25 µg/d) raises testosterone levels. **Zinc** deficiency lowers testosterone levels but over-supplementation has no effect on serum testosterone.**

*Livera G, Rouiller-Fabre V, Pairault C, Levacher C, Habert R (Aug 2002). "Regulation and perturbation of testicular functions by vitamin A". *Reproduction*. 124 (2): 173–80

**Prasad AS, Mantzoros CS, Beck FW, Hess JW, Brewer GJ (May 1996). "Zinc status and serum testosterone levels of healthy adults". *Nutrition*. 12 (5): 344–48

Phytoceuticals factors to stimulate testosterone:

**Black walnut (Juglans nigra),
Cardamon pod and seed (Elettaria
cardamomum), Ginger (Zingiber
officiale), Ginseng (Elutherococcus),
Nettle leaf, Oat seed (avens sativa),
Sarsaparilla (Smilax officialis), Saw
Palmetto (Serenoa repens), Yarrow
(Achillea millefoliu).**

**Natural products in the treatment
of male hormone imbalance.**

Saw Palmetto

Saw Palmetto is a type of (dwarf) Palm normally regarded and used as an Herb.

Botanical Names

Serenoa repens

Serenoa serrulata

Saw Palmetto inhibits the conversion of Testosterone to DHT in the prostate by inhibition of the **5-alpha reductase** enzyme and blocks the attachment of DHT to cellular binding sites by inhibition of the enzyme **3-ketosteroid**, thus increasing the breakdown and excretion of DHT.

Eric Pierotti Natural products in the treatment of male hormone imbalance 2006??

Part of the beneficial effect of **Saw Palmetto** in the treatment of enlarged prostate relates to its ability to relax the smooth muscle at the bladder outlet (thereby preventing the urinary urgency and frequent urination that occurs in enlarged prostate patients).

Eric Pierotti Natural products in the treatment of male hormone imbalance 2006??

Saw Palmetto reduces the activity of **Epidermal Growth Factor (EGF)** in the prostate by up to 66% (excessive prostate EGF activity has been implicated in enlarged prostate).

Saw Palmetto also acts directly on the prostate in cases of enlarged prostate to reduce the pain and inflammation associated with enlarged prostate (due to various lipids in Saw Palmetto).

Stinging Nettle Root

Urtica dioica (Common perennial Nettle; Stinging Nettle)

Urticaria urens (Annual Nettle; Dog Nettle; Small Nettle)

Nettle (root) is an effective adjunct to Saw Palmetto for the treatment of Enlarged Prostate.

In one human study, a daily dosage of 240 mg of **Nettle root** combined with 320 mg of **Saw palmetto** (for 12 weeks) caused a 26% increase in -

maximum urinary flow, a 29% increase in **mean urinary flow**, a 45% reduction in residual urine, a 50% reduction in **Nocturia**, a 62% reduction in **Dysuria** and a 53% decrease in **post-void dribbling** in Enlarged Prostate patients.

Inhibits the ***aromatase and 5-alpha reductase*** enzymes.

Inhibits the **transformation of the benign cells** involved in Enlarged Prostate to the malignant Cells involved in Prostate Cancer.

Inhibits the binding of DHT to Prostate cells thereby preventing DHT from stimulating the proliferation of Prostate cells that leads to Enlarged Prostate.

Contraindicated in hypertension as it can further raise blood pressure in some patients.

Inhibits the binding of
Testosterone to Sex Hormone
Binding Globulin (SHBG),
resulting in lower levels of
“bound” Testosterone and **higher
levels of “free” Testosterone**, this
effect occurs as a result of Nettle
binding to SHBG in place of
Testosterone.

Eric Pierotti Natural products in the treatment of male hormone imbalance 2006??

Chrysin

Is a type of Isoflavonoid, found in Propolis, Chinese Skull cap and Passion flower.

Studies have shown it increases (male) Sexual Desire (libido).

Inhibits the conversion of androstenedione to estrone by inhibiting *aromatase*.

Inhibits the conversion of testosterone to estradiol by inhibiting the aromatase enzyme.

In one study, 3,000 mg of **Chrysin per day caused an increase in Testosterone levels of at least 20% in males.**

Eric Pierotti Natural products in the treatment of male hormone imbalance 2006??

Alleviates Gout by inhibiting the *xanthine oxidase* (2p 372nm) which subsequently causes a reduction in Uric Acid production.

Chrysin may stimulate muscle growth by inhibiting the conversion of testosterone to estradiol.

In animal studies **Chrysin** caused significant increases in muscle mass (up to 20%).

In chronically ill humans **Chrysin** caused gains in lean body mass of 1.5 - 3 kg in after several weeks of therapy.

Eric Pierotti Natural products in the treatment of male hormone imbalance 2006??

The dosage of **Chrysin** required to inhibit the conversion of Testosterone to estrogens is 1,000 - 1,500 mg per day.

Unfortunately **Chrysin** is poorly absorbed orally, however;

Eric Pierotti Natural products in the treatment of male hormone imbalance 2006??

Piperine

Is an alkaloid of piper nigrum (black pepper).

Low doses of **Piperine** have been found to greatly enhance the absorption and bioavailability of most nutrients by inhibiting enzymes in the liver that normally metabolize various nutrients.

Eric Pierotti Natural products in the treatment of male hormone imbalance 2006??

Tribulus terrestris

**A type of herb also known as
Burra Gokhru; Gokshura;
Puncture Vine; Small Caltrops.**

Tribulus terrestris is speculated to enhance the conversion of Androstenedione to Testosterone.

It is speculated that this conversion occurs under the influence of LH which Tribulus terrestris is claimed to increase production of.

Eric Pierotti Natural products in the treatment of male hormone imbalance 2006??

Some studies have shown that daily intake of 750 mg of **Tribulus terrestris** results in an increase in free Testosterone levels of 30% (only in males) within five days which results in improvement of; Male impotence, infertility, low semen, sexual desire and performance.

Eric Pierotti Natural products in the treatment of male hormone imbalance 2006??

Maca

A type of Herb (a tuber) native to the high Andes plateau of Peru

Botanical Name

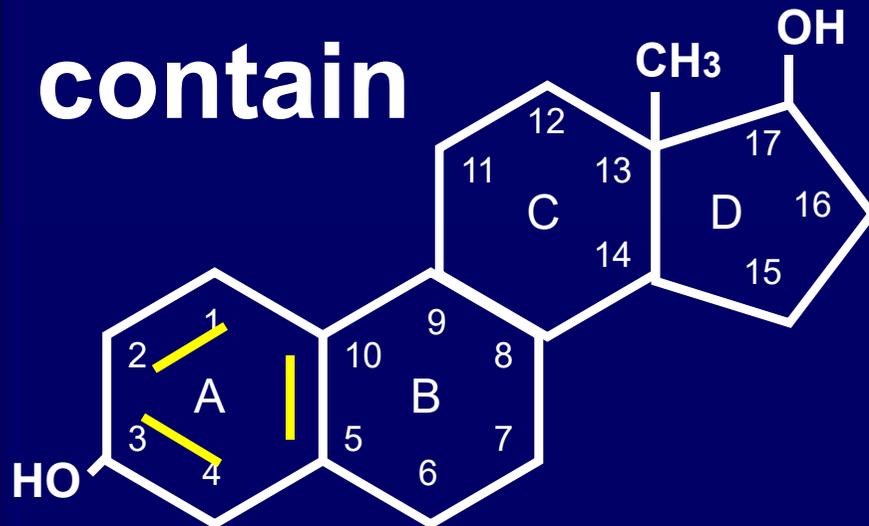
Lepidium meyenii

Lepidium peruvianum Chacon

Estrogen Synthesis

All **naturally occurring** estrogens

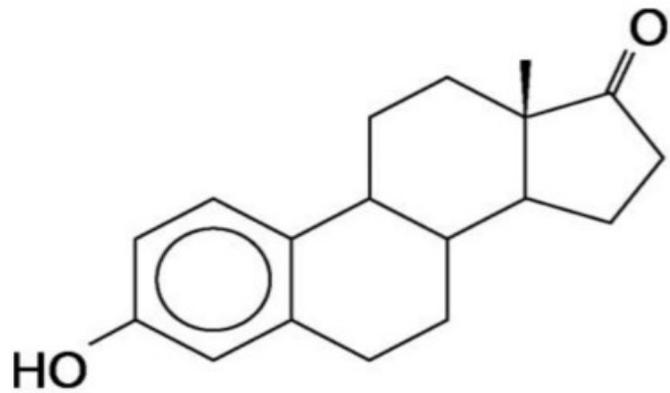
contain



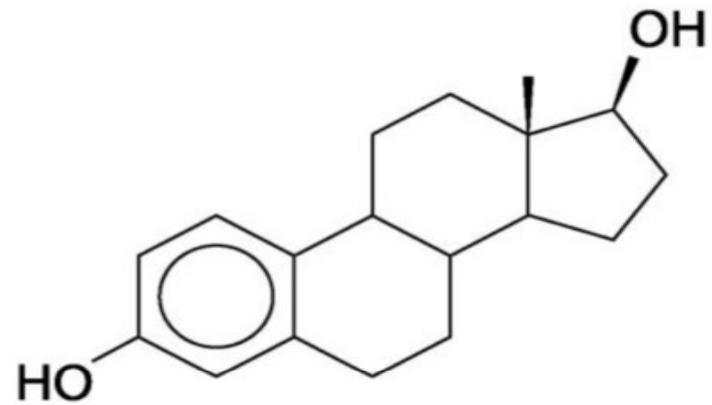
1. an unsaturated A ring

2. a phenolic hydroxyl group at C3

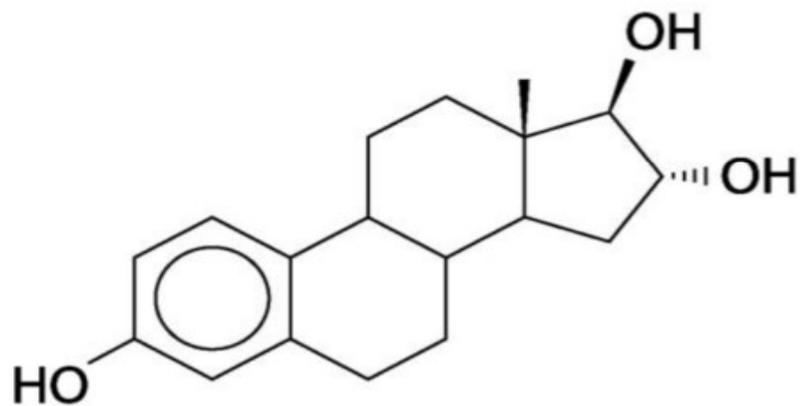
3. a methyl group at C13



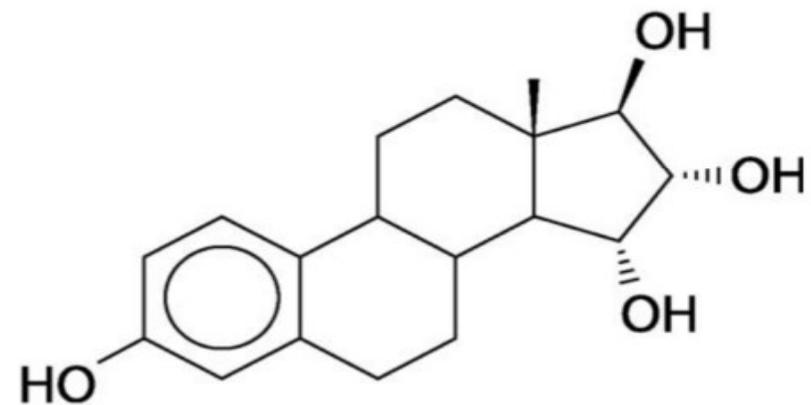
E₁ Estrone



E₂ Estradiol



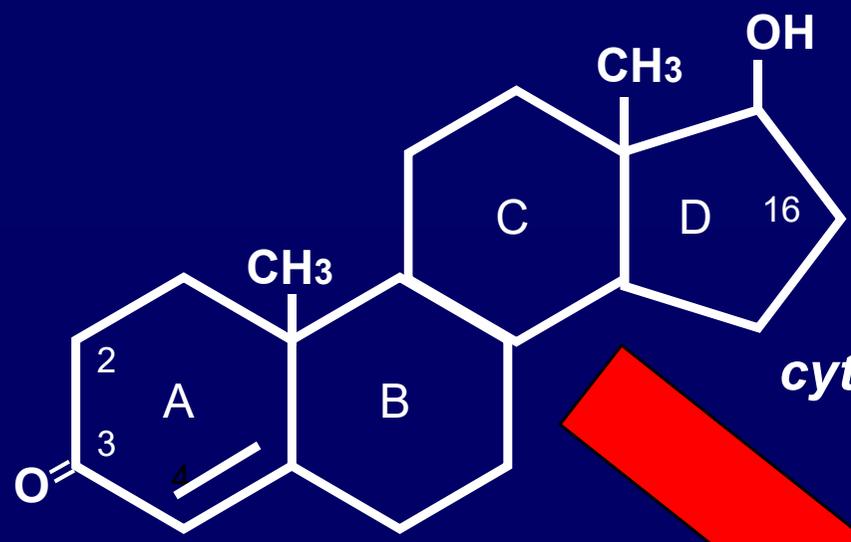
E₃ Estriol



E₄ Estetrol

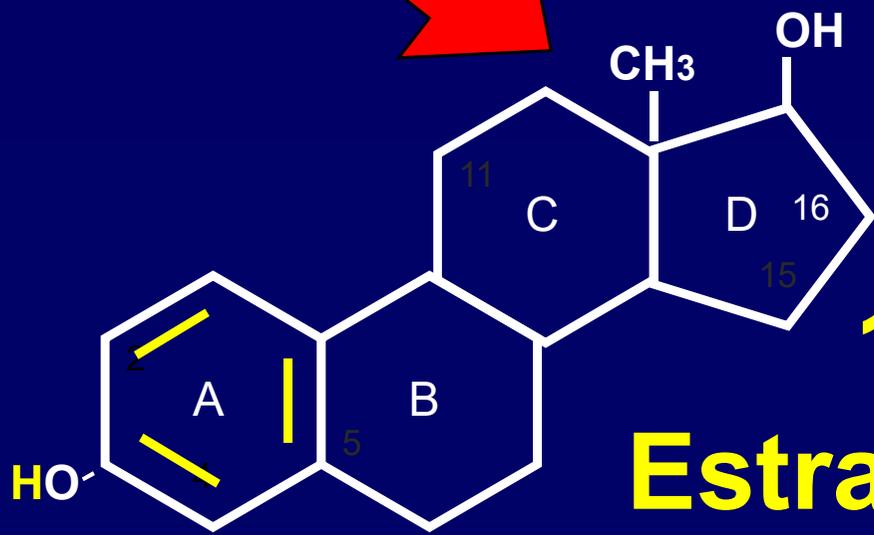
Only in pregnancy

Testosterone



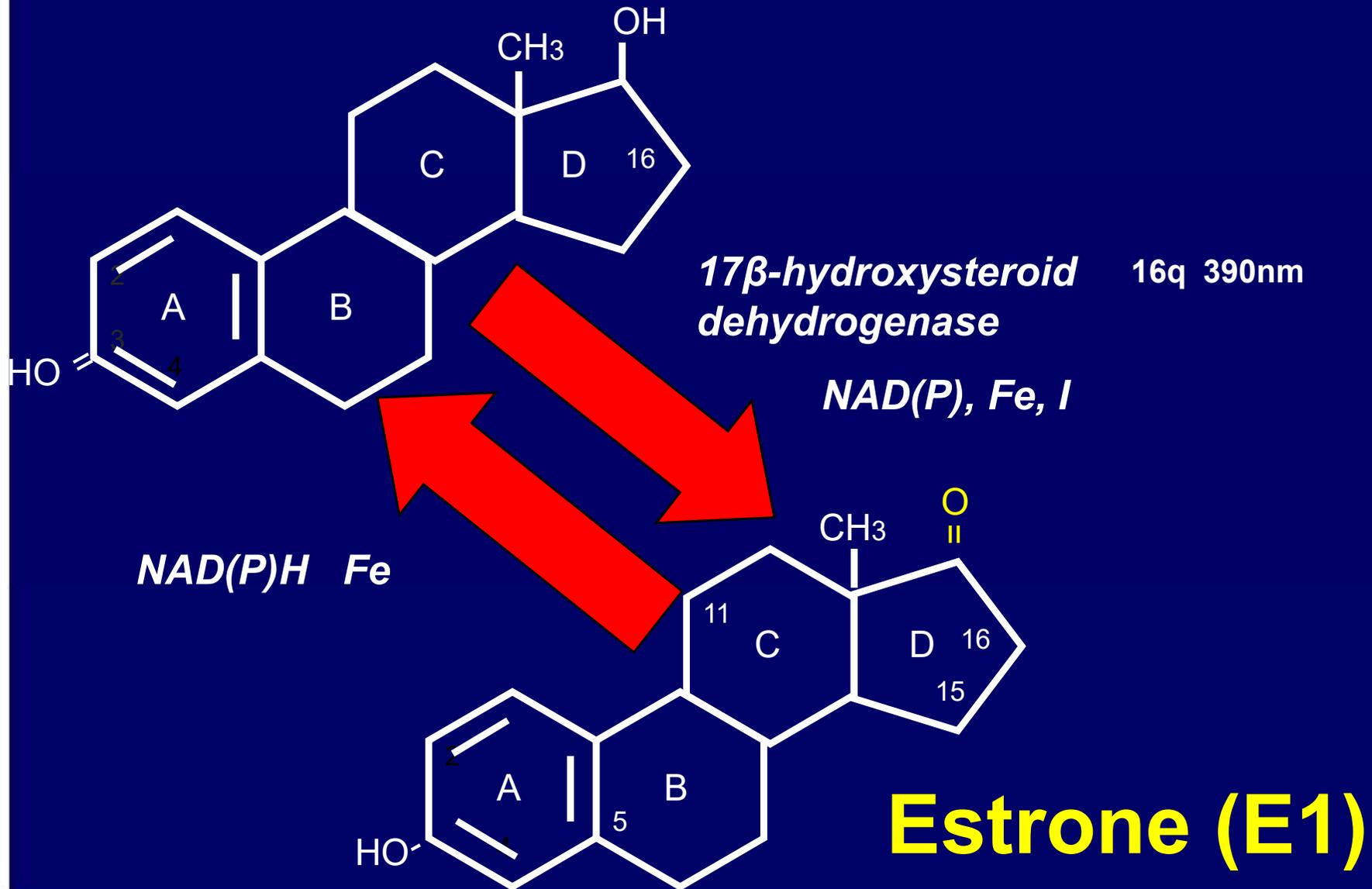
15q 388nm
cytochrome p450 (aromatase)

*FADH₂, NADPH,
Fe, O₂, Mg, B, Vit E*



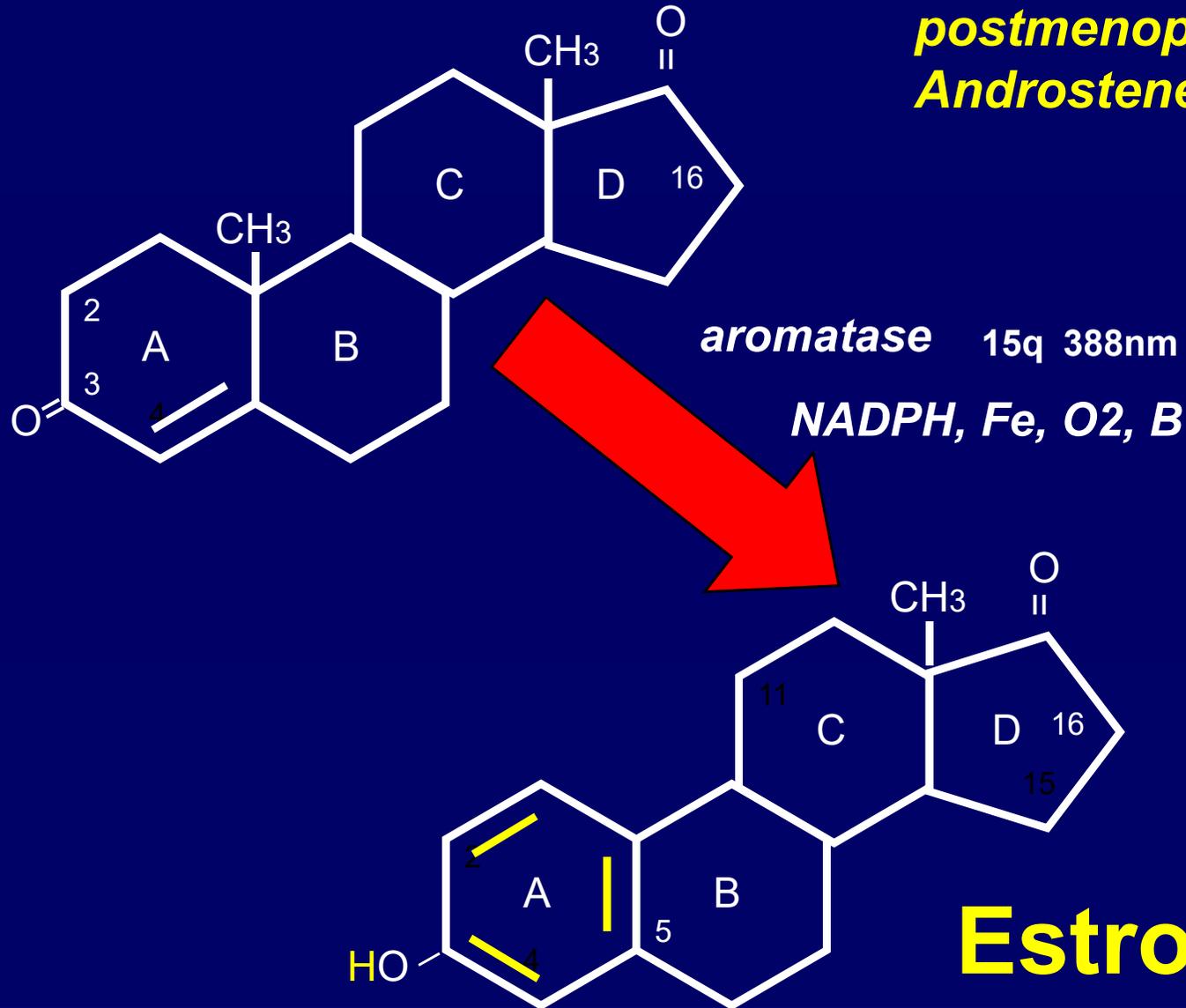
**17-β
Estradiol (E2)**

17-β Estradiol (E2)



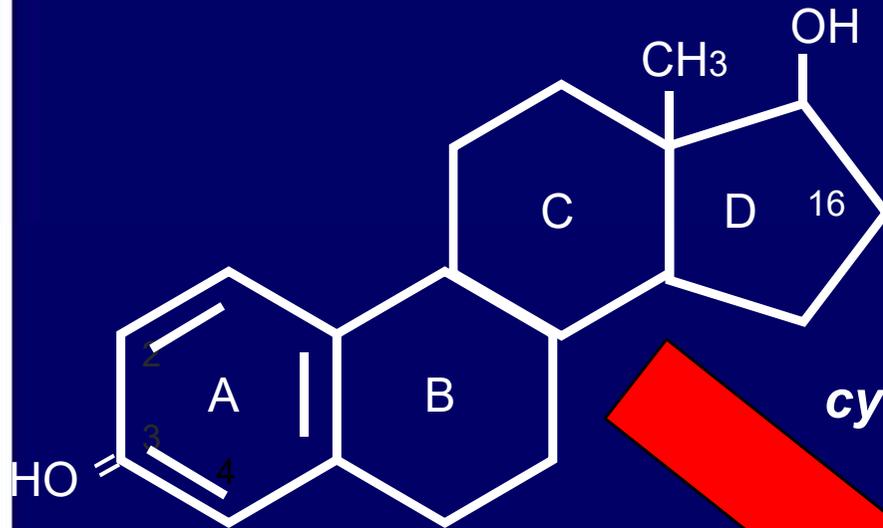
Androstenedione

An alternative route to synthesizing estrone postmenopausally is from Androstenedione



Estrone (E2)

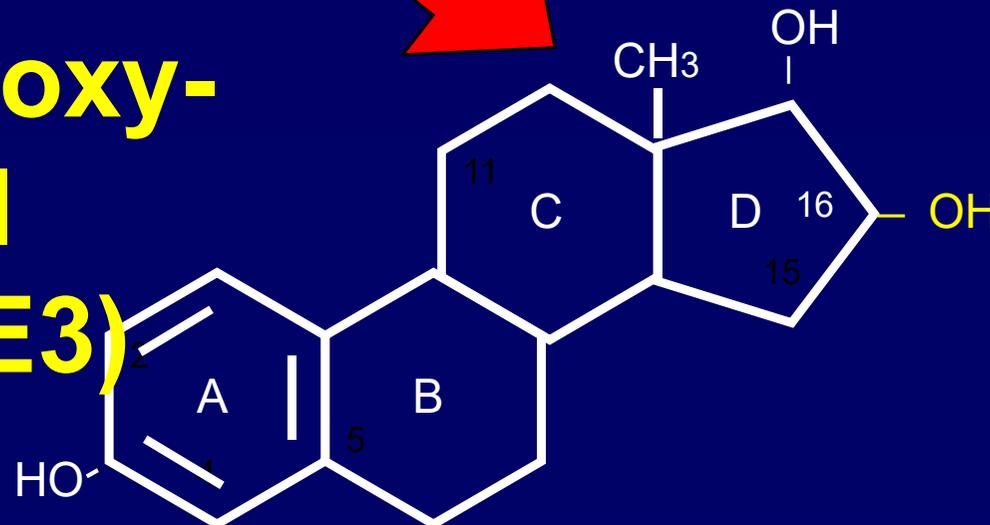
17- β Estradiol (E2)



cytochrome p450 CYP 1A2 15q 388nm

NADPH (Mg), Fe, O₂

16 α -hydroxy- estradiol (Estriol E3)



Estrogens influence the growth,
differentiation and function of
tissues of the female
reproductive system

i.e. Uterus

Ovaries

Breast

Estradiol (E2)

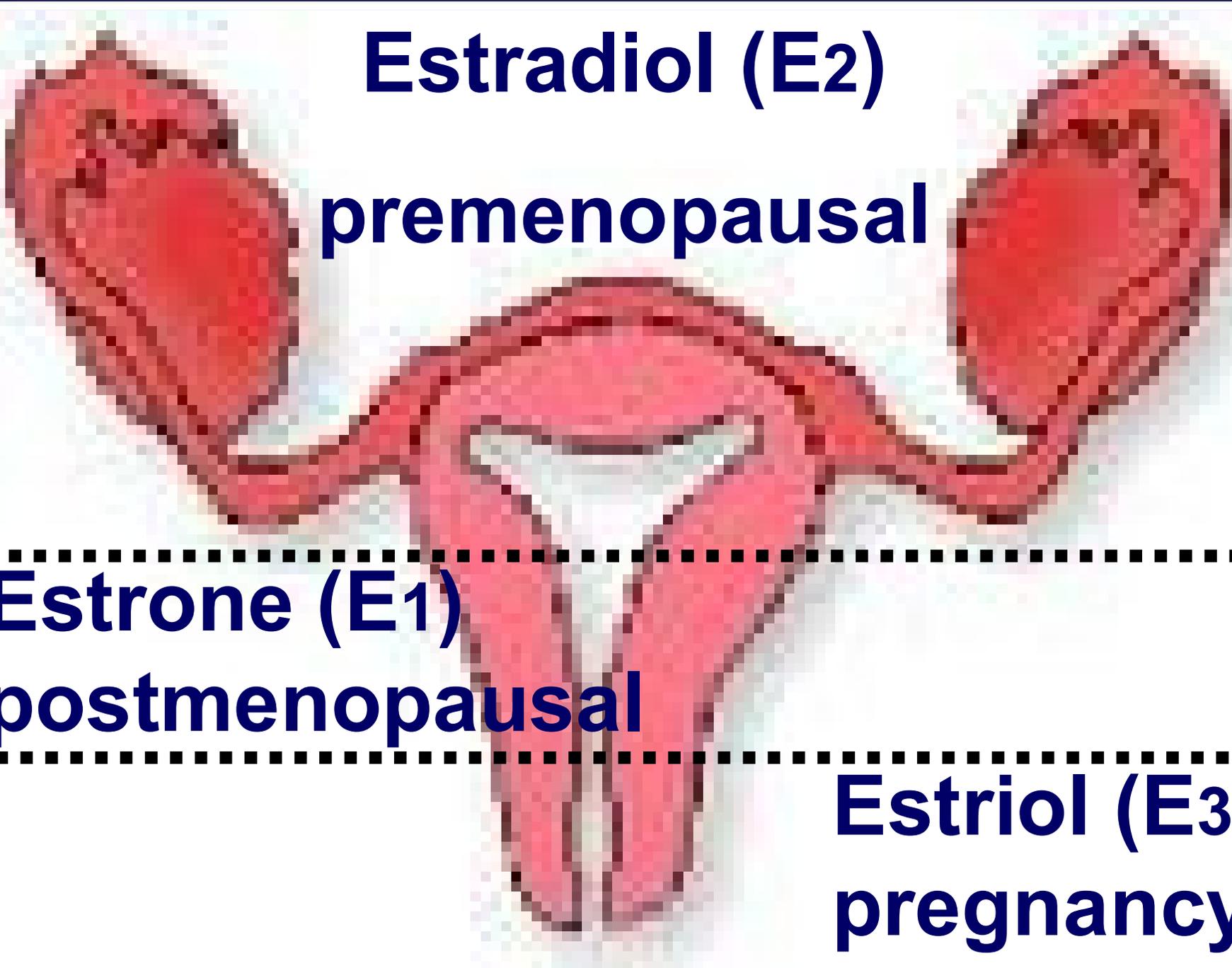
premenopausal

Estrone (E1)

postmenopausal

Estriol (E3)

pregnancy



Estradiol mainly targets the ovaries, fallopian tubes, the upper third of the uterus and the breast tissue.

Estrone mainly targets the mid portion of the uterus.

Estriol mainly targets the lower one third of the uterus and the vagina.

Estrogens stimulate the development of tissues involved with reproduction.

They stimulate the size and number of cells by increasing the rate of protein synthesis.

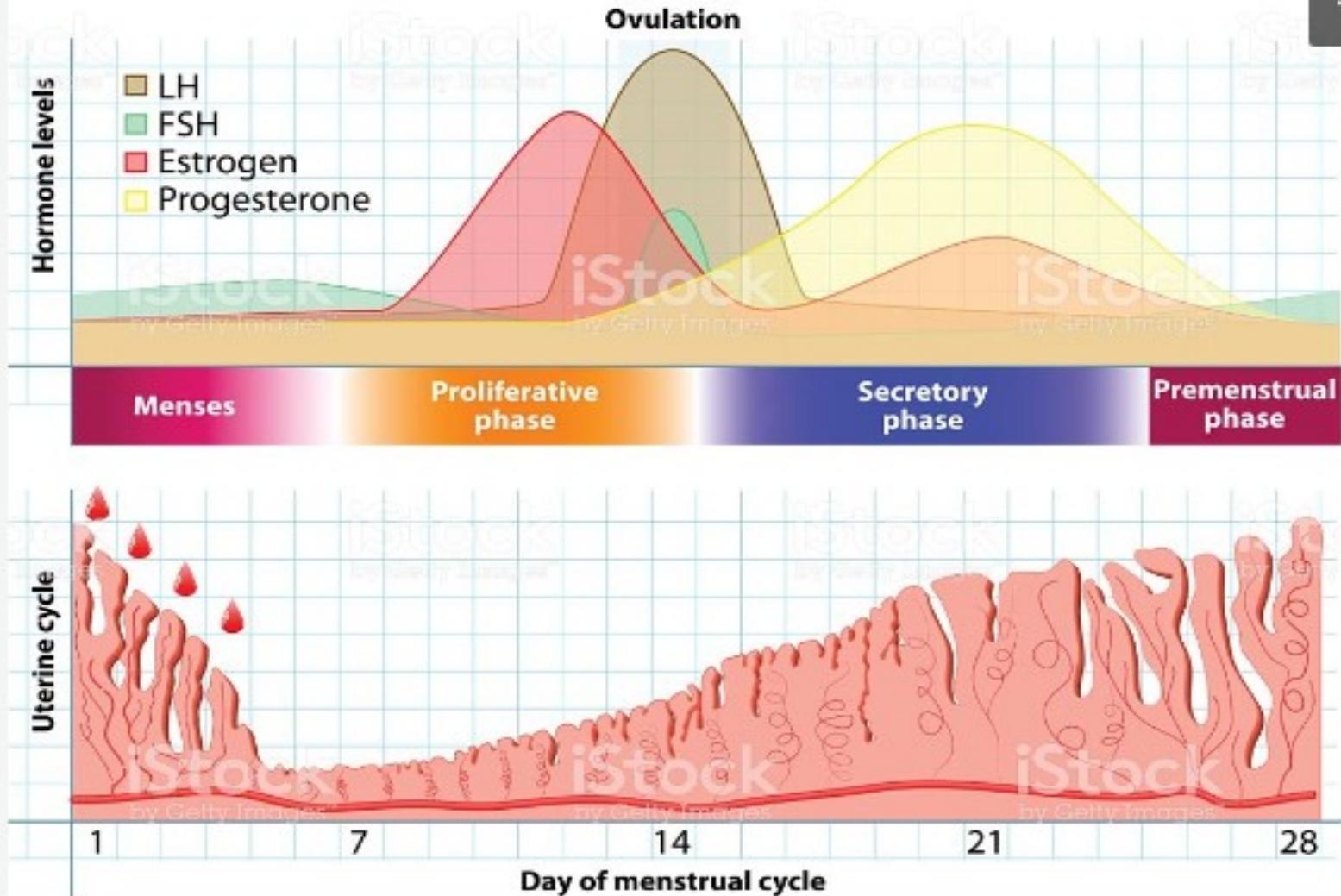
There is **proliferation** of the vaginal epithelium, the uterine endometrium and glandular hypertrophy.

The myometrium develops an intrinsic rhythmical motility and the breast ducts proliferate.

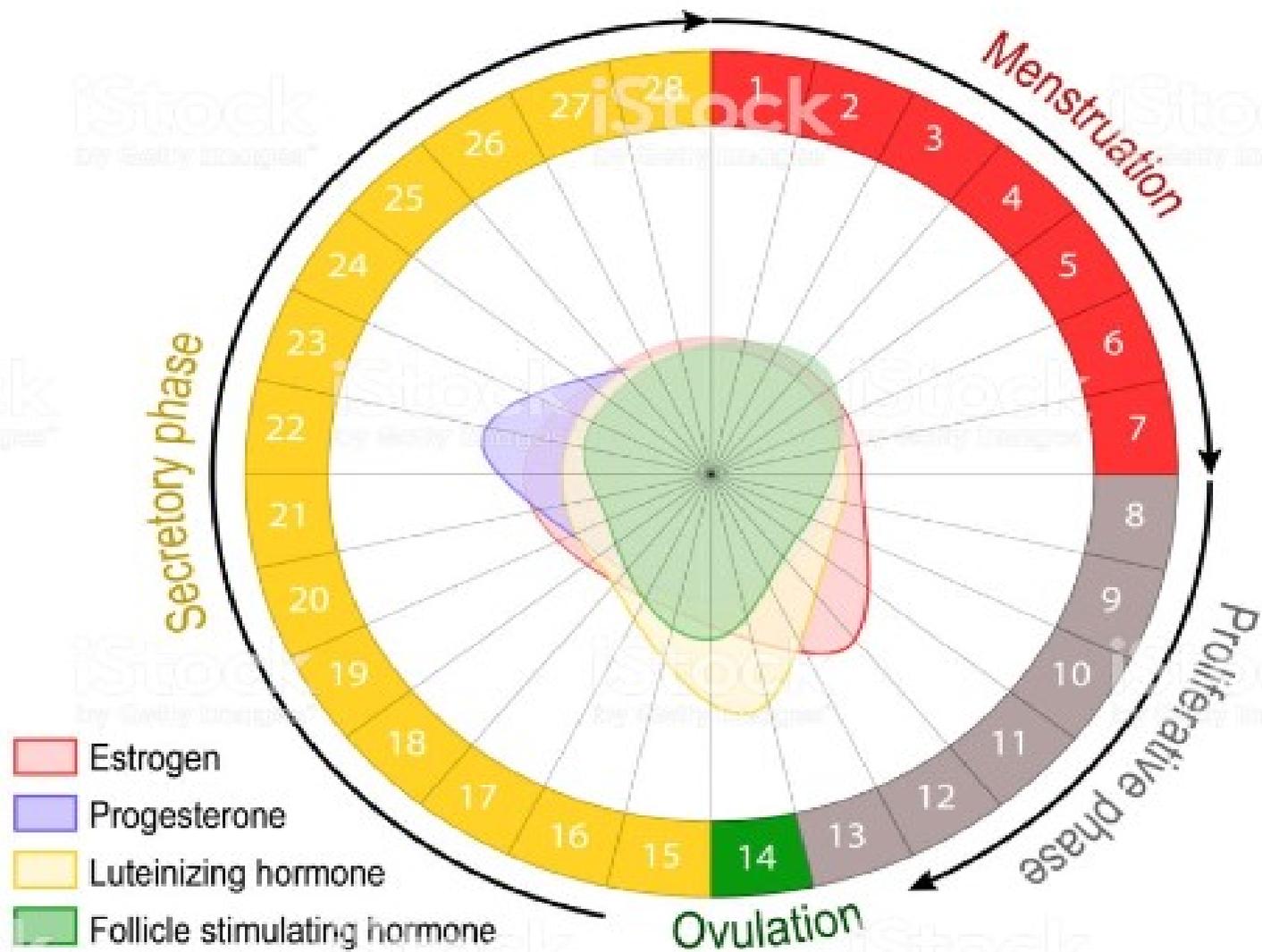
Estrogens have some **anabolic** effects on bone and cartilage but largely function by inhibiting the breakdown of bone cells.



MENSTRUAL CYCLE



Menstrual cycle



Osteoclasts reabsorb bone

Stimulated by

Vitamin A

Parathyroid hormone

1,25 OH D3

IL1 and IL6

TNF

TGF- α

Inhibited by

Calcitonin

Estrogens

TGF- β

INF α

PgE2

There are two estrogen receptors **α and β** which are expressed to varying extents in most organs including the uterus, ovaries, breast, brain, lung, liver, gastrointestinal tract, bone kidney, genitourinary tract, prostate and testes.

They are expressed to a much greater level in carcinomas.

Mechanisms of action

- 1. Bind to cell membrane ER and stimulate secondary messengers.**
- 2. Bind to nuclear ER and regulate gene expression.**
- 3. E1 and E2 are metabolized to catechol estrogens which maybe carcinogenic.**

How your diet could influence the age of your menopause

1/5/2018

The research was published in **the Journal of Epidemiology & Community Health** and the women were asked what their typical diet contained.

A diet high in legumes, which includes peas, beans, lentils and chickpeas, delayed menopause by one-and-a-half years, on average.

Eating lots of refined carbs, particularly rice and pasta, was linked to menopause coming earlier by one-and-a-half years.



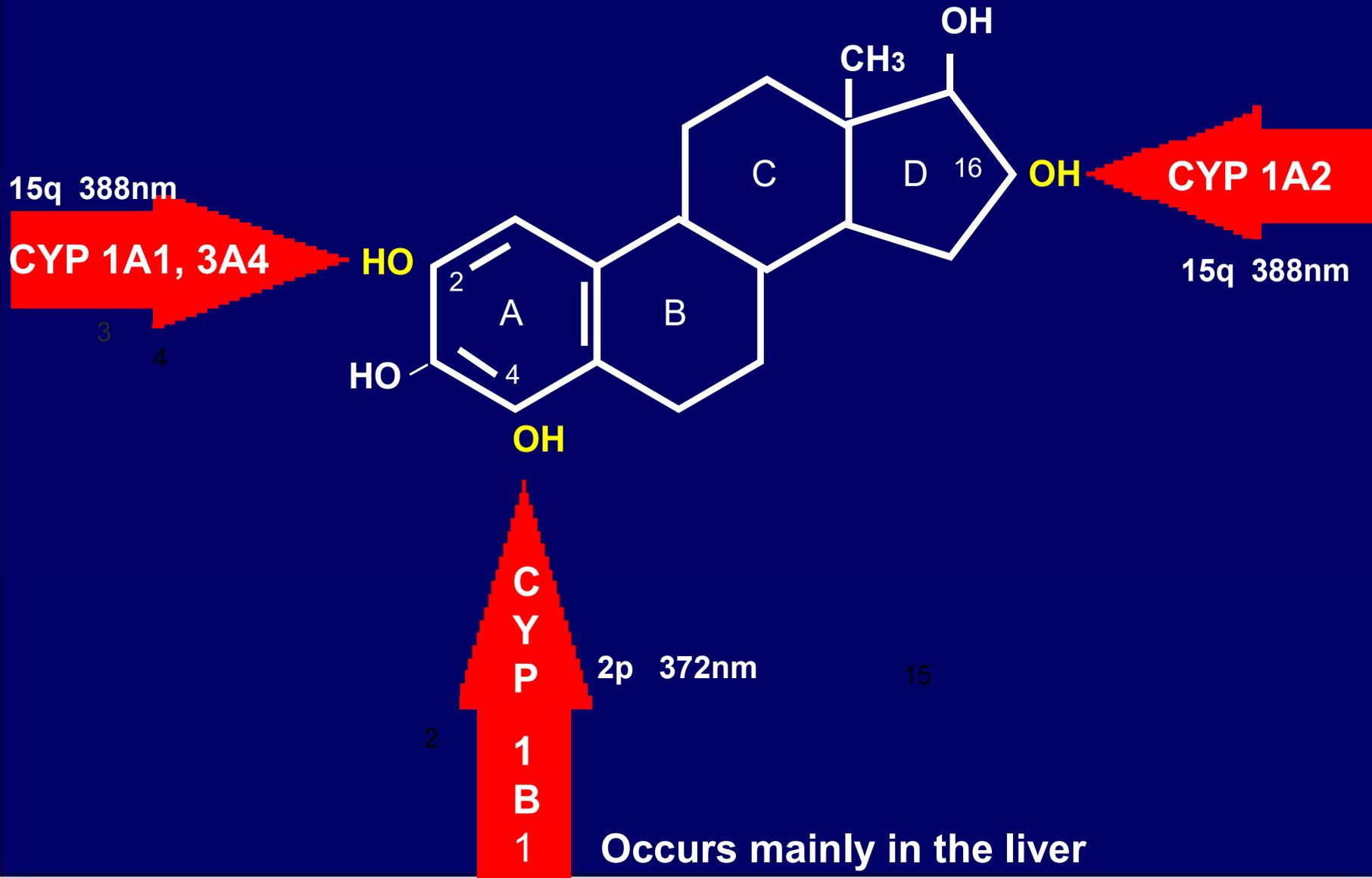
A diet high in carbs could bring on an earlier menopause, a study suggests.

Eating lots of pasta and rice was associated with reaching menopause one-and-a-half years earlier than the average age of women in the UK of 51.

However, the University of Leeds study of 914 UK women, also found that a diet rich in oily fish and peas and beans may delay natural menopause.

The Metabolism of 17 β -ESTRADIOL

17-β Estradiol (E2) hydroxylation



CYP 1A1

Stimulated by
NADPH
Fe⁺⁺, O₂
Indole-3-carbinols
Rosemary
Smoking
Retinol

15q 388nm

Stimulated by
NADPH
Fe⁺⁺, O₂
Char grilling
Tobacco

Inhibited by
Sulforaphanes

2p 372nm

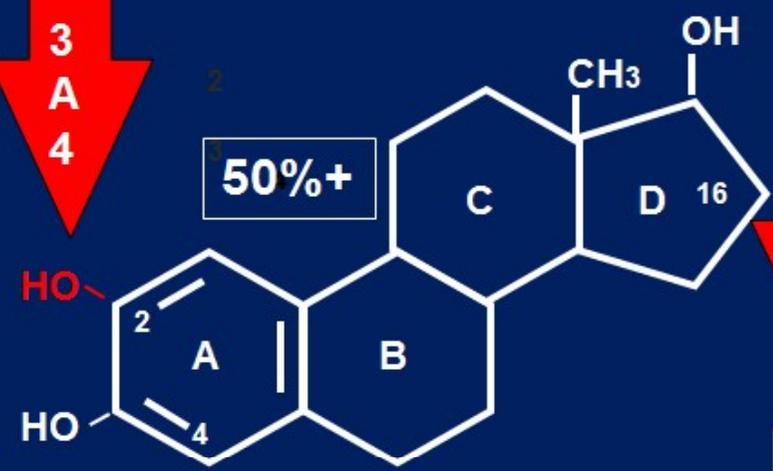
CYP 1B1

Stimulated by
NADPH, Fe⁺⁺, O₂
Omega 3, Brassicas, Smoking
Retinol, iodide

15q 388nm

CYP 1A2

3A4



2 Hydroxyestradiol
(2-OHE2)

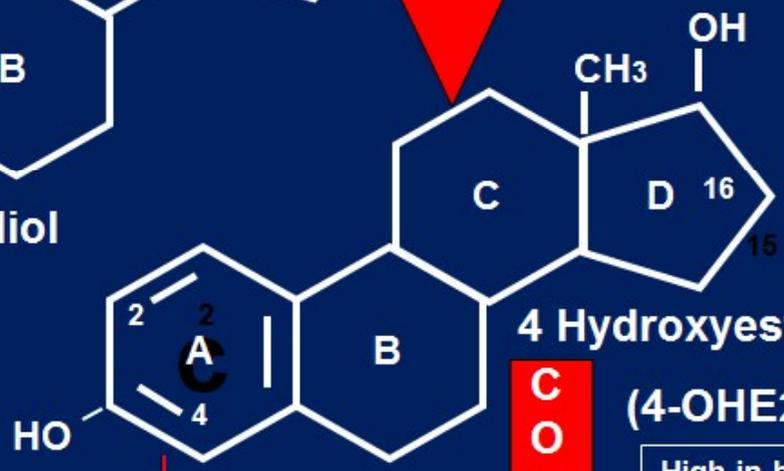
COMT

CYP 1B1



16α-Hydroxyestradiol
(16-OHE2) (Estrinol or E3)

COMT



4 Hydroxyestradiol
(4-OHE2)

COMT

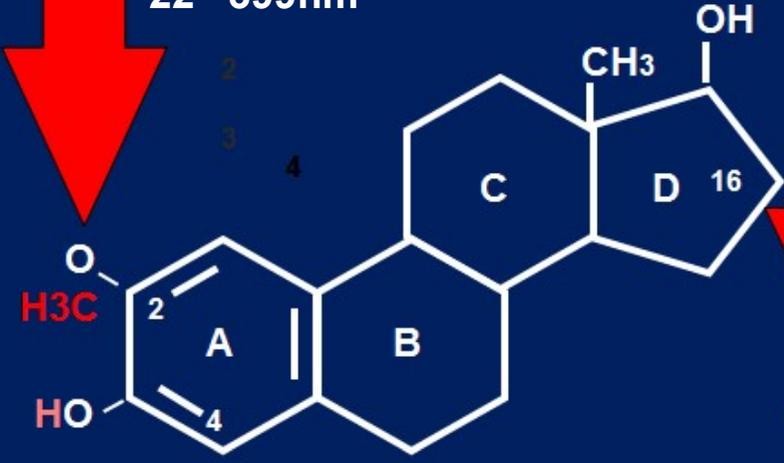
High in benign and malignant growths

COMT

Stimulated by
SAM
Mg⁺⁺

Inhibited by
Catechins
Bioflavonoids
Catcholamines
Homocysteine
SAH

22 399nm



2 Methoxyestradiol

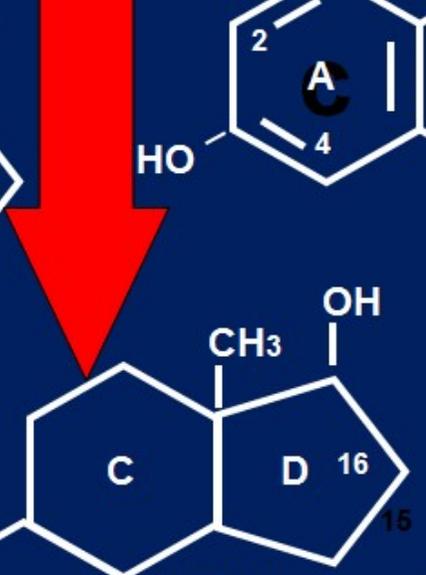
(2-MeOE2)

COMT

Stimulated by
SAM
Mg⁺⁺

Inhibited by
Catechins
Bioflavonoids
Catcholamines
Homocysteine
SAH

22 399nm



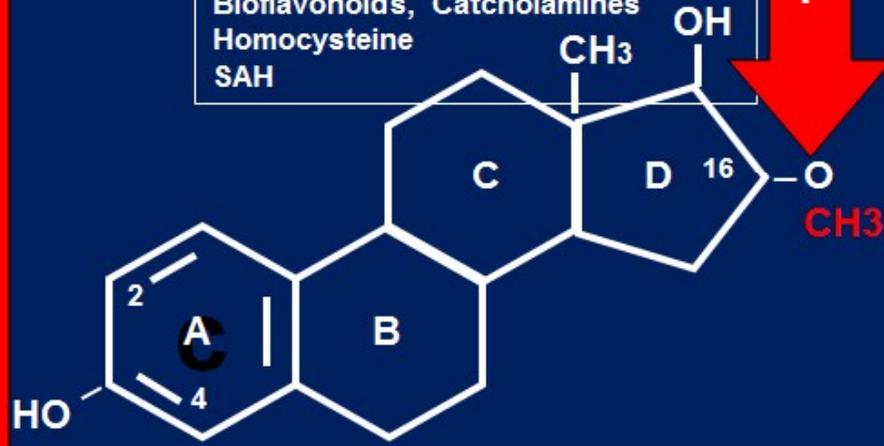
4 Methoxyestradiol

(4-MeOE2)

22 399nm

Stimulated by
SAM, Mg⁺⁺

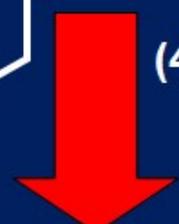
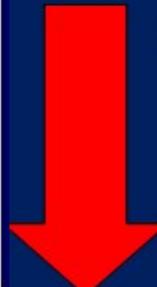
Inhibited by Catechins
Bioflavonoids, Catcholamines
Homocysteine
SAH



16α- Methoxyestradiol

(16-MeOE2)

COMT



Glutathione conjugation from various *glutathione-s-transferase enzymes* using glutathione as the cofactor. NAC, Zn⁺⁺, P5P, Selenium. Spinach, Onion, Garlic, Rosemary, Watercress.

Sulfation from various *sulfotransferase enzymes* using PAPS or Sulfur as the cofactor. MSM. Broccoli, Asparagus, Garlic, Onions, Dill, Parsnip, Horseradish, Cabbage, Stinging nettle.

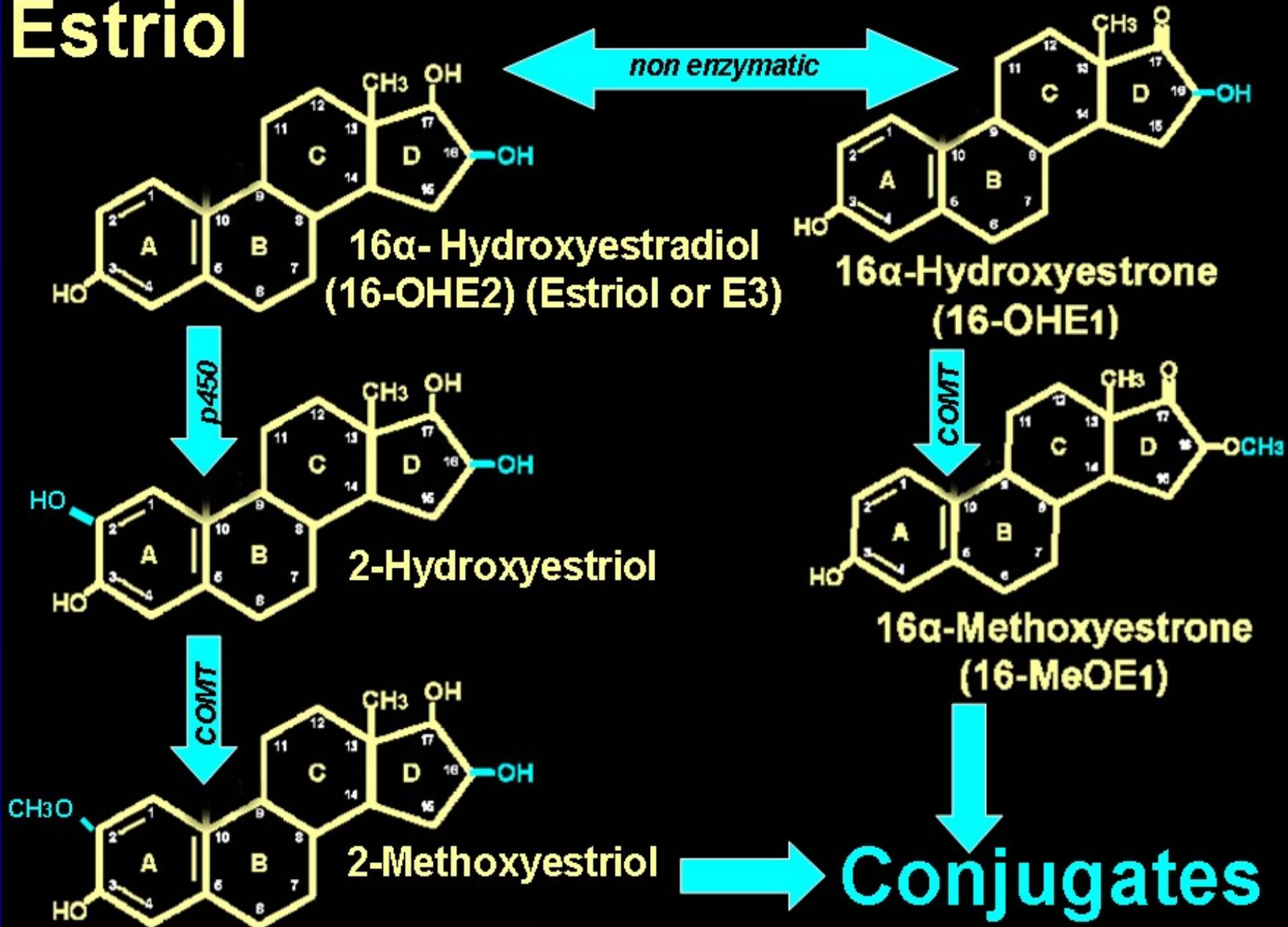
Glucuronidation from various *glucuronosyl transferase enzymes* using UDP-glucuronic acid as the cofactor. Cashew, Soy, Licorice, Flax, Alfalfa.

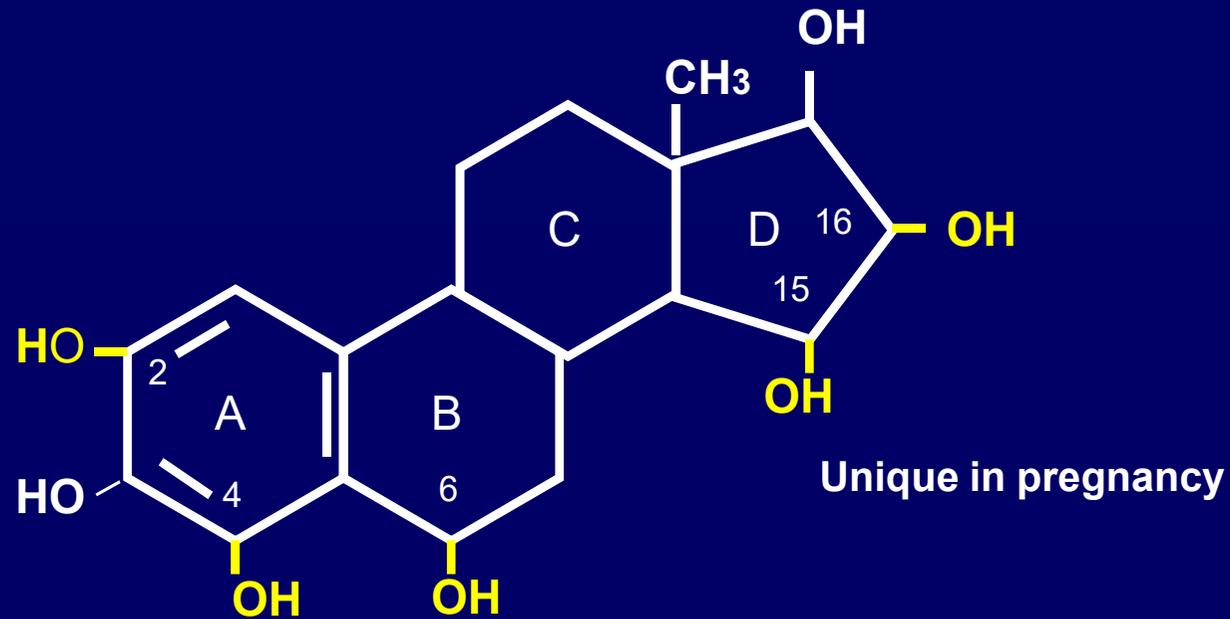
Acetylation using AcetylCoA as the acetyl donor. Pantethine. Endive, Pea, Cucumber, Watercress, Tomato.



Methoxyestradiol conjugates excreted in the urine and bile

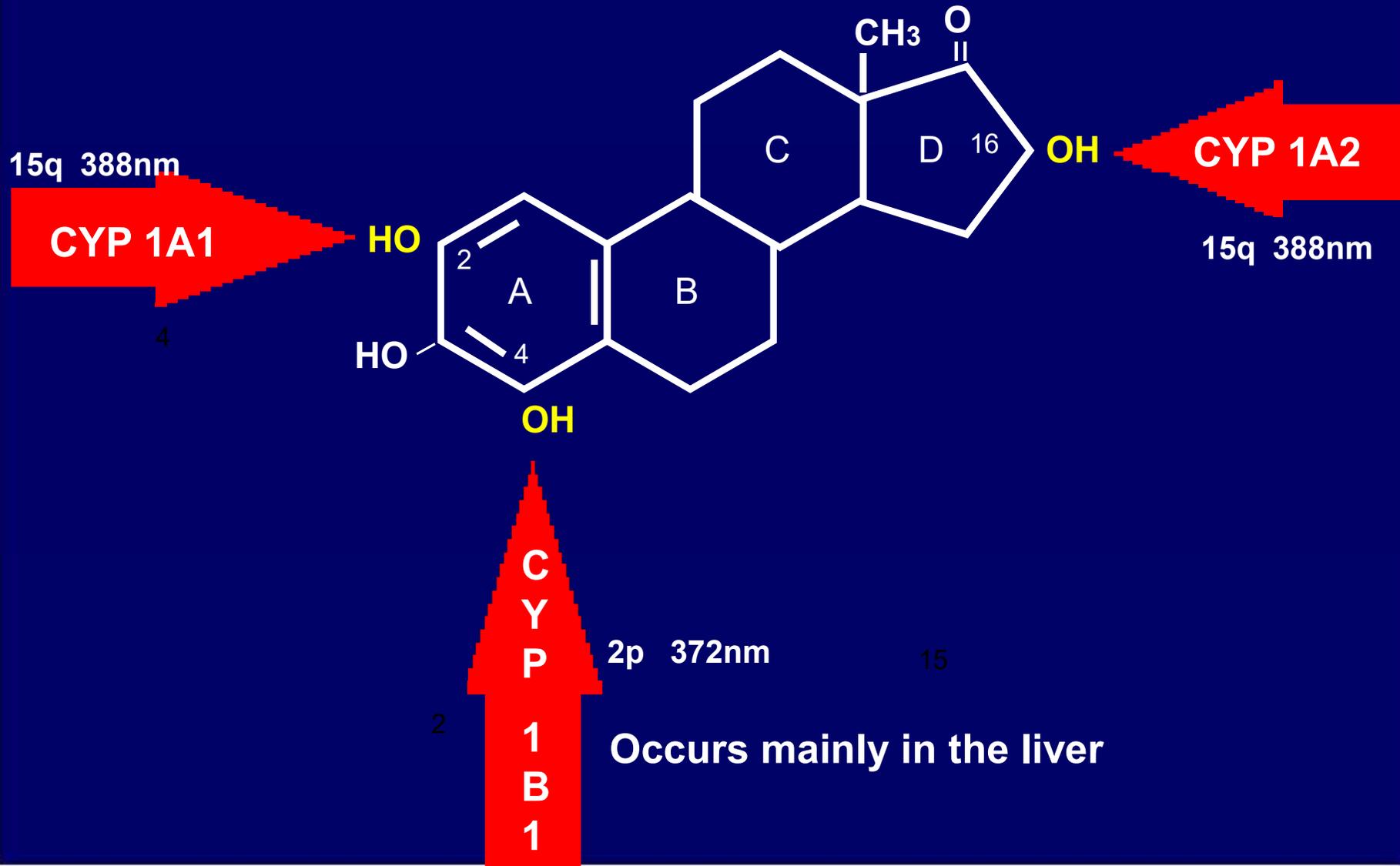
Estriol

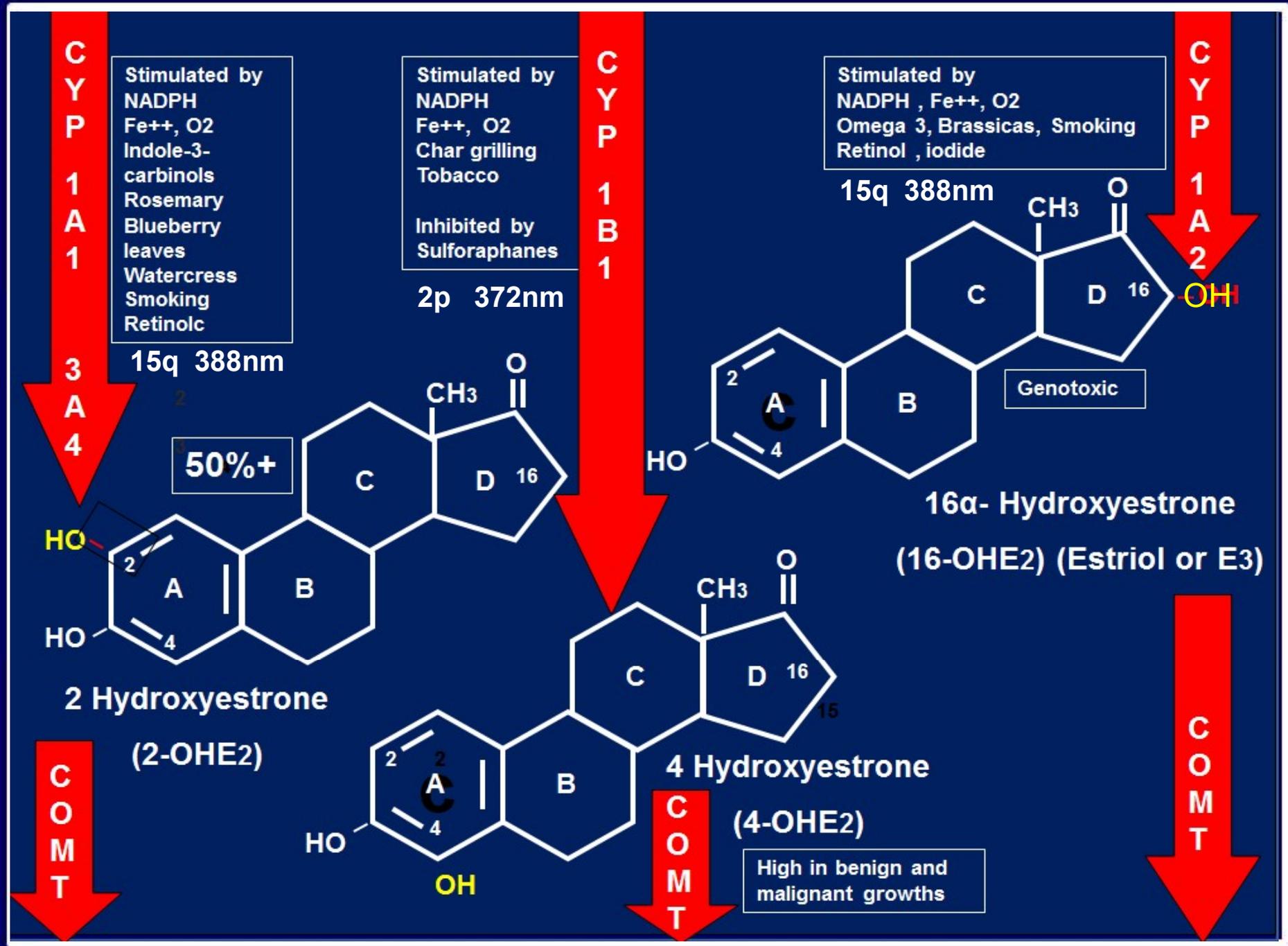


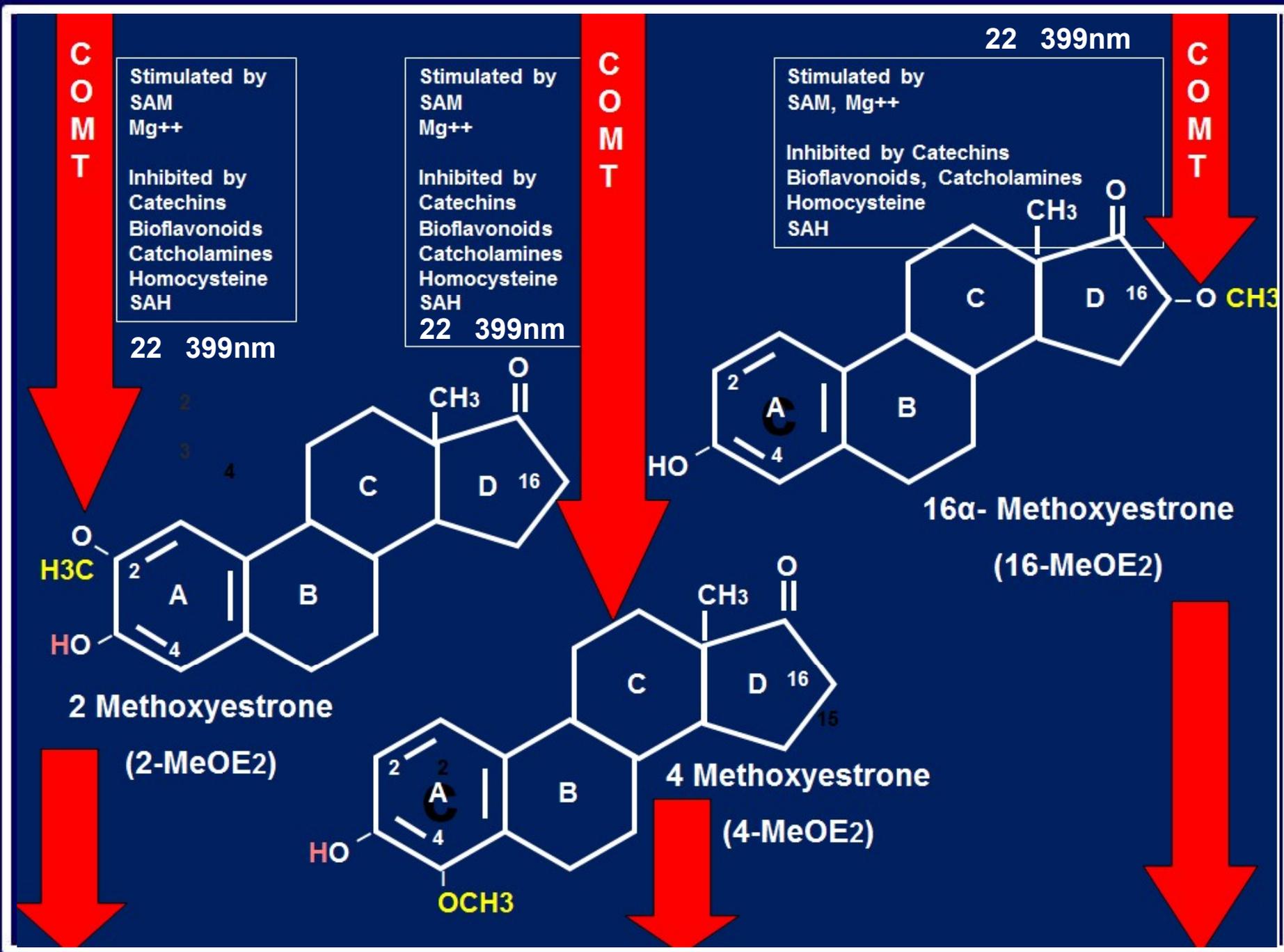


Sites of hydroxylation of Estrone¹⁵ (E1) and 17- β Estradiol (E2)²

Estrone (E1) hydroxylation







Glutathione conjugation from various *glutathione-s-transferase enzymes* using glutathione as the cofactor. NAC, Zn⁺⁺, P5P, Selenium. Spinach, Onion, Garlic, Rosemary, Watercress.

Sulfation from various *sulfotransferase enzymes* using PAPs or Sulfur as the cofactor. MSM. Broccoli, Asparagus, Garlic, Onions, Dill, Parsnip, Horseradish, Cabbage, Stinging nettle.

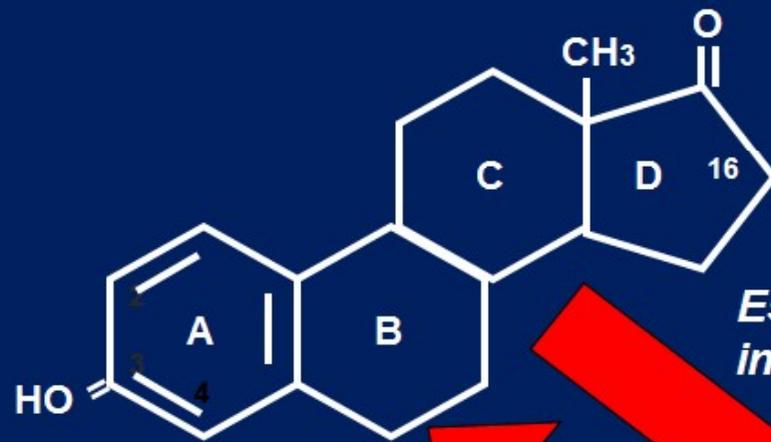
Glucuronidation from various *glucuronosyl transferase enzymes* using UDP-glucuronic acid as the cofactor. Cashew, Soy, Licorice, Flax, Alfalfa.

Acetylation using AcetylCoA as the acetyl donor. Pantethine. Endive, Pea, Cucumber, Watercress, Tomato.



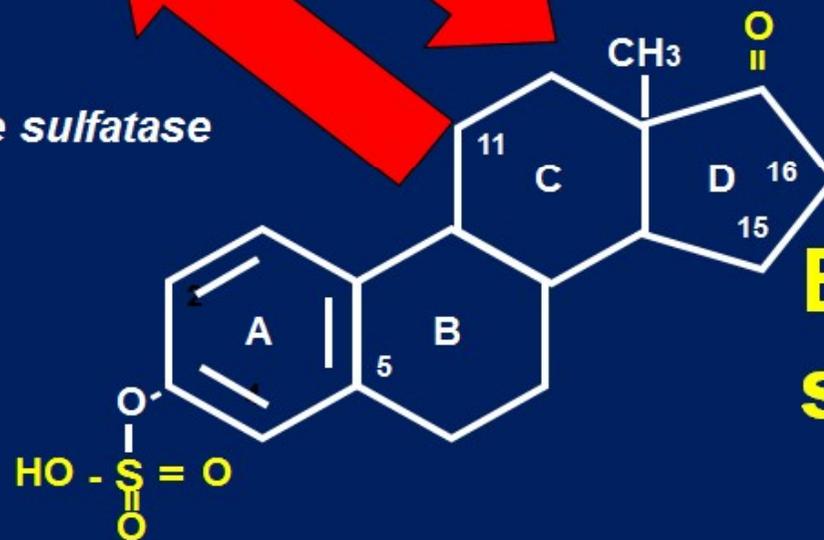
Methoxyestrone conjugates excreted in the urine and bile

Estrone (E1)



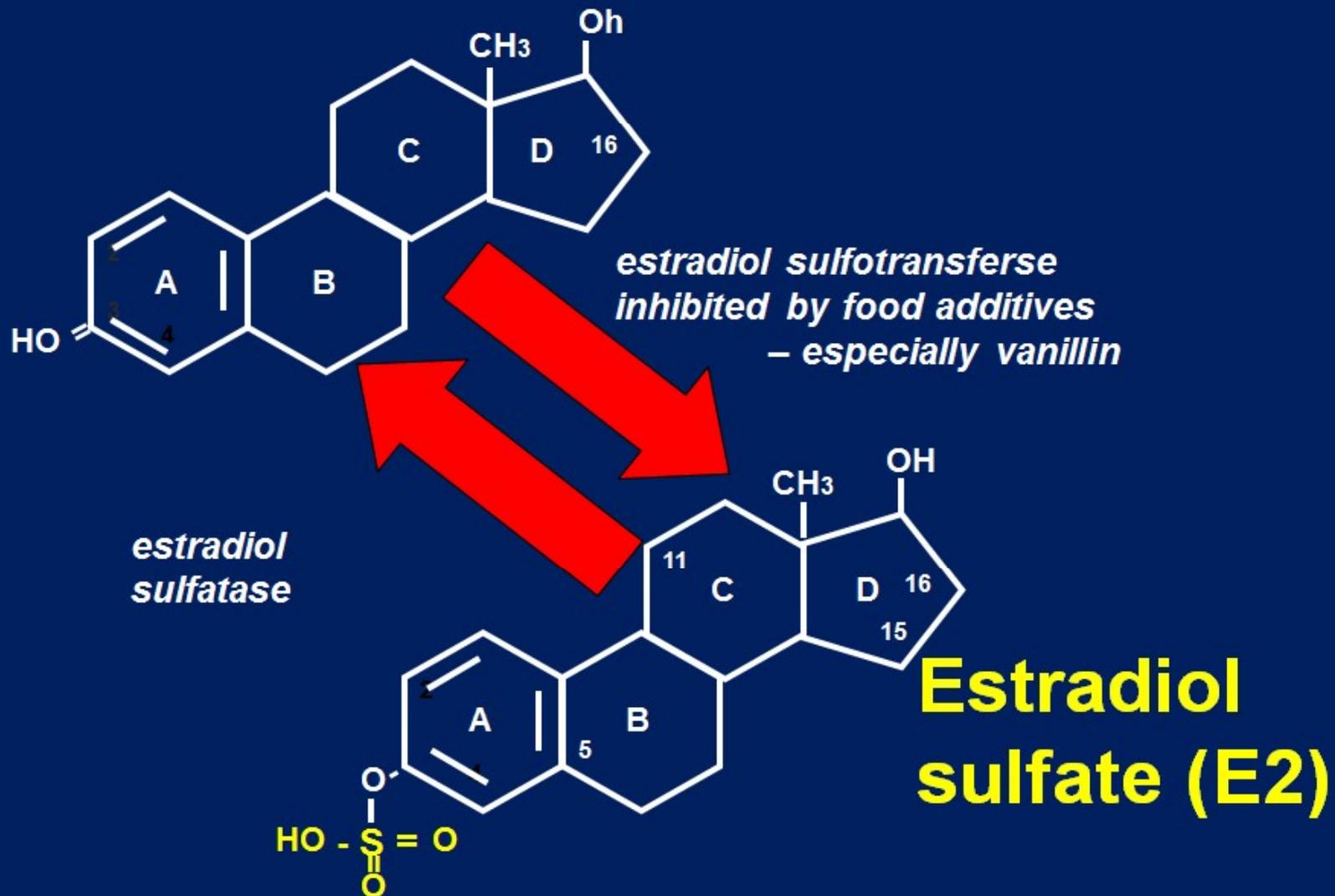
Estrone sulfotransferase 16p 389nm
inhibited by food additives
– especially vanillin

estrone sulfatase



Estrone sulfate (E1)

Estradiol (E2)



Enzyme co-enzymes and co-factors

P450 Aromatase – NADPH, FADH₂, O₂,
B, Vit E

17 β -HSD – NAD, Fe, I

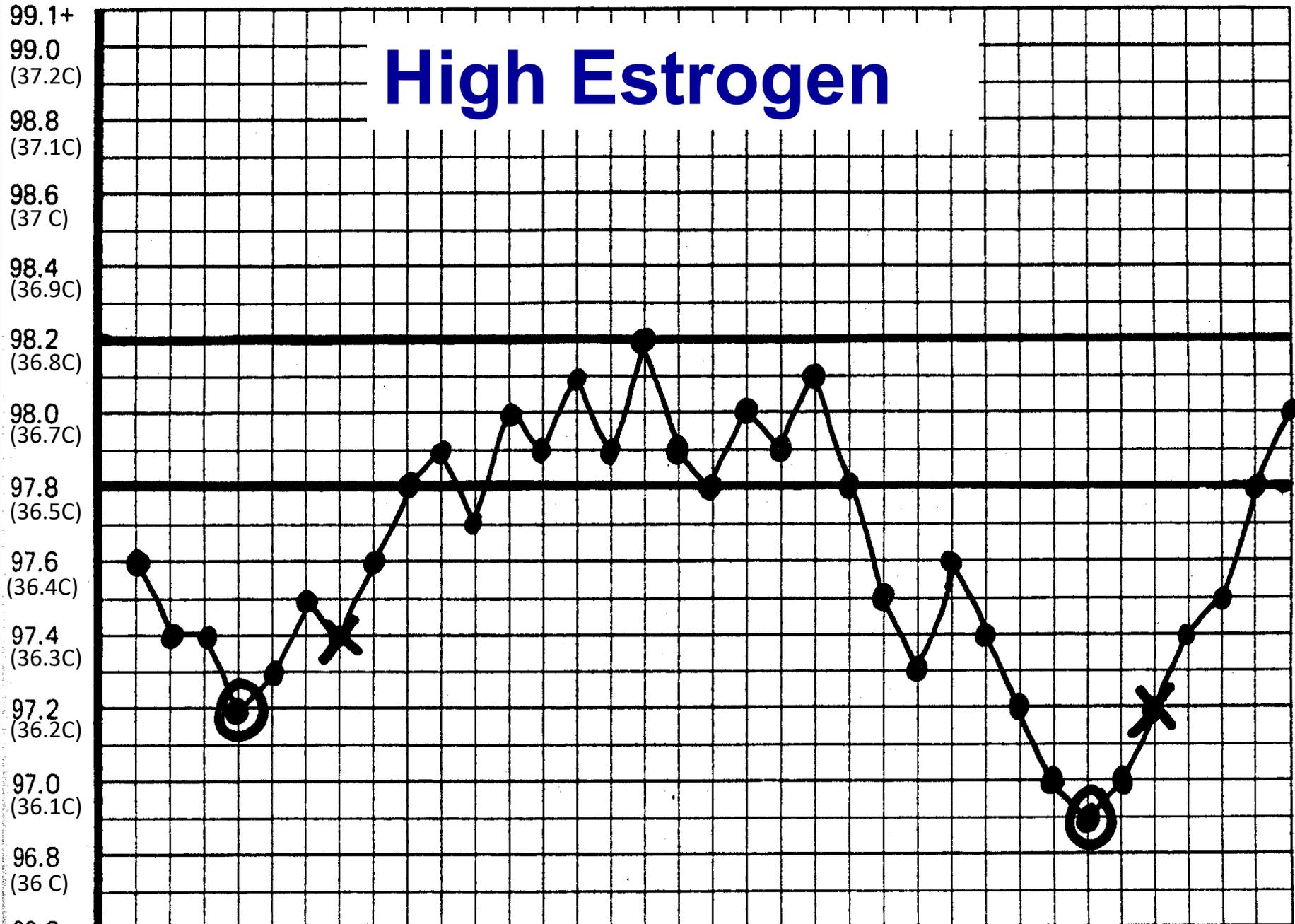
P450 (*CYP1A1* etc) - NADPH, (Mg), Fe, O₂

COMT – SAM, Mg, ATP, Zn,

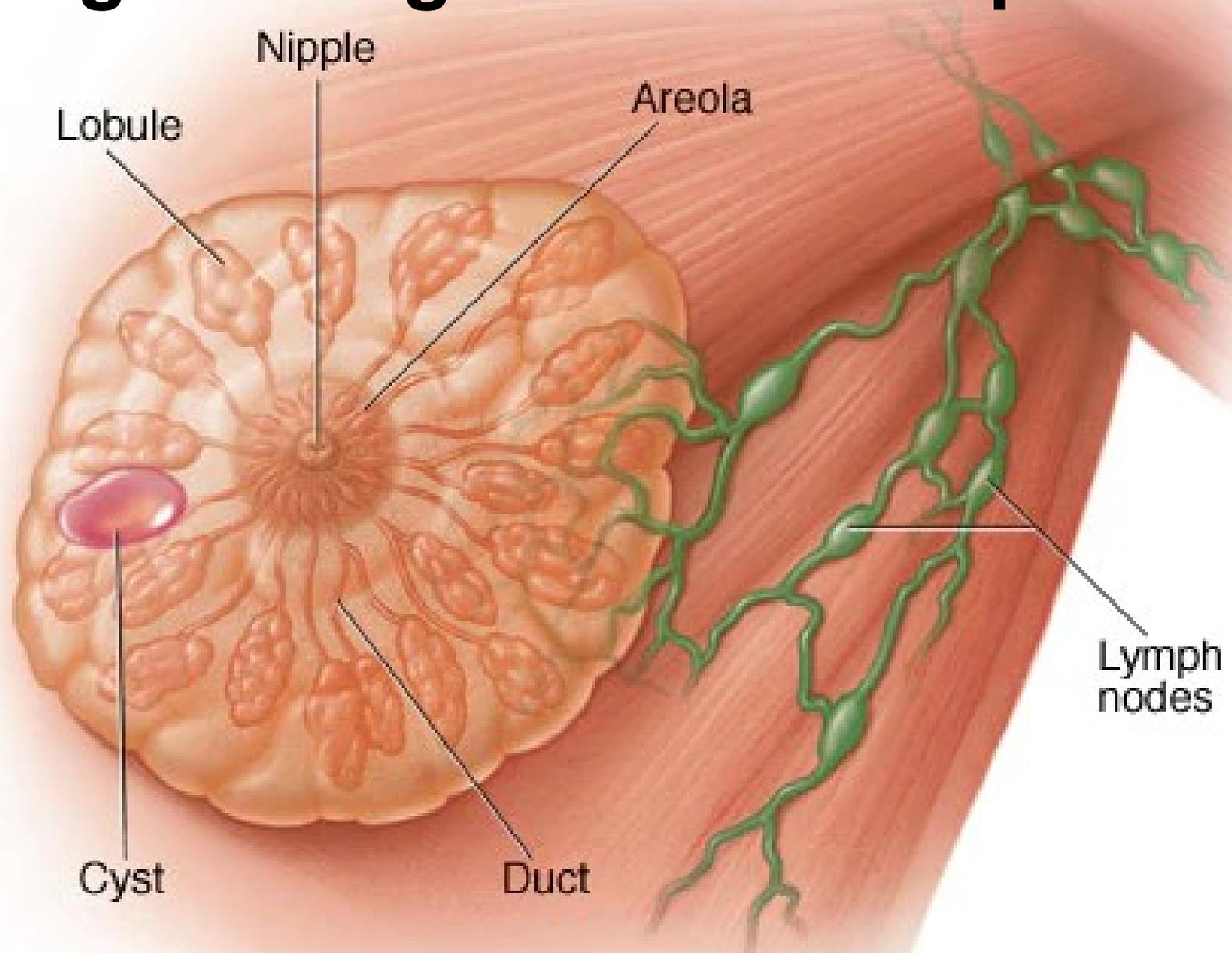
Sulfotransferase – S

G-S-T

High Estrogen



High estrogen breast lumps



High estrogen breast lumps

- 1. Therapy localise breast lump (cyst).**
- 2. Identify negating meridian .(usually Liver or Large intestine).**
- 3. Give sustained drainage to meridian Neurolymphatic reflex point.**

Glucosinolates are secondary metabolites that are mainly found in members of the Brassicaceae (Cruciferae) family. Glucosinolates consist of a common glycone group and a variable aglycone side-chain.



Upon tissue disruption, glucosinolates rearrange to **isothiocyanates, thiocyanates, or nitriles**. Natural isothiocyanates are effective chemoprotective agents that block chemical carcinogenesis and prevent several types of cancer in rodent models.



Isothiocyanates target mammalian Phase 1 and Phase 2 drug-metabolizing enzymes and their coding genes, resulting in decreased carcinogen-DNA interactions and in increased carcinogen detoxification.



e.g. methionine-derived isothiocyanate, **sulforaphane**, inhibits Phase 1 enzyme-mediated activation of procarcinogens, induces Phase 2 detoxification enzymes in hepatoma cells, and blocks **mammary tumour** formation in rats.



Sulforaphane

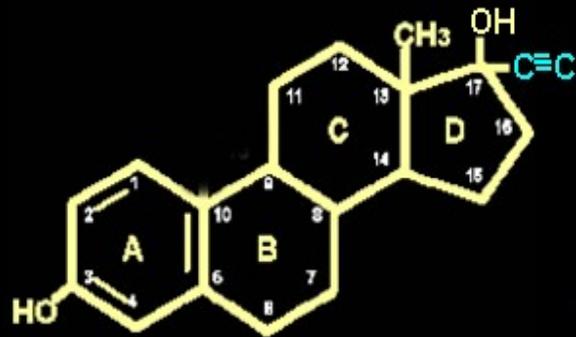
is the most powerful natural inducer of chemo-protective enzymes thus far reported.





The Contraceptive Pill

Oral Contraceptives



Ethinylestradiol



8-Dehydroestrone



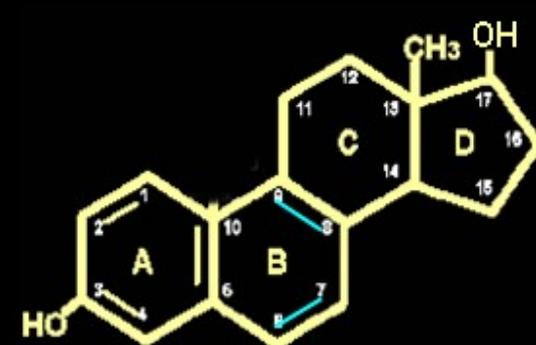
Equilin



Equilenin



17 α -Dihydroequilin



17 α -Dihydroequilenin

Sex drive is dependent on androgen levels only in the presence of estrogen, but without estrogen, free testosterone level actually decreases sexual desire (instead of increases sex drive), as demonstrated for those women who have hypoactive sexual desire disorder, ----

Warnock JK, Swanson SG, Borel RW, Zipfel LM, Brennan JJ (2005). "Combined esterified estrogens and methyltestosterone versus esterified estrogens alone in the treatment of loss of sexual interest in surgically menopausal

women". Menopause. 12 (4): 374-84.

and the sexual desire in these women can be restored by administration of estrogen (using oral contraceptive).*

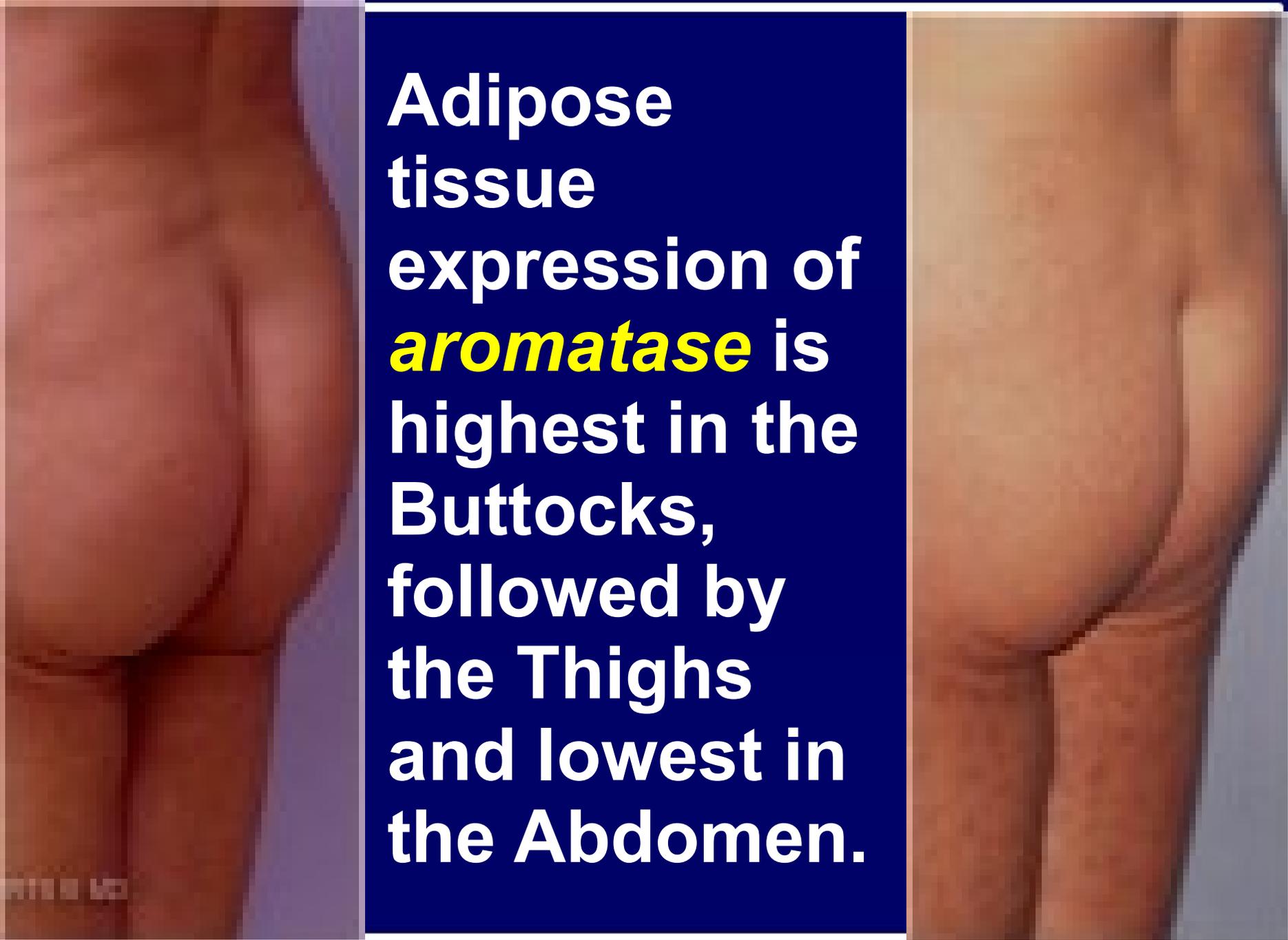
***Heiman JR, Rupp H, Janssen E, Newhouse SK, Brauer M, Laan E (May 2011). "Sexual desire, sexual arousal and hormonal differences in premenopausal US and Dutch women with and without low sexual desire". Hormones and Behavior. 59 (5): 772–9.**

Large quantities of **Estrone and Estriol** are produced by the placenta during pregnancy.

These are also the primary estrogens produced by adipose tissue in men and postmenopausal women.

Extragonadal
conversion of
Androstenedione
to **Estrone** pre
and post
menopausally
occurs mainly in
fibroblasts
surrounding
adipose tissue.





Adipose
tissue
expression of
aromatase is
highest in the
Buttocks,
followed by
the Thighs
and lowest in
the Abdomen.

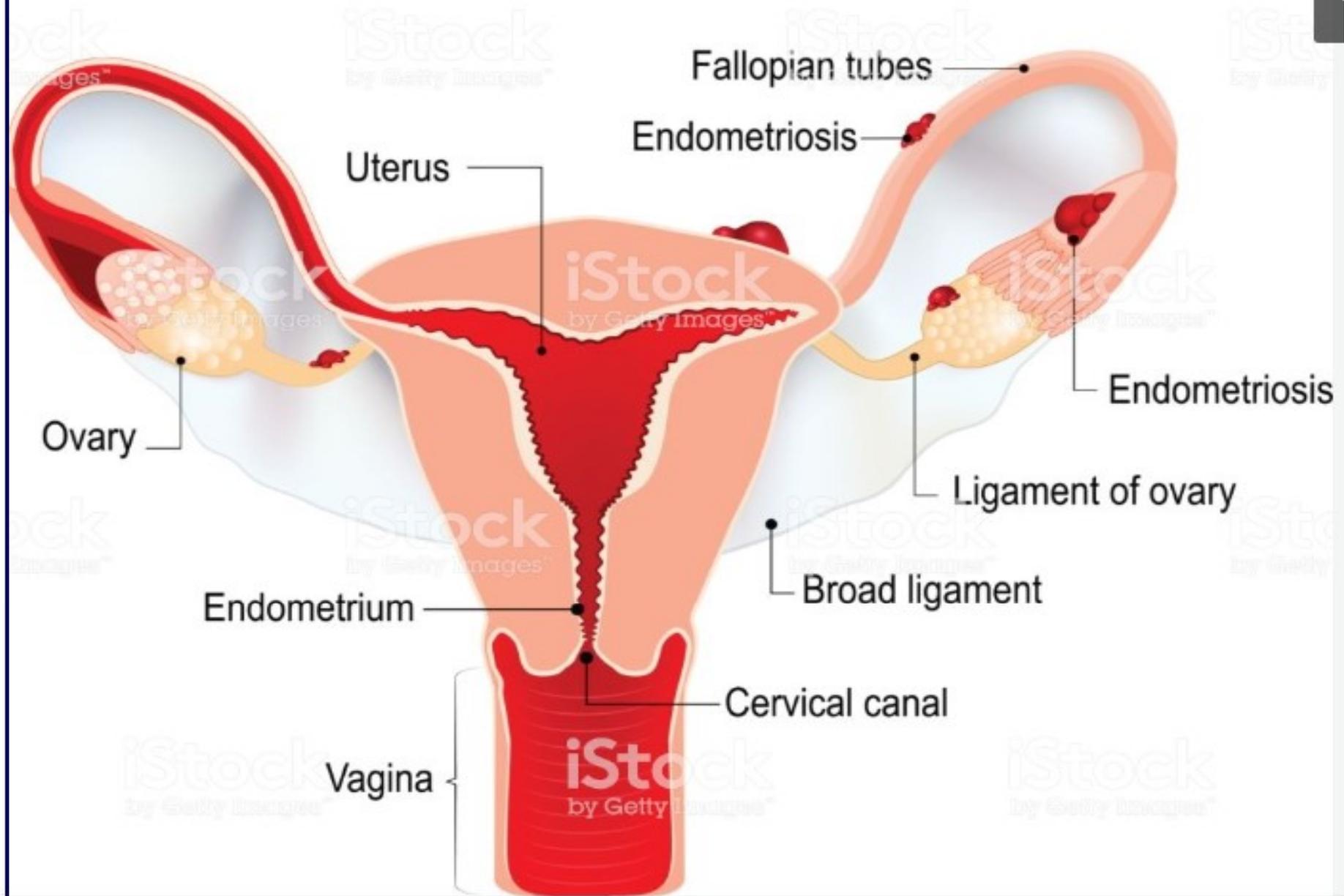
Methoxyestrones
are clinically the
most active at
adipose
deposition to the
buttocks and
thighs.





Estriols are clinically most active at adipose deposition to the abdomen.

ENDOMETRIOSIS





Estrogen risk factors

Enzymatic regulators of Estradiol levels in breast tissue.

INCREASE	DECREASE
Cytochrome P450 aromatase	Cytochrome P450 1A1 P450 1A2
17β-hydroxysteroid dehydrogenase	Cytochrome P450 1B1
Estradiol sulfatase	Estrone & Estradiol sulfotransferase

1. Age of menarche.
Higher risk the earlier the menarche, thus longer overall estrogen exposure.



Early menarche is a well established but weak positive risk factor for breast cancer. The risk factor is **1.2 for** women in whom menarche occurred before the age of 12 years compared with women in whom it occurred at the age of 14 years. Studies show higher levels of E2 in these girls.

2. Parity.

**Higher risk
in nulliparity.
Nuns have
20% higher
estrogen
levels.**



3. Age of first birth.

Higher risk with first birth after 30 years.

Lowest risk with first birth before 20 years (higher prolactin levels).



4. Breastfeeding



5. Women born prematurely before 33 weeks of gestation have increased risk.



6. Women with a twin brother have higher estrogens. (Greater exposure to estrogens in the placenta)



**7. Later the
menopause
the longer the
overall
estrogen
exposure.**



For every **one year increase** in age at menopause, the risk of breast cancer increases by 3%. This is compounded by an early menarche leading to much longer exposure to estrogen.



8. Width and Height.

**Increased risk
postmenopausally.
Increased
protection
premenopausally
due to lower
ovulations and
increase
sequestration of E2
in adipose tissue.**



As Body Mass Index (BMI) increases so do circulating estrogens. Breast cancer risk is 18% higher in obese women.

Dr Lesley Walker of Cancer Research,
Oxford University 20/8/03



Women are 25% more at risk to breast cancer for every **2½ inch** increase in height above 5ft 2in. Maybe due to high calorie diet during puberty.

(British Journal of Cancer July 2003)



A similar link occurs in males and the risk of testicular cancer. Men taller than **6ft 1in** have almost double the risk of contacting testicular cancer than those under 5ft 9in.

(British Journal of Cancer July 2003)



9. Diet. Higher risk with **high saturated fat** intake.

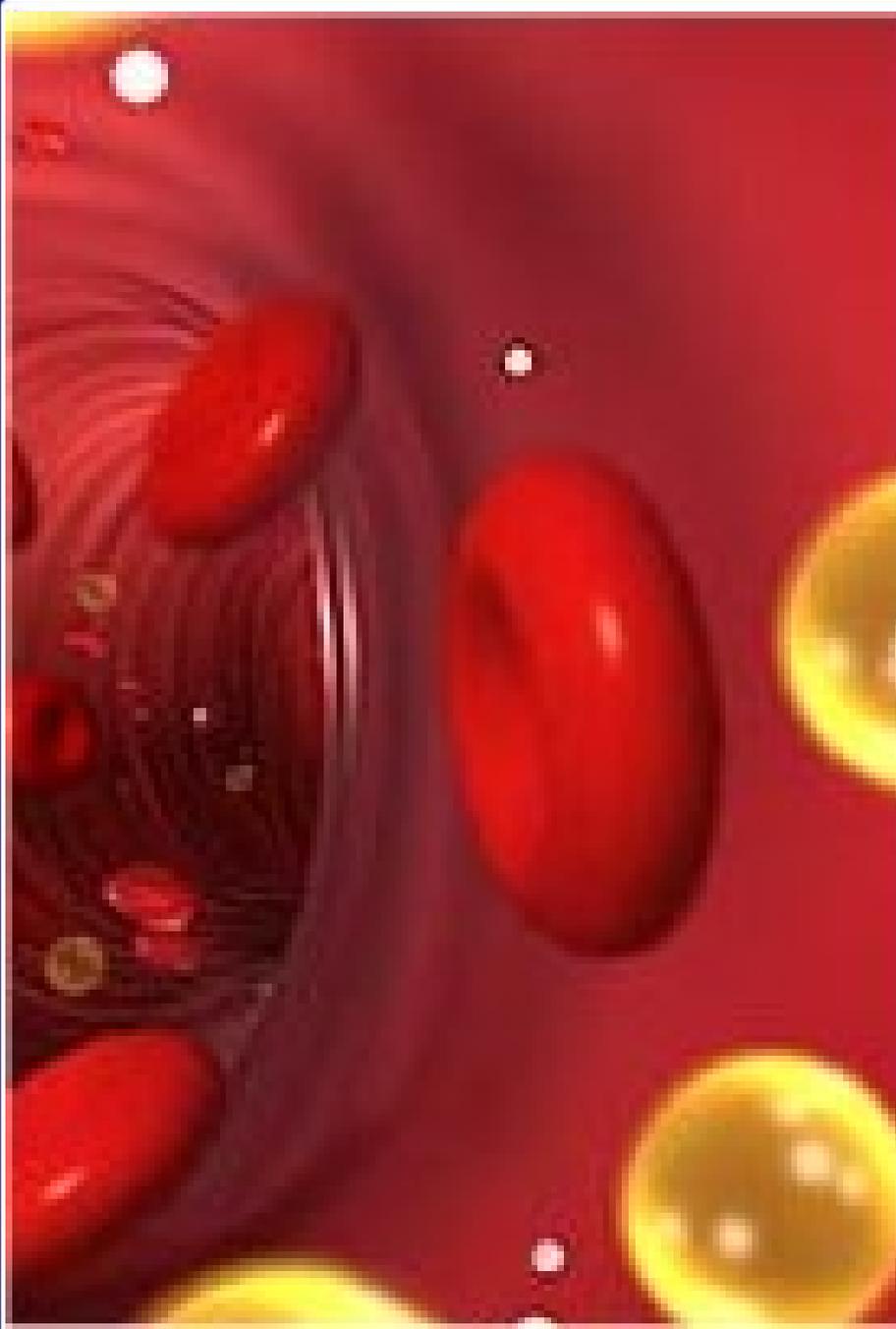
Lowest risk with high oleic fatty acid and Omega 3 oil intake.



**The ratio of Omega 3 to Omega 6
fatty acids in adipose tissue**



**shows an inverse association
with breast cancer risk.**



**No correlation
between serum
cholesterol and
triglyceride
concentrations
and breast
cancer rates.**

Women who eat more than **90gm of fat** a day have 2x the risk of developing breast cancer. Women eating less than 40gm fat per day have least incidence.
(Lancet July 2003)



Asian women who consume 15% or less of their energy as fat have significantly lower plasma E2 levels than their Western counterparts on a 40% higher fat diet.



Reduction of fat intake to **20% of total calorie** and/or increased dietary fibre consumption for at least 2 months resulted in a 20% reduction in serum E2 and a 5% reduction in E1.

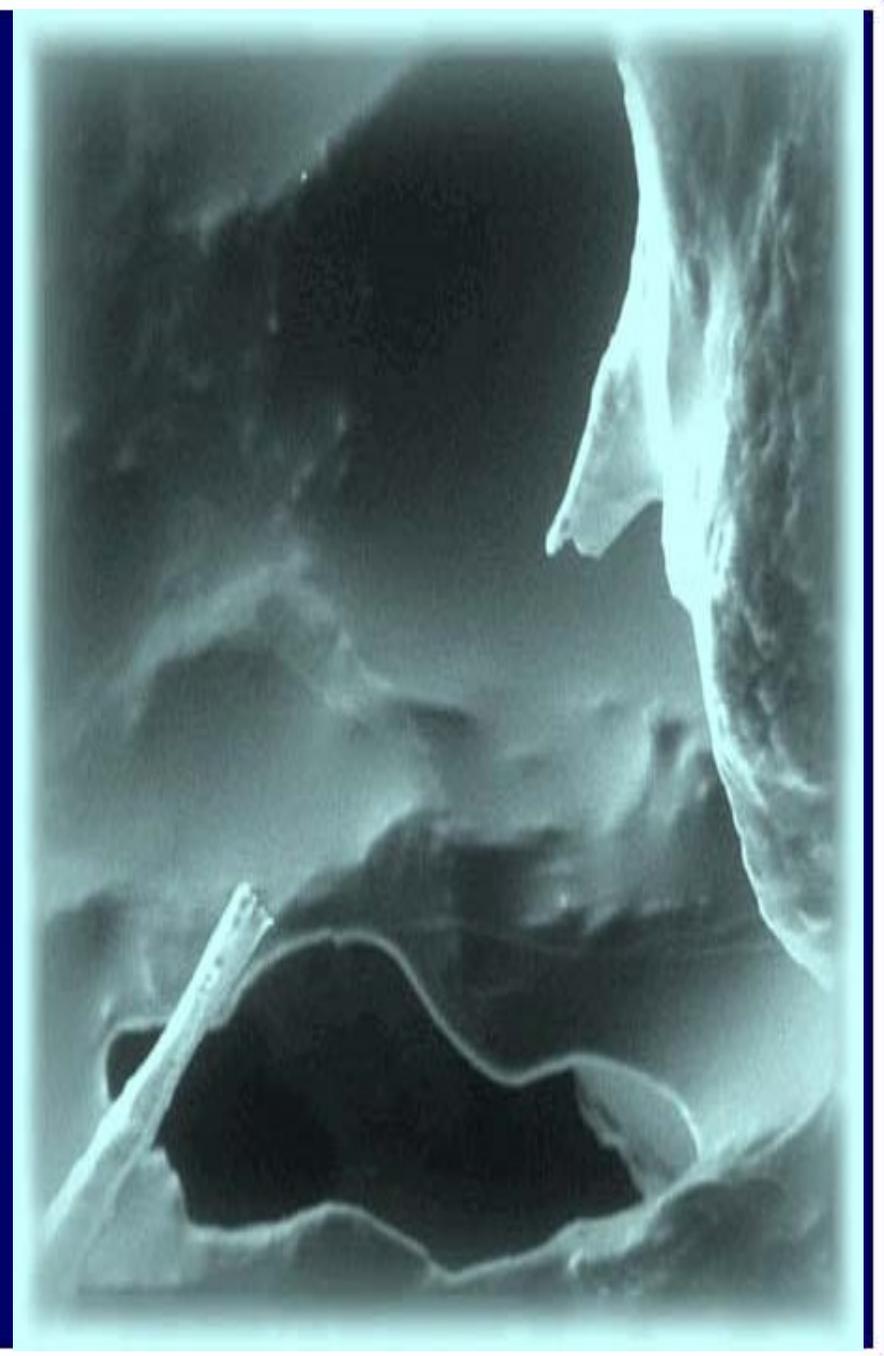


High alcohol intake induces liver aromatase.



Postmenopausal women receiving estrogen replacement therapy experienced a **sustained increase** in circulating E2 following ingestion of alcohol

10. Bone density
depends in part
on estrogen
levels.



E2 affects bone mass most likely via the ER in osteoblasts.

Women with hip fractures have a 16% lower risk of breast cancer and women with forearm fractures an even greater reduction of 58% compared to women without fractures.





11. Family history. Increased likelihood of inheriting various polymorphisms.

Evidence of CYP polymorphisms and some evidence with COMT polymorphisms.

Women whose mother and sister both have a history of breast cancer have a relative risk of 2.5 compared with those without a **family history.**



12. Enzyme polymorphisms

Evidence that polymorphisms in CYP 1A1 or CYP 1B1 are of significance.

Studies of COMT gene polymorphisms G>A increased the risk by 2 fold due to significantly decreased enzyme activity.

Example A *BRCA* mutation is a mutation in either of the ***BRCA1*** and ***BRCA2*** genes, which are tumour suppressor genes. Hundreds of different types of mutations in these genes have been identified, some of which have been determined to be harmful, while others have no proven impact.

BRCA1 Chromosome 17q
BRCA2 Chromosome 13q
TP53 Chromosome 17p

Harmful mutations in these genes may produce a hereditary breast-ovarian cancer syndrome in affected persons. Only **5-10%** of breast cancer cases in women are attributed to *BRCA1* and *BRCA2* mutations (with *BRCA1* mutations being slightly more common than *BRCA2* mutations).

Women with harmful mutations in either ***BRCA1*** or ***BRCA2*** have a risk of breast cancer that is about five times the normal risk, and a risk of ovarian cancer that is about ten to thirty times normal. The risk of breast and ovarian cancer is higher for women with a high-risk ***BRCA1*** mutation than with a ***BRCA2*** mutation.

High-risk mutations, which disable an important error-free DNA repair process (homology directed repair), significantly increase the person's risk of developing **breast cancer, ovarian cancer and certain other cancers.**

Why ***BRCA1*** and ***BRCA2*** mutations lead preferentially to cancers of the breast and ovary is not known, but lack of ***BRCA1*** function seems to lead to non-functional X-chromosome inactivation.

Mutations can be inherited from either parent and may be passed on to both sons and daughters. Each child of a genetic carrier, regardless of sex, has a **50% chance of inheriting the mutated gene from the parent who carries the mutation.**

As a result, half of the people with **BRCA** gene mutations are male, who would then pass the mutation on to 50% of their offspring, male or female.

The risk of *BRCA*-related breast cancers for men with the mutation is higher than for other men, but still low.

However, ***BRCA* mutations** can increase the risk of other cancers, such as colon cancer, pancreatic cancer, and prostate cancer.

72 previously unknown genes mutations have been recently found that lead to the development of breast cancer. **BRCA1** mutation contains 125,950 base pairs. A mutation is a misspelling such that the gene cannot code the proper protein.

According to the **National Cancer Institute** 55% - 65% of women who inherit the BRCA1 mutation and around 45% of women who inherit the BRCA2 mutation will develop breast cancer by the age of 70. However only 1% of women have these mutations which is only a small fraction of all inherited breast cancer.

Only about 10% of breast cancers are hereditary.

Most of the newly identified variants are in regions of the genome that **regulate nearby genes**

Holly Yan (2013-05-14). "What's the gene that led to Angelina Jolie's double mastectomy?. Health. CNN.

HER2 (from human epidermal growth factor receptor 2) is a member of the human epidermal growth factor receptor family. Over-expression of this **oncogene** has been shown to play an important role in the development and progression of certain aggressive types of breast cancer.

HER2 Chromosome 17q

In recent years the protein has become an important biomarker and target of therapy for approximately **30% of breast cancer** patients.

HER2 is so named because it has a similar structure to human epidermal growth factor receptor, or HER1. It is so named because it was derived from a rodent glioblastoma cell line, a type of neural tumour.

Mitri Z, Constantine T, O'Regan R (2012). "The HER2 Receptor in Breast Cancer: Pathophysiology, Clinical Use, and New Advanc in Therapy". *Chemotherapy Research and Practice*. 2012: 743193. PMC 3539433. PMID 23320171.

An **oncogene** is a gene that has the potential to cause cancer. In tumour cells, they are often mutated and/or expressed at high levels.

Activated oncogenes can cause mutant cells designated for apoptosis to survive and proliferate instead.

13. Endogenous estrogen concentration.

It appears that differences in serum E2 concentration could be etiologically important especially in post-menopausal women.

14. Exogenous estrogen concentration from oral contraceptives and hormone replacement therapy increase risk.

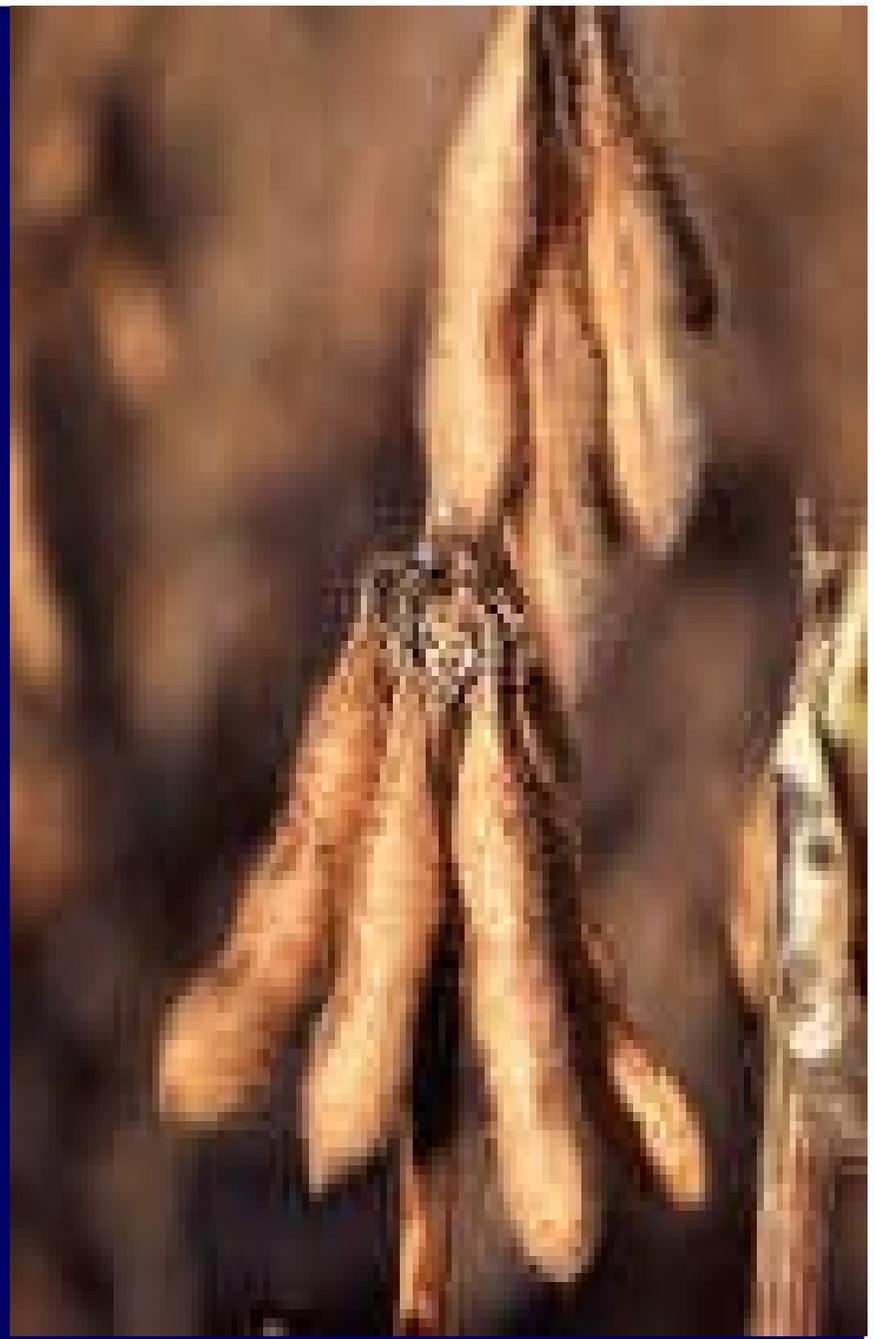


15. Phytoestrogens

**Formed from
lignans
(enterolactone)
and from
isoflavones
(equols) by
colonic bacterial
fermentation.**



**Work by inhibiting
aromatase and
17 β -
hydroxysteroid
dehydrogenase
enzymes and by
increasing serum
binding globulin
thus lowering free
estrogens.**

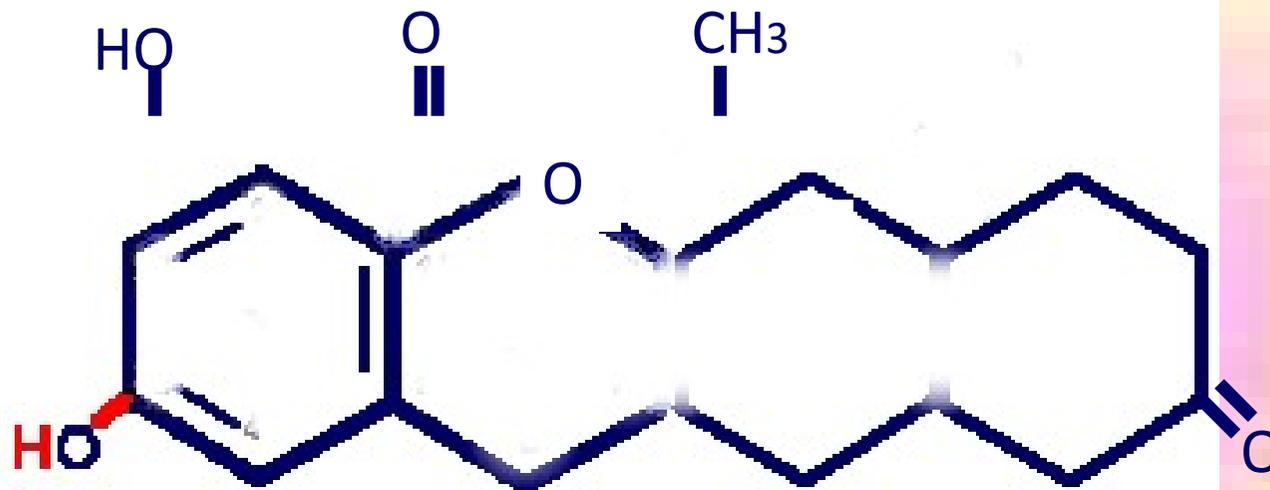


16. Xenoestrogens.

Organochlorides
(DDT, DDE), 
carbamates, PCB's,
plasticizers,
styrenes,
nonylphenols all
can have weak
estrogen like
effects.



Zearalenone - Zearalanol



Zearalenone and its reduced derivative, **Zearalanol**, are fungal or mycoestrogens from fusarium moulds.

They have been associated with estrogenizing syndromes in animals fed mould infected grain.

They have been shown to interact with the ER and to promote weight gain in rats.

100-1000 fold higher doses than E2 are required to achieve equivalent responses.

High fibre diet linked to lower breast cancer risk

Source: *CANCER, ACS*

By **Nikki Hancocks** 

08-Apr-2020 - Last updated on 08-Apr-2020 at 1

"Fiber consumption and breast cancer incidence: a systematic review and meta-analysis of prospective studies."

Farvid. M. S., et al



istock | fibre sources

**Phytoceuticals to
stimulate Progesterone:**

**Dang quai (*Angelica
sinensis*), Sarsaparilla
(*Smilax officinalis*),
White deadnettle
(*Lamium alba*), Yarrow
(*Achillea millefolium*).**



**Yarrow (*Achillea
millefolium*)**

Phytochemicals to stimulate

Estrogens: Angelica
(*Angelica archangelica*),
Aniseed (*Pimpinella anisum*),
Black cohosh (*Cimicifuga
racemosa*), Fenugreek
(*Trigonella foenum-graecum*),
Ginseng (*elutherococcus*),
Hops (*Humulus lupulus*),
Nettle (*Urtica dioica*), Oats
(*Avena sativa*), Sarsaparilla
(*Smilax officinalis*), Wild yam
(*Dioscorea villosa*), Yarrow
(*Achillea millefolium*)



**Yarrow (*Achillea
millefolium*)**

Indole-3-carbinol

Indole-3-Carbinol is a type of Indole.

Chemically, it is a metabolite of Glucobrassicin, which in turn is a hydrolytic product of Glucosinolates

Indole-3-Carbinol is metabolized to **Diindolylmethane (DIM)** in the stomach, which recent research indicates is the compound that is actually responsible for the benefits formerly attributed to Indole-3-Carbinol.

Chemically, Diindolylmethane (DIM) consists of two molecules of Indole-3-Carbinol bound together.

Indole-3-Carbinol stimulates the endogenous production of **Glutathione** by hepatocytes.

Indole-3-Carbinol facilitates the binding of various substances (including carcinogens) to **Glucuronic Acid** to form **Glucuronides** for excretion.

Indole-3-Carbinol inhibits the conversion of Estrone to 16-Hydroxyestrone (a carcinogenic metabolite of Estrone).

And redirects Estrone to be converted to 2-Hydroxyestrone (a safe metabolite of Estrone).

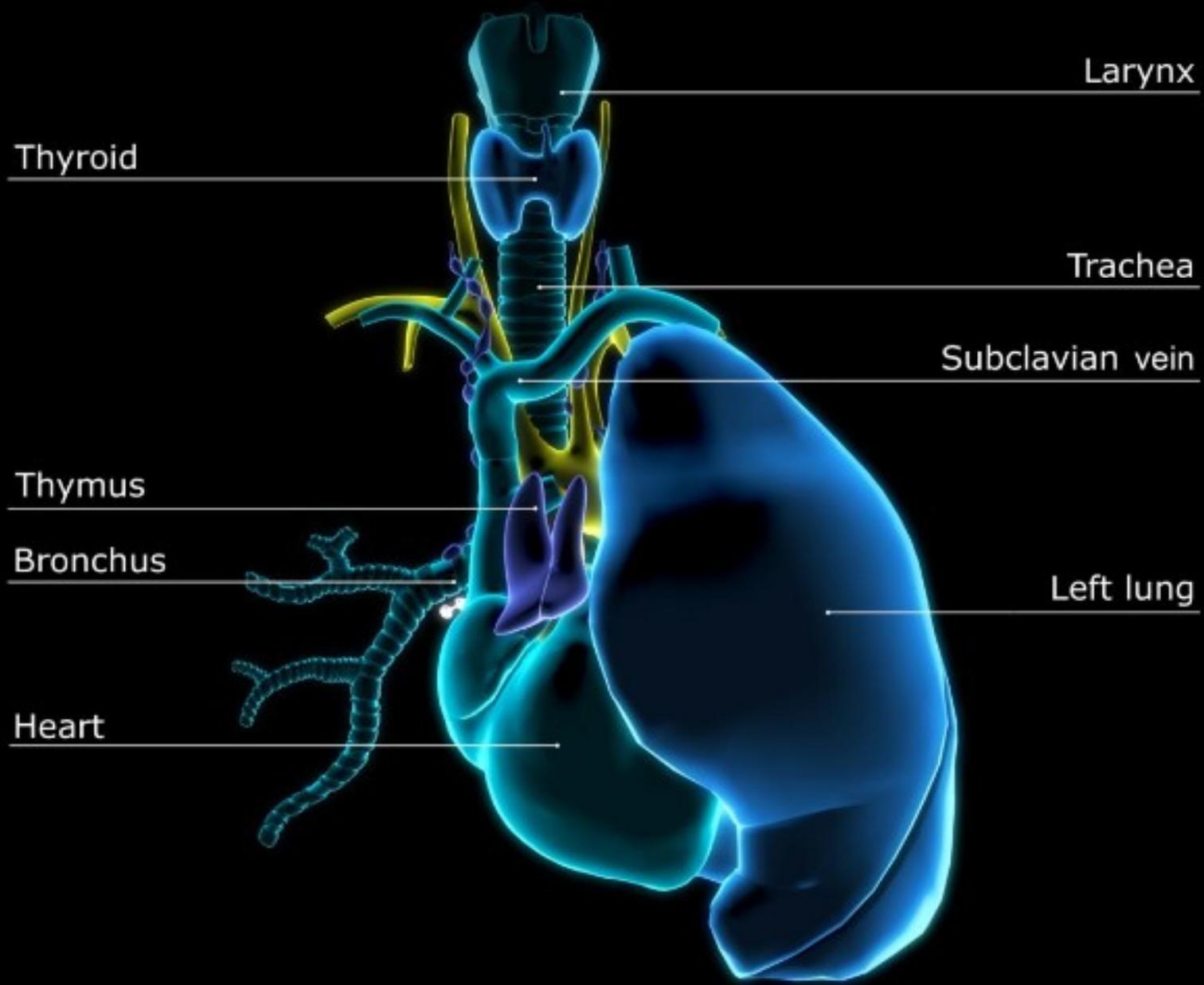
Chaste Berry

Is a shrubby herb with botanical name *Vitex agnus-castus*

Chaste Berry may mimic the ability of Luteinizing Hormone (LH) to stimulate the production of Progesterone in the Corpus Luteum during the Luteal Phase of the Menstrual Cycle.

Some studies have shown that Chaste Berry also stimulates the actual secretion of LH.

The Thymus Gland



Larynx

Thyroid

Trachea

Subclavian vein

Thymus

Bronchus

Left lung

Heart

The Thymus Gland is the main organ of the lymphatic system. The gland's primary function is to promote the development of cells of the immune system called T lymphocytes. T lymphocytes, or T-cells, are white blood cells that protect against foreign organisms (bacteria and viruses) that manage to infect body cells.

They also protect the body from itself by controlling cancerous cells. From infancy to adolescence, the thymus is relatively large in size. After puberty, the thymus begins to shrink, which continues with age.

The thymus is a two-lobed structure in the upper chest cavity that partially extends into the neck.

The thymus is above the pericardium of the heart, in front of the aorta, between the lungs, below the thyroid, and behind the breastbone. The thymus has a thin outer covering called a capsule and consists of three types of cells: epithelial cells, lymphocytes, and Kulchitsky, or neuroendocrine, cells.

- **Epithelial cells:** Tightly packed cells that give shape and structure to the thymus
- **Lymphocytes:** Immune cells that protect against infection and stimulate an immune response
- **Kulchitsky cells:** Hormone-releasing cells

Each lobe of the thymus contains many smaller divisions called lobules. A lobule consists of an inner area called the medulla and an outer region called the cortex. The cortex contains immature T lymphocytes. These cells haven't developed the ability to distinguish cells of the body from foreign cells.

The medulla contains the larger, mature T lymphocytes, which have the ability to identify self and have differentiated into specialized T lymphocytes.

While T lymphocytes mature in the thymus, they originate from bone marrow stem cells.

Immature T-cells migrate from the bone marrow to the thymus via the blood. The "T " in T lymphocyte stands for thymus-derived.

The thymus functions chiefly to develop T lymphocytes.

Once mature, these cells leave the thymus and are transported via blood vessels to the lymph nodes and spleen.

T lymphocytes are responsible for cell-mediated immunity, an immune response that involves the activation of certain immune cells to fight infection.

T-cells contain proteins called T-cell receptors that populate the T-cell membrane and are capable of recognizing various types of antigens (substances that provoke an immune response).

T lymphocytes differentiate into three major classes in the thymus:

- Cytotoxic T cells: Directly terminate antigens**
- Helper T cells: Precipitate the production of antibodies by B-cells and also produce substances that activate other T-cells**
- Regulatory T cells: Also called suppressor T cells; suppress the response of B-cells and other T-cells to antigens**

The thymus produces hormone-like proteins that help T lymphocytes mature and differentiate. Some thymic hormones include thymopoietin, thymulin, thymosin, and thymic humoral factor (THF).

Thymopoietin and thymulin induce differentiation in T lymphocytes and enhance T-cell function.

Thymosin increases immune responses and stimulates certain pituitary gland hormones (growth hormone, luteinizing hormone, prolactin, gonadotropin-releasing hormone, and adrenocorticotrophic hormone).

Thymic humoral factor increases immune responses to viruses.

Thymic hormones influence structures of the endocrine system, including the pituitary gland and adrenal glands, to assist in the growth and sexual development.

The thymus and its hormones influence other organs and organ systems, including the kidneys, spleen reproductive system, and central nervous system.

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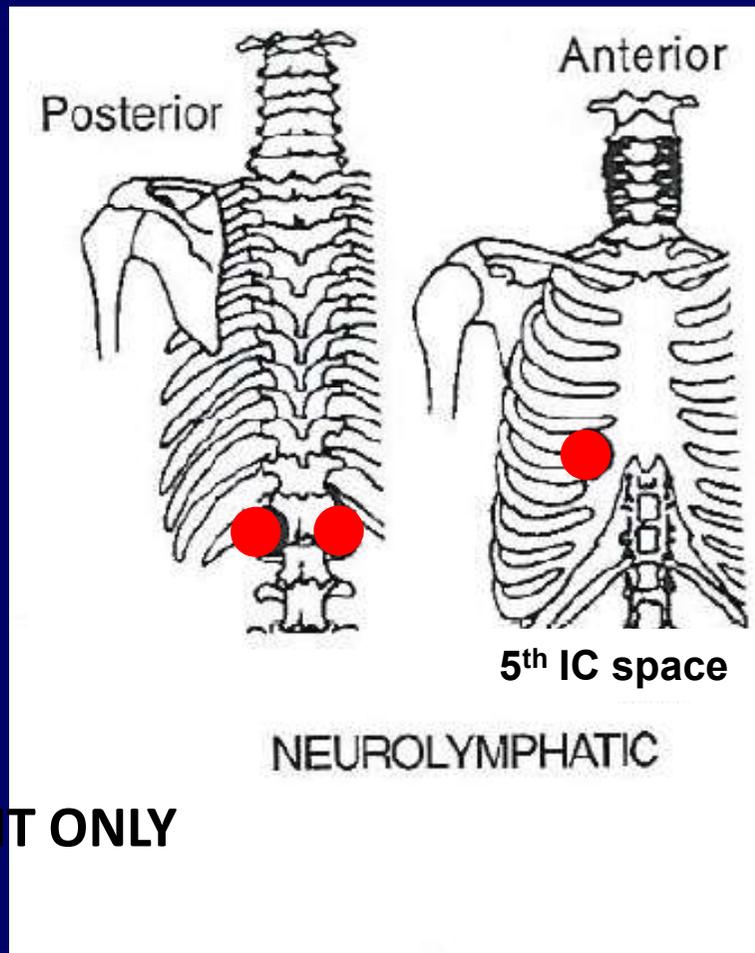
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Chapman's Reflexes Points

Thymus

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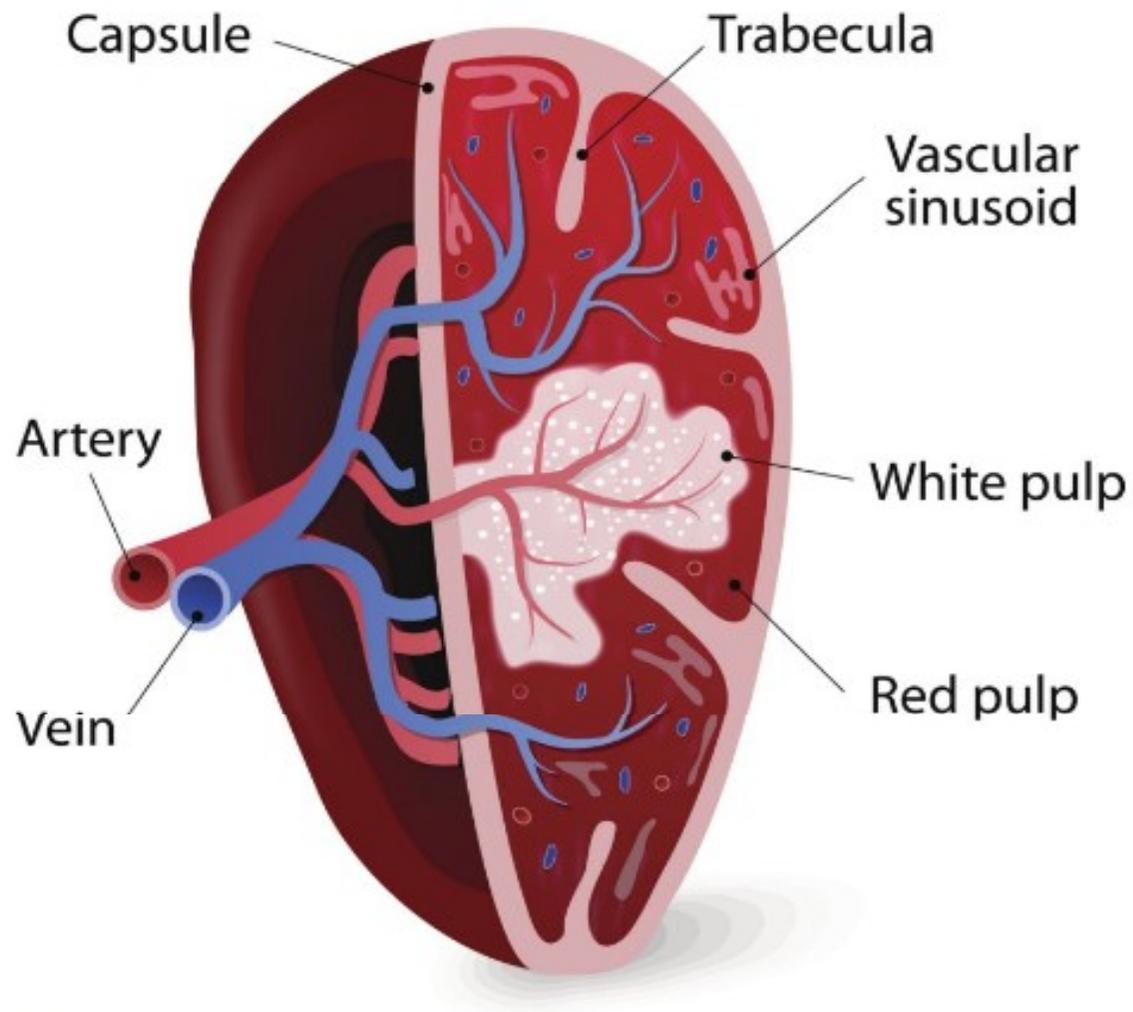
Remember that blood flows through all our organs every few minutes.

Rubbing the Neurolyphatic reflexes decongests the organ enabling it to carry out it function.

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The Spleen

SPLEEN ANATOMY



The spleen is often described as being about the size of a small fist. It is positioned under the rib cage, below the diaphragm, and above the left kidney. The spleen is rich in blood supplied via the splenic artery. Blood exits this organ through the splenic vein.

The spleen also contains efferent lymphatic vessels, which transport lymph away from the spleen. Lymph is a clear fluid that comes from blood plasma that exits blood vessels at capillary beds. This fluid becomes the interstitial fluid that surrounds cells.

Lymph vessels collect and direct lymph toward veins or other lymph nodes.

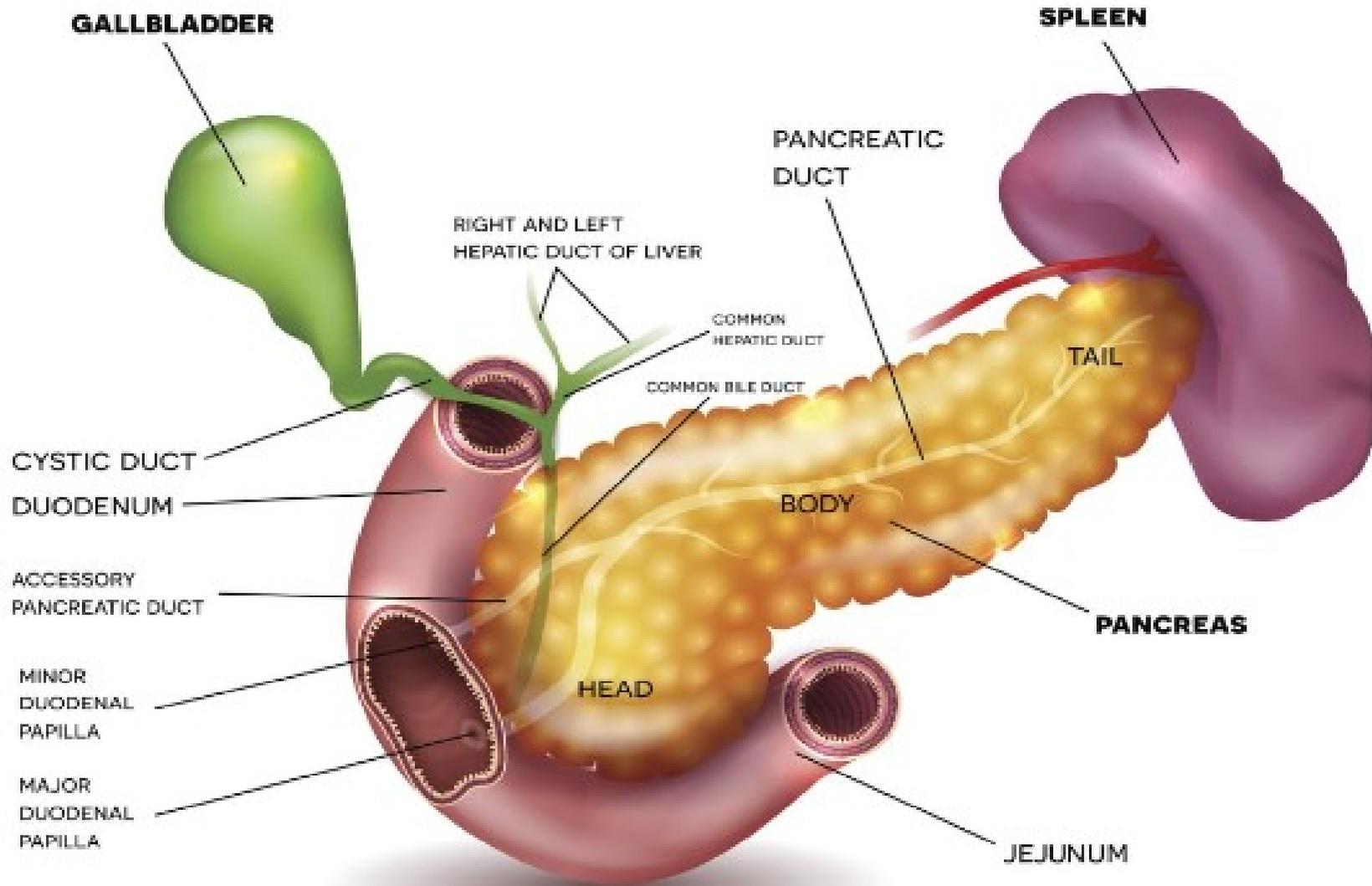
The spleen is a soft, elongated organ that has an outer connective tissue covering called a capsule. It is divided internally into many smaller sections called lobules.

The spleen consists of two types of tissue: red pulp and white pulp.

White pulp is lymphatic tissue that mainly consists of lymphocytes called B-lymphocytes and T-lymphocytes that surround arteries.

Red pulp consists of venous sinuses and splenic cords.

Venous sinuses are essentially cavities filled with blood, while splenic cords are connective tissues containing red blood cells and certain white blood cells (including lymphocytes and macrophages).



The major role of the spleen is to filter blood. The spleen develops and produces mature immune cells that are capable of identifying and destroying pathogens.

Contained within the white pulp of the spleen are immune cells called B and T-lymphocytes.

T-lymphocytes are responsible for cell-mediated immunity, which is an immune response that involves the activation of certain immune cells to fight infection.

T-cells contain proteins called T-cell receptors that populate the T-cell membrane.

They are capable of recognizing various types of antigens (substances that provoke an immune response).

T-lymphocytes are derived from the thymus and travel to the spleen via blood vessels.

B-lymphocytes or B-cells originate from bone marrow stem cells. B-cells create antibodies that are specific to a specific antigen. The antibody binds to the antigen and labels it for destruction by other immune cells.

Both white and red pulp contains lymphocytes and immune cells called macrophages.

These cells dispose of antigens, dead cells, and debris by engulfing and digesting them.

While the spleen functions chiefly to filter blood, it also stores red blood cells and platelets.

In instances where extreme bleeding occurs, red blood cells, platelets, and macrophages are released from the spleen.

Macrophages help to reduce inflammation and destroy pathogens or damaged cells in the injured area. Platelets are blood components that help the blood clot to stop blood loss. Red blood cells are released from the spleen into blood circulation to help compensate for blood loss.

Sources

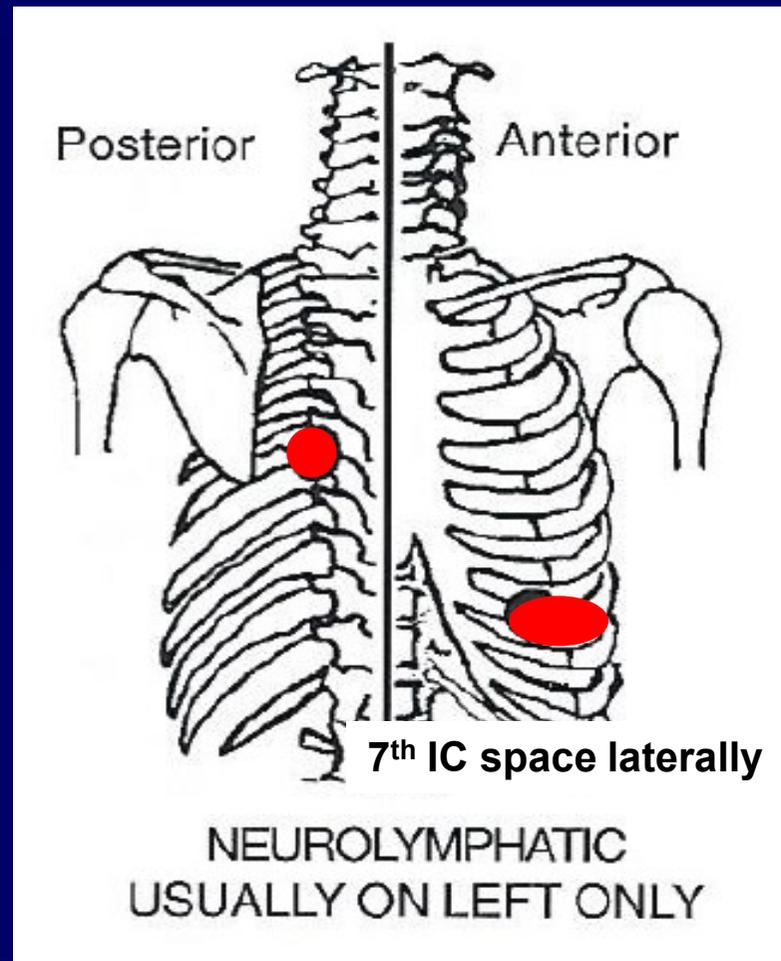
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Spleen

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The Liver



The liver is an important vital organ that also happens to be the largest internal organ in the body. Weighing between 3 and 3.5 pounds, the liver is located in the upper right area of the abdominal cavity and is responsible for hundreds of different functions.

Some of these functions include nutrient metabolism, detoxification of harmful substances, and protecting the body from germs. The liver has a unique ability to regenerate itself. This ability makes it possible for individuals to donate part of their liver for transplantation.

Liver tissue is composed of two main types of cells. Hepatocytes are the most numerous type of liver cells. These epithelial cells are responsible for most of the functions performed by the liver. Kupffer cells are immune cells that are also found in the liver.

They are thought to be a type of macrophage that rids the body of pathogens and old red blood cells.

The liver also contains numerous bile ducts, which drain bile produced by the liver into larger hepatic ducts. These ducts join to form the common hepatic duct.

The cystic duct extending from the gallbladder joins the common hepatic duct to form the common bile duct. Bile from the liver and gallbladder drain into the common bile duct and are delivered to the upper portion of the small intestines (duodenum).

The liver receives blood from organs including the stomach, small intestines, spleen, pancreas, and gallbladder through the hepatic portal vein. The liver then processes filters and detoxifies the blood before sending it back to the heart via the inferior vena cava.

1. Fat Digestion: A key function of the liver in the digestion of fats. Bile produced by the liver breaks down fat in the small intestines so that it can be used for energy.

2. Metabolism: The liver metabolizes carbohydrates, proteins, and lipids in the blood that are initially processed during digestion. Hepatocytes store glucose obtained from the break down of carbohydrates in the foods we eat. Excess glucose is removed from the blood and stored as glycogen in the liver.

When glucose is needed, the liver breaks down glycogen into glucose and releases the sugar into the blood.

The liver metabolizes amino acids from digested proteins. In the process, toxic ammonia is produced which the liver converts to urea.

Urea is transported to the blood and is passed to the kidneys where it is excreted in the urine.

The liver processes fats to produce other lipids including phospholipids and cholesterol.

These substances are necessary for cell membrane production, digestion, bile acid formation, and hormone production. The liver also metabolizes hemoglobin, chemicals, medications, alcohol and other drugs in the blood.

3. Nutrient Storage: The liver stores nutrients obtained from the blood for use when needed. Some of these substances include glucose, iron, copper, vitamin B12, vitamin A, vitamin D, vitamin K (helps blood to clot), and vitamin B9 (folate - aids in red blood cell synthesis).

Synthesis and Secretion: The liver synthesizes and secretes plasma proteins that act as clotting factors and help to maintain proper blood fluid balance. The blood protein fibrinogen produced by the liver is converted to fibrin, a sticky fibrous mesh that traps platelets and other blood cells.

Another clotting factor produced by the liver, prothrombin, is needed to convert fibrinogen to fibrin.

The liver also produces a number of carrier proteins including albumin, which transports substances such as hormones, fatty acids, calcium, bilirubin, and various drugs.

Hormones are also synthesized and secreted by the liver when needed. Liver-synthesized hormones include insulin-like growth factor 1, which aids in early growth and development.

Thrombopoietin is a hormone that regulates platelet production in the bone marrow.

5. Immune Defence: The Kupffer cells of the liver filter the blood of pathogens such as bacteria, parasites, and fungi. They also rid the body of old blood cells, dead cells, cancer cells, and cellular refuse. Harmful substances and waste products are secreted by the liver into either the bile or the blood.

Substances secreted into bile are eliminated from the body through the digestive tract. Substances secreted into the blood are filtered by the kidneys and excreted in the urine.

Source

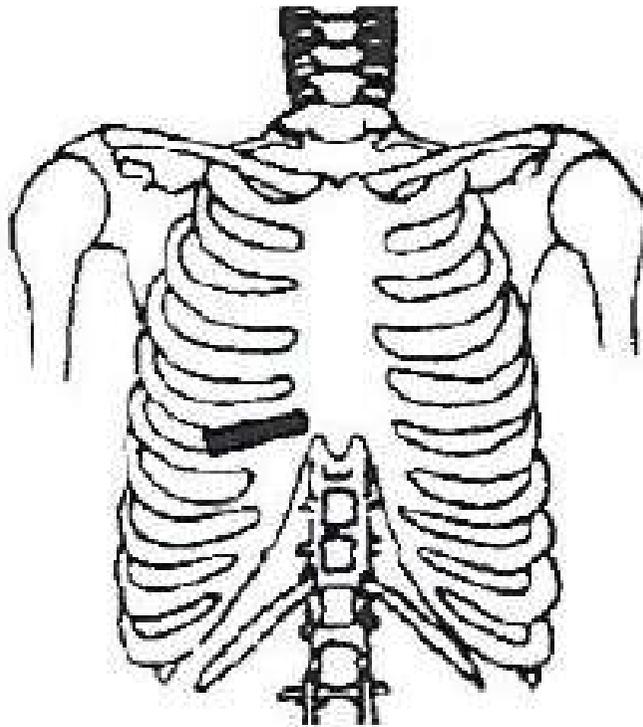
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Liver

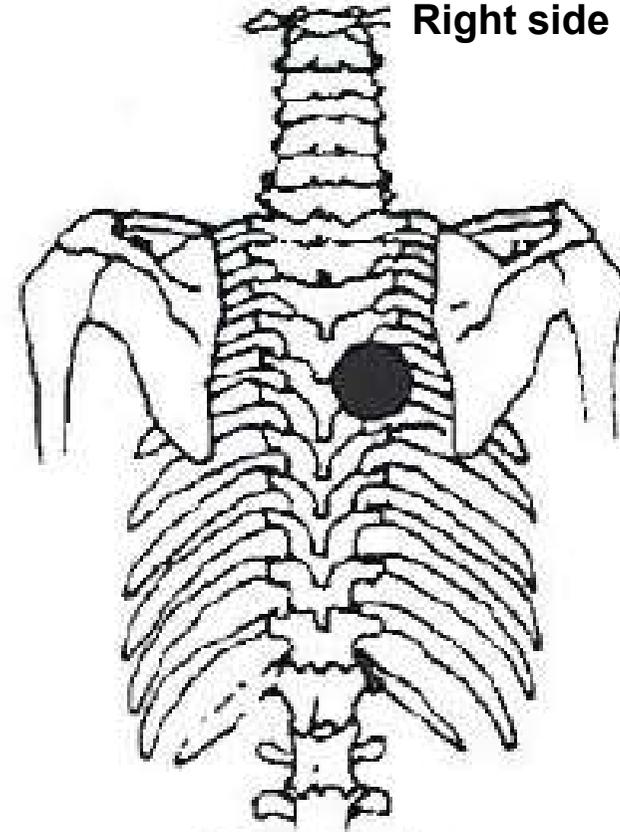
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5th IC space from mamillary line to the sternum right side only



Anterior

Between T5/T6.
Right side only



Posterior

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Bone Marrow

Bone marrow is the soft, flexible connective tissue within bone cavities. A component of the lymphatic system bone marrow functions primarily to produce blood cells and to store fat. Bone marrow is highly vascular, meaning that it is richly supplied with a large number of blood vessels.

There are two categories of bone marrow tissue: red marrow and yellow marrow. From birth to early adolescence, the majority of our bone marrow is red marrow. As we grow and mature, increasing amounts of red marrow are replaced by yellow marrow.

On average, bone marrow can generate hundreds of billions of new blood cells every day.

In the body, the major function of bone marrow is to produce blood cells.

Bone marrow also helps to remove old cells from the circulation.

Bone marrow has both a vascular component and a non-vascular component.

Disease can impact the body's bone marrow. Low blood cell production is often a result of damage or disease.

Bone marrow is separated into a vascular section and non-vascular sections.

The vascular section contains blood vessels that supply the bone with nutrients and transport blood stem cells and mature blood cells away from the bone and into circulation.

The non-vascular sections of the bone marrow are where hematopoiesis or blood cell formation occurs. This area contains immature blood cells, fat cells, white blood cells (macrophages and plasma cells), and thin, branching fibres of reticular connective tissue.

While all blood cells are derived from bone marrow, some white blood cells mature in other organs such as the spleen, lymph nodes, and thymus gland.

The major function of bone marrow is to generate blood cells. Bone marrow contains two main types of stem cells.

Hematopoietic stem cells, found in red marrow, are responsible for the production of blood cells.

Bone marrow mesenchymal stem cells (multipotent stromal cells) produce the non-blood cell components of marrow, including fat, cartilage, fibrous connective tissue (found in tendons and ligaments), stromal cells that support blood formation, and bone cells.

Red Marrow

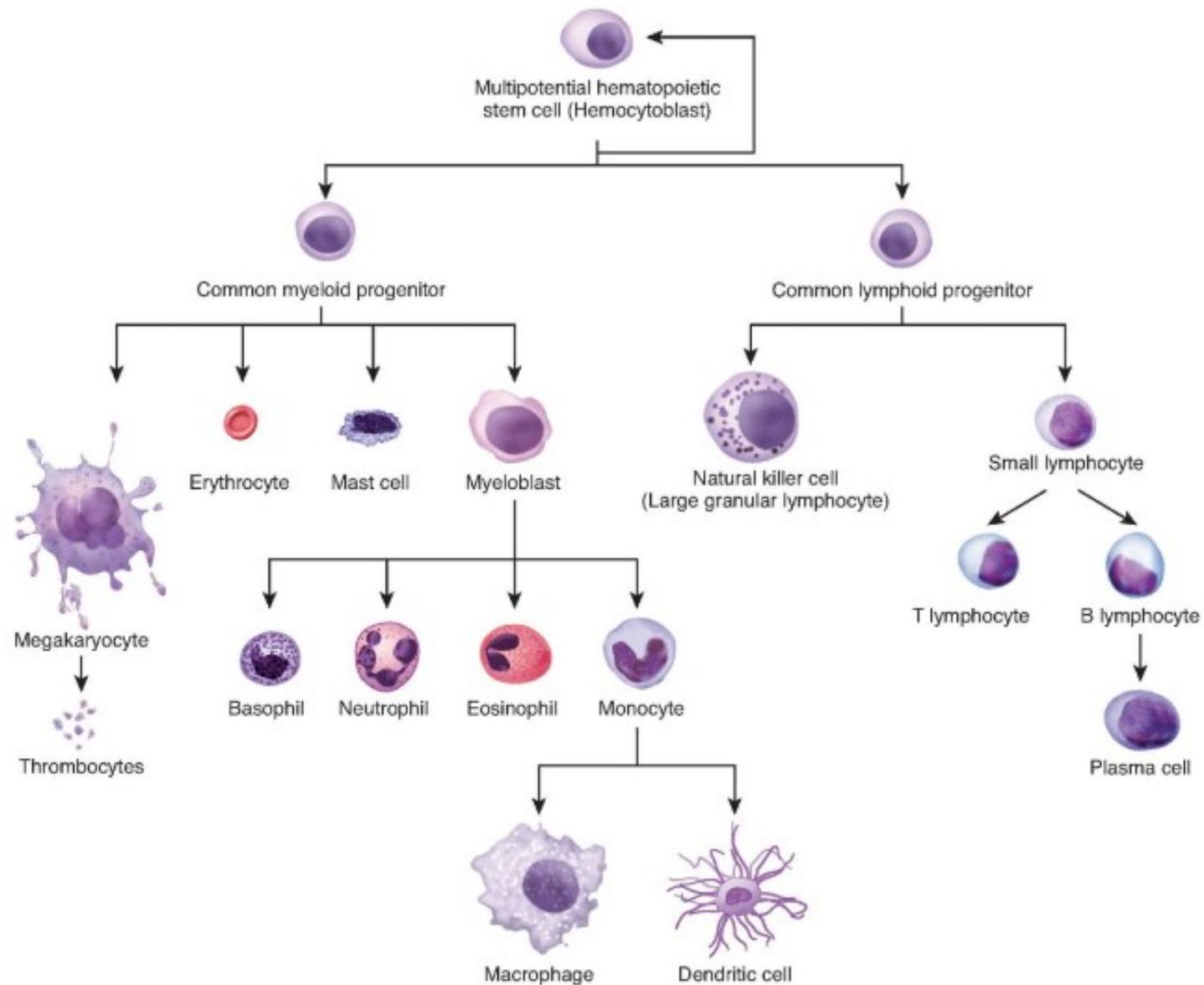
In adults, red marrow is confined mostly to skeletal system bones of the skull, pelvis, spine, ribs, sternum, shoulder blades, and near the point of attachment of the long bones of the arms and legs. Not only does red marrow produce blood cells, but it also helps to remove old cells from circulation.

Red marrow contains hematopoietic stem cells that produce two other types of stem cells: myeloid stem cells and lymphoid stem cells.

These cells develop into red blood cells, white blood cells, or platelets.

Yellow marrow consists primarily of fat cells. It has poor vascular supply and is composed of hematopoietic tissue that has become inactive. Yellow marrow is found in spongy bones and in the shaft of long bones.

When blood supply is extremely low, yellow marrow can be converted to red marrow in order to produce more blood cells.



 This image shows the formation, development, and differentiation of blood cells.

OpenStax, Anatomy & Physiology / [Wikimedia Commons/CC BY 4.0](https://commons.wikimedia.org/wiki/File:Blood_cell_differentiation.png)

Red bone marrow contains hematopoietic stem cells that produce two other types of stem cells: myeloid stem cells and lymphoid stem cells.

These cells develop into red blood cells, white blood cells, or platelets.

Myeloid Stem Cells - develop into red blood cells, platelets, mast cells, or myeloblast cells.

Myeloblast cells develop into granulocyte and monocyte white blood cells.

- **Red Blood Cells** — also called erythrocytes, these cells transport oxygen to body cells and deliver carbon dioxide to the lungs.

- **Platelets** —also called thrombocytes, these cells develop from megakaryocytes (huge cells) that break into fragments to form platelets. They aid in the blood clotting process and tissue healing.

Myeloblast Granulocytes (white blood cells) — develop from myeloblast cells and include neutrophils, eosinophils, and basophils. These immune cells defend the body against foreign invaders (bacteria, viruses, and other pathogens) and become active during allergic reactions.

• **Monocytes** — these large white blood cells migrate from blood to tissues and develop into macrophages and dendritic cells. Macrophages remove foreign substances, dead or damaged cells, and cancer cells from the body by phagocytosis.

Dendritic cells aid in the development of antigen immunity by presenting antigenic information to lymphocytes. They initiate primary immune responses and are commonly found in the skin, respiratory tract and gastrointestinal tract.

Mast Cells — these white blood cell granulocytes develop independently from myeloblast cells. They are found throughout body tissues, particularly in the skin and lining of the digestive system. Mast cells mediate immune responses by releasing chemicals, such as histamine, stored in granules.

Lymphoid Stem Cells — develop into lymphoblast cells, which produce other types of white blood cells called lymphocytes. Lymphocytes include natural killer cells, B lymphocytes, and T lymphocytes.

- **Natural Killer Cells** — these cytotoxic cells contain enzymes that cause apoptosis (cellular self-destruction) in infected and diseased cells. They are components in the body's innate immune response protecting against pathogens and tumour development.

- **B Cell Lymphocytes** — these cells are important for adaptive immunity and long lasting protection against pathogens. They recognize molecular signals from pathogens and produce antibodies against specific antigens.

• **T Cell Lymphocytes** — these cells are active in cell-mediated immunity. They help to identify and destroy damaged, cancerous, and infected cells.

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