The Thyroid

BCH 120 — Metabolic & Endocrine Biochemistry · Dr. Radi

By the end of this unit, you can…

- Describe the thyroid gland/follicle and the systemic actions of thyroid hormone, and draw the structures of T4 and T3
- Explain thyroid hormone synthesis on thyroglobulin — iodide trapping, TPO-catalyzed iodination (MIT/DIT) and coupling to T3/T4 — plus storage, secretion, and the inhibitors of synthesis
- Explain plasma transport (bound reservoir vs active free fraction; T4 vs T3) and peripheral deiodination (selenium deiodinases; T4 → active T3 vs inactive reverse-T3)
- Trace the hypothalamic–pituitary–thyroid axis and its feedback, and how T3 regulates transcription by flipping the thyroid receptor from repressor to activator
- Describe the biological actions of T3 and the major thyroid disorders (hyperthyroidism/Graves', hypothyroidism/Hashimoto's, CIDS), their symptoms, and treatment

Today's route

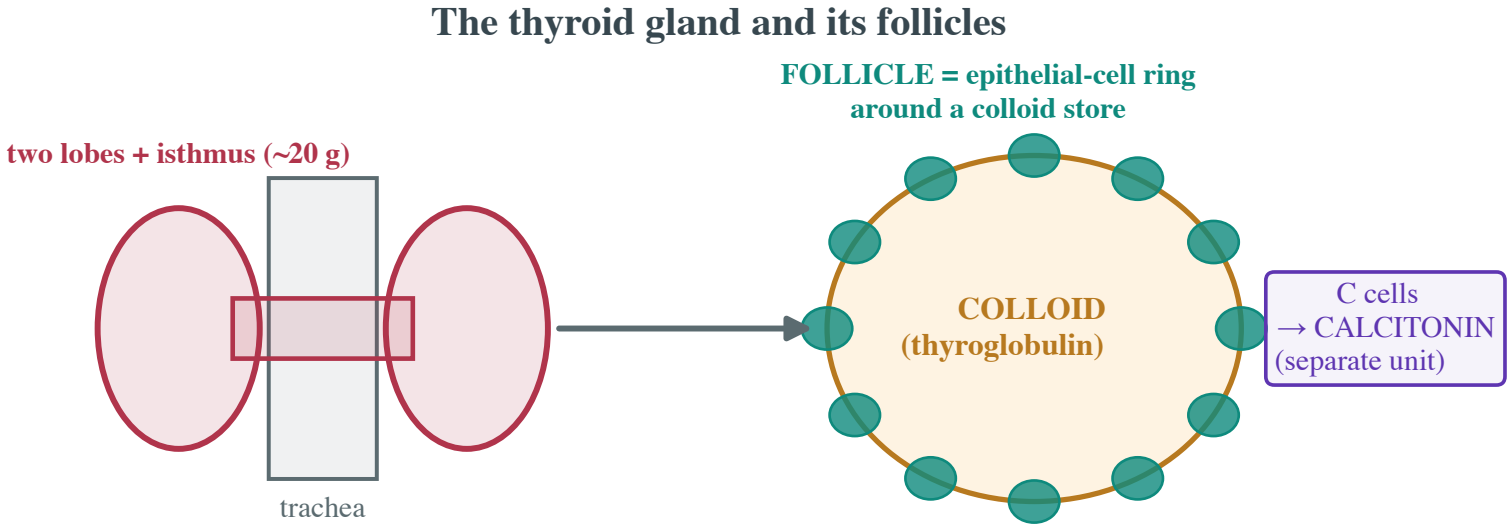
1. The Thyroid Gland & Its Hormones
2. Making Thyroid Hormone — Iodination & Coupling
3. Transport & Deiodination
4. The HPT Axis & T_3's Gene Switch
5. T_3 Actions & Thyroid Disorders

1 · The Thyroid Gland & Its Hormones

"The thyroid is the body's metabolic thermostat — a butterfly-shaped gland that touches nearly every cell. It makes two iodine-studded hormones, T4 and T3, and you need to know both their jobs and their structures."

A gland built from follicles

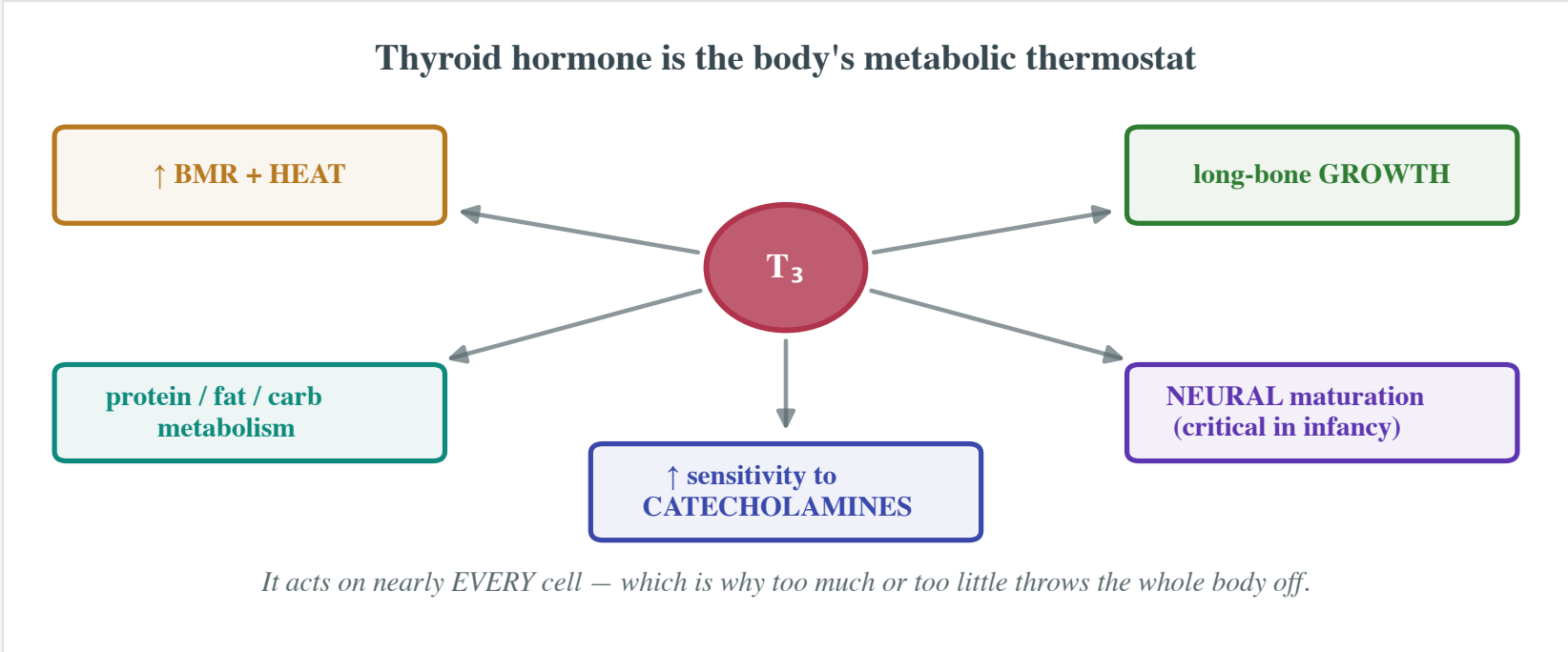
The **thyroid** sits over your trachea — **two lobes joined by an isthmus**, about 20 grams. Its working unit is the **follicle**: a single ring of **epithelial cells** wrapped around a lake of **colloid**. The epithelial cells are the **factory** (they trap iodine and build hormone); the colloid is the **warehouse** (stored hormone, weeks' worth). Scattered between the follicles are **C cells**, which make **calcitonin** — a calcium hormone we'll meet in its own unit.



The follicle is the factory: epithelial cells trap iodine and build hormone; the colloid is the warehouse.

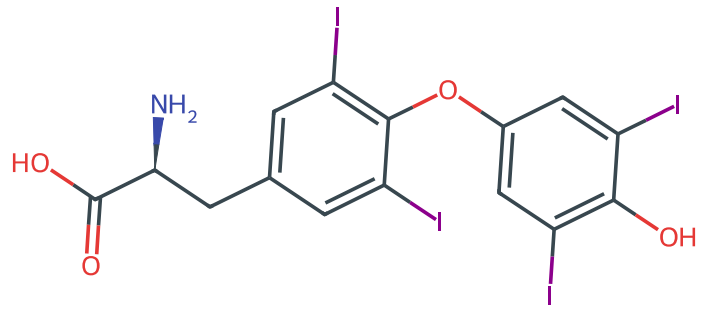
The body's metabolic thermostat

Why does the thyroid matter so much? Because its hormone acts on **nearly every cell**. It sets your **basal metabolic rate** and **heat production**, tunes **carbohydrate, fat, and protein** metabolism, drives **long-bone growth** and **neural maturation** (critical in infancy), and **sharpens your response to catecholamines** like adrenaline. When it's off — too high or too low — the **whole body** feels it. That's why thyroid disease is so common and so consequential.

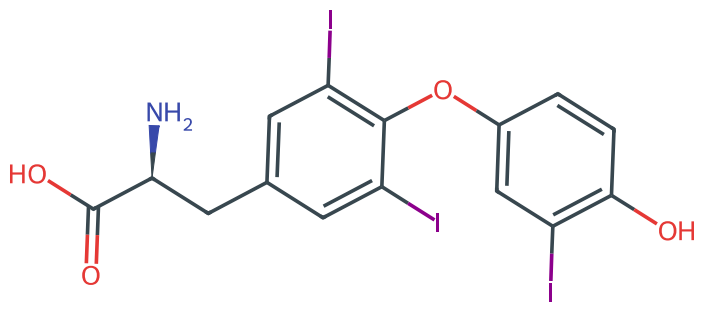


T4 and T3 — know these structures

Here are the two hormones, and **you need to be able to draw them**. Both are built from **two tyrosine-derived rings joined by an ether**, studded with **iodine**. **T4 (thyroxine)** carries **four** iodines — positions **3, 5, 3′, 5′** — and is the main form released, a long-lived **pro-hormone**. **T3** carries **three** iodines (**3, 5, 3′**) and is the **active** hormone. The count is the whole story: four = storage, three = go.



T4 (thyroxine) 4 iodines



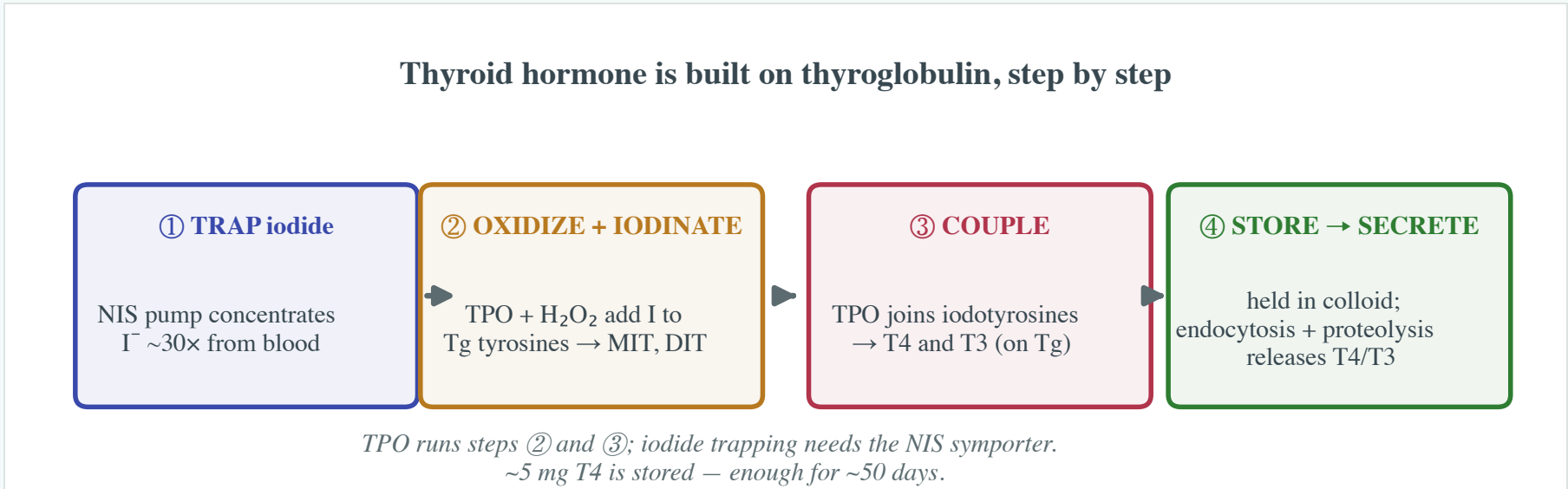
T3 (active) 3 iodines

2 · Making Thyroid Hormone — Iodination & Coupling

"Thyroid hormone is unique — it's built on a giant scaffold protein, thyroglobulin, one iodine at a time. Learn the four steps and one enzyme (thyroid peroxidase), and you'll understand both the biochemistry and every drug that treats an overactive thyroid."

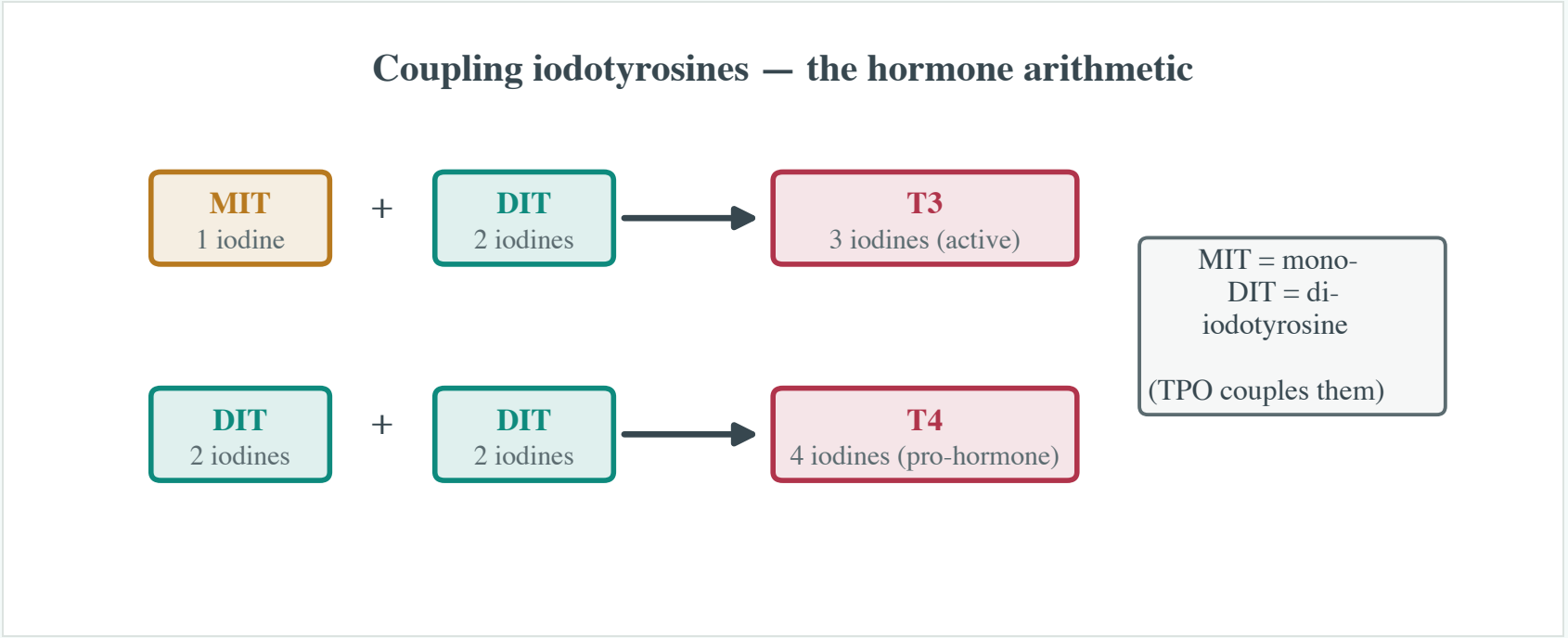
Built on thyroglobulin, step by step

Thyroid hormone synthesis is a **four-step assembly line**, and it all happens **on a scaffold protein, thyroglobulin**. **① Trap** — a pump (NIS) concentrates **iodide ~30×** from the blood. **② Iodinate** — **thyroid peroxidase (TPO)**, using **H_2O_2**, tacks iodine onto **tyrosines** in thyroglobulin (making MIT and DIT). **③ Couple** — TPO joins those iodotyrosines into **T3 and T4**. **④ Store & secrete** — the hormone waits in the **colloid** until the cell takes it back in and cuts it loose. One enzyme, TPO, runs the two chemistry steps.



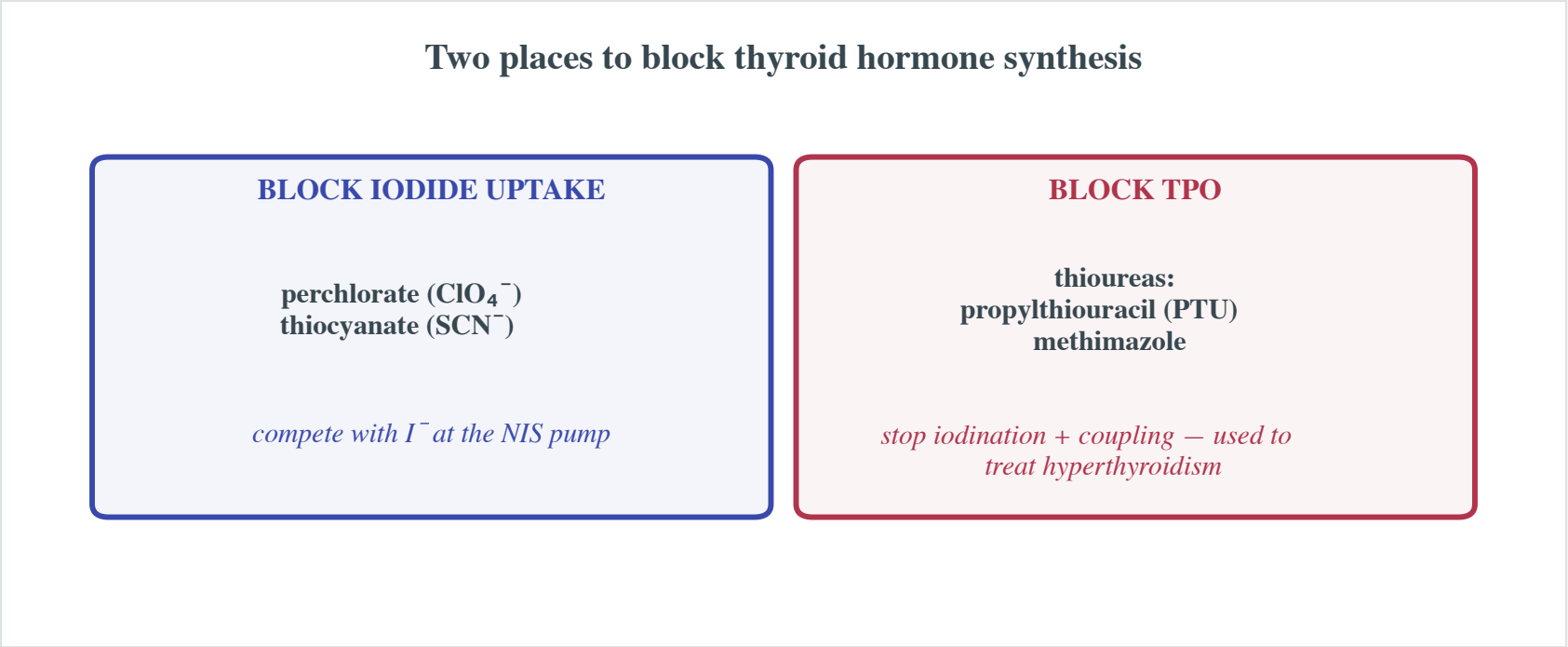
The coupling arithmetic

Here's the part students love, because it's just addition. Iodinated tyrosines come in two sizes: **MIT** (one iodine) and **DIT** (two iodines). Couple a **MIT + DIT** and you get **T3** — three iodines, the active hormone. Couple **DIT + DIT** and you get **T4** — four iodines, the pro-hormone. That's it: the number of iodines on each partner adds up to the hormone. TPO does the joining.



Two places to block it

Because synthesis is a defined pathway, we can **stop it at two points** — which is exactly how we treat an **overactive** thyroid. **Block iodide uptake**: **perchlorate** and **thiocyanate** compete with iodide at the NIS pump. **Block TPO**: the **thioureas** — **propylthiouracil (PTU)** and **methimazole** — shut down iodination and coupling directly. Know the two targets and you know the drug classes: no iodine in, or no enzyme to use it.

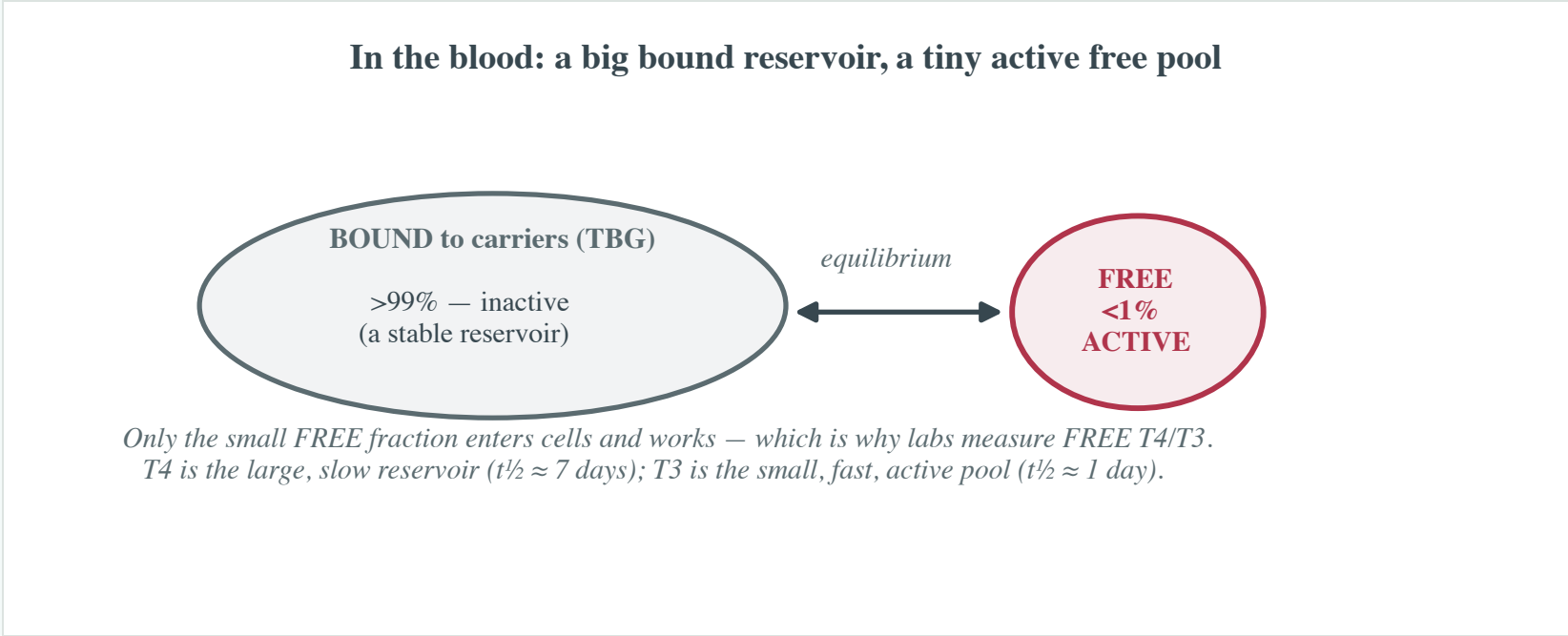


3 · Transport & Deiodination

"Once thyroid hormone hits the blood, two things happen that shape its whole biology: almost all of it rides bound to carrier proteins (only the free bit works), and the tissues get the final say — activating T4 into T3, or shutting it down into reverse-T3."

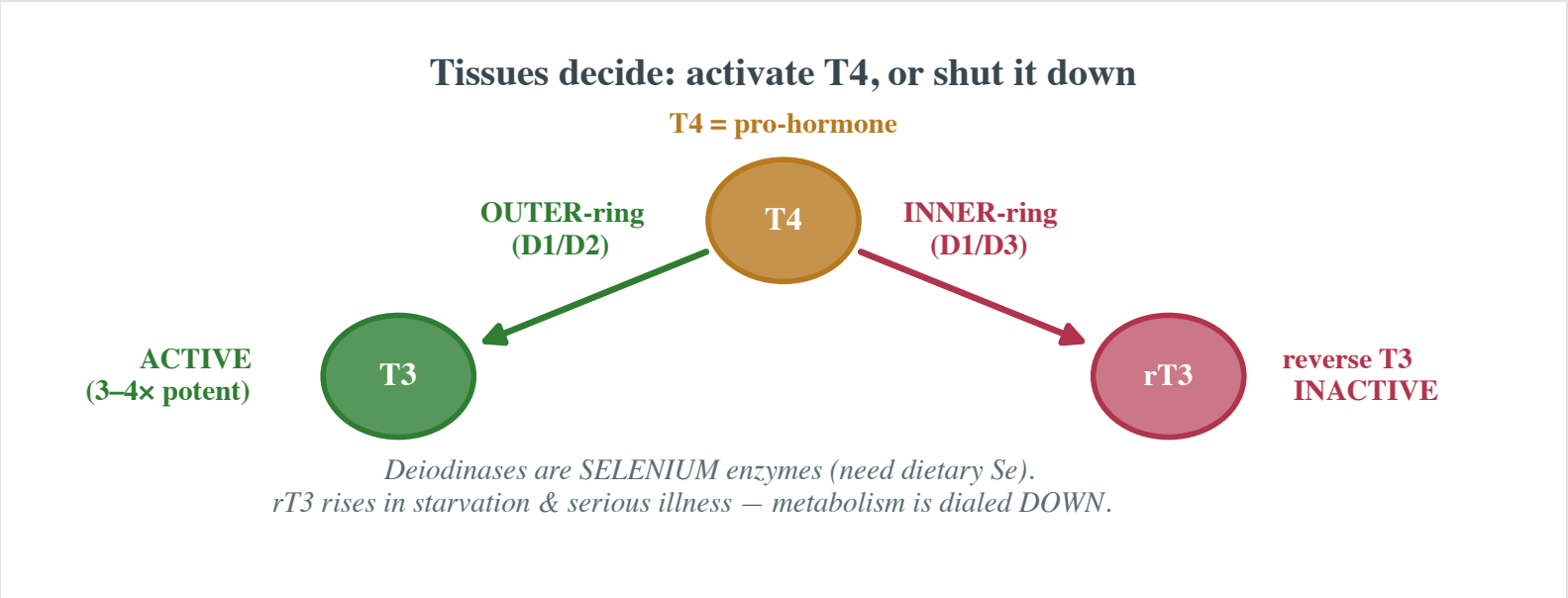
A big bound reservoir, a tiny active pool

In the blood, **over 99%** of thyroid hormone rides **bound to carrier proteins** (thyroxine-binding globulin and friends) — and while it's bound, it's **inactive**. Only the **small free fraction** can enter cells and act. That's why the lab measures **free T4/T3**, not total. And the two hormones play different roles: **T4** is the **large, slow reservoir** (half-life ~7 days); **T3** is the **small, fast, active** pool (half-life ~1 day). Bulk storage versus the working currency.



Tissues activate — or silence — T4

Here's the elegant control: **T4 is a pro-hormone**, and each tissue decides what to do with it using **deiodinases** (which are **selenium** enzymes — so you need dietary selenium). Chop an iodine off the **outer ring** (D1/D2) → **T3**, the **active** hormone. Chop one off the **inner ring** (D1/D3) → **reverse T3 (rT3)**, which is **inactive**. So the same T4 can be turned **up** or **down** locally. In **starvation and serious illness**, the body shunts toward rT3 — dialing metabolism **down** to conserve fuel.

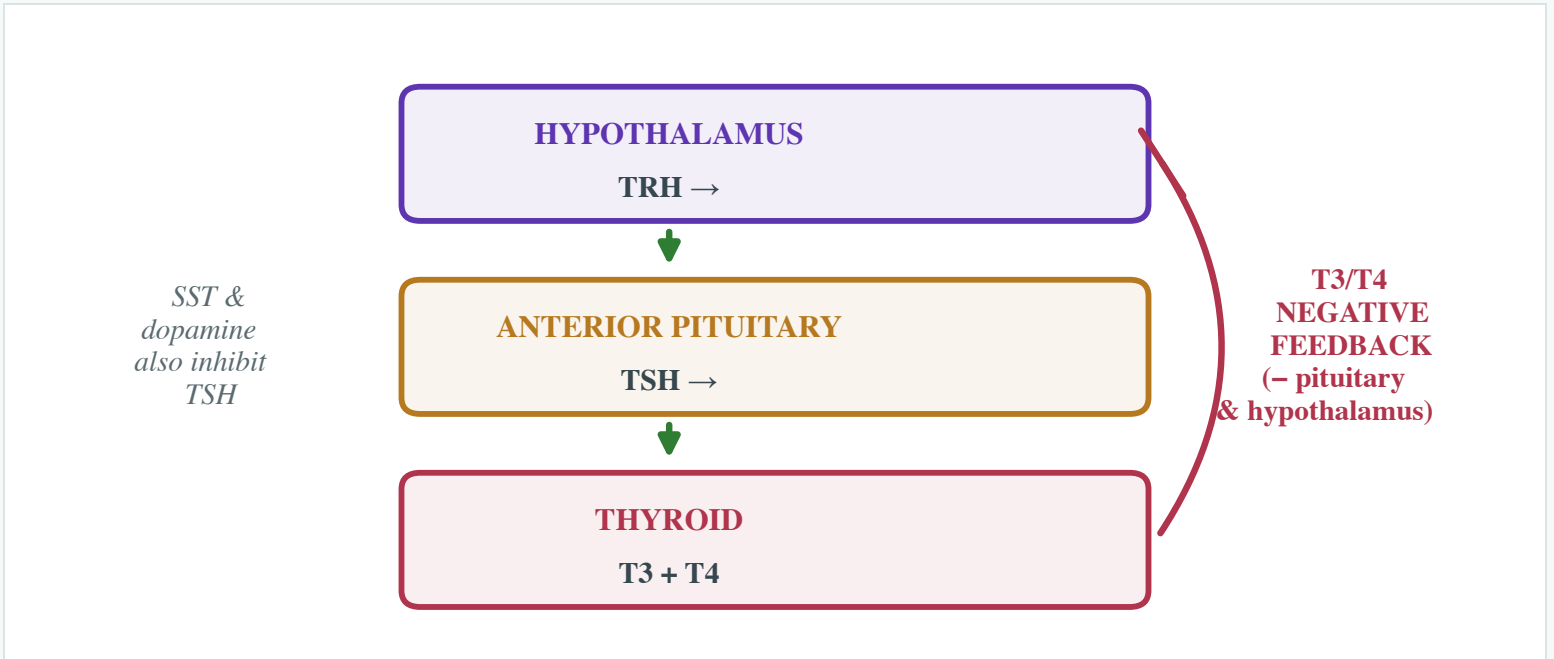


4 · The HPT Axis & T_3's Gene Switch

"Thyroid output is governed by the classic three-tier feedback loop — hypothalamus, pituitary, thyroid. And down at the molecule, T_3 does something clever: it doesn't just turn a gene on, it releases a brake that was actively holding it off."

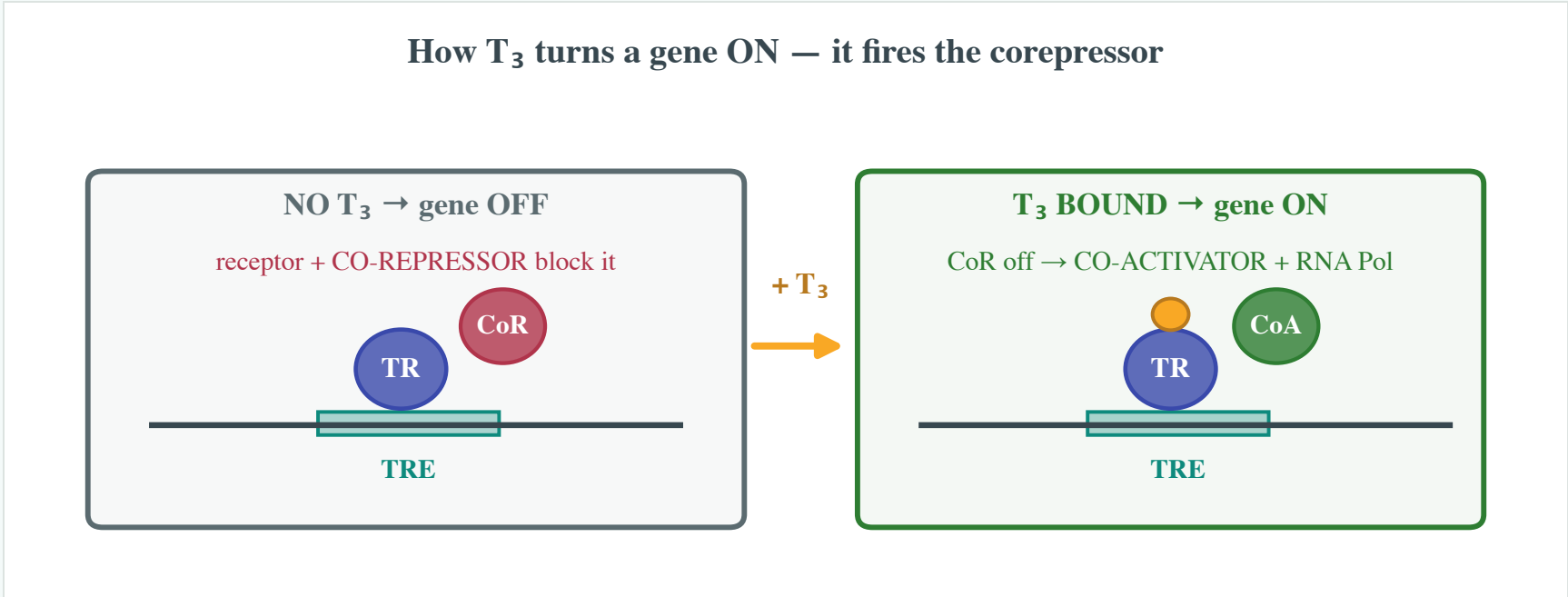
The HPT axis and its feedback

Thyroid hormone runs on a **three-tier axis**. The **hypothalamus** sends **TRH**, which tells the **anterior pituitary** to release **TSH**, which drives the **thyroid** to make **T3 and T4**. Then comes the control knob: circulating **T3/T4 feed back negatively** on both the pituitary and hypothalamus, throttling TSH so levels stay steady. A neat detail — the **pituitary makes its own T3** (via deiodinase) so it can **sense** the T4 in your blood. Somatostatin and dopamine nudge TSH down too.



How T_3 flips a gene ON

Now the molecular trick, and it's not what you'd guess. The **thyroid receptor (TR)** is already sitting on the DNA at a **thyroid response element** — but with a **co-repressor** bound, it's **actively holding the gene OFF**. When **T3 arrives** and binds the receptor, it triggers a shape change that **kicks the co-repressor off** and pulls in **co-activators and RNA polymerase**, switching the gene **ON**. So T3 doesn't push the gas — it **releases the brake**. Elegant, and worth remembering.

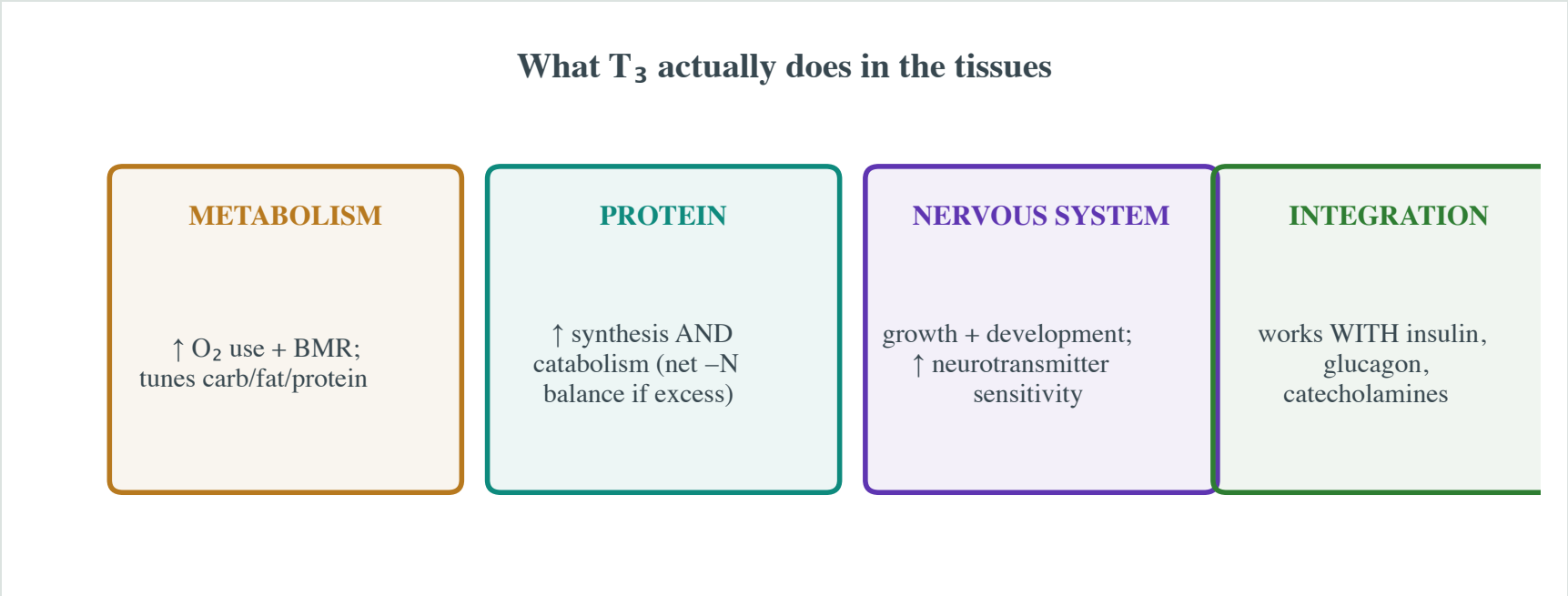


5 · T_3 Actions & Thyroid Disorders

"Put it together: what T_3 actually does in your tissues, and what happens when the thyroid runs too hot or too cold. Two of the most common autoimmune diseases in medicine live here — Graves' and Hashimoto's — and they're mirror images."

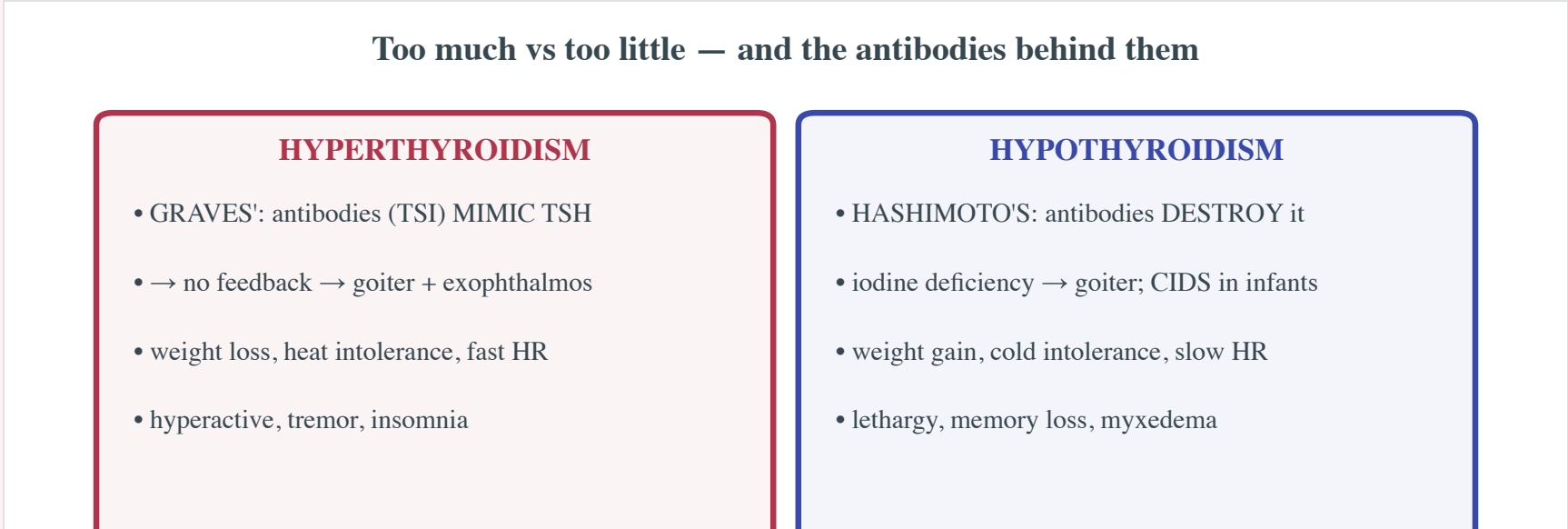
What T_3 does in the tissues

Once T3 is inside and switching genes, the effects are **body-wide**. It **raises oxygen consumption and BMR** (the metabolic engine). It boosts **protein synthesis — but also catabolism**, so in excess it pushes you into **negative nitrogen balance**. It's essential for **nervous-system growth and development** and cranks up **neurotransmitter sensitivity**. And it **integrates** with insulin, glucagon, and catecholamines to touch **all** of intermediary metabolism. One hormone, wired into everything.



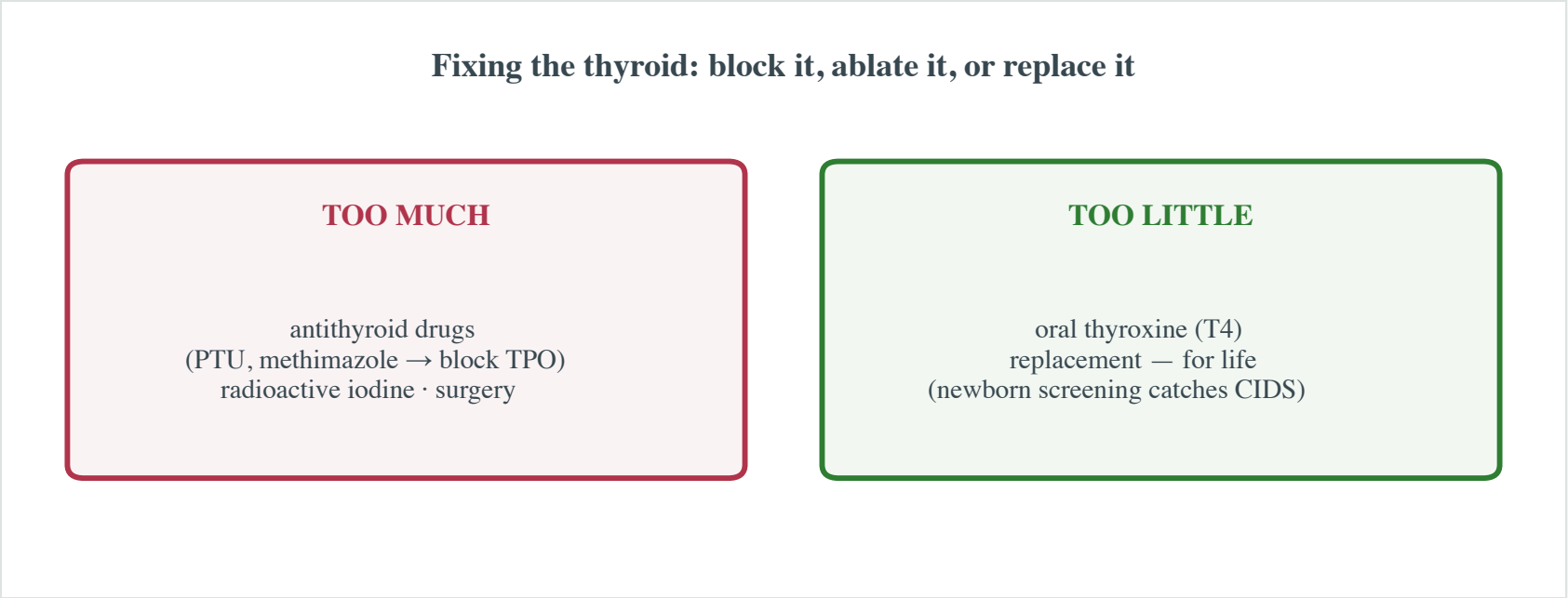
Too hot, too cold — and the antibodies

When the thyroid misfires, it's often **autoimmune**, and the two big diseases are **mirror images**. **Hyperthyroidism** — usually **Graves'** — is antibodies (**TSI**) that **mimic TSH** and won't stop: goiter, bulging eyes (**exophthalmos**), weight loss, heat intolerance, racing heart. (A **hot nodule or adenoma** can also do it.) **Hypothyroidism** — often **Hashimoto's** — is antibodies that **destroy** the gland (iodine deficiency does it too → **CIDS** in infants): weight gain, cold intolerance, slow heart, lethargy, **myxedema**. One antibody flips it on, the other tears it out — and **TSH is the first test** that tells them apart.



Fixing it: block, ablate, or replace

Treatment follows straight from the biochemistry. For a thyroid that's **too active**, you **block synthesis** (**PTU, methimazole** — the TPO inhibitors), or you **ablate** the gland with **radioactive iodine** or surgery. For a thyroid that's **too quiet**, you simply **replace** the hormone: oral **thyroxine (T4)**, taken for life, which the body deiodinates to T3 as needed. And because untreated infant hypothyroidism is devastating, every newborn is **screened** — catching CIDS before it can do harm.



Can you…?

- □ describe the thyroid gland/follicle and the systemic actions of thyroid hormone, and draw the structures of T4 and T3?
- □ explain thyroid hormone synthesis on thyroglobulin — iodide trapping, TPO-catalyzed iodination (MIT/DIT) and coupling to T3/T4 — plus storage, secretion, and the inhibitors of synthesis?
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- □ describe the biological actions of T3 and the major thyroid disorders (hyperthyroidism/Graves', hypothyroidism/Hashimoto's, CIDS), their symptoms, and treatment?

If any box stays empty, the practice site has a drill for it.

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