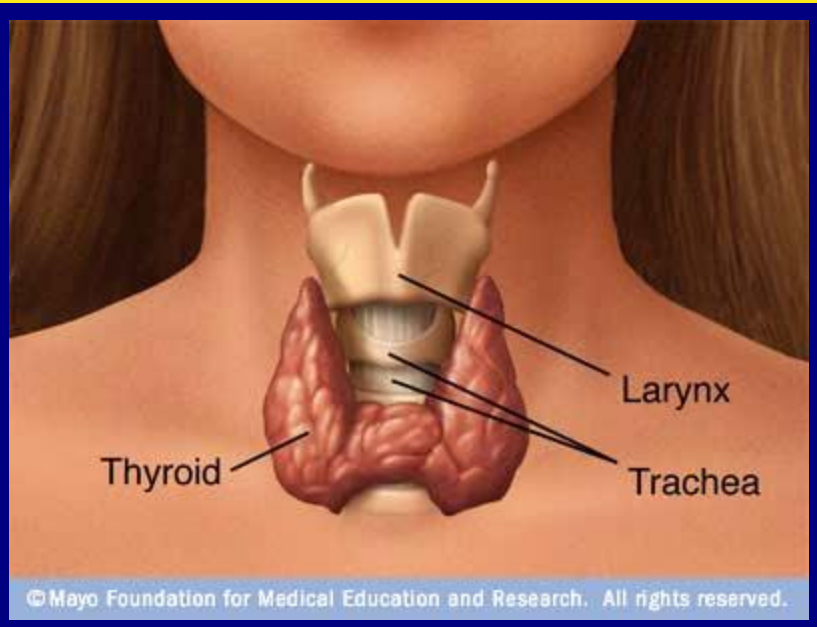
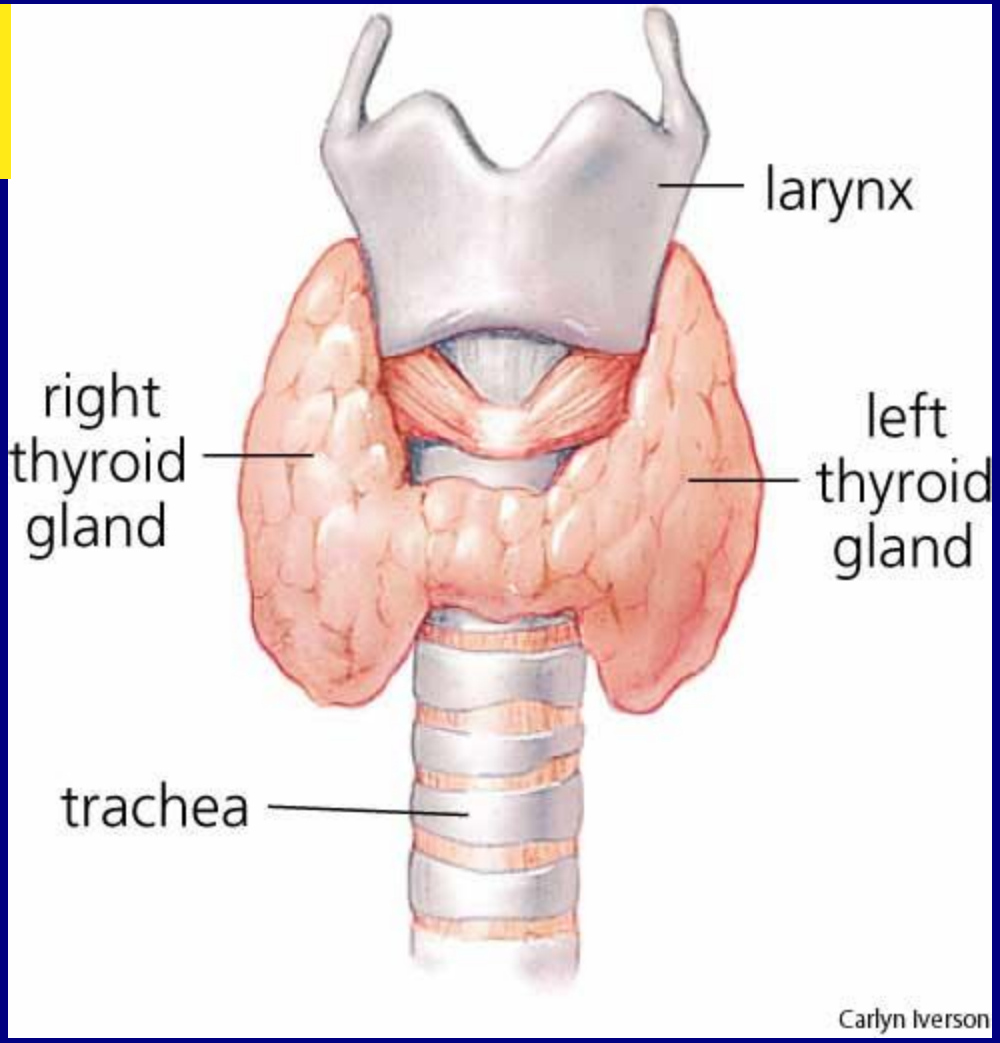
The Thyroid Gland

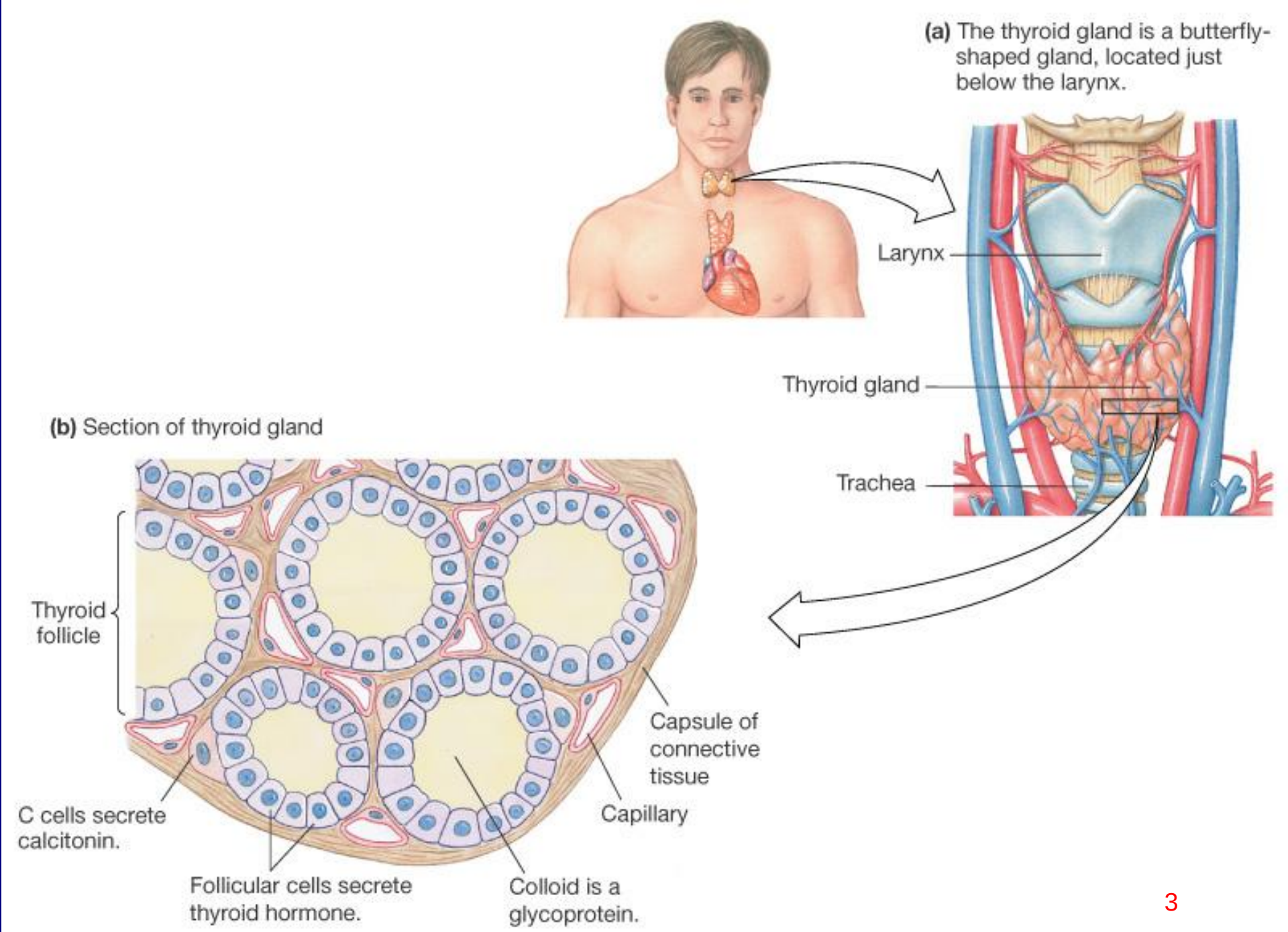
Anatomy

- Two lateral lobes, anterior to the trachea weight, 10-20g.
- Consists of follicles, contain colloid.
- Follicles synthesize thyroglobulin.
- Thyroglobulin → lumen, synthesis T_4/T_3.

Thyroid Gland







Thyroid Hormone Synthesis and Secretion

Hormone Synthesis

1. Active transport of I^- into thyroid cells (iodide trapping).
2. Iodide oxidation and iodination of tyrosine in Tg.
3. Coupling to T_3 and T_4.
4. Tg proteolysis.
5. Deiodination of iodotyrosines.
6. Intrathyroidal 5'- deiodinase $T_4 \rightarrow T_3$

Synthesis and secretion of T_3 and T_4

(1) Iodide trapping

(2) Synthesis of thyroglobulin (TGB)

(3) Oxidation of iodide

Catalysed by peroxidase enzyme

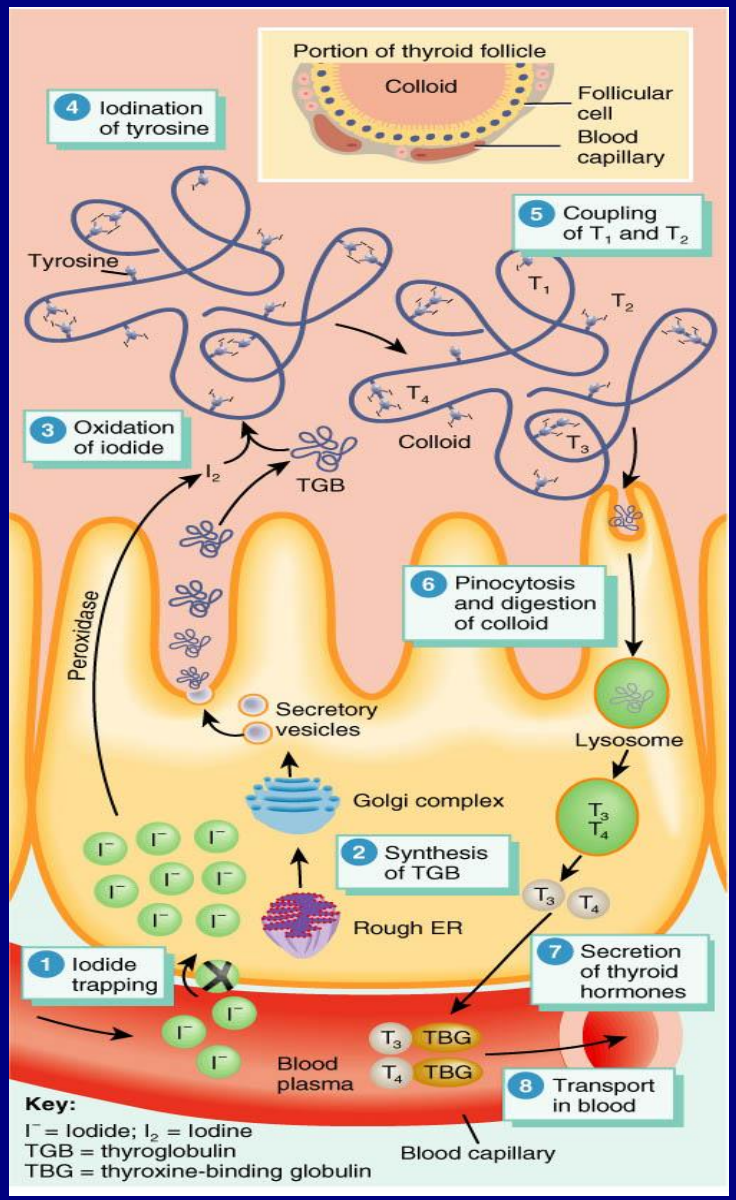
(4) Iodination of tyrosine

1-2 iodine ions bind to tyrosine to form MIT (T_1) or DIT (T_2)

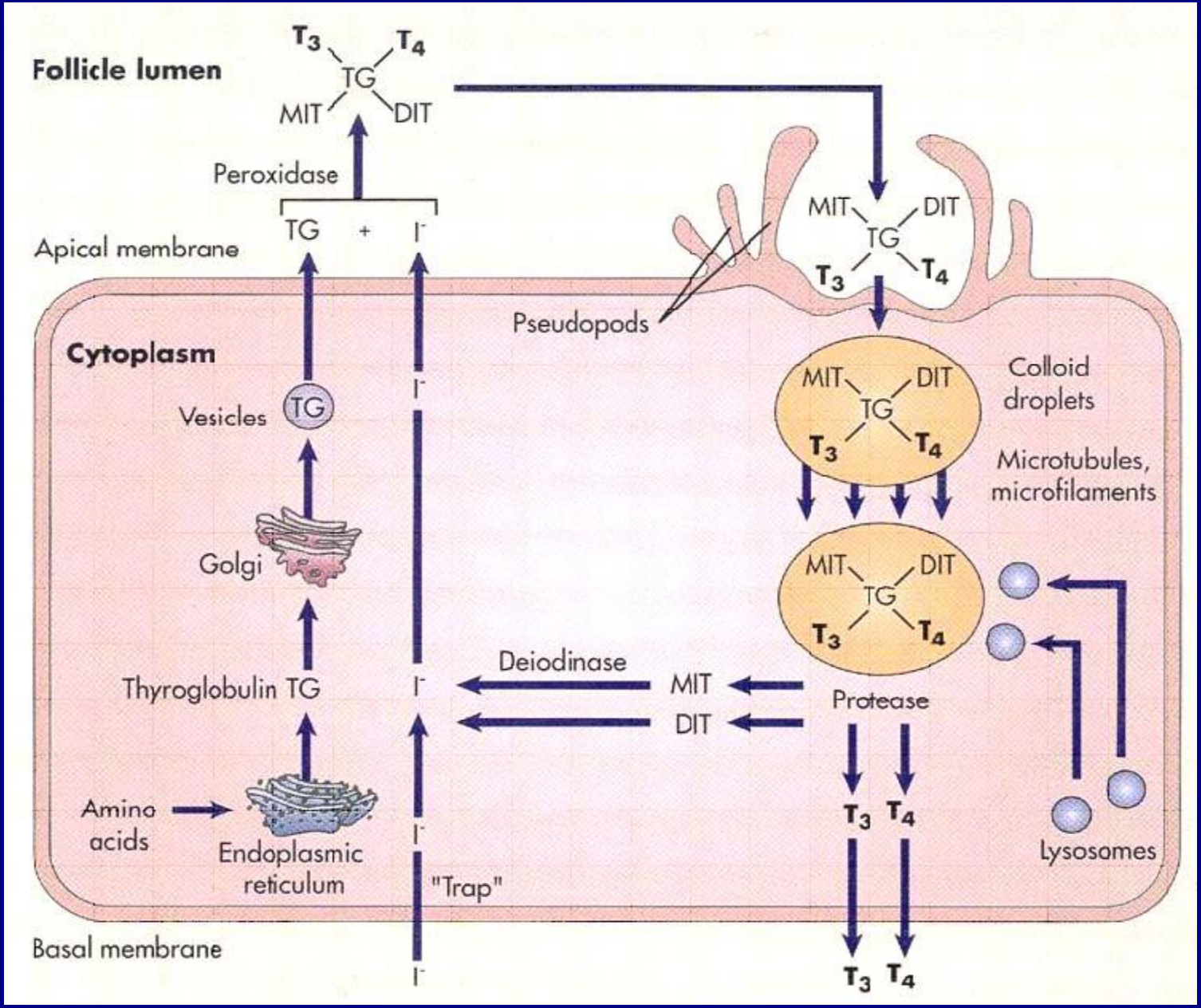
(5) Coupling of T_1 and T_2

2 x DIT molecules join to form T_4

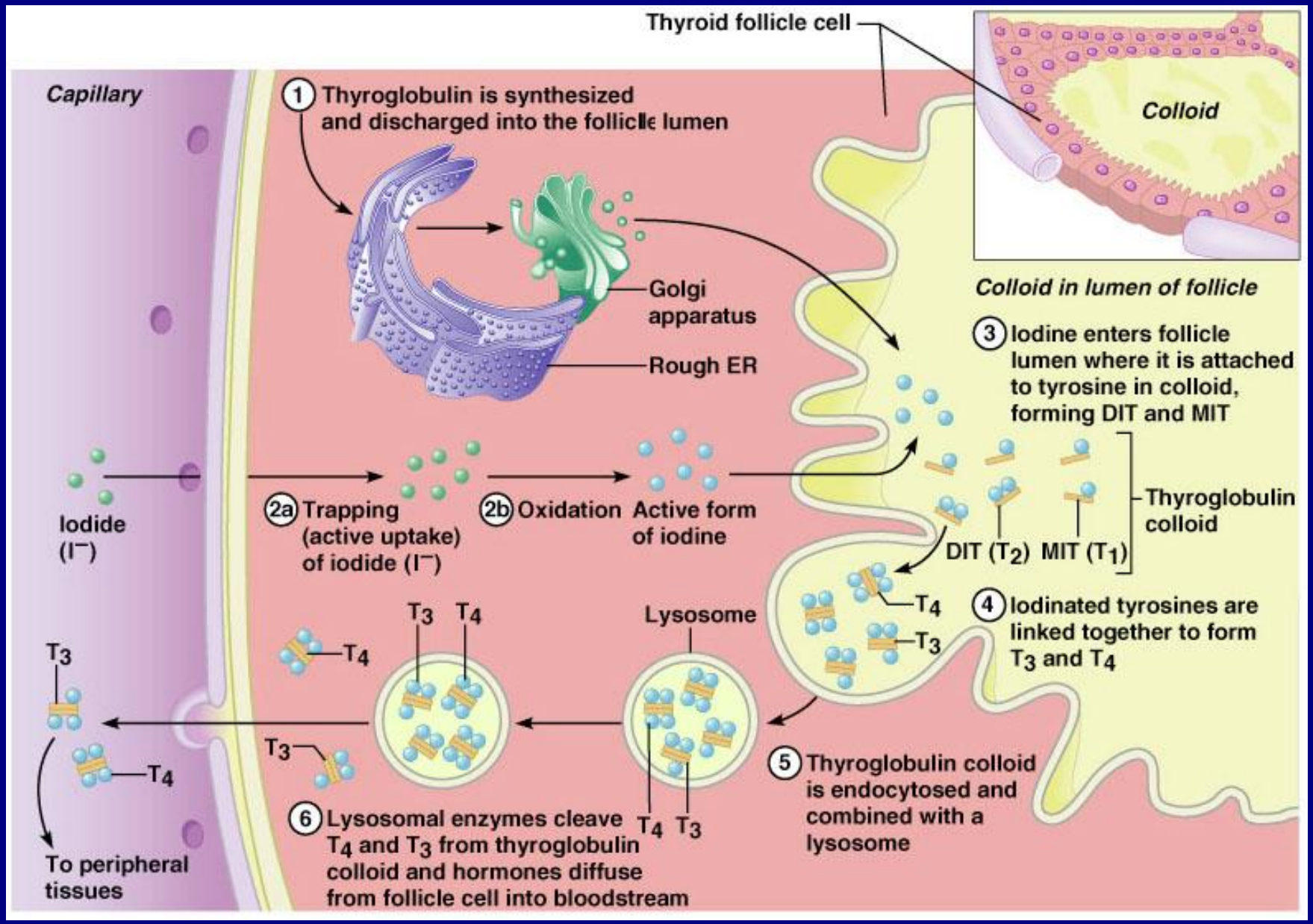
1 x MIT + 1 x DIT join to form T_3



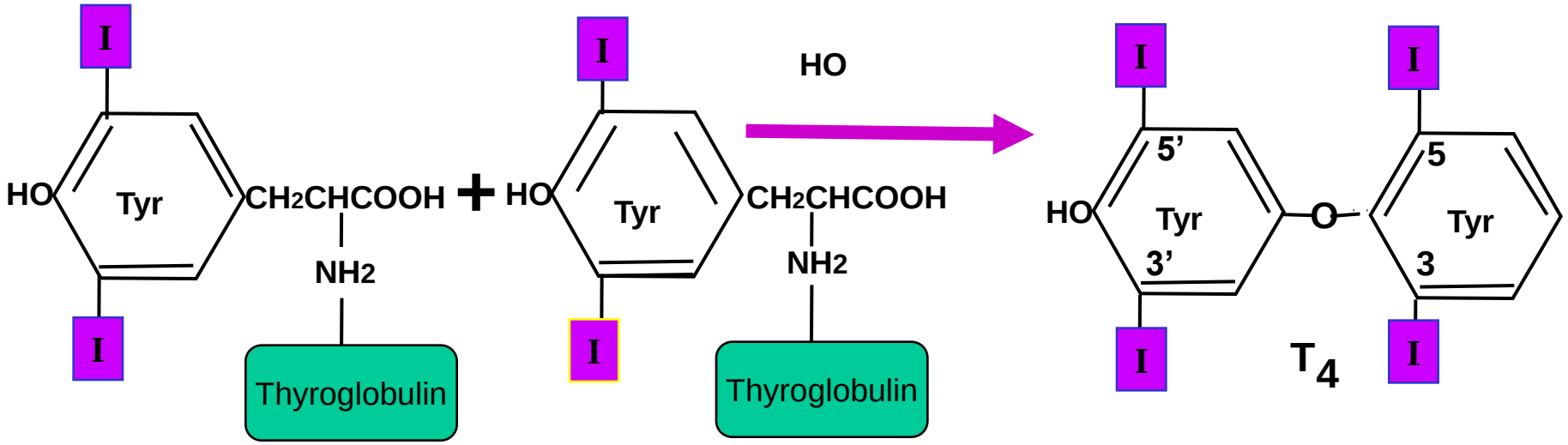
Synthesis and secretion of T_3 and T_4



Synthesis and secretion of T_3 and T_4



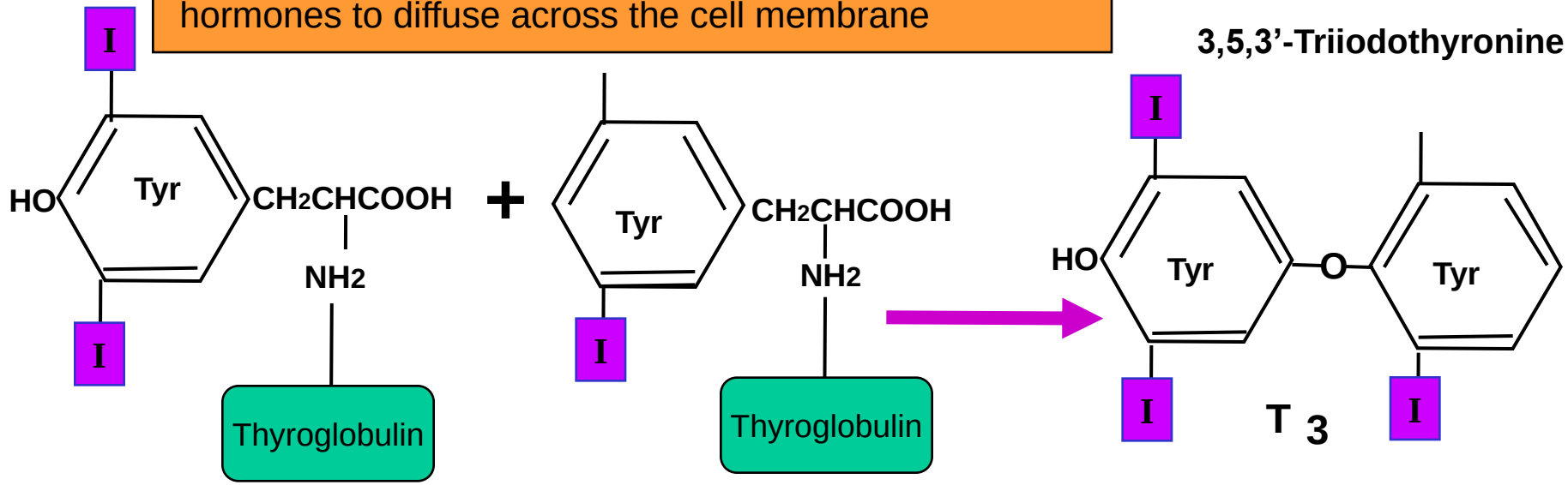
SYNTHESIS OF THYROID HORMONES: STEP- 2 COUPLING OF IODOTYROSINES



3,5,3'5'-tetraiodothyronine

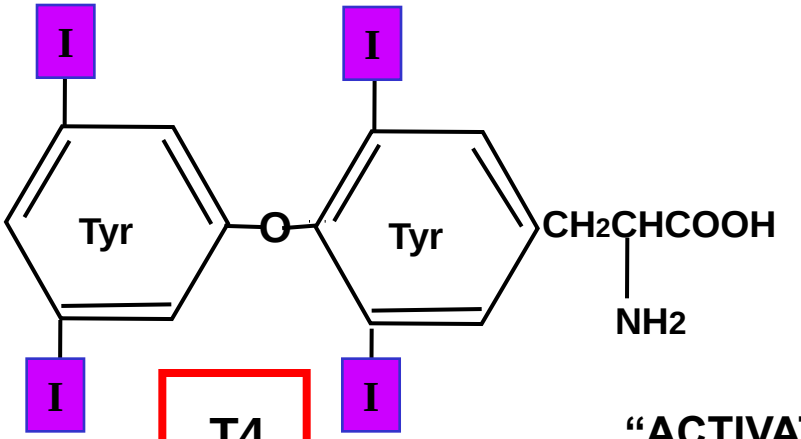
Coupling of iodotyrosine moities results in the loss of the peptide linkage to thyroglobulin allowing thyroid hormones to diffuse across the cell membrane

3,5,3'-Triiodothyronine



STEP 3
DEIODINATION

3,5,3'5'-tetraiodothyronine



"DEACTIVATION" PATHWAY

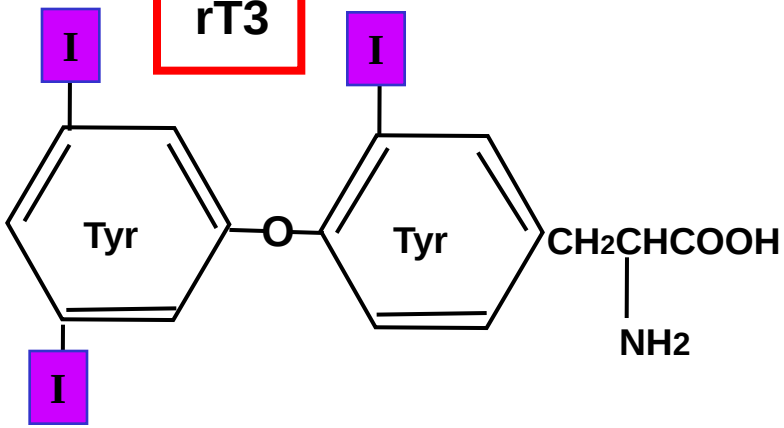
T4

"ACTIVATION" PATHWAY

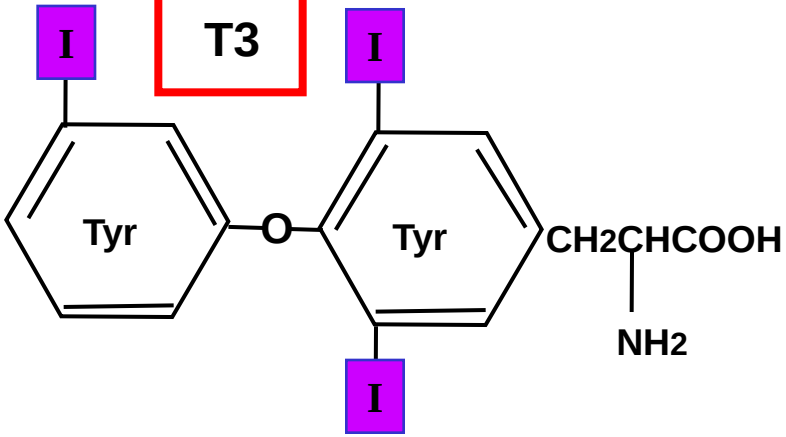
5-deiodination

5'- deiodination

rT3



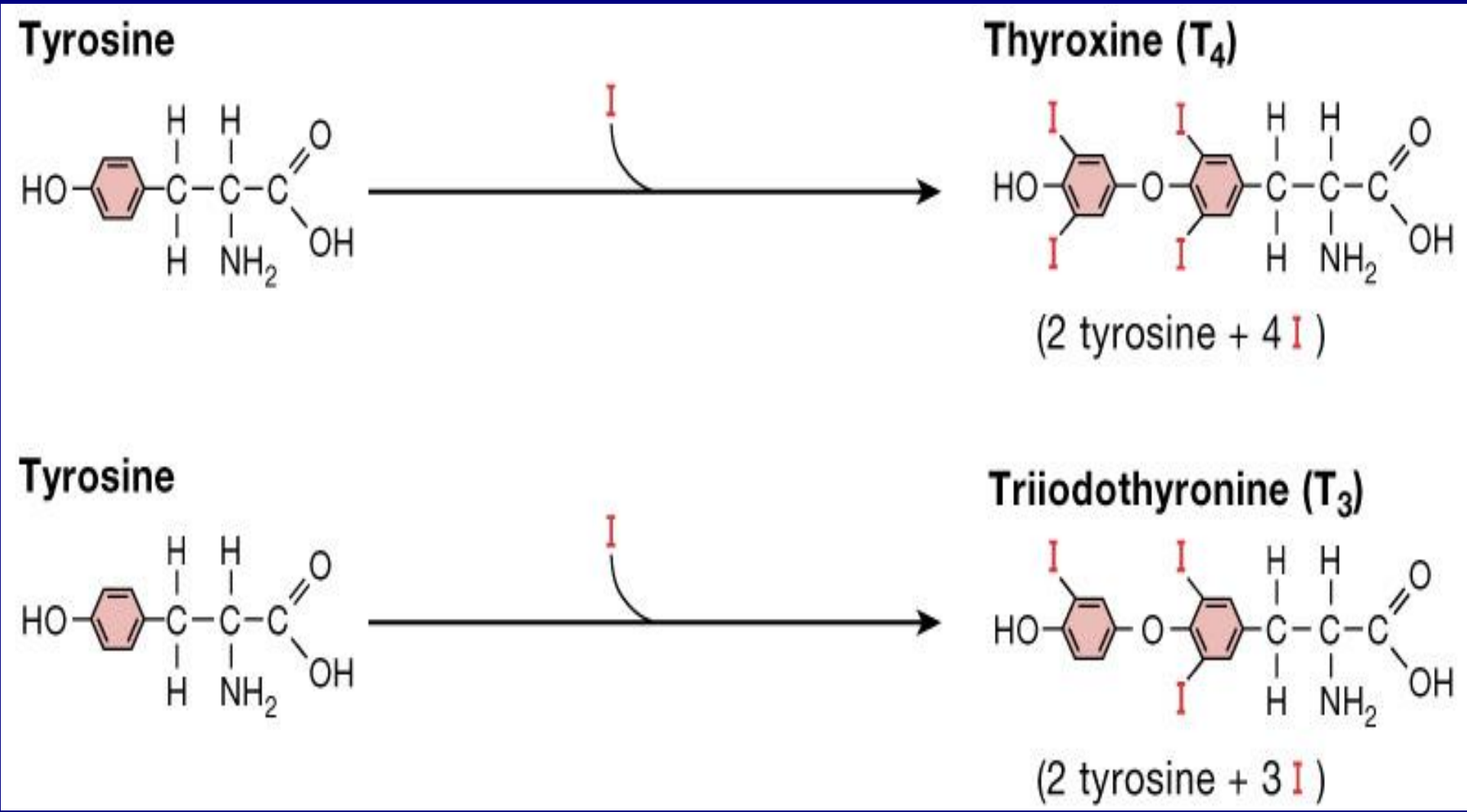
T3



3,3',5'-Triiodothyronine (reverse T3)

3,5,3'-Triiodothyronine (T3)

Thyroxine and its precursors: Structure & Synthesis



Dietary Iodine

- Food, coastal area
- Thyroid traps iodide
- RDA: 150 µg - adults

Thyroglobulin

- Large glycoprotein, MW 660,000. Dimer.
- Four tyrosyl sites for hormogenesis on Thyroglobulin (Tg).
- TSH ↑ , T_3↓ Tg gene.
- mRNA → RER → Golgi (glycosylation) exocytotic vesicles.
- Release Tg into the follicular lumen.

Iodide Trap (Iodide transport)

- Na^+/I^- symporter (NIS), intrinsic membrane protein, basement membrane.
- Apical surface: pendrin carries I^- → colloid
- TSH ↑ NIS
- TSH receptor stimulated antibody (Grave's disease) ↑ NIS
- Perchlorate (ClO_4^-), SCN^-, NO_3^- ↓ NIS

Thyroid Peroxidase

- Membrane – bound glycoprotein MW 102,000 (apical cell surface) Oxidation of iodide ions by H_2O_2.
- NADPH: generation of H_2O_2.
- Iodination of tyr on Tg.
- RER → Golgi → exocytotic vesicles to apical cell surface.
- TSH ↑ thyroidal peroxidase.

Thyroperoxidase

- **Iodination of Tyrosines in Thyroglobulin**

  (H_2O_2) generated by NADPH

- **Coupling of Iodotyrosines**

  Dimeric structure of Tg is essential.

  DIT + DIT $\rightarrow T_4$, DIT + MIT $\rightarrow T_3$

- Thiocarbamide drugs (Polythiouracil PTU, carbimazole) $\rightarrow \downarrow$ thyroperoxidase (treatment of hyperthyroidism).

Proteolysis of Thyroglobulin

- Lysosomal enzymes fused with colloid vesicles.
- Releasing T_4, T_3, DIT, MIT, peptide fragments, a.as.
- T_3/T_4 released into circulation (stimulated by TSH).
- DIT/MIT deiodinated (I^- conserved)
- Lithium ↓ Tg proteolysis.

Abnormalities in Thyroid Hormone Synthesis

- **Inherited metabolic Defects**

  Dyshormonogenesis (any phase)

  Thyroid enlargement – goiter

  Mild-severe hypothyroidism

  ↓ T_3/T_4, ↑ TSH

- **Effect of Iodide deficiency**

  Low iodine diet: ↑ MIT/DIT, ↑ T_3/T_4 ratio (↑ 5'- deiodinase) , ↓ T_4 secretion, ↑ TSH, goiter.

  Neonate: Cretinism

Abnormalities in Thyroid Hormone Synthesis…

Effect of iodine Excess

- Wolff – Chaikoff Effect: ↑ Iodide (diet) initially ↑organification up to a certain level then ↓ organification due to ↓ H_2O_2

- Effect is transient, normal gland "escapes“ from I^- effect

Thyroid Hormone Transport

T_3/T_4 transport in serum bound to:

1. Thyroxine – binding globulin (TBG) 70%
2. Thyroxine – binding prealbumin (TBPA) or transthyretin
3. Albumin 15%

Free Hormone "active"

0.04% T_4, 0.4% T_3

Metabolism of thyroid Hormones

T_4 100 nmol/day, T_3 5 nmol, rT_3 < 5 nmol

5' - Deiodination

Type 1 (5' – deiodinase)

In liver, kidney, thyroid, muscle

To provide T_3 to the plasma

↑ in hyperthyroidism ↓ in hypothyroidism

Inhibited by PTU

Dietary deficiency of Selenium inhibits $T_4 \rightarrow T_3$

Type 2 (5' – deiodinase)

Brain and pituitary, maintain intracellular T_3 to CNS

Resistant to PTU, sensitive to T_4

Metabolism of thyroid Hormones …

5’ – Deiodination …

Type 3 (5 – deiodinase)

Placenta, glial cells

Inactivation of T4 and T3

$T_4 \rightarrow rT_3$

$T_3 \rightarrow 3,3' - T_2$

↑ in hyperthyroidism (protects fetus and brain from ↑ or ↓ T4)

Function of Deiodinases

- Local Tissue and cellular control of thyroid activity
- Adapt to environment such as state of I^- deficiency
- 80% of T_4 metabolized by deiodination:

  35% to T_3, 45% to rT_3

Half – Life

T_4 7 days, T_3 1 day, rT_3 0.2 day.

Control of Thyroid Function

1. Hypothalamic – pituitary thyroid axis

   TRH → ↑ TSH → ↑ thyroid gland growth and hormone secretion

1. Deiodinases $T_4 \rightarrow T_3$
2. Iodine supply
3. TSH – receptor autoantibodies

   (Agonists, Antagonists)

Thyrotropin – Releasing Hormone -TRH

- TRH binds to thyrotrophs and Lactotrophs ↑ TSH and PRL
- T_3 ↓ TRH receptor, E_2 ↑ TRH receptors and sensitivity.
- TRH: release of stored TSH, ↑ hormone synthesis.
- THR receptor: seven–transmembrane – GTP

  ↑ phospholipase C IP_3 → ↑ Release

  ↑1,2 DAG → PKC → ↑ hormone synthesis
- TRH ↑ glycosylation of TSH (full biological activity)

Control of Thyroid Function: Effect of T_3

- T_3 directly inhibits TRH gene transcription.
- $T_4 \downarrow$ TRH synthesis and release (through T_3)

TSH secretion

- Circadian rhythm, pulsatile (nocturnal surge)
- Cold (animals and newborn only): ↑ TRH, TSH (not in adults).
- T_3, T_4, α-adrenergic agonists, ADH → ↑ TRH.

TSH: Effects

- Accelerates Tg resorption, ↑ lysosomal formation → Tg hydrolysis
- Cell growth → thyroid enlargement
- ↑ All phases of I^- metabolism:

  ↑ I^- uptake, transport, iodination of Tg → secretion of T_3/T_4.

  cAMP → ↑ I^- transport

  IP_3, Ca^{++} → iodination of Tg.

TSH: Effects …

- ↑ mRNA for Tg and thyroperoxidase.
- ↑ Type 1 5'- deiodinase.
- Glucose uptake, O_2 consumption, glucose oxidation via HMP (NADPH) and krebs cycle (ATP).

TSH Secretion

- Intrathyrotroph T_3 controls TSH mRNA, TSH release
- TRH: glycosylation, activation and release of TSH
- Somatostatin, dopamine, (bromocriptine), Glucocorticoids: ↓ TSH

The Actions of Thyroid Hormones:
1. Thyroid Hormone Receptor

- **Structure**
  - Within the cell $T_4 \rightarrow T_3$ by 5'- deiodinase.
  - Receptor family: T_3, glucocorticoids, mineralocorticoids, estrogens, progestins, vitamin D_3, retinoic acid, retrovirus v-erb A.

The Actions of Thyroid Hormones:
1. Thyroid Hormone Receptor …

- **TR Gene**
  - **Two genes**: α and β (TR α1 & 2; TR β1 & 2).

    TR α2: does not bind T_3, inhibits T_3 action.
  - Thyroid receptor: three domains:

    N-terminal (ligand-independent).

    DNA binding: two cysteine – Zn "fingers".

    C-terminal (ligand binding).

The Actions of Thyroid Hormones:
1. Thyroid Hormone Receptor …

DNA binding

- Thyroid hormone receptors (TR) bind to specific thyroid hormone response element (TRE) sites on DNA.
- Form heterodimers: with retinoid × receptor (R×R) or retinoic acid receptor (RAR).
- In absence of T_3, corepressors suppress gene.

The Actions of Thyroid Hormones:
1. Thyroid Hormone Receptor …

T_3 binding

- Disruption of TR homodimers or heterodimers on TRE.
- Displacement of corepressors.
- Binding of coactivators.
- Activates gene transcription.

Physiologic Effect of Thyroid Hormones

- **Genomic actions**: tissue growth, brain maturation, ↑ heat production and O_2 consumption due to ↑ Na^+-K^+ ATPase and ↑ β-adrenergic receptors.
- **Non-genomic Action**: ↓ pituitary type 2 5'- deiodinase ↑ glucose and amino acid transport.

Physiologic Effect of Thyroid Hormones…

1. Effect on Fetal Development:

- Thyroid in fetus begins 11 wks, T_3/T_4 secretion 18-20 wks.
- Placental type 3 5-deiodinase → inactivation of most T_3/T_4.
- ↓ fetal T_3: cretinism (mental retardation and dwarfism).

Physiologic Effect of Thyroid Hormones…

2. **Effect on O_2 consumption and Heat Production**
   - Due to ↑ Na^+– K^+ ATPase except in brain, spleen, testis
3. **Cardiovascular Effects**
   - ↑ myosin heavy chain α improving cardiac output
   - ↑ Ca^{++} ATPase in sarcoplasmic reticulum
   - ↑ β adrenergic receptors.
   - ↑ Cardiac output, heart rate in hyperthyroidism

Physiologic Effect of Thyroid Hormones…

4. Sympathetic Effects

- T_3 ↑ β-adrenergic receptors in heart, skeletal, adipose tissue.
- Sensitivity to catecholamine ↑ in hyperthyroidism
- β-adrenergic blockers controls tachycardia and arrhythmias.

5. Hematopoietic Effects

- T_3 ↑ erythropoietin – erythropoiesis.
- ↑ 2,3- DPG ↑ O_2 dissociation from Hb.

Physiologic Effect of Thyroid Hormones…

6. G.I. Effects

- T_3 ↑ gut motility, diarrhea.
- (Hyperthyroidism) → weight loss
- (Hypothyroidism) → weight gain

7. Skeletal Effects

- T_3 ↑ bone turnover, ↑ bone resorption,
- Hyperthyroidism → osteopenia, hypercalcemia, hypercalciuria.

Physiologic Effect of Thyroid Hormones…

8. Neuromuscular Effects

- Hyperthyroidism: ↑ protein turnover, myopathy, hyperflexia
- T_3: CNS development + function
- Adults: hypothyroidism → sluggishness

9. Endocrine Effect

- T_3 ↑ cortisol turnover; ↑ Rate of cortisol production.
- Ovulation impaired in hypo- and hyperthyroidism (infertility).

Physiologic Effect of Thyroid Hormones…

10. Effects on Lipids and Carbohydrates

- T_3 ↑ hepatic gluconeogenesis, glycogenolysis, ↑G.I. Glucose absorption (exacerbate diabetes mellitus).
- ↑Cholesterol synthesis and degradation (↑LDL receptors) →↓ chol.
- ↑ lipolysis
- Hypothyroidism: ↑ chol. levels

Tests of Thyroid Function

1. Thyroid Hormones in Blood

- Total T_4/T_3, Free T_4/T_3, rT_3, Tg (metastasis)
- Free T_4 (FT_4) estimated using FT_4 index (FT_4I)
- FT_4 doesn't measure T_3 (early Graves' disease, T_3 toxicosis), FT_4 low, hyperthyroid state.

Tests of Thyroid Function …

2. Hypothalamic –Pituitary – Thyroid Axis

- Serum TSH: (TRH = not clinically feasible)
- FT4 α 1/log TSH
- TSH pituitary tumors: FT4 ↑, FSH not suppressed
- Hypothyroidism: ↑ TSH, ↓FT4.
- Hypothyroidism (pituitary or hypothalamic tumor): FT4 ↓, TSH not elevated, no TSH response to TRH.

Tests of Thyroid Function …

Serum TSH

Most sensitive convenient, specific test for hypothyroidism, and hyperthyroidism.

Tests of Thyroid Function …

Cardiac muscle contractility

- Time QRS complex to opening of aortic value.
- Left ventricular ejection time (LVET).
- Prolonged in hypothyroidism, shortened in hyperthyroidism.

Thyroid Autoantibodies.

- Thyroglobulin antibody (Tg Ab)
- Thyroperoxidase antibody (TPO Ab)
- TSH receptor antibody (TSH-R Ab [stim] or [block])

Disorders of the Thyroid

Patients usually complain of:

1. Thyroid enlargement (diffuse or nodular)
2. Thyroid deficiency (hypothyroidism)
3. Thyroid hormone excess (hyperthyroidism)
4. Complications of a specific form of hyperthyroidism: Graves' disease (with exophthalmos) and thickening of the skin over the lower legs (thyroid dermopathy)

Hypothyroidism

1. primary (thyroid failure).
2. Secondary (due to pituitary TSH deficit).
3. Tertiary (due to hypothalamic TRH deficiency).
4. Peripheral Resistance (to the action of thyroid hormone).

Hypothyroidism …

Etiology

1. Hashimoto's thyroiditis (autoimmune thyroiditis) with or without goiter. In older patients: gland destroyed by thyroperoxidase autoantibodies.
2. Radioactive iodine therapy for Graves' disease.
3. Iodine deficiency (developing countries).
4. Excessive iodide intake.
5. Drugs: Lithium carbonate (depression), PTU.

Hypothyroidism …

Pathogenesis

- Accumulation of glycosaminoglycans.
- ↑ hyaluronic acid in interstitial tissues.
- ↑ Capillary permeability to albumin.
- Interstitial edema (skin, heart muscle, striated muscle).

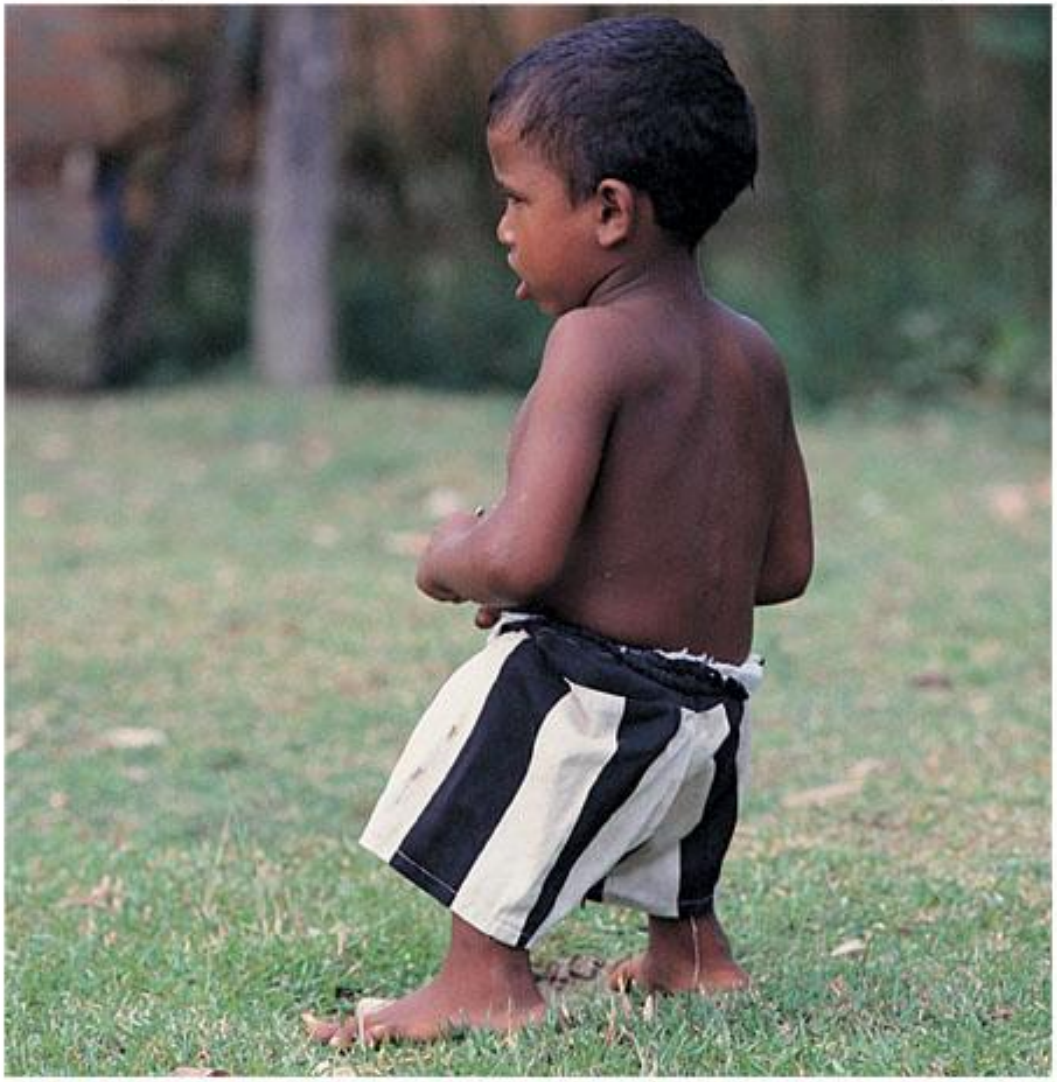
Hypothyroidism …

Clinical Presentations

a. Newborn Infants (Cretinism)

- Goiter, mental retardation, short stature, puffy face and hands, deaf.
- Due to:
  - Failure of thyroid to descend.
  - Placental transfer of TSH-R Ab [block] from mother with Hashimoto's thyroiditis.
  - Inherited defects of T_3/T_4 biosynthesis.
- Serum T_4 < 6 µg/dL or TSH > 25 µU/ml = neonatal hypothyroidism.

Cretinism



Hypothyroidism …

Clinical Presentations ….

b. Children

- Retarded growth, mental retardation, obesity
- In adolescence: precocious puberty, short stature

Hypothyroidism …

Clinical Presentations ….

c. Adults

- Easy fatigability, coldness, weight gain, constipation, menstrual irregularities, and muscle cramps.
- Physical finings: cool, rough, dry skin; puffy face and hands; slow reflexes.
  1. Cardiovascular signs
  2. Pulmonary function
  3. Intestinal peristalsis
  4. Renal function
  5. Anemia: ↓ Hb synthesis; Fe, Folate, B_{12} deficiency
  6. Neuromuscular system
  7. CNS symptoms

Hypothyroidism …

Complications

a. Myxedema Coma

- End stage of untreated hypothyroidism.
- Progressive weakness, hypothermia, hypoventilation, hypoglycemia, water intoxication, shock and death.

b. Neuropsychiatric disease

- Depression, confusion, paranoid.

Diagnosis of Hypothyroidism

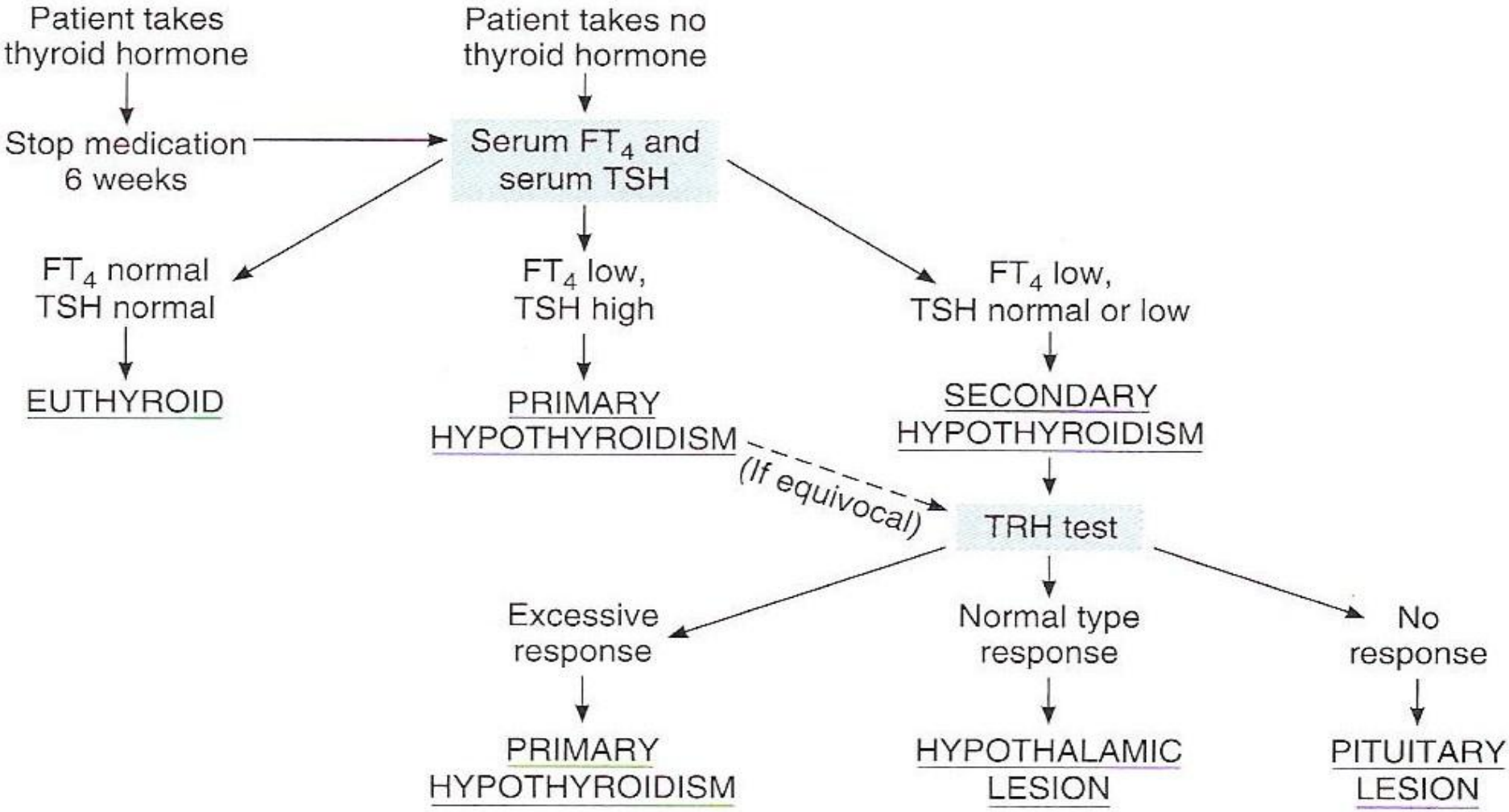


Figure 7–36. Diagnosis of hypothyroidism. Either free thyroxine (FT_4) or free thyroxine index (FT_4I) may be used with TSH for evaluation.

Hyperthyroidism and Thyrotoxicosis

Thyrotoxicosis:

Clinical syndrome when tissues are exposed to high levels of thyroid hormones.

Graves' Disease
Diffuse Toxic Goiter

Features

- Thyrotoxicosis.
- Goiter.
- Ophthalmopathy (exophthalmos).
- Dermopathy (peritibial myxedema).

Graves' Disease …

Etiology

- Autoimmune disease.
- Antibodies against TSH receptors.
- Antibodies have the capacity to stimulate. thyroid gland (growth and function).
- Antibodies: TSH–R Ab [stim].
- Genetic predisposition.

Graves' Disease …

Exophthalmos

- Cytotoxic lymphocytes (killer cells) and cytotoxic antibodies sensitized to a common antigen as TSH-R in orbital fibroblasts, orbital muscles, and thyroid tissues.
- Inflammation of orbital fibroblasts, swollen orbital muscles, periorbital edema.

- **Graves' Disease …**

Graves' Disease …

Thyroid Dermopathy

- Thickening of the skin (particularly over lower tibia).
- Accumulation of glycosaminoglycans.

Thyroid Osteopathy

- Bone swelling
- Separation of fingernails

Relationship between free T4 and TSH

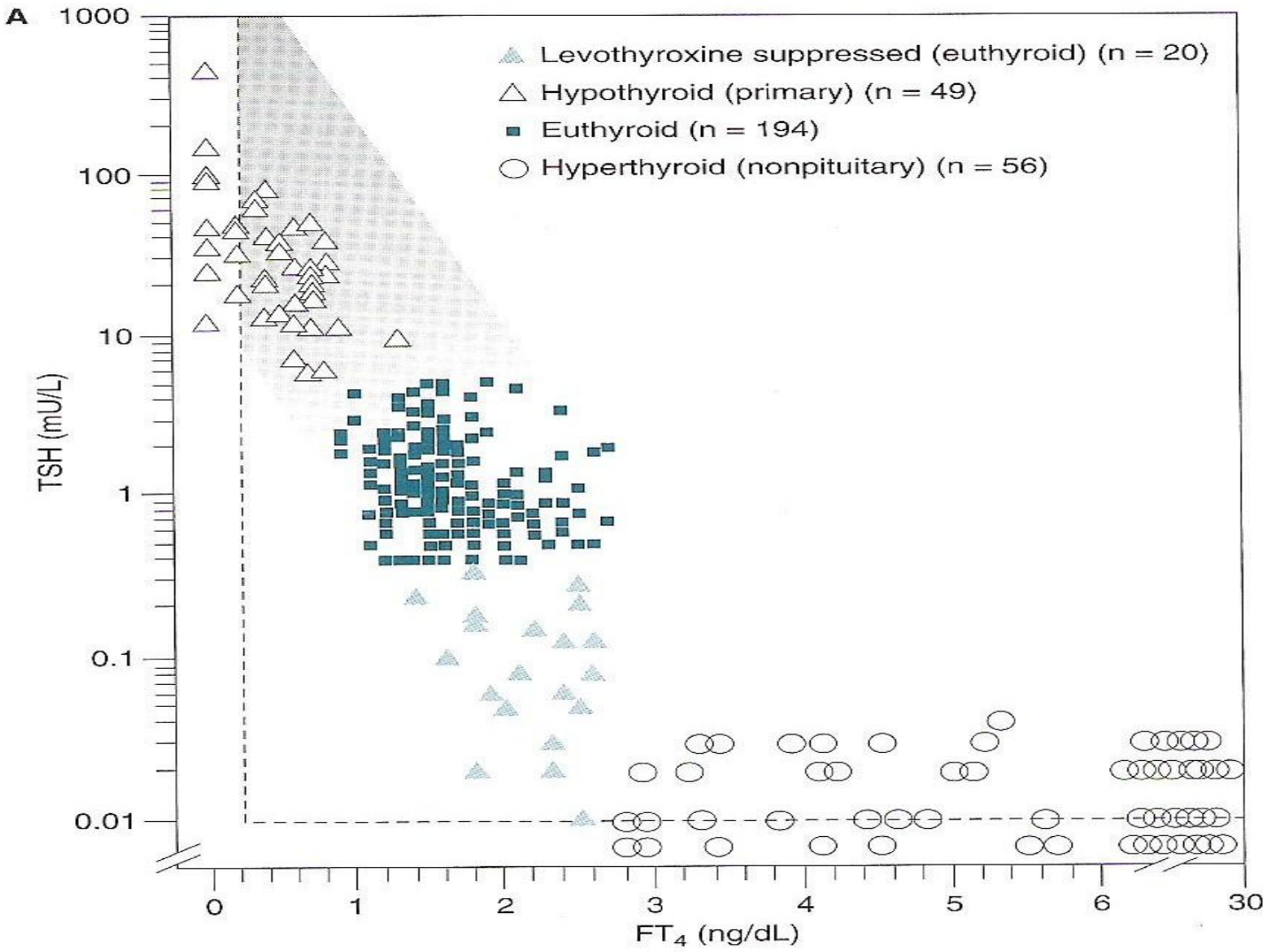


Figure 7–28. ***A:*** Relationship between serum free thyroxine by dialysis (FT_4) ng/dL and $\log_{10}$ TSH in euthyroid, hyperthyroid, hypothyroid, and L-T_4-suppressed euthyroid individuals. Note that for each unit change in T_4 there is a logarithmic change in TSH.