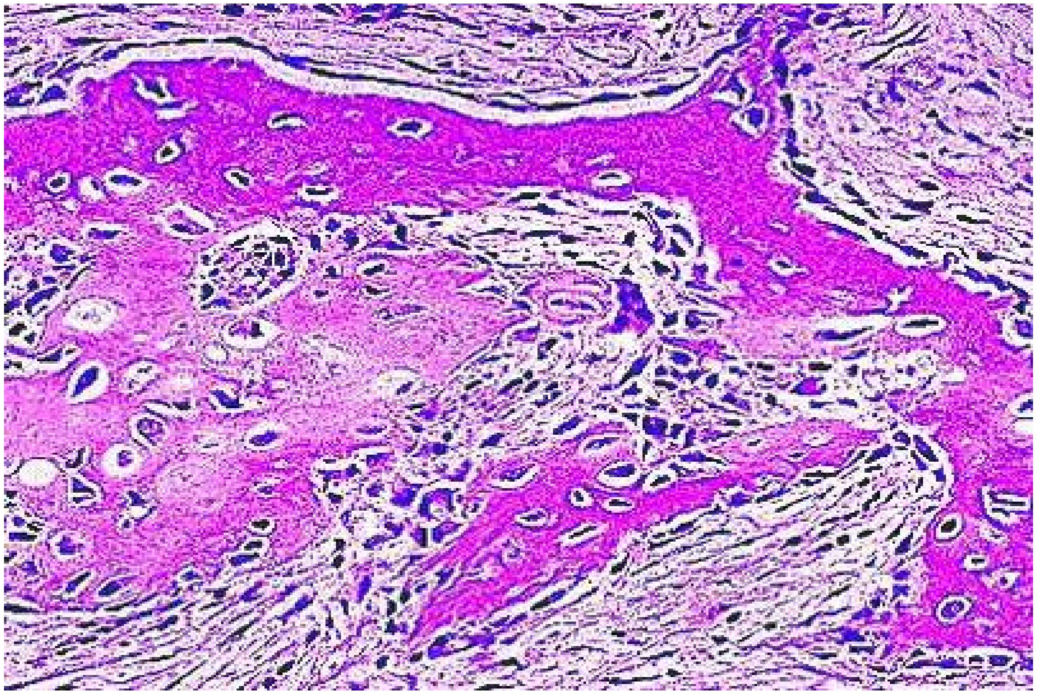
BONE STRUCTURE AND HORMONAL CONTROL

D.HAMMOUDI.MD

Bone

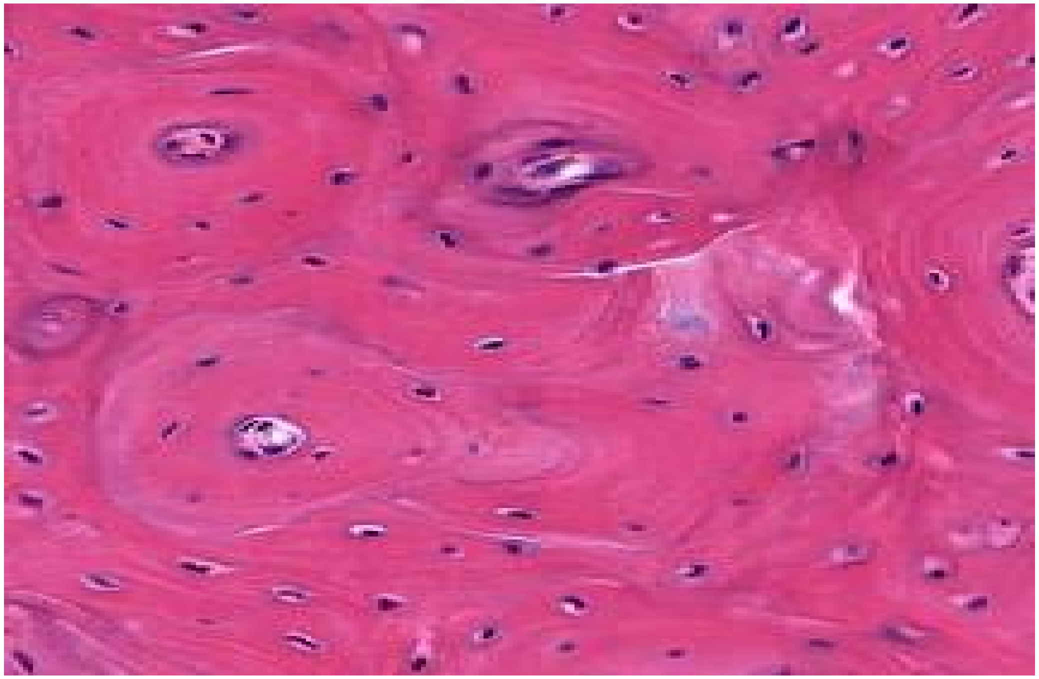
Woven bone

1. Immature bone formed rapidly as in the fetus or repair of an injury.
2. Collagen is irregularly arranged.



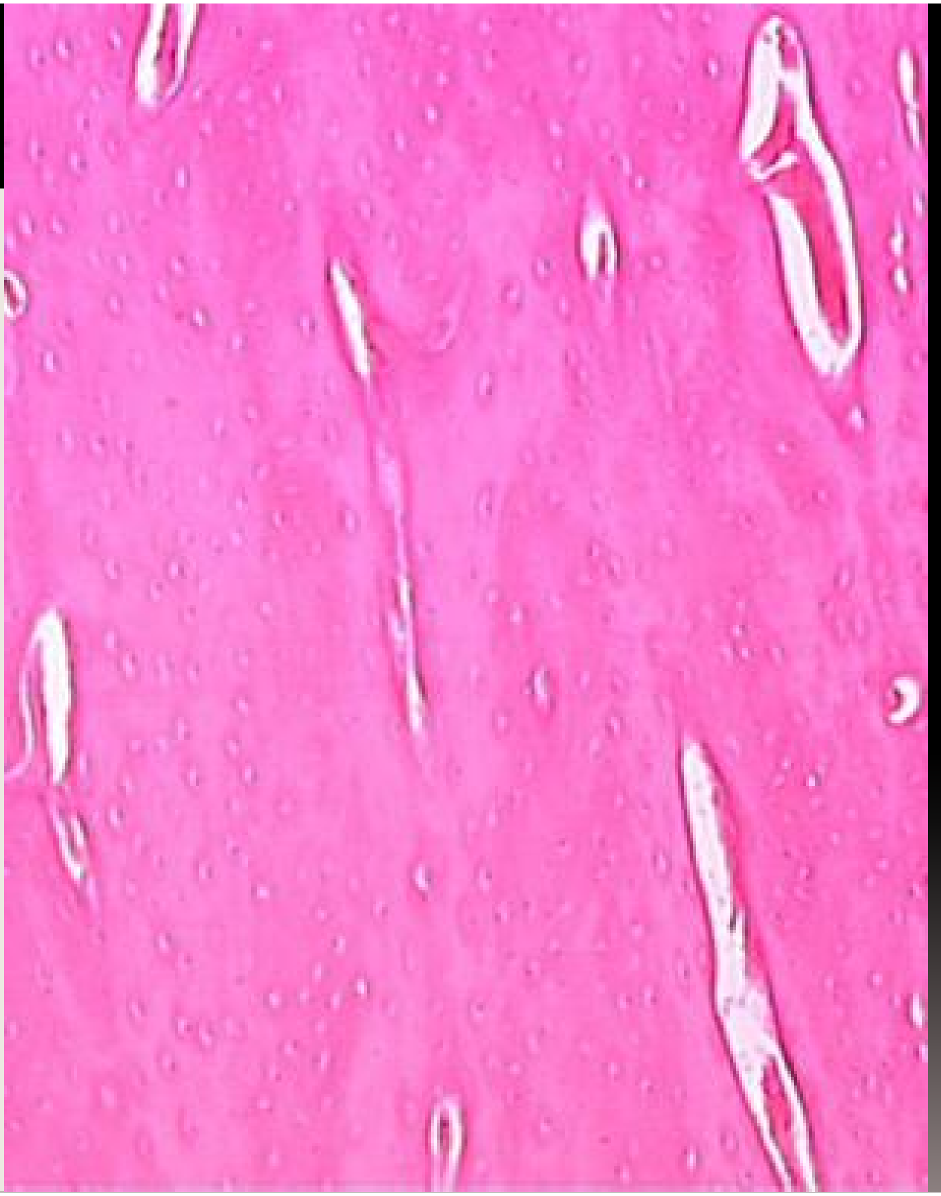
Lamellar bone

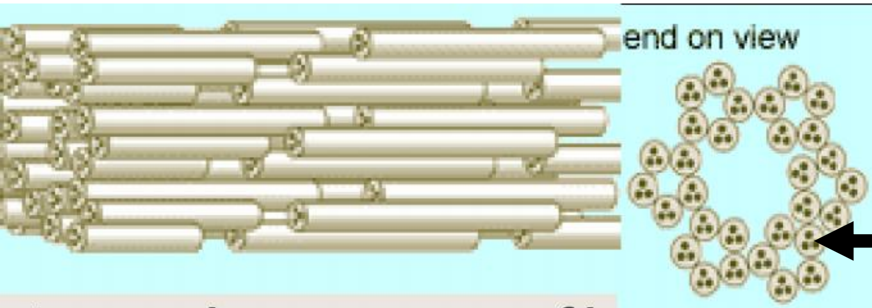
1. Mature bone that is physically stronger.
2. Collagen is regularly arranged



Bone Structure

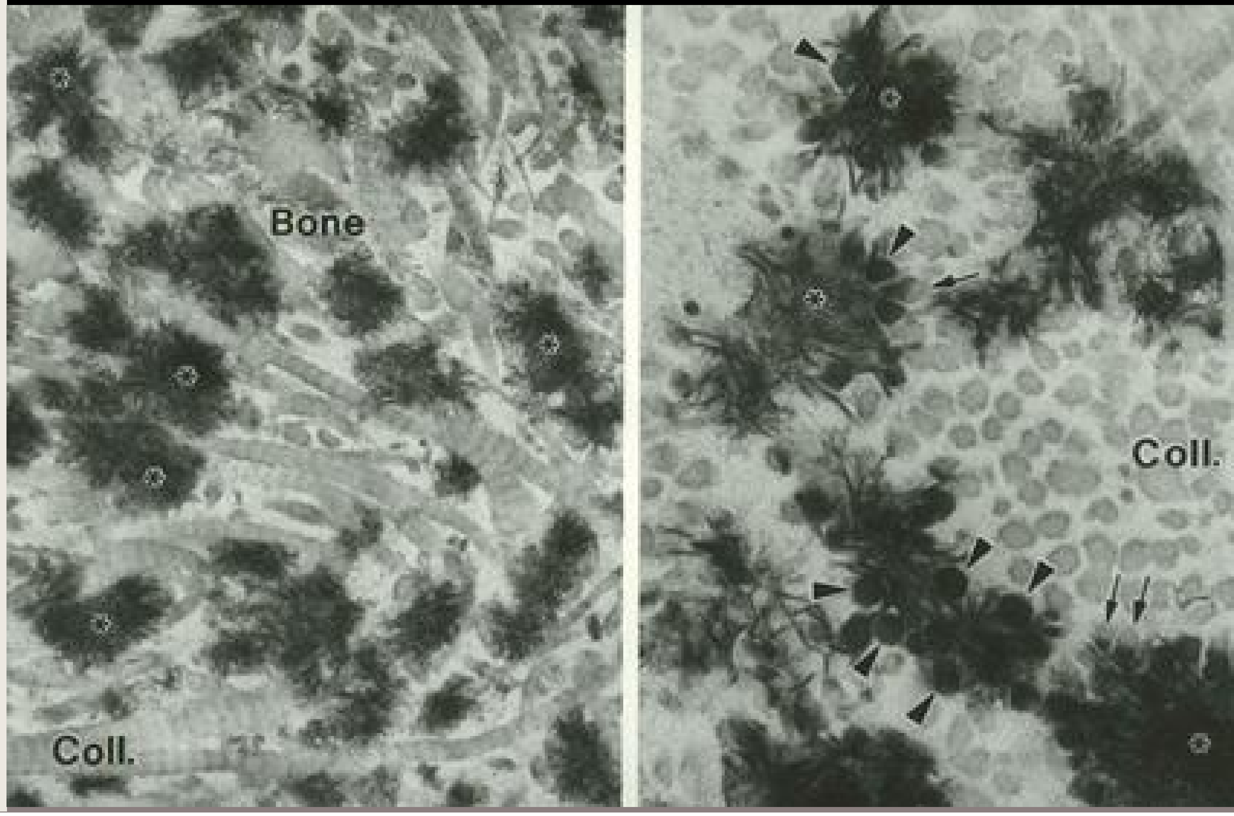
- **Bone Matrix:**
  - Consists of **organic and inorganic components.**
  - **1/3 organic and 2/3 inorganic by weight**.
    - **Organic component consists of several materials that are secreted by the osteoblasts:**
      - **Collagen fibers and other organic materials**
        - These (particularly the collagen) provide the bone with resilience and the ability to resist stretching and twisting.





Three-dimensional array of collagen molecules. The rod-shaped molecules lie in a staggered arrangement which acts as a template for bone mineralization. Bone mineral is laid down in the gaps.

Note collagen fibers in longitudinal & cross section and how they occupy space btwn the black bone cells.



Inorganic component of bone matrix

- Consists mainly of 2 salts:

-**calcium phosphate**

-calcium hydroxide.

- These 2 salts interact to form a compound called **hydroxyapatite.**

  - **Bone also contains smaller amounts of magnesium, fluoride, and sodium.**
  - These minerals give bone its characteristic hardness and the ability to resist compression.

This bone:

a. Has been demineralized

b. Has had its organic component removed

Hormonal control

Hormones important to bone growth and homeostasis:

- **Growth Hormone (GH)** –
- **The thyroid hormones (e.g. thyroxine)** –
- **Testosterone -**
- Estrogens -
- **Calcitonin –**
- **Parathyroid hormones**
- **Insulin**
- **Glucocorticoids**

Hormones important to bone growth and homeostasis:

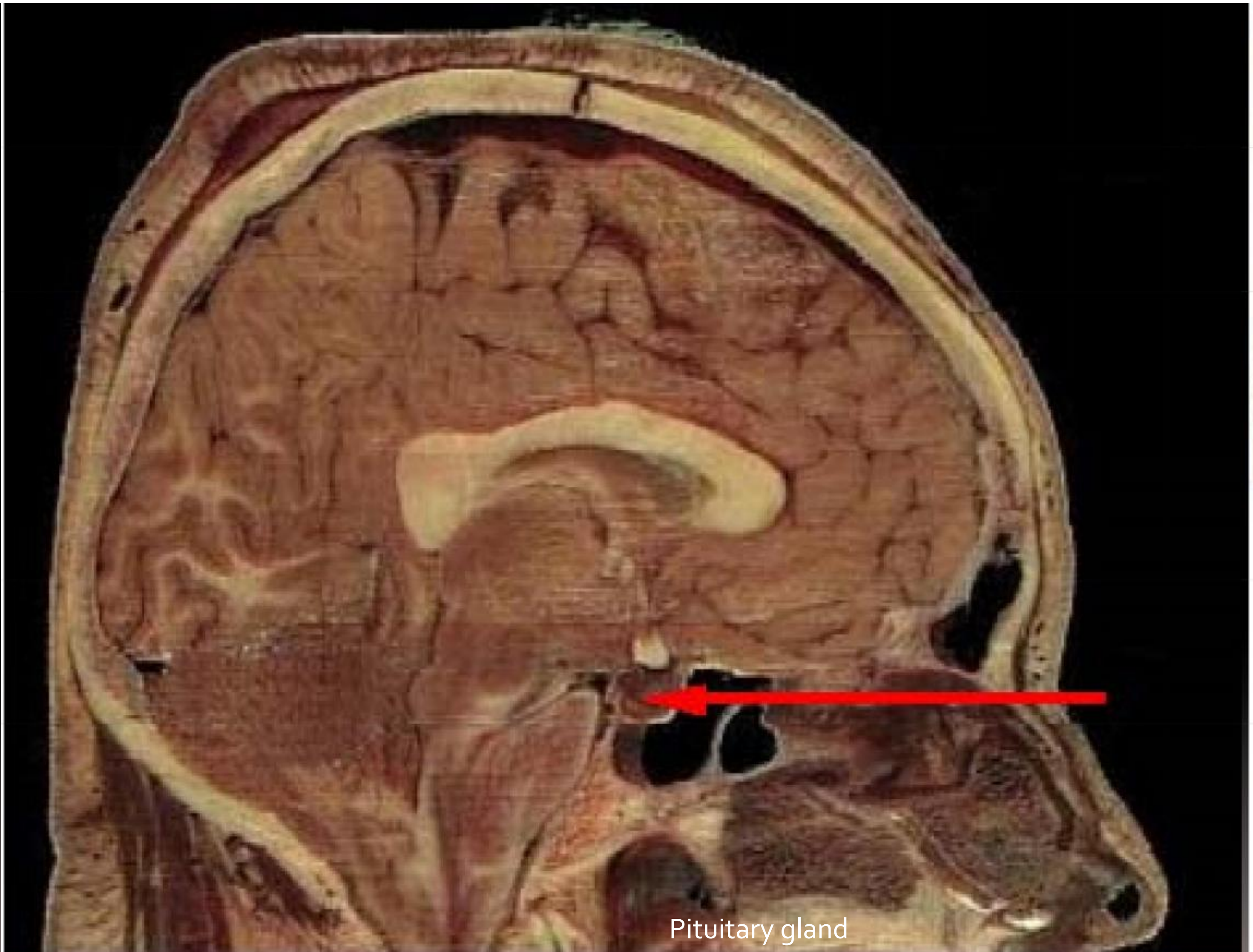
•**Growth Hormone (GH)** - from the **anterior pituitary**, this hormone is necessary for normal growth and development of the skeleton.
A deficiency (hyposecretion) of GH during childhood produces a **dwarf**,
An excess (hypersecretion) produces a **giant.**
Hypersecretion in adulthood produces **acromegaly,** a disorder in which the shape of many bones, especially those in the face becomes exaggerated.

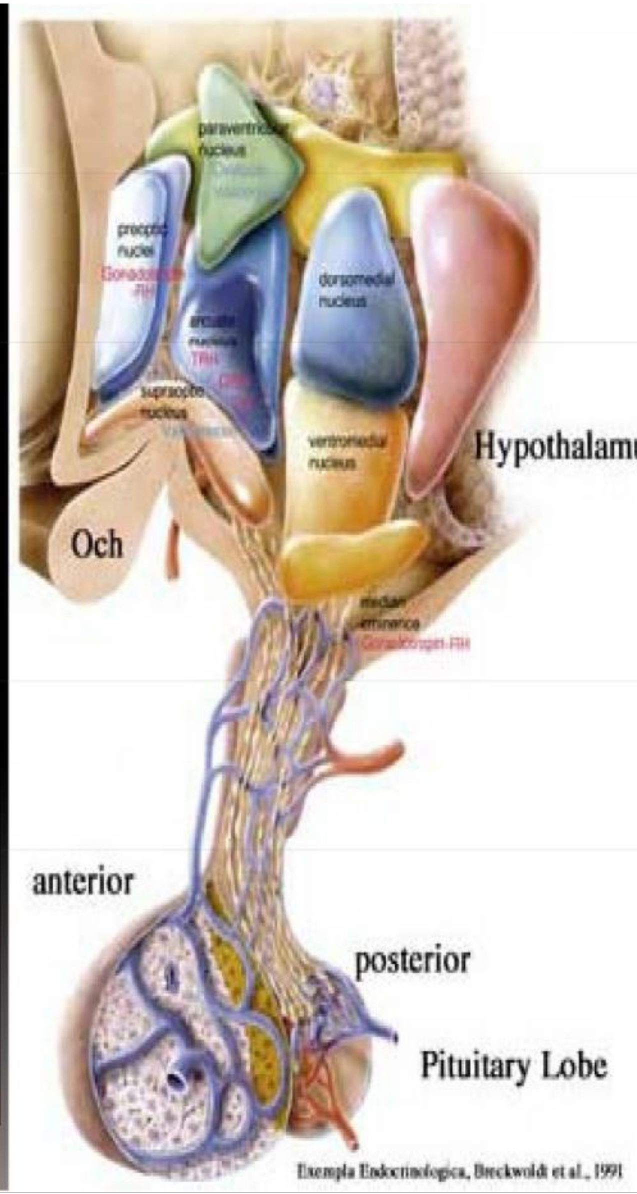
•**The thyroid hormones (e.g. thyroxine)** - regulate metabolism of most cells including those in bone.

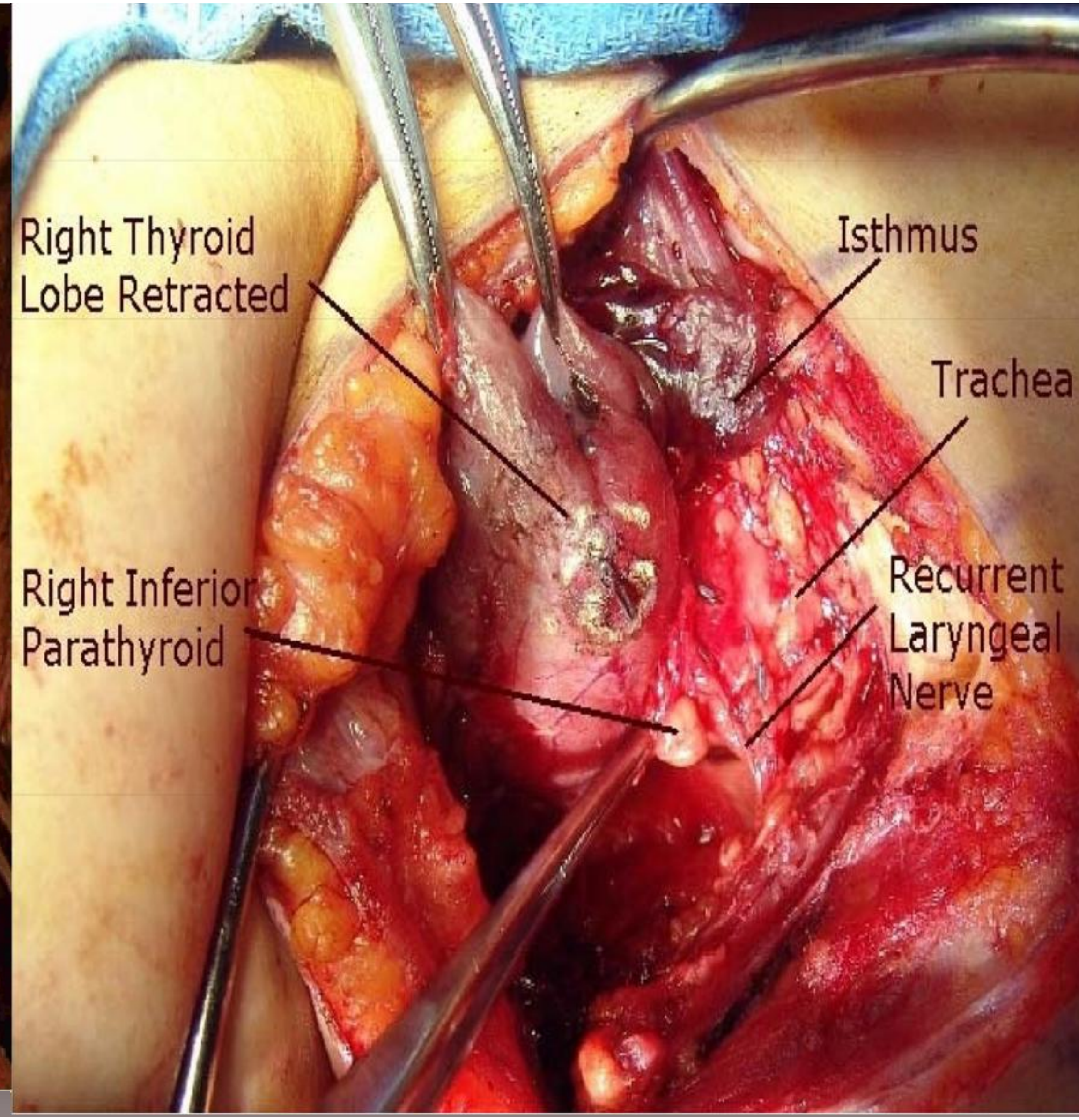
•**Testosterone -** this and other androgens are important for growth in mass and density of bone. Testosterone is present in both males and females in varying amounts.

• **Estrogens** - these hormones are important for growth in length of bone and for bone maintenance. They too are present in varying amounts in both sexes.

•**Calcitonin - Normally important only in children**, this hormone is secreted by special cells in the thyroid. Its function is to stimulate the uptake of calcium into growing bone and the deposition of bone matrix. It is not produced, nor is it effective therapeutically, in adults.

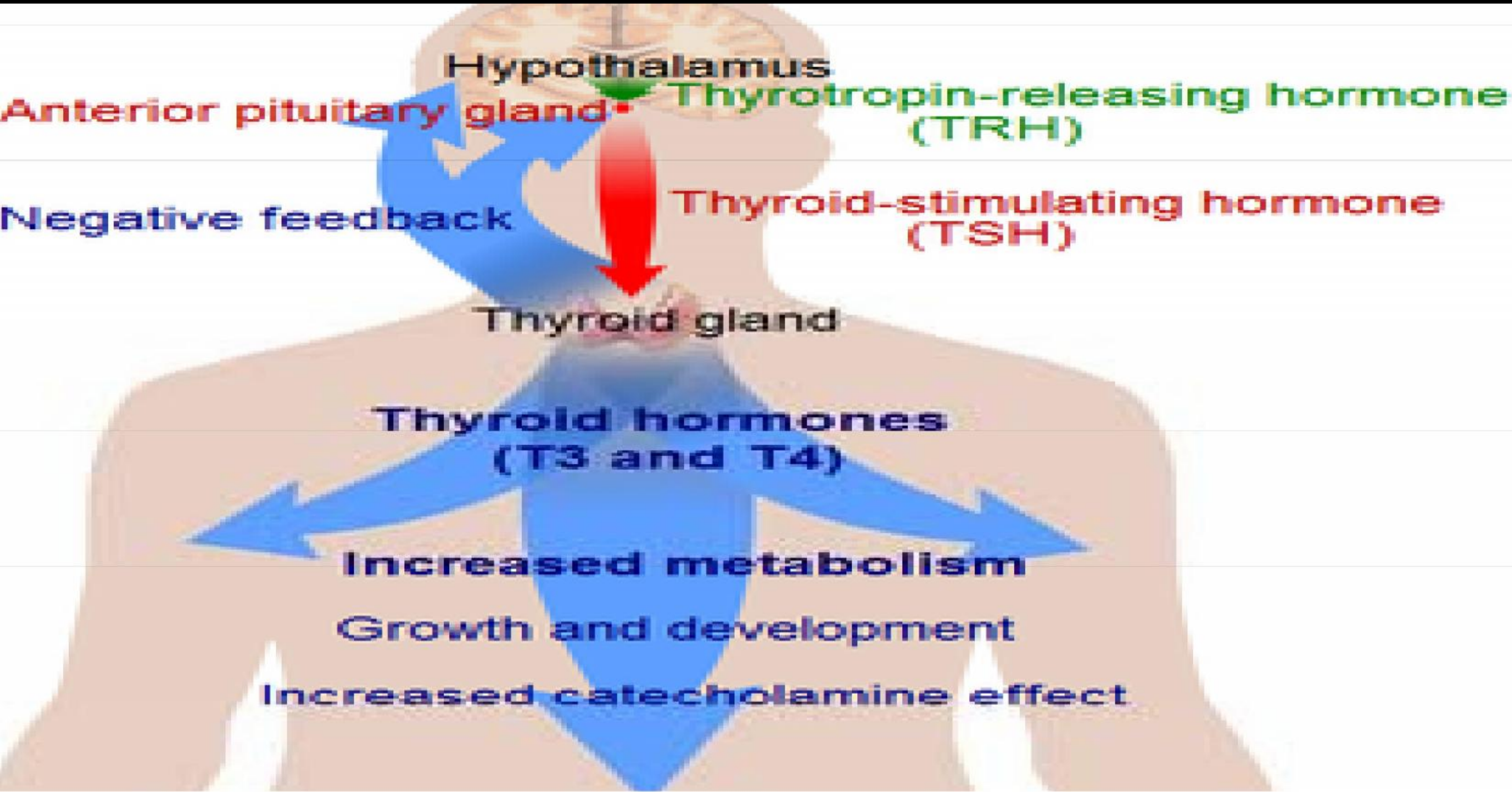

Pituitary gland

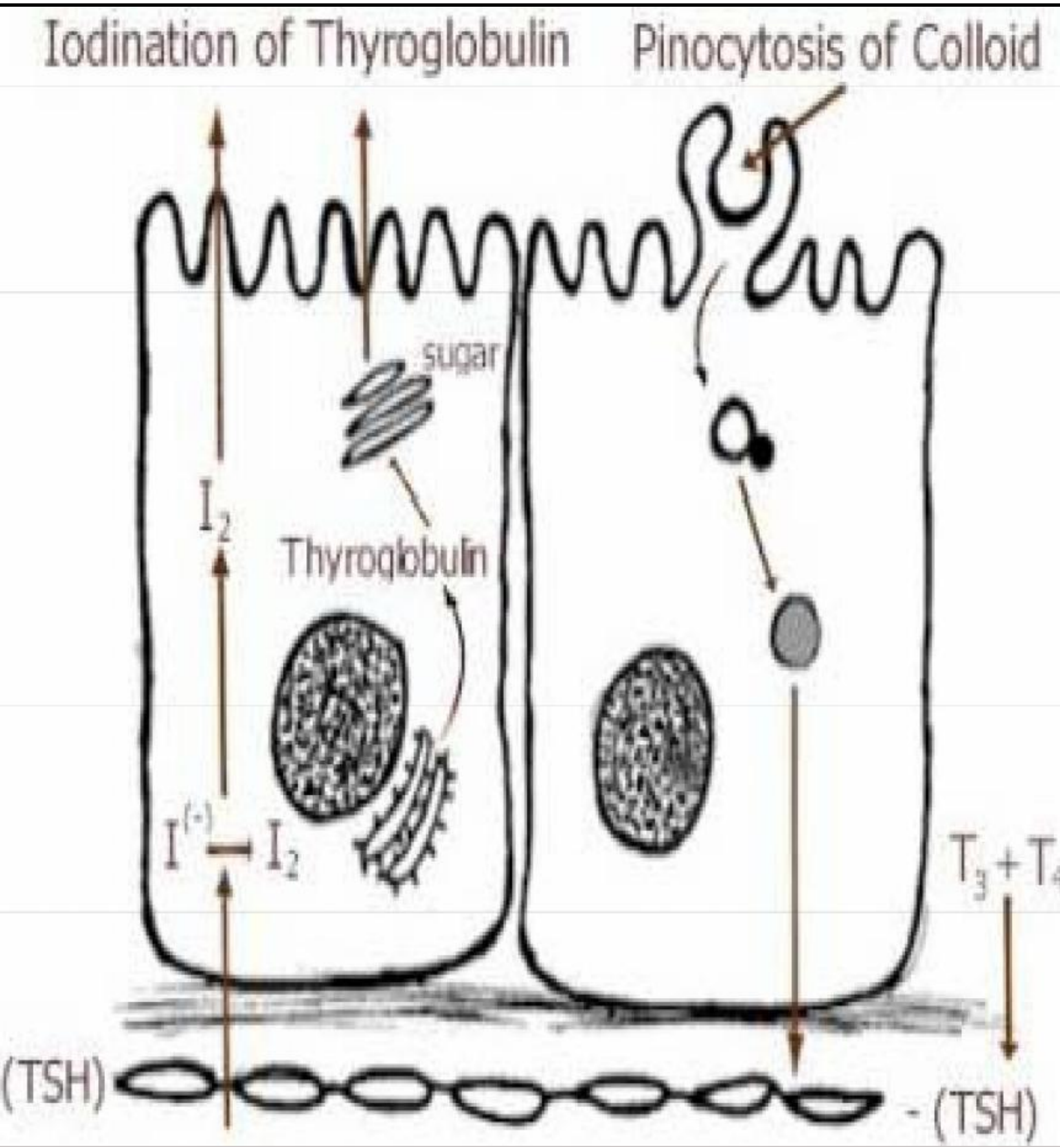

paraventricular nucleus
preoptic nuclei
dorsomedial nucleus
supraoptic nucleus
ventromedial nucleus
Hypothalamu
Och
median eminence
anterior
posterior
Pituitary Lobe
Exempla Endocrinologica, Breckwoldt et al., 1991



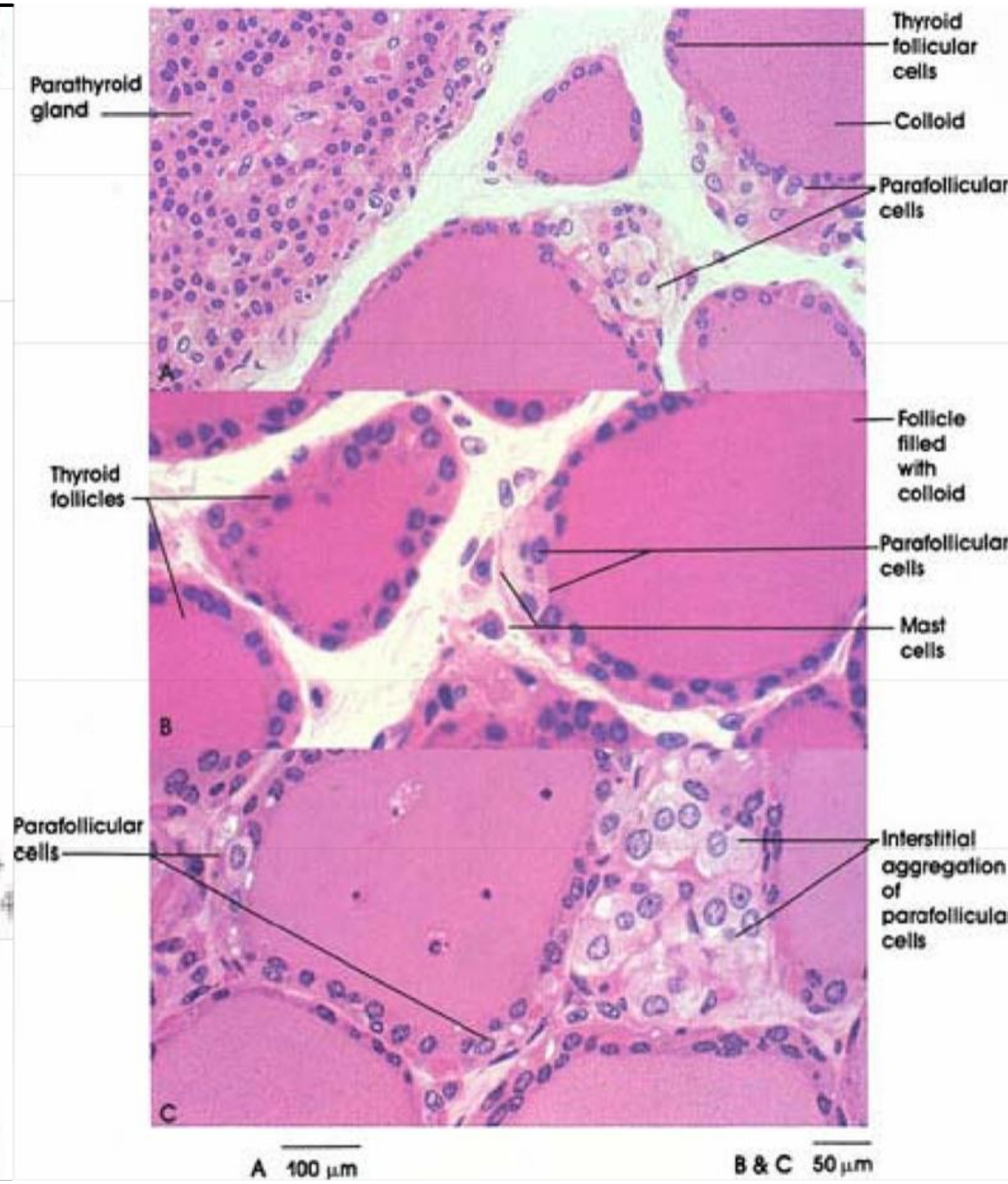
Right Thyroid
Lobe Retracted
Isthmus
Trachea
Right Inferior
Parathyroid
Recurrent
Laryngeal
Nerve

Thyroid system

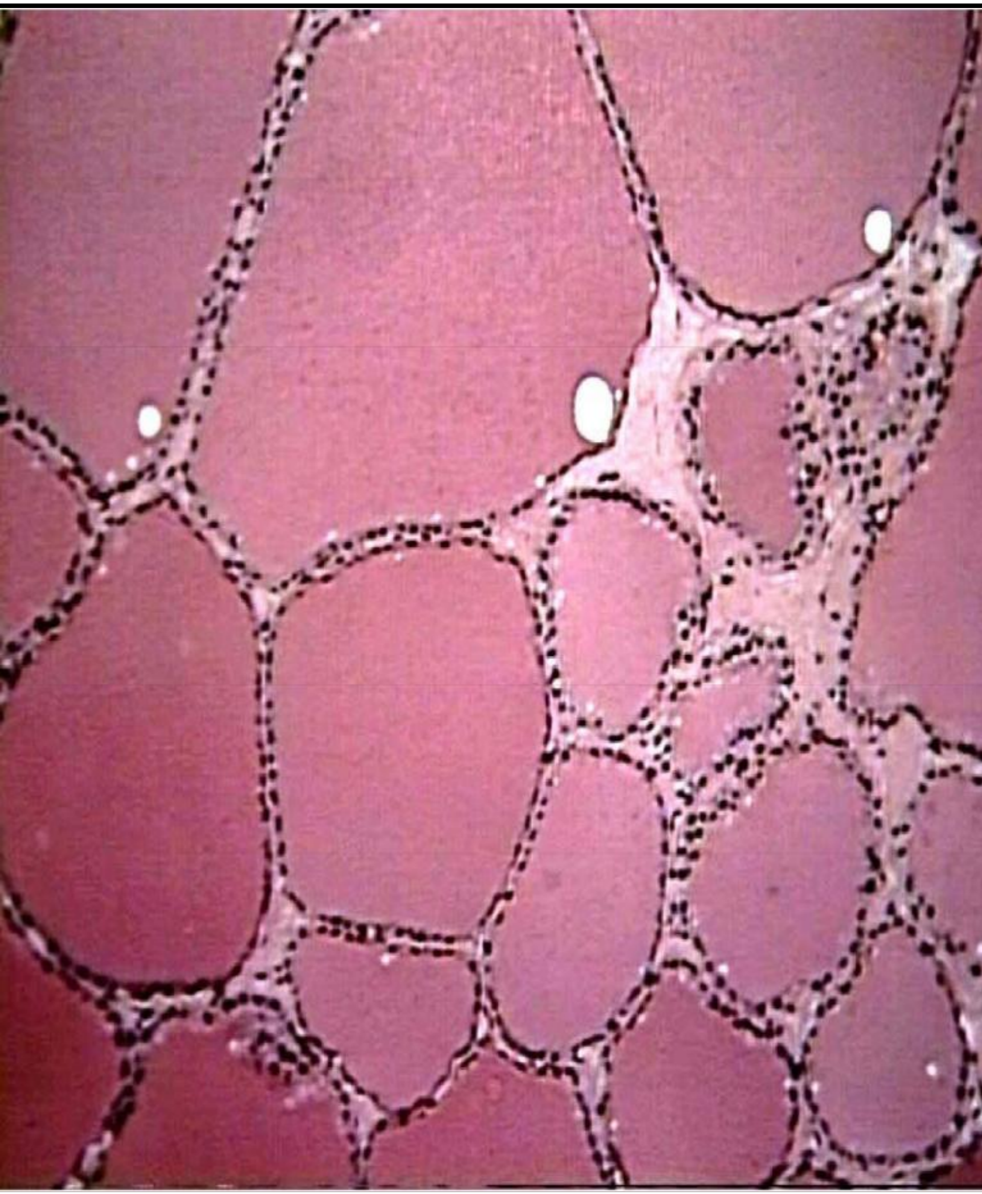


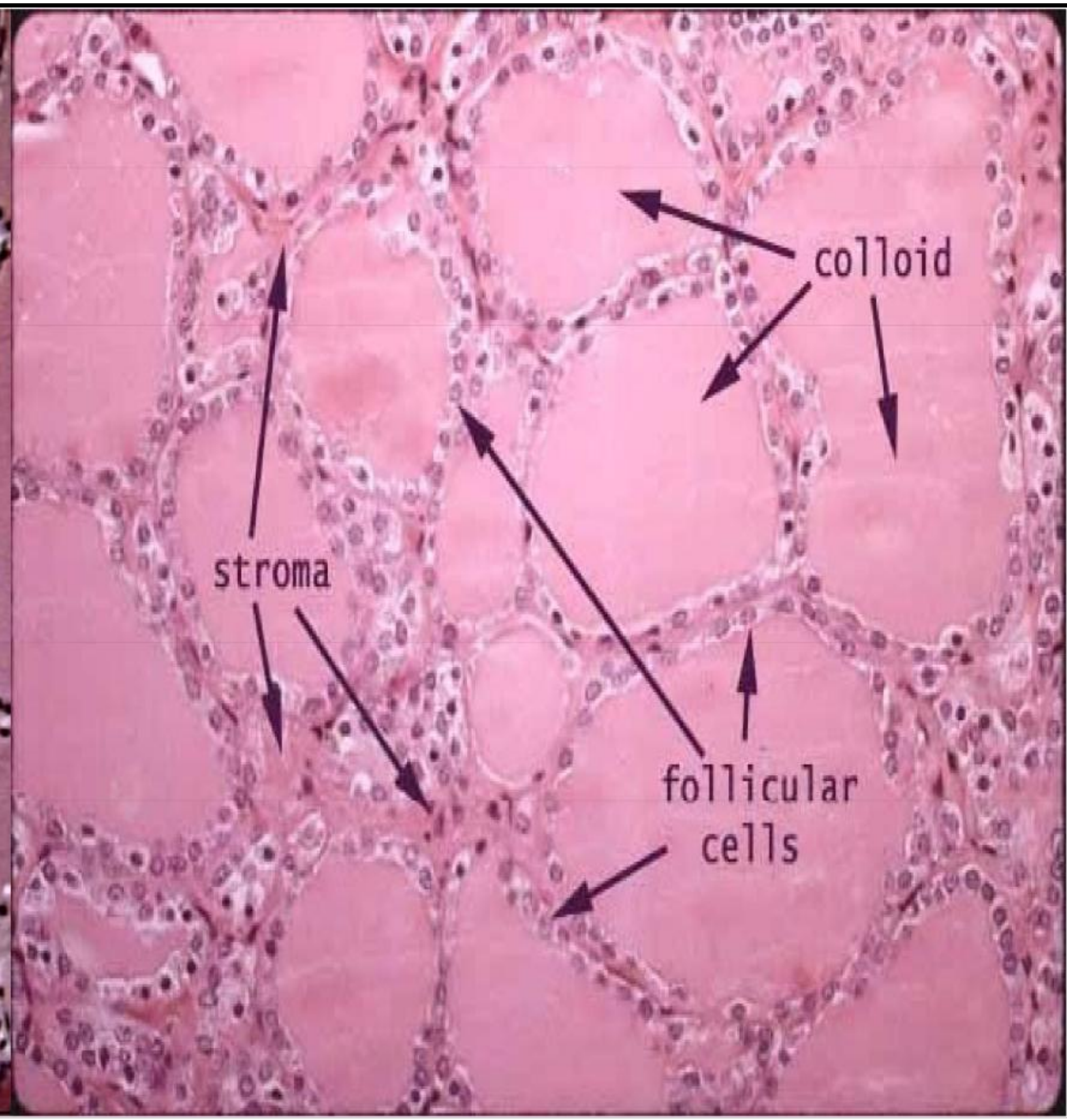


Iodination of Thyroglobulin
Pinocytosis of Colloid
sugar
I_2
Thyroglobulin
$I^{(-)} \rightarrow I_2$
$T_3 + T_4$
(TSH)
- (TSH)



Parathyroid gland
Thyroid follicular cells
Colloid
Parafollicular cells
A
Thyroid follicles
Follicle filled with colloid
Parafollicular cells
Mast cells
B
Parafollicular cells
Interstitial aggregation of parafollicula cells
C
A 100 µm
B & C 50 µm




colloid
stroma
follicular
cells

Parathyroid hormone -

- this hormone exerts the primary control in calcium homeostasis.
- Calcium is necessary in the blood for many functions and when its level falls parathyroid hormone is secreted.

This hormone uses several methods to raise calcium levels in the blood:

1) increased Vitamin D production. Vitamin D is a hormone whose precursor is produced in the skin in response to sunlight and then processed in the liver and kidney to become active Vitamin D3. Vitamin D3 increases calcium absorption in the gut. Without this vitamin calcium is not absorbed to any great degree.

2) Increased reabsorption of calcium in the kidney. Much calcium is lost to the urine, so when you need more in the blood this is an important source.

3) Resorption of bone. PTH increases osteoclastic activity to release calcium into the blood.

Other hormones that affect bone growth include **insulin** and the **glucocorticoids**.

- **Insulin stimulates bone formation**
- **Glucocorticoids inhibit osteoclast activity.**

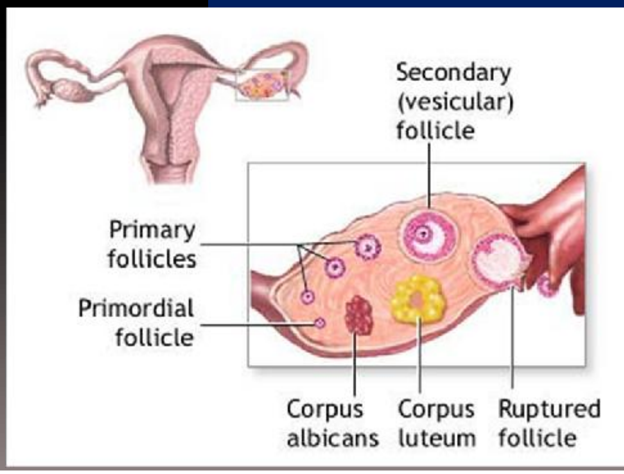
Testosterone

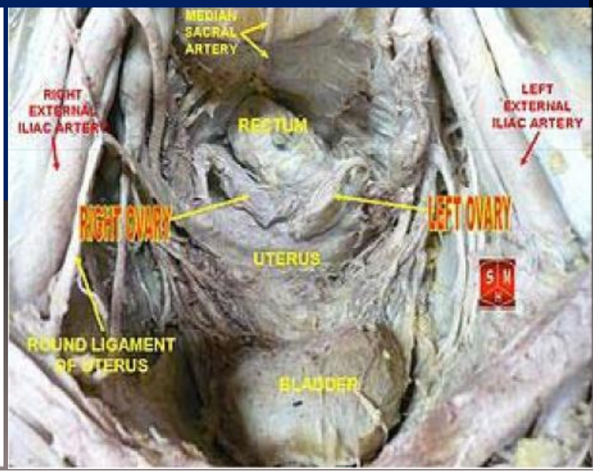
is primarily secreted in the testicles of males and the ovaries of females, although small amounts are also secreted by the adrenal glands.

In the testes **the leydig cells** [**interstitial cells of Leydig]** produce the testosterone

Estrogens

- are produced primarily by developing follicles in the
- ovaries, the corpus luteum, and the placenta.
- Follicle-stimulating hormone (FSH) stimulates the production of estrogen in the granulosa cells of
- the ovaries.
- Some estrogens are also produced in smaller amounts by other tissues such as the liver, adrenal glands, and the breasts.
- Fat cells also produce estrogen



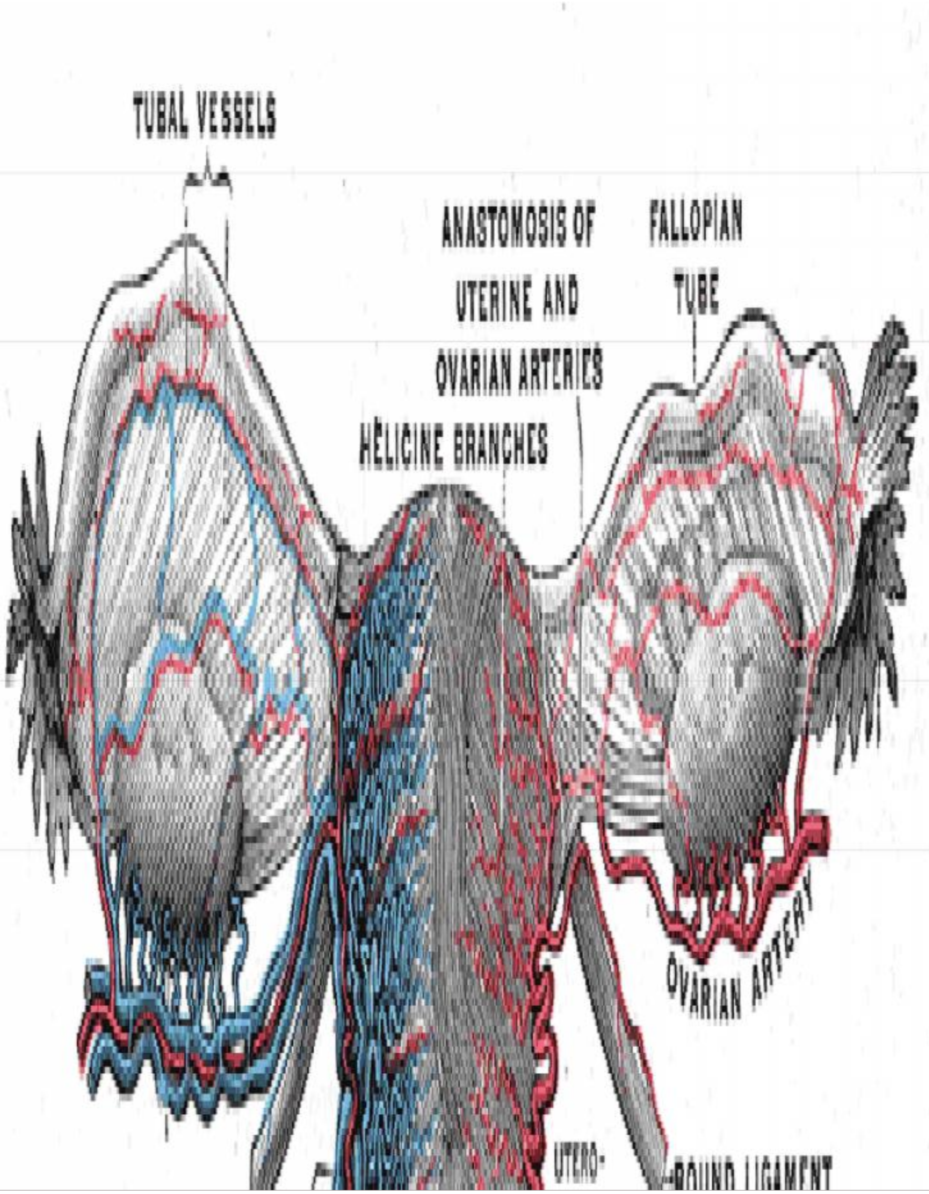


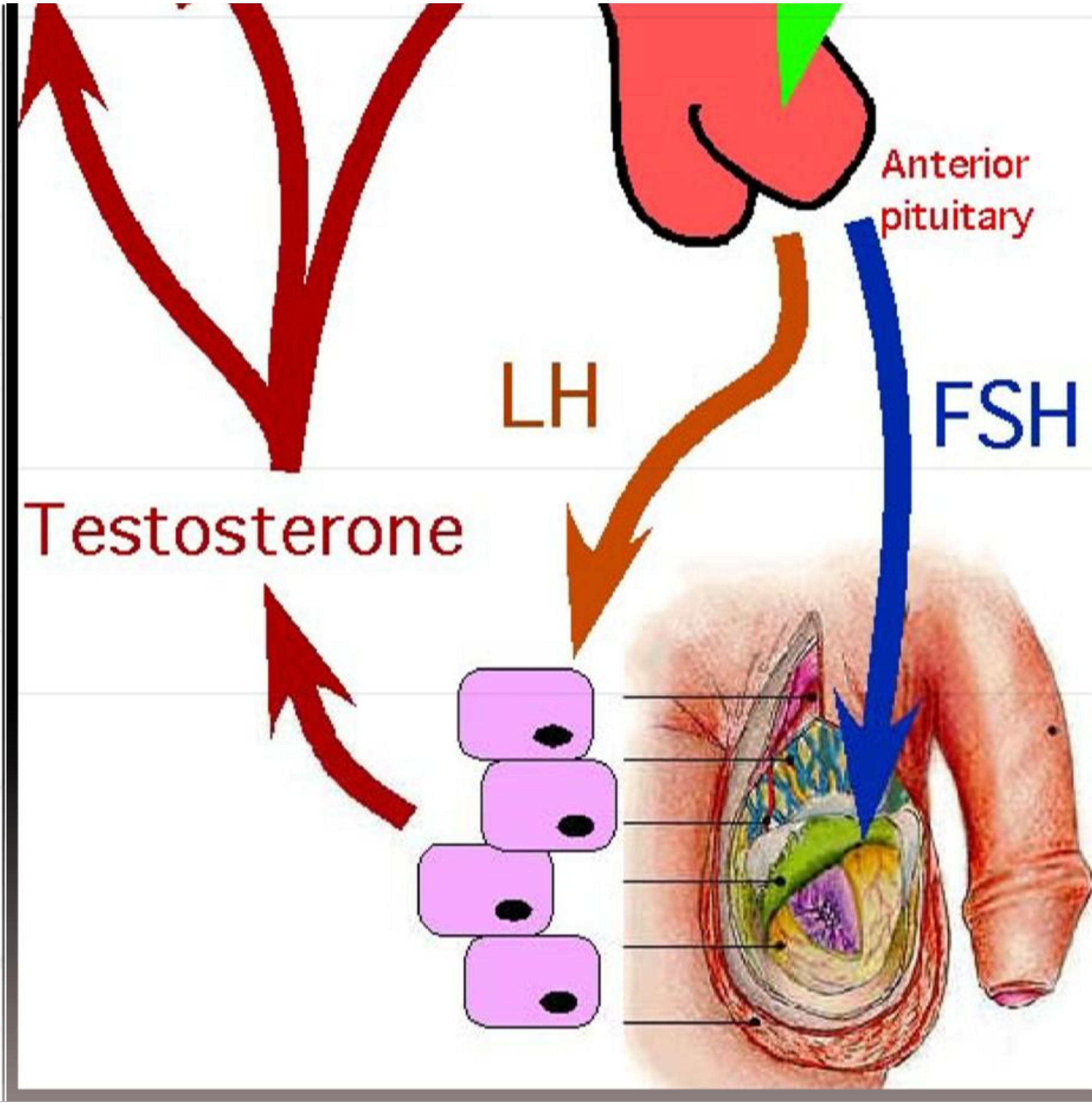
- At puberty, the rising levels of sex hormones (estrogens in females and androgens in males) cause osteoblasts to produce bone faster than the epiphyseal cartilage can divide.

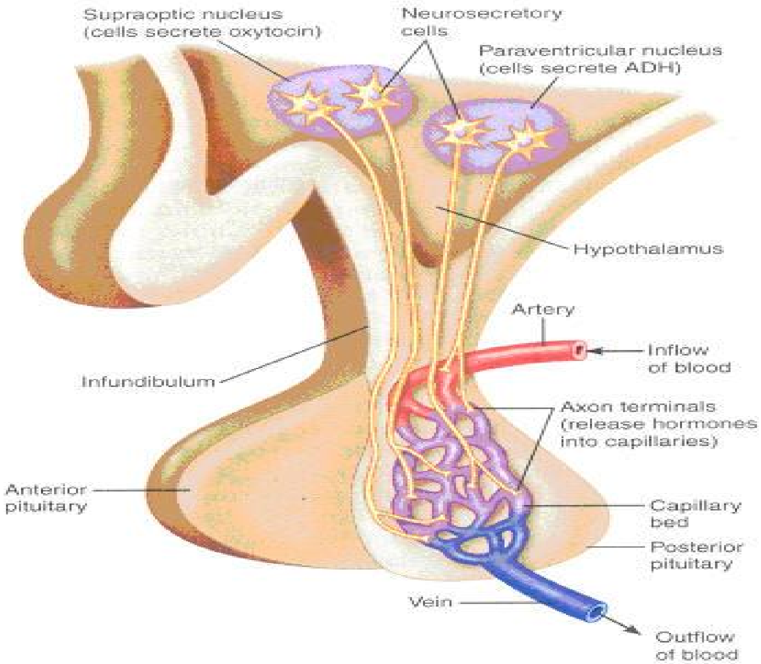
- This causes the characteristic growth spurt as well as the ultimate closure of the epiphyseal plate.

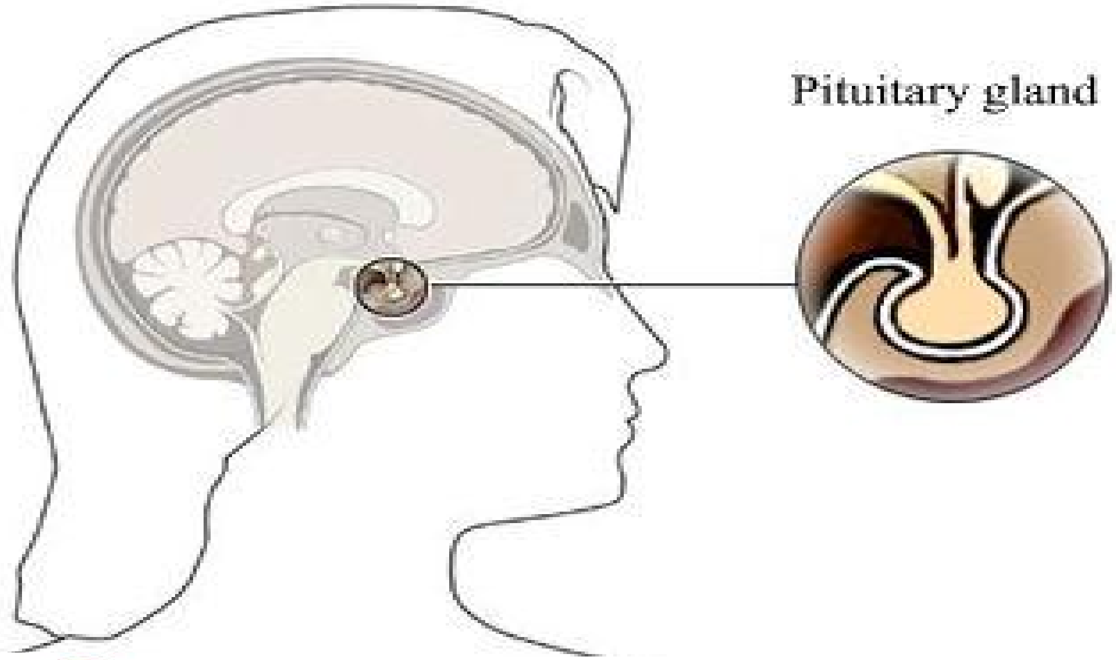
- Estrogens cause faster closure of the epiphyseal growth plate than do androgens.

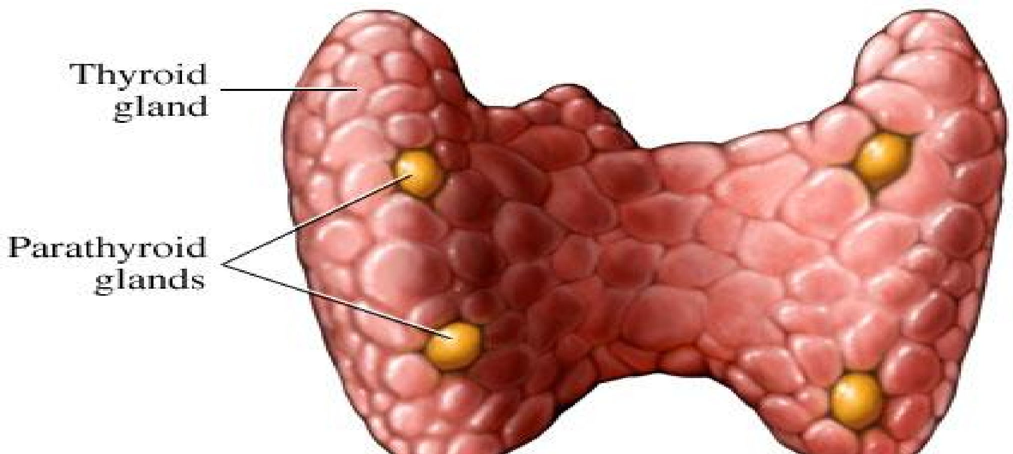
- Estrogen also acts to stimulate osteoblast activity


TUBAL VESSELS
ANASTOMOSIS OF UTERINE AND OVARIAN ARTERIES
FALLOPIAN TUBE
HÉLICINE BRANCHES
OVARIAN ARTERY
UTERO-
ROUND LIGAMENT

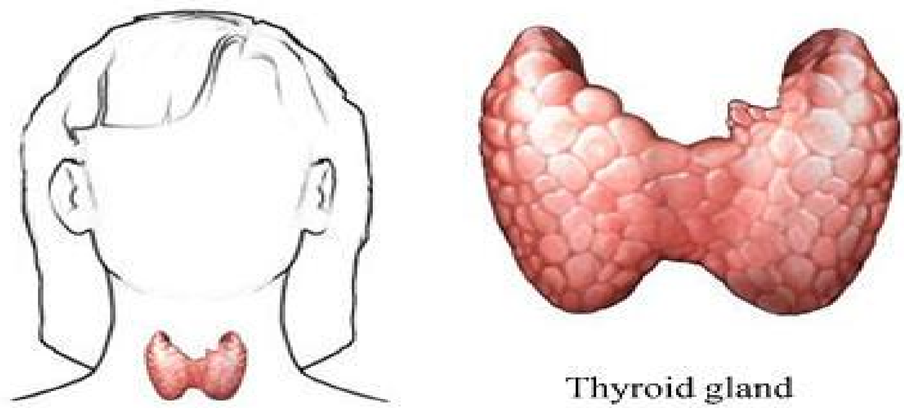

Anterior pituitary
LH
FSH
Testosterone





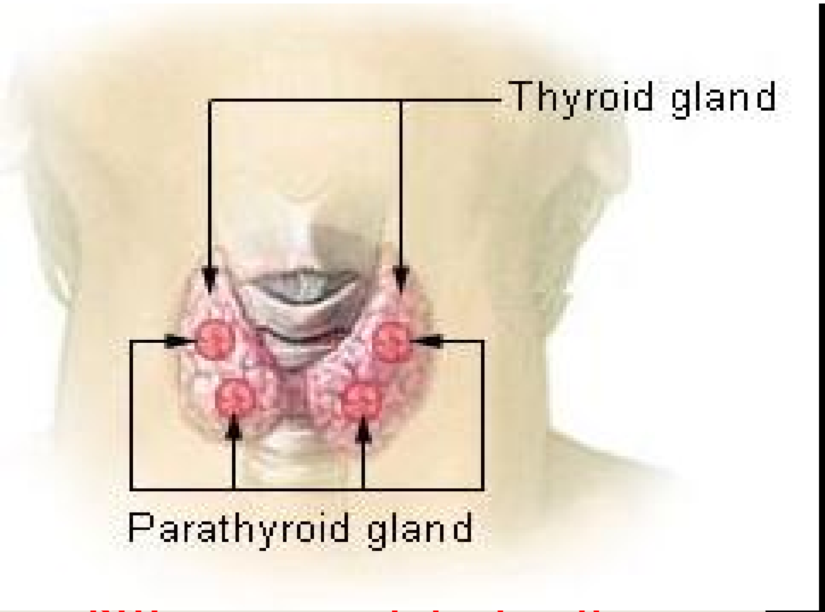


Back view

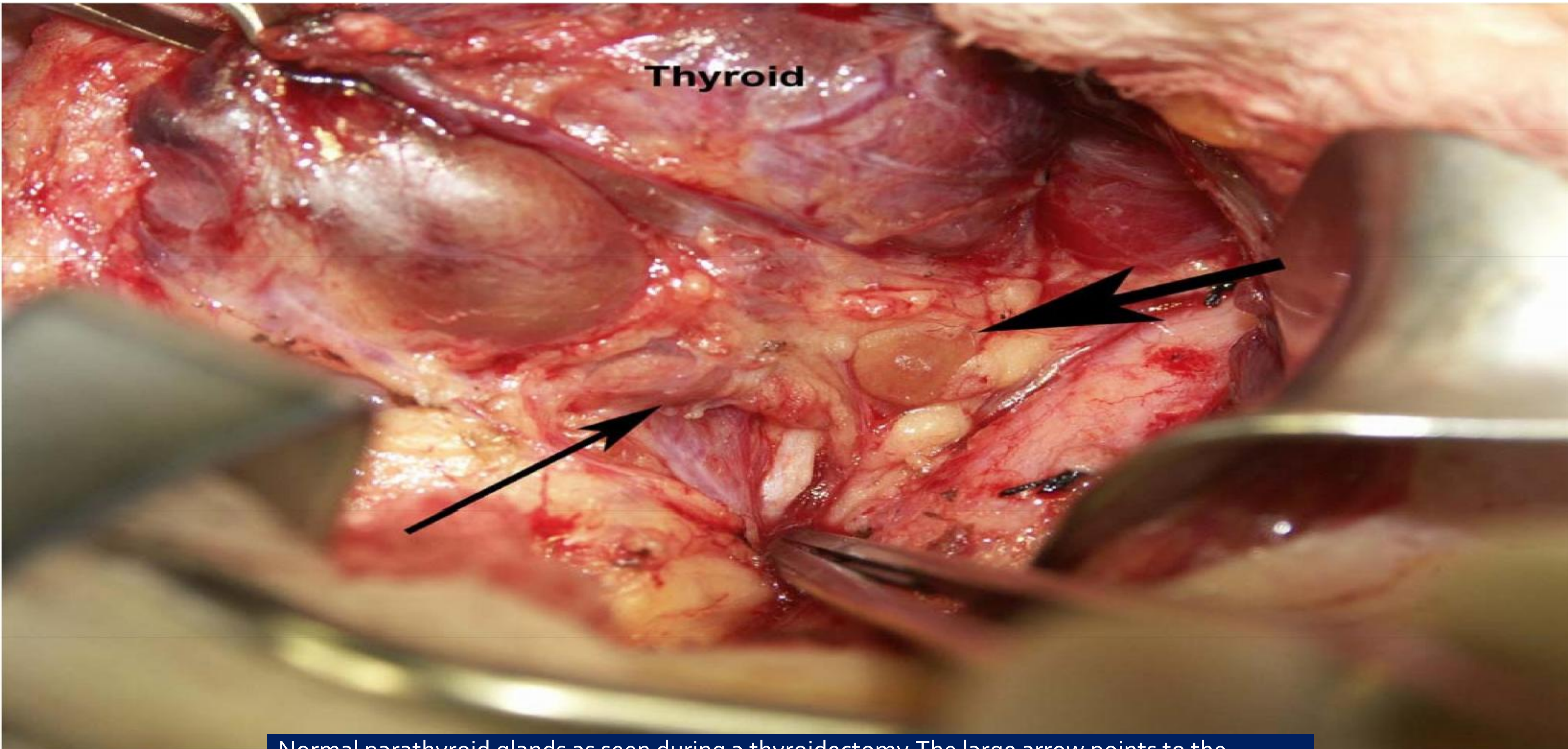

Thyroid gland

Parathyroid Hormone

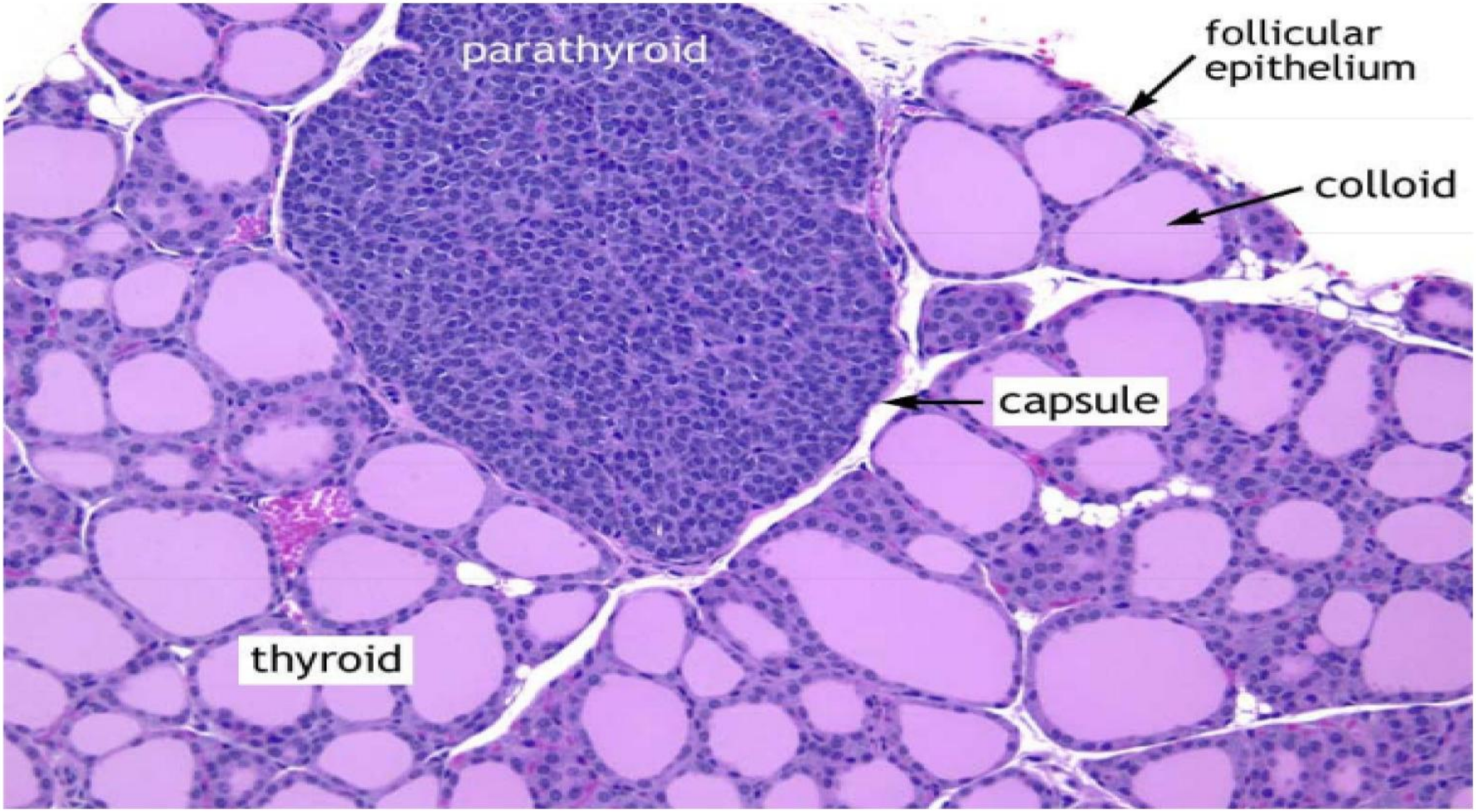
- Released by the cells of the parathyroid gland in response to low blood [Ca^{2+}].Causes blood [Ca^{2+}] to increase.
- PTH will bind to osteoblasts and this will cause 2 things to occur:
  - The osteoblasts will decrease their activity and they will release a chemical known as *osteoclast-stimulating factor*.
  - Osteoclast-stimulating factor will increase osteoclast activity.

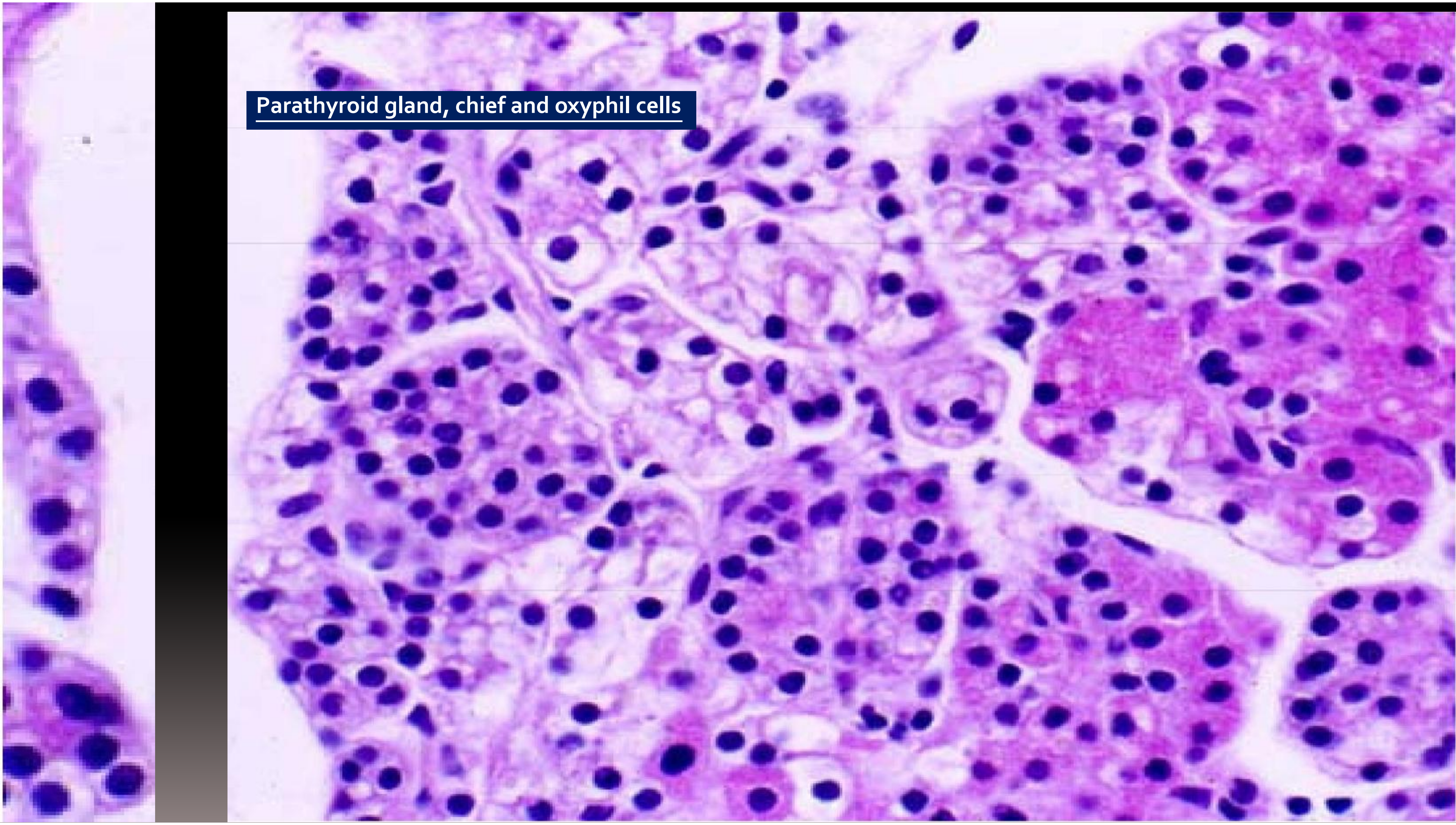


- PTH increases calcitriol synthesis which increases Ca^{2+} absorption in the small intestine.
- PTH decreases urinary Ca^{2+} excretion and increases urinary phosphate excretion.



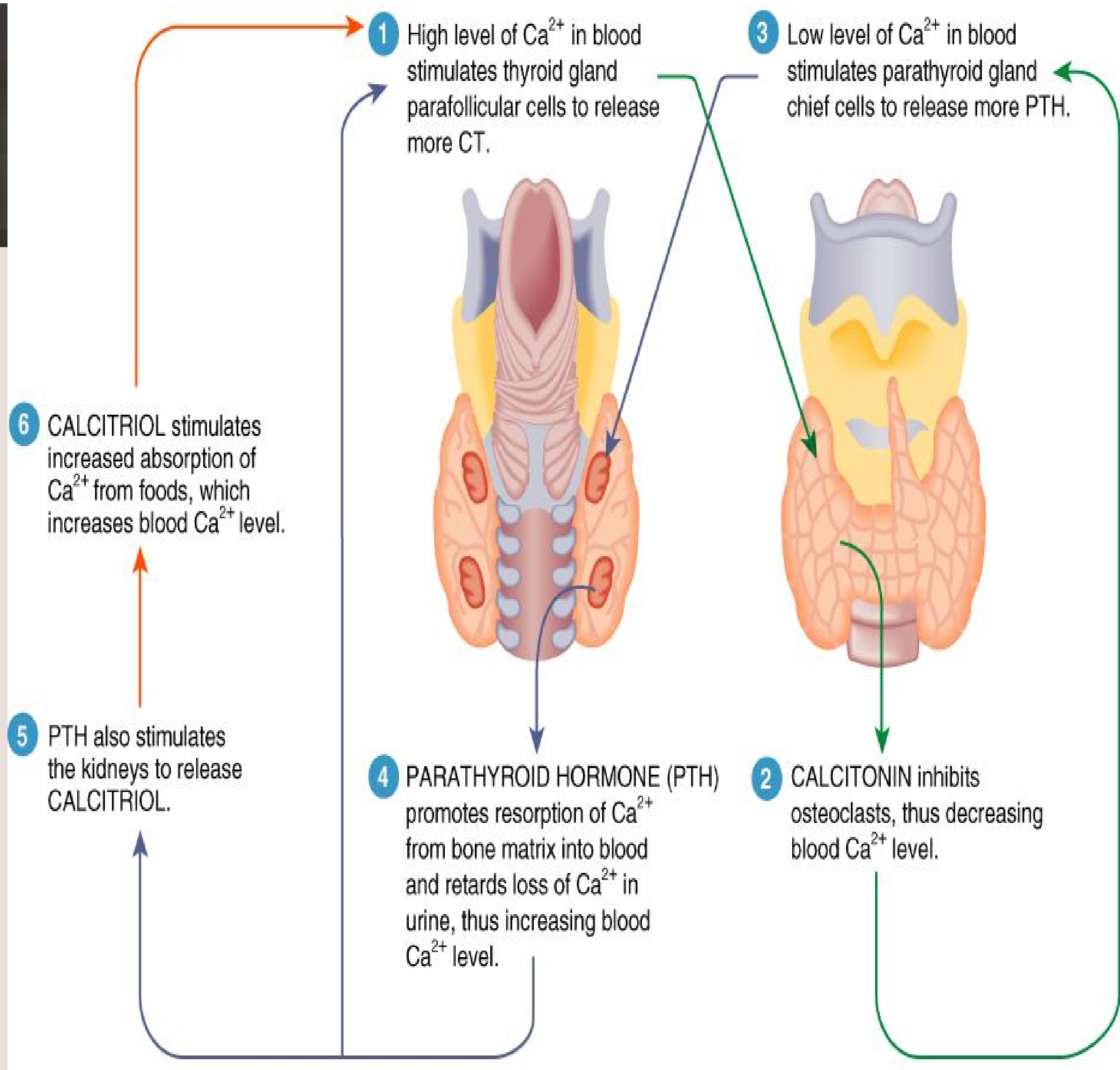
Normal parathyroid glands as seen during a thyroidectomy. The large arrow points to the superior parathyroid. The thinner arrow points to the inferior parathyroid. The forceps points toward the recurrent laryngeal nerve. The patient's head is toward the right.


parathyroid
follicular
epithelium
colloid
capsule
thyroid


Parathyroid gland, chief and oxyphil cells

Hormonal control of remodelling

- **Hormonal control of remodelling acts to maintain blood calcium homeostasis rather than integrity of skeleton**
- **Blood calcium homeostasis**
  - **Parathyroid hormone (PTH) released when blood Ca^{2+} low - stimulates osteoclasts**
    - Also promotes Ca^{2+} absorption in GI tract and reduces filtration at kidney
  - **Calcitonin released when blood Ca^{2+} high**
    - **inhibits osteoclasts**
    - **stimulates osteoblasts**

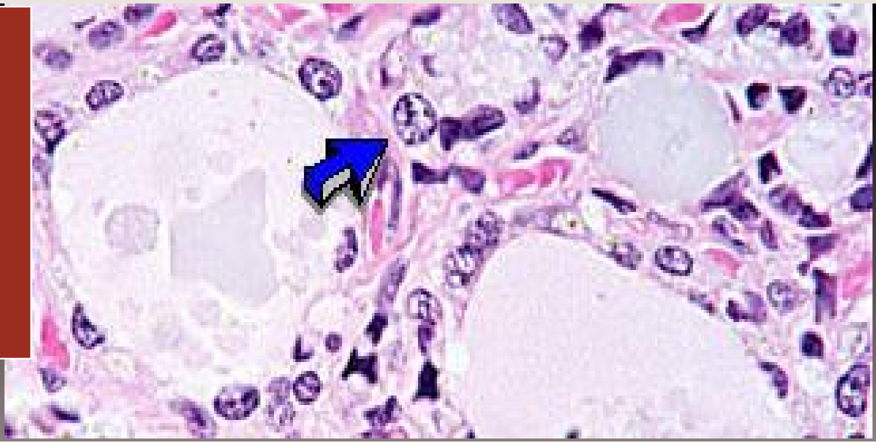


18.14

Calcitonin = thyrocalcitonin

- Released by the C cells = clear cells =parafollicular cells of the thyroid gland in response to high blood [Ca^{2+}].
- Calcitonin acts to "*tone down*" blood calcium levels (reduce calcemia).
- Calcitonin causes decreased osteoclast activity which results in decreased break down of bone matrix and decreased calcium being released into the blood.
- Calcitonin also stimulates osteoblast activity which means calcium will be taken from the blood and deposited as bone matrix.

Notice the thyroid follicles on the right. The arrow indicates a C cell



- Stimulate the uptake of calcium into growing bone and the deposition of bone matrix
- Calcitonin stimulate osteoblast toproduce bone and store calcium

Secretion of calcitonin is stimulated by:

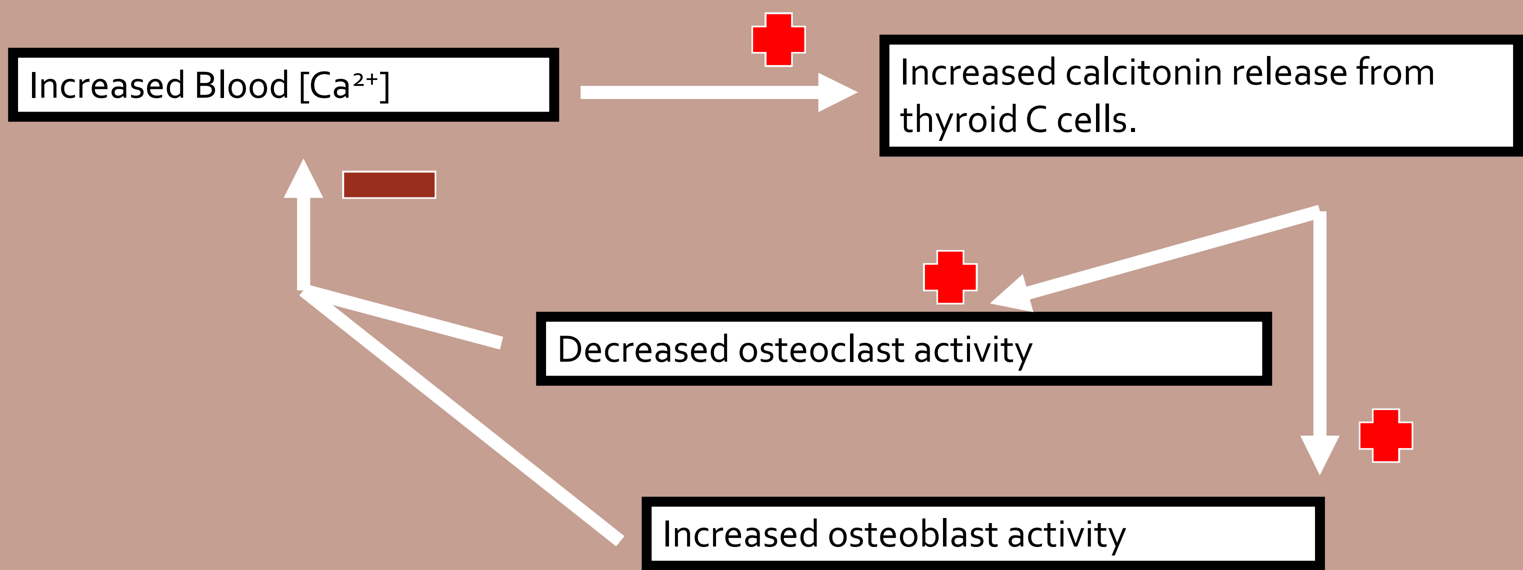
- increase in serum calcium
- Gastrin and pentagastrin

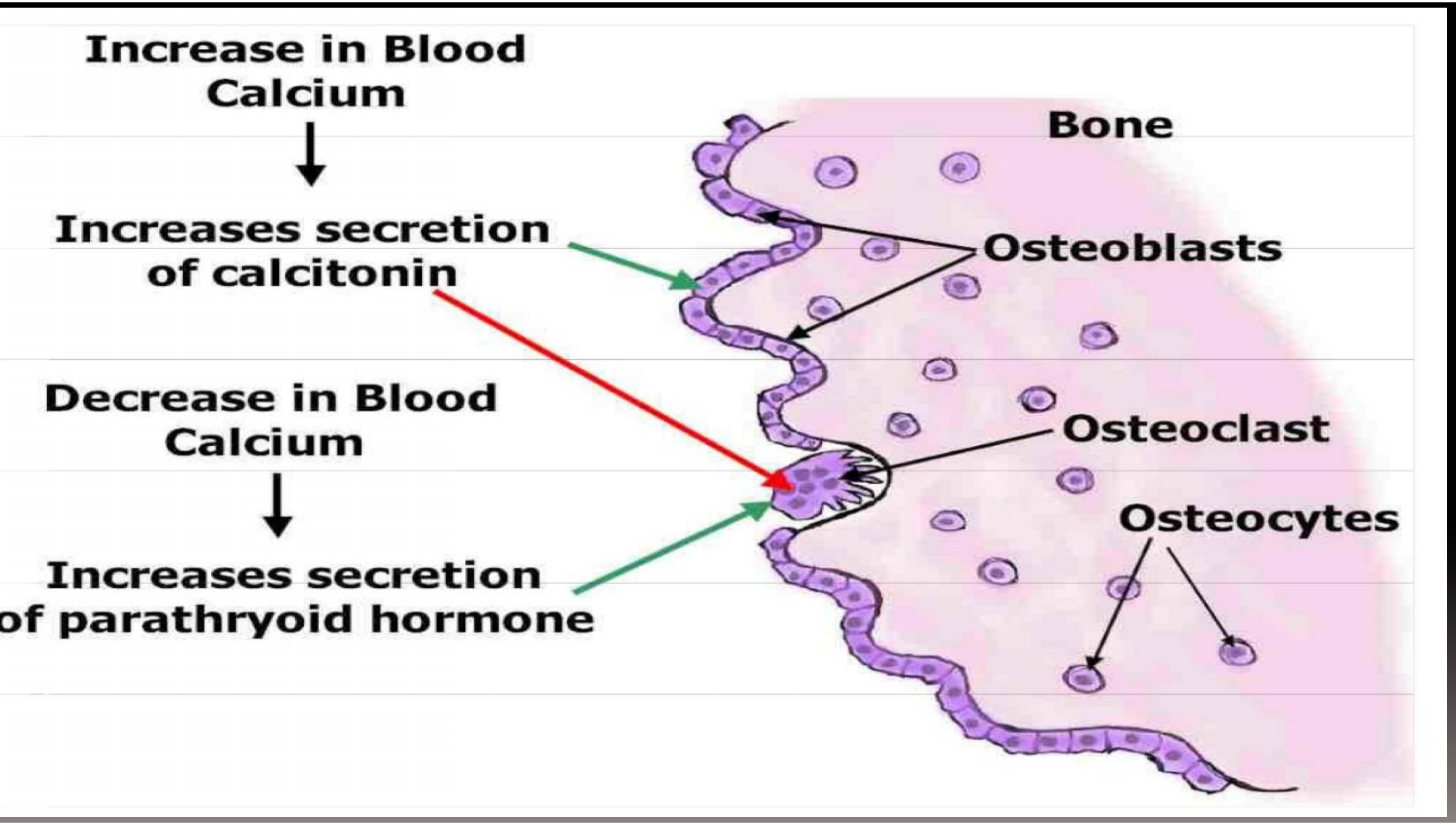
More specifically, calcitonin lowers blood Ca^{2+} levels in three ways:

- Inhibits Ca^{2+} absorption by the intestines
- Inhibits osteoclast activity in bones
- Inhibits renal tubular cell reabsorption of Ca^{2+} allowing it to be secreted in the urine

- **Vitamin D regulation**
- **calcitonin protects against calcium loss from skeleton during periods of calcium mobilization, such as pregnancy and, especially, lactation**

Calcitonin Negative Feedback Loop




Increase in Blood Calcium
Increases secretion of calcitonin
Decrease in Blood Calcium
Increases secretion of parathryoid hormone
Bone
Osteoblasts
Osteoclast
Osteocytes

Calcium

- **Important signal molecule**
- **Part of intercellular cement that holds cells together at tight junction**
- **Cofactor in the coagulation cascade**
- **Affects the excitability of neurons**

Calcium is the most abundant mineral in the human body.

•The average adult body contains in total approximately 1 kg, 99% in the skeleton in the form of calcium phosphate salts.

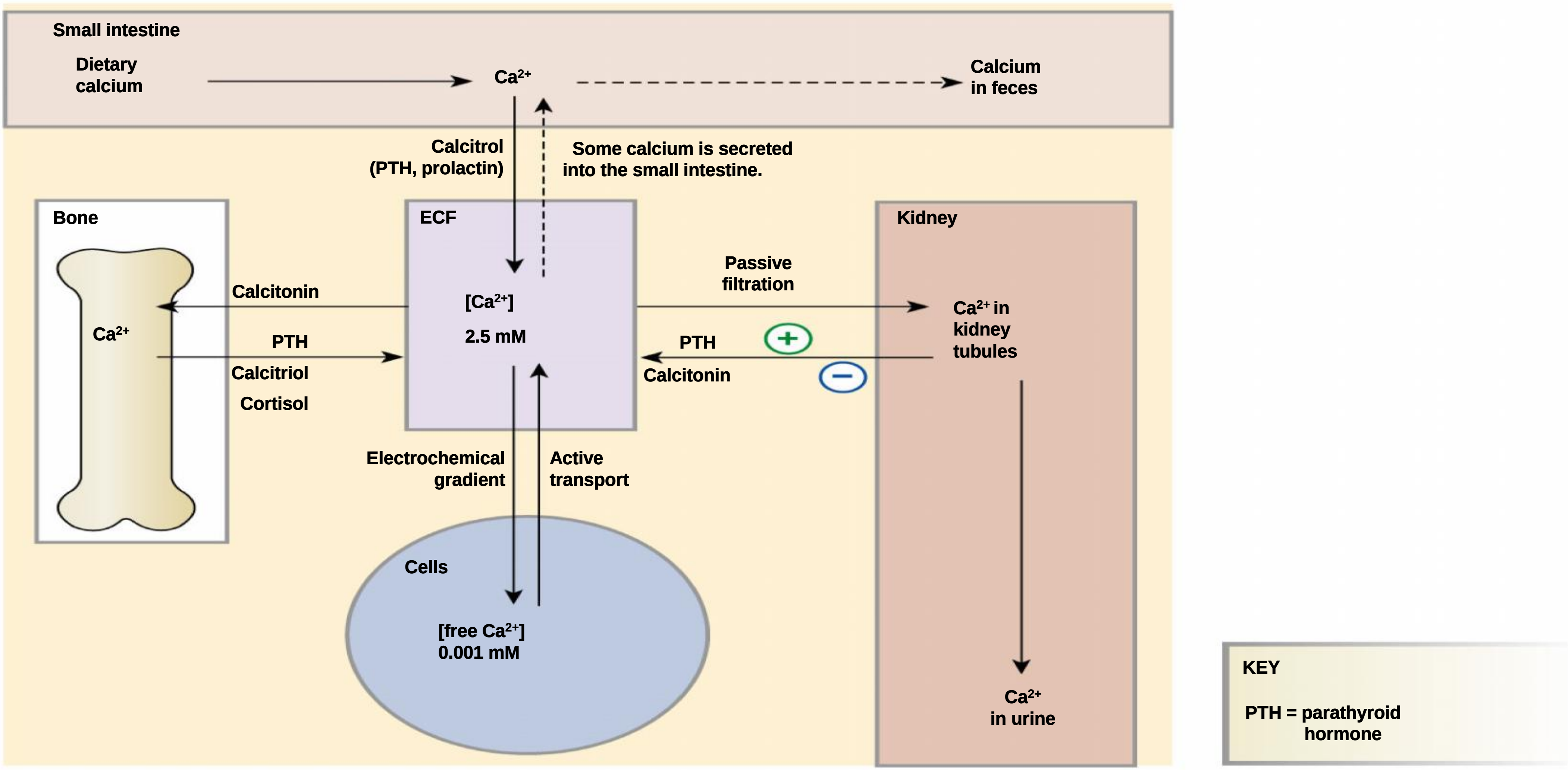
•The extracellular fluid (ECF) contains approximately 22.5 mmol, of which about 9 mmol is in the serum.

•Approximately 500 mmol of calcium is exchanged between bone and the ECF over a period of twenty-four hours

•The amount of total calcium varies with the level of serum albumin, a protein to which calcium is bound.

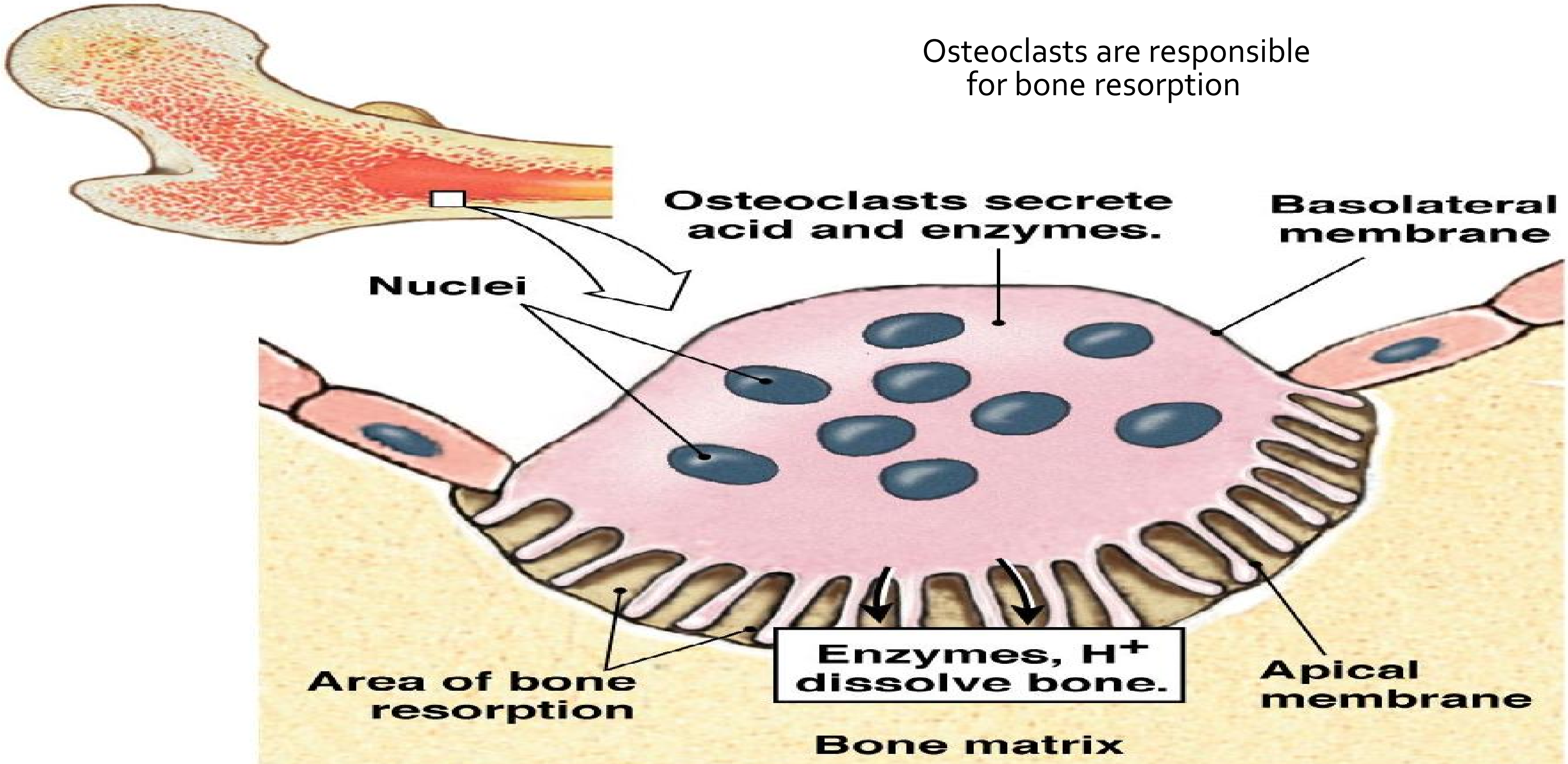
The serum level of calcium is closely regulated with a normal *total calcium* of 2.2-2.6 mmol/L (9-10.5 mg/dL) and a normal *ionized calcium* of 1.1-1.4 mmol/L (4.5- 5.6 mg/dL).

Calcium Balance in the Body



Calcium Balance

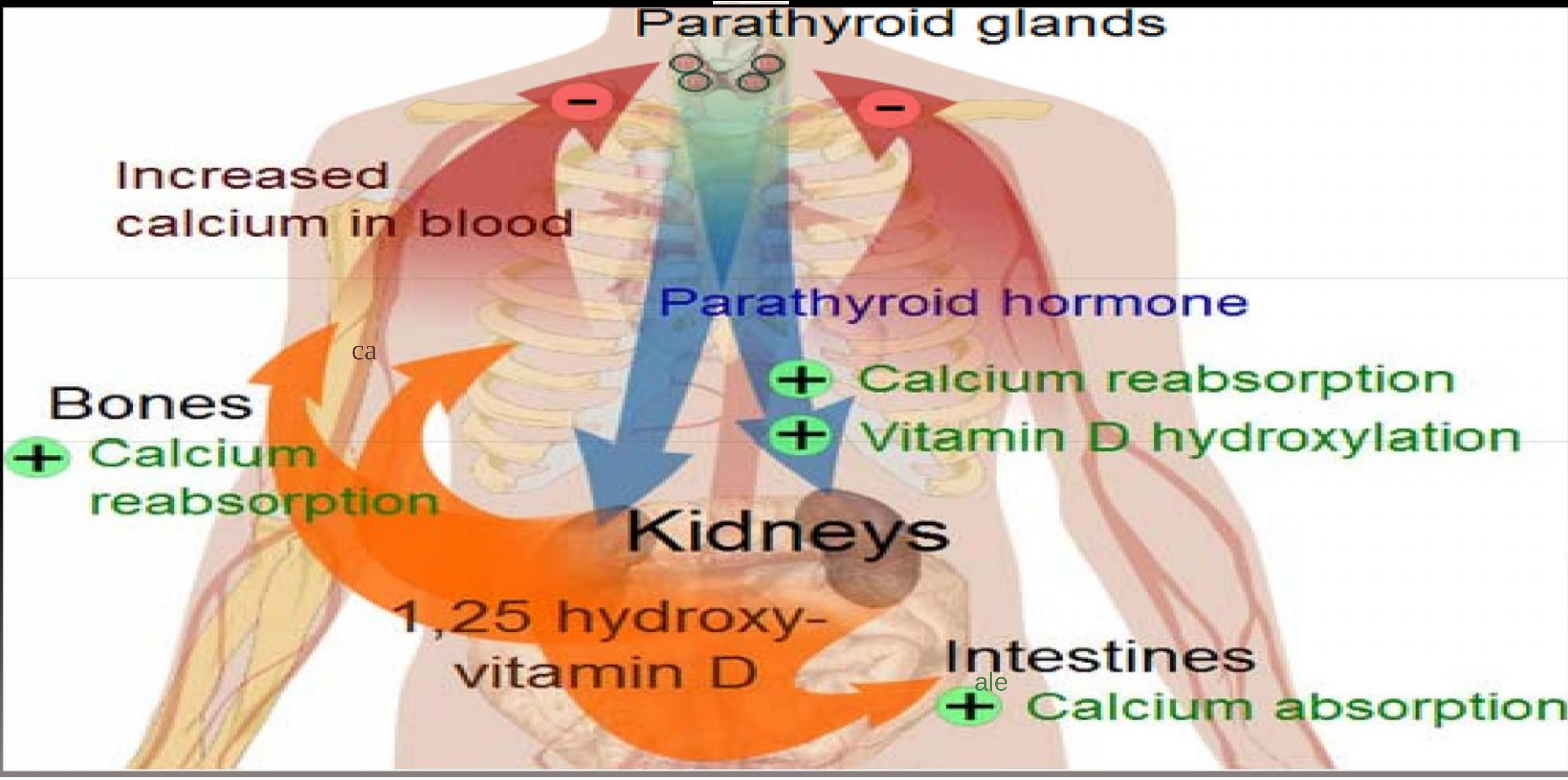
Osteoclasts are responsible for bone resorption



Calcium Balance

- **<u>Parathyroid hormone</u>**
  - Mobilizes calcium from bone
  - Enhances renal reabsorption
  - Indirectly increases intestinal absorption
- **<u>Vitamin D (Calcitriol)</u>**
- **<u>Calcitonin (from Thyroid)</u>**

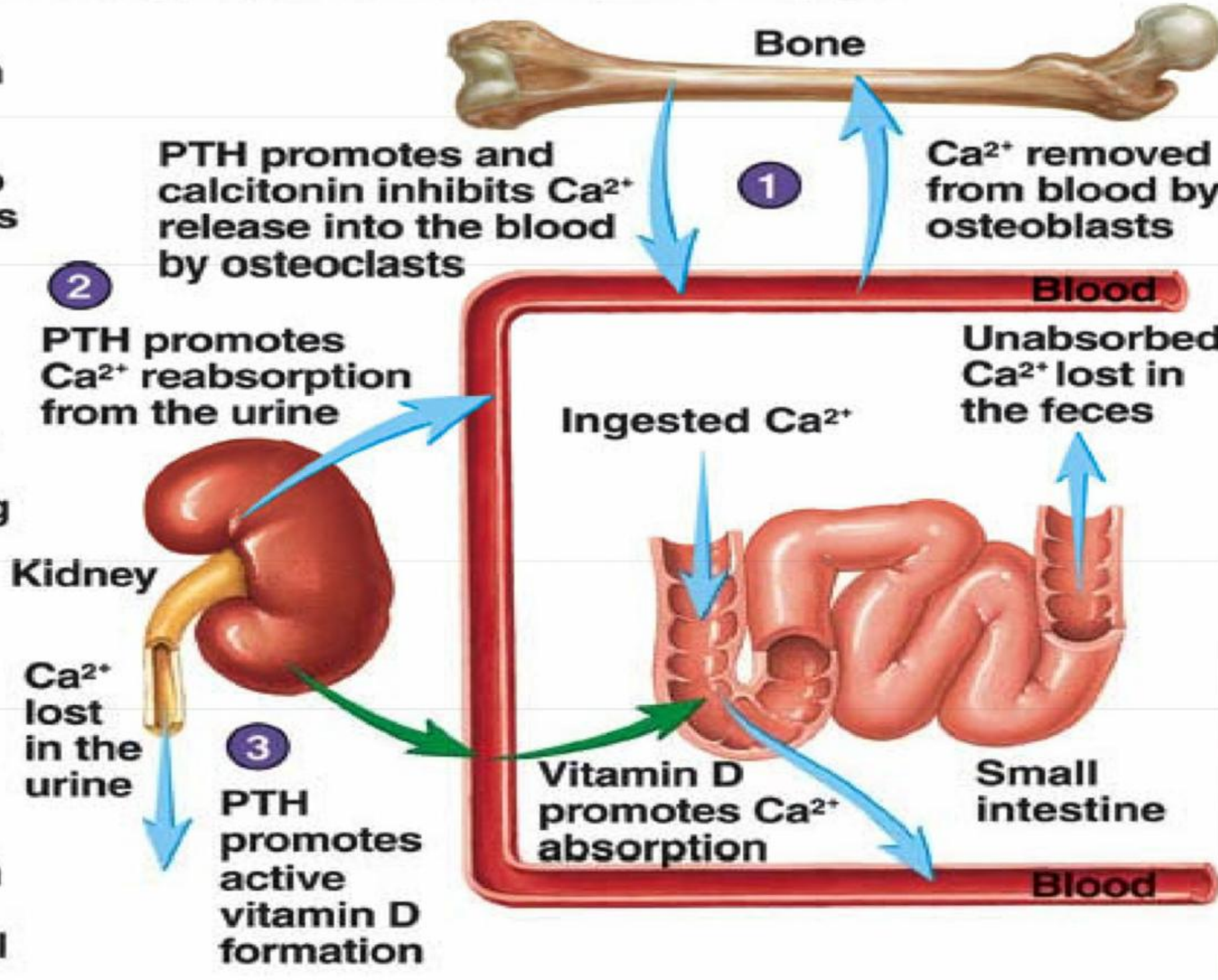
Calcium regulation



1. Osteoclasts break down bone and release calcium into the blood, and osteoblasts remove calcium from the blood to make bone. PTH regulates blood calcium levels by indirectly stimulating osteoclast activity, resulting in increased calcium release into the blood. Calcitonin plays a minor role in calcium maintenance by inhibiting osteoclast activity.

2. In the kidneys, PTH increases calcium reabsorption from the urine.

3. In the kidneys, PTH also promotes the formation of active vitamin D, which increases calcium absorption from the small intestine.



Bone homeostasis

- **Bones continually being remodelled**
  - 5-7% of bone mass turned over each week
- **Remodelling regulated by two control mechanisms:**
  - **Hormonal control of blood Ca^{2+} homeostasis**
  - **Mechanical stress**

Nutritional Effects on Bone

- Normal bone growth/maintenance cannot occur w/o sufficient dietary intake of calcium and phosphate salts.
- Calcium and phosphate are not absorbed in the intestine unless the hormone calcitriol is present.
- Calcitriol synthesis is dependent on the availability of the steroid *cholecalciferol* (a.k.a. Vitamin D) which may be synthesized in the skin or obtained from the diet.
- Vitamins C, A, K, and B_{12} are all necessary for bone growth as well.

Different Forms of Vitamin D

Cholecalciferol

vitamin D3

Cholecalciferol: is the naturally occurring form of vitamin D.

Cholecalciferol is made in large quantities in your skin when sunlight strikes your bare skin.

It can also be taken as a **supplement.**

Calcidiol

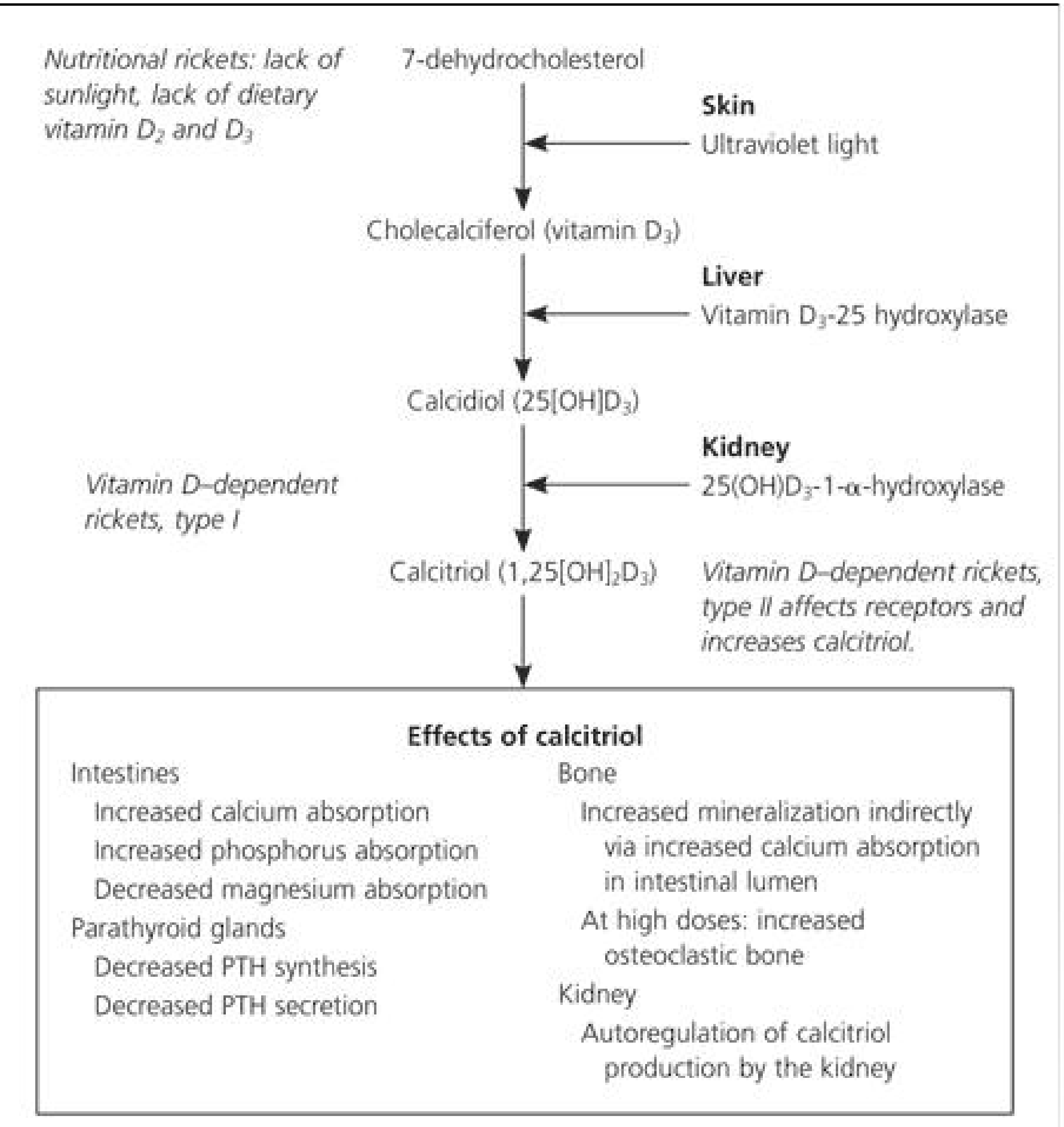
25(OH)D or 25D Calcidiol Made in Liver AFTER BEING ABSORBED BY SKIN OR INJESTION

Calcidiol (25-hydroxyvitamin D) is a prehormone in your blood that is directly made from cholecalciferol. When being tested for vitamin D deficiency, **calcidiol is the only blood test that should be drawn**. When someone refers to vitamin D blood levels, they are referring to calcidiol levels. Your doctor can order calcidiol levels but the lab will know calcidiol as 25-hydroxyvitamin D.

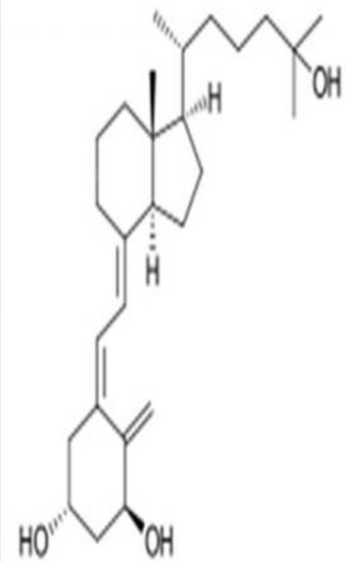
Calcitriol

1,25(OH)2D3 or 1,25D3

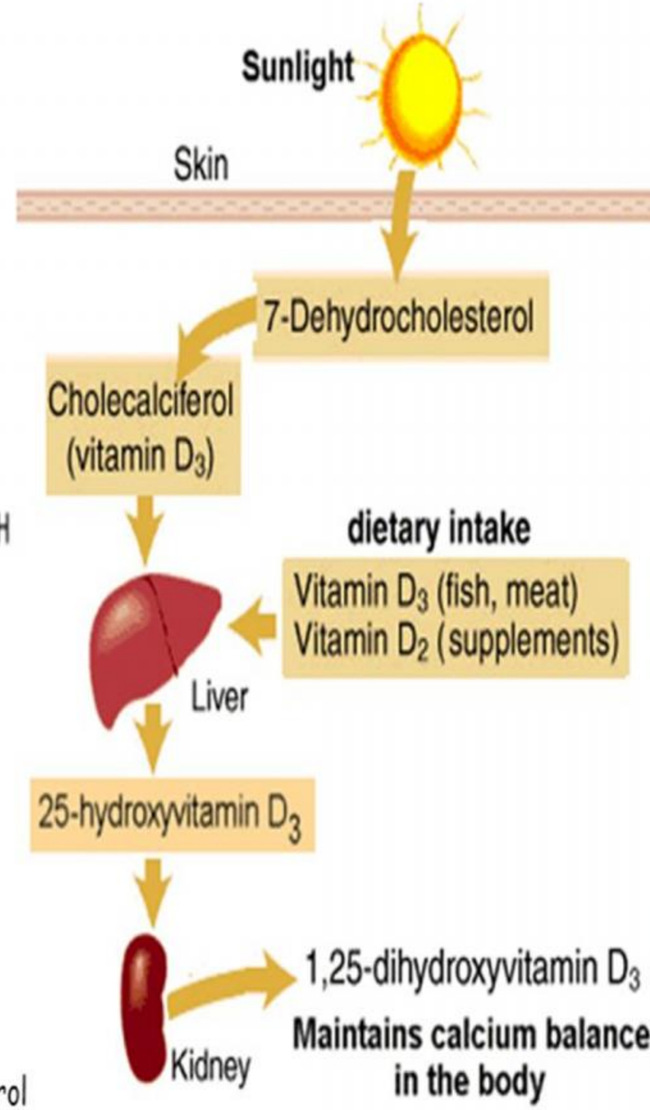
Calcitriol (1,25-dihydroxyvitamin D) is a made from calcidiol in both the kidneys and in other tissues and is the most potent steroid hormone derived from cholecalciferol. Calcitriol has powerful anti-cancer properties. It is sometimes **referred to as the active form of vitamin D**. Calcitriol levels should never be used to determine if you are deficient in vitamin D.



Both ergocalciferol and cholecalciferol are metabolized in liver



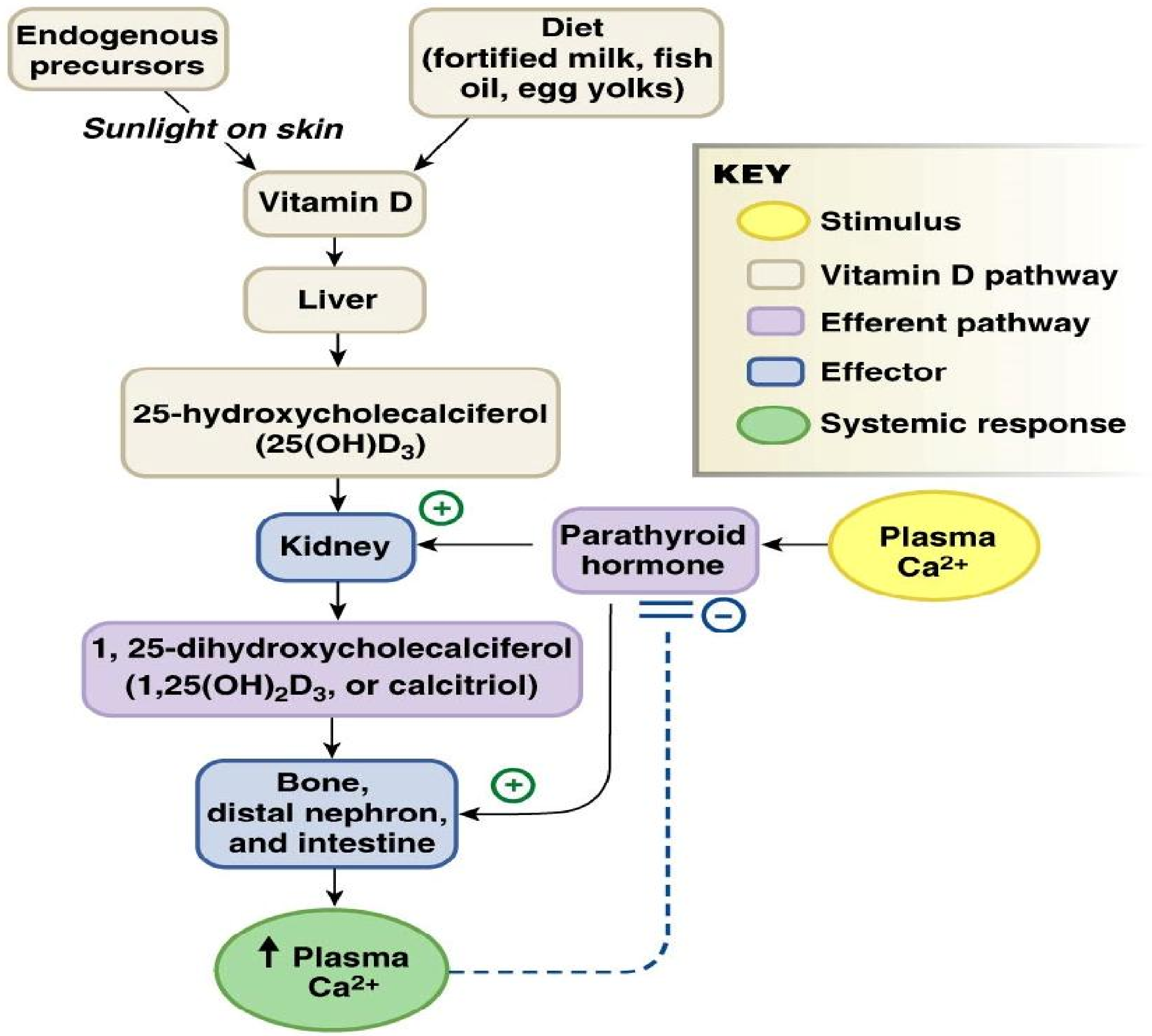
1,25-dihydroxycholecalciferol



Calcium Balance

	Parathyroid Hormone (PTH)
Cell of origin	Parathyroid glands
Chemical nature	84-amino acid peptide
Biosynthesis	Continuous production, little stored
Transport in the circulation	Dissolved in plasma
Half-life	Less than 20 minutes
Factors affecting release	↓ Plasma Ca^{2+}
Target cells or tissues	Kidney, bone, intestine
Target receptor	Membrane receptor acts via cAMP
Whole body or tissue action	↑ Plasma Ca^{2+}
Action at cellular level	↑ Vitamin D synthesis; ↑ renal reabsorption of Ca^{2+}; ↑ bone resorption
Action at molecular level	Rapidly alters Ca^{2+} transport but also initiates protein synthesis in osteoclasts
Onset of action	2–3 hours for bone, with increased osteoclast activity requiring 1–2 hours; 1–2 days for intestinal absorption; within minutes for kidney transport
Feedback regulation	Negative feedback by ↑ plasma Ca^{2+}
Other information	Osteoclasts have no PTH receptors, so are affected by PTH-induced paracrines. PTH is essential for life; absence causes hypocalcemic tetany.

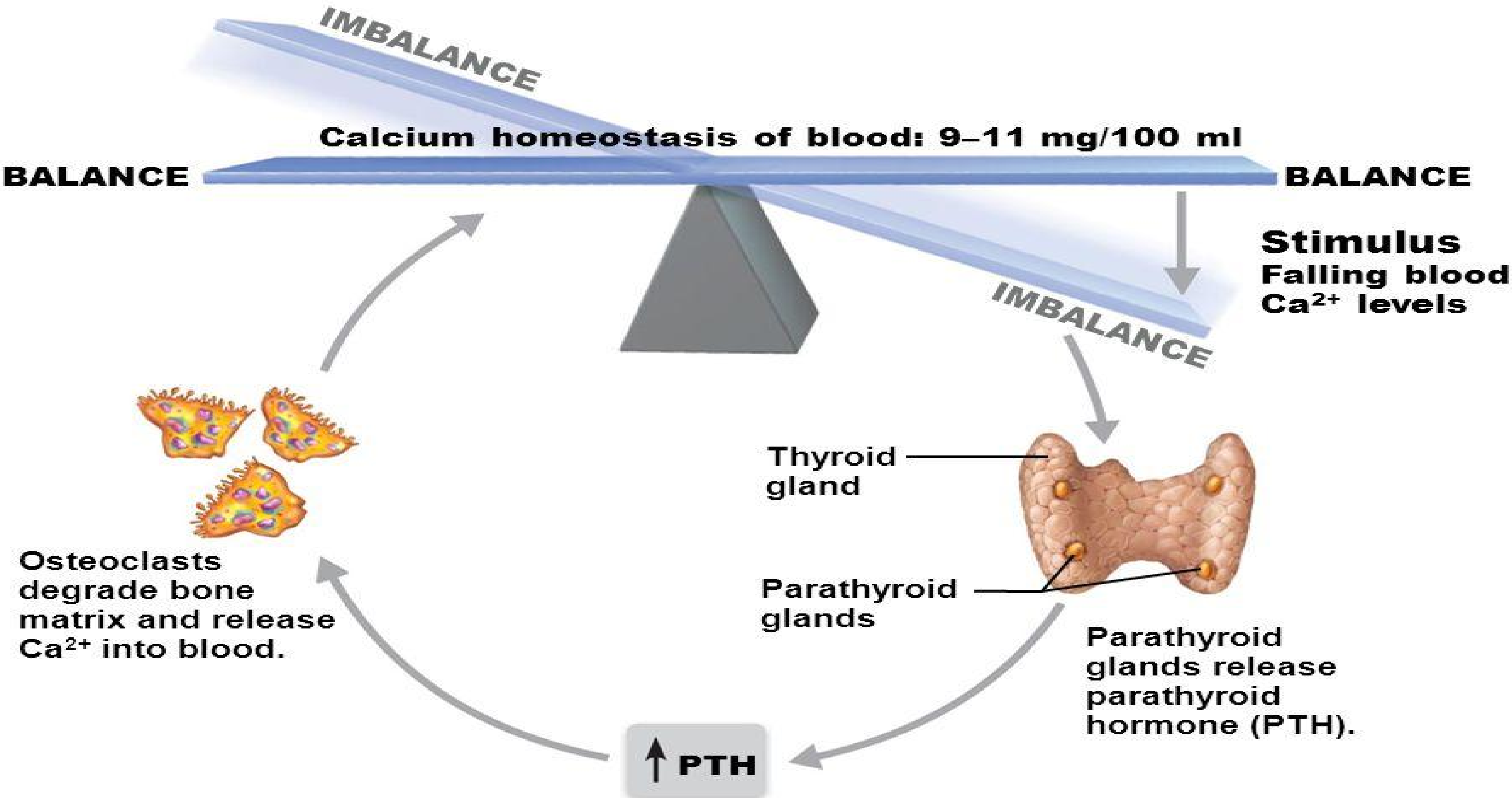
Endocrine Control of Calcium Balance

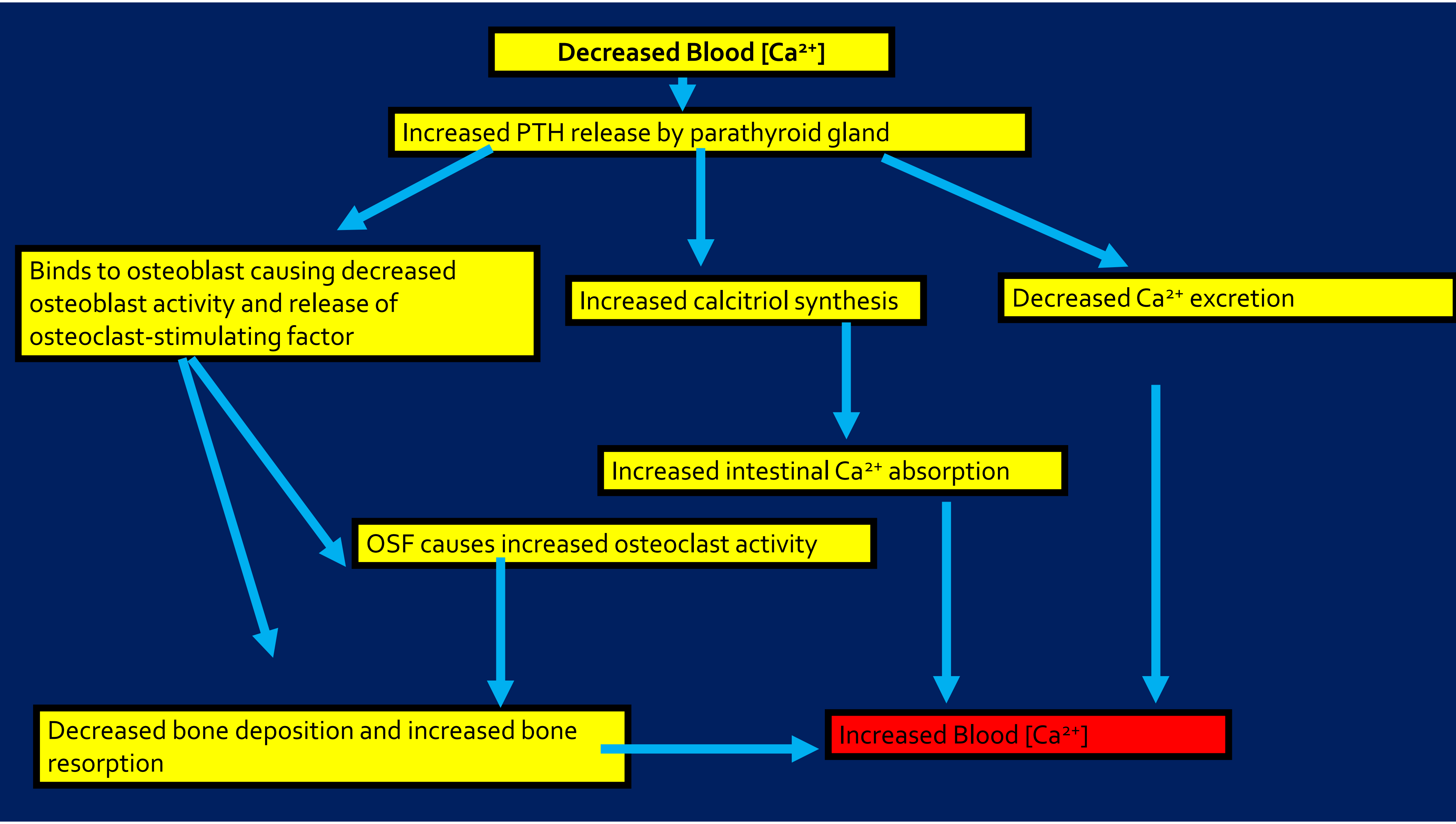


Calcitonin

	Calcitonin
Cell of origin	C cells of thyroid gland (parafollicular cells)
Chemical nature	32-amino acid peptide
Biosynthesis	Typical peptide
Transport in the circulation	Dissolved in plasma
Half-life	<10 minutes
Factors affecting release	↑ Plasma $[Ca^{2+}]$
Target cells or tissues	Bone and kidney
Target receptor	G protein-coupled membrane receptor
Whole body or tissue action	Prevents bone resorption; enhances kidney excretion
Action at molecular level	Signal transduction pathways appear to vary during cell cycle
Other information	Experimentally decreases plasma $[Ca^{2+}]$ but has little apparent physiological effect in adult humans; possible effect on skeletal development; possible protection of bone Ca^{2+} stores during pregnancy and lactation

Figure 6.12 Parathyroid hormone (PTH) control of blood calcium levels.





Decreased Blood [Ca^{2+}]
Increased PTH release by parathyroid gland
Binds to osteoblast causing decreased osteoblast activity and release of osteoclast-stimulating factor
Increased calcitriol synthesis
Decreased Ca^{2+} excretion
Increased intestinal Ca^{2+} absorption
OSF causes increased osteoclast activity
Decreased bone deposition and increased bone resorption
Increased Blood [Ca^{2+}]

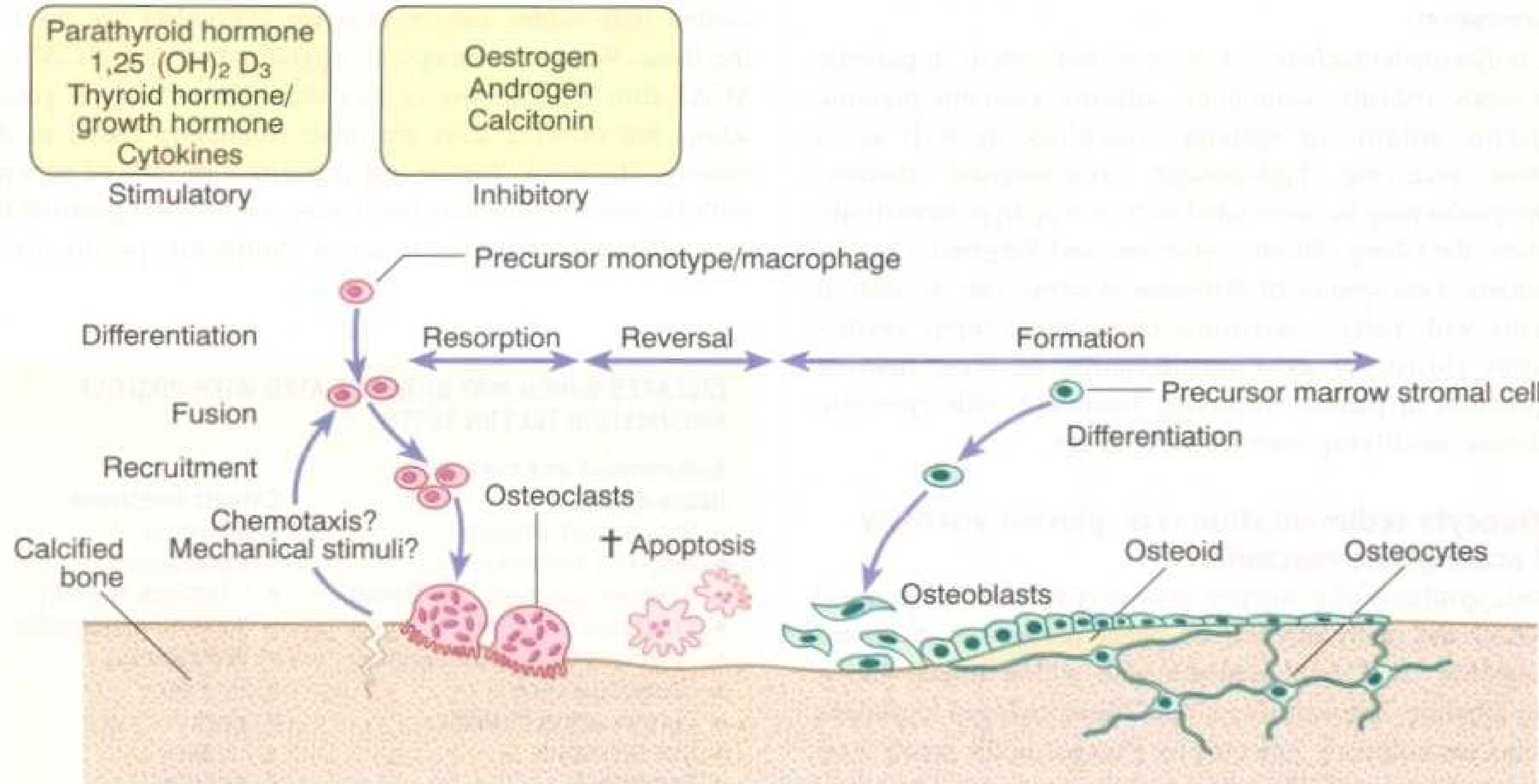
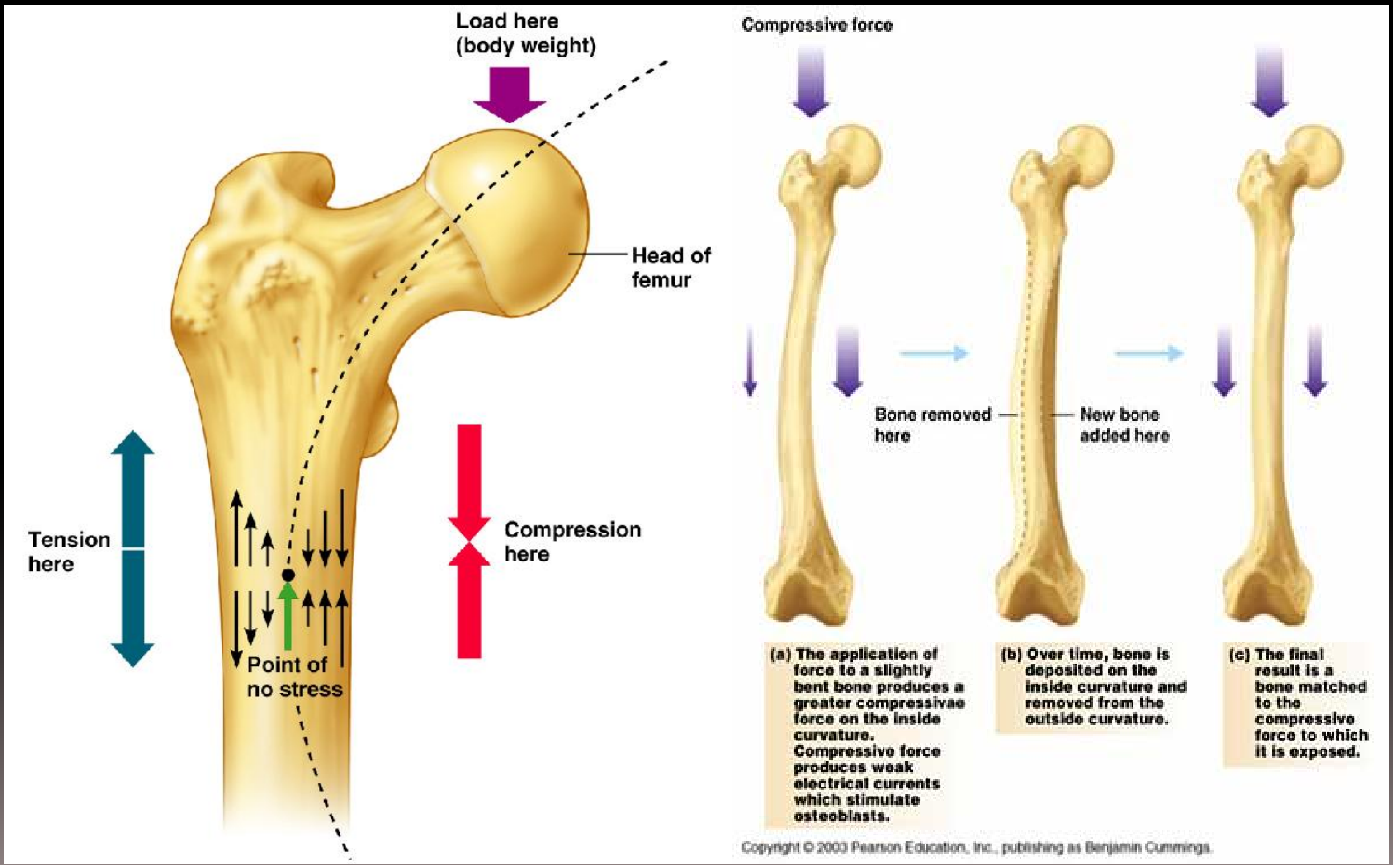
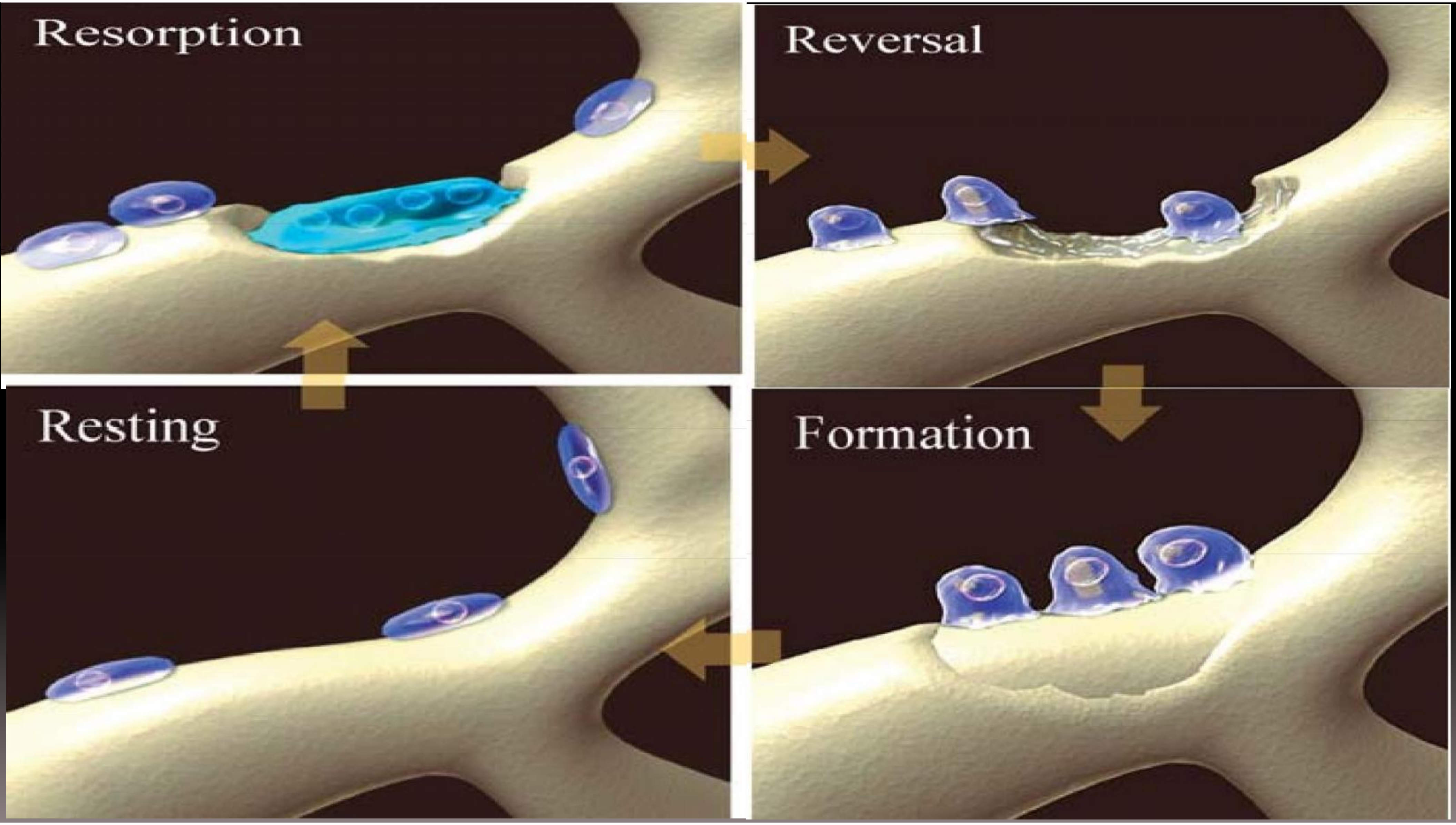


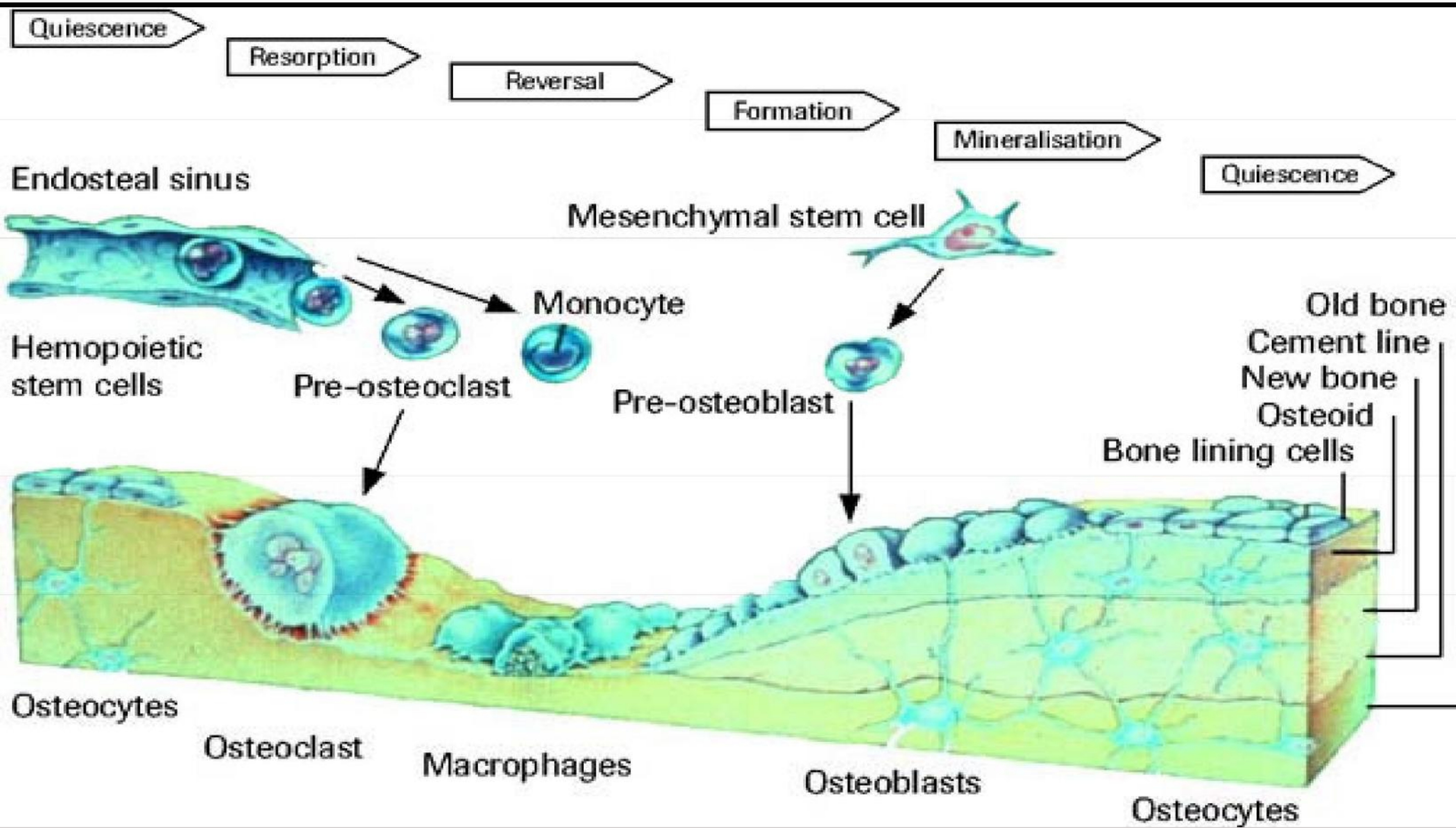
Fig. 12.4 The bone remodelling cycle. (1,25 $(OH)_2$ D = 1,25 dihydroxyvitamin D)

Response to Mechanical Stress

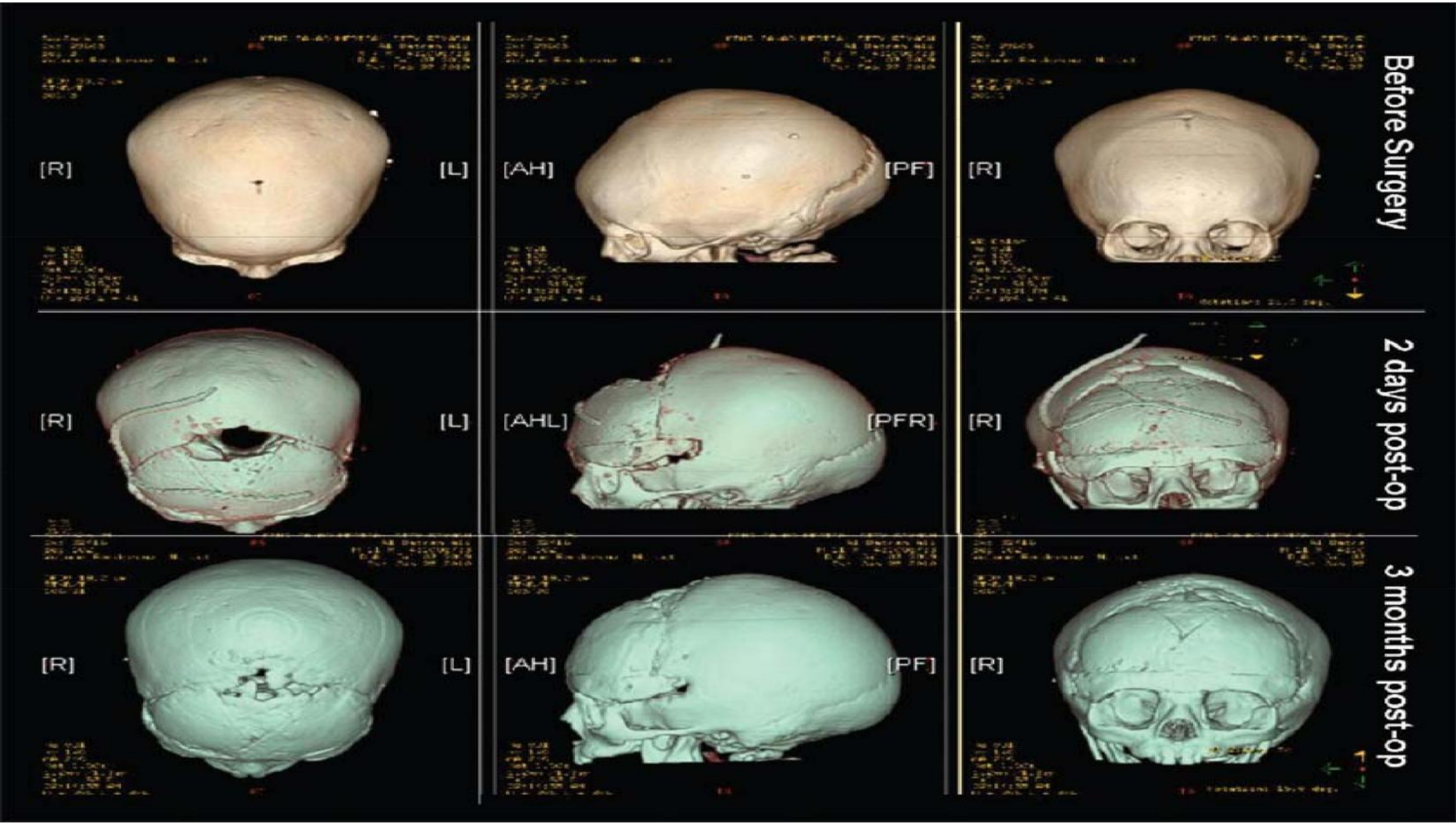
Wolff's law – a bone grows or remodels in response to the forces or demands placed upon it

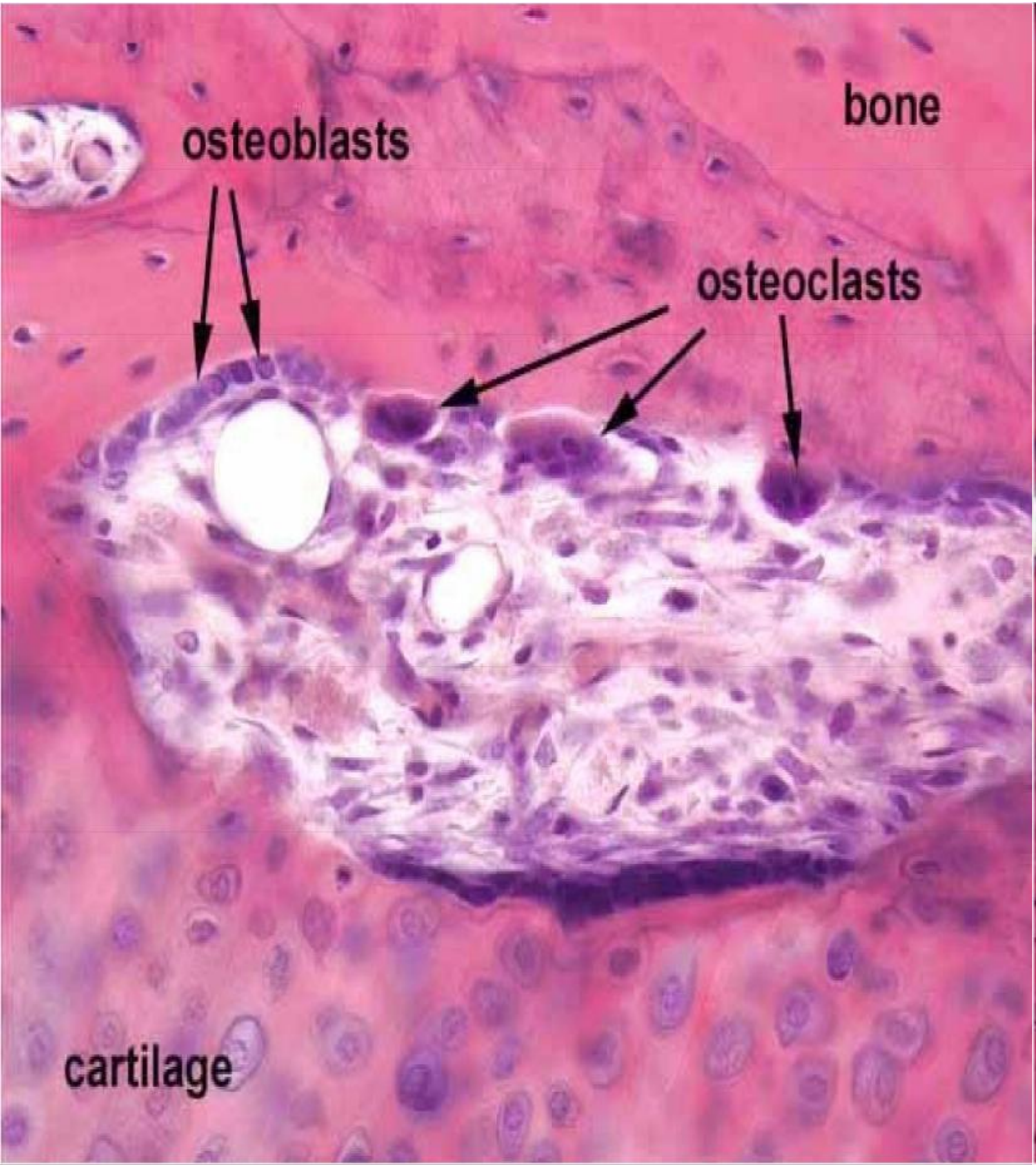


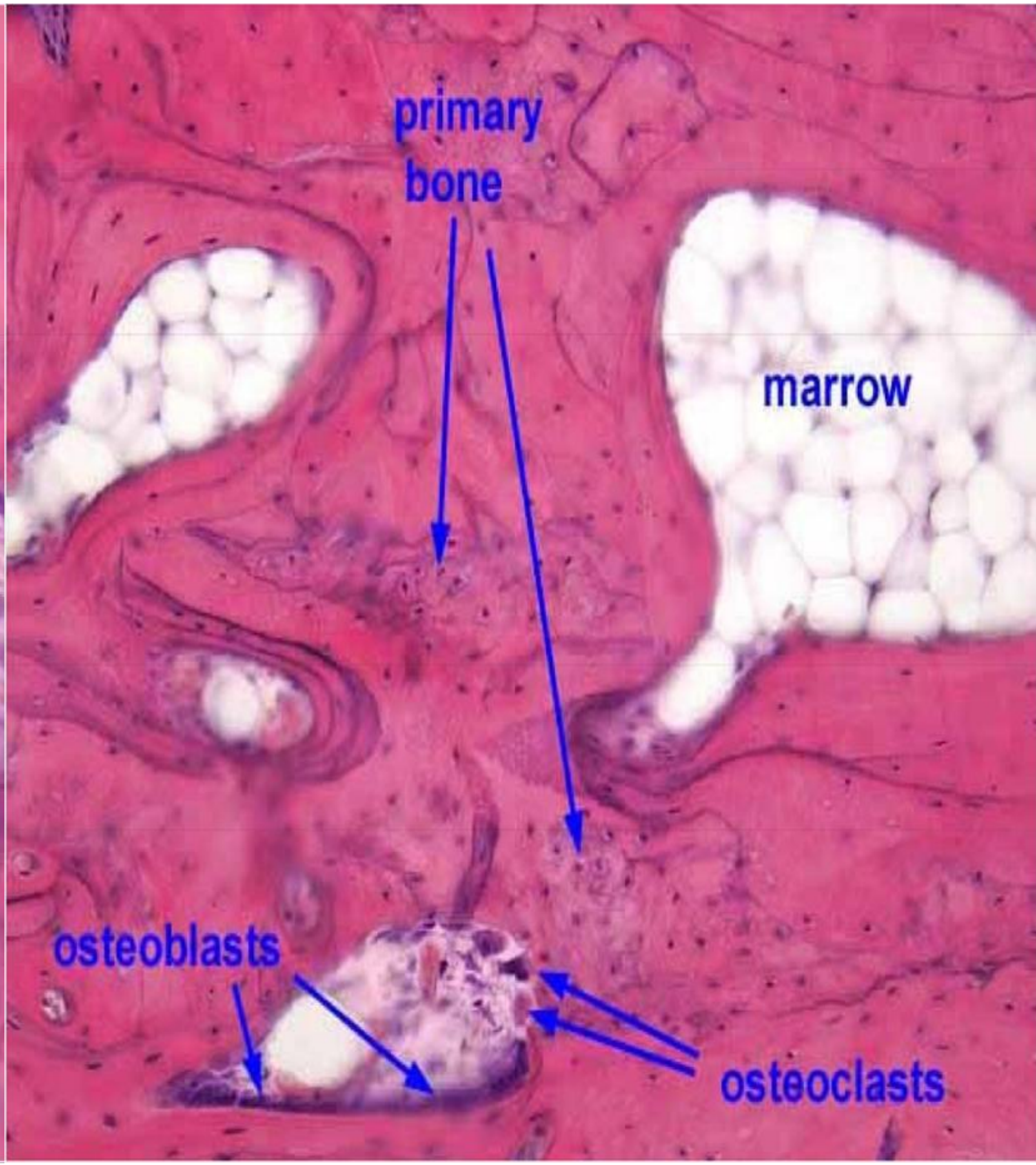

Resorption
Reversal
Resting
Formation



Quiescence
Resorption
Reversal
Formation
Mineralisation
Quiescence
Endosteal sinus
Mesenchymal stem cell
Monocyte
Hemopoietic stem cells
Pre-osteoclast
Pre-osteoblast
Old bone
Cement line
New bone
Osteoid
Bone lining cells
Osteocytes
Osteoclast
Macrophages
Osteoblasts
Osteocytes


Before Surgery
2 days post-op
3 months post-op
[R]
[L]
[AH]
[PF]
[AHL]
[PFR]


bone
osteoblasts
osteoclasts
cartilage

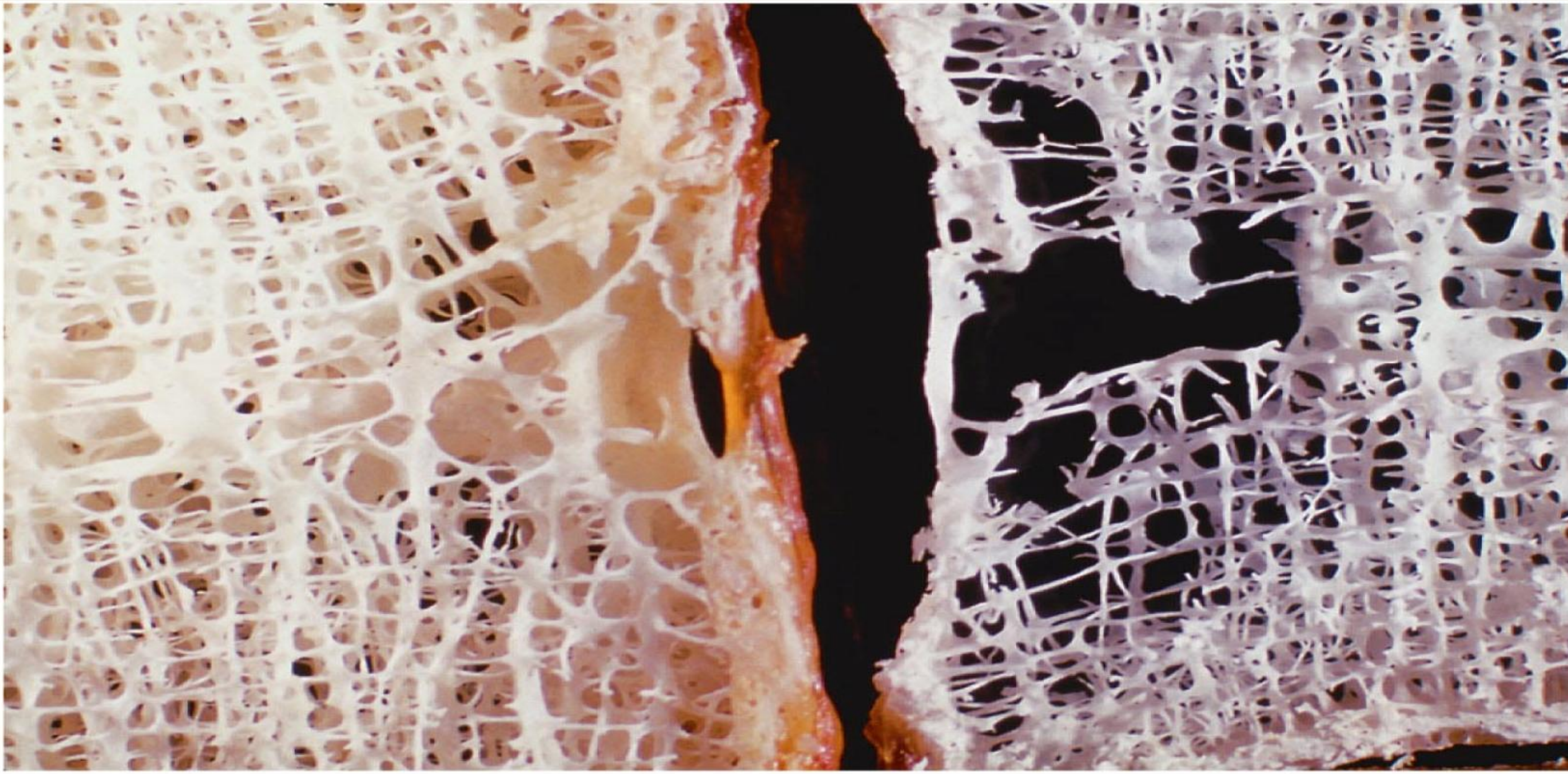

primary
bone
marrow
osteoblasts
osteoclasts

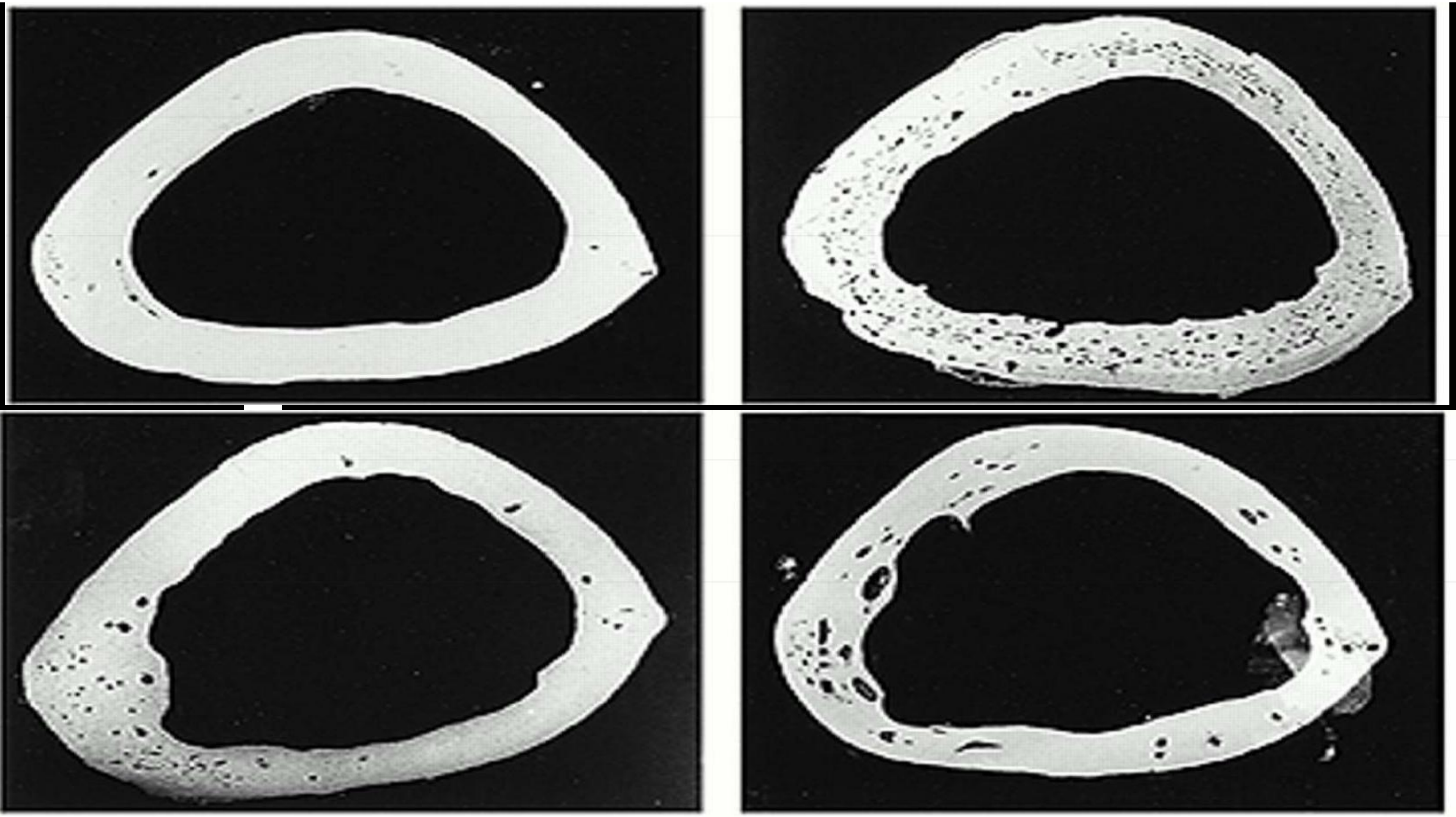
Mechanical control of remodelling

- Hormonal control determines **when** remodelling will occur
- Mechanical stress determines **where** remodelling occurs
  - Mechanical loading reduces osteoclast sensitivity to PTH

Osteoporosis

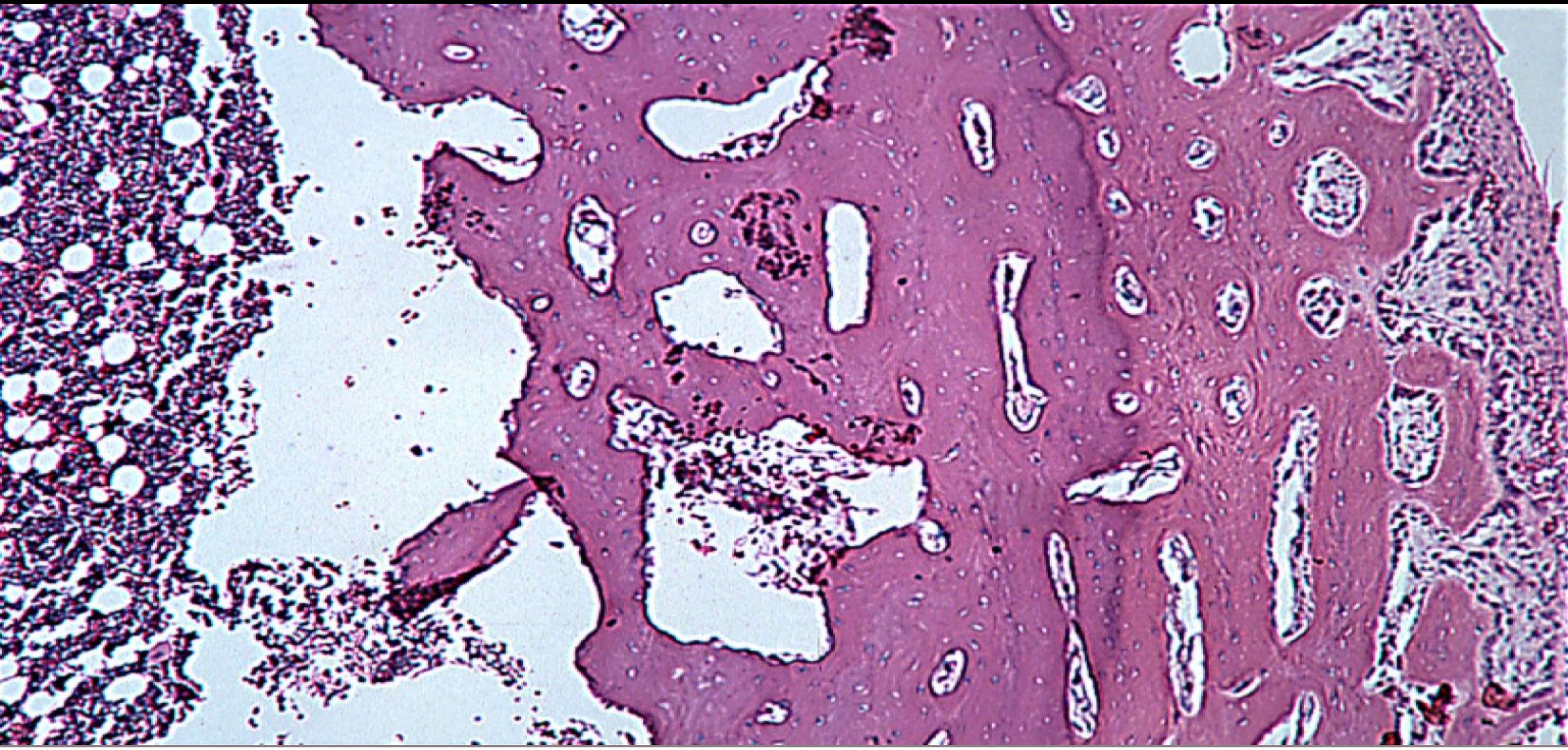
Normal bone (left) and bone loss in osteoporosis (right)

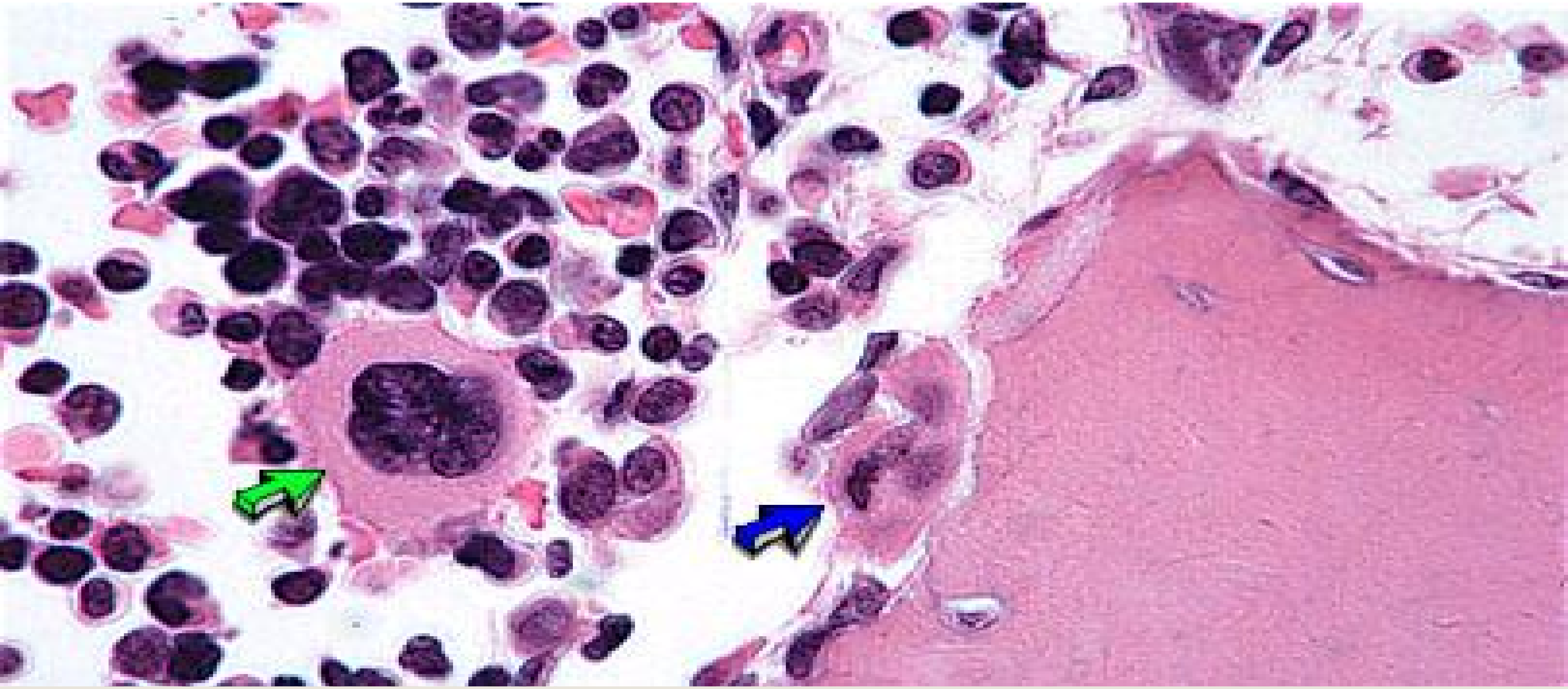




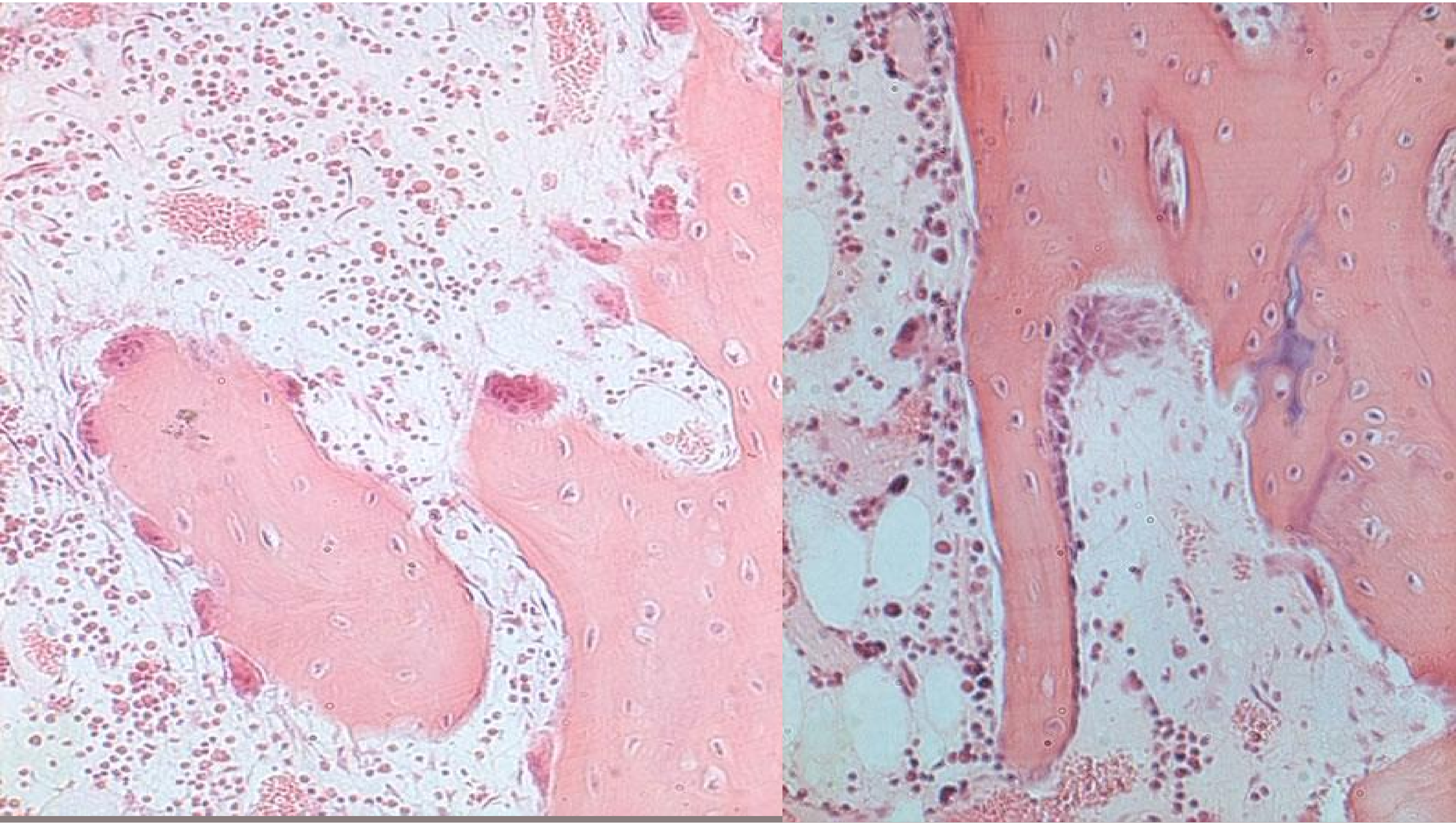
Decalcified Bone Matrix

This cross section of a long bone shows cortical bone to the right and bone marrow to the left. The white circles in the marrow are fat cells. In this preparation calcium has been removed during tissue processing.



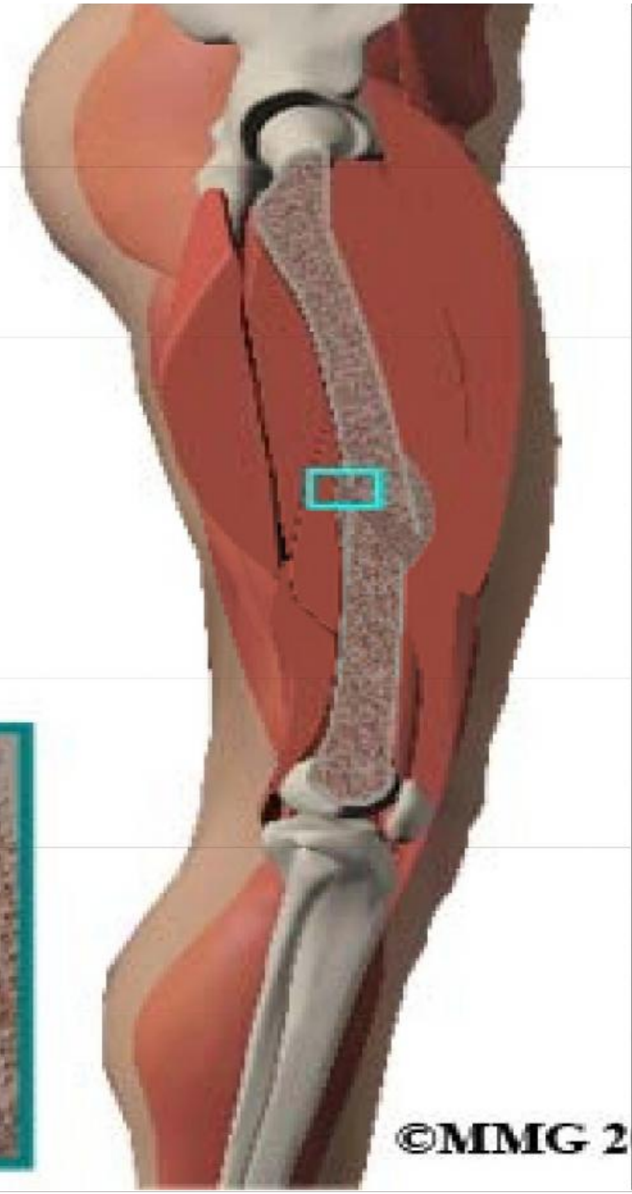


- Decalcified Bone Matrix
  Osteoclasts (blue) are responsible for degradation of old bone.
- Be careful, do not mistake the large multinucleate osteoclast with the equally large megakaryocyte.
- The megakaryocyte (green) has a single multi-lobed nucleus.

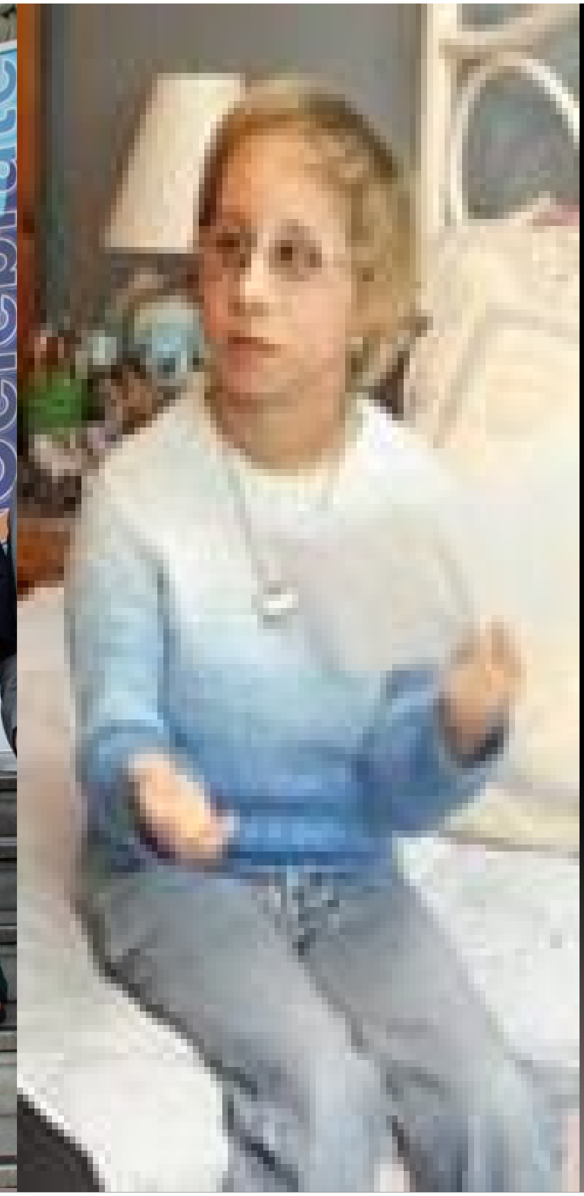


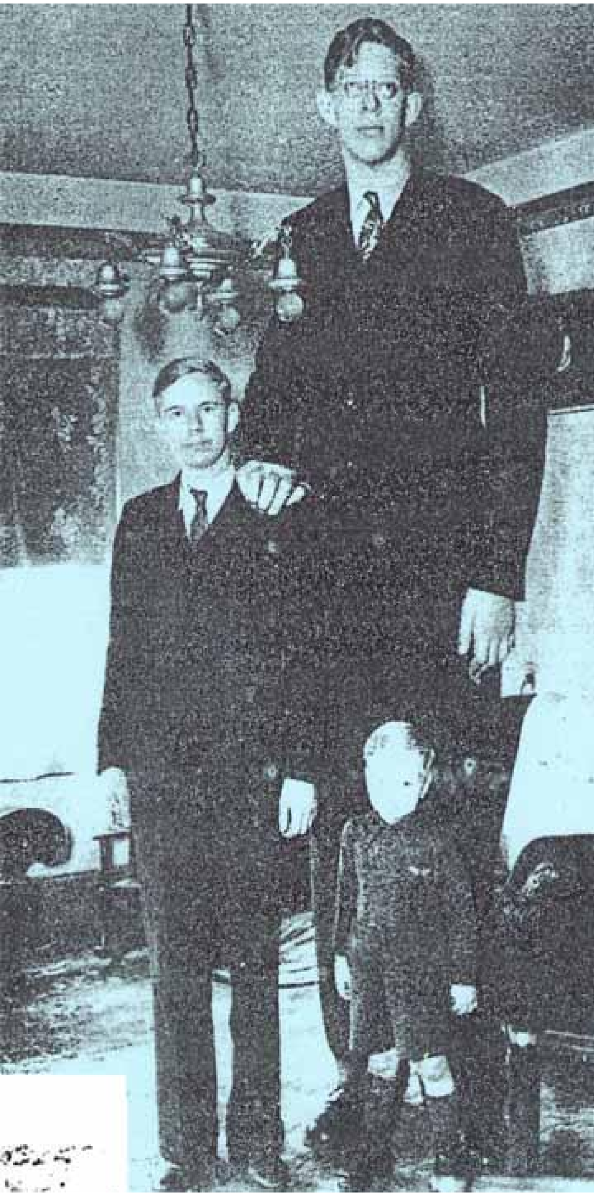

callus

Bone remodeling

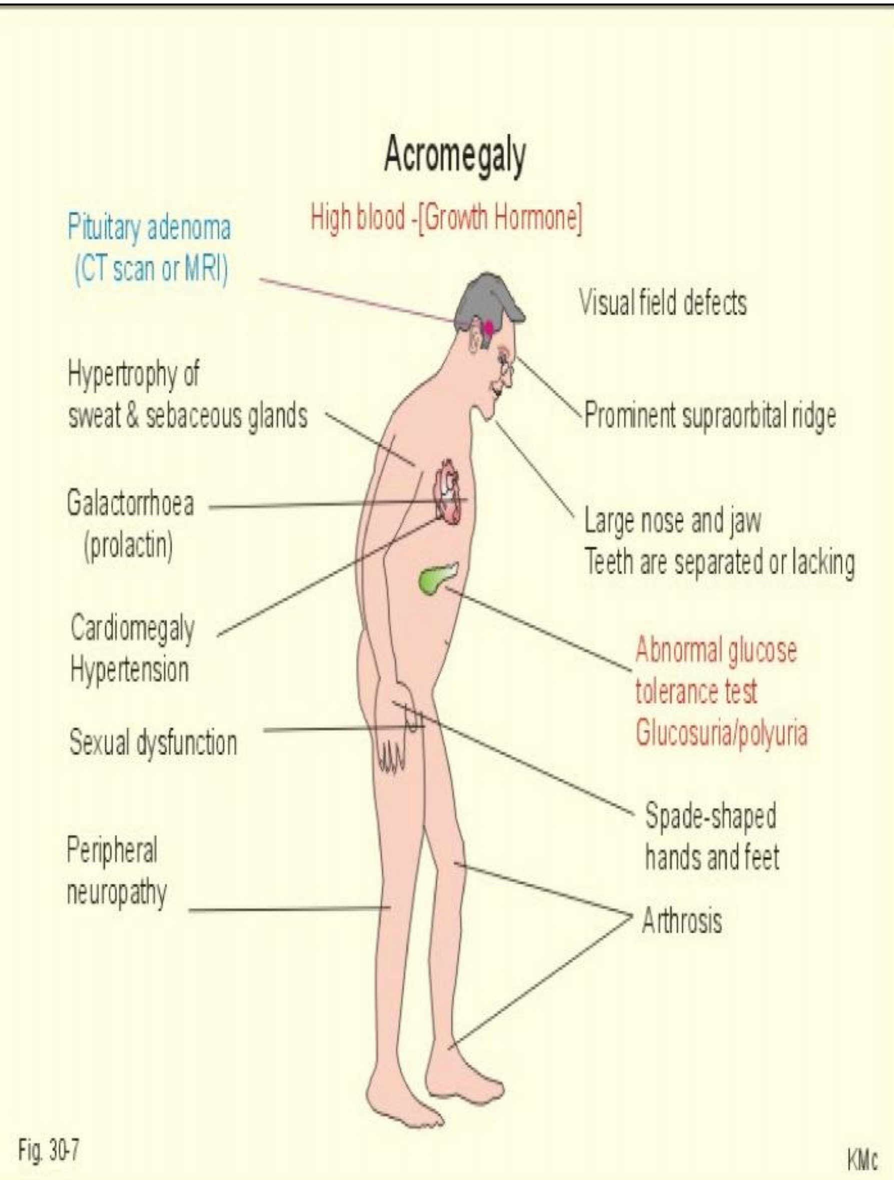



Belfast
Celebrate





Anna Swan with her parents


Acromegaly
High blood -[Growth Hormone]
Pituitary adenoma
(CT scan or MRI)
Visual field defects
Hypertrophy of
sweat & sebaceous glands
Prominent supraorbital ridge
Galactorrhoea
(prolactin)
Large nose and jaw
Teeth are separated or lacking
Cardiomegaly
Hypertension
Abnormal glucose
tolerance test
Glucosuria/polyuria
Sexual dysfunction
Spade-shaped
hands and feet
Peripheral
neuropathy
Arthrosis
Fig. 30-7
KMc

Hyperparathyroidism

Increased Blood -[Ca^{2+}]

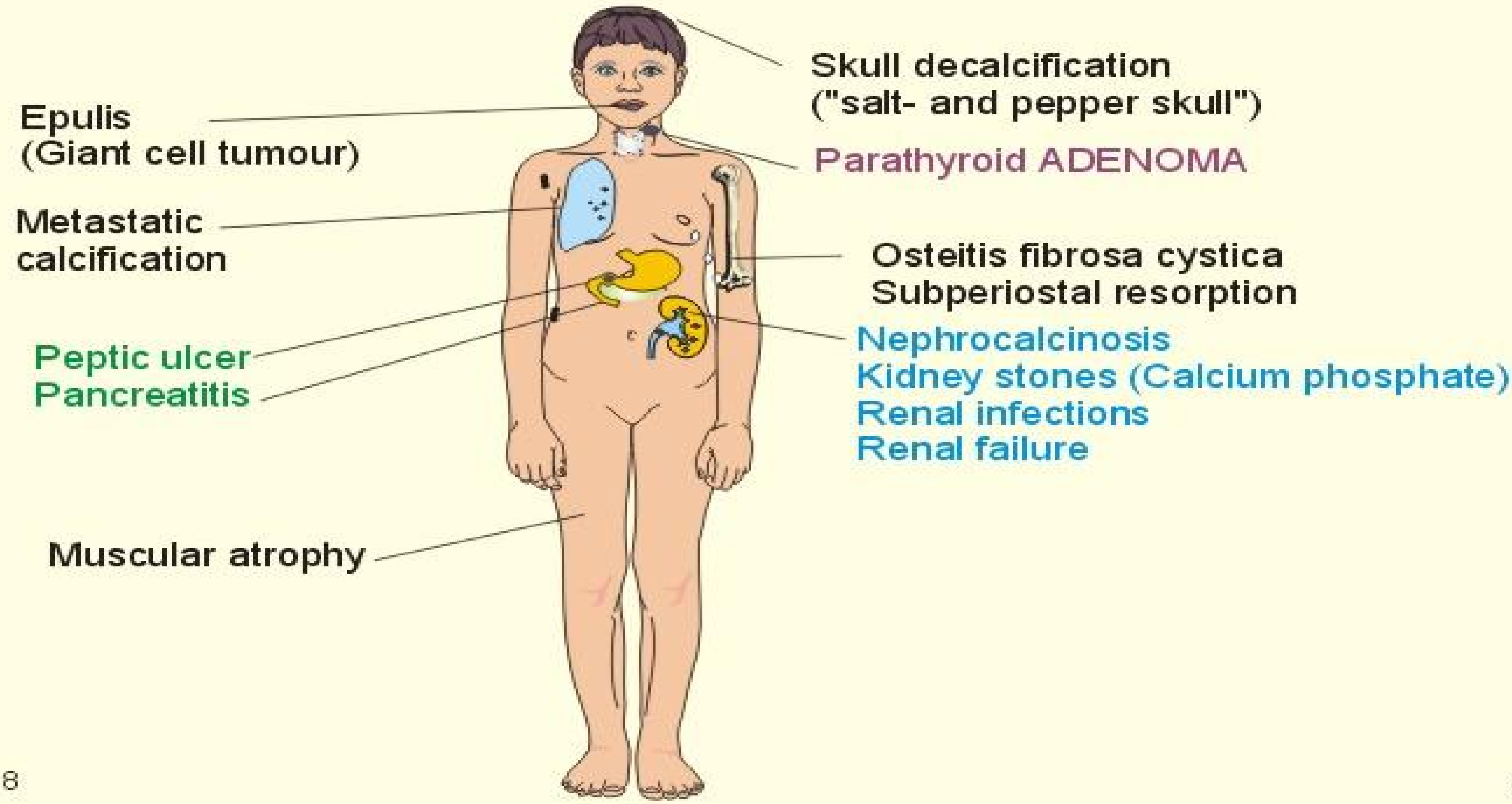
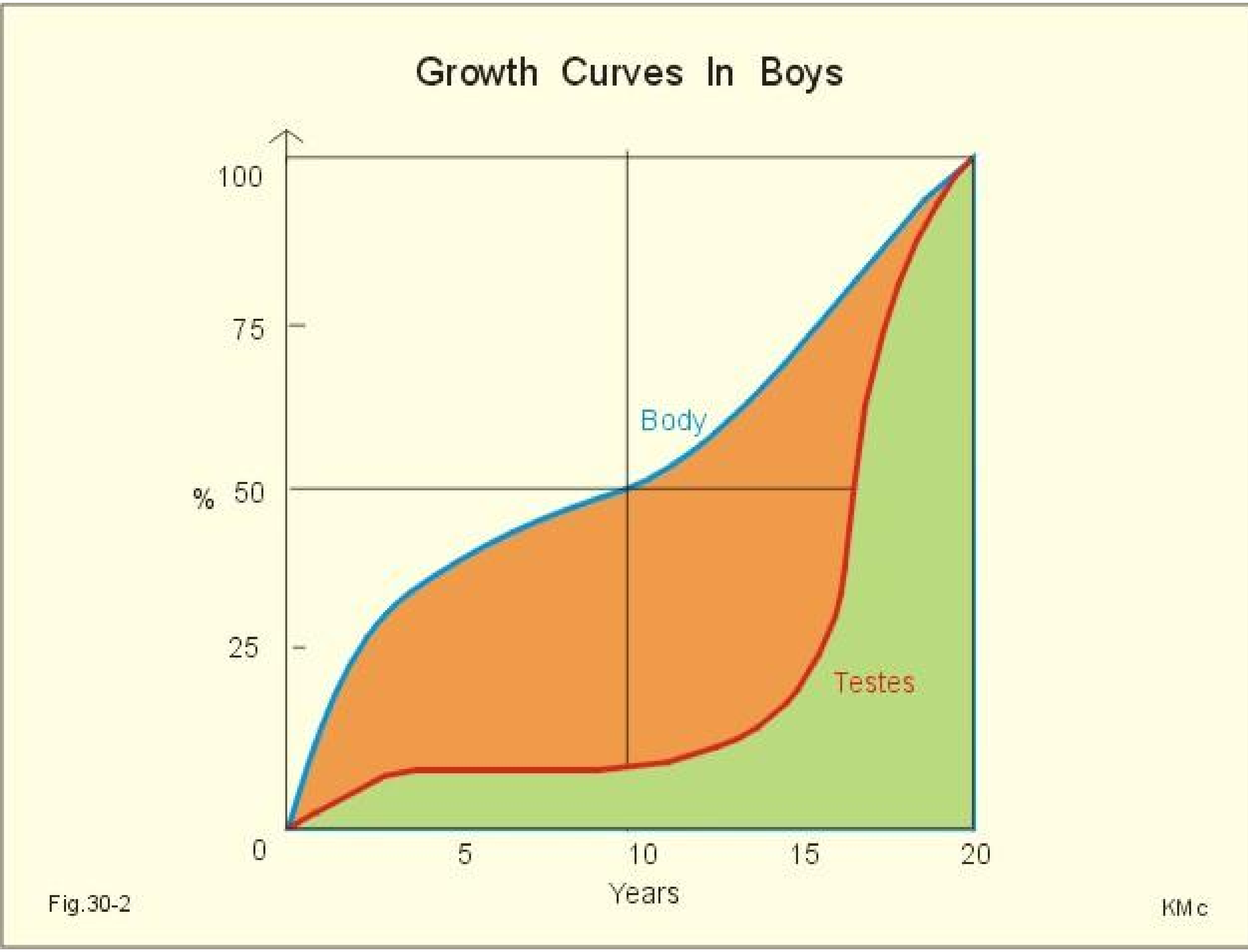


Fig. 30-8

KMc



Growth Curves In Boys
100
75
% 50
25
0
5
10
15
20
Years
Body
Testes
Fig.30-2
KMc