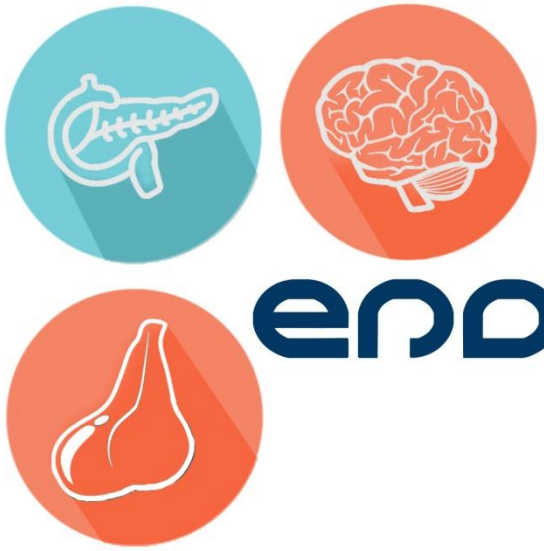

endocrine system

Pharmacology

Sheet Slide

number	4
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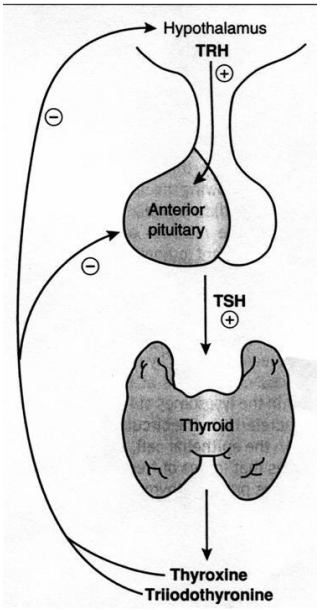
Thyroid Hormones

Regulation of thyroid hormones' secretion:

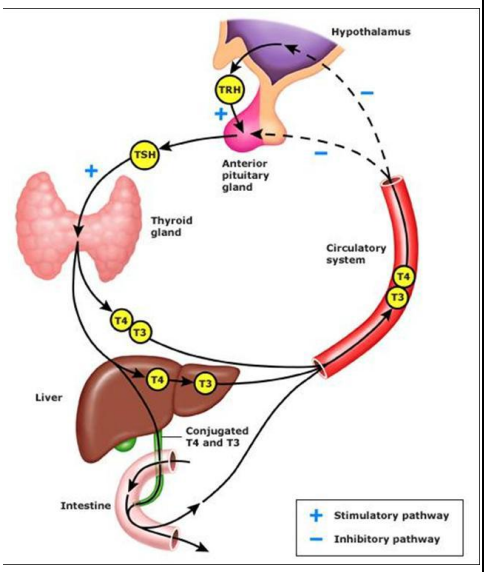
Thyroid hormones are essential for many physiological functions including development (of skeletal tissue,…) and are important for metabolism. They are synthesized in and released from the thyroid gland which is located in the neck.

The thyroid gland is under the regulation of the hypothalamus and the anterior pituitary gland. The regulation of synthesis and release of the thyroid hormones has great clinical significance.



The hypothalamus controls most of the anterior pituitary hormones. It releases **TRH** (Thyrotropin Releasing Hormone) which is a small peptide (3 amino acids). TRH reaches the anterior pituitary through portal system (network of capillaries), it then interacts with a specific membrane receptor (because it is a peptide) on the anterior pituitary resulting in the synthesis and release of **TSH** (Thyroid Stimulating Hormone); a glycoprotein with αβ subunits. TSH in turn interacts with specific membrane receptor on the thyroid gland leading to increased synthesis and release of **thyroid hormones** (**T3**, **T4**).

Thyroid hormones are released whenever they are needed. All hormones are needed in very minute quantities. They reach target cells and interact with specific receptors leading to the biological response.



After producing the desired effect, the action has to be terminated. The action of most hormones is terminated by a highly specific negative feedback mechanism. T3 and T4 feedback mainly on the **pituitary gland** and little on the hypothalamus; it is a highly-regulated system. In addition, T3 and T4 could be metabolized in the liver through conjugation reactions.

*What is the clinical significance of knowing this regulatory mechanism?

- It lies in the fact that understanding such regulatory and negative feedback mechanisms as endocrine pharmacologists and surgeons allowed us to understand the basis of certain endocrine diseases, helped in the **diagnosis** of endocrine diseases affecting endocrine secreting cells, and helped in putting a strategy to deal with such diseases.

→Here are several **examples** to understand the importance of these regulatory and negative feedback mechanisms:

- Deficiency states are more common.

- Hyperthyroidism is sometimes treated by surgery (removal of the thyroid) ending up with hypothyroidism.

EXAMPLE1: In hypothyroidism patients, there is no production of thyroid hormones and the manifestations of this disease are going to be due to the deficiency in thyroid hormones.

Now, is it possible that the thyroid gland is normal and the patient *has* hypothyroidism??

- Yes. It could be due to the *deficiency of **TSH*** for example. The major function of TSH is to produce and release thyroid hormones, so its deficiency leads to no synthesis and release of thyroid hormones; a condition known as **secondary hypothyroidism** (thyroid is normal but the problem results from the hormones controlling the gland directly like TSH).

Let's go a step further. Would a patient with normal thyroid and anterior pituitary have hypothyroidism?

- Yes. This could be **tertiary hypothyroidism** which is due to ***TRH*** *deficiency*.

So, hypothyroidism can be primary, secondary or tertiary.

To know where the defect is (in the thyroid, pituitary or hypothalamus), we do some tests. Such tests are very expensive.

*Why do we pay much money when the manifestations are the same (mainly due to T3, T4 deficiency)? Why don't we give T3 and T4 and that's it?

- Hypothyroid patients are indeed treated by exogenous administration of thyroid hormones (tablets, IV…).

Remember: the main (or only) job of **TRH** is to synthesize and secrete **TSH**, as with **TSH** that causes the synthesis and release thyroid hormones (T3 and T4).

If we do these diagnostic tests and we found out that the defect is in the hypothalamus (pituitary and thyroid are normal), hypothyroidism in such patients could be successfully treated by **TRH** administration. In many situations, using TRH is preferred above exogenous T3 and T4. Why is that? Because even with large doses of TRH it will only affect the releasable amount of TSH (it will not cause high release of TSH) because of *saturation* (with an increase of the dose, there is no further increase in the response). But one has to be careful though. Also, the system could be better controlled when using TRH. With T3 and T4 administration, you must keep eye on the dose and you must follow the patient (the regulation would be better if we used TRH). Side effects will also be more. And so on. On the other hand, TRH administration beautifully controls tertiary hypothyroidism (it is very effective although it is a 3-a.a peptide). It is also easy to modify the structure of TRH and it has different agonists with **less** side effects and **more** potency.
First, we have to make sure the pituitary and thyroid glands are okay. Otherwise, **TRH** will not be of value in the management of hypothyroidism. **TSH** is a complex protein and is not that widely used but it could be used.

If the defect is in the pituitary, you can replace with human recombinant TSH preparations.

All types of hypothyroidism could be successfully treated with T3, T4. But if the exam was specific (1^o, 2^o or 3^o), the treatment will be as discussed above.

The synthesis of a specific hormone happens in several steps involving enzymes, and it usually takes time. But after the synthesis of that particular hormone, it is stored in the endocrine gland (**storage** pool) and released whenever it is needed. The amount available for release (**releasable** pool) is a small amount and release is very quick. So, drugs which hit the synthetic machinery usually have **a delayed onset of action**. While drugs that affect release have **a rapid onset of action.**

00:00-10:30

EXAMPLE2: Could a patient with thyroid cancer be treated with thyroid hormones? Can the growth of this tumor be controlled by administration of exogenous T3 and T4?

- Yes, they could be used for **TSH-dependent cancer** (cancer that depends on TSH in its growth and even metastasis). By giving T3, T4 from outside, you suppress TSH release by negative feedback. Hence, this could be of value in the management of this type of cancer.

EXAMPLE3: The endocrine system is a highly sensitive system. Don't play with the hormonal environment of your body. If, for example, your GH level is normal, do not take GH to gain extra 2 or 3 cm (it is misuse/abuse).
When sex hormones (estrogen and progesterone) are given to a lady as contraceptives, it damages the whole axis and there is **5-10% possibility of irreversibility (she may become infertile)**. Sometimes IVF and IVM procedures are not beneficial.

Synthesis of thyroid hormones:

T3 and **T4** are iodinated tyrosines, and the precursor for their synthesis is **tyrosine**. Iodine is also needed.

- Tyrosine residues are present on a storage protein known as **thyroglobulin (TG)** in the thyroid gland.
- Iodide is only needed for thyroid hormone synthesis. And for its importance, it is added to our salt. So nowadays we don't have conditions of iodide deficiency and hypothyroidism resulting from it (in countries that add iodide to salt0.
  In iodide deficiency, there is no production of T3 and T4, so **TSH** levels rise causing goiter (enlarged thyroid). Iodide is trapped by thyroid follicles and added to tyrosines. **Sources:**
  -Iodized salt
  -Iodated bread
  -Dairy products
  Daily requirement: 75 micrograms which is about 10g of iodized salt.

T4 (thyroxine) is tetra iodothyronine (2 **tyrosines** +4 **I**) while **T3** is tri iodothyronine (2 **tyrosines** +3 **I**). **Reverse T3** (rT3) is a mirror image of T3; the position of the iodines is different. Reverse T3 (inactive) is only synthesized in a very little amount if any (5-15%). Most of the thyroid hormones synthesized is T4.

1. The first step is **<u>iodide trapping</u>**; iodide is trapped by thyroid follicles.

2. The second step is **<u>oxidation</u>** of iodide(I^-) to iodine(I_2). Iodide has to be oxidized <u>in order to be added to tyrosine</u>.

3. Following that is **<u>iodination reaction</u>**; the addition of iodine to tyrosine residues that are present on thyroglobulin. Iodination reaction occurs while tyrosine residues are still on thyroglobulin forming of **mono-iodotyrosine (MIT)** and **diiodotyrosine (DIT)**.

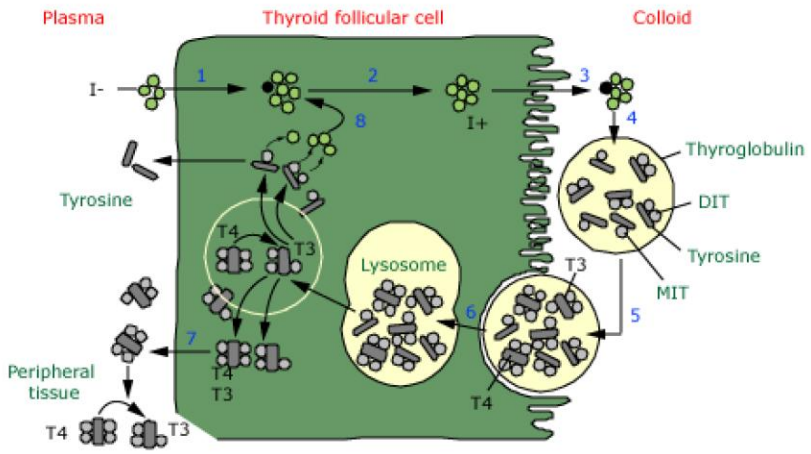
4. **<u>Coupling reaction</u>** (combination) of MITs and DITs:
    - MIT + DIT = T3
    - DIT + DIT = T4 (thyroxine)

   This coupling reaction occurs while tyrosine residues are still on **thyroglobulin** not on free tyrosine residues.

→ The oxidation, iodination, and coupling reactions are catalyzed by iodine or **thyroid peroxidase** enzyme

5. Thyroglobulin has now to be **<u>hydrolyzed</u>** by lysosomal enzymes releasing MIT, DIT, T3 and T4 in the follicle. What are really available for release into the blood are T3 and T4 while MIT and DIT are recycled to preserve iodide.

10:30-20:30



rT3 is secreted in a very little amount. <u>Most of the thyroid hormones that are synthesized in the thyroid gland are belonging to T4</u> (80-90% of thyroid hormones). T3 is about 10% of thyroid hormones secreted. Both T3 and T4 are

released into the blood stream. Thyroid hormones travel in blood bound to a specific **thyroxine binding globulin (TBG)** that facilitates their delivery to target cells. It also provides storage for these hormones.

In the peripheral tissues (kidney, liver, neuronal tissue, etc.), most of T4 synthesized is converted to T3 by **deiodinase enzyme**. This enzyme removes one iodine from T4 ending up with T3(more active).

The actions of thyroid hormones are mainly through T3 rather than T4. There are no receptors recognized for T4 in the nucleus. Both have similar mechanism of action, but what mainly binds nuclear receptors is T3.

The enzymes used in the synthetic pathway are considered receptors for drugs; we identify a specific enzyme to inhibit it. Drugs that could hit this synthetic machinery could be utilized in the management of disorders affecting the thyroid gland; where those which increase synthesis could be utilized in the management of hypothyroidisim, and those which inhibit synthesis could be utilized in the management of hyperthyroidisim. But ***remember*** that the drugs which hit the synthetic machinery usually have a delayed onset of action. Why? In hyperthyroidism for example, you have already synthesized thyroid hormones. Only when the already synthesized hormones are used up (stroage pool), these drugs start to act (and inhibit the oxidation reaction for example). Whereas drugs that hit the release have an immediate/rapid onset of action.

Mechanism of action of thyroid hormones:

Thyroid hormones reach target cells by the aid of the carrier protein **(TBG)**. They are highly lipid soluble (**lipophilic**) and easily pass plasma membrane in target cells.
Most of T4 is converted to T3 in target cells. Only the T3 form enters the nucleus (and little of T4) and binds nuclear receptor protein. The **hormone-receptor complex** binds specific response elements on DNA leading to a direct effect on the level of transcription. The mRNA produced then codes for specific proteins that mediate the biological responses of thyroid hormones.
After mediating the response, we don't need the hormones any more. The action is terminated by negative feedback and conjugation.

Differences between T3 and T4:

- **Thyroid content:**
  In the thyroid gland: T4 (Thyroxine) > T3 (4:1) ----> 80% is T4 and 20% is T3

- **Major source:**
  T4 → thyroid gland; **T3 →** deiodination of T4 **(80% of T3 is formed by deiodination of T4 in peripheral tissues)**

- **Potency:**
  T3 > T4 (Free T3 is **3-5** times more active than free T4)
  Potency is not that important in pharmacology. whatever the drug is, our major concern is to reach Vmax (the **efficacy**). Potency is related to the dose; less potent drug is given in larger doses and if it has no side effects there is no problem in increasing the dose since we achieve efficacy.

- **Protein binding:**
  T4 > T3 (T4 **99.97**% bound; T3 **99.5**% bound)
  This reflects long duration of action of T4 since it is more extensively bound to the globulin.

- **Half-life:**
  T4 = 1 week; **T3 =** 1 day
  The half-life of T4 is more, so the administration of T4 is less frequent when compared with T3. The dose of T3 is less because it is more potent.

General effects of thyroid hormones:

1. Thyroid hormones increase everything; **they increase the basal metabolic rate**, oxygen consumption, etc.

2. **Promote growth & development** (essential for growth in childhood).
   There are cases of **dwarfism** (called cretinism) due to hypothyroidism.
   They are very essential during fetal life for the development **of neuronal tissue.** If a baby is born with hypothyroidism, the **causes** could be:
   - Baby born without the thyroid.
   - the presence of certain antibodies directed toward the thyroid that are produced in the pregnant lady and easily cross the placenta

- the use of anti-thyroid drugs during pregnancy that easily cross the placenta and suppress the function of the thyroid in the fetus

Irrespective of the causes, if the baby is born with hypothyroidism, he usually acts normally **up to one year** and you don't see any serious obvious manifestations until then. By the age of one**, mental retardation appears on the baby**. This is very dangerous. Now, many hospitals usually screen for thyroid function of the baby after delivery by an easy blood test that measures T3 and T4 concentration.

- Calorigenic effect:
  ↑BMR; ↑ O2 consumption; ↑ general metabolism; ↑ CHO metabolism

3. ↑lipolysis; ↑ lipid breakdown.

4. **↓Cholesterol blood level**.
   Thyroid hormones were extensively used in weight reduction programs in the past. Now there are better drugs to lower blood cholesterol level.

5. **↑ β-adrenergic receptors in most tissues especially the heart** (over activity of sympathetic system). This is responsible for the **major manifestations of hyperthyroidism**. Hyperthyroidism patient are usually very anxious and nervous, have sweating, increased activity, and reduction of weight despite increased appetite.

20:30-31:00

6. ↑ **GIT motility** that could lead to **diarrhea**.

Disorders affecting the thyroid gland:

1) Hypothyroidism

In Children → **Cretinism**
In adults → **Myxedema**

Causes:

- **Surgical removal** of thyroid.
- **Thyroiditis** (Hashimoto's= chronic lymphocytic thyroiditis): an autoimmune inflammatory disease causing atrophy of thyroid; infectious; transient; postpartum hemorrhage.

- **Severe deficiency or excess of iodine**. Iodine could be used in the management of **hyperthyroidism**.
  *How does iodine acts as an anti-thyroid agent? How does excess of iodine cause hypothyroidism?
  The first proposed mechanism on how it is an anti-thyroid agent is that it has an auto regulatory mechanism; after entering the follicles it feeds back on its own tracking but only with large doses. This theory is obsolete; it is proved that this is not due to the effect of iodide inside the follicle on its tracking. But still we say that excess iodine inhibits the release of T3 and T4 and could lead to hypothyroidism.
- **Severe deficiency of one or more of the synthesis enzymes** (ex: peroxidase).
- **Severe pituitary or hypothalamic dysfunction**.
- Drug induced. When you see a patient always ask about his/her previous medications. Anti-thyroid drugs cause hypothyroidism.

Symptoms:

- Cold intolerance
- Lethargy
- Constipation
- Slowing of mental function and motor activity
- Weight gain but appetite decreased
- Abnormal menses
- dry/thick skin, hair loss, and hoarse voice
- Stroke volume and heart rate decreased; non pitting edema

Non pitting edema is the one in which the indentation made by a pressure on the affected area does not persist. While in edema of heart or renal failure, the skin doesn't return back to normal very quickly when you press on it (pitting edema).
These symptoms are easily detected.

Treatment:

The treatment is with hormonal replacement therapy (HRT); you replace with the deficient hormone.

Thyroid hormones preparations:

We have **animal sources** and **synthetic sources**. Animal preparations are easy to get (available) and cheap BUT they are **more allergic**. Synthetic preparations can also be allergic. Actually, allergy is considered a universal side effect of most hormones and anti-histamines.
Synthetic sources are more pure and their synthesis is not that difficult but they are a little bit more expensive.

Thyroid hormone structure is the same between human and animal unlike GH which is highly species-specific. That's why we can't use GH from animal sources, but we can use thyroid hormones or insulin for example.

1. Animal preparations:

- Thyroid USP (bovine, ovine, porcine); oral: They take the thyroid of the animal, dry it, and make tablets out of it (not pure; contains proteins, cellular debris, etc.). USP means according to the regulations of United States with respect to iodine content in the tablet (to not exceed a certain percent of the weight of the tablet), more likely to develop allergy.

- Thyroid extract (Thyroglobulin); oral: they "cleaned" the gland and **extracted thyroglobulin**. It is cleaner when compared with Thyroid USP but it is still contaminated with certain animal proteins. It is orally effective because it is stable orally. It reaches the intestine and gets hydrolyzed releasing T3 and T4 which are then absorbed (remember they are lipophilic).

2. Synthetic preparations:

- ℓ- thyroxine sodium; **synthetic T4**, oral
- Liothyronine sodium, **synthetic T3**, oral & I.V
- Liotrix, synthetic **T4 & T3** (**4:1** →the same ratio in the thyroid), oral

All have $t_{1/2}$ of 1 week except liothyronine ($t_{1/2}$ of 1 day).
Liotrix and Liothyronine have **no over advantage above synthetic T4** because synthetic T4 is going to be totally converted to T3. T3&T4 is expensive and have a shorter duration of action as compared to T4.

Clinical uses to thyroid hormones:

- **Hypothyroidism** in very little amounts (physiological doses; HRT). Pharmacological doses as those used for glucocorticoids (cortisol) for example are mainly used for diseases not related to endocrine system (ex: inflammatory diseases, immunosuppression, anti-allergic).
- **Thyroid cancer** (for TSH-dependent cancer)
- **Weight reduction** (abuse!!!): weight is best managed by diet and exercise; there is no need for the use of drugs.
- d- isomer as compared to l- isomer:
  d- is **equipotent** to the l- with respect to its effects on **blood cholesterol levels**, but the d- isomer has ¼ the potency with respect to other effects (e.g. growth and development, calorigenic effect, etc.). So, we use the **d-isomer for the management of hypercholesterolemia**, but we have better drugs nowadays.

Side effects to thyroid hormones:

- **Allergic** reactions -**Hyperthyroidism**

31:00-43:00

2) Hyperthyroidism

Thyrotoxicosis: excess production of T3 and T4.

A patient has to fulfill 3 things to say that he has Grave's disease; he must have: Hyperthyroidism, hyperplasia (or hypertrophy) of thyroid, and exophthalmos.

Symptoms:

- Increased bowel movements (diarrhea)
- Abnormal menses
- Tachycardia and atrial arrhythmias (atrial fibrillation)
- Heat intolerance
- Nervousness, irritability, emotional instability
- Fatigue
- Weight loss but increased food ingestion

Treatment:

- Propranolol (a non-selective β-blocker): It controls the manifestations of thyrotoxicosis; it has ***no*** anti-thyroid activity. Before surgery, we give propranolol to control **the manifestations** of hyperthyroidism; it works beautifully. It also controls anxiety without affecting the mental ability (not sedative).

- Anti-thyroid drugs: the drugs which hit the synthetic machinery (act on synthesis of thyroid hormones). They are highly effective and in most cases surgery is not needed.
- Surgery

❖ **Anti-thyroid drugs:**

1. Thiourea derivatives (Thionamides):

- Methimazole, Carbimazole, Propylthiouracil. They differ in their **pharmacokinetic** properties. Carbimazole (pro-drug) is converted to Methimazole.

- **Potency**:
  Methimazole > Carbimazole > Propylthiouracil

- All of them are effective **orally**. There are dosage forms with immediate release and forms with sustained release. Those with sustained release are released slowly and have longer duration of action.

- **MOA (Mechanism of Action)**:
  - Inhibitors of **thyroid peroxidase** enzyme. So they interfere with oxidation, iodination, and coupling reactions.
  - In addtition to this, **Propylthiouracil** also inhibits peripheral deiodination of T4.

- **Disadvantages**:
  - They have ***no*** effect on the ***release*** of T3 and T4. Thus, they have **delayed onset of action** (12-18 hrs).
  - **Prolonged treatment** for at least 1.5 years.
  - Side effects (mentioned below)

- **High relapse rate**; when you stop treatment, hyperthyroidism recurs. It is as if you are saying that treatment should be given for life (more side effects), but they are still used.

- **Side effects:**
  - Allergy
  - Hepatic dysfunction
  - **Agranulocytosis** (also an absolute contraindication to their use).
  - **Methimazole** is **teratogenic** (aplasia cutis congenita); **propylthiouracil** is not.

2. Iodide (K+ or Na+):

- **Dosage forms**: Available in solution and oral tablets.

- **MOA**:
  ↓oxidation, **↓release of T4 and T3**
  ↓uptake? (questionable)

- Major **side effects**:
  - **Allergy**: It can sometimes cause a life threatening allergic reaction. Therefore, a test for iodide hypersensitivity is essential. This test is done by putting a small amount of it on the skin using the tip of a pin.

- Widely used before thyroid surgeries to **↓ vascularity of the thyroid gland.**

3. Radioactive iodine=RAI (^{131}I):

- Available in solution and capsule **dosage forms**.

- It is now considered **the best treatment** for hyperthyroidism. If you wanted to remove the thyroid you end up with hypothyroidism and give hormonal replacement (**subtotal thyroidectomy** is preferred to preserve the **parathyroid glands**), so these drugs are better.

- **Uses:**
  - Diagnostic use to assess the function of the thyroid (**small** dose).
  - Rx (treatment) of hyperthyroidism and Grave's disease (**intermediate** dose).
  - Rx of thyroid Cancer (**large** doses).

- **Advantages**: higher remission rates - It is 100% successful in improving the manifestations of hyperthyroidism. It is given in one dose and only 10% will fail first treatment and require a second dose of ^{131}I.

- In the US, over 60% of endocrinologists select radioiodine as first-line therapy for Grave's disease. It is the preferred therapy for women desiring pregnancy in the near future. After RAI therapy, they must wait 4-6 months before conceiving.

- **Disadvantages**: hypothyroidism (**dose dependent**).

- **Contraindications**:
  - **pregnancy** (absolute) because of **teratogenicity** of radiation.
  - **ophthalmopathy** (relative – RAI therapy may cause or worsen this condition)

- **Side effects**:
  - Pulmonary fibrosis
  - Teratogenicity and carcinogenicity

  Side effects could appear 10 years after the treatment.

4. Lithium carbonate:

- Also considered as the drug of choice to treat cases of manic depressive psychosis (a condition between schizophrenia and depression). Many of the cases treated with it had hypothyroidism.
- Oral; S.R (sustained release) tablets.
- Has similar **MOA** to iodide mainly inhibiting **release**.
- Has **narrow therapeutic window**
- Side effects:
  - Nausea, diarrhea, drowsiness, blurred vision

- Ataxia, tinnitus and **diabetes insipidus** (by suppression of **ADH**)
- Hypothyroidism

5. Iodinated contrast media:

- e.g. Ipodate
- Given **orally**
- **MOA**: They contain iodide so **they inhibit release of T4 & T3**. They also **inhibit peripheral conversion of T4 to T3** (unlike iodide that doesn't have this effect).
- Similar **side effects** to iodide;
  - Allergic reactions

43:00-56:00

Parathyroid Gland & Calcium Metabolism

Calcium is present in dairy products and many foods. It is very essential; it is considered **the 5th most important element in the body.**
Importance/**functions** of calcium:

- It is essential **for bone formation**
- It is an important **2nd messenger**; mediating the effects of hormones and neurotransmitters
- Important **for the release of many hormones** including insulin
- **Blood coagulation**
- **Contraction of muscles** (both voluntary and non-voluntary muscles)

Calcium is very important especially during childhood and puberty up to the age of 30. If you eat calcium or take calcium tablets, all ingested calcium will be **directed immediately to bone**.

Calcium in the blood is either bound to phosphate ($PO4^{--}$) or albumin or is free (Ca^{++}). If all calcium stays in the bone, it is a problem. So I have to have a mechanism from which I can bring calcium back from bone to blood; this is known as **bone resorption**. Anything that increases bone resorption moves calcium from bone to blood, and anything that inhibits bone resorption keeps calcium in bones (99% of calcium is present in bones).

There are 3 factors that **regulate** free calcium in blood: **PTH** and **vit.D** (have major roles), and **calcitonin** (doesn't play a major role).

Parathyroid Hormone (PTH) is a hormone (84 a.a peptide) that is synthesized in the parathyroid glands from a larger precursor (preproPTH) as follows:

PreproPTH → proPTH → PTH

Calcitonin is a hormone that is produced by **the parafollicular cells** (C cells) of the thyroid. It does not play a major role. The evidence came from the fact that excess calcitonin is *not* associated with **severe manifestations of hypocalcemia** and vice versa. Deficiency of calcitonin has no bad consequences with respect to the blood level of free calcium. This is not true regarding PTH and vitamin D; deficiency of PTH causes hypocalcemia and high vitamin D causes intoxication and so on.

All these hormones act on 3 different **tissues**: Bone, Intestine, and Kidneys.

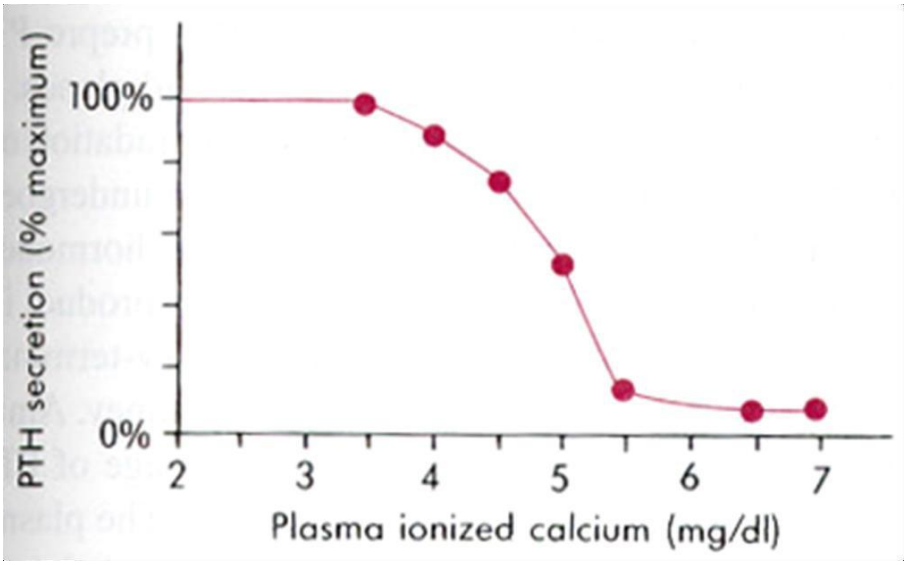
Parathyroid Hormone (PTH)

PTH is a **polypeptide** so it has a surface membrane-receptor.

Regulation of its synthesis and release from parathyroid gland is controlled by calcium blood level where hypocalcemia increases PTH synthesis and release and hypercalcemia inhibits PTH synthesis and release. Little if any regulation by $PO4^{--}$.

↓ [Ca++] → ↑ PTH ↑ [Ca++] → ↓ PTH

The figure below correlates blood level of PTH with plasma concentration of free calcium.



- Maximum secretion of PTH occurs at plasma Ca++ below 3.5 mg/dl
- At Ca++ above 5.5 mg/dl, PTH secretion is maximally inhibited

Effects of PTH:

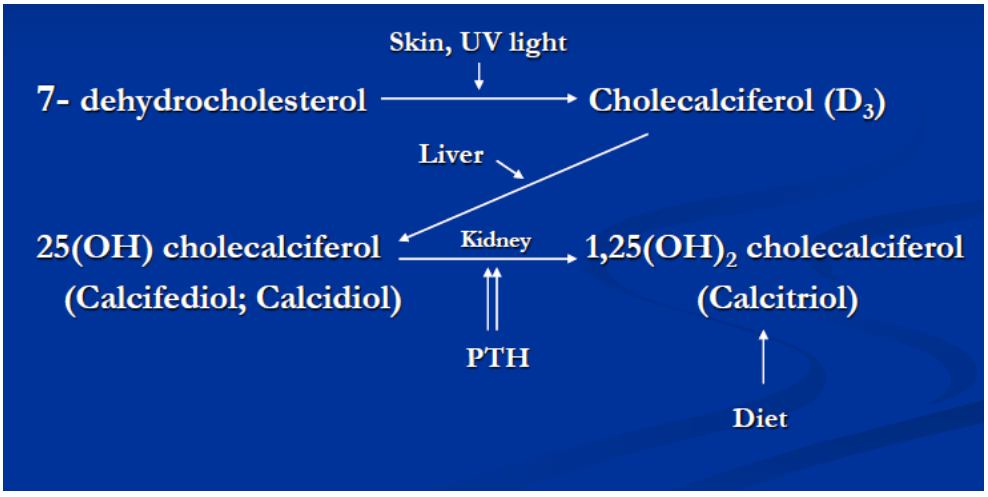
- **On bone (1º target tissue)**: It reaches bone and interacts with specific membrane receptors and mediates its effect through cAMP.
  - **↑ resorption of Ca^{++}& $PO4^{--}$**
- **On intestine**:
  - **An indirect effect through ↑ vitamin D synthesis**
  - **↑absorption** of Ca^{++}& $PO4^{--}$
- **On kidneys**:
  - **cAMP** mediated effect
  - **↑ reabsorption** of Ca^{++}, **↑↑↑ excretion of $PO4^{-}$**

** The amount of $PO4^{-}$excreted by the kidney exceeds the amount that is moved from bone and absorbed in the intestine; the **net result** is **hypercalcemia** and **hypophosphatemia**.

** Measurement of cAMP level in urine could be used to assess the function of the parathyroid gland; high levels reflect hyperparathyroidism and low levels reflect hypoparathyroidism.

Vitamin D

Synthesis:



**PTH enhances the final activation of vit.D in the kidney.

*Normal daily requirement 400 IU/day

Effects of Vitamin D:

- On intestine (1º target tissue):
  ↑ Absorption of Ca^{++}& $PO4^{--}$
- On bone:
  ↑bone resorption
- On kidney:
  ↑ Reabsorption of Ca^{++}& $PO4^{-}$

** The **net effect** is <u>high calcium and phosphate</u>

** While **Calcitonin** reduces both Ca^{++}& $PO4^{-}$

End of the sheet, sorry if there are any mistakes.