

Hyperthyroidism

Mechanisms, clinicopathologic effects and etiologic diagnosis

A pathology-led approach to the thyrotoxic syndrome

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Learning objectives

Distinguish thyroid hyperfunction from other causes of thyrotoxicosis.

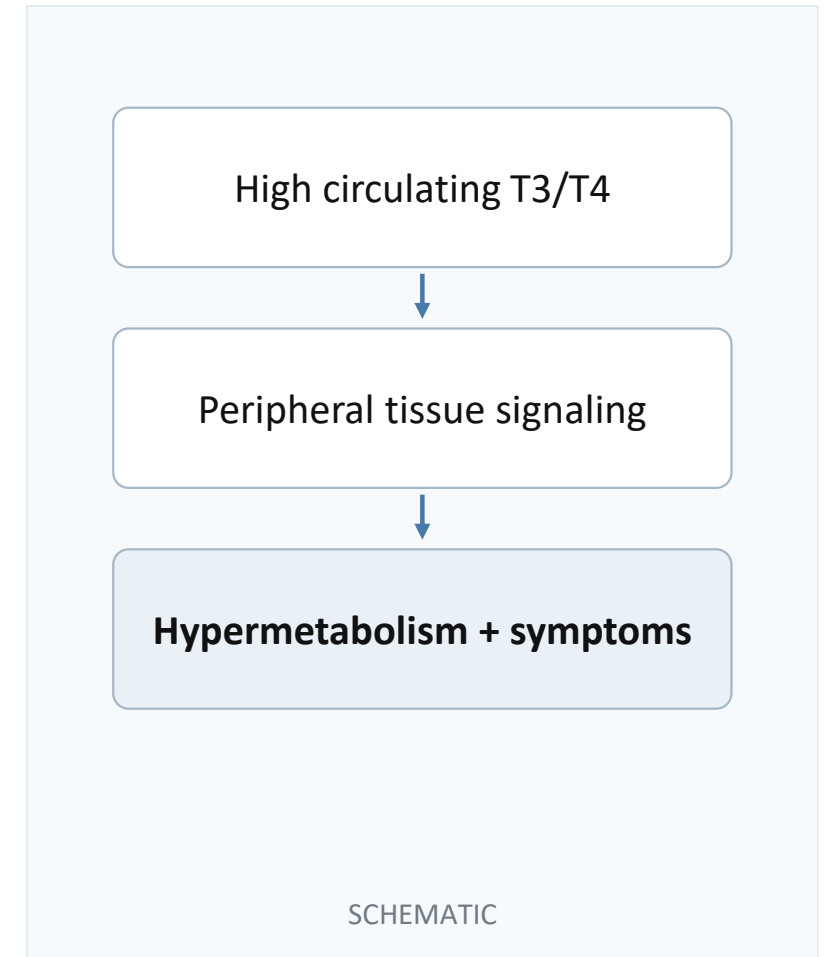
Explain the major systemic effects of excess thyroid hormone.

Interpret TSH, free T4, T3, uptake patterns, and Graves-associated antibodies.

Connect therapeutic interventions to their mechanistic targets.

Thyrotoxicosis is a clinical hormone-excess state

- Elevated circulating free thyroid hormone produces systemic hypermetabolism.
- The clinical syndrome reflects excess T3/T4 action in peripheral tissues.
- The source of excess hormone is not necessarily increased gland synthesis.



Hyperthyroidism is narrower than thyrotoxicosis

- Hyperthyroidism: The thyroid gland synthesizes and secretes excessive hormone.
- Destructive thyroiditis: Stored hormone leaks from injured follicles.
- Exogenous hormone or ectopic tissue may produce thyrotoxicosis without intrinsic gland hyperfunction.

Hyperthyroidism	Increased synthesis / gland function
Other thyrotoxicosis	Release, extrathyroidal production, or ingestion

The distinction predicts uptake patterns and treatment response.

Classifying the source changes the diagnostic question

- First ask whether circulating hormone excess is due to new thyroid synthesis.
- Then identify diffuse, nodular, pituitary-driven, destructive, or extrathyroidal mechanisms.
- Symptoms establish the syndrome but rarely determine etiology alone.

Synthesis in gland

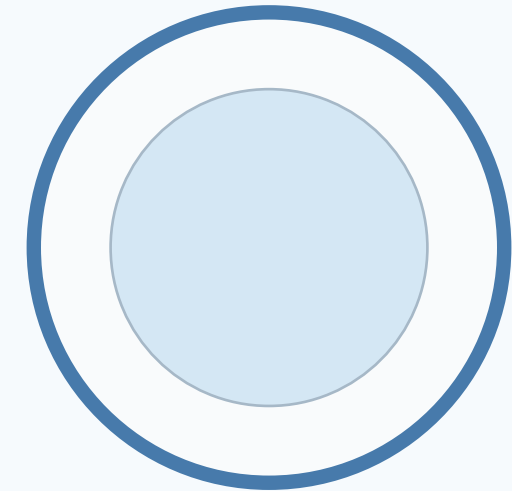
Release of stored hormone

Ectopic or exogenous supply

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Follicles are the functional unit of the thyroid

- Thyroid follicular epithelium surrounds a lumen containing stored colloid.
- A functioning follicle synthesizes and releases thyroid hormones.
- Follicular growth and colloid dynamics change across different thyroid diseases.



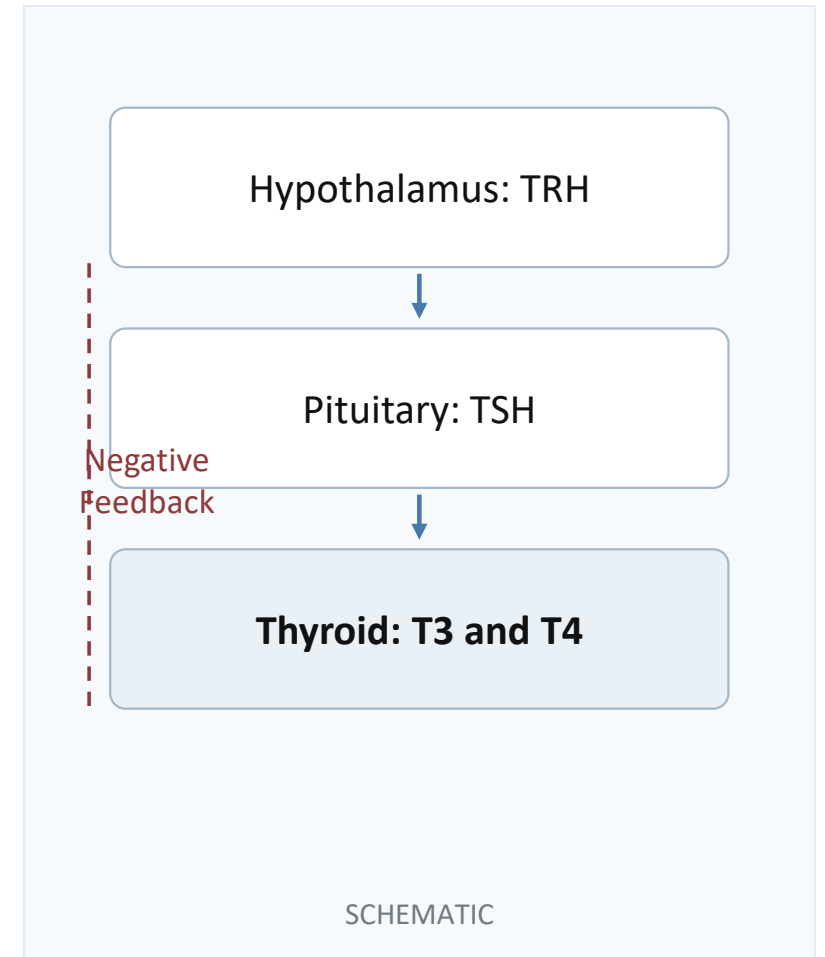
Follicular epithelium

Colloid (stored hormone)

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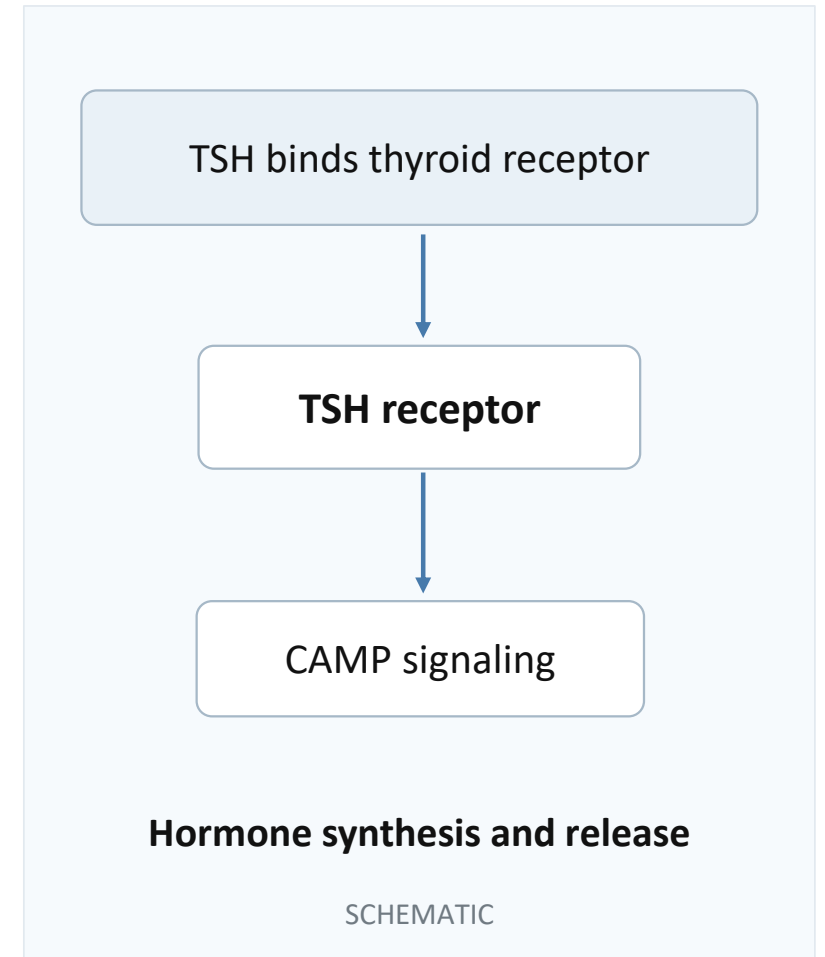
The hypothalamic–pituitary–thyroid axis

- Hypothalamic TRH stimulates pituitary thyrotrophs.
- Pituitary TSH stimulates thyroid follicular hormone synthesis and release.
- Circulating T3/T4 suppress TRH and TSH through negative feedback.



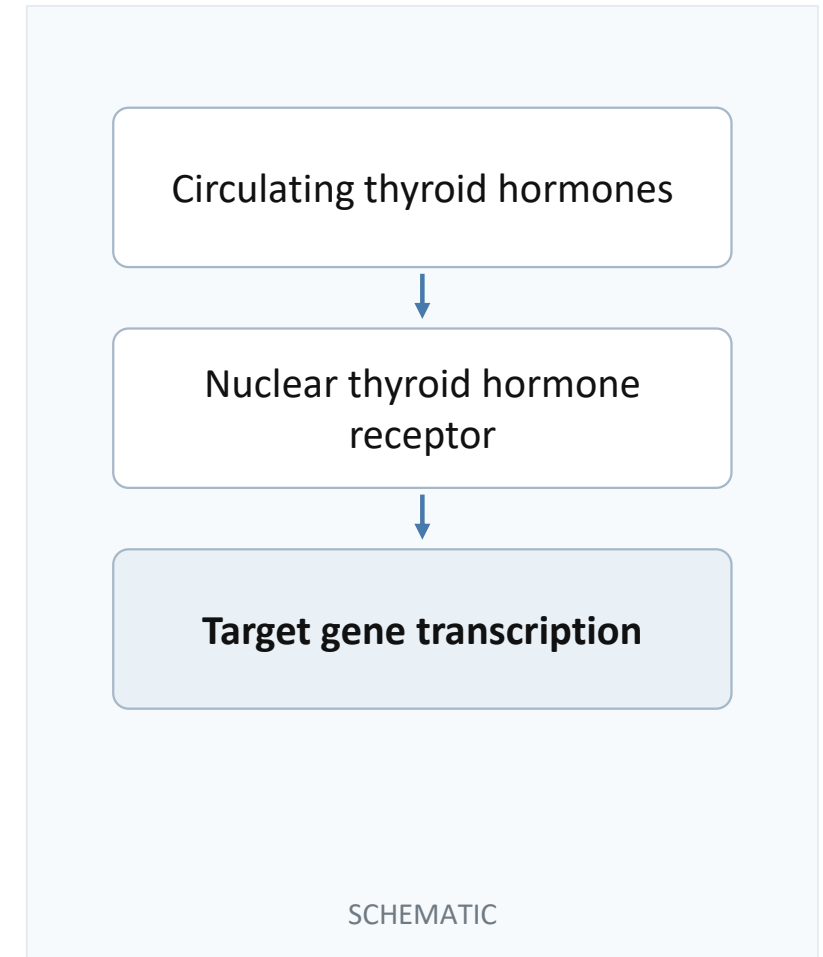
TSH receptor signaling drives hormone production

- TSH binds a receptor on thyroid follicular epithelium.
- Receptor activation engages G proteins and cyclic AMP signaling.
- The pathway increases thyroid hormone synthesis and release.



Thyroid hormones act through gene regulation

- T3 and T4 enter peripheral tissues; Thyroid hormone receptors act in cell nuclei.
- Hormone–receptor complexes regulate transcription of responsive genes.
- Multiorgan manifestations follow altered metabolic and physiologic programs.



Three mechanistic routes to circulating hormone excess

- Increased synthesis: Graves disease, toxic nodules, or excess TSH signaling.
- Destructive release: Painful or painless thyroiditis releases preformed hormone.
- Other supply: Ectopic thyroid tissue or ingested thyroid hormone.

Synthesis in gland

Release of stored hormone

Ectopic or exogenous supply

SCHEMATIC

Primary and secondary hyperthyroidism

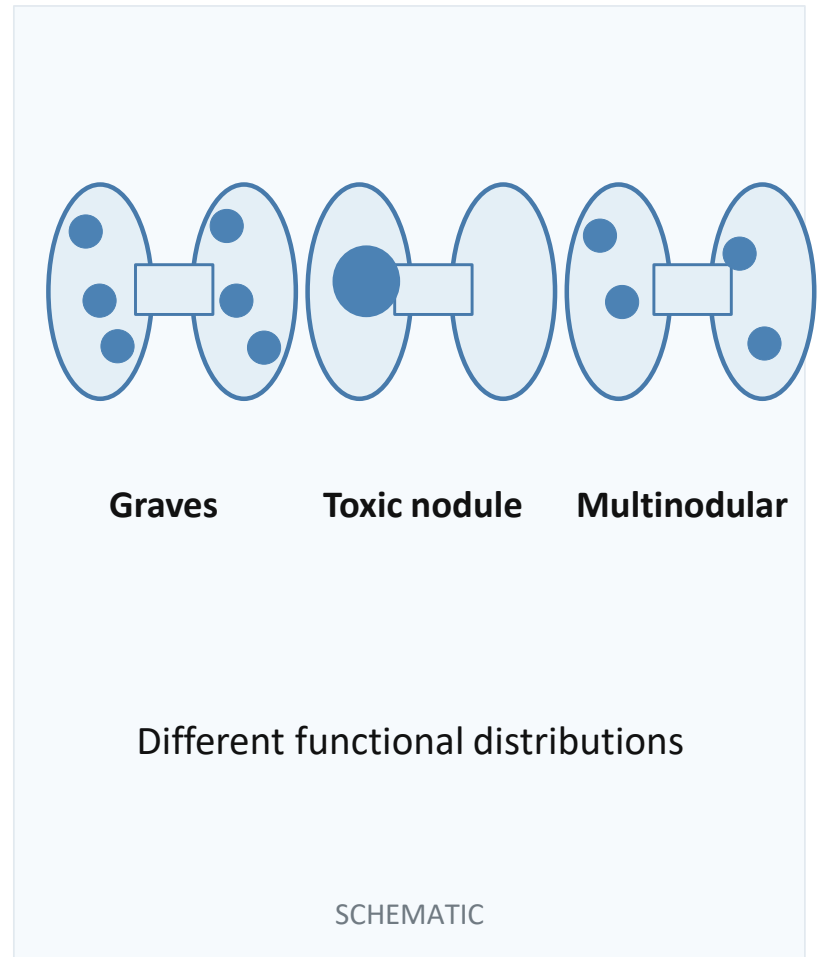
- Primary hyperthyroidism originates in the thyroid gland.
- Rare secondary hyperthyroidism can result from a TSH-secreting pituitary neuroendocrine tumor.
- Primary disease generally suppresses TSH; Pituitary-driven disease may not.

Primary	Thyroid autonomy / stimulation	TSH suppressed
Secondary	TSH-secreting PitNET	TSH normal or raised

Interpret TSH in the context of concurrent free hormone levels.

Principal endogenous causes

- Graves disease is the predominant cause account (approximately 85%).
- Other major causes are hyperfunctioning multinodular goiter and toxic adenoma.
- These three mechanisms involve increased glandular hormone production.



Additional thyroid-hyperfunction causes

- Iodine-induced hyperthyroidism is listed among primary glandular causes.
- Maternal Graves disease can produce neonatal thyrotoxicosis.
- Rare pituitary TSH excess produces secondary hyperthyroidism.

Primary	Iodine-related; Neonatal maternal Graves
Secondary	TSH-secreting pituitary tumor

Clinical context is needed to recognize less common causes.

Causes without increased gland production

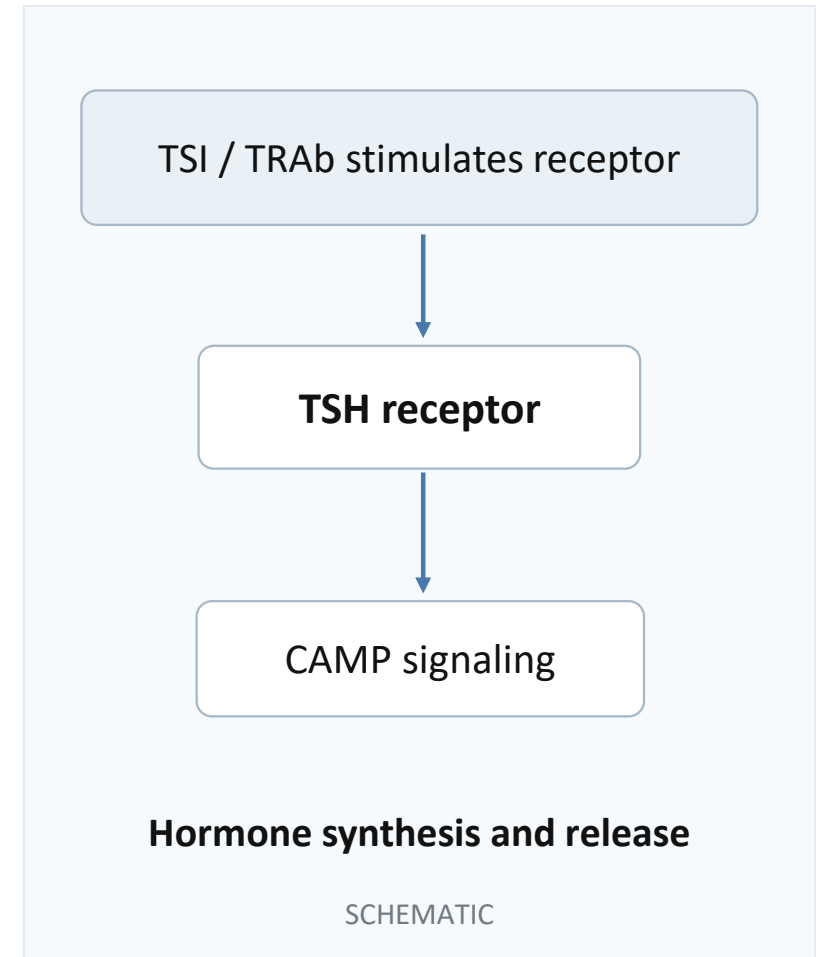
- Subacute granulomatous (de Quervain) thyroiditis is typically painful.
- Lymphocytic thyroiditis may be painless.
- Struma ovarii and factitious thyrotoxicosis are extrathyroidal supply routes.

Release from thyroid	Painful or painless thyroiditis
Extrathyroidal source	Struma ovarii; Exogenous thyroxine

A low-uptake gland may coexist with elevated circulating hormone.

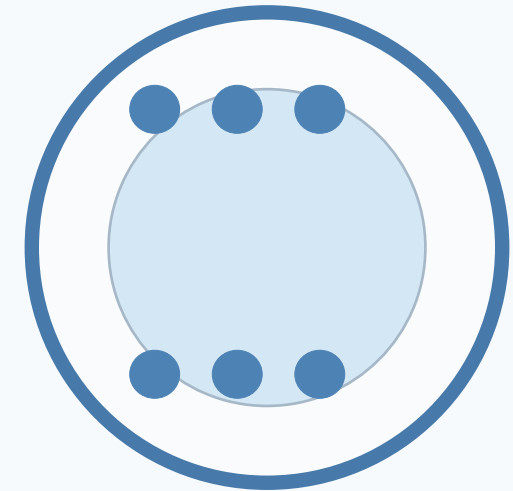
Graves disease: Receptor-directed autoimmunity

- Autoantibodies target the TSH receptor, mimicking TSH stimulation.
- Thyroid-stimulating immunoglobulins (TSI) activate adenyl cyclase signaling.
- Hypersecretion continues despite pituitary TSH suppression.



Graves disease: The characteristic gland

- The untreated gland is usually diffusely and symmetrically enlarged.
- Follicular epithelium is crowded and tall, sometimes forming small papillary projections.
- Colloid margins are scalloped because hormone-producing epithelium actively resorbs colloid.

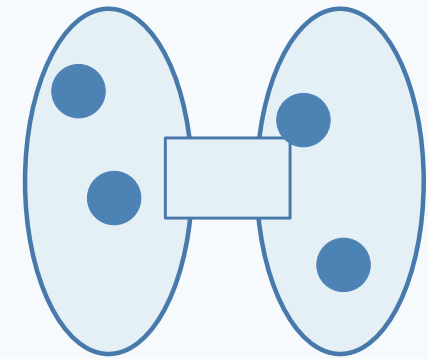


Scalloped colloid

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Toxic multinodular goiter: Functional heterogeneity

- Recurrent follicular hyperplasia and involution create an irregular, nodular gland.
- Some nodules become functionally autonomous, while others are relatively inactive.
- Radioiodine uptake is consequently patchy rather than uniform.

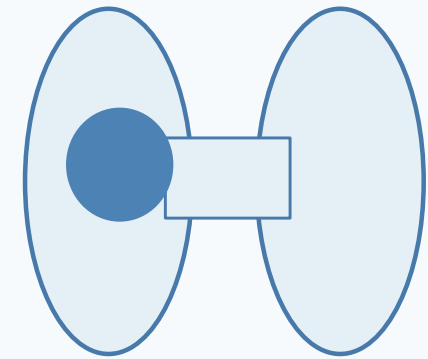


Heterogeneous activity

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Toxic adenoma: A focal source of excess hormone

- A solitary hyperfunctioning nodule can dominate hormone production.
- On radionuclide imaging, uptake is increased in the functional nodule.
- Pituitary TSH suppression reduces activity in surrounding thyroid tissue.



Solitary active nodule

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Iodine-associated and neonatal thyrotoxicosis

- Iodine-induced hyperthyroidism belongs to the increased-production group.
- Neonatal thyrotoxicosis may occur with maternal Graves disease.
- In both settings, history and clinical context direct etiologic interpretation.

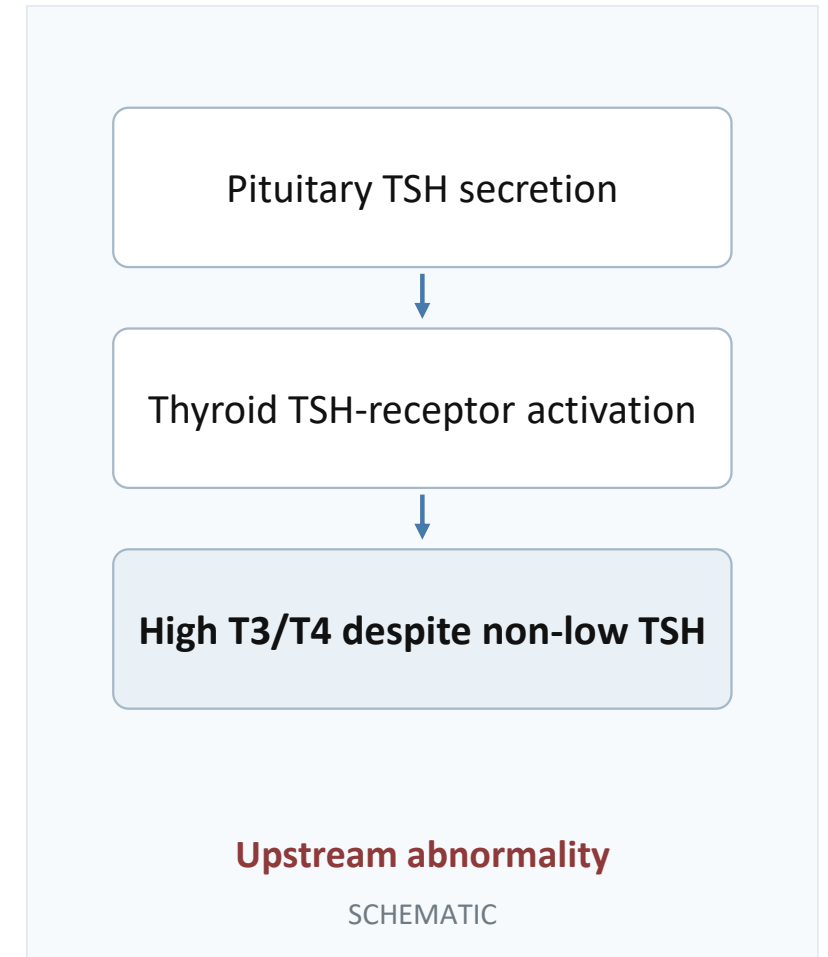
CLINICOPATHOLOGIC LINK

These are contextual causes—not interchangeable with destructive thyroiditis.

Interpretation

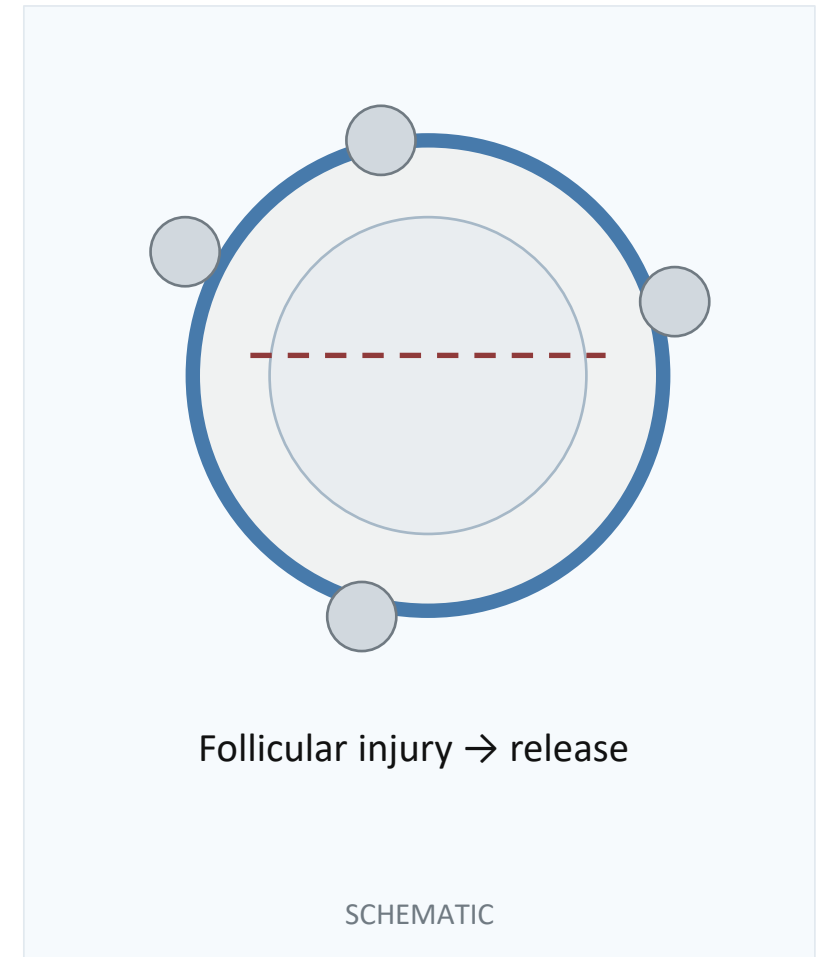
TSH-secreting pituitary tumors are exceptional

- The source of stimulation is pituitary rather than autonomous thyroid tissue.
- Serum TSH is inappropriately normal or elevated in the presence of hormone excess.
- Treatment may include pituitary surgery, somatostatin analogs, or irradiation.



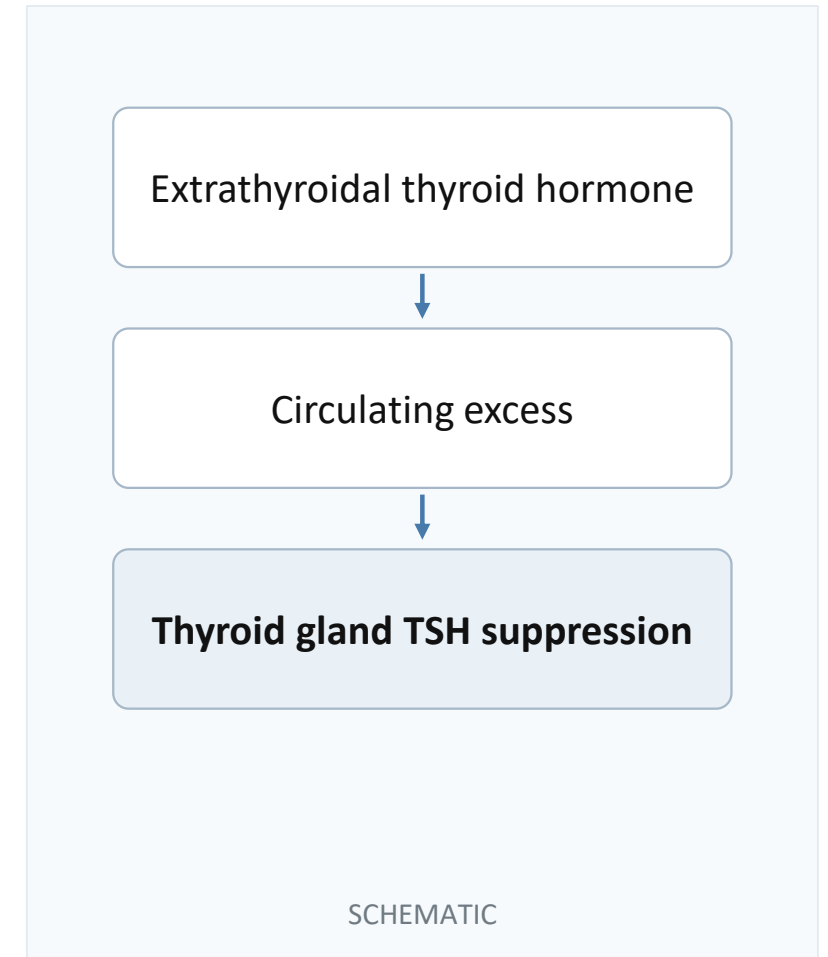
Destructive thyroiditis releases preformed hormone

- Follicular injury can discharge stored hormone into circulation.
- Biochemical thyrotoxicosis occurs without an increase in hormone synthesis.
- The textbook distinguishes painful de Quervain from painless lymphocytic thyroiditis.



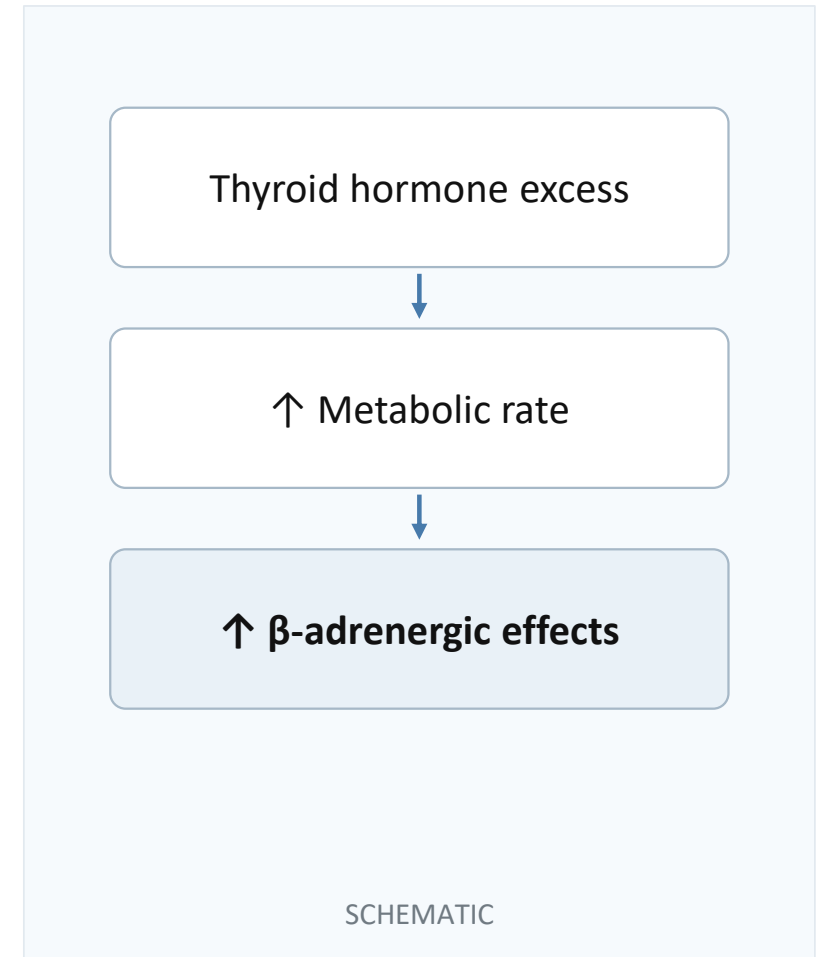
Extrathyroidal sources bypass gland hyperfunction

- Struma ovarii contains functional thyroid tissue in an ovarian teratoma.
- Factitious thyrotoxicosis follows ingestion of exogenous thyroid hormone.
- A suppressed pituitary TSH does not locate the hormone source.



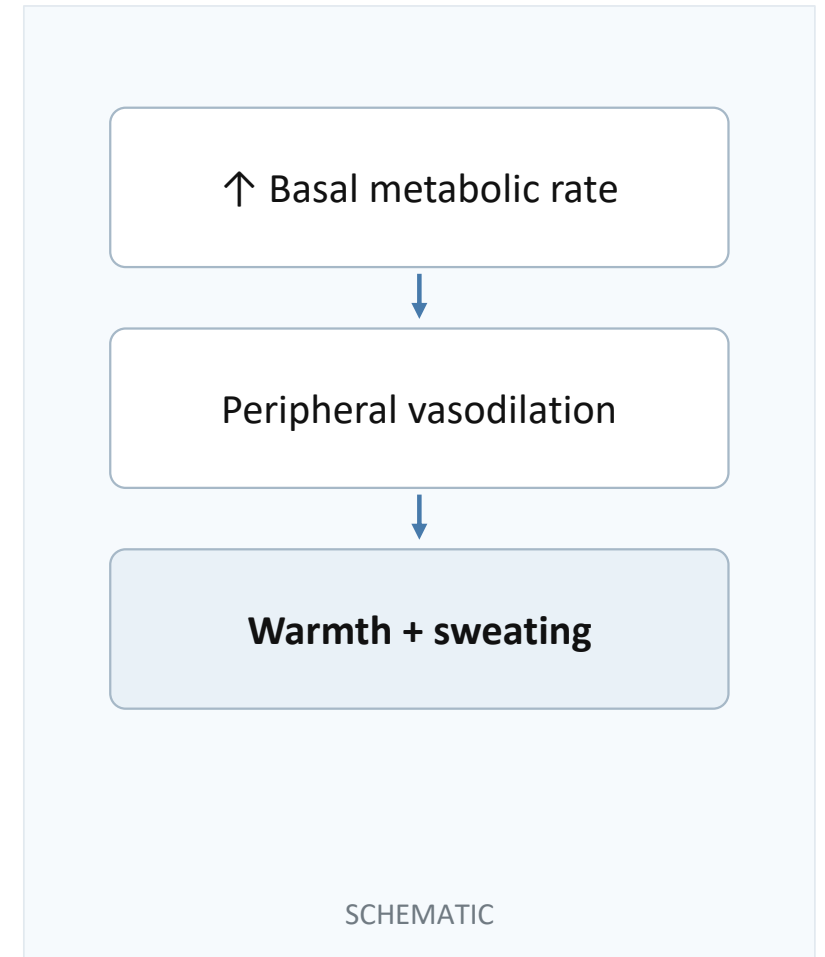
The symptom complex has two principal drivers

- Hypermetabolic effects reflect elevated thyroid hormone signaling.
- Enhanced sympathetic / β -adrenergic tone contributes tremor and neurobehavioral changes.
- Cardiovascular manifestations often reflect both increased demand and adrenergic effects.



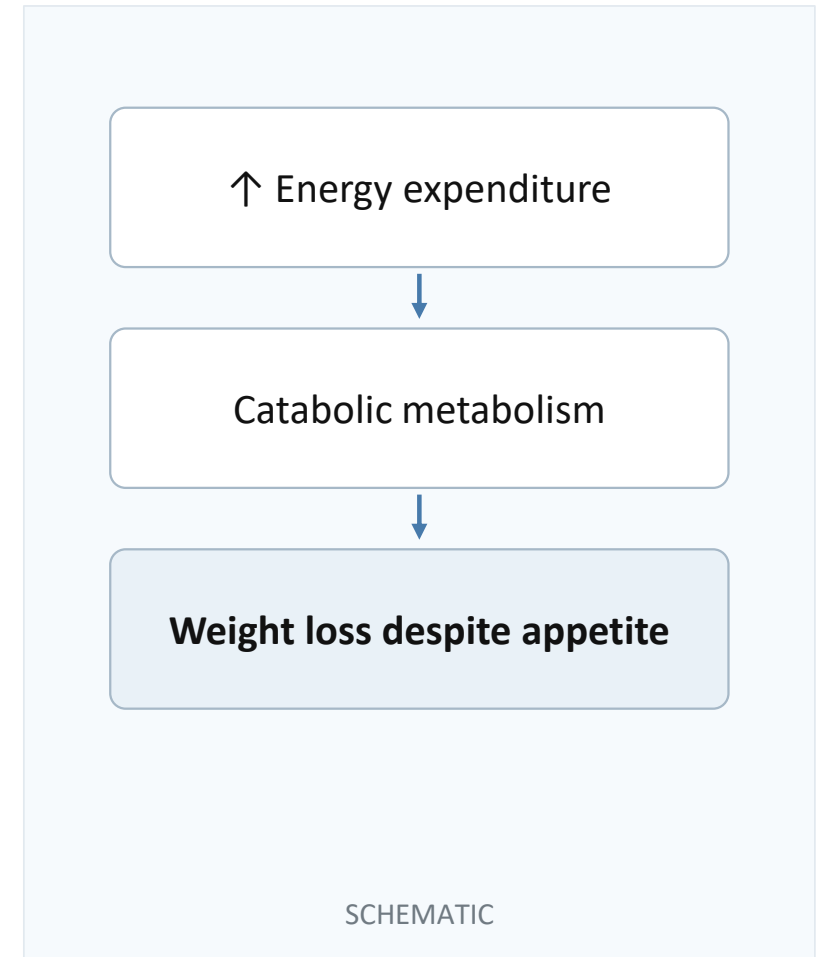
Raised basal metabolic rate produces heat intolerance

- Thyroid hormone increases basal metabolic activity.
- Peripheral vasodilation and increased cutaneous blood flow facilitate heat loss.
- Patients report warmth, sweating, and difficulty tolerating hot environments.



Weight loss reflects heightened catabolism

- Catabolic metabolism increases energy consumption.
- Weight loss may occur despite a paradoxically increased appetite.
- Unexplained weight decline therefore requires endocrine consideration.



Skin and thermoregulatory findings

- Thyrotoxic skin is often soft, warm, and flushed.
- Sweating increases along with peripheral heat dissipation.
- These findings are consequences of a systemic metabolic state, not a skin-specific disease.

CLINICOPATHOLOGIC LINK

Peripheral perfusion links hormone excess to physical examination findings.

Interpretation

Cardiovascular adaptation to increased oxygen demand

- The hypermetabolic state increases systemic oxygen requirements.
- Cardiac contractility and cardiac output often rise to meet demand.
- Persistent hemodynamic stress contributes to cardiomegaly and dysfunction.

↑ Peripheral O₂ requirement



↑ Contractility / output



Cardiac workload + risk

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Tachycardia and palpitations

- Tachycardia is a common and often early cardiovascular manifestation.
- Patients may become aware of forceful or rapid heartbeats.
- β -adrenergic overactivity contributes to the symptom burden.

Rapid rhythm (schematic)



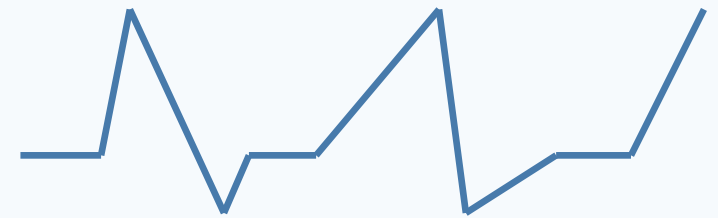
Illustrative waveform; Not a clinical ECG

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Atrial fibrillation is an important complication

- Arrhythmias, particularly atrial fibrillation, are frequent in older patients.
- Palpitations or worsening cardiovascular disease may be the first clue.
- The underlying thyrotoxic state should be considered during evaluation.

Irregular rhythm (schematic)



Illustrative waveform; Not a clinical ECG

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Thyrotoxicosis may precipitate heart failure

- Existing cardiac disease increases vulnerability to thyroid hormone excess.
- Heart failure may emerge in older adults with compromised reserve.
- A subset develops potentially reversible thyrotoxic cardiomyopathy.

↑ Peripheral O₂ requirement



↑ Contractility / output



Cardiac workload + risk

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Myocardial changes described in thyrotoxicosis

- Focal lymphocytic and eosinophilic infiltrates.
- Mild interstitial fibrosis and myofibril fatty changes have been described.
- Mitochondria may increase in size and number in affected myocardium.

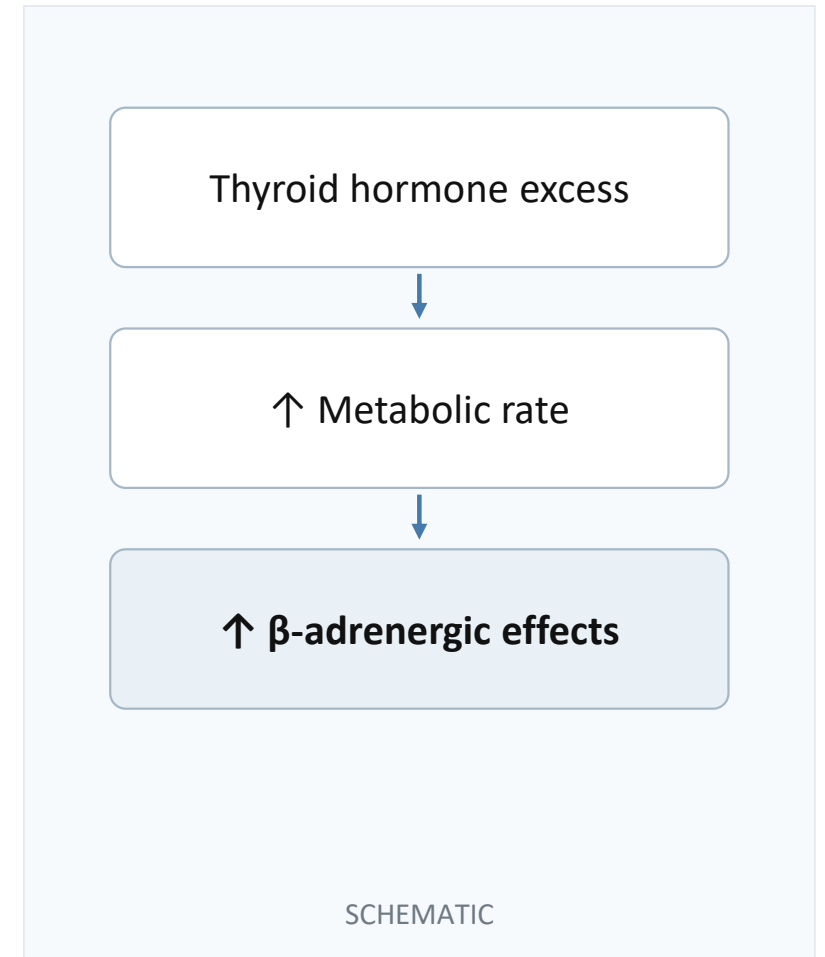
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These are reported tissue changes, not a specific biopsy-based diagnostic signature.

Interpretation

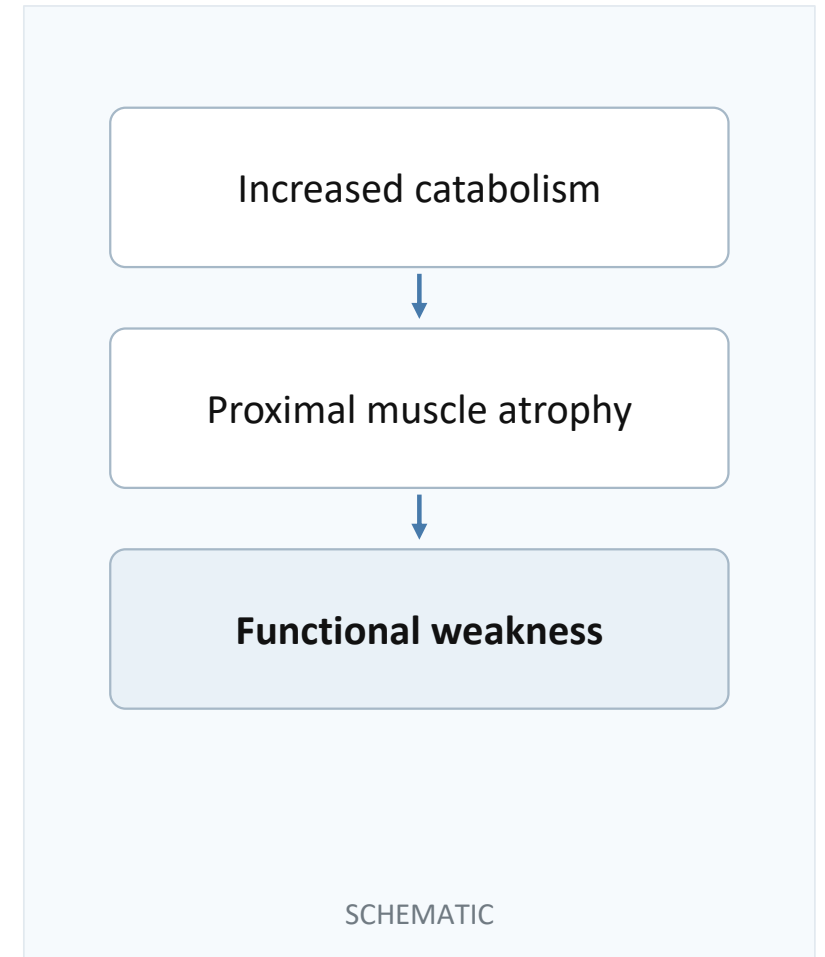
The nervous system reflects adrenergic activation

- Tremor and hyperactivity are common expressions of sympathetic overactivity.
- Anxiety, emotional lability, and poor concentration may be prominent.
- Insomnia further amplifies neurobehavioral complaints.



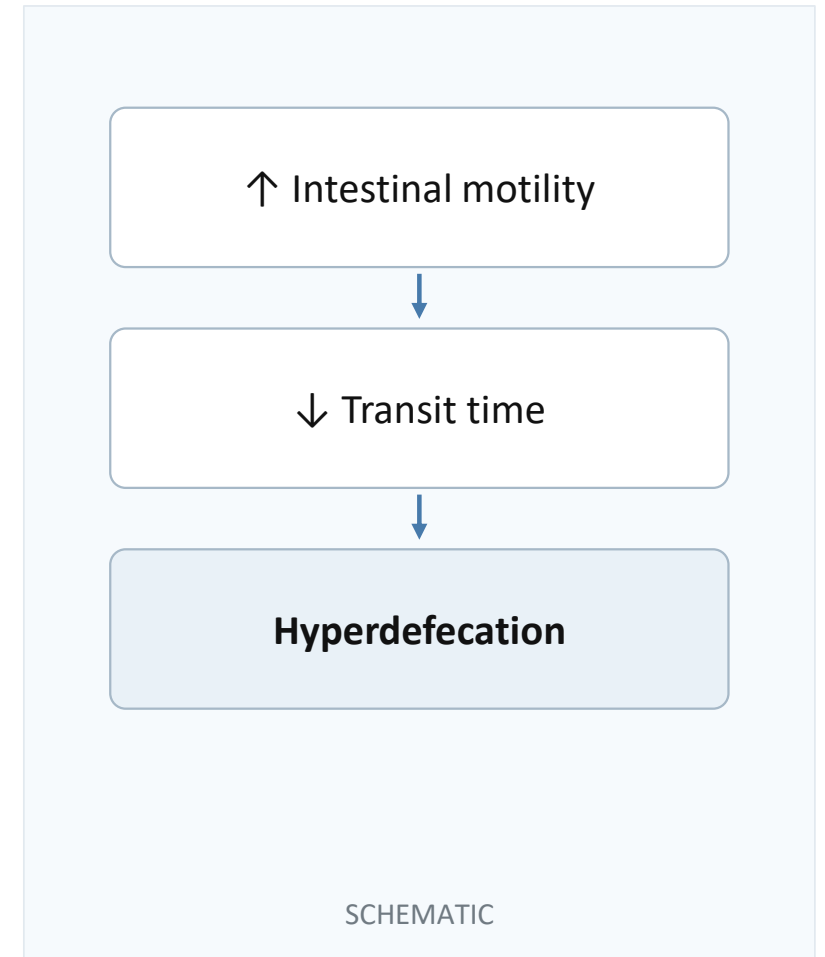
Thyroid myopathy is predominantly proximal

- Proximal muscle weakness can accompany decreased muscle mass.
- Muscle atrophy with fatty infiltration and focal inflammatory changes.
- Motor complaints may coexist with other classic thyrotoxic symptoms.



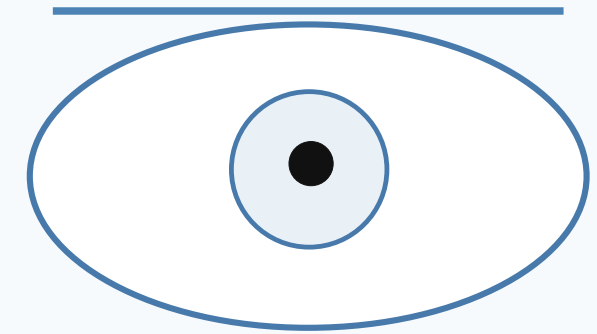
Gastrointestinal transit is accelerated

- Intestinal hypermotility shortens transit time.
- Frequent bowel movements or hyperdefecation may result.
- Some patients develop fat malabsorption.



Lid retraction and stare are adrenergic findings

- Sympathetic stimulation of the superior tarsal (Müller) muscle elevates the upper lid.
- A wide-eyed stare and lid lag may occur in hyperthyroidism.
- These findings alone do not establish Graves orbitopathy.



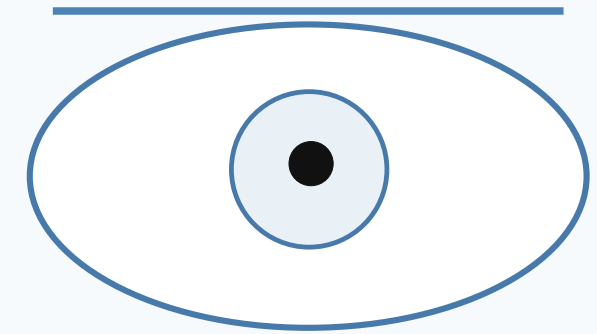
Upper eyelid retraction

Sympathetic Müller muscle tone

SCHEMATIC

True infiltrative orbitopathy points toward Graves

- Graves-associated orbital disease may cause genuine proptosis / exophthalmos.
- Retro-orbital connective tissue and extraocular muscles expand and become edematous.
- This process is distinct from adrenergic stare and may persist after hormone control.



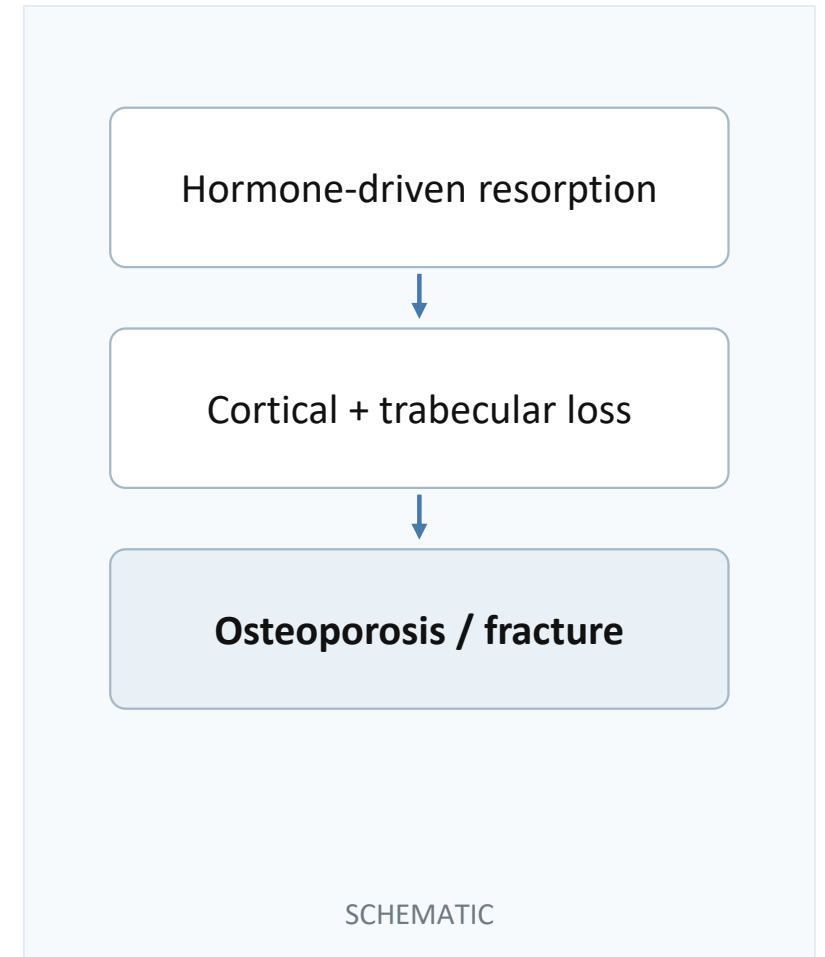
Retro-orbital tissue expansion

Graves-specific tissue process

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Excess thyroid hormone reduces skeletal strength

- Thyroid hormone stimulates bone resorption.
- Cortical bone becomes more porous and trabecular bone volume decreases.
- The net result is osteoporosis and increased fracture susceptibility.



Other tissue consequences of hormone excess

- Hepatic steatosis may lead to mild hepatomegaly.
- Skeletal muscle may show atrophy and fatty infiltration.
- Graves disease may be associated with lymphoid hyperplasia and lymphadenopathy.

CLINICOPATHOLOGIC LINK

Systemic organ findings reflect both hormone effects and disease-specific biology.

Interpretation

Graves-specific manifestations extend beyond thyrotoxicosis

- Diffuse thyroid enlargement may be associated with increased blood flow and a bruit.
- Infiltrative ophthalmopathy produces true exophthalmos.
- Localized pretibial dermatopathy occurs in a minority of patients.

Diffuse hyperthyroid gland

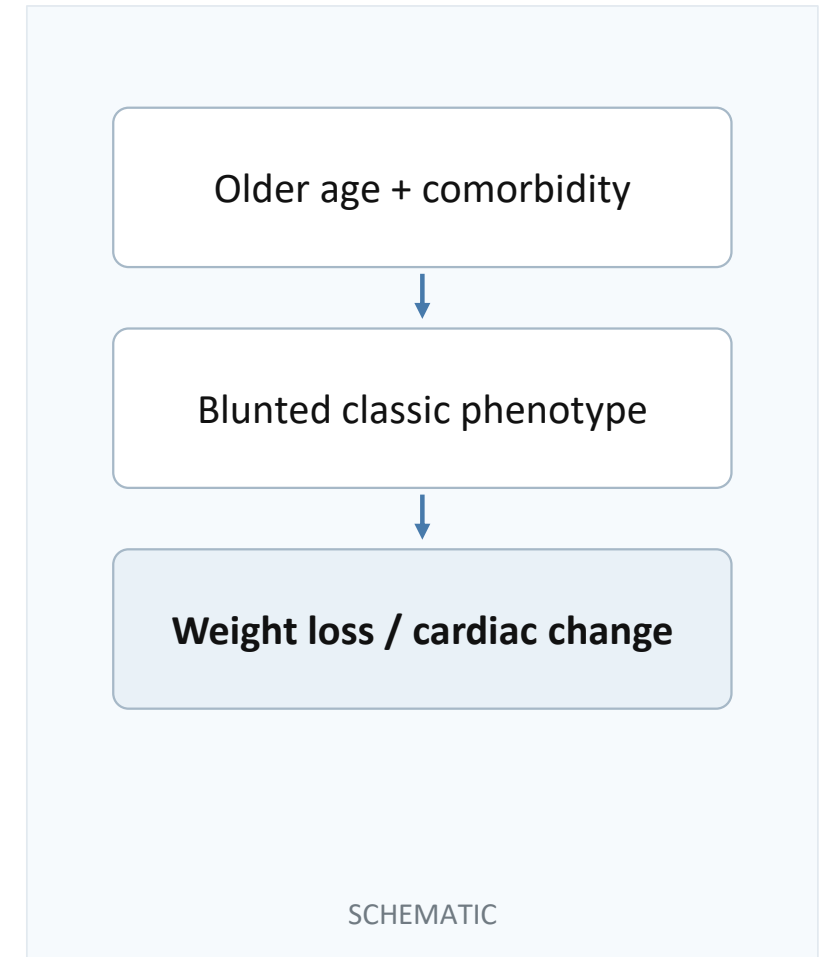
Infiltrative orbitopathy

Pretibial dermatopathy (minority)

SCHEMATIC

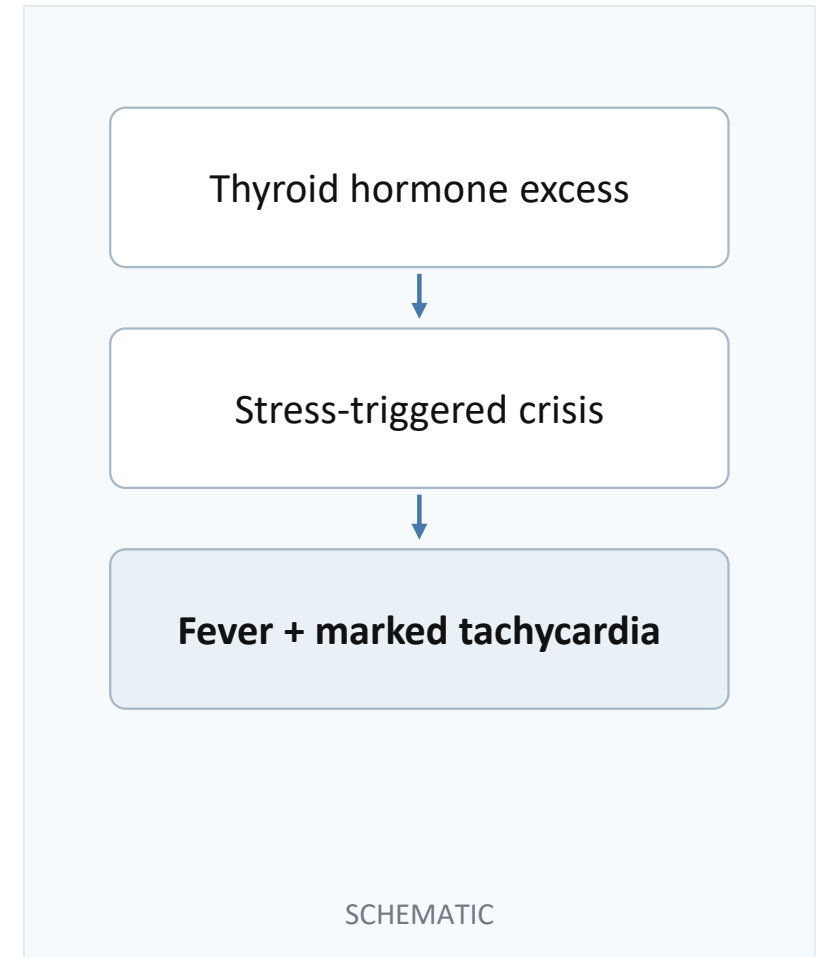
Apathetic hyperthyroidism can mask the classic picture

- Older adults may lack conspicuous tremor, hyperactivity, or heat intolerance.
- Weight loss or worsening cardiovascular disease may prompt investigation.
- Comorbidity and age blunt the usual clinical phenotype.



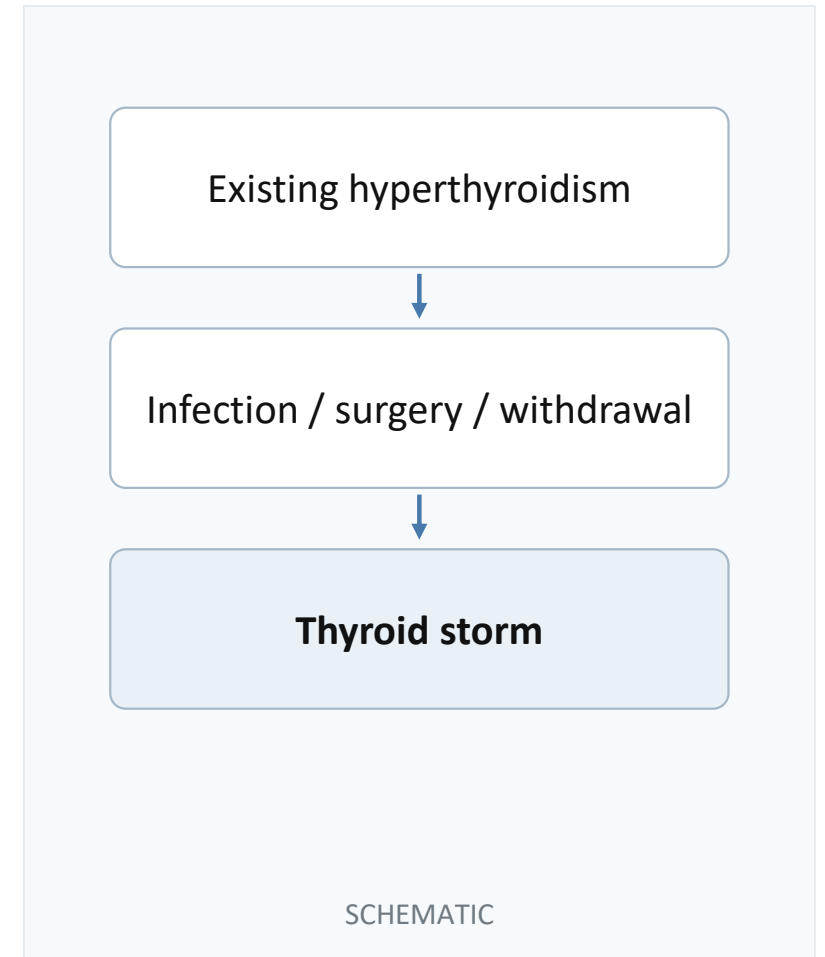
Thyroid storm: Abrupt severe decompensation

- Thyroid storm is an acute, severe manifestation of thyrotoxicosis.
- In the source, it occurs most commonly in patients with Graves disease.
- It is a medical emergency with significant untreated arrhythmic mortality.



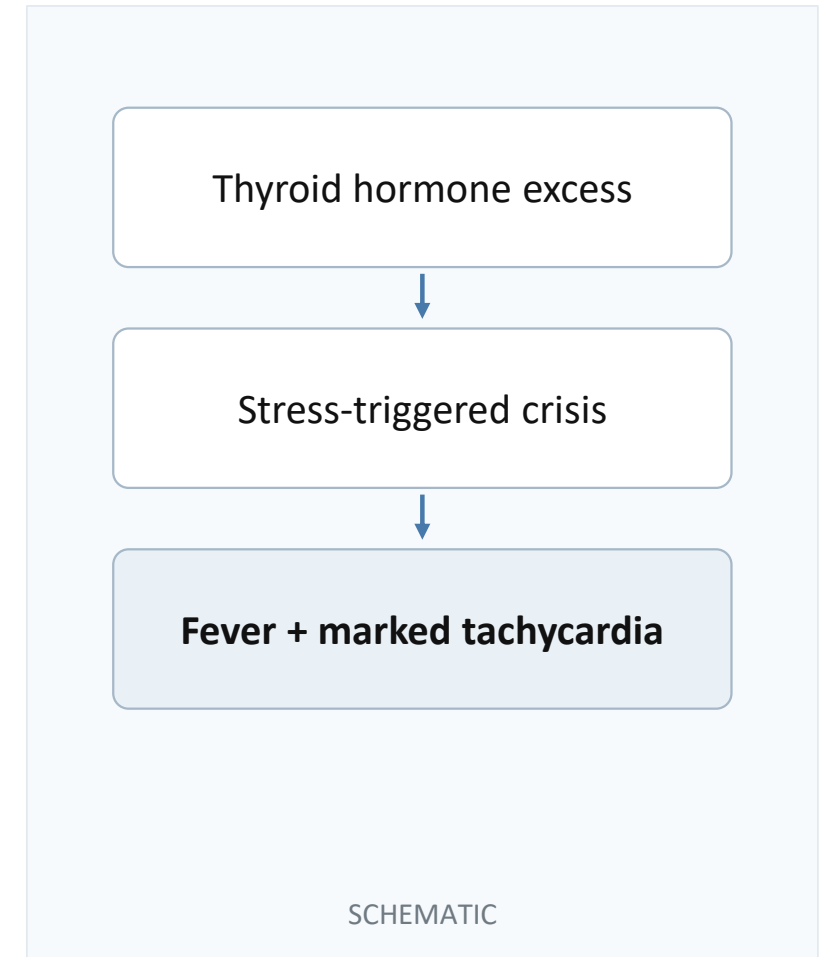
Common precipitants of thyroid storm

- Infection or another acute physiologic stress may precipitate decompensation.
- Surgery is a recognized setting.
- Stopping antithyroid medication may precipitate an acute episode.



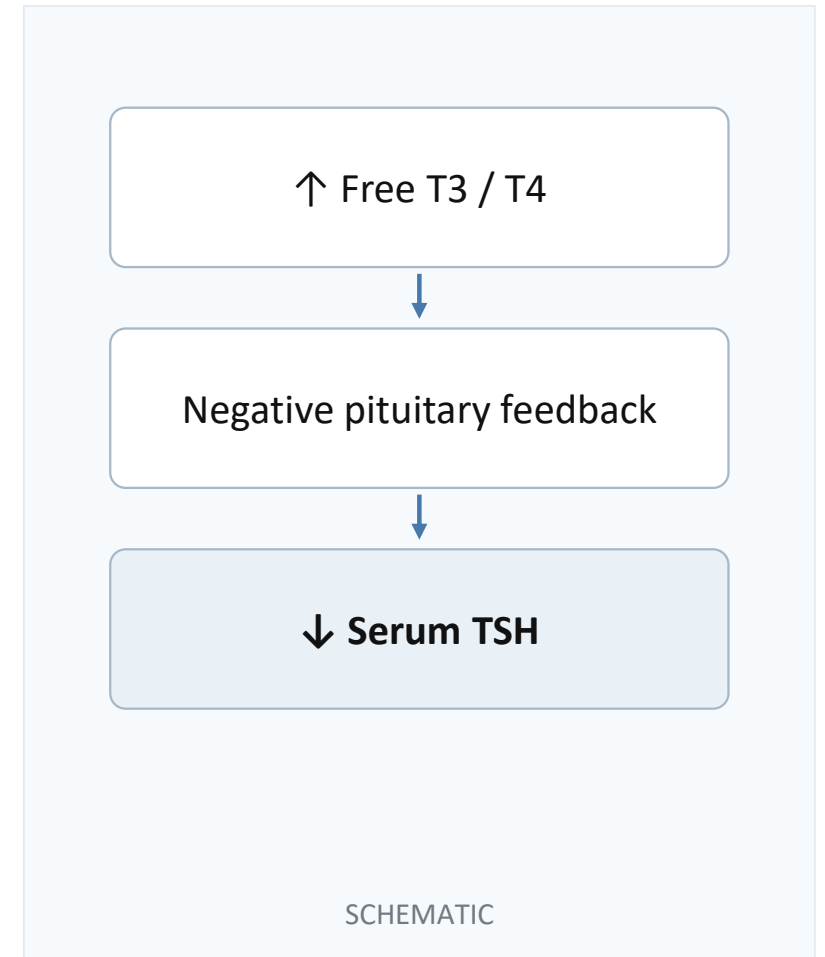
Recognizing the storm phenotype

- Marked fever may accompany severe thyrotoxicosis.
- Tachycardia may be disproportionate to the degree of fever.
- Cardiac arrhythmias are a principal life-threatening complication.



Start biochemical evaluation with serum TSH

- TSH is the most useful single screening test for primary hyperthyroidism.
- Negative feedback suppresses TSH early, sometimes before overt hormone elevation.
- An isolated TSH value must be interpreted alongside clinical context and free hormones.



Overt primary hyperthyroidism: The expected pattern

- Suppressed serum TSH indicates pituitary feedback inhibition.
- Elevated free T4 supports overt thyroid hormone excess.
- T3 measurement is useful if the pattern is discordant or T3-predominant.

TSH	Low
Free T4	Elevated
Interpretation	Overt primary hormone excess

The free hormone concentration distinguishes overt disease from earliest subclinical forms.

Subclinical hyperthyroidism is a biochemical stage

- TSH suppression may precede an overt rise in circulating thyroid hormones.
- Free T4 can still be within its laboratory reference interval.
- An appropriate assessment also accounts for circulating T3.

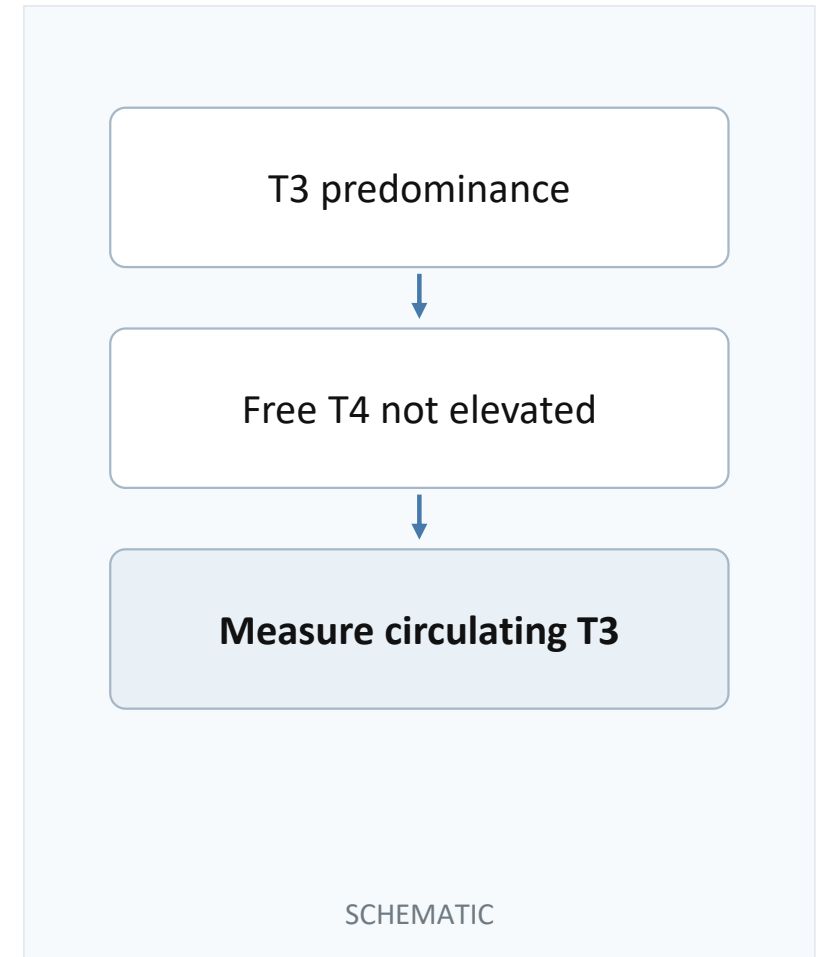
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Use assay-specific reference intervals; No arbitrary numeric cutoff is required here.

Interpretation

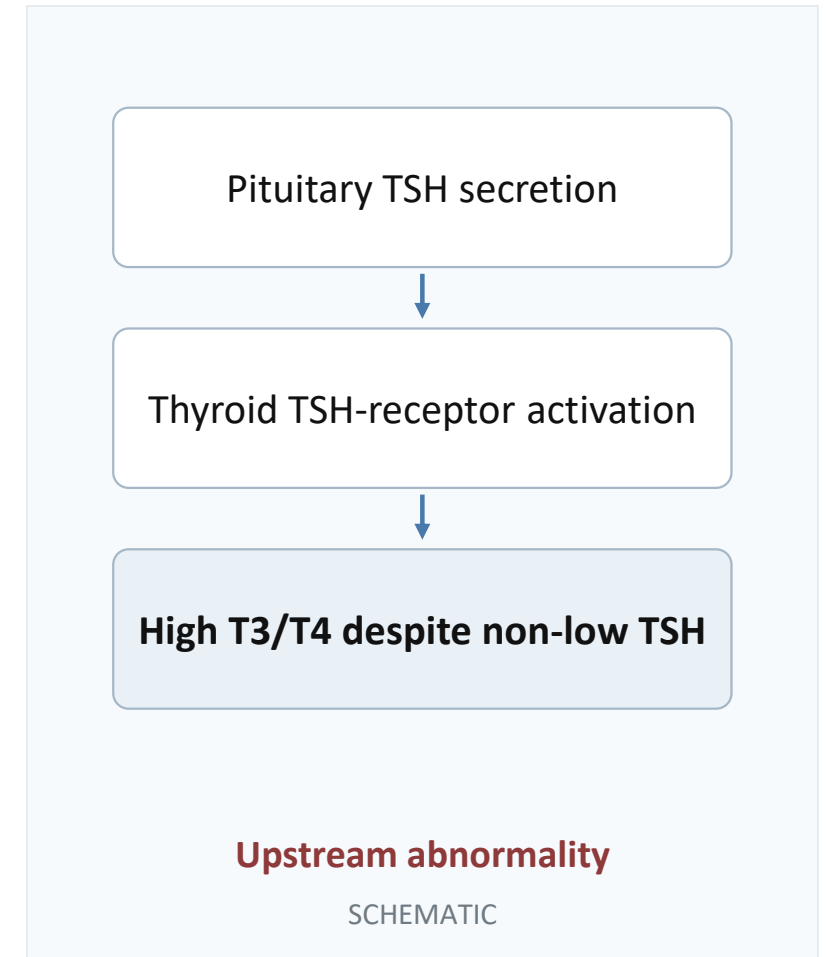
T3-predominant thyrotoxicosis can obscure diagnosis

- Some patients have increased circulating T3 without elevated free T4.
- Free T4 may even be decreased in the Robbins description.
- Direct T3 measurement can resolve suspected discordant biochemical findings.



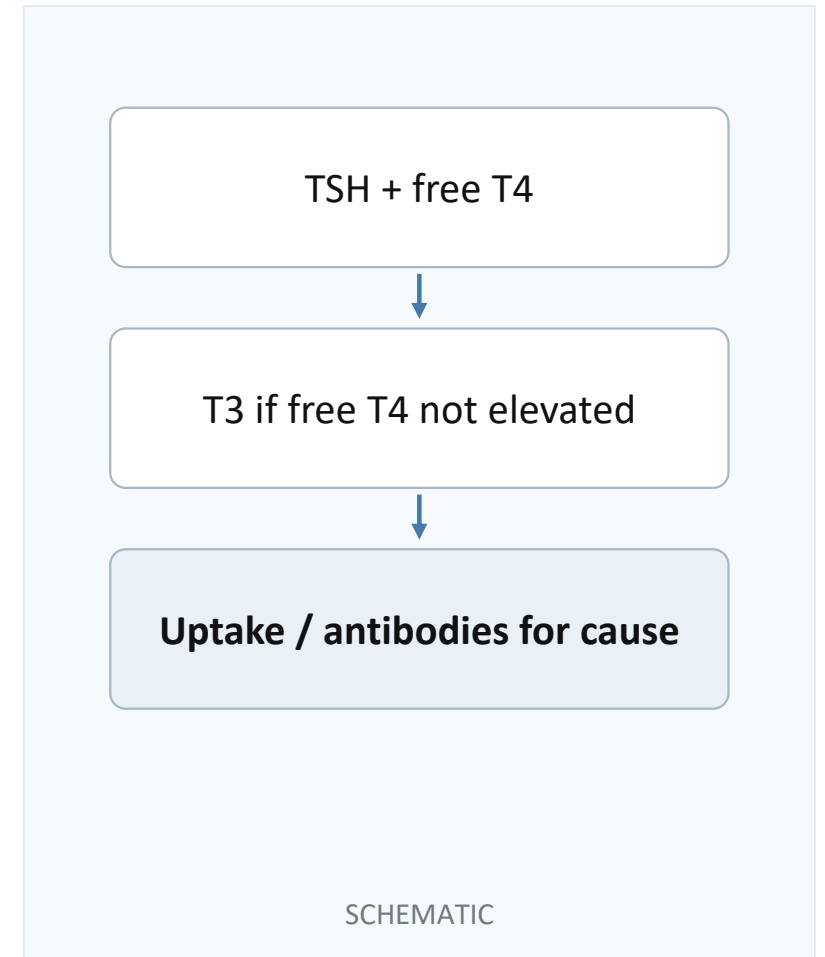
Non-suppressed TSH changes the differential

- Pituitary-associated secondary hyperthyroidism is rare.
- TSH may be inappropriately normal or elevated despite excess free hormone.
- This differs from expected feedback suppression in primary disease.



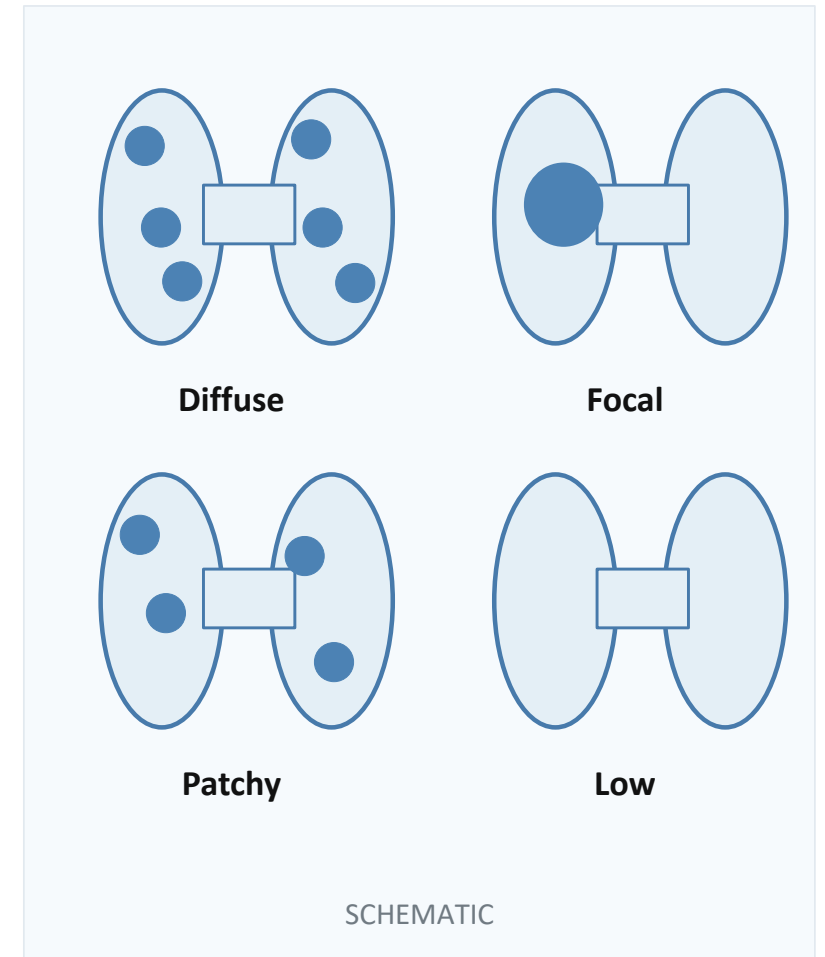
A stepwise laboratory interpretation pathway

- First assess TSH and free thyroid hormone concentrations.
- If TSH is suppressed and free T4 is not raised, consider measuring T3.
- After confirming biochemical thyrotoxicosis, determine the mechanism and source.



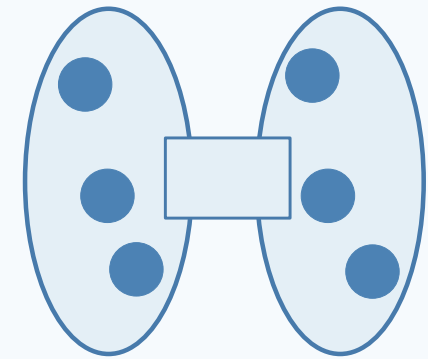
Radioiodine uptake evaluates functional activity

- Uptake is a mechanistic study of hormone-producing thyroid tissue.
- Diffuse, focal, patchy, and low-uptake patterns discriminate key causes.
- Pattern interpretation follows confirmation of biochemical hormone excess.



Diffuse increased uptake favors Graves disease

- TSH receptor-stimulating antibodies act throughout the gland.
- A radionuclide scan typically shows diffuse increased uptake.
- TSI or TRAb can provide complementary etiologic evidence.

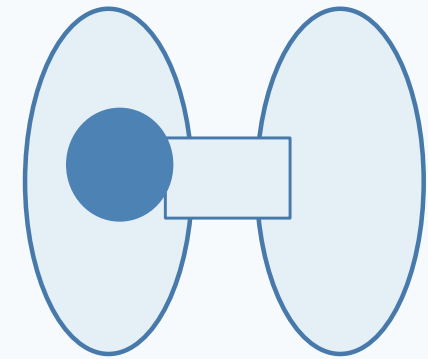


Diffuse increased uptake

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Focal increased uptake favors a toxic adenoma

- One autonomous nodule produces a focal functional hot spot.
- TSH suppression reduces uptake in surrounding follicles.
- The resultant distribution differs from Graves-associated diffuse activity.

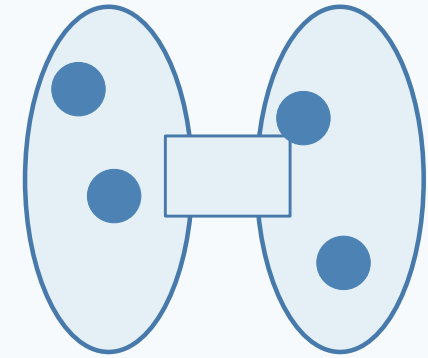


Focal increased uptake

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Patchy uptake supports toxic multinodular disease

- Different nodules exhibit differing functional activity.
- Autonomous hot nodules may coexist with less active or cold nodules.
- The heterogeneity follows uneven follicular functional autonomy.

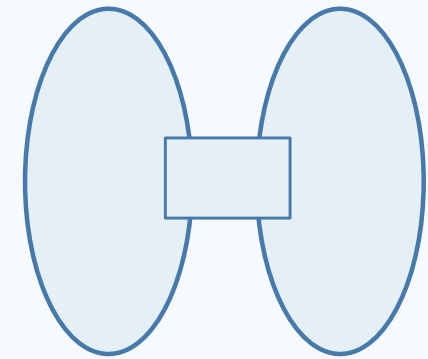


Patchy uptake

SCHEMATIC

Low uptake suggests hormone release or outside supply

- Inflammatory follicle damage may release stored hormone without new synthesis.
- Extrathyroidal hormone intake does not require cervical thyroid stimulation.
- Low thyroid uptake therefore contrasts with synthesis-driven hyperfunction.

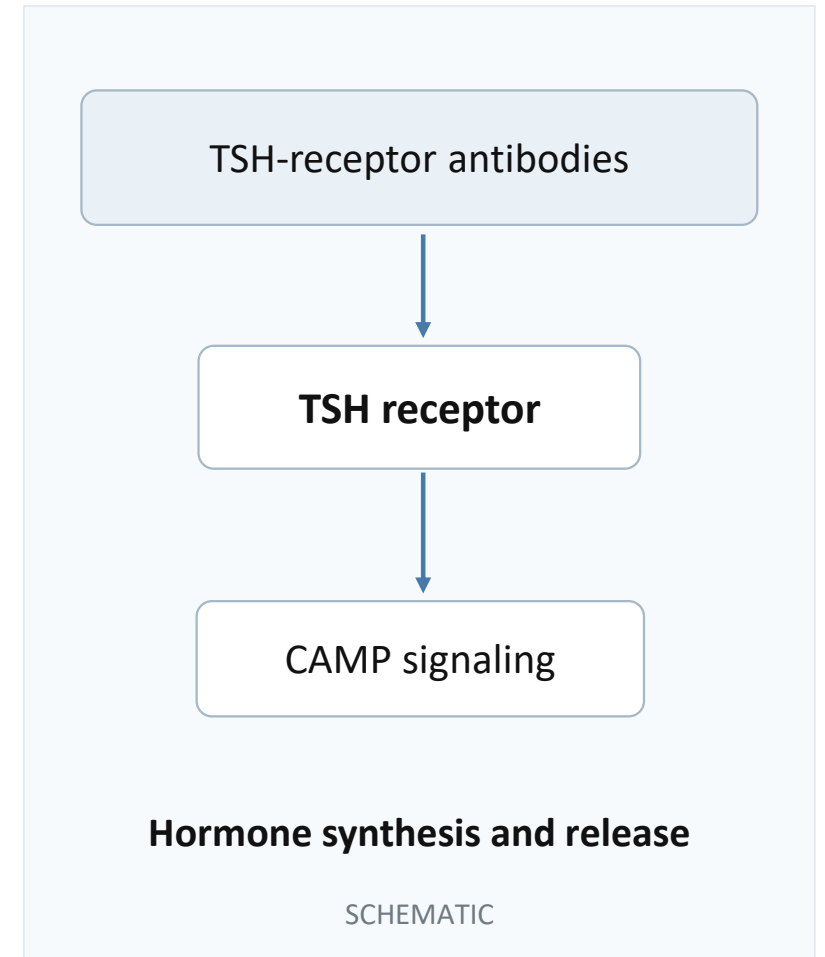


Low cervical uptake

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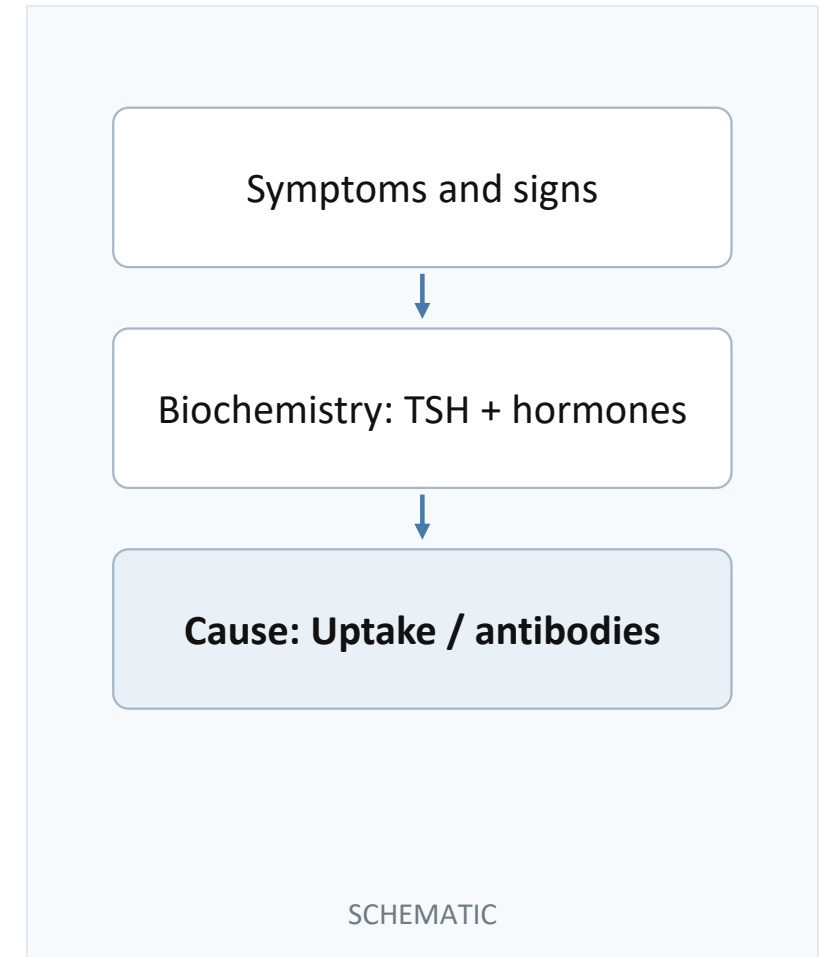
TRAb and TSI support Graves etiology

- Thyroid-stimulating immunoglobulins activate the TSH receptor.
- TSI and/or TSH-receptor antibody positivity generally supports Graves disease.
- Antibody testing is particularly helpful when biochemical thyrotoxicosis has been established.



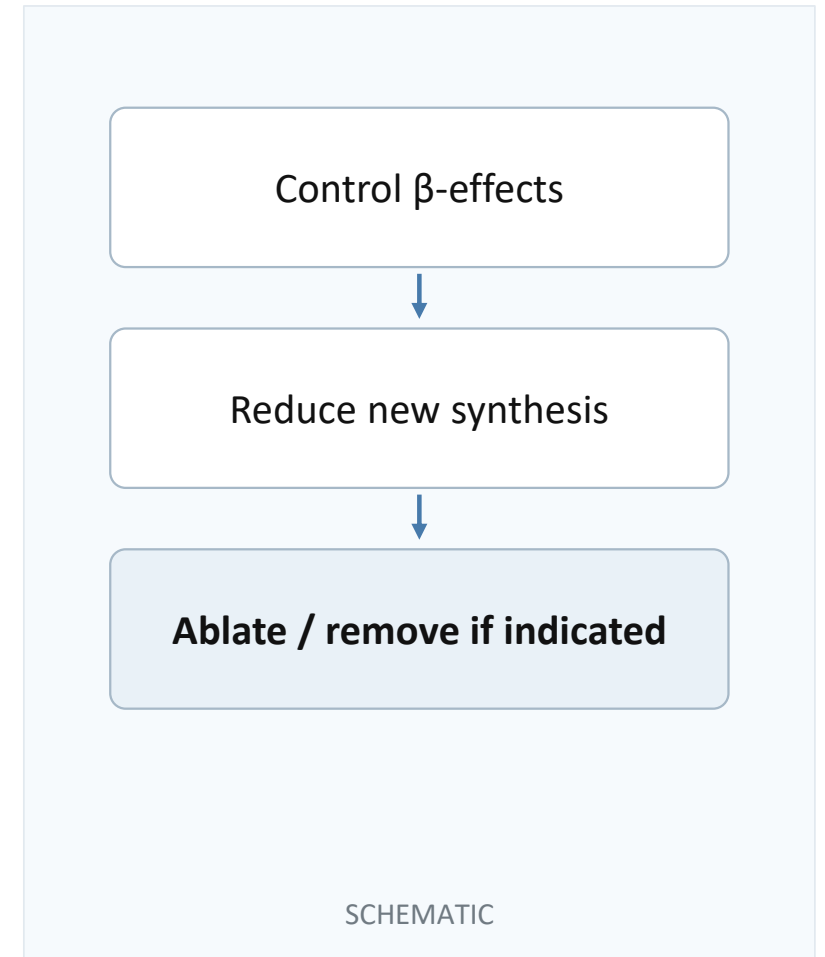
Clinical and laboratory evidence must converge

- Symptoms establish physiologic consequences of hormone excess.
- TSH and free hormones support or challenge biochemical thyrotoxicosis.
- Uptake distribution and antibodies identify the causative mechanism.



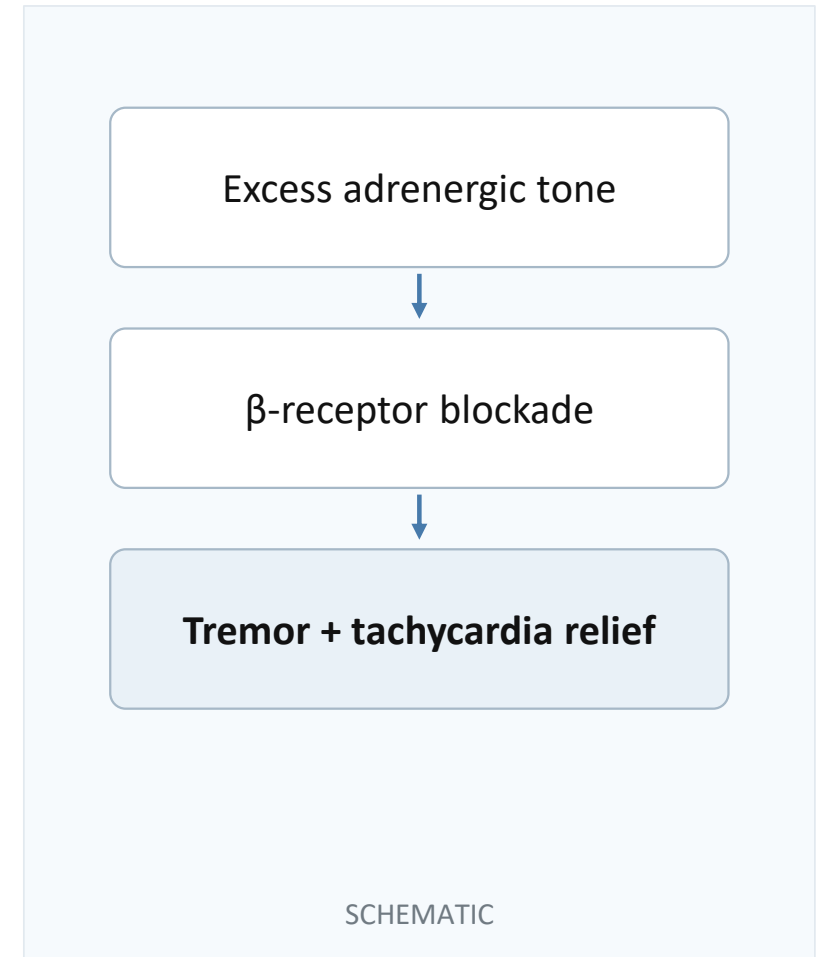
Treatment works at several distinct targets

- β -blockers dampen consequences of excess adrenergic tone.
- Thionamides reduce new thyroid hormone synthesis.
- Iodide, conversion inhibitors, ablation, and surgery act at different steps.



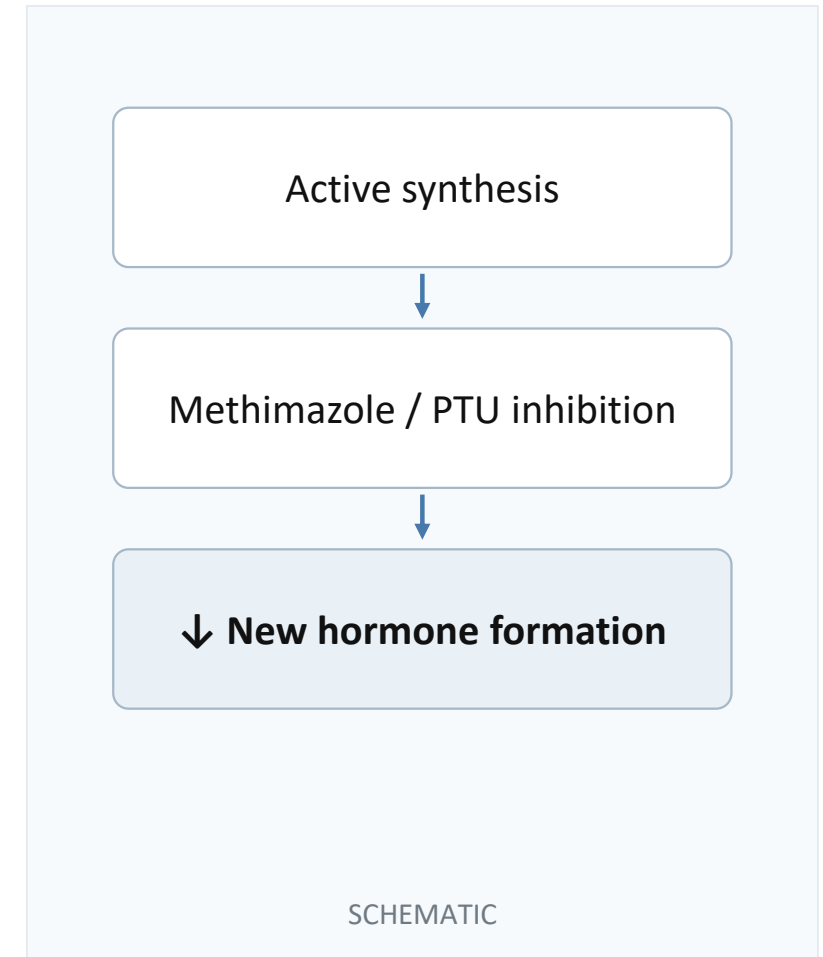
β -blockers relieve adrenergic symptoms

- β -blockade improves tachycardia, palpitations, tremulousness, and anxiety.
- This strategy targets hormone-driven sympathetic manifestations.
- It does not itself remove the underlying source of excess thyroid hormone.



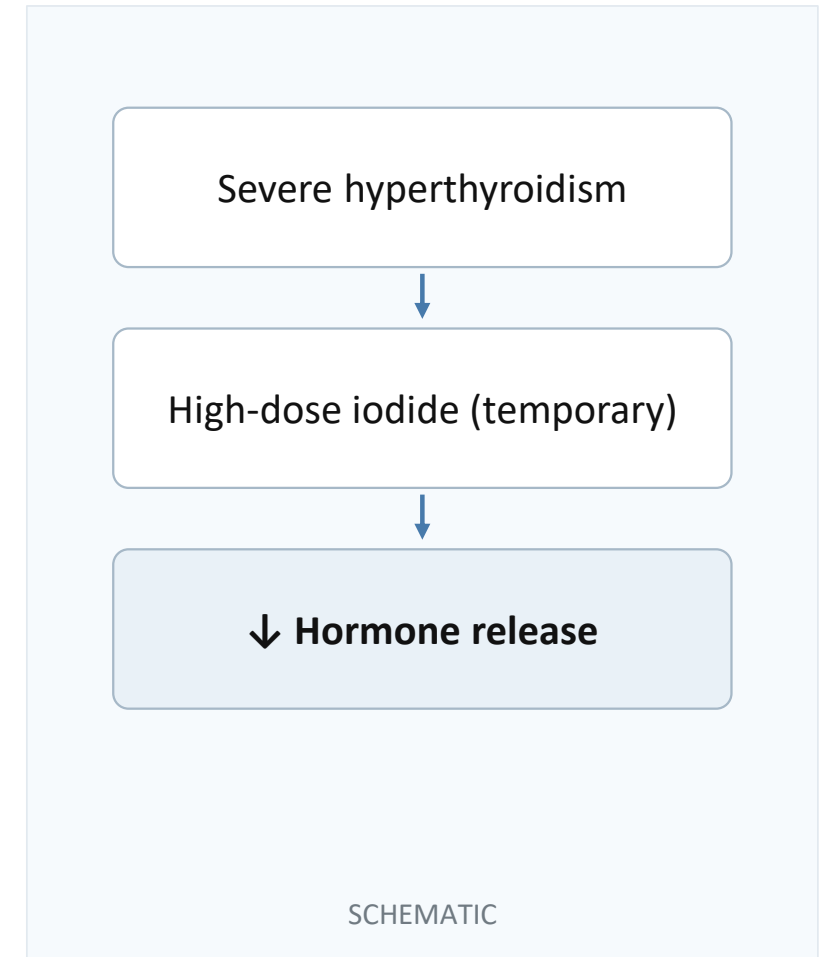
Thionamides inhibit new hormone synthesis

- Methimazole and propylthiouracil inhibit thyroid hormone production.
- Their action is mechanistically appropriate for active synthesis-driven causes.
- They do not reverse immediate release of hormone already stored in destroyed follicles.



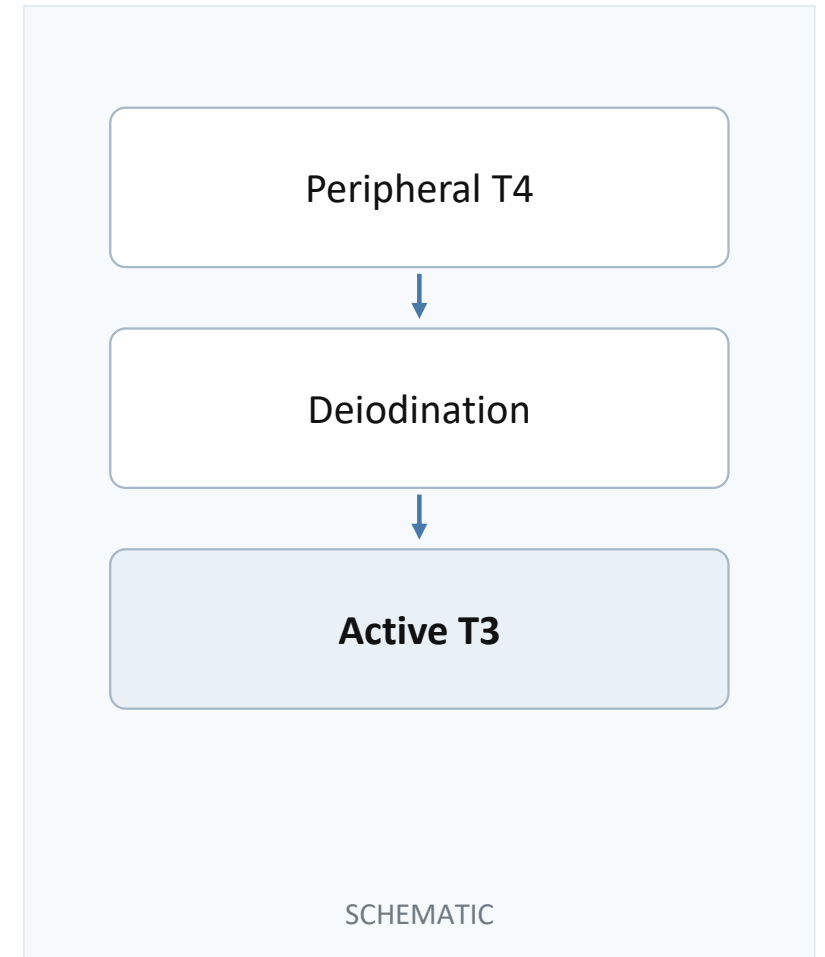
High-dose iodide has a temporary suppressive role

- In severe thyrotoxicosis, iodide can acutely inhibit hormone release.
- Use of iodine solution in severe disease and thyroid storm.
- This is a temporary intervention rather than a stand-alone definitive cure.



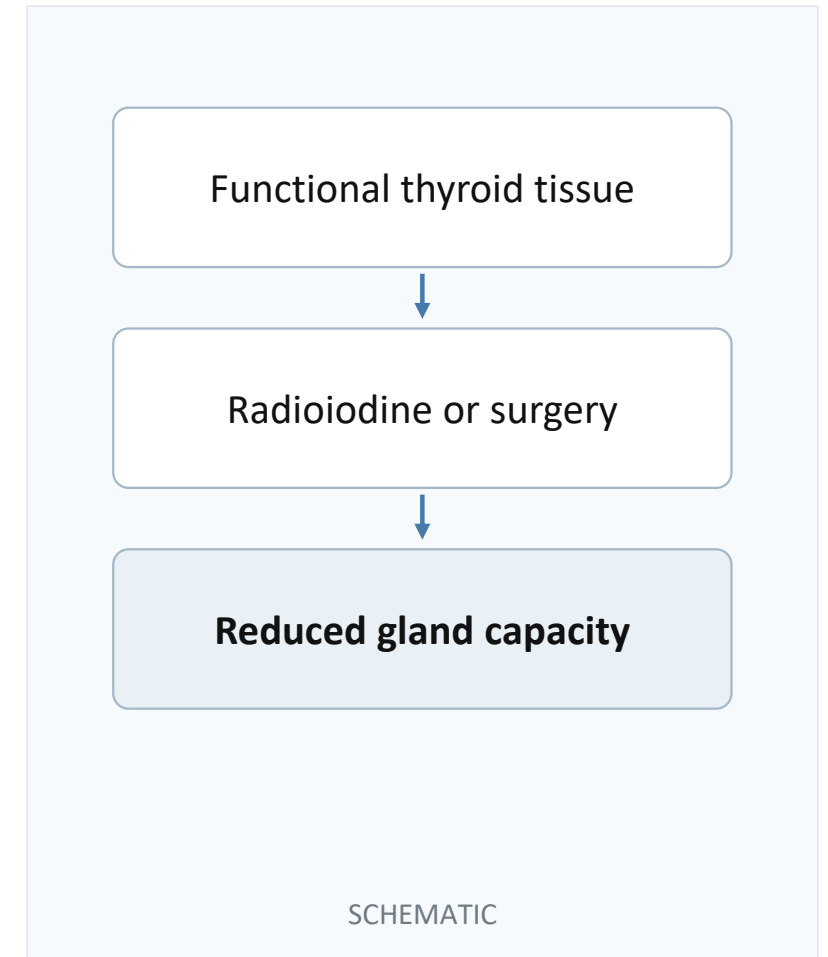
Peripheral T4-to-T3 conversion is another target

- T4 is converted to biologically potent T3 in peripheral tissues.
- Propylthiouracil inhibits this conversion in addition to inhibiting synthesis.
- The textbook also notes other agents capable of reducing peripheral conversion.



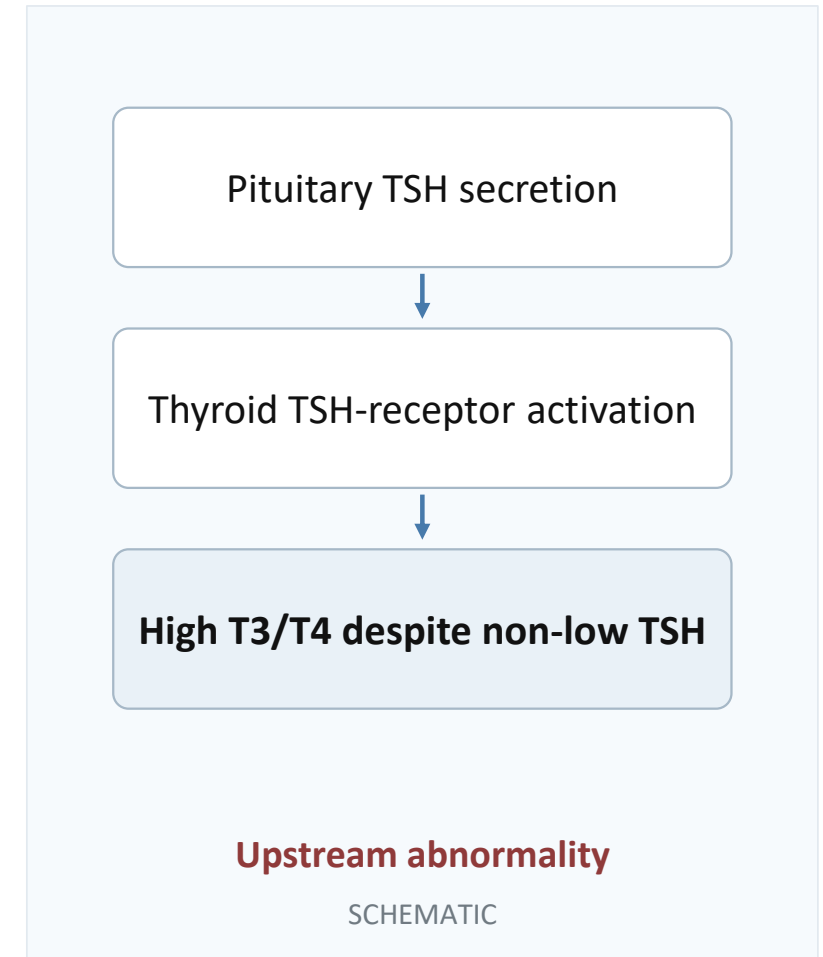
Definitive therapy removes functional thyroid tissue

- Radioactive iodine is taken up by thyroid tissue and ablates gland function.
- Thyroidectomy surgically removes hormone-producing tissue.
- Choice of definitive therapy depends on the underlying disease and clinical setting.



Pituitary-driven disease requires a different strategy

- TSH-secreting pituitary tumors are not autonomous thyroid disorders.
- Pituitary surgery, somatostatin analogs, or irradiation among options.
- Therapeutic logic must address the inappropriate upstream TSH stimulus.



Case: Diffuse thyrotoxicosis with a thyroid bruit

CLINICAL REASONING

- Illustrative case: Weight loss, tremor, diffuse enlarged thyroid, and suppressed TSH.
- Elevated free T4 and diffusely increased uptake support active glandular synthesis.
- A thyroid bruit and positive TSI would further favor Graves disease.

Which evidence localizes the cause?

Diffuse uptake and receptor antibodies favor Graves-mediated hyperfunction.

Illustrative teaching case

Case: Painful thyroid illness with hormone excess

CLINICAL REASONING

- Illustrative case: Neck pain, transient thyrotoxic symptoms, and suppressed TSH.
- Low uptake supports destructive release rather than increased synthesis.
- The underlying thyroiditis mechanism is central to treatment selection.

Why is the uptake low despite high thyroid hormone?

Stored hormone enters blood while new hormone synthesis is not increased.

Illustrative teaching case

Case: One active nodule

CLINICAL REASONING

- Illustrative case: Low TSH, excess hormone, and a dominant focal uptake region.
- A solitary hot nodule suggests toxic adenoma physiology.
- Surrounding relatively suppressed thyroid activity reinforces focal autonomy.

How does pituitary feedback shape the scan?

TSH suppression quiets surrounding nonautonomous thyroid tissue.

Illustrative teaching case

Case: New atrial fibrillation in an older adult

CLINICAL REASONING

- Illustrative case: Weight loss, new atrial fibrillation, and few obvious adrenergic signs.
- Apathetic hyperthyroidism remains plausible despite muted classic symptoms.
- Serum TSH followed by free hormone assessment provides the biochemical pathway.

What is the key diagnostic pitfall?

Older patients may exhibit predominantly cardiovascular manifestations.

Illustrative teaching case

Case: Severe febrile tachycardia after a stressor

CLINICAL REASONING

- Illustrative case: Known Graves disease, infection, fever, and marked tachycardia.
- Thyroid storm should be recognized as an urgent clinical syndrome.
- Arrhythmias can be fatal without emergency management.

What makes the presentation emergent?

Sudden decompensation with disproportionate tachycardia and systemic instability.

Illustrative teaching case

Integrating patterns at the bedside

- Graves: Diffuse production; Typically diffuse uptake; TRAb / TSI can be positive.
- Toxic adenoma: Focal production and a solitary increased-uptake nodule.
- Thyroiditis / extrathyroidal supply: Hormone excess despite low cervical uptake.

Pattern	Mechanism	Uptake
Graves	Diffuse stimulation	Diffuse high
Toxic adenoma	Focal autonomy	Focal high
Thyroiditis	Release of stores	Low

Biochemical similarity does not imply etiologic equivalence.

Five diagnostic errors to avoid

- Do not equate thyrotoxicosis with increased glandular synthesis.
- Do not mistake lid lag or stare for Graves-specific infiltrative orbitopathy.
- Do not exclude T3 thyrotoxicosis solely because free T4 is not elevated.
- Do not overlook biochemical hyperthyroidism in an older patient with arrhythmia.

CLINICOPATHOLOGIC LINK

A fifth error: Interpreting uptake or antibodies before establishing the hormonal state.

Interpretation

Synthesis: From hormones to mechanism

Clinical excess arises from hypermetabolism plus increased adrenergic tone.

TSH and free hormone tests establish the biochemical pattern.

Uptake and receptor antibodies help distinguish major etiologies.

Therapeutic targets differ for synthesis, release, and extrathyroidal supply.

Source

Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th edition (2026).

Primary section: Hyperthyroidism; contextual sections: Thyroid Gland, Graves Disease, and Multinodular Goiter.

All process diagrams and gland drawings in this lecture are original schematics, not clinical or histologic specimens.