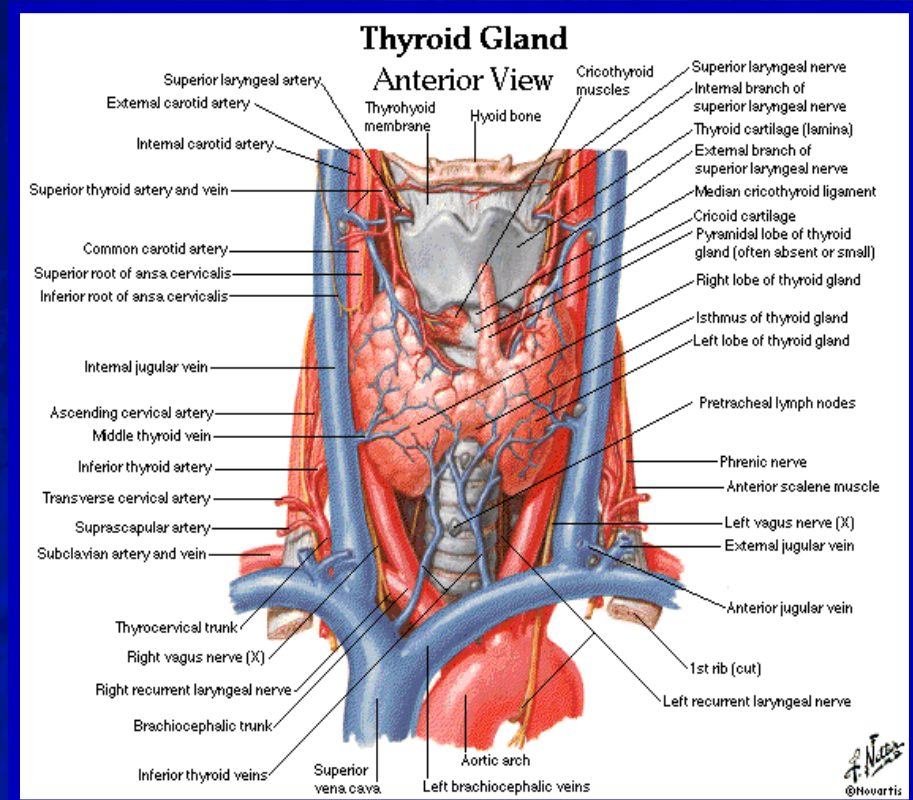
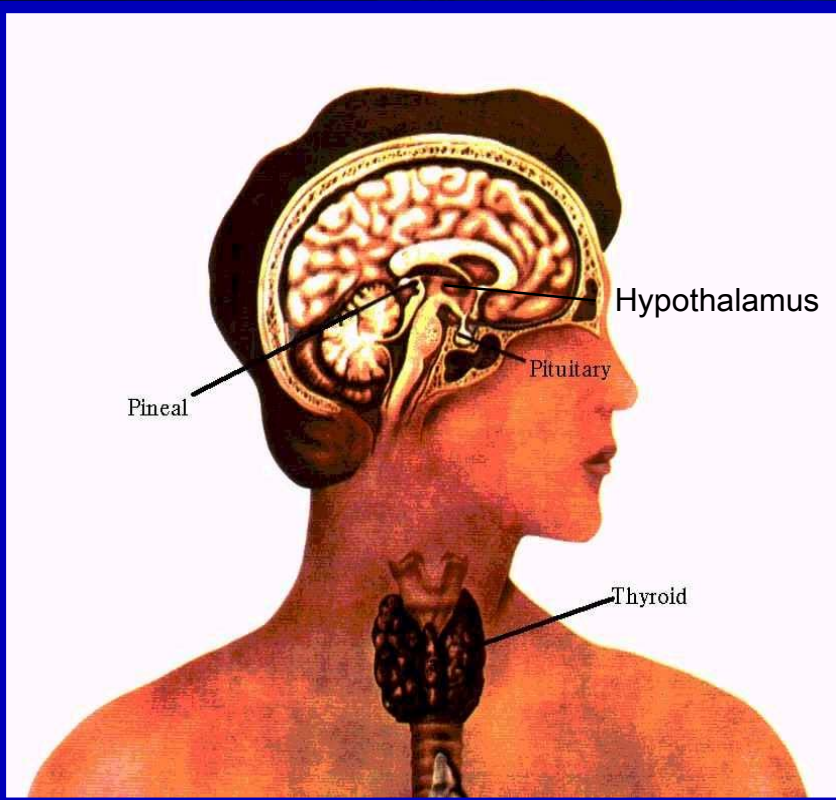
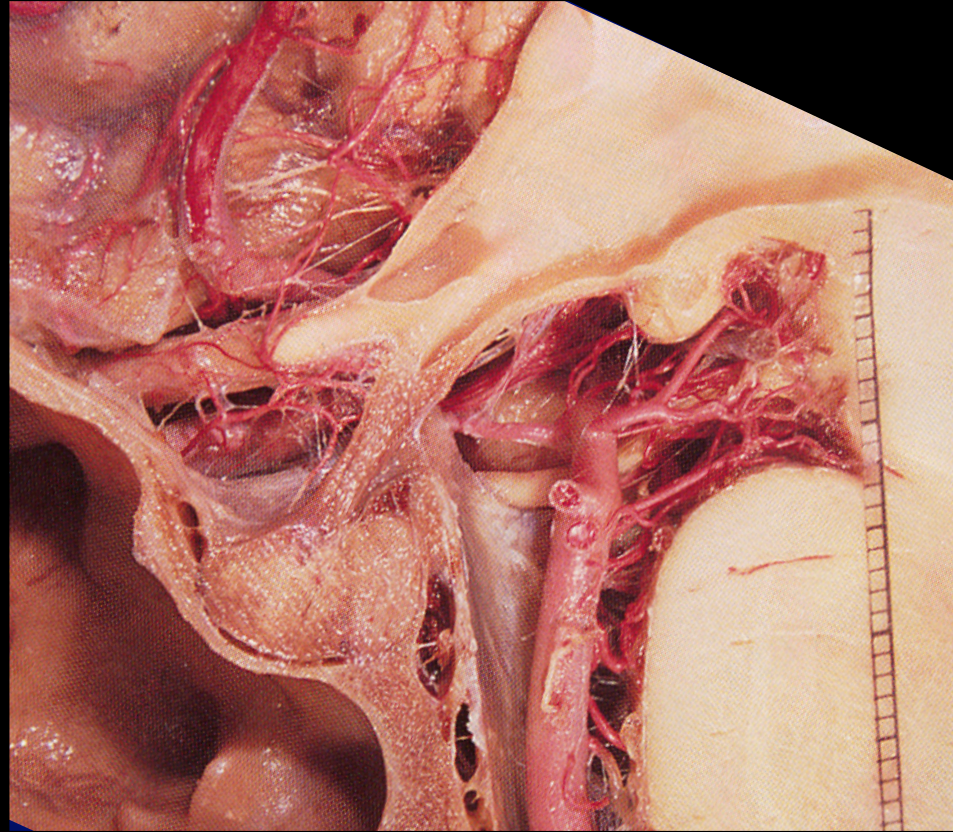


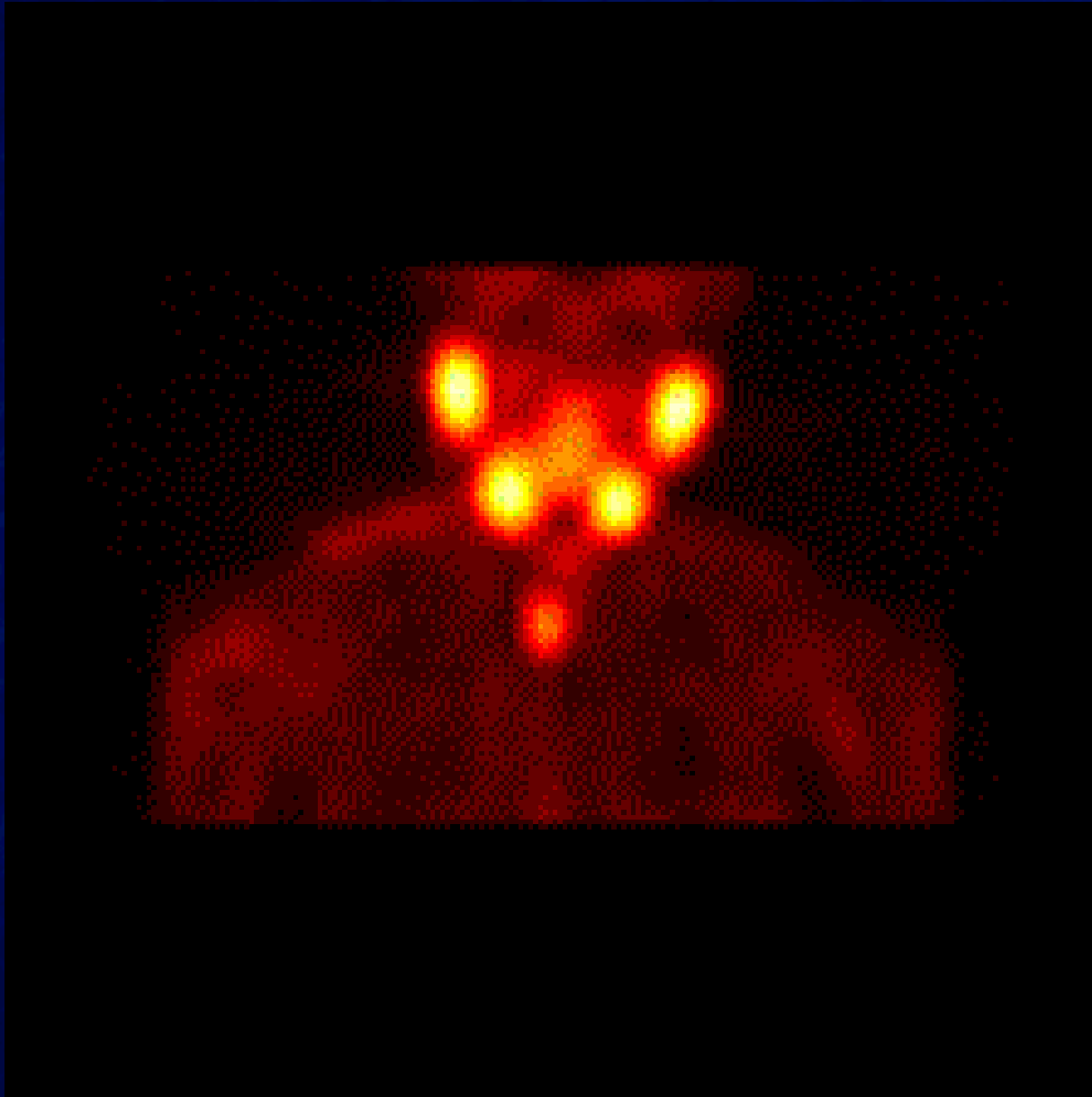
Biochemistry of the Thyroid gland



Features of the thyroid axis:

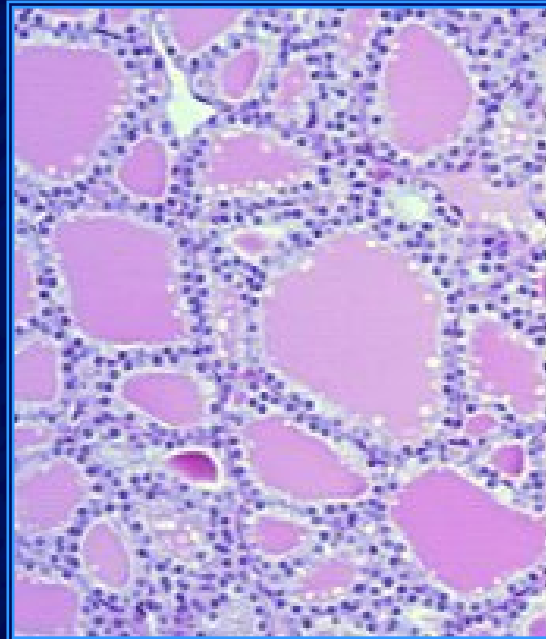
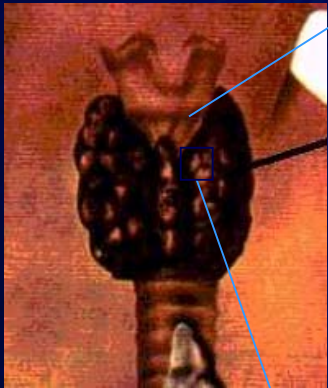


Thyroid imaging:

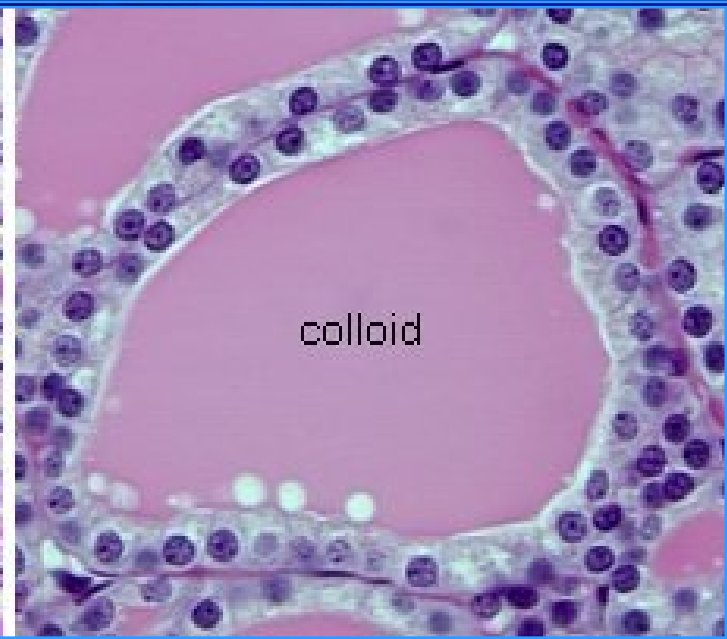


Features of the thyroid gland:

- Endocrine organ, key component in regulating body metabolism
- Highly vascularized tissue, should feel smooth / solid upon palpation
- Hypo- / hyperthyroidism related to a variety of mood / anxiety syndromes
- Thyroid dysfunction can reduce the effectiveness of antidepressants
- Goiter: enlargement of thyroid gland



Follicular epithelium



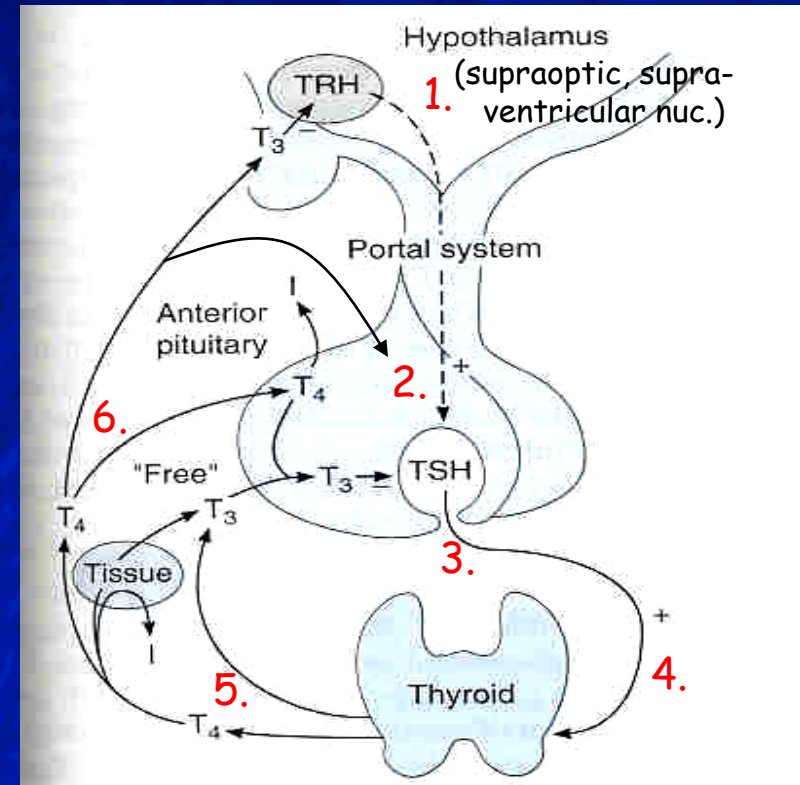
Colloid (stores thyroglobulin)
normally amber in color

Role of TH in hypothalamic-pituitary axis:

1. Thyrophin Releasing Hormone (TRH) - hypothalamic tri-peptide (glu-his-pro)
2. TRH binds to TRH receptors in the anterior pituitary (G protein coupled)
3. Stimulates the release of thyroid stimulating hormone (TSH)
4. Binds TSH receptors on thyroid gland (G protein)
5. Stimulates production of thyroid hormones, growth of thyroid cells (pathologic = goiter).
6. Thyroid hormones negatively regulates TRH secretion and TRH receptor levels in the ant. pituitary. Thyroid hormones also inhibit TSH production by inhibiting the TSH beta gene.

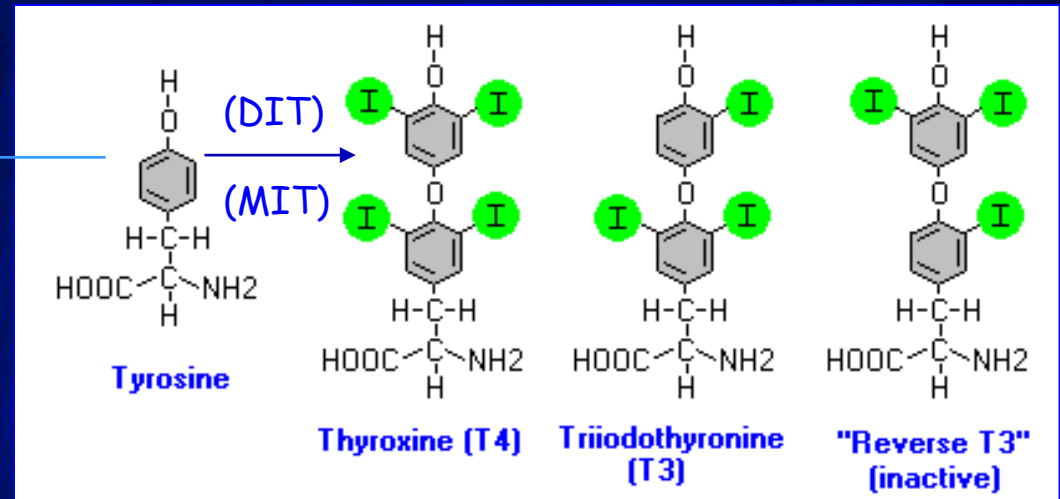
Notes:

Circadian rhythm (sleep) - increased TRH
Nonspecific stress - decreases TRH
TSH - pituitary glycoprotein (28kDa)
composed to alpha and beta strands



Thyroid hormones:

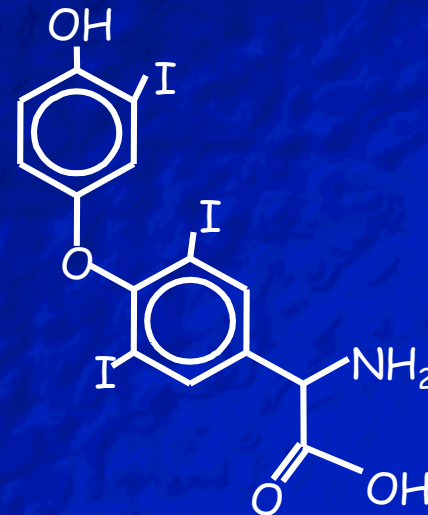
Catecholamines



(4-10x)



Thyroxine (T₄)

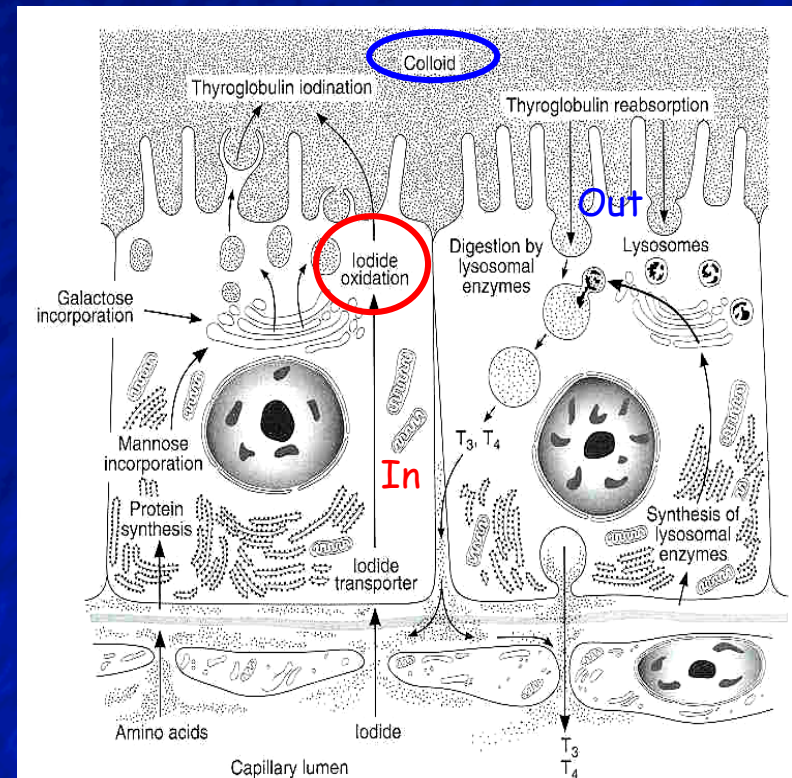


3,5,3'-Triiodothyronine (T₃)

Production of thyroid hormones:

- equivalent of ~150 ug/day iodine ingested - taken in and transferred to blood as iodide.
- Iodide taken up and concentrated in thyroid gland (20-100x blood plasma levels). Uptake blocked by perchlorates and thiocyanates.
- Iodide becomes oxidized to iodine when it reached the apical side of the follicular epithelium through the action of thyroidal peroxidase.
- Specifically iodine is added to tyrosine residues within thyroglobulin (MIT and DIT).
- Subsequent oxid. form T3 and T4 precursors.
- Iodinated thyroglobulin (TG) is stored in the acini of the gland, giving it its characteristic pink color (eosin staining).
- Following stimulation, TG is endocytosed to the follicular lumen and hydrolyzed by lysosomal enzymes. T4 and a small amount of T3 is then released into the blood.

Note: Under normal dietary conditions T4 is the major product (>90%). Under conditions of low iodine intake proportion of T3 may rise.



Thyroid peroxidase catalyzed TH formation:

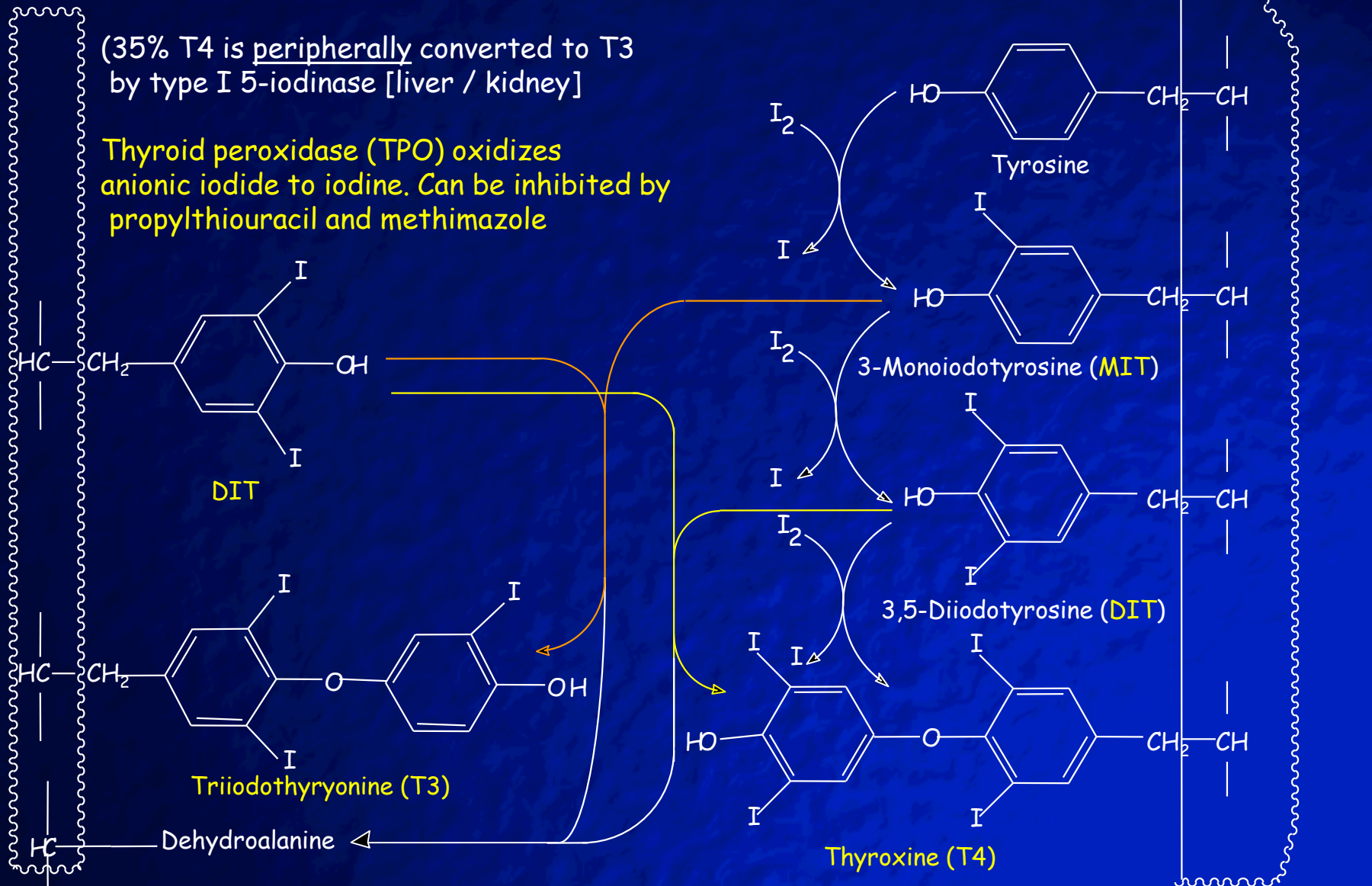
THYROGLOBULIN

FOLLICULAR COLLOID

THYROGLOBULIN

(35% T4 is peripherally converted to T3 by type I 5-iodinase [liver / kidney])

Thyroid peroxidase (TPO) oxidizes anionic iodide to iodine. Can be inhibited by propylthiouracil and methimazole



Transport of thyroid hormones:

The majority of thyroid hormones are bound to serum proteins, **thyroxine binding globulin** (75% of bound TH), as well as **thyroxine binding pre-albumin/transthyretin** and **serum albumin**). Unbound TH's is considered to be the primary biologically active form (0.05% T4, 0.3% T3)

Free TH's are more readily metabolized compared to bound forms.

T3 exhibits a shorter half-life (2 days) than T4 (7 days) but is 4-5 fold more active.

Free TH's and TSH levels are considered medically to be a more sensitive measure of thyroid function. Normal values are: FT4 11-24 pmol/L, FT3 3.3-8.2 pmol/L. However serum TSH is still typically the initial measure of choice for thyroid disease (0.5-5.0 mU/L).

Note: The thyroid gland produces some T3. However most is produced by de-iodination of T4 in peripheral tissues (T4 "prohormone" theory). Drugs such as aspirin and dicumarol can decrease the binding of thyroid hormones to their carriers.

Thyroid hormones are catabolized primarily by de-iodination (T3 reverse) and by glucuronidation in the liver.

Conditions which affect TBG levels:

Agent known to increase thyroxine binding globulin (TBG) levels:

Estrogen Effects -pregnancy, oral contraceptives

Infectious Hepatitis

Biliary Cirrhosis

Tamoxifen

Clofibrate

Agents known to decrease TBG levels:

Androgens and Anabolic Steroids

Large doses of Glucocorticoids

Nephrotic Syndrome

Major Systemic Non-thyroidal Illness

Active Acromegaly

Chronic Liver Disease

Drugs - Dilantin, Tegretol

Metabolic effects of thyroid hormones:

Growth and development:

- Stimulation of protein synthesis (skeletal)
- Increases basal metabolic rate (O₂ consumption)
- Critical for basal metabolism (temperature)
- TH important in brain development (axonal and dendritic development, myelination, cell mig.)

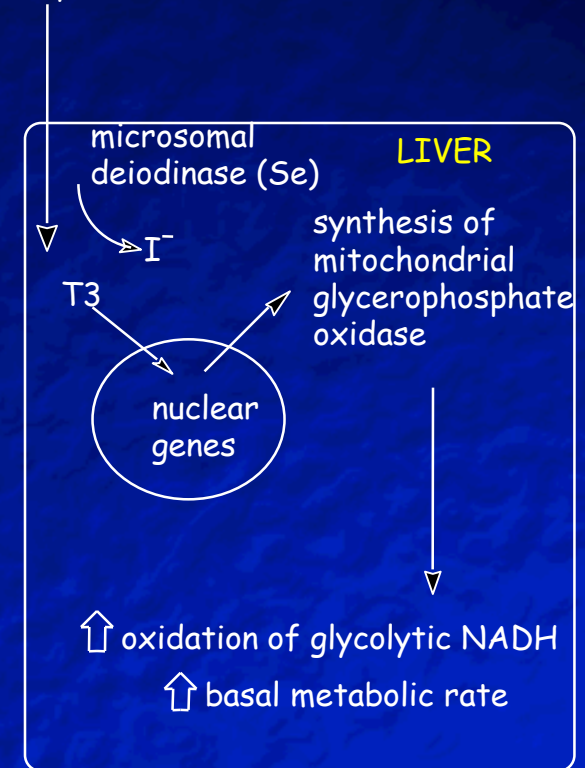
Uncoupling oxidative phosphorylation:

- Less effective ATP utilization
- Greater heat production

Additional activities:

- Increased cardiac output and systolic blood pressure
- Increased gastric motility
- Increased O₂ consumption by muscles leading to muscular weakness
- TH increases sensitivity of target tissues to catecholamines, thereby elevating lipolysis, glycogenolysis, and gluconeogenesis.

Plasma thyroxine (T₄) + T₃



Thyroid syndromes, overview:

- Benign Nontoxic Conditions
 - Diffuse and Nodular Goiter
- Benign Toxic Conditions (hyperthyroid)
 - Toxic Multinodular Goiter
 - Graves' Disease
 - Toxic Adenoma
- Inflammatory Conditions (hypothyroid)
 - Chronic (Hashimoto's) Thyroiditis
 - Subacute (De Quervain's) Thyroiditis
 - Riedel's Thyroiditis

Causes of hyperthyroidism:

Excess
thyroxine



hyperthyroidism
(high metabolism)



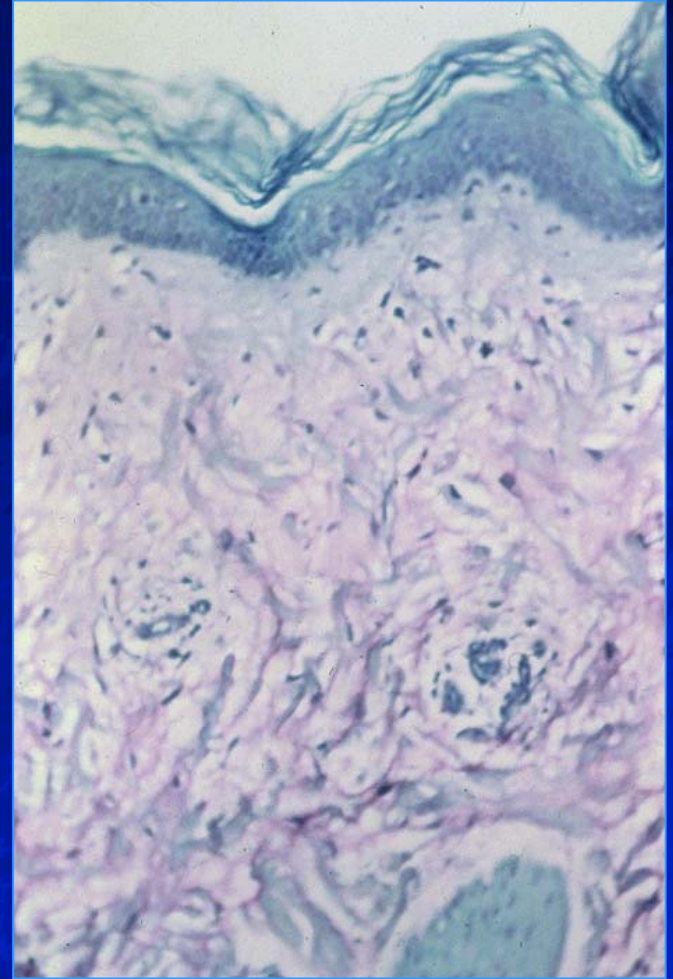
- Graves disease
- Metastatic thyroid cancer
- Hyperthyroidism in nodular goiter.

[Graves disease, Basedow's disease, diffuse toxic goiter, exophthalmic goiter]

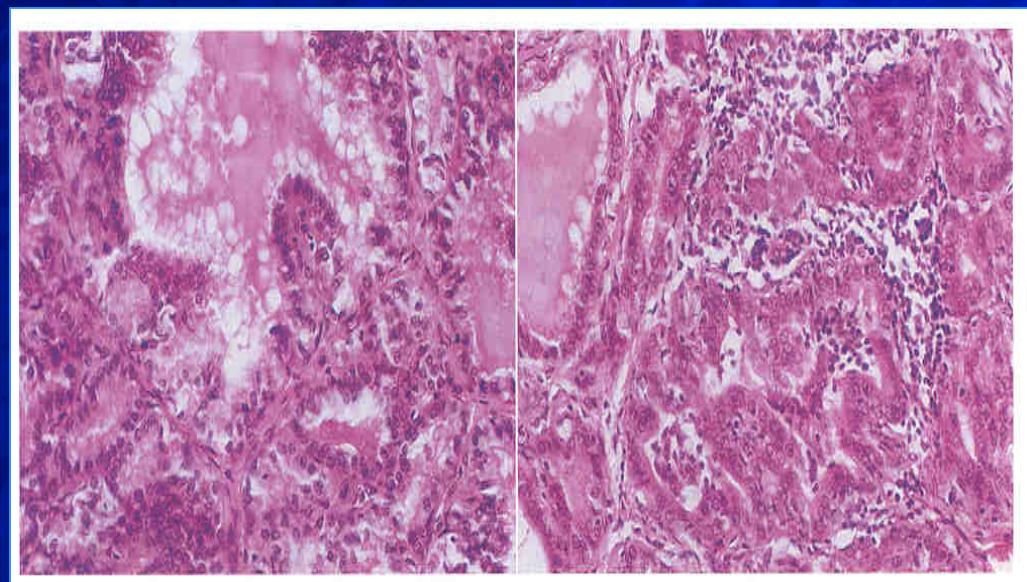
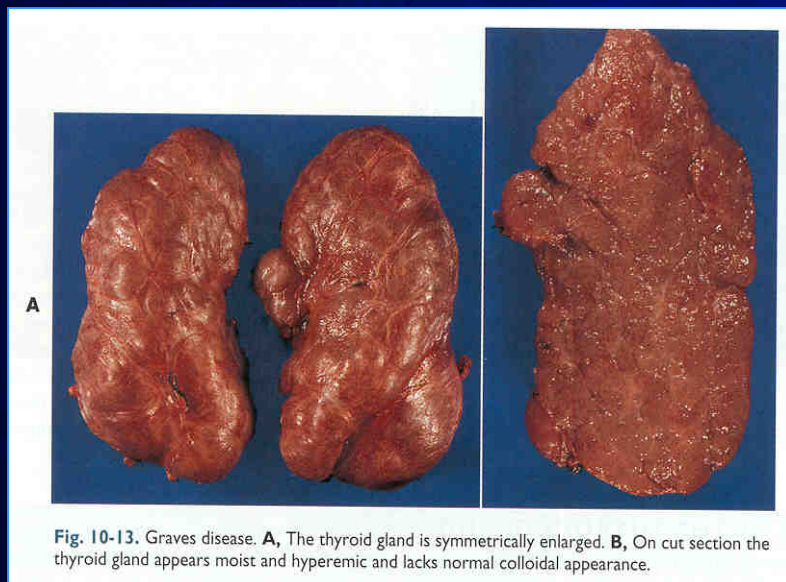
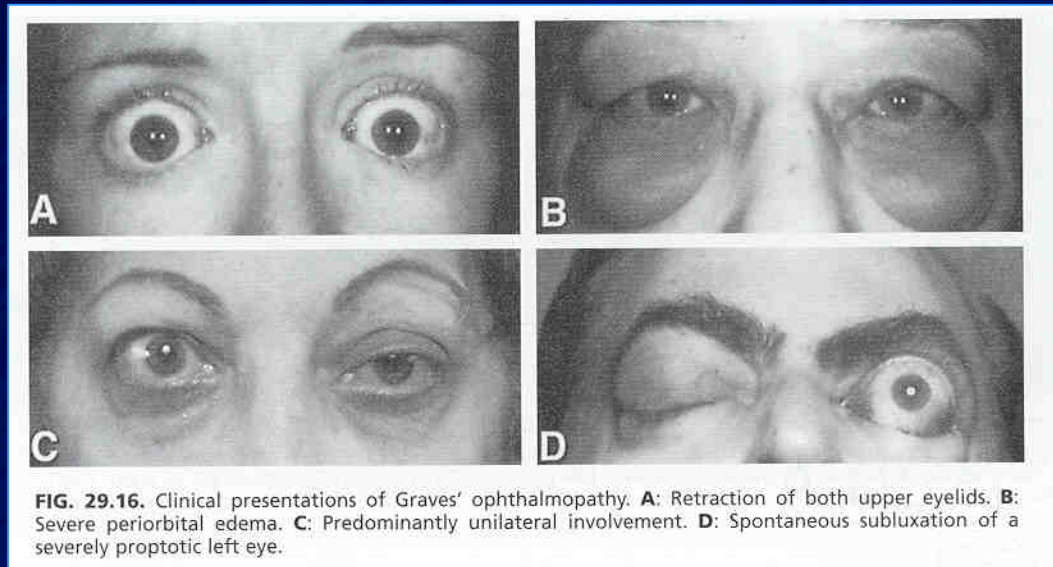
- Graves: most common cause of thyrotoxicosis in humans
- Impairment of skeletal tissues, CNS, lipid metabolism, protein synthesis
- Increased O₂ consumption, appetite, pulse rate, systolic pressure, sweating, tremor, weight loss.
- HLA-D IgG auto-antibodies activate TSH receptors, stimulating the gland
- Increased metabolic rate, rapid pulse, weight loss, excess heat production
- Diffuse goiter, heat intolerance, exophthalmos, brittle hair, myxedema

Clinical tests: high thyroxine (T₄), low TSH (Iodine tracer test)

Pathology of hyperthyroidism, general:



Graves disease, pathology:



Graves disease:

Features:

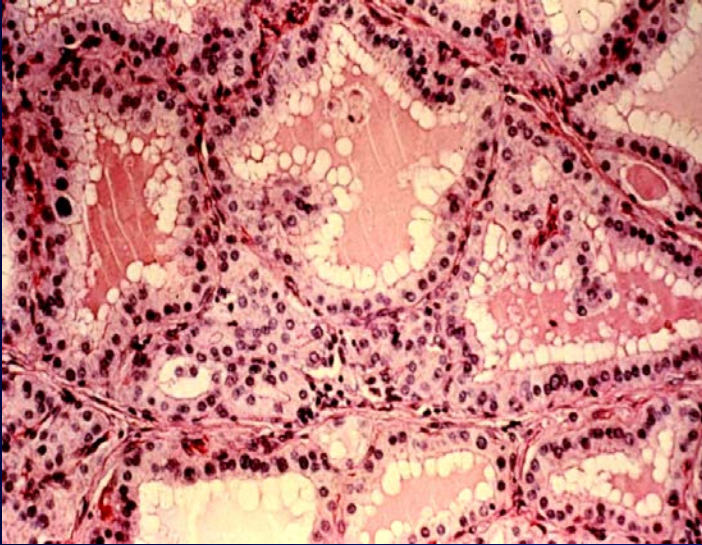
- Hyperthyroid syndrome.
- Most common form of thyrotoxicosis in humans (80%).
- Autoimmune etiology with familial predisposition.
- Affects females three to five times more often than males.
- Autoantibodies to thyroid stimulating hormone receptor. Other auto-antibodies also present (TgAb, TPOAb).
- Antibodies activate TSH receptors causing thyroid enlargement, hormone overprod.
- The result is that circulating T4 levels are elevated (TSH levels reduced).

Note: This relationship is true only in individuals with an intact hypothalamic-pituitary-thyroid axis. Patients who present with a normal or detectable TSH level and elevated thyroid hormone concentrations require further evaluation to exclude central causes of hyperthyroidism.

Symptoms:

- Thyrotoxicosis: palpitations, nervousness, easy fatigability, diarrhea, excessive sweating, intolerance to heat, weight loss
- Abnormal eye position
- Diffuse goiter upon palpation

Treatments for hyperthyroidism:



Treatments:

- a) Propylthiouracil, methimazole
(inactivates thyroid peroxidase)
- b) radioactive iodine
("inactivates" thyroid peroxidase)
- c) Iodide (inhibits hormone release)
- d) surgery (removal of source)
- e) high caloric/protein diet
(if severe weight loss/muscle waste)
- f) ionic inhibitors thiocyanate and perchlorate (mimics which inhibit iodide uptake). These are no longer in wide use due to significant risk of aplastic anemia, agranulocytosis.

Note:

Propranolol is frequently given in addition to anti-thyroid drugs in order to control cardiac/vascular symptoms associated with hyperthyroid state.

Graves, Treatments:

- Anti-thyroid Drugs
 - May require prolonged therapy
- Radioactive iodine
 - May worsen ophthalmopathy unless followed by steroids
- Surgery
 - Make patient euthyroid prior to surgery
 - Potassium iodide two weeks prior to surgery can decrease the vascularity of the gland

Graves, Treatments continued:

- Anti-thyroid drugs
- Propylthiouracil—PTU—(100mg tid or methimazole (30mg qd)
- Treat pregnant patients with PTU as methimazole can cause aplasia cutis in the fetus
- If anti-thyroid drugs are continued for 1-2 years after euthyroid state is reached, ~one-half of patient attain remission.

Side effects:

- Agranulocytosis: rare (1/200-500)
- Hepatotoxicity: Fulminant Hepatitis with necrosis in PTU; Cholestatic jaundice with methimazole
- Rashes can range from limited erythema to an exfoliative dermatitis

Thyroid Storm and Thyrotoxicosis

Thyroid storm is an acute, life-threatening, thyroid hormone-induced hypermetabolic state. Common clinical presentation includes fever, tachycardia, neurologic abnormalities, and hypertension, followed by hypotension and shock. Because thyroid storm is invariably fatal if left untreated, rapid diagnosis and aggressive treatment are critical.

Precipitating factors:

- Infection, Surgery, Trauma, Radioactive iodine treatment, Pregnancy, Anticholinergic and adrenergic drugs, TH ingestion, Diabetic ketoacidosis (DKA).

Treatment:

- Thyroid storm: manage aggressively with beta-blockers, calcium channel blockers, PTU, methimazole, sodium iodide, digitalis or diuretics for heart failure, fluid and electrolyte management.

Thyroid storm, medications:

Potassium iodide (Pima, SSKI, Thyro-Block) - Used to inhibit TH release from thyroid gland.

Propylthiouracil (PTU - Propyl-Thyracil) - inhibits synthesis of TH by preventing organification and trapping of iodide to iodine / inhibition of coupling of iodotyrosines. Also inhibits peripheral conversion of T4 to T3.

Methimazole (Tapazole) - Inhibits synthesis of TH by preventing organification of iodide to iodine and coupling of iodotyrosines. Although at least 10 times more potent than PTU on a weight basis, it does not inhibit peripheral conversion of T4 to T3.

Propranolol (Inderal) - Widely used for thyroid storm, propranolol is a nonselective beta-adrenergic antagonist. Decreases heart rate, myocardial contractility, blood pressure, and myocardial oxygen demand. Often the only adjunctive drug necessary to control thyroid storm symptoms.

Hypothyroidism:

Iodine deficiency

Insufficient
thyroxine



hypothyroidism
(low metabolism)

low thyroxine



high TSH



thyroid growth

Symptoms: constant fatigue, muscle aches,
cold intolerance, swelling (puffy face)

Indicators:

- iodide deficiency
- dietary goitrogens
(inactivate peroxidase)
eg. raw cabbage (thiocyanate)
- HASHIMOTO'S THYROIDITIS
(autoimmune TPO antibody
with a genetic basis)
- MYXEDEMA -coma,
tissue swelling, weight gain
- CRETINISM - in children
decreased bone/nervous development
stunted growth, delayed development
- Protruding tongue



Treatment:

- Thyroxine daily for life
- Iodized salt / flour iodate

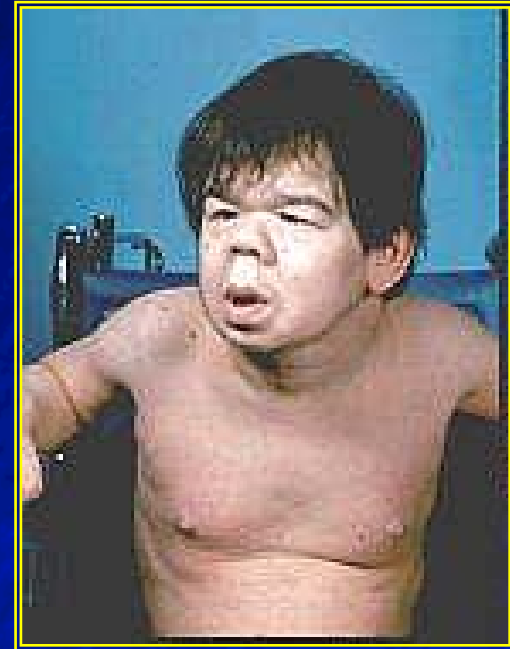
Need 200ug I /day

Caution: High doses of
iodide leads to necrosis of follicular
Cells in hypothyroidism.

Hypothyroidism, developmental:



Juvenile Hypothyroidism



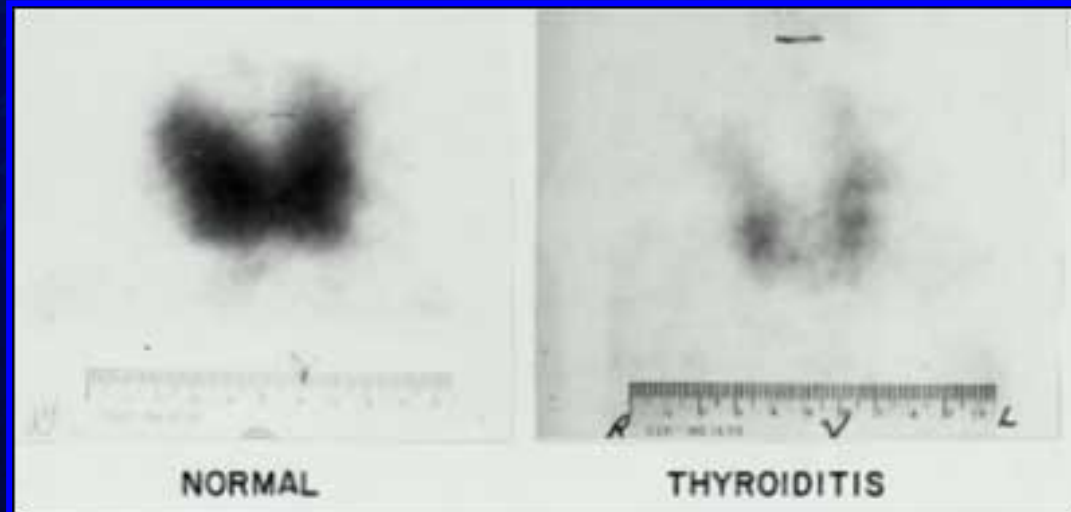
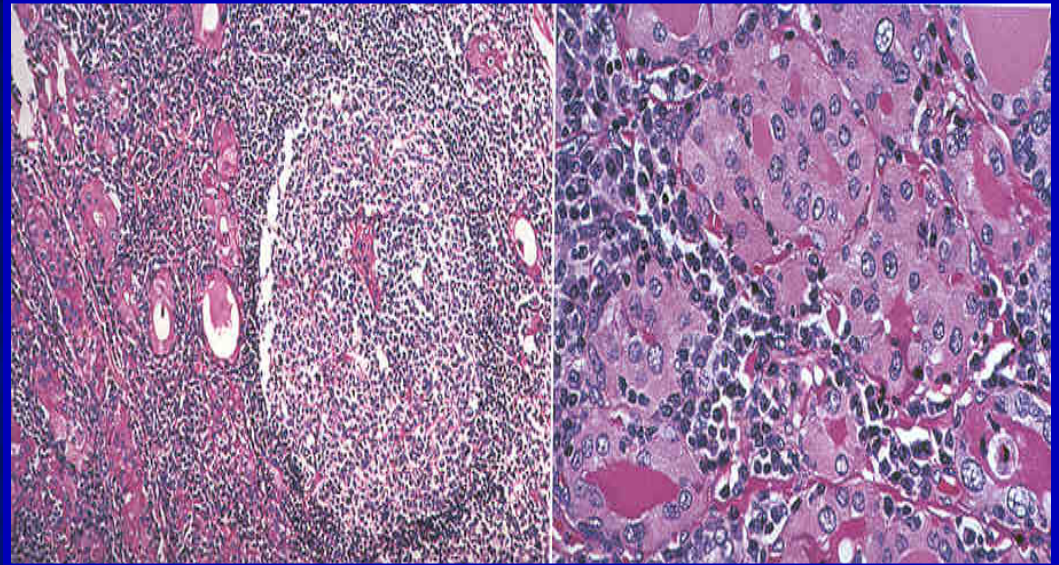
Congenital Hypothyroidism

- **Cretinism** is the term for the constellation of defects resulting from untreated **neonatal hypothyroidism**. This remains one of the most common causes of mental retardation in the world today.

Chronic Thyroiditis (typically Hashimoto's):

- Also known as Hashimoto's disease, often slow onset
- Most common cause of hypothyroidism in North America
- Auto-antibodies include: thyroglobulin antibody, **thyroid peroxidase antibody, TSH receptor blocking antibody**
- Reidel's thyroiditis is also a chronic syndrome
- Presents as a multi-nodular, firm, asymmetric goiter
- Tends to occur in women and also occurs in their daughters in an autosomal dominant type transmission
- Usually has high titers of anti-thyroid peroxidase (**anti-TPO**) antibodies
- Most common causes: Hashimoto's thyroiditis OR I131-induced hypothyroidism after treatment for Graves' disease
- Patients often present with some or all of the following: fatigue, cold intolerance, weight gain, constipation, hair loss, apathy

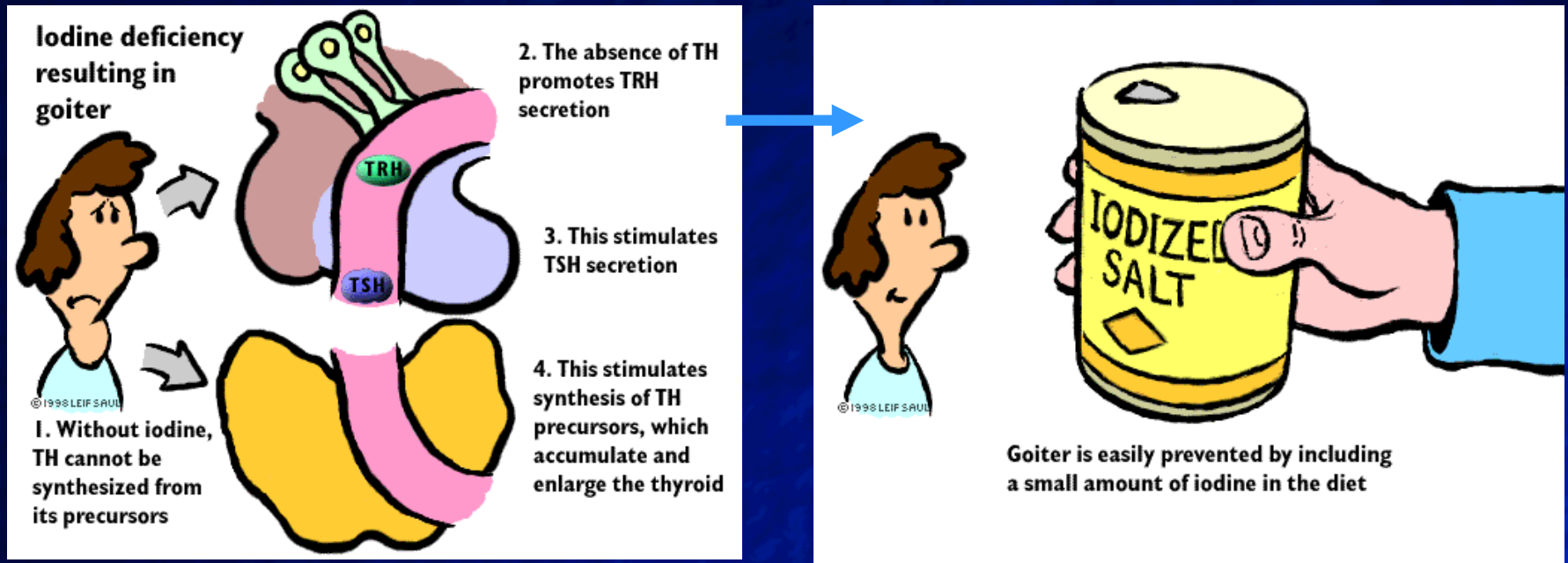
Chronic Thyroiditis (Hashimoto's):



Chronic Thyroiditis - Treatments:

- Similar to subclinical hypothyroidism, treatment of patients with subclinical hyperthyroidism have not been studied enough to have conclusive arguments
- The theoretical benefits of treatment include prevention of osteoporosis and subsequent bone fractures and prevention of atrial fibrillation.
- Therapy is either anti-thyroid drugs or ablation with either surgery or iodine
- Risk of progression to overt hypothyroidism is highest for those with antibodies to thyroperoxidase; pregnant patients are at increased risk for fetal death; increased risk for hypercholesterolemia .
- Low dose Levothyroxine is now generally given to patients with these conditions and the lab findings of subclinical hypothyroidism

Iodine deficiency and goiter:



Thyroid preparations:

Thyroglobulin - (Proloid) purified pig thyroid.

Levothyroxin sodium - (Synthroid) (Sodium salt of natural isomer of thyroxine)
liothyronin (Cytomel), Liotrix (Thyrolar) used similarly

Protirelin - synthetic TSH which can be used to stimulate the thyroid.

Note: there are OTHER causes of goiter.

These include: **Cassava root**, Brussels sprouts, cabbage, cauliflower
Milk from regions where goitrogens are present in the grass.

Best guides to establish diagnosis

- A) measure serum anti-thyroid AB
 - B) measure serum thyroglobulin levels
 - C) measure serum thyroid stimulating immunoglobulins
 - D) RAIU uptake and scan
 - E) Needle aspiration and biopsy of thyroid
-
- Check TSH---if it is >5 mU/L, check free thyroxine: low free thyroxine indicates overt hypothyroidism; normal free thyroxine indicates sub-clinical hypothyroidism.
-
- Treatment: for overt hypothyroidism is levothyroxine (T4) alone. T4 has a very long half life and takes weeks to equilibrate and TSH levels should be rechecked 6-8 weeks for response to therapy