# Thyroid and Anti-Thyroid Drugs

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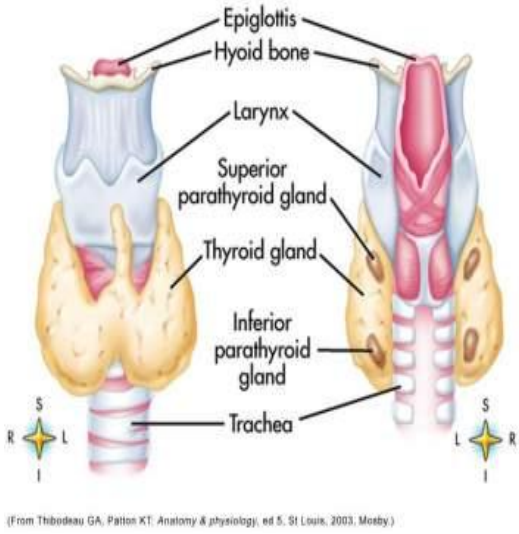
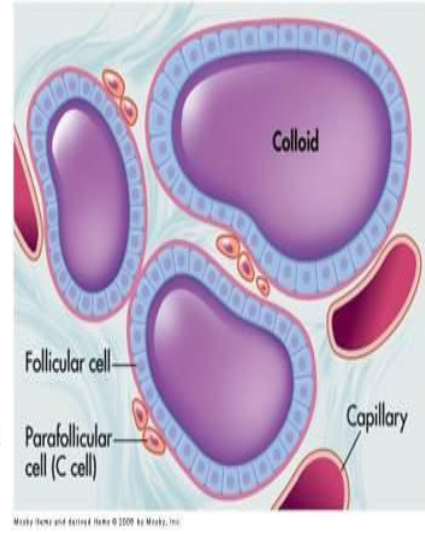
## Anatomy and Physiology of the Thyroid Gland

- Member of the Endocrine System
  - Secretes thyroid hormones, thyroxine T4, triiodothyronine T3, which regulate metabolism, growth, development, body temperature, and energy levels.

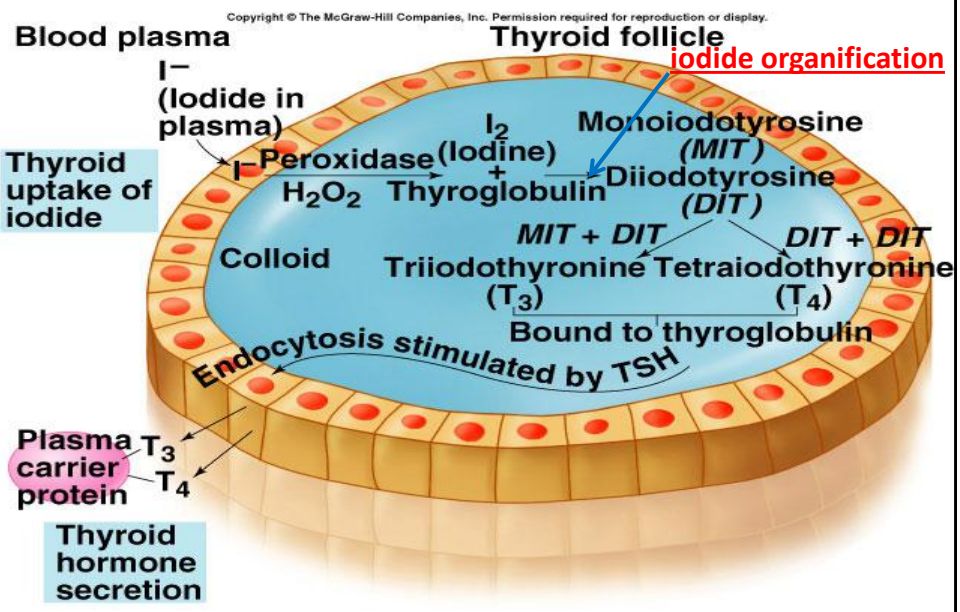
    And calcitonin which is important in the regulation of calcium metabolism.
  - Located in neck adjacent to the 5$^{th}$ cervical vertebra (C5).
  - Butterfly shaped w/2 lobes connected by an isthmus



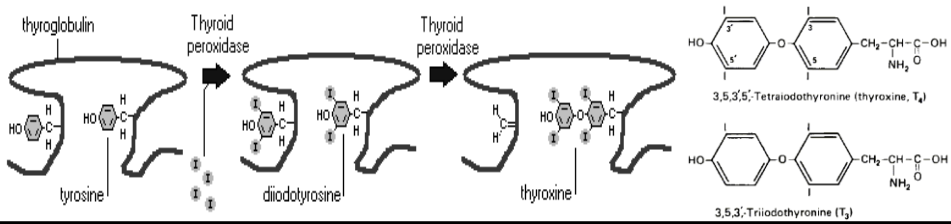

- Made up of 2 types of cells
  - **Follicle cells** (simple cuboidal epithelium) make up the follicle & produce a glycoprotein called ***thyroglobulin***
    - The lumen of the follicle contains thyroglobulin which attached Iodine molecules
    - **Thyroid hormone (TH)** is produced from the iodinated thyroglobulin
  - **Parafollicular cells** are interspersed b/t follicular epithelium
    - **Calcitonin** is produced here (It acts to reduce blood calcium ($Ca^{2+}$))

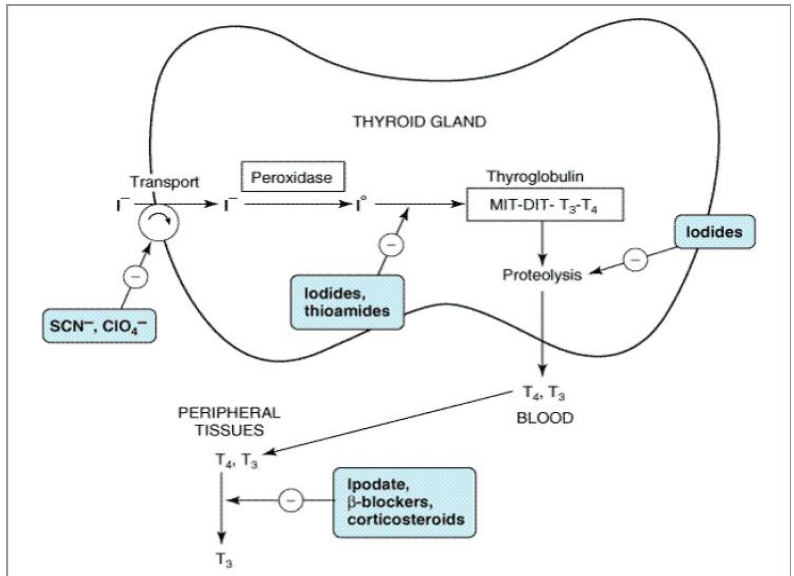
## Biosynthesis of Thyroid Hormones



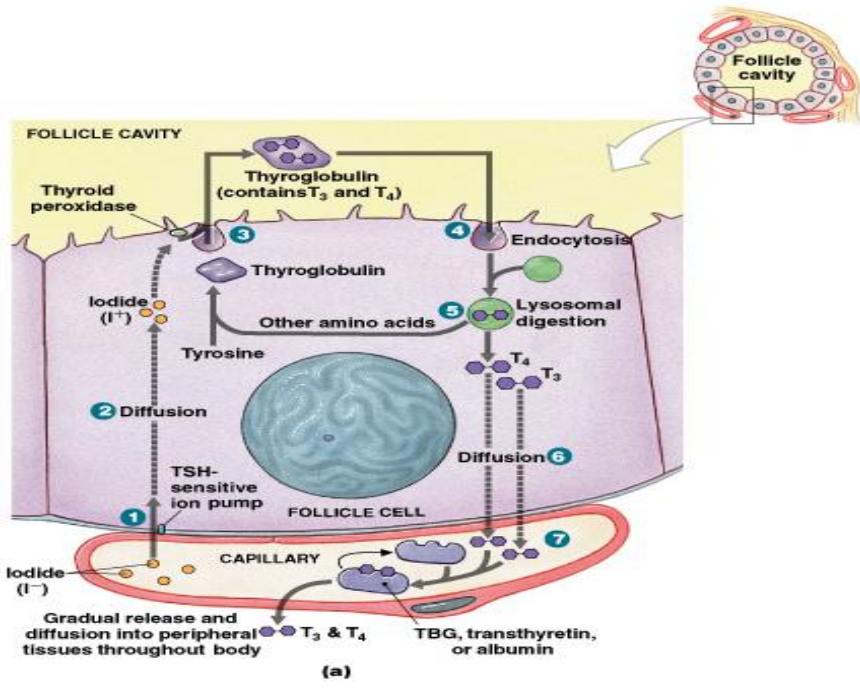

## Biosynthesis of Thyroid Hormones

- Thyroid peroxidase (TPO) catalyzes the conversion of iodide ($I^-$) to iodine ($I_2$) using $H_2O_2$ as a cofactor.
- TPO then catalyzes the addition of iodine to the C-3 and C-5 position of a tyrosine residue of thyroglobulin.
- Two iodinated thyrosine rings condense to form thyroxine, or T4, with four iodine substituents.
- The ratio of T4 to T3 within thyroglobulin is approximately 5:1, so that most of the hormone released is thyroxine.





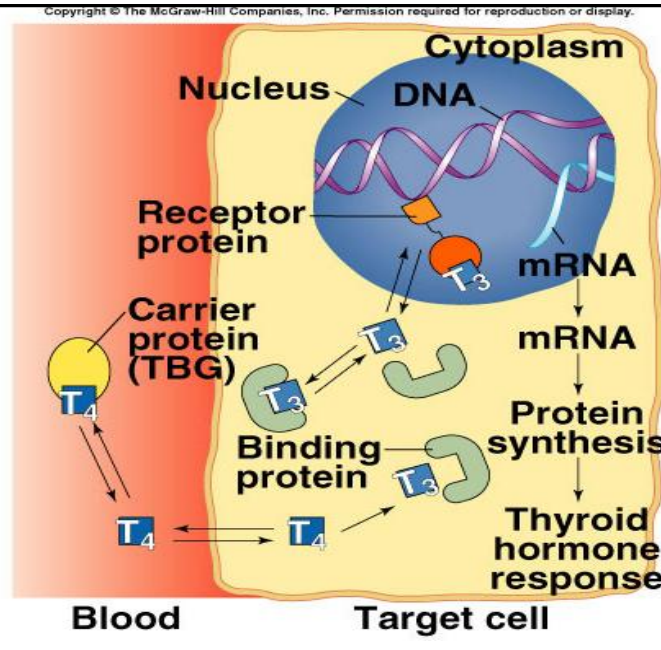

Biosynthesis of thyroid hormones. The sites of action of various drugs that interfere with thyroid hormone biosynthesis are shown.



## Mechanism of action of thyroid hormones

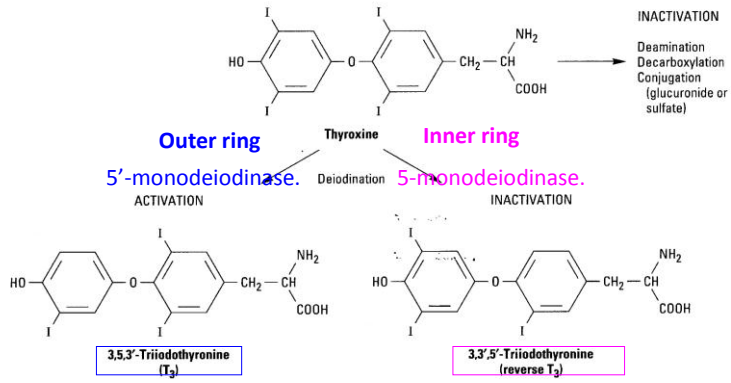
- Hydrophobic molecule transported in the bloodstream with a requisite carrier protein, TBG. Albumin also serves as a TH carrier protein.
- T4 dissociate from thyroxine binding globulin in plasma before entry into the target cells.
- In the cells, T4 is enzymatically deiodinated to T3 which enters nucleus and attaches to specific receptors which promotes protein synthesis.





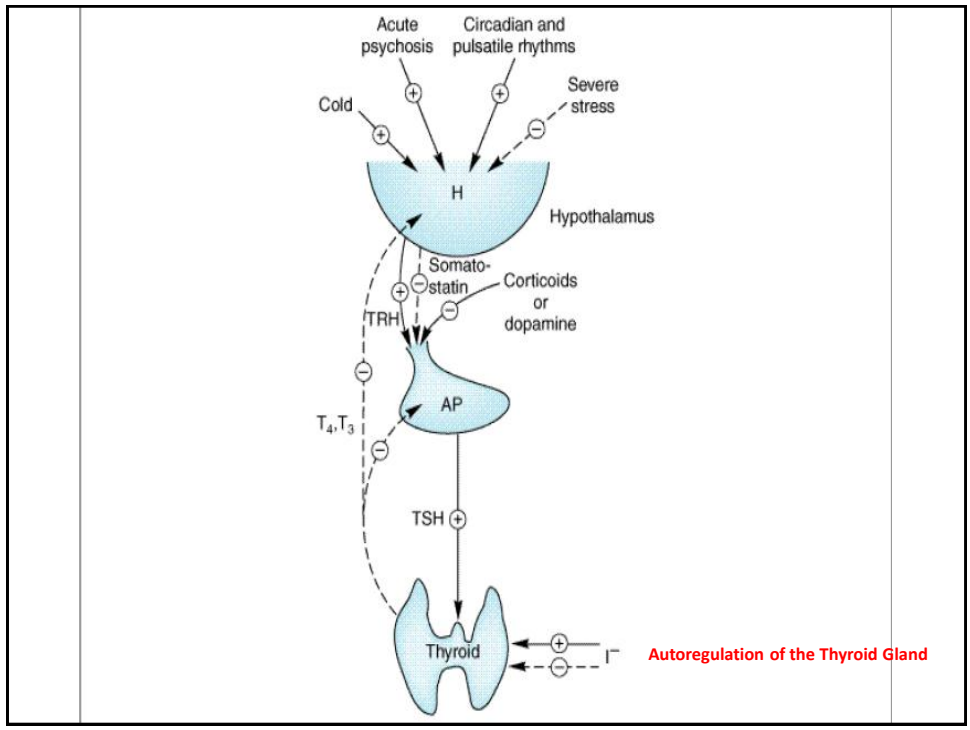

**the affinity of the receptor site for T4 is about ten times lower than that for T3.**

- The primary metabolism of thyroxine is deiodination.
- Deiodination of T4 may occur by monodeiodination of outer ring producing 3,5,3'- triiodothyronine - T3 ( T3 is 4 times more potent than T4) by 5'-monodeiodinase.
- Deiodination of inner ring produce 3,3',5' – reverse triiodothyronine – rT3 (inactive) by 5 monodeiodinase.

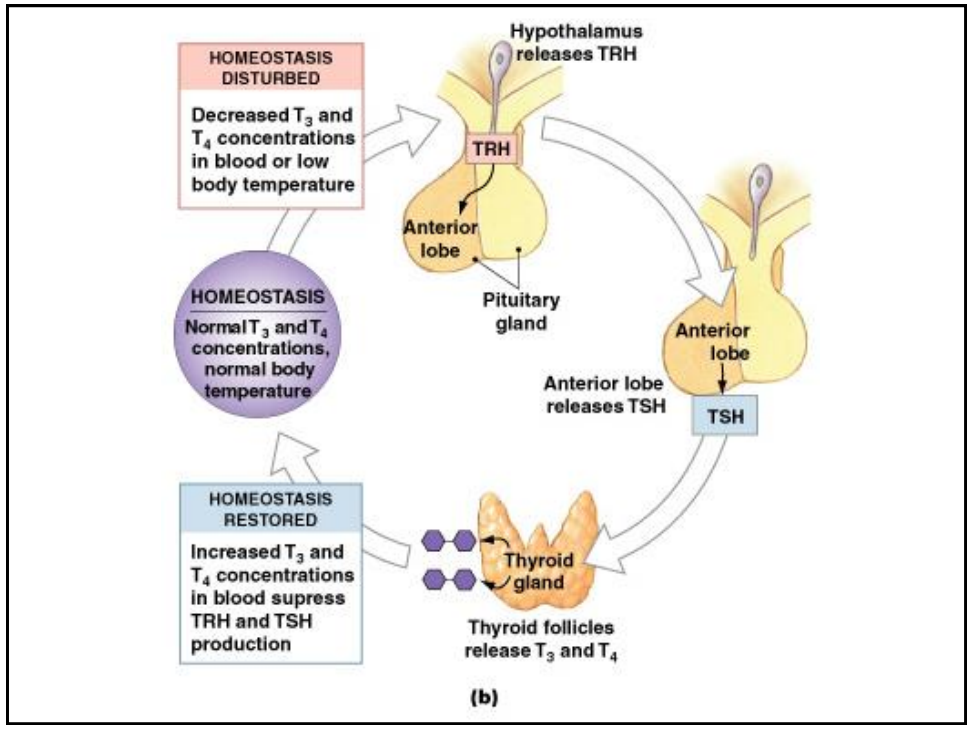



## Thyroid-Pituitary Relationships

- The hypothalamus in the brain secretes thyroid releasing hormone, TRH, that target the pituitary gland which, in turn, secretes thyroid stimulating hormone, TSH.
- The pituitary gland's sensitivity toward TRH varies with the body's need for thyroid hormones.
- TSH is absorbed into the thyroid, stimulating the thyroid to absorb iodine and synthesize hormones.
- Thyroid hormones provide negative feedback for TSH production via a"homeostatic feedback loop."




Autoregulation of the Thyroid Gland



## Thyroid Hormones

### Pharmacokinetics

Table 38–1. Summary of Thyroid Hormone Kinetics.

| Variable | $T_4$ | $T_3$ |
|---|---|---|
| Volume of distribution | 10 L | 40 L |
| Extrathyroidal pool | 800 µg | 54 µg |
| Daily production | 75 µg | 25 µg |
| Fractional turnover per day | 10% | 60% |
| Metabolic clearance per day | 1.1 L | 24 L |
| Half-life (biologic) | 7 days | 1 day |
| Serum levels | | |
| Total | 5–11 µg/dL (64–132 nmol/L) | 95–190 ng/dL (1.5–2.9 nmol/L) |
| Free | 0.7–1.86 ng/dL (9–24 pmol/L) | 0.2–0.52 ng/dL (3–8 pmol/L) |
| Amount bound | 99.96% | 99.6% |
| Biologic potency | 1 | 4 |

## Effects of Thyroid Hormones

- The thyroid hormones are responsible for optimal growth, development, function, and maintenance of all body tissues.

- Excess or inadequate amounts result in the signs and symptoms of thyrotoxicosis or hypothyroidism.

- Thyroid hormone is critical for nervous, skeletal, and reproductive tissues.
- TH effects depend on protein synthesis as well as potentiation of the secretion and action of growth hormone. Thyroid deprivation in early life results in irreversible mental retardation and dwarfism.

- Effects on growth and calorigenesis are accompanied by an influence on metabolism of drugs as well as carbohydrates, fats, proteins.

- Many of the manifestations of thyroid hyperactivity resemble sympathetic nervous system overactivity, although catecholamine levels are not increased.

- Possible explanations include increased numbers of receptors or enhanced amplification of the receptor signal.

Table 38–4. Manifestations of Thyrotoxicosis and Hypothyroidism.

| System | Thyrotoxicosis | Hypothyroidism |
|---|---|---|
| Skin and appendages | Warm, moist skin; sweating; heat intolerance; fine, thin hair; Plummer's nails; pretibial dermopathy (Graves' disease) | Pale, cool, puffy skin; dry and brittle hair; brittle nails |
| Eyes, face | Retraction of upper lid with wide stare; periorbital edema; exophthalmos; diplopia (Graves' disease) | Drooping of eyelids; periorbital edema; loss of temporal aspects of eyebrows; puffy, nonpitting facies; large tongue |
| Cardiovascular system | Decreased peripheral vascular resistance, increased heart rate, stroke volume, cardiac output, pulse pressure; high-output heart failure; increased inotropic and chronotropic effects; arrhythmias; angina | Increased peripheral vascular resistance; decreased heart rate, stroke volume, cardiac output, pulse pressure; low-output heart failure; ECG: bradycardia, prolonged PR interval, flat T wave, low voltage; pericardial effusion |
| Respiratory system | Dyspnea; decreased vital capacity | Pleural effusions; hypoventilation and $CO_2$ retention |
| Gastrointestinal system | Increased appetite; increased frequency of bowel movements; hypoproteinemia | Decreased appetite; decreased frequency of bowel movements; ascites |
| Central nervous system | Nervousness; hyperkinesia; emotional lability | Lethargy; general slowing of mental processes; neuropathies |
| Musculoskeletal system | Weakness and muscle fatigue; increased deep tendon reflexes; hypercalcemia; osteoporosis | Stiffness and muscle fatigue; decreased deep tendon reflexes; increased alkaline phosphatase, LDH, AST |
| Renal system | Mild polyuria; increased renal blood flow; increased glomerular filtration rate | Impaired water excretion; decreased renal blood flow; decreased glomerular filtration rate |
| Hematopoietic | Increased erythropoiesis; anemia[1] | Decreased erythropoiesis; anemia[1] |
| Reproductive system | Menstrual irregularities; decreased fertility; increased gonadal steroid metabolism | Hypermenorrhea; infertility; decreased libido; impotence; oligospermia; decreased gonadal steroid metabolism |
| Metabolic system | Increased basal metabolic rate; negative nitrogen balance; hyperglycemia; increased free fatty acids; decreased cholesterol and triglycerides; increased hormone degradation; increased requirements for fat- and water-soluble vitamins; increased drug metabolism | Decreased basal metabolic rate; slight positive nitrogen balance; delayed degradation of insulin, with increased sensitivity; increased cholesterol and triglycerides; decreased hormone degradation; decreased requirements for fat- and water-soluble vitamins; decreased drug metabolism |

# Hypothyroidism

➢ Hypothyroidism is a syndrome resulting from deficiency of thyroid hormones and is manifested largely by a reversible slowing down of all body functions.

➢ In infants and children, there is retardation of growth and development ⇨ dwarfism and irreversible mental retardation.

➢ The laboratory diagnosis of hypothyroidism in the adult is easily made by the combination of a low free thyroxine and elevated serum TSH.

➢ *Causes*:

- Primary hypothyroidism is typically caused by Hashimoto's Disease (also known as chronic lymphocytic thyroiditis, causes goiters due to the accumulation of lymphocytes), an auto-immune disorder in which the thyroid is destroyed by antibodies.
- Impaired hypothalamus and pituitary function, can inhibit the secretion of TSH, causing secondary hypothyroidism.
- A diet insufficient in iodine causes hypothyroidism as well.

# Hypothyroidism

➢ Presenting *clinical manifestations*

- Weight gain
- Constipation
- Fatigue
- Irregular menstrual cycle in women
- Edema
- More common in females than males

Colloidal goiter

## Management of Hypothyroidism

- Hypothyroidism caused by drugs, can be treated by simply removing the depressant agent.
- The general strategy of replacement therapy is appropriate. The most satisfactory preparation is levothyroxine.
- Infants and children require more T4 per kilogram of body weight than adults.
- Because of the long half-life of thyroxine, the dose can be given once daily.
- Serum TSH and free thyroxine should be measured at regular intervals and maintained within the normal range.
- It takes 6–8 weeks after starting a given dose of thyroxine to reach steady state levels in the bloodstream.

## Special Problems in Management of Hypothyroidism

**Myxedema and Coronary Artery Disease**

- Myxedema is frequently occurs in older persons, it is often associated with underlying coronary artery disease.
- Correction of myxedema must be done cautiously to avoid provoking arrhythmia, angina, or acute myocardial infarction.

**Myxedema Coma**

- Myxedema coma is an end state of untreated hypothyroidism.
- It is associated with progressive weakness, hypothermia, hypoventilation, hypoglycemia, hyponatremia, shock, and death.
- Management of myxedema coma is a medical emergency.
- The treatment of choice in myxedema coma is to give a loading dose of levothyroxine intravenously.

## Thyroid Preparations

- Synthetic (levothyroxine, liothyronine, liotrix):
  - *Synthetic levothyroxine* is the preparation of choice for thyroid replacement and suppression therapy because of:
    - its stability, content uniformity, low cost,
    - lack of allergenic foreign protein,
    - easy laboratory measurement of serum levels,
    - and long half-life (7 days), which permits once-daily administration.
    - In addition, $T_4$ is converted to $T_3$ intracellularly; thus, administration of $T_4$ produces both hormones.
  - *Synthetic liothyronine* is three to four times more potent than levothyroxine, it is not recommended for routine replacement therapy because of:
    - its shorter half-life (24 hours), which requires multiple daily doses;
    - its higher cost;
    - the greater difficulty of monitoring its adequacy of replacement by conventional laboratory tests.
    - because of its greater hormone activity and consequent greater risk of cardiotoxicity, $T_3$ should be avoided in patients with cardiac disease.
  - *Synthetic liotrix* (mixture of thyroxine and liothyronine )

- or of animal origin (desiccated thyroid): is never justified.

## Hyperthyroidism (thyrotoxicosis)

- Is the clinical syndrome that results when tissues are exposed to high levels of thyroid hormone.

- *Causes*:
  - Grave's disease, and autoimmune disorder in which antibodies serve as agonists to the TSH receptors on the thyroid's surface, causing thyroid growth and activation of hormone synthesis and secretion.

  - Thyroid tumors which cause the uncontrolled synthesis and secretion of thyroid hormones.

- T3, T4, will be elevated and TSH is suppressed.

## Clinical Manifestations

- Diarrhea
- Increased appetite
- Muscle weakness
- Fatigue
- Heart palpitations
- Irritability
- Nervousness
- Sleep disturbances
- Heat intolerance

Exophthalmos

## Management of Hyperthyroidism

**Antithyroid Agents**

- **Thioamides**
- **Anion Inhibitors**
- **Iodides**

**Radioactive Iodine**

**Thyroidectomy**

**Adjuncts to Antithyroid Therapy**

## Antithyroid Agents

### ➢ Thioamides

- Methimazole or propylthiouracil
- are major drugs for treatment of thyrotoxicosis.
- Methimazole is about ten times more potent than propylthiouracil.
- Propylthiouracil, giving the drug every 6–8 hours. Since a single dose of methimazole exerts an antithyroid effect for longer than 24 hours.
- Both thioamides cross the placental barrier and are concentrated by the fetal thyroid, ⇨ caution in pregnancy.
- Propylthiouracil is preferable in pregnancy because it crosses the placenta less readily.
- Propylthiouracil is not secreted in sufficient quantity in breast milk to preclude breast-feeding.

### ➢ Thioamides

***Pharmacodynamics***

- The thioamides act by multiple mechanisms:
  - The major action is to prevent hormone synthesis by inhibiting the thyroid peroxidase-catalyzed reactions and blocking iodine organification.
  - they block coupling of the iodotyrosines.
  - They do not block uptake of iodide by the gland.
  - Propylthiouracil and (to a much lesser extent) methimazole inhibit the peripheral deiodination of T4 and T3.
- Since the synthesis rather than the release of hormones is affected, the onset of these agents is slow, often requiring 3–4 weeks before stores of T4 are depleted.

## ➢ Anion Inhibitors

➢ perchlorate ($ClO_4^-$), and thiocyanate ($SCN^-$):
- can block uptake of iodide by the gland through competitive inhibition of the iodide transport mechanism.

➢ Since these effects can be overcome by large doses of iodides, their effectiveness is somewhat unpredictable.

## ➢ Iodides

➢ Today they are rarely used as sole therapy.

➢ Iodides have several actions on the thyroid:
- They inhibit organification
- And inhibit hormone release
- and decrease the size and vascularity of the hyperplastic gland.

➢ Rapid improvement in thyrotoxic symptoms occurs within 2–7 days.

➢ Valuable as preoperative preparation for surgery.

➢ Chronic use of iodides in pregnancy should be avoided, since they cross the placenta.

## Radioactive Iodine

- $^{131}I$ is the only isotope used for treatment of thyrotoxicosis.
- Administered orally in solution as sodium $^{131}I$.
- Its therapeutic effect depends on emission of rays with an effective half-life of 5 days.
- Within a few weeks after administration, destruction of the thyroid parenchyma is evidenced by epithelial swelling and necrosis, follicular disruption, edema, and leukocyte infiltration.
- Advantages of radioiodine include easy administration, effectiveness, low expense, and absence of pain.
- Should not be administered to pregnant women or nursing mothers, since it crosses the placenta and is excreted in breast milk.

## Thyroidectomy

- A near-total thyroidectomy is the treatment of choice for patients with very large glands or multinodular goiters.
- Patients are treated with antithyroid drugs until euthyroid (about 6 weeks). In addition, for 2 weeks prior to surgery, they receive saturated solution of potassium iodide, to diminish vascularity of the gland and simplify surgery.
- About 80-90% of patients will require thyroid supplementation following near-total thyroidectomy.

## Adjuncts to Antithyroid Therapy

- During the acute phase of thyrotoxicosis, ***beta-adrenoceptor-blocking agents*** without intrinsic sympathomimetic activity are extremely helpful. Propranolol will control tachycardia, hypertension, and atrial fibrillation. Propranolol is gradually withdrawn as serum thyroxine levels return to normal.

- ***Diltiazem***, can be used to control tachycardia in patients in whom beta-blockers are contraindicated, eg, those with asthma. Other calcium channel blockers may not be as effective as diltiazem.

- ***Barbiturates*** accelerate T4 breakdown (by hepatic enzyme induction) and may be helpful both as sedatives and to lower T4 levels.