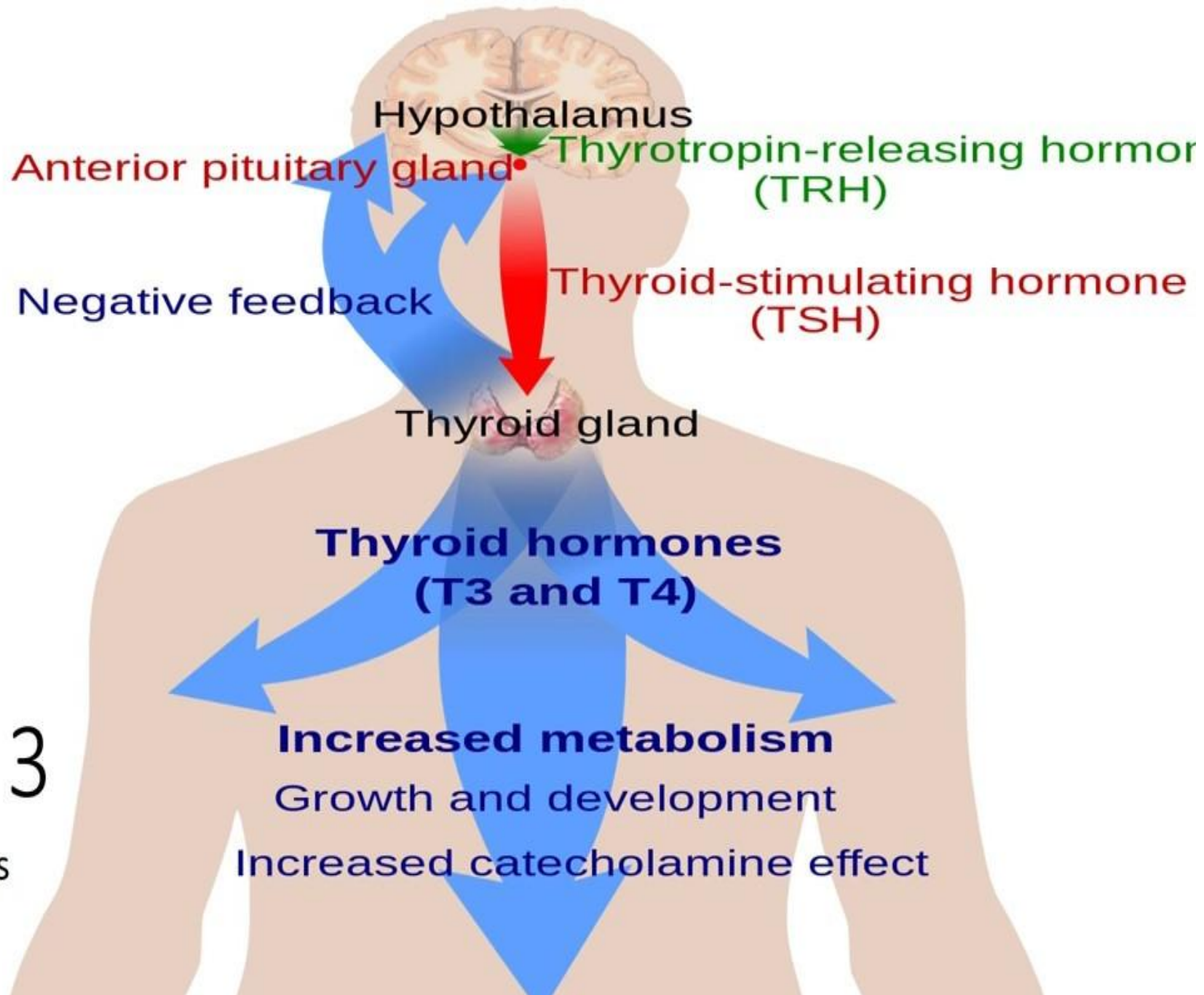


Thyroid system



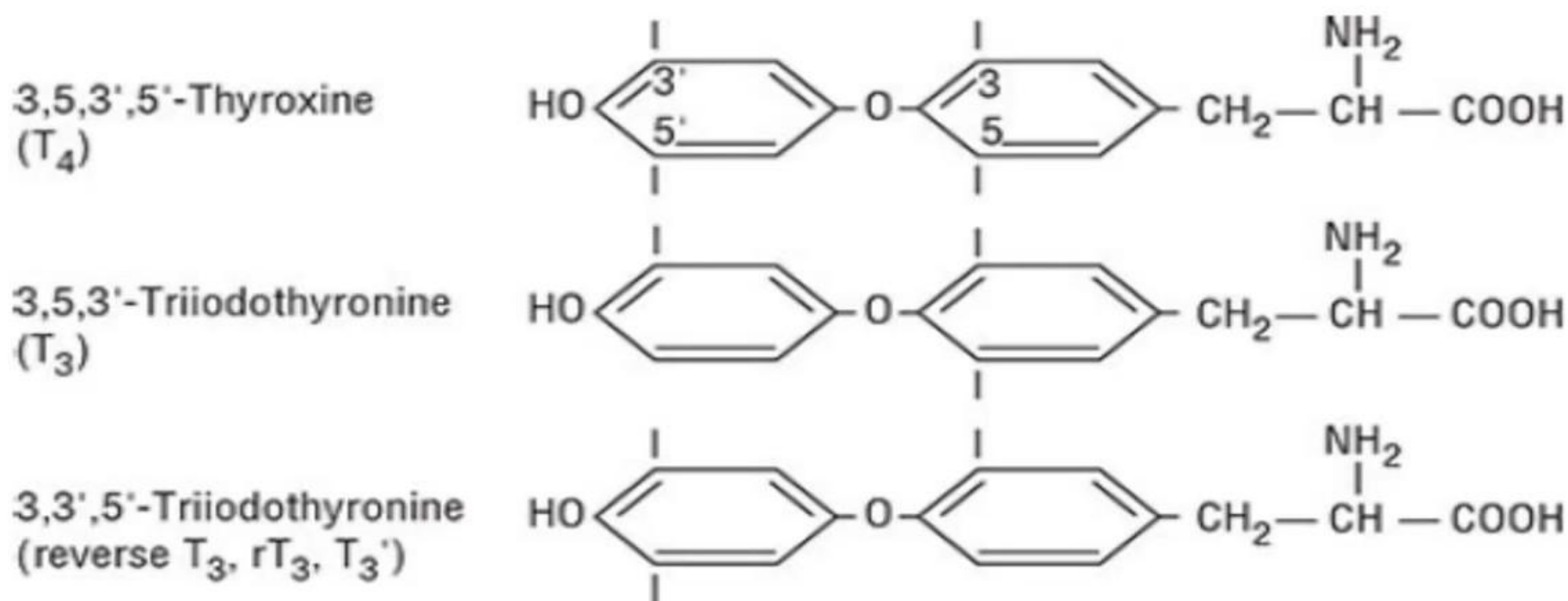
Endocrine 3

Dr. Samaher Younis

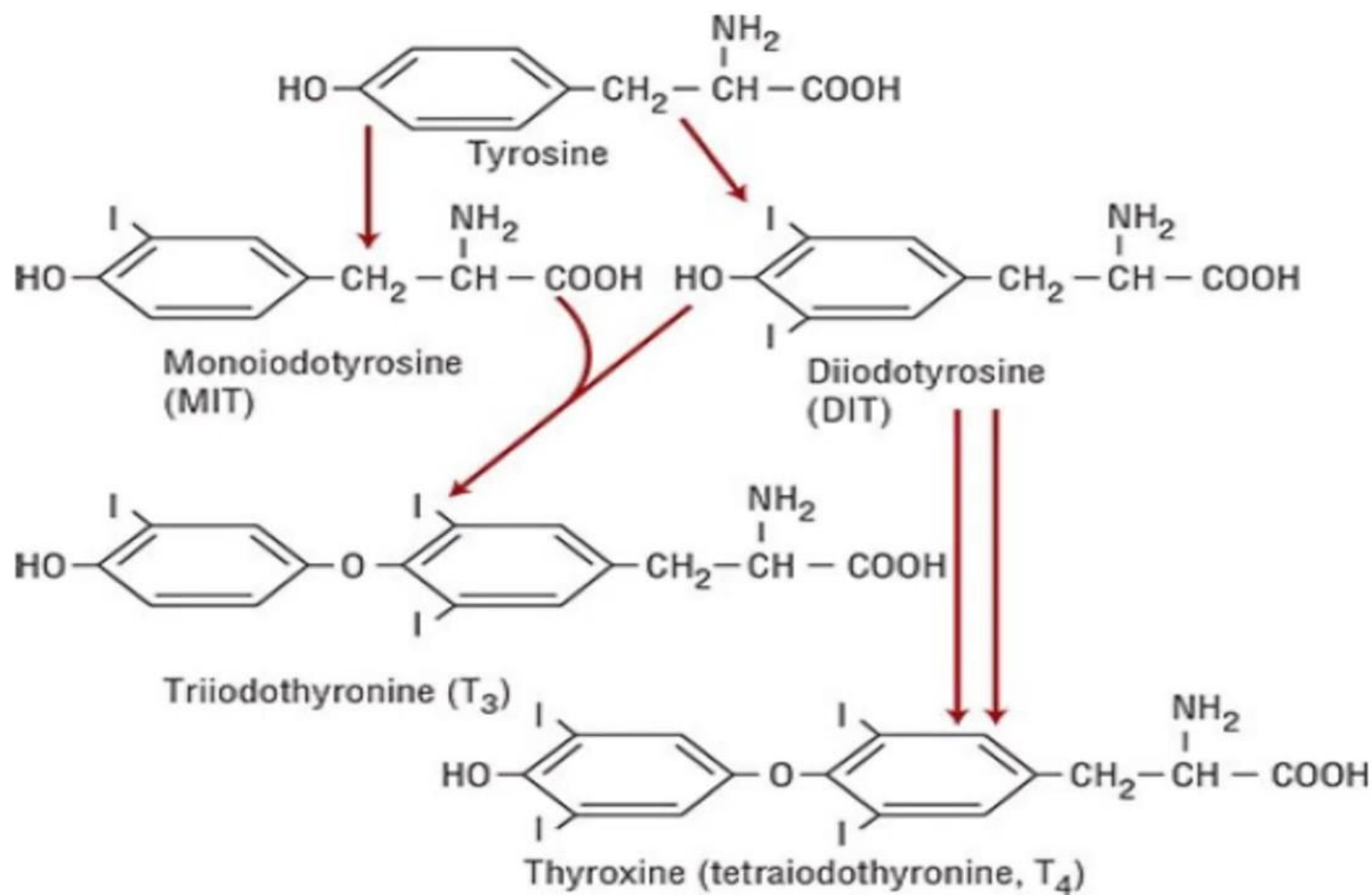
BCPS

THYROID DISORDERS

Hyperthyroid Disorders (thyrotoxicosis)



Structure of thyroid hormones.



Treatments for Hyperthyroidism Caused by Graves' Disease

Treatment	Advantages	Disadvantages	Comment
Methimazole (first-line pharmacotherapy)	Noninvasive	Low cure rate (average 40%-50%)	First-line treatment in children, adolescents, and pregnancy
Propylthiouracil (second-line pharmacotherapy)	Low initial cost Low risk of permanent hypothyroidism Possible remissions due to immune effects	Adverse drug reactions Drug compliance	Initial treatment in severe cases or preoperative preparation
Radioactive iodine (^{131}I)	Cure of hyperthyroidism Lowest cost, before adjustment for quality of life	Permanent hypothyroidism almost inevitable Might worsen ophthalmopathy Pregnancy must be deferred for 6-12 months; no breast-feeding Small potential risk of exacerbation of hyperthyroidism	Best treatment for toxic nodules and toxic multinodular goiter
Surgery	Rapid, effective treatment, especially in patients with large goiters	Most invasive Least costly in long term after quality-of-life adjustment Permanent hypothyroidism Pain, scar	Potential choice in pregnancy (2nd trimester) if major side effect from antithyroid drugs Potential complications (recurrent laryngeal nerve damage, hypoparathyroidism) Useful when coexisting suspicious nodule present Option for patients who refuse radioiodine

Therapy goals

- a. Minimize or eliminate symptoms, improve quality of life
- b. Minimize long-term damage to organs (heart disease, arrhythmias, sudden cardiac death, bone demineralization, and fractures)
- c. Normalize free T4 and TSH concentrations

Therapeutics

- a. Ablative therapy: Treatment of choice for Graves disease, toxic nodule, multinodular goiter; radioactive iodine ablative therapy and surgical resection for adenomas according to patient preferences or comorbidities.
- Ablative therapy often results in hypothyroidism

Antithyroid pharmacotherapy

usually reserved for:

i. Those awaiting ablative therapy or surgical resection

(a) Depletes stored hormone

(b) Minimizes risk of post treatment hyperthyroidism caused by thyroiditis

ii. Those who are not ablative or surgical candidates (e.g., serious cardiovascular disease, candidate

unlikely to be adherent to radiation safety)

iii. When ablative therapy or surgical resection fails to normalize thyroid function

iv. Those with a high probability of remission with oral therapy for Graves disease

(a) Mild disease

(b) Small goiter

(c) Low or negative antibody titers

v. Those with limited life expectancy

vi. Those with moderate to severe active Graves ophthalmopathy

- **Antithyroid Medications**

- **Thionamide Drugs** Two drugs within this category, MMI (methimazole) and PTU (propylthiouracil), are approved for the treatment of hyperthyroidism in the United States.

Mechanism of Action MMI and PTU share several mechanisms to inhibit the biosynthesis of thyroid hormone.

- First, These drugs serve as preferential substrates for the iodinating intermediate of thyroid peroxidase and divert iodine away from potential iodination sites in TG (thyroglobulin). This prevents subsequent incorporation of iodine into iodotyrosines and ultimately iodothyronine (**“organification”**).
- Second, they inhibit coupling of MIT and DIT to form T4 and T3. (**The coupling**) reaction may be more sensitive to these drugs than the iodination reaction.
- Third, Propylthiouracil PTU can block T4/T3 (**conversion**) in the periphery as well

Pharmacokinetics

Both antithyroid drugs are well absorbed (80%-95%) from the gastrointestinal tract, with peak serum concentrations about 1 hour after ingestion.

The plasma half-life ranges of PTU and MMI are **1 to 2.5** and 6 to 9 hours, respectively, and are not appreciably affected by thyroid status.

Urinary excretion is about 35% for PTU and less than 10% for MMI.

These drugs are **actively concentrated in the thyroid gland**, which may account for the disparity between their relatively short plasma half-lives and the effectiveness of once daily dosing regimens even with PTU.

Approximately **60% to 80% of PTU is bound to plasma albumin**, whereas MMI is not protein bound.

MMI readily crosses the **placenta** and appears in breast milk.

Dosing

Propylthiouracil

- (1) Initial: 100 mg by mouth three times daily
- (2) Maximal: 400 mg three times daily
- (3) Once euthyroid, can reduce to 50 mg two or three times daily

Methimazole

- (1) Preferred agent for Graves disease according to the American Association of Clinical Endocrinologists (AACE) for most patients unless in first trimester of **pregnancy**; then use propylthiouracil

(A) American Thyroid Association **recommends propylthiouracil in the first trimester because of the risk of embryopathy.**

- (B) Change to methimazole in the second trimester.
- (2) Initial: 10–20 mg by mouth once daily
- (3) Maximal: 40 mg three times daily
- (4) Once euthyroid, may reduce to 5–10 mg/day

Monthly dosage titrations as needed (depending on symptoms and free T4 concentrations); TSH may remain low for months after therapy begins

Adverse effects

(a) Hepatotoxicity risk with propylthiouracil (boxed warning): AACE recommends baseline liver function tests. Routine evaluation of liver function while receiving antithyroid agents has not been shown to prevent severe hepatotoxicity.

(b) Rash

(c) Arthralgia, lupus-like symptoms

(d) Fever

(e) Agranulocytosis early in therapy (usually within 3 months): AACE recommends a baseline complete blood cell count; no routine monitoring recommended. Can repeat if patient becomes febrile or develops pharyngitis

Efficacy

- (a) Slow onset in reducing symptoms (6-8 weeks). Maximal effect may take 4–6 months.
- (b) Neither drug appears superior to the other in efficacy.
- (c) On a milligram-to-milligram basis, methimazole is 10-fold more potent than propylthiouracil.
- (d) Remission rates low: 20%–30%. Remission is defined as normal TSH and T4 for 1 year after discontinuing antithyroid therapy.
- (e) Therapy duration in Graves disease (oral agents unlikely to cause remission in those with nodular thyroid disease)
 - (1) Usually 12–18 months; length of trial might not affect remission rate
 - (2) Consider trial off oral therapy if TSH is normal; antibody titers can help guide decision.
 - (3) Monitor thyroid concentrations every 1–3 months for up to 12 months for relapse (abnormal TSH or T4 return).

Nonselective β -blockers (primarily propranolol; sometimes nadolol)

➤ Mechanism of action: Blocks many hyperthyroidism manifestations mediated by β -adrenergic receptors; also may block (less active) T4 conversion to (more active) T3

➤ Propranolol dosing

(a) Initial: 20–40 mg by mouth three or four times daily

(b) Maximal: 240–480 mg/day

Iodines and iodides (e.g., Lugol's solution, saturated solution of potassium iodide)

➤ Mechanism of action: Inhibits the release of stored thyroid hormone. Minimal effect on hormone synthesis. Helps decrease vascularity and size of gland before surgery

➤ Dosing

(a) Lugol's solution (6.3–8 mg of iodide per drop)

(b) Saturated solution of potassium iodide (38–50 mg of iodide per drop)

(c) Potassium iodide tablets: 130-mg tablets contain 100 mg of iodide.

(d) Usual daily dose: 120–400 mg mixed with juice or water, split three times daily

Do not use in the days before ablative iodine therapy (may reduce uptake of radioactive iodine).

- Limited efficacy after 7–14 days of therapy because thyroid hormone release will resume
- Primary use is temporary before surgery (7–10 days) to shrink the gland.
- Can be used after ablative therapy (3–7 days) to inhibit thyroiditis-mediated release of stored hormone
- Used acutely in thyroid storm

Radioactive Iodine

Although other radioisotopes have been used to ablate thyroid tissue, ^{131}I is considered to be the agent of choice for Graves' disease, toxic autonomous nodules, and toxic MNGs.⁹ RAI is administered as a colorless and tasteless liquid that is well absorbed and concentrates in the thyroid. ^{131}I is a β - and γ -emitter with a tissue penetration of 2 mm and a half-life of 8 days. Other organs take up ^{131}I , but the thyroid gland is the only organ in which organification of the absorbed iodine takes place. Initially, RAI disrupts hormone synthesis by incorporating into thyroid hormones and TG. Over a period of weeks, follicles that have taken up RAI and surrounding follicles develop evidence of cellular necrosis, breakdown of follicles, and destruction of small vessels within the gland, leading to edema and fibrosis of the interstitial tissue. Pregnancy is an absolute contraindication to the use of RAI since radiation will be delivered to the fetal tissue, including the fetal thyroid.

Thyroid Storm

Pharmacotherapy

a. **Propylthiouracil**

- i. 500- to 1000-mg loading dose; then 250 mg every 4 hours
 - ii. Blocks new hormone synthesis
 - iii. Can use methimazole 60–80 mg daily
- b. Iodide therapy 1 hour after propylthiouracil initiation (dosed as stated earlier) to block hormone release

c. **β -Blocker therapy:** Propranolol or esmolol commonly used to control symptoms and block conversion of T4 to T3

d. **Acetaminophen as antipyretic therapy**, if needed (avoid nonsteroidal anti-inflammatory drugs because of displacement of protein-bound thyroid hormones)

e. **Corticosteroid therapy:** Prednisone 300-mg intravenous loading dose; then 100 mg every 8 hours (or equivalent dosages of, for example, dexamethasone, hydrocortisone). Provides prophylaxis against relative adrenal insufficiency and can block conversion of T4 to T3

Hypothyroid Disorders

Therapy goals

- a. Minimize or eliminate symptoms; improve quality of life
 - b. Minimize long-term damage to organs (myxedema coma, heart disease)
 - c. Normalize free T4 and TSH concentrations
- **Levothyroxine** (drug of choice)

Dosing

- (a) Initial
 - (1) In otherwise healthy adults, 1.6 mcg/kg (use ideal body weight) per day
 - (2) In patients age 50–60, consider 50 mcg/day.
 - (3) In those with existing cardiovascular disease, consider 12.5–25 mcg/day.

Usually dosed in the morning on an empty stomach 30–60 minutes before breakfast or at bedtime 4 hours after last meal; dosed separately from other medications (particularly calcium or iron supplements and antacids)

Daily requirements are higher in pregnancy

Monitoring

4–8 weeks is appropriate to assess patient response in TSH after initiating or changing therapy (about a 7-day half-life for T₄). May take longer for TSH to achieve steady-state concentrations

Myxedema Coma

Pharmacotherapy

➤ **Intravenous thyroid hormone** replacement

- i. T4: 100- to 500-mcg loading dose, followed by 75–100 mcg/day, until the patient can tolerate oral therapy. Lower the initial dose in frail patients or patients with established cardiovascular disease.
- ii. Some advocate the use of T3 over T4, given that T3 is more biologically active and that T4/T3 conversion may be suppressed in myxedema coma. Cost and availability limit intravenous T3 use.

➤ **Antibiotic therapy:** Given common infectious causes, some clinicians advocate empiric therapy with broad-spectrum antibiotics.

➤ Corticosteroid therapy

- i. **Hydrocortisone** 100 mg every 8 hours (or equivalent steroid)
- ii. Can be discontinued if random cortisol concentration not depressed