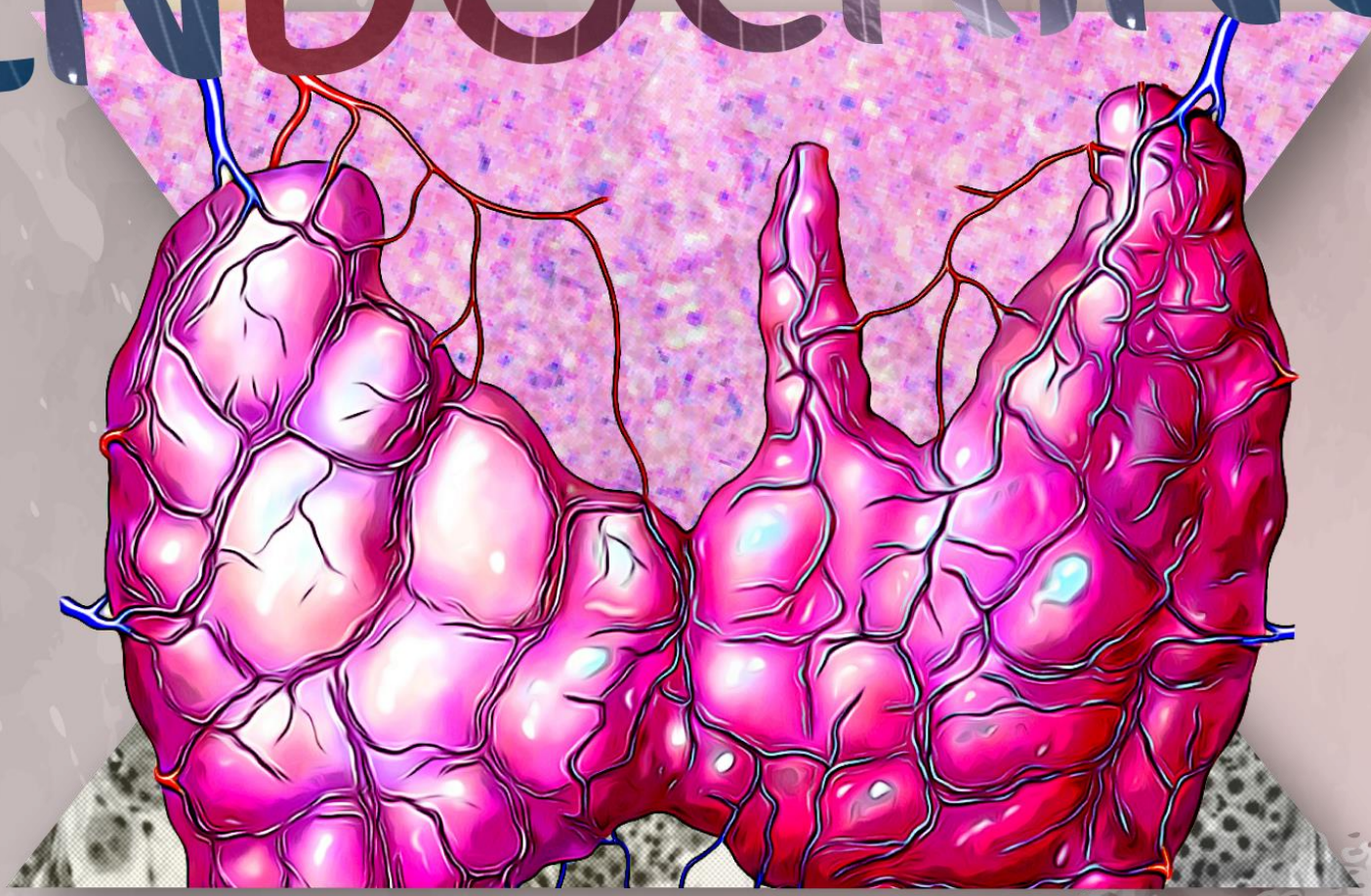
ENDOCRINE No 6



SUBJECT: physiology

DONE BY: 2016

CORRECTED BY: Bayan Abusheikha

DOCTOR: Saleem

There are a lot of information from the book that weren't mentioned by the doctor so don't be confused if you didn't hear them in the record, I know it's a long sheet but studying it won't be hard I promise.

Metabolism of thyroxine (T4):

-As we said it's **a pro-hormone** from which other hormones are synthesized. T4 either produces inactive substances; reverse T3 (95%), or it produces active substances; T3 (75%) or (DIT) diiodotyrosine.

-Thyroid hormones are very dangerous, therefore, they are found mostly in their protein-binding form; 99.5% of T3 and 99.98% of T4 are bound to plasma proteins. Notice how only 0.02% of T4 is free and 0.5% of T3 is free and if the percentages increase, death might occur.

-Three proteins can bind to thyroid hormones: thyronine-binding globulin (TBG) , Albumin and thyroxine-binding pre-albumin (TBPA) .

	Actual binding T4 %	Actual binding T3 %
TBG	75	75
Albumin	10	25
TBPA	15	0 T3 doesn't bind to TBPA.

-The percentage of free T4 is lower than T3 because it's a prohormone with very little activity.

-Binding of thyroid hormones to proteins has two advantages:

1- Prevention of filtration, since they are small molecules.

2- Elongation of their half-life.

Functions of the thyroid hormones:

-The figure below summarizes thyroid hormone functions and mechanism of action:

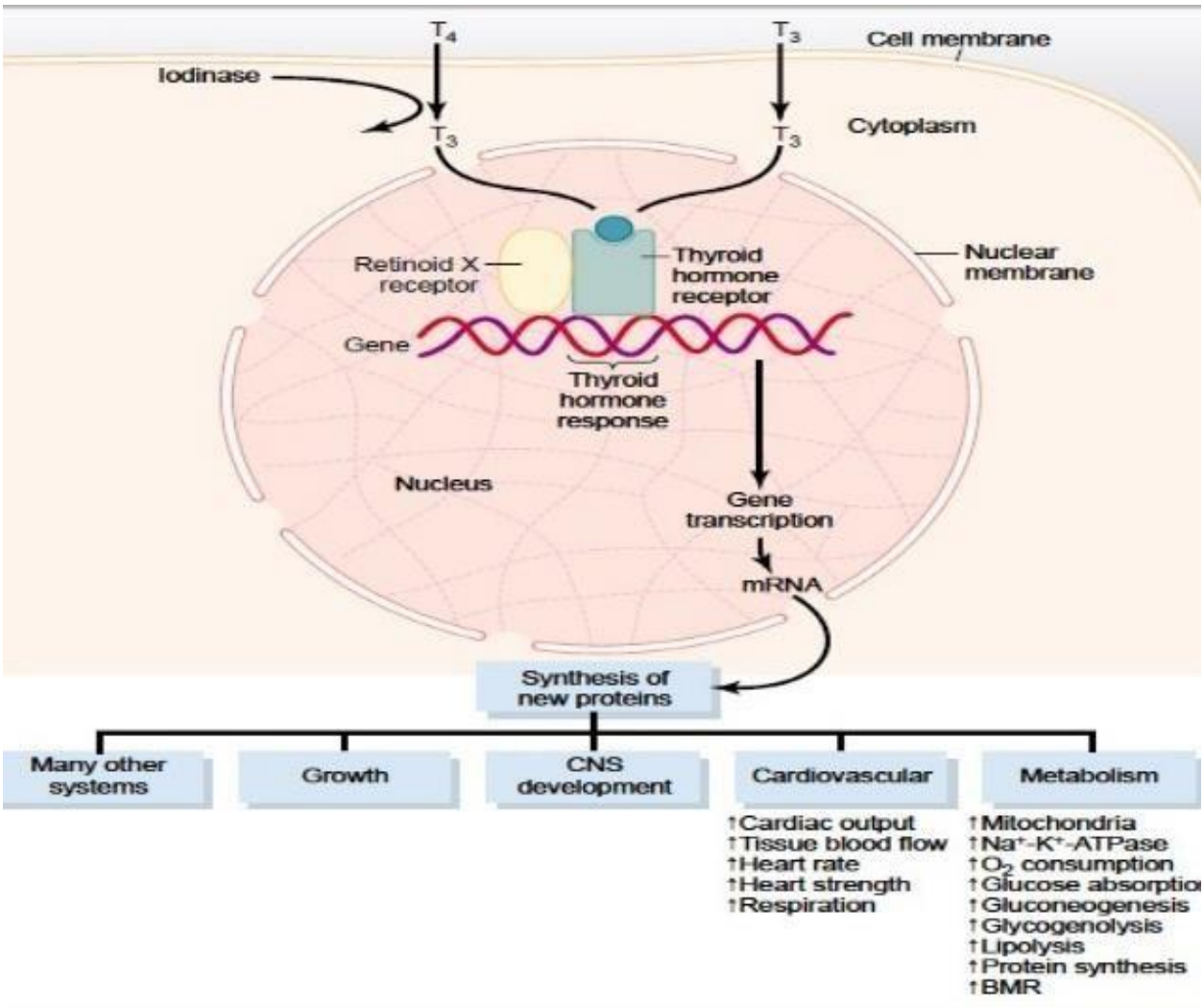


Figure: thyroid hormones activation of target cells. Thyroxine (T4) and triiodothyronine (T3) enter the cell membrane by a carrier-mediated adenosine triphosphate-dependent transport process. Much of the T4 is deiodinated to form T3, which interacts with the thyroid hormone receptor, bound as a heterodimer with retinoid X receptor. This action affect gene transcription and formation of many proteins, thus providing a hormone response. The main actions on different
cells are: increasing basal metabolic rate (BMR), mRNA synthesis and activity of the sodium-potassium ATPase.

CNS development: deficiency of thyroid hormones during fetal life causes no CNS development

Factors affecting thyroid hormones secretion:

TABLE 9–8. Factors Affecting Thyroid Hormone Secretion

Stimulatory Factors	Inhibitory Factors
TSH	I^- deficiency
Thyroid-stimulating immunoglobulins	Deiodinase deficiency
Increased TBG levels (e.g., pregnancy)	Excessive I^- intake (Wolff-Chaikoff effect)
	Perchlorate; thiocyanate (inhibit I^- pump)
	Propylthiouracil (inhibits peroxidase enzyme)
	Decreased TBG levels (e.g., liver disease)

*Deiodinase deficiency: T4 cant be converted to t3 (thyroid hormone deficiency)

*Multiple hormones, including growth hormone (GH), insulin-like growth factors (IGF-I and -II), insulin, thyroid hormones, glucocorticoids, androgens & estrogens contribute to the growth process in humans. Among these, GH & IGF-I have been implicated as the major determinants of growth in normal post-uterine life.

*Thyroid hormones are essential in normal amounts for growth; excess does not produce overgrowth as with GH, but causes increase catabolism of proteins & other nutrients.

*Thyroxine at normal concentrations has a **permissive** effect on the action of GH on protein synthesis. In the absence of thyroxine, amino acids uptake & protein synthesis are not much stimulated.

*Thyroid hormone has a permissive effect on lipids and protiens

*Adrenaline cant function of lipids unless they are first affected by thyroid hormone.

Diseases of the thyroid:

1-Hypothyrodism:

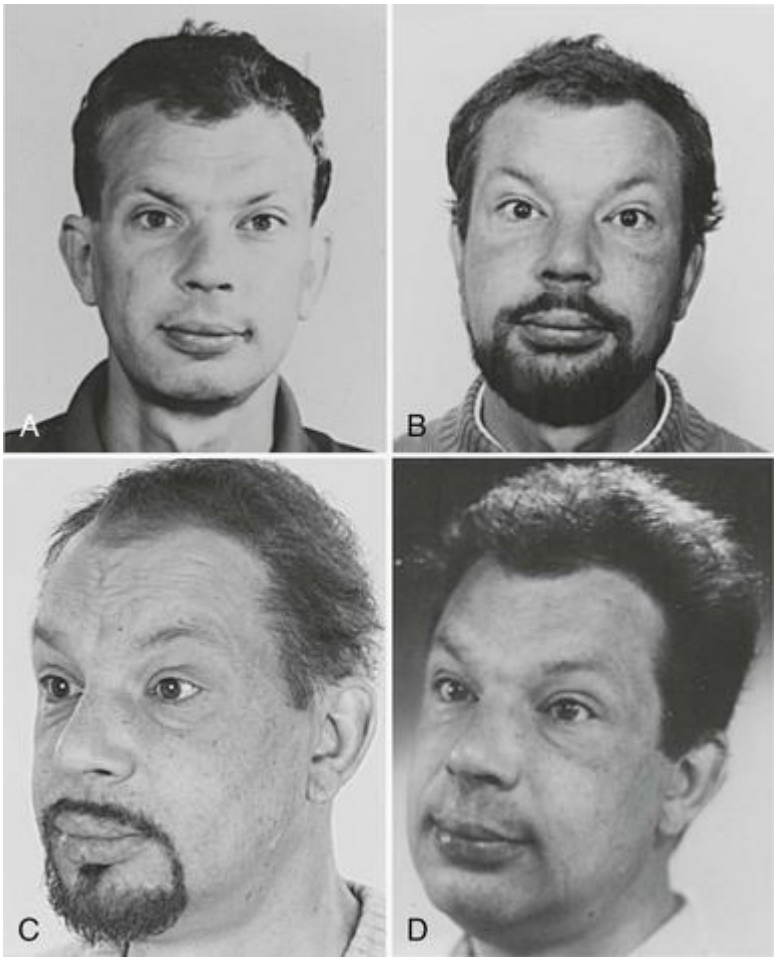
-Whether the cause of hypothyroidism was surgical removal of the thyroid gland, destruction by irradiation, thyroiditis, iodine deficiency or autoimmune diseases, the physiological effects are the same. These effects which are mainly seen in Myxedema include:

- Fatigue and somnolence.
- Decreased tissue oxidation and gut movements (constipation).

- Decreased Basal Metabolic Rate (BMR), Heart and Respiratory Rates.
- Body temperature falls, thought processes decrease, Blood Cholesterol increases, slow husky voice, Appetite is reduced, weight increases and a dry brittle hair.

-The main diseases associated with hyperthyroidism are:

A. ***Myxedema***: develops in adults with almost total lack of thyroid hormones. Such a patient demonstrates bagginess under eyes, swelling of the face (its said to be "doll like") and edematous appearance throughout the body. They are also sterile



Apearance of a 47-year-old man 12 years (A), 5 years (B), and 3 years (C) before hypothyroidism secondary to atrophic myxedema (D) was diagnosed. Note the typical myxedema face characterized by puffy nonpitting swelling of the skin and coarse facial feature

B. ***Cretinism***: caused by extreme hypothyroidism during feta life, infancy, or childhood. This condition is characterized by mental retardation and failure of body growth and sexual development and. It result from congenital lack of thyroid gland (congenital cretinism), or genetic deficiency and iodine deficiency (endemic cretinism).

Note: dwarfism results from growth hormone deficiency that mainly affect body growth **without** mental retardation.

2-Hyperthyrodism:

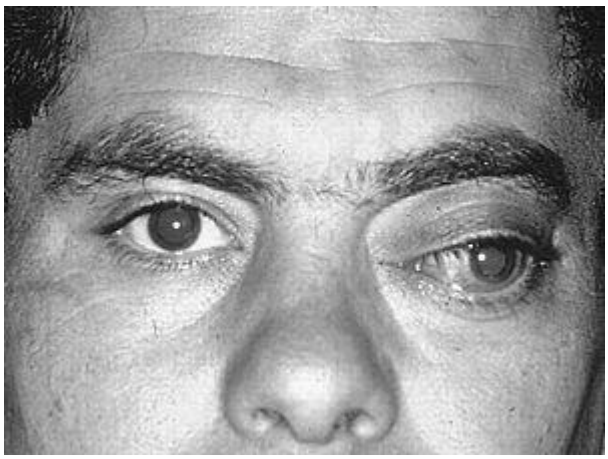
The main symptoms are: increased sweating, muscle weakness, nervousness or other psychic disorders, extreme fatigue but inability to sleep, tremor of hands and intolerance to heat.

Causes of hyperthyroidism are toxic goiter and Graves' disease.

Graves' disease: the most common form of hyperthyroidism, it is an autoimmune disease in which antibodies called thyroid-stimulating immunoglobulins (TSIs) form against TSH receptor in the thyroid gland leading to continuous activation of these receptors.

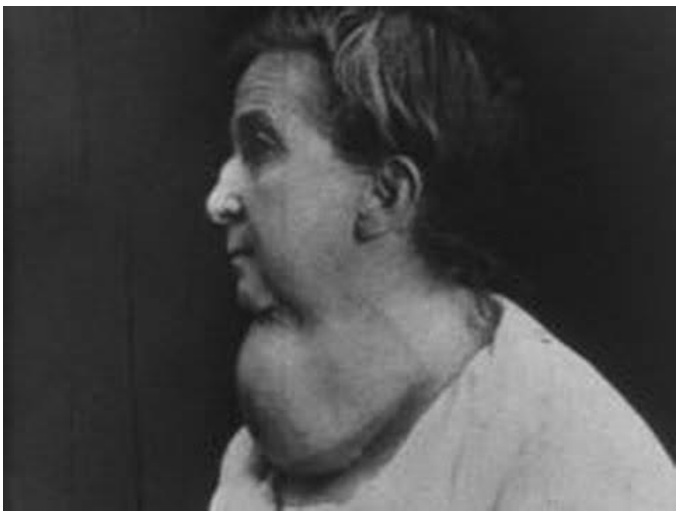
In Graves' disease there is:

1-Exophthalmus: the protrusion of the eye balls. Most but not all patients with hyperthyroidism develop some degree of protruding of eye balls, It usually occurs due to increased production of antibody called Thyroid Stimulating Immunoglobulin (TSI) which acts against a protein of the extraocular muscles and the connective tissue behind the eye which causes these tissues to swell, It is not due to an excess of the thyroid hormones .The patient cannot close his eyes and he is exposed to blindness.



Exophthalmos can be either bilateral (as is often seen in Graves' disease) or unilateral (as is often seen in an orbital tumor).

2-Goiter(neoplasm of the thyroid) : enlargement of the thyroid gland, it does occur in both hypothyroidism and hyperthyroidism because of the continuous stimulation of thyroid cells. Goiter can be either nontoxic and benign or toxic and malignant and we have to take a biopsy to know.



(Exophthamlus and goiter relate together but one can happen alone)

●When T3, T4 levels are low, this is simple nontoxic goiter (benign goiter).

● When T3, T4 levels are high, this is toxic malignant goiter (hyperthyroidism).

●Sometimes although there is high or low levels of T3, T4 but there is no goiter.

●Even when it's enlarged, your thyroid may produce normal amounts of hormones.

Thyroid gland questions:

1-Which is false about the thyroid: Iodine deficiency doesn't cause goiter.

2- Which is false about T4: It acts more rapidly than T3.

3-Which is true about thyroglobulin: Contains MIT & DIT.

4-True about Thyroxin synthesis: Iodide (I-) is oxidized to Iodine (I2)

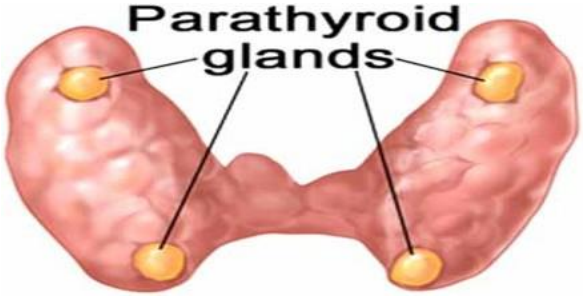
5-Which of the following when found in excess amounts causes protein catabolism: T3.

6-What happens to most of T4? Converted to T3

7-which of the following does not occur in thyroid hormone synthesis: >>> 4 molecules of iodine bind to one molecule of tyrosine to form tetraiodothyronine (2 molecules).

8-Most abundant thyroid hormone produced is: T4 and most potent? T3.

Parathyroid Glands



We have **normally** *four* small glands and they **normally** locate *posterior* to the *thyroid gland.* **Abnormally**, some people have *more than four* and others may **abnormally** have their parathyroids somewhere other than behind the thyroid (*ectopic*).

Note: humans ideally have **four parathyroid glands**, frequently surgeons mistakenly while performing **thyroidectomy**, they remove parathyroid because it is difficult to locate parathyroid glands during thyroid operations due to the *close anatomical relation* between both glands. Needless to say, if *one or two glands* were missed, the remaining ones would *be sufficient* to perform the function of all the glands because of the capability of the tissue of hypertrophying.

(extra: removal of three out of the four parathyroid glands causes transient hypoparathyroidism, hypertrophying of remaining tissue is possible too)

**The parathyroid glands develop at 5-14 weeks of gestation, they develop almost before the development of thyroid gland, there are variations between individuals, though.

** In adults, Each gland weighs 20-50 milligrams(mg)

(extra, these glands usually become enlarged in many **physiological cases** such as during pregnancy, lactation and some **pathological cases** at which decreased calcium concentration persists and results in hypertrophy of the glands like what happens in rickets)

Parathyroid Glands are Composed of two types of cells:-

a) ChiefCells

A**lmost** all of the parathyroid hormone (PTH) is synthesized and secreted by the chief cells, **almost all** of PTH is synthesized and secreted by chief because,

1- there is a small portion secreted by **another organ** (the doctor has not mentioned what is it)

2- another explanation is that some other cells **secrete another protein** called parathyroid hormone-related protein**PTHrP** (which is paracrine and it is also produced by many other organs), this protein hormone is similar to PTH in function but with less activity

((this PTHrP also increases the formation of second messengers (cAMP, I, Diacylglycerol) to normalize plasma calcium level, like PTH))

The aim of the presence of Chief Cells is that they play the main role in regulating Ca^{2+}via PTH secretion

b) Oxyphil (eosinophil) Cells

(unknown function), although their function is uncertain, it is suggested that they may be modified or depleted chief cells that no longer secrete PTH.

(EXTRA: it might play role in the metabolism of the parathyroid glands.)

DON'T secrete PTH

The parathyroid hormone

1- It is **synthesized** and **secreted** by the chief cells.

2- It is released into **capillaries**, from there it goes to the general circulation, then to **all tissues** of the body BUT it doesn't act on all tissues, only some are sensitive to it (remember: parathyroid is an endocrine gland)

3- It acts on *Kidney Tubules*, *Bone* and *Gut*

4- The dominant regulator of PTH secretion is the **plasma Ca++ level** (potent regulator).

Ca++ also regulates the size & the number of parathyroid cells

Extra Note *to explain what is underlined:* if there was a slight decrease in calcium concentration, PTH secretion would increase, when this decrease persisted for a long period of time, the gland would undergo hypertrophy. But, if Calcium concentration increased due to any reason, the activity of the gland would decrease which leads to reduction of the gland's size.

5- Its main function is to **maintain/ normalize ionized blood calcium** normal level at 11mg/ 100 millilitre plasma (necessary for normal muscle excitability), this is why PTH is essential for life, because without it, Ca++ falls in plasma, as a result, neuromuscular excitability increases, tetany & death occurs when tatany reaches lungs and heart.

6- **Magnesium**, like calcium, increases resorption -when its concentration is low-, **Hypomagnesemia** stimulates PTH secretion such as hypocalcaemia but less potent. ((Although it *has* low potency, magnesium is needed too, when deficient, no mineralization occurs))

7- **phosphate metabolism**, i.e., A rise in plasma phosphate concentration **indirectly** causes a transient increase in PTH secretion. This explains the normal function of PTH, how it reduces phosphate concentration.

8- 1,25 (OH)2 -D **directly** reduces PTH secretion, this is how vitamin D helps keep your PTH levels in check.

Notes: 1,25 (OH)2 -D is the most potent metabolite of vitamin D.

An increase in 1,25 (OH)2 –D and Calcium concentration **directly** inhibits the release of PTH by negative feedback inhibition mechanism, while low concentration of Calcium **stimulates** the gland to secrete PTH

9- It is a **protein** hormone, meaning that:

- it is **free** (not protein-bound) in plasma with short half life
- it **interacts with receptors** on the surface of target cells (on the cell membrane) increasing the formation of cAMP, IP & diacylglycerol.

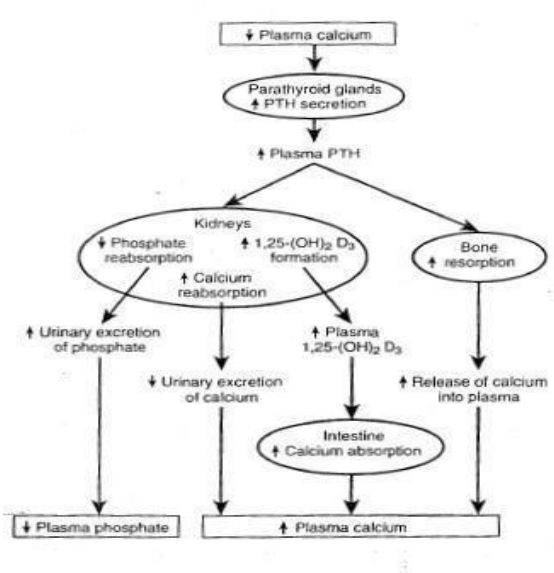
PTH is a single chain protein (9600 molecular weight) that contains **84** amino acids. (The biologic activity of the hormone resides within a.a 1-34, meaning that the biological activity of PTH is found in the first **34** amino acids which are adjacent to the N terminus), the doctor said that there might be differences between people in the number of amino acids but where activity resides is the same in everyone, ((extra: for example, there have been compounds isolated from the parathyroid glands that have as few as 34 amino acids exhibit full PTH activity))

The doctor gave another example which is thyroglobulin which has 70- 100 amino acids, but there is no change in where the activity resides)

ExtraNote: PTH is first synthesized by ribosome in the form of preprohormone which is a polypeptide chain of 110 amino acids, then in the ER and Golgi apparatus preprohormone is cleaved into prohormone of 90 amino acids , and then to the hormone itself with 84 amino acids .

Effects of PTH on calcium and phosphate metabolism :

why do we study calcium and phosphate together? Because the homeostasis for both is closely associated and many factors that regulate Calcium also regulate phosphate from the diagram on the right, we notice that when plasma calcium **decreases**, parathyroid glands **secrete more** PTH, as a result, PTH plasma level **rises**, ((extra: because when the free ionized Ca++ concentration decreases in the blood, sensors in the theparathyroid gland cell membrane called (calcium – sensing receptors) detect this decrease and start to secrete PTH to normalize the situation.))it acts on Kidneys, Bones and Gut, but how?



PTH's main function is to control the extracellular concentration of calcium and phosphate by regulating:

1)Renal Excretion:

PTH acts directly on kidneys,

- more 1,25-$(OH)_2$ D_3Formation which increases plasma levels of

  1,25$(OH)_2$ D_3.(by conversion of 25-$(OH)_2D_3$into 1,25-$(OH)_2D_3$ the active and potent form of vitamin D needed to allow the entry of both Calcium and Phosphate from the gut into the blood circulation)

  Note that PTH stimulates the conversion.

- less phosphate reabsorption (PTH Inhibits renal tubular resorption of phosphate), which increases urinary excretion of phosphate.This effect quantitatively offsets entry of phosphate from bone and gut. Therefore, plasma phosphate level decreases.
- more calcium reabsorption which reduces urinary excretion of calcium

2) Bone Resorption PTH acts directly on bone

- More bone resorption which increases calcium release into plasma. PTH controls the action of releasing calcium (+phosphate) from the bone, *Here is the mechanism: (slides)*

Bone resorption by osteoclasts. Parathyroid hormone (PTH) binds to receptors on osteoblasts, causing them to release RANKL which is also called osteoprotegerin ligand (OPGL), Which binds to receptors on preosteoclast cells (osteoclast precursors) -such as RANK-. This causes the cells to differentiate into mature osteoclasts. The mature osteoclasts then **develop a ruffled borde**r (villus-like projections), these villi secrete two types of substances: ((that promote resorption))**1)Enzymes released from lysosomes of the osteoclasts. 2) several acids**

*__To summarize__, PTH activates osteoblasts, the osteoblasts activate osteoclasts which resorb bone releasing calcium and phosphate into blood by releasing *enzymes* and *acids* that promote resorption

__Why doesn't PTH directly activate osteoclasts__? Because osteoclast cells do not themselves have PTH receptors. Instead the osteoblasts signal osteoclast precursors, a major signal is RANKL which activates receptors on osteoclast precursors (extra: osteocytes could also send signals to osteoclasts)

Extra: How the previous mechanism could be suppressed? By OPG, OPG binds to RANKL (OPGL) preventing it from interacting with its receptor, and thus inhibiting differentiation of preosteoclasts into mature osteoclasts that resorb bone, this is why PTH decreases OPG

3) Intestinal Absorption,

PTH indirectly increases absorption via 1,25(OH)2–D that facilitates the entry of ions through the epithelium of the gut

- It responds to the increase in the plasma levels of 1,25-$(OH)_2D_3$ by increasing calcium ions absorption (and phosphate ions too)

(ExtraNote: notice that the percentage of dietary calcium absorbed from the gut is inversely related to intake)

The overall final result of all the previous is to maintain ion levels by both *decreasing plasma phosphate* and increasing plasma calcium.

Note: Any disease that decreases the release of PTH will affect its functions in the intestine, kidney and bone on the contrary of its normal functions.

Parathyroids' Underactivity (hypofunction of parathyroid glands)

of **Removal** or (**Atrophy** Glands Parathyroid Hypofunction of Parathyroid tissue) causes hypocalcaemia, often with resultant tetany because of inadequate production of PTH which affects the kidneys, bones and gut in the following means respectively:

1) **Diminished** tubular **reabsorption** of calcium and decreased phosphate excretion (but increases calcium levels in urine)
2) **Reduced mobilization** of calcium and phosphate from bones
3) **Vitamin D** metabolites **not converted** to 1:25 $(OH)_2$ D_3, this insufficient production of 1:25 $(OH)_2$ D_3leads to diminished absorption of dietary calcium from gut.

All the previously mentioned points, lead to fall in BLOOD CALCIUM level and [rise in plasma phosphate]If more falling of blood calcium occurs (if concentration of blood calcium falls below 6-7mg/100mL plasma), this leads to more increase in excitability of Neuromuscular tissue, this leads to severe convulsive disorder -TETANY- why? Because calcium regulates sodium, low levels of calcium leads to continuous Na+ entry (continuous repolarization) which causes tetany.

Tetany when occurs can spread to **lungs**, when tetanisation affects the respiratory system, **death** occurs (hypocalcaemic tetany) ***extra:*** *why it is lethal? because tetanic spasms affect laryngeal muscles, spasm of these muscles obstructs respiration*

If calcium levels fall below 5mg/100 mL death occurs

ExtraNote: (2015 sheet) Heart cannot be affected with tetany, but why? Because the action potential of the heart occupies the mechanical response which means that there is no difference between the electrical and the mechanical response.(the doctor's answer) The heart cannot be tetanized, or go into sustained involuntary contractions, because of the long refractory period of the muscle, during which it does not respond to stimulus.(another correct answer).

FROM SLIDES

Calcium plays a key role in nerve and muscle function, enzyme function, and mineral balance in bone.

Calcium affects nerve and muscle excitability, neurotransmitter release from axon terminals, and excitation- contraction coupling in muscle cells. It serves as a second or third messenger in several intracellular signal transduction pathways. Some enzymes use calcium as a cofactor, including some in the blood-clotting cascade. Finally,calcium is a major constituent ofbone. Of all of these roles the one that demands the most careful regulation of plasma calcium is the effect of calcium on nerve excitability. Calcium affects the **sodium** permeability of membranes, which influences the ease with which actionpotentials are triggered. Low plasmacalcium (**hypocalcaemia**)-about 50 percent below normal- can lead to the generation of spontaneous action potentials in nerves. When motor neurons are affected, tetany of the muscles of the motor unit may occur, this conditionis called **hypocalcaemic tetany.**

Hypocalcaemic Tetany is the involuntary tetanic contraction of skeletal muscles that occurs when the extracellular Ca 2+concentration falls to about 40 percent of its normal value. · · This may seem surprising,because we have seen that Ca2+ isrequired for excitationcontraction coupling. However, recall that this Ca2+issarcoplasmic reticulumC2+, not extracellular Ca2+. The effect of changes in extracellular Ca 2+ is exerted not on the sarcoplasmic reticulum Ca2+but directly on the plasma membrane. Low extracellular Ca2+ (hypocalcemia) increases the opening of Na+ channels in excitable membranes, leading to membrane depolarization and the spontaneous firing of action potentials. This causes the increased muscle contractions, which are similar to muscular cramping ..

((Note the Inverse relationship between Plasma Calcium and Inorganic Phosphate.))

Usual Manifestations:TWITCHINGS,NERVOUSNESS,OCCASIONAL SPASMS OF FACIAL AND LIMB MUSCLES

Symptoms are relieved by injection of Calcium, large doses of Vitamin D compound and PTH.

NOTE:- **hypercalcemia** causes the neurons to become depressed (not excitable) while **hypocalcaemia** cause the nervous system to be more excited which might cause tetany (why more excitable? Because of increased neuronal membrane permeability to sodium ions, facilitating initiation of action potentials)

Parathyroids' Overactivity (hyperactivity)

PTH normally supplies Calcium from synovial fluid around the bone, not from the texture of the bone. However, This would change if there was an ABNORMAL hyperfunction (often due to tumour) which causes overproduction of PTH (hyperparathyroidism) the prolonged secretion of PTH finally results in very evident resorption and even development of large cavities filled with osteoclasts, generally there would be consequences on Bones, Kidney, Intestine

A) Greatly increased **mobilization** of calcium and phosphate (Excess Amounts of Calcium and Phosphate are Withdrawn from Stores in Bones)- leading to fragile bone (bone softening)

B) Greatly **increased** tubular **reabsorption** of calcium and tubular secretion of phosphate (leading to great loss of phosphate in urine)

C) Very high 1:25 DHCC levels which act on gut and leads to great increase in absorption of dietary calcium

Then this leads to a great rise in BLOOD CALCIUM level (possibly over 1617mg/100 mL which contributes to increased viscosity of plasma, which facilitates deposition of calcium in unusual sites such as kidney, and eventually to **OSTEITIS FIBROSA CYSTICA** (eventual softening and deformity of bones).

OSTEITIS FIBROSA CYSTICA: a disease caused due to persistent secretion of PTH which leads to more release of Calcium and Phosphate from the bone . it differs from osteoporosis

Other Symptoms: signs of toxicity (calcium toxicity) such as nausea, vomiting, loss of appetite,

Note: The Increased Level of Blood Calcium Eventually Leads to Excessive Loss of Calcium in Urine (in spite of increased reabsorption) and also of Water Since the Salt Excreted in Solution. The Manifestations are **Polyuria and Thirst** (this explains why the patient is always thirsty like diabetics but to a lesser extent)

How to Abolish the disease? Excision of the Overactive Parathyroid Tissue.

TO SUM UP, Hyperparathyroidism causes **extreme osteoclastic activity** in the bones/ which **elevates calcium** ion concentration while **depressing** concentration of **phosphate** ions

(Extra: high levels of ALP is diagnostic in hyperparathyroidism, because of the secretion of large quantities of ALP)

VitaminD, (Hormone D)

It has been debated on whether to call it a vitamin or a hormone, It is a **vitamin** (because it can be taken from diet), a vitamin in the sense that when it cannot be synthesized in sufficient quantities, it must be ingested in minimal amounts for health to be maintained. and it is a **hormone** (because it can be synthesized in the body and released into the blood). A hormone in the sense that it is synthesized in the body, although not by an endocrine gland; after further processing, it is transported via the circulation to act on target cells… and it functions as a type of "hormone" to promote absorption of calcium specifically in its 1,25 $(OH)_2D_3$ form.

- in conjunction with PTH, Vitamin D is the second major regulatory **hormone** for calcium and phosphate metabolism.
- The roles of PTH and vitamin D can be distinguished as follows. **The role of PTH** is to maintain the plasma Ca^{2+} concentration, and its actions are coordinated to *increase* Ca^{2+} the ionized concentration toward normal.

The role of vitamin D is to promote **mineralization** of new bone,and its actions are coordinated to increase *both* Ca^{2+}andphosphate concentrations in the plasma so that these elements can be deposited in new bone mineral.Phosphate concentrations in plasma so that these elements can be deposited in new bone mineral.

(phosphate metabolism is the main difference)

Therefore, Free Ca++ not the phosphate that is regulated so precisely ..
hormonal control of free Ca+++ level is via dual hormone system: PTH and Vitamin D

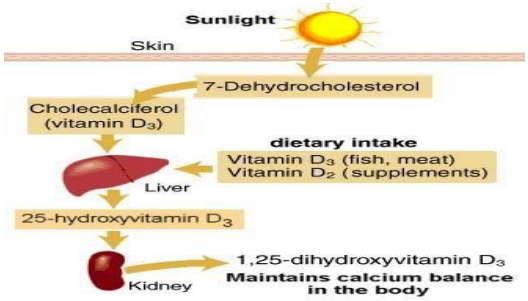
In **Bone**, 1,25-dihydroxycholecalciferol acts synergistically with PTH to stimulate osteoclast activity and bone resorption. This action may seem paradoxical, since the overall action of 1 ,25dihydroxycholecalciferol is to promote bone mineralization. However, mineralized "old" bone is resorbed to provide more Calcium ions and phosphate to ECF so that "new" bone can be mineralized (bone remodelling).

((NOTE that Bone remodelling is influenced by PTH and active form of Vitamin D))

Vitamin D & its Metabolism

As mentioned before, Vitamins **D3 & D2** are essentially prohormones that undergo **identical processing** that converts them to molecules with identical qualitative & quantitative actions.

Vitamin D itself is not the active substance that actually causes the effects. Instead, it be converted through a succession of reactions in the liver and kidneys to the final active product. Once vitamin D enters **the circulation** whether it is synthesized in the skin (D3)when exposed to sun or ingested and then absorbed from gut (D2), both undergo 25-hydroxylation in the liver, this step is the first step in the activation of D_3, meaning that it is concentrated in the **liver**, where it is processed (hydroxylated to 25-0HD), this molecule is transported to the **kidney** where it is further hydroxylated, but it undergoes alternative fates. (i.e.**two different** pathways, each of which is mediated by a special enzyme



i. the alpha-hydroxylase enzyme

it is activated when more biological activity, thereby it is further hydroxylated in 1 position to form 1,25-$(0H)_2$-D, this occurs as a result of:

- vitamin D deficiency
- calcium deficiency
- phosphate deficiency
- the presence of PTH (its secretion from parathyroids)kidney with the help of PTH, coverts 25- hydroxycholecalciferol into 1,25- hydroxycholecalciferol
- production of insulin from pancreas
- production of GH,PRL from pituitary glands

extra: the absence of kidneys makes vitamin D loses its effectiveness, because the most potent form 1,25-$(0H)_2$-D is formed in the kidneys, also this conversion requires PTH, this is why this active form will not be present in the absence of PTH)

ii. another enzyme (24-hydroxylase)

it is activated to hydroxylze 24 position when less biological activity is required, to form 24,25-(0H)2-Din the following conditions:

- calcium excess
- phosphate excess
- the presence of 1,25-(OH2)-D

it mainly depends on the **concentration of calcium**, 25-(OH)2-D is either converted to 1,25-(OH)2-D or 24,25-(OH)2-D. when Calcium is needed, meaning that calcium concentration is below the normal level, 25(OH)2-D is converted to 1,25-(OH)2D, but when Calcium level is significant, (calcium levels are high when PTH is suppressed) 25-(OH)2-D is converted into 24,25-OH)2-D.

Both **1,25-(0H)2-D** and 24,25-(0H)2-D can be found in the plasma normally but **the former** is more potent, i.e. 24,25-(0H)2-D is only 1/20th as potent as 1,25-(0H)2-D & mainly serves to dispose of excess vitamin D.

Potency of the known Vitamin D metabolites from the most potent to the least: - *1,25-(OH)2-D* then *24,25-(OH)2-D* then *25-(OH)2-D*, they all have the same function but differ in their potencies.

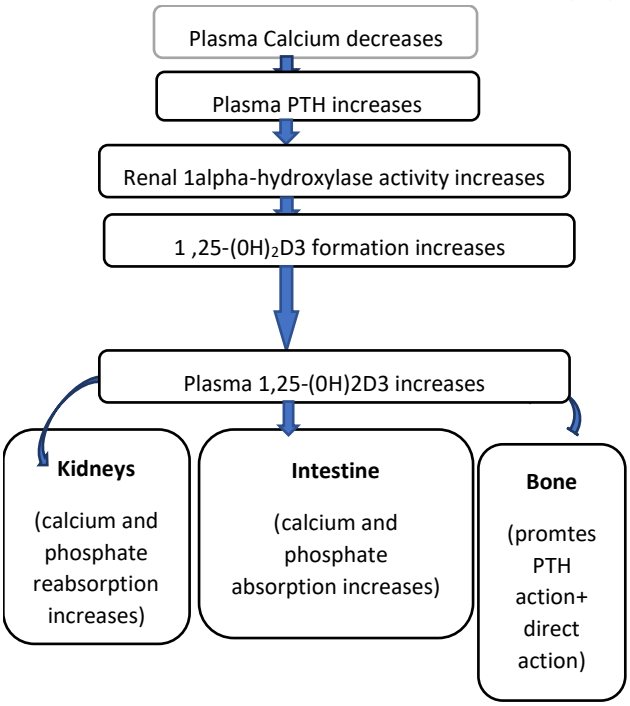
	Plasma concentration (µg/L)	**Estimated Production Rate (µg/day)**	**Plasma Half-Life (day)**
1,25 $(OH)_2$-D_3	0.03	1	1 to 3
24,25$(OH)_2$-D_3	2	1	15 to 40
25-(OH)-D_3	20	10	5 to 20

In addition to the three vitamin D metabolites there **are 15 other** metabolites of Vitamin D found in the blood! but their physiological function is unclear yet.

Vitamin D, 25-0H-D & 1,25-(0H)-D circulate bound to a protein carrier. 1,25-(0H)-D has by far the lowest concentration & the shortest half-life of the three.

Mineral Transfer	**Mineral Homeostasis**
AVIAN SHELL GLAND	KIDNEY
MAMMARY GLAND	INTESTINE
PLACENTA	BONE
SKIN	

What are the Effects of 1;25-$(0H)_2$D3 on Calcium and Phosphate metabolism



The result of what happens in kidney, intestine and bone as explained in the diagram, is a decrease in urinary excretion of both phosphate and calcium which results in increasing plasma calcium and phosphate (the net effect)

REMEMBER that PTH increase calcium but reduces the phosphate BUT Vitamin D raises the level of both calcium and phosphate to do its function which is bone mineralization which needs both Calcium and Phosphate. Although vitaminD increases the phosphate concentration, it has a synergistic relation with PTH. (no antagonism)

As mentioned before, the synthesis of the active form of vitamin D sequentially occurs in the skin then the liver then the kidney. Sometimes though, after vitamin D is converted to the 25OH form in the liver, it can be stored in fat tissue, obese people especially teenagers have a type of fat in their abdomen which captures vitamin D and does not allow it to be released so they suffer from problems effecting their **bone** and **hearts**. But why the heart? we know that Vitamin D increases the level of calcium and thus helps the heart to function well.

**teenagers who suffer from vitamin D deficiency, they usually have problems with heart, blood pressure, blood sugar

Before talking about Vitamin D deficiency, let's see from where we can **obtain** it,

- **Vitamin D_3** is mainly produced in the skin, but it is also available from other natural sources, such as:-
  Fish (Cod/ Halibut), liver, fortified milk, eggs, bird
- **vitamin D_2** can be obtained from nowhere except from diet and largely from vegetables.

Vitamin D deficiency

Vitamin D is fat soluble vitamin *stored* in the liver and fat tissues of our bodies and only 1-2% of the store is burned each day, therefore several years of very low dietary intake as well as diminished endogenous synthesis is required for deficiency to develop. In other words, deficiency does not develop unless low intake was simultaneous with depleted stores. We need both Vitamin D_2 and Vitamin D_3, from diet and sun respectively. Neither Vitamin D_3 nor Vitamin D_2 is sufficient alone

without the other. Let's suppose there was a man who is exposed to the sun daily, this would not protect them from vitamin D deficiency if their diet was not rich in vitamin D.

**What are the Causes of deficiency of 1:25-dihydroxycalciferol:

- Failure to synthesize cholecalciferol in the skin (this occurs in darkskinned people in a (temperature climate)?
- Dietary deficiency of cholecalciferol (relatively less important)
- Failure to hydroxylate cholecalciferol in the 25 position (this-occurs in chronic liver disease; hepatic osteodystrophy)
- Rapid metabolism of cholecalciferol and its active metabolites (this occurs when hepatic enzymes are induced and is seen in patients taking anticonvulsants)
- Failure to hydroxylate 25-cholecalciferol in the 1 position (this occurs in patients with chronic renal failure; renal osteodystrophy)

**Deficiency of vitamin D leads to ○ failure of bone mineralization&results

in:

- softening of the bones(osteomalacia)in adults, (aka adult rickets)
- the classic disease of rickets in children what is the difference between poliomyelitis and rickets diseases ?

Poliomyelitis >>> caused by viral infection

Rickets >>> caused by a deficiency in vitamin D

What are physiological actions of phosphate

1. functions as part of the intracellular buffer system
2. constituent of a variety of macromolecules, such as nucleic acids, phospholipids, metabolic intermediates, phosphoproteins
3. constituent of bone

***What are physiological actions of calcium*

1. required for the maintenance of normal sodium permeability in nerves
2. Involved in triggering the release of acetylcholine from nerve endings at the neuromnuscular junction
3. Involved in excitation-contraction coupling in muscle cells
4. Serves as an intracellular signal' for some hormones
5. Required by someenzymes for normal activity
6. Required· for blood clotting to occur normally
7. Required for protein secretion
8. Constituent of Bone.

Major inorganic constituents of Bone

CONSTITUENT	**TOTAL BODY CONTENT PRESENT IN BONE (%)**
Calcium	99 (total body content present in bone)
Phosphate	85
Carbonate	80
Magnesium	50
Sodium	35
Water	9 (but adipose tissue contains much less water)

***Factors that affect bone formation and calcium metabolism*

- parathyroid hormone
- 1,25-0thydroxycholecaldferol
- Calcitonin
- Glucocorticoids
- Growth hormone and somatomedins
- Thyroid hormones
- Estrogens
- Insulin
- IGF-1
- Epidermal growth factor
- Fibroblast growth factor
- Platelet-derived growth factor
- Prostaglandin E2
- Osteoclast activating factor

good luck and please don't hesitate to ask me anything