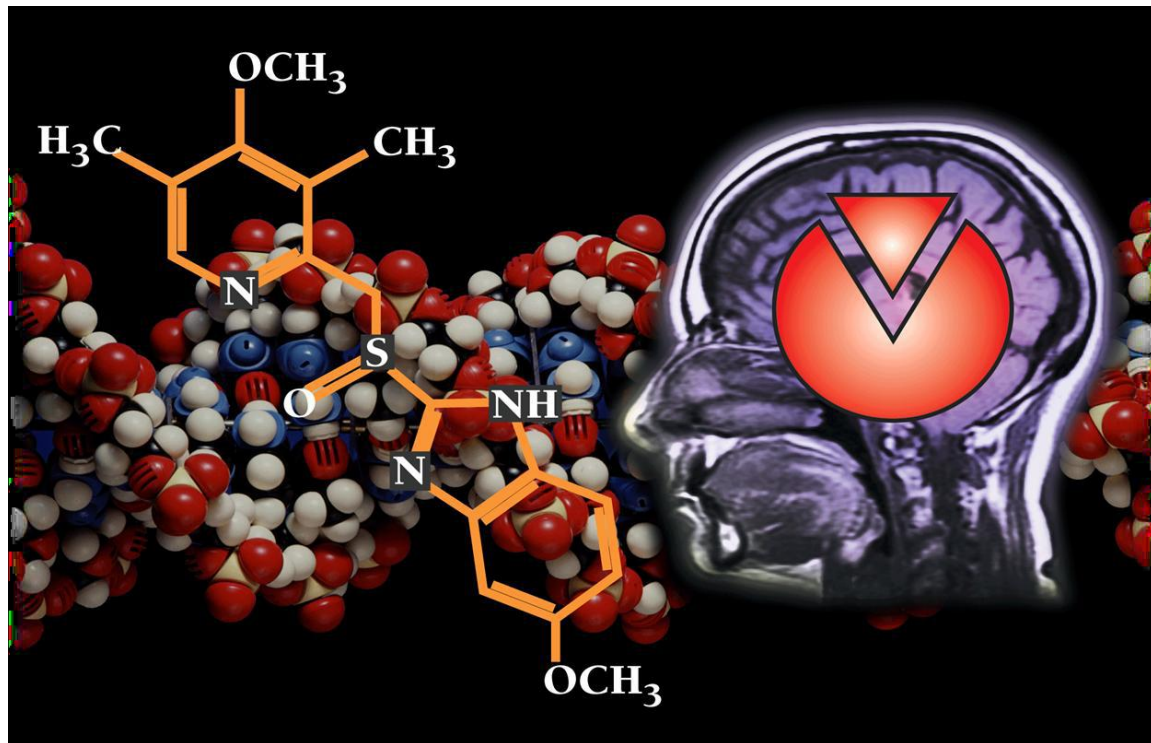


Thyroid & Anti-thyroid Drugs



Note: First page is an introduction. **Texts in red are important information.** Text boxes with Thick maroon margins are additional info.

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Introduction

Normal thyroid gland secretes:

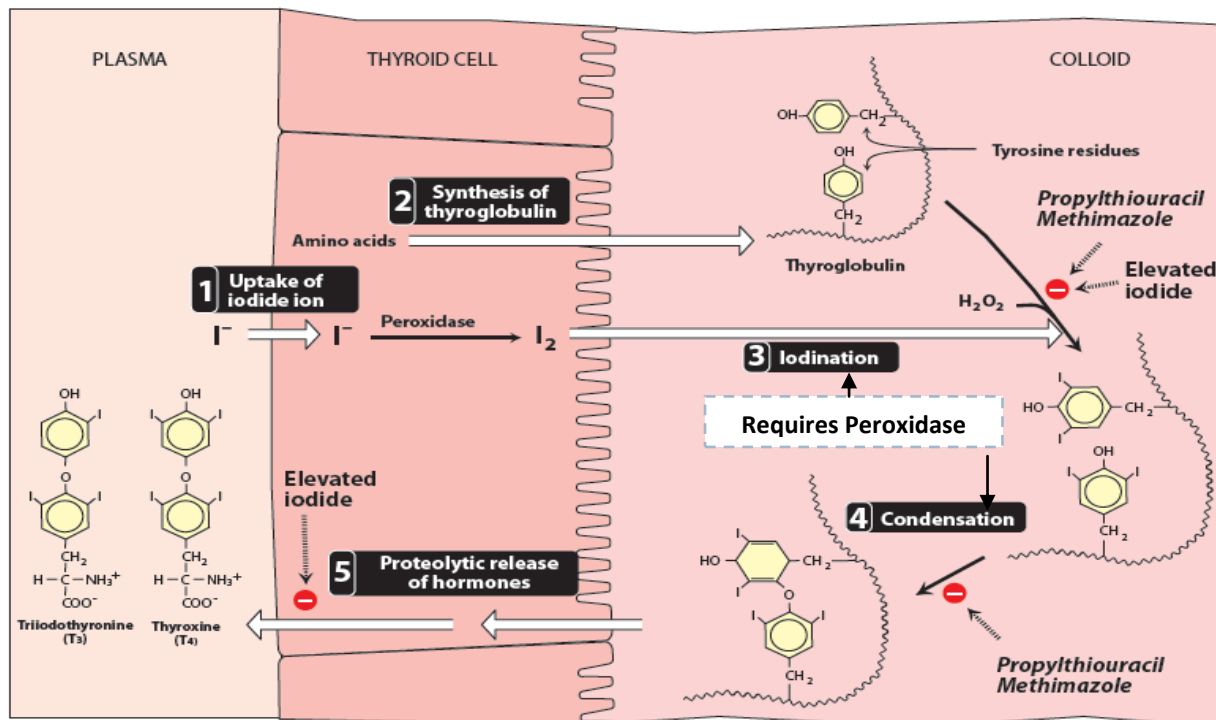
T3 (**triiodothyronine**)

T4 (**tetraiodothyronine**).

To maintain

- Normal growth and development of **Nervous, Skeletal** and **Reproductive** systems
- It also controls metabolism of **Fats, Carbohydrates, Proteins** and **Vitamins**

Biosynthesis of Thyroid Hormones



After release from the gland, **T4** and **T3** are transported in the blood by **thyroxine-binding globulin (TBG)**, a protein synthesized in the liver.

Hyperthyroidism

Over activity of the thyroid gland

Graves' disease

- Most common cause of hyperthyroidism 60-80%.
- It is autoimmune disorder associated with circulating immunoglobulins that bind to and stimulate the thyrotropin (TSH) receptor, resulting in sustained thyroid over activity & it can be familial.

Manifestations of Hyperthyroidism

- | | | |
|---|--------------------|-----------------|
| • Restlessness, nervousness, Irritability | • Heat intolerance | • Light periods |
| • Tremors | • Diarrhea | • Exophthalmos |
| • palpitation | • short breath | |
| • Weight loss | • Itching | |
| • sweating | | |

Treatment of Hyperthyroidism

1. Thioamides[antithyroid drugs]
2. Iodides
3. Radioactive iodine
4. Beta blockers
5. Surgery

1-Thioamides

- Methimazole [meth-IM-ah-zole]
- Propylthiouracil [proe-pil-thye-oh-YOOR-ah-sil]

Note: In the United Kingdom, **carbimazole(pro-drug)**, which is converted to **methimazole** in vivo, is widely used. **Methimazole** is about ten times more potent than **propylthiouracil**.

Mechanism of Action

- Inhibit synthesis of thyroid hormones
- Inhibit **thyroid peroxidase- mediated iodination** of tyrosine residues in thyroglobulin
- Block **coupling(Condensation)** of **iodotyrosines(MIT and DIT)**
- Block the conversion of **T₄ to T₃** within the **thyroid & in peripheral** tissues

Note: Since the **synthesis** rather than the **release** of hormones is affected, the onset of these **agents are slow**, often requiring 3–4 weeks before **stores of T₄** are depleted.

Note: **Thioamides** do not block uptake of iodide by the gland, but block The oxidation of Iodide. **Propylthiouracil** and **(to a much lesser extent) methimazole** inhibit the peripheral **deiodination of T₄ and T₃**

Pharmacokinetic comparison between Propylthiouracil and Methimazole

	Propylthiouracil	Methimazole
Absorption	Rapidly absorbed from GIT	Same
Protein binding	80-90% is bound	Most of drug is free
accumulation	In thyroid	Similar
Excretion	Kidneys as inactive metabolite within 24 hrs	Excretion slow, 60-70% of drug is recovered in urine in 48 hrs
Absorption	Rapidly absorbed from GIT	Same
Half life	1.5 -2hrs (short half-life)	6 hrs (long half-life)
Administration	Every 6-8 hrs	As a single dose
Pregnancy	Preferred, though cross placenta and is conc .in fetal thyroid but is highly protein bound ,crossing placenta is less readily	Cross placenta and concentrated by fetal thyroid Not recommended
Breastfeeding	Less secreted in breast milk Recommended	secreted Not recommended

Adverse Effects

- **Cutaneous reactions: [maculopapular rash]**
- Arthralgia (pain in the joints)
- GI upset: Hepatotoxicity , **cholestatic jaundice (mainly with methimazole)**
- **Agranulocytosis** [very rare and most dangerous complication occur within 90 days of treatment]
 - ✓ This reaction is usually **reversible** when the drug is immediately discontinued.
 - ✓ **Colony stimulating factor** is administered to hasten the recovery of the **granulocytes**
- There is **cross sensitivity** between **propylthiouracil** and **methimazole**. ; therefore, switching drugs in patients with severe reactions is not recommended.

Note: A minor rash can often be controlled by antihistamine therapy. Because the more severe reaction of agranulocytosis is often suspected when a sore throat or high fever develops, patients receiving **thiomides** must be instructed to **discontinue the drug** and seek immediate medical attention if these symptoms develop. White cell and differential counts and a throat culture are indicated in such cases, followed by appropriate **antibiotic therapy**.

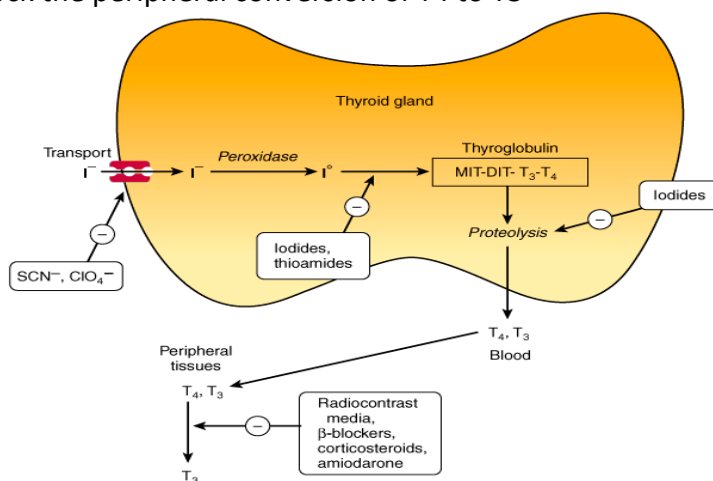
Note: **Colony stimulating factors** are secreted **glycoproteins** that bind to receptor proteins on the surfaces of hemopoietic stem cells, thereby activating intracellular signaling pathways that can cause the cells to proliferate and differentiate into a specific kind of blood cell (usually white blood cells).

2-Iodides:

Organic iodides as iopanoic acid or ipodate are used commonly

Mechanism of action:

- **Inhibit hormone release**
- **Block the peripheral conversion of T₄ to T₃**



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology*, 12th Edition. <http://www.accessmedicine.com>
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Biosynthesis of thyroid hormones. The sites of action of various drugs that interfere with thyroid hormone biosynthesis are indicated.

Note: The effect (the so-called “acute Wolff-Chaikoff effect”), is to reduce the **rate of iodide trapping**, so that the rate of **iodination** of tyrosine to **form thyroid hormones** is **also decreased**. Even more important, the **normal endocytosis of colloid** from the follicles by the thyroid glandular cells is **paralyzed** and the **proteolysis is inhibited** by the high iodide concentrations (**how it is paralyzed and inhibited is not fully understood**). Because this is the first step in release of the thyroid hormones from the storage colloid, **there is almost an immediate shutdown** of thyroid hormone secretion into the blood.

In short, when iodides are present in the blood in high concentration, most activities of the thyroid gland are decreased, but often they remain **decreased for only a few weeks. (Iodides lose their inhibitory effect after a few weeks)**

Clinical uses:

- As adjunctive therapy
- **Before surgery** to reduce size, fragility & vascularity of hyperplastic gland.
- E.g. **iopanoic acid** or **ipodate** are used commonly
- Should not be given alone

Iodides are not used in the routine treatment of hyperthyroidism because of paradoxical (contradictory) increase in hormone release with prolonged use. As the gland will escape from iodide block in 2-8 weeks, this may produce severe exacerbation of thyrotoxicosis in an iodinated – enriched gland

Note: Because iodides in high concentrations decrease all phases of thyroid activity, they slightly decrease the size of the thyroid gland and especially decrease its blood supply.

Precautions and Toxicity in the use of iodides

- Should be **avoided in pregnancy** (since they cross the placenta and can cause fetal goiter.)
- produces increase in the **intraglandular stores of iodine** which **delays the effect of thioamides** and **prevents use of radioactive iodine**; Therefore, iodides should be initiated after thioamides
- **Iodism** (acneiform rash, swelling of salivary glands, mucous membrane ulcerations, metallic taste, bleeding disorders and rarely anaphylaxis).

3-Radioactive Iodine

- **¹³¹I isotope** (therapeutic effect depends on emission of **β rays**, produce long-term decrease in thyroid hormone production)
- **Rapidly absorbed**, concentrated in thyroid gland and stored in follicles.
- Half-life 5 days
- **Cross placenta & excreted in breast milk**
- **Easy administration** (orally), effective, painless and less expensive

Note: Radioactive iodine (¹³¹I) is taken up and concentrated in the thyroid gland specifically that a dose large enough to severely damage the gland can be given **without** endangering other tissues.

Clinical uses :

- Hyperthyroidism mainly in old patients (above 40)
 - Graves' disease
 - Patients with toxic nodular goiter
 - Diagnostic uses
- ❑ Should not be given to pregnant women or nursing mothers

Disadvantages:

- High incidence of delayed hypothyroidism
- Large doses have cytotoxic actions (necrosis of the follicular cells followed by fibrosis)
- May cause genetic damage
- May cause leukemia & neoplasia (carcinogenic) especially in young age

4-Adrenoceptor Blocking Agents:

- Relief the adrenergic symptoms of hyperthyroidism such as tremor, palpitation, heat intolerance and nervousness.
- E.g. **Propranolol, Atenolol**
- Contraindicated in **asthmatic patients**, **Diltiazem A Ca channel blocker is used instead.**
- Can be given in pregnancy

5-Thyroidectomy

- A near-total thyroidectomy is the treatment of choice in **very large gland or multinodular goiter**
- In case of **large or multinodular goiter** and to simplify surgery (to diminish vascularity) saturated solution of **potassium iodide** 5 drops twice daily for **two weeks** prior to surgery

Special problems of Hyperthyroidism

1-Management of Grave's disease

- A. Drug therapy
- B. surgical thyroidectomy
- C. Destruction of the gland with radioactive iodine

❑ In young patient with small gland and mild disease :

- **Methimazole / propylthiouracil** until disease undergoes spontaneous remission.
- Take 1-2 years (60-70 % relapse).
- Start with **large divided** doses
- Then **maintenance** as **a single daily dose.**
- Propylthiouracil is preferred.
- Reactivation of the autoimmune process may occur leading to increase in TSH and stimulation of thyroid; this can be prevented by addition of **levothyroxine.**

2-Thyroid Storm

- Sudden acute exacerbation of all of the symptoms of thyrotoxicosis, presenting as a life threatening syndrome.
- Vigorous(effective) management is mandatory. **Propranolol** 1-2mg slow I.V. or 40-80 mg orally every 6 hours(**To control CVS manifestations**)
- **Potassium iodide** 10 drops **orally** daily (**To prevent release of hormones**) or
- **Propylthiouracil** 250 mg orally every six hours or 400 mg every six hours rectally.(**To prevent synthesis of hormones**)
- **Hydrocortisone** 50 mg I.V. every 6 hours to prevent shock.
- If above methods fail **peritoneal dialysis** or plasmaphoresis is performed to lower the levels of circulating T4

Peritoneal dialysis is a treatment used to clean the blood of extra fluid and waste that builds up in the body usually when the kidneys do not work.

Plasmapheresis is a process involving the following steps: 1- Whole blood is withdrawn from the person. 2-The liquid portion or plasma is removed from the blood and replaced. 3- The blood, with all its red and white blood cells, is transfused back into the person.

3-Thyrototoxicosis during pregnancy:

- Definitive therapy with ^{131}I or subtotal thyroidectomy **prior to pregnancy** to avoid acute exacerbation during pregnancy or after delivery
- During pregnancy radioiodine is contraindicated.
- **Propylthiouracil** is a better choice during pregnancy. Dose must be kept minimum i.e., <300 mg daily. (Because it may affect the fetal thyroid gland.)

Hypothyroidism

Introduction

Thyroid gland does not produce enough hormone

Can be caused by:

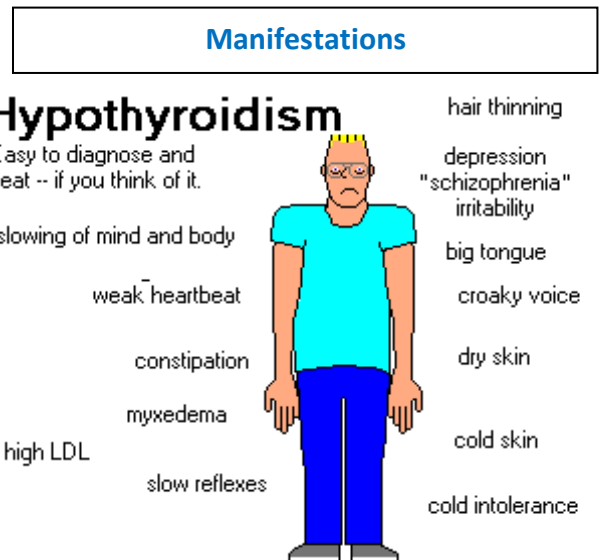
- Autoimmune disorder Hashimoto's thyroiditis (most common)
- Irradiation
- Surgical removal of thyroid gland
- Medications that reduce thyroid hormone levels

People who are most at risk include those over age 50 & females (while in hyperthyroidism the young people are at risk)

Infants and children suffer severely, results in dwarfism and irreversible mental retardation

Diagnosed by: low free thyroxine and elevated serum TSH

For treatment: replacement therapy is appropriate



Treatment

- Daily dose of a **synthetic thyroid** hormone preparations
- Serum **TSH** is the reliable guide to adjust thyroxine (thyroid hormone) dose (to see how the patient's health is improving)

Thyroid preparations:

1-LEVOTHYROXINE:(T4):

- This is the preparation of choice for thyroid replacement and suppression therapy, because it is stable and has a **long half life** (7 days), to be administered once daily.
- **Oral preparations** available are from 0.025 to 0.3 mg tablets
- **Absorption is increased when hormone is given on empty stomach**
- For **parenteral** use 200-500 μg (100 $\mu\text{g}/\text{ml}$ when reconstituted) for injection.

You don't have to memorize the doses

- In long standing condition, in old patients and in patients with cardiac disease, treatment is started with **reduced dosage**.
- Can restore normal thyroid levels **within 2-3 weeks**.
- **levothyroxine** is given in a dose of 12.5 – 25 $\mu\text{g}/\text{day}$ for two weeks and then increasing it after every two weeks.

ADVERSE EFFECTS OF OVER DOSE:

Children :

- (CNS disorders mainly like : Restlessness, insomnia)
- accelerated bone maturation.(The growth effect differs according to the place):
 - ❖ In epiphysis →will be closed quickly→ ↓growth
 - ❖ In the shaft of long bone →↑growth

ADULTS : (same any other drug toxicities and some symptoms of hyperthyroidism –nothing characteristic)

- Agitation , heat intolerance , pain (headache, muscle pain)
- Intestinal & metabolic symptoms (change in appetite, diarrhea, weight loss)

Adverse effects of under-dosing (when it's lower than the therapeutic dose)

- Sluggishness
- Mental dullness
- Feeling cold
- Muscle cramps (pain)

Note:The adverse effects of under dosing are more dangerous than the over dosing because it's like hypothyroidism symptoms or even worse

2- Liothyronine(T3)

- More potent (3-4 times) and more rapid than levothyroxine but has a short half life and is not recommended for routine replacement therapy, it requires multiple daily doses.
- It should be avoided in cardiac patients (Since it is more potent it will precipitate to arrhythmia).
- It is best used for short –term suppression of TSH.
- Oral preparation available are 5-50µg tablets
- For parenteral use 10µg/ml

Special problems of Hypothyroidism

Myxedema coma:

- It is an end state of untreated hypothyroidism.
- It develops quite and progress slowly to stupor, coma and death.
- The treatment of choice is loading dose of **levothyroxine** intravenously 300-400µg initially followed by 50µg daily.
- I.V **T3** can be used but it may provoke **cardiotoxicity**
- I.V hydrocortisone may be used in case of **adrenal and pituitary insufficiency**.

Hypothyroidism and pregnancy:

In pregnant hypothyroid patient 20-30 % increase in **thyroxine** is required because of elevated maternal TBG induced by **estrogen** and because of early development of fetal brain which depends on **maternal thyroxine**

Note:Since myxedema frequently occurs in older persons, it is often associated with underlying coronary artery disease. In this situation, the low levels of circulating thyroid hormone actually protect the heart against increasing demands that could result in angina pectoris or myocardial infarction. Correction of myxedema must be done cautiously to avoid provoking arrhythmia, angina, or acute myocardial infarction. If coronary artery surgery is indicated, it should be done first, prior to correction of the myxedema by thyroxine administration.

Conditions affecting thyroid hormone replacement requirements

Because thyroid hormone is highly protein bound, any medical conditions or drugs that alter amount of binding hormones may affect the level of free hormones:

Conditions that cause an increase in serum binding proteins

- **High estrogen states** (pregnancy, oral contraceptive use, postmenopausal estrogen replacement
- The dosage of **levothyroxin**(T4) must be increased

Increase the dose



Conditions that cause a decrease in serum binding proteins

- Androgens decrease levels of thyroid binding proteins
- Old patients also, have lower serum protein levels
- Nephrosis , Cirrhosis (Have lower serum protein level)
- All these conditions need reduction of hormone replacement dosages

Decrease the dose



Medications that reduce the absorption of thyroid hormone from intestine , such as :

- Cholestyramine
- Aluminum containing antacids
- Calcium preparations
- Ferrous preparations

Increase the dose



Medications that accelerate metabolism of thyroid hormones such as :

- Rifampin (Thorough hepatic induction of P450)
- Phenytoin (Thorough hepatic induction of P450)
- Phenobarbital (Thorough hepatic induction of P450)
- Oral hypoglycemic drugs

Note: These medications have a minor effect



Summary:

- ✓ **Thioamides** (e.g **Methimazole** or **Propylthiouracil**) inhibit thyroid **peroxidase**- mediated iodination.(They **block the synthesis of new thyroid hormones**)
- ✓ **Propylthiouracil** and (to a much lesser extent) **methimazole** **inhibit** the peripheral& **thyroid deiodination of T₄ and T₃** (weak effect)
- ✓ Since the **synthesis** rather than the **release** of hormones is affected, the onset of these **agents are slow**
- ✓ **Propylthiouracil** **is** highly protein bound, has a short half-life, and is preferred in pregnancy and lactation; however, **Methimazole** **is** mostly free in the circulation, and has a long half-life.
- ✓ ADRs includes **maculopapular rash**,**Arthralgia**,**cholestatic jaundice (mainly with methimazole)**,and **Agranulocytosis**(rare but dangerous)
- ✓ **This reaction** is usually **reversible** when the drug is immediately discontinued.
- ✓ **Colony stimulating factor** is administered to hasten the recovery of the **granulocytes**
- ✓ There is **cross sensitivity** between **propylthiouracil** and **methimazole**.
- ✓ **Iodides** **Inhibit** hormone release by probably **inhibiting** both **iodination** and **proteolysis** of **thyroglobulin**
- ✓ Since they inhibit the release rather than synthesis of T₃ & T₄ they **are rapidly acting**
- ✓ They also **Block** the peripheral conversion of **T₄ to T₃**
- ✓ **Clinical uses:** as adjunctive therapy, before **surgery** to reduce size & vascularity of hyperplastic gland.
- ✓ the gland **will escape** from **iodide block in 2-8 weeks**, this may produce severe exacerbation of thyrotoxicosis in an iodinated – enriched gland
- ✓ Produces increase in the **intraglandular stores of iodine** which **delays the effect of thioamides** and **prevents use of radioactive iodine**; therefore, iodides should be initiated after thioamides, and should not be used with radioactive iodine.
- ✓ **They may produce iodism** (acneiform rash, swelling of salivary glands, mucous membrane ulcerations, metallic taste ,bleeding disorders and rarely anaphylaxis).
- ✓ They Should be **avoided in pregnancy**
- ✓ **Radioactive Iodine** therapeutic effect depends on emission of **β rays that specifically damage the thyroid**.
- ✓ They have **High incidence** of delayed **hypothyroidism**
- ✓ Large doses have cytotoxic actions (necrosis of the follicular cells followed by fibrosis)
- ✓ **Adrenoceptor Blocking Agents:** E.g. **Propranolol**, **Atenolol** are used to Relief the adrenergic symptoms of hyperthyroidism
- ✓ Contraindicated in **asthmatic patients**, **Diltiazem A Ca channel blocker is used instead**.
- ✓ A near-total thyroidectomy is the treatment of choice in **very large gland or multinodular goiter**
- To treat the hypothyroidism the replacement therapy is appropriate **And LEVOTHYROXINE(T₄)is the preparation of choice** , also we can use Serum TSH as the reliable guide to adjust thyroxine dose.
- **LEVOTHYROXINE(T₄)** has long half-life so **we use it as routine replacement therapy** however Liothyronine(T₃) has short half-life and not recommended as a routine therapy
- **LEVOTHYROXINE(T₄)** has Oral preparations used as routine therapy which has best if it was given on empty stomach also it has parenteral preparation for emergency situations , however **Liothyronine(T₃)** is just used for short –term suppression of TSH (acute emergency) but be aware it should be avoided with cardiac patient, since it has a more potent effect
- The adverse effect of using **LEVOTHYROXINE(T₄)** differs according to the dosing (over –below the therapeutic dose)
 - ❖ over dosing in adult same like any toxicities of other drugs but **in children (CNS disorders mainly like : Restlessness, insomnia) and accelerated bone maturation**.
 - ❖ under-dosing **it's more dangerous including** :Sluggishness ,Mental dullness, Feeling cold and Muscle cramps (**pain**)
- for the pregnant women we use **LEVOTHYROXINE(T₄)**

Review questions

1. Preparation of choice for thyroid replacement?

- A. dessicated thyroid
- B. liothyronine
- C. levothyroxine
- D. propylthiouracil
- E. methimazole

2-Which of the following best describes the effect of propylthiouracil on thyroid hormone production?

- A. It blocks the release of thyrotropin-releasing hormone.
- B. It inhibits uptake of iodide by thyroid cells.
- C. It prevents the release of thyroid hormone from thyroglobulin.
- D. It blocks iodination and coupling of tyrosines in thyroglobulin to form thyroid hormones.
- E. It blocks the release of hormones from the thyroid gland.

3-Hyperthyroidism can be treated by all but which one of the following?

- A. Triiodothyronine.
- B. Surgical removal of the thyroid gland.
- C. Iodide.
- D. Propylthiouracil.
- E. Methimazole.

4- Methimazole reduces serum concentrations of T3 primarily by which of the following?

- A. Accelerating the peripheral metabolism of T3
- B. Inhibit the proteolysis of TBG
- C. Inhibits the secretion of TSH
- D. Inhibit the uptake of iodide by cells in the Thyroid
- E. Prevents the addition of iodine to tyrosine residues on thyroglobulin.

5-Though rare, a serious toxicity associated with thiomides is which of the following?

- A. Torsade de pointes arrhythmia
- B. Lupus like syndrome
- C. Thrombotic thrombocytic purpura (TTP)
- D. Agranulocytosis

6- A 65 year old man with multi nodular goiter is scheduled for a near-total thyroidectomy. Which of the following drugs will be administered for 10-14 days before surgery to reduce the vascularity of his thyroid gland?

- A. Levothyroxine
- B. Liothyronine
- C. Potassium iodide
- D. Radioactive iodine
- E. Prednisone.

7-When initiating T4 therapy for an elderly patient with long standing hypothyroidism, it is important to begin with small doses to avoid which of the following?

- A. A flare-up of exophthalmos
- B. Acute renal failure
- C. Seizures
- D. Hemolysis
- E. Overstimulation of the heart