

Graves Disease

Autoimmune thyroid hyperfunction and extrathyroidal lesions

Mechanism • Morphology • Clinicopathologic correlation

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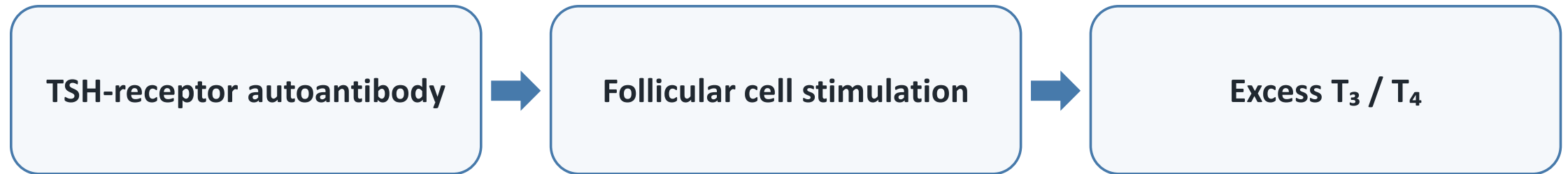
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Learning outcomes

- Explain how stimulating TSH-receptor autoantibodies create primary hyperthyroidism.
- Recognize the characteristic thyroid and extrathyroidal morphology.
- Integrate clinical findings, hormone tests, antibodies, and uptake patterns.
- Distinguish Graves disease from other major causes of thyrotoxicosis.

Graves disease: Receptor-driven hyperthyroidism

- An autoimmune disorder in which TSH-receptor stimulation drives excess thyroid hormone production.
- Produces diffuse enlargement and hyperfunction of the thyroid gland.
- Characteristic extrathyroidal lesions are orbitopathy and, less commonly, dermopathy.

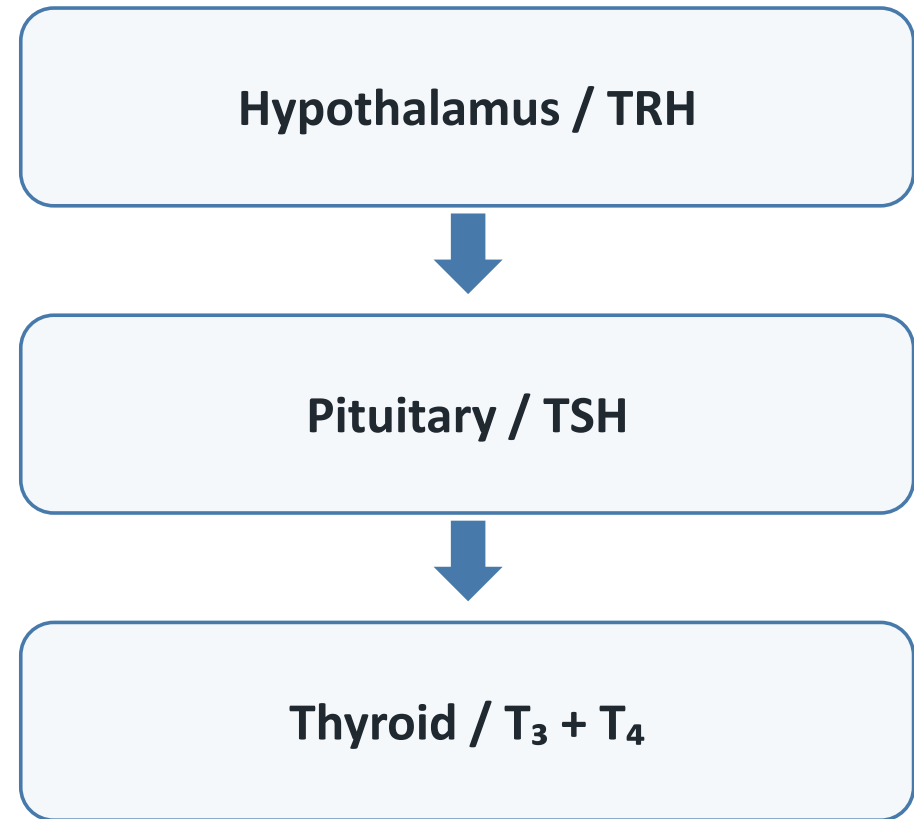


Hyperthyroidism versus thyrotoxicosis

Concept	Thyrotoxicosis	Hyperthyroidism
Meaning	Hormone excess in tissues	Increased gland production
Graves disease	Present	Present
Destructive thyroiditis	May be present	Not the cause

Normal hypothalamic–pituitary–thyroid feedback

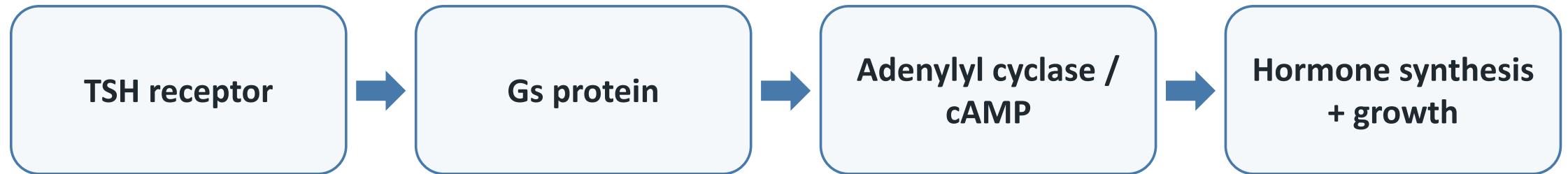
- Hypothalamic TRH promotes pituitary TSH secretion.
- TSH binds the follicular-cell receptor and stimulates hormone synthesis and release.
- T_3 and T_4 suppress TRH and TSH by negative feedback.



T_3/T_4 inhibit TRH and TSH

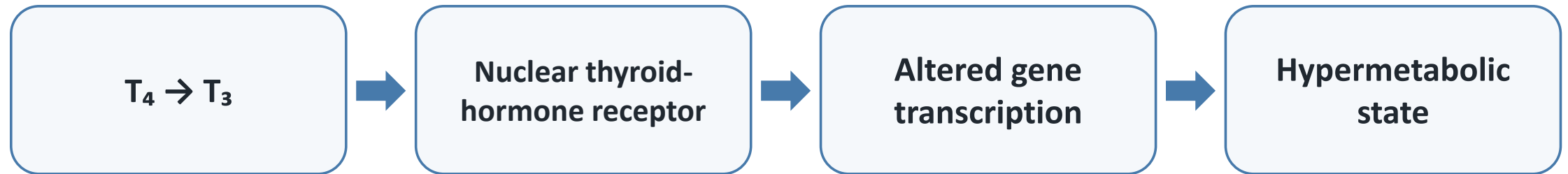
TSH receptor: A cAMP-linked signaling pathway

- TSH receptor activation couples to Gs-protein signaling.
- Increased intracellular cAMP activates downstream effector pathways.
- Follicular-cell growth and thyroid hormone production increase.



Why excess thyroid hormone produces symptoms

- T_4 is converted in peripheral tissues to the more active T_3 .
- Thyroid hormone receptors regulate target-gene expression.
- Increased metabolic activity and β -adrenergic responsiveness generate the clinical syndrome.



Causes of thyrotoxicosis: Source matters

Mechanism	Examples	Typical gland output
Increased synthesis	Graves; toxic nodules	Increased
Hormone leakage	Granulomatous / painless thyroiditis	Not increased
Outside source	Exogenous thyroid hormone	Not increased

The characteristic Graves clinical triad

Diffuse toxic goiter

**Infiltrative
ophthalmopathy**

Pretibial dermopathy

The three manifestations do not necessarily coexist in every patient.

Epidemiologic profile

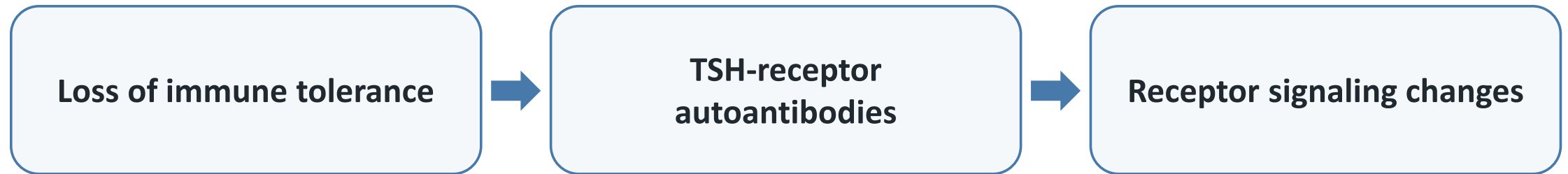
- Peak incidence occurs between 20 and 50 years of age.
- Females are affected approximately 5–10 times more frequently than males.
- The disease is the leading cause of endogenous hyperthyroidism.

Clinical / pathologic inference

The demographic pattern
increases suspicion;
Laboratory and etiologic tests
establish the diagnosis.

Graves disease is an autoimmune receptoropathy

- Multiple thyroid-directed autoantibodies may circulate.
- The most pathophysiologically important target is the TSH receptor.
- Autoantibody effects on the receptor can be stimulating or blocking.

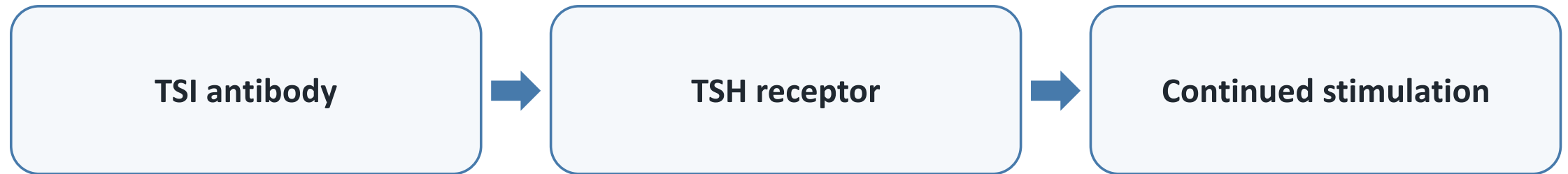


Stimulating and blocking TSH-receptor antibodies

Receptor antibody	Functional effect	Possible phenotype
Stimulating	Mimics TSH signaling	Hyperthyroidism
Blocking	Opposes receptor activation	Hypothyroidism in some patients

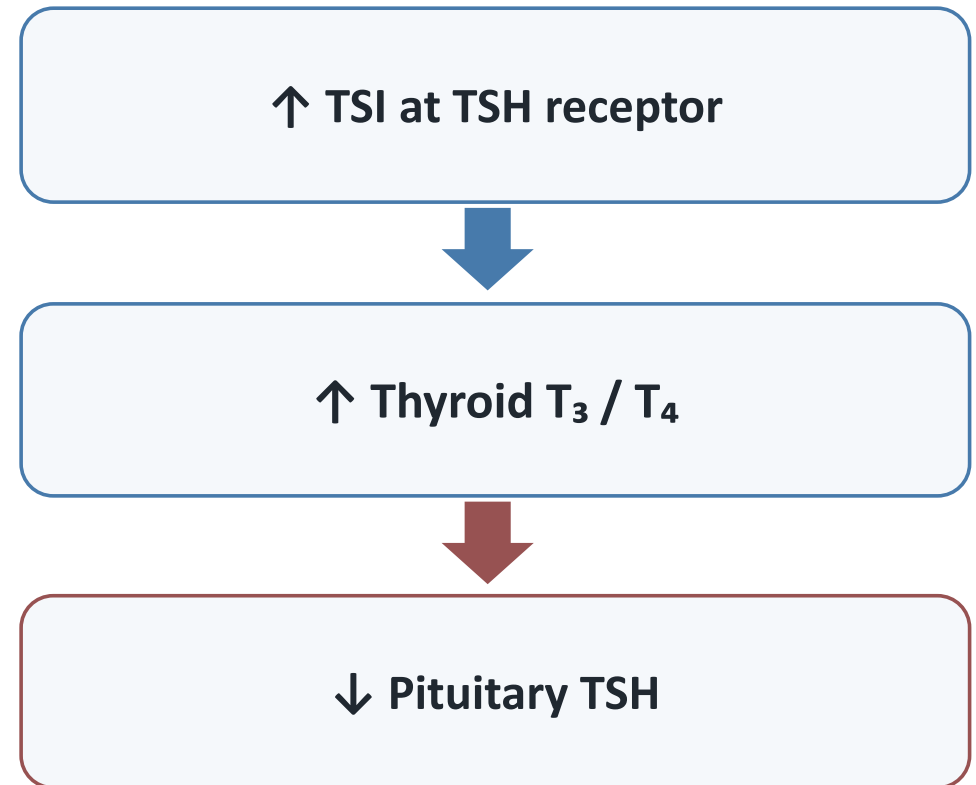
Thyroid-stimulating immunoglobulin (TSI)

- TSI is the most common antibody subtype described in Graves disease.
- TSI in approximately 90% of patients.
- TSI directly mimics the action of pituitary TSH at the receptor.



A ligand mimic bypasses normal feedback

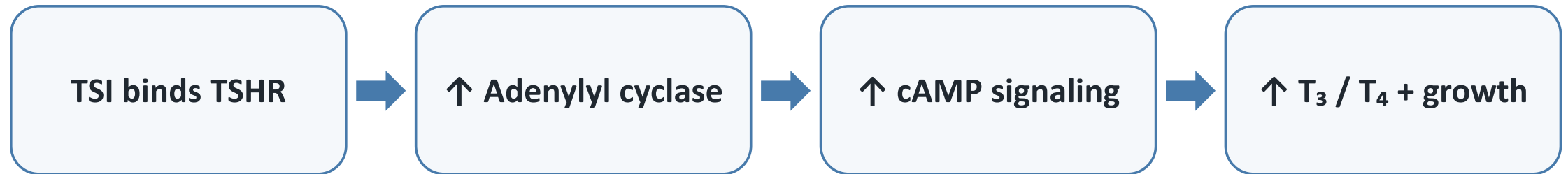
- TSI occupancy stimulates the thyroid even when pituitary TSH is low.
- Normal feedback appropriately decreases circulating TSH.
- Autoantibody-driven receptor signaling nevertheless persists.



Autoantibody stimulation persists

The direct mechanism of hormone excess

- TSI binds to the TSH receptor on follicular epithelial cells.
- Receptor activation increases adenylyl cyclase activity.
- Enhanced signaling drives thyroid hormone release and follicular growth.



Autoantibody specificity: TSI versus anti-TPO

Antibody	Main significance
TSI / stimulating TRAb	Direct receptor-mediated hyperfunction
Anti-thyroid peroxidase	Marker of thyroid autoimmunity
Anti-thyroglobulin	Marker of thyroid autoimmunity

Genetic susceptibility is substantial, not deterministic

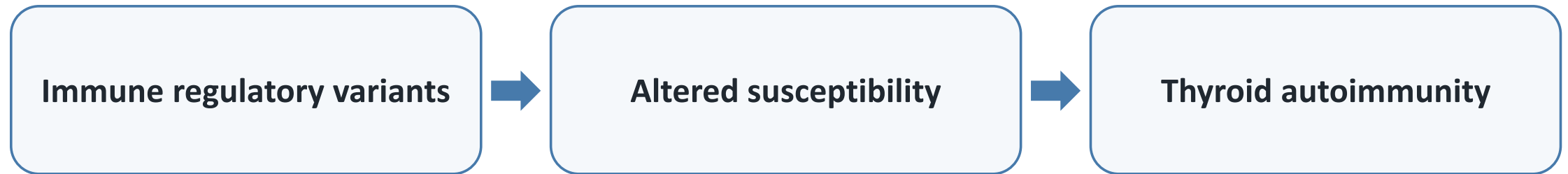
- Monozygotic twin concordance is reported at approximately 30–40%.
- Dizygotic twin concordance is less than 5%.
- Incomplete concordance supports influences beyond inherited genotype.

Clinical / pathologic inference

Twin concordance demonstrates heritable predisposition but does not establish a single-gene disorder.

Immune-function loci in Graves susceptibility

- Robbins implicates variants associated with CTLA4, PTPN22, and IL2RA.
- These loci have roles in immune regulation.
- Their shared associations support an autoimmune predisposition.



TSHR genetic variation contributes to risk

- Genome-wide association studies implicate TSHR susceptibility variants.
- This connects the principal autoantigen with inherited disease risk.
- Susceptibility variants are not themselves diagnostic of active Graves disease.

Clinical / pathologic inference

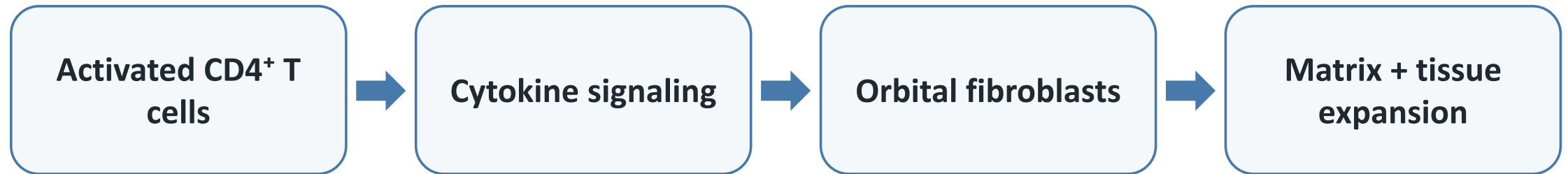
TSHR is simultaneously the principal pathogenic autoantibody target and a susceptibility locus.

Why Graves and Hashimoto disease overlap

Feature	Graves disease	Hashimoto thyroiditis
Dominant outcome	Hyperfunction	Destructive failure
Principal mechanism	TSHR stimulation	Immune follicular injury
Common clinical course	Thyrotoxicosis	Hypothyroidism

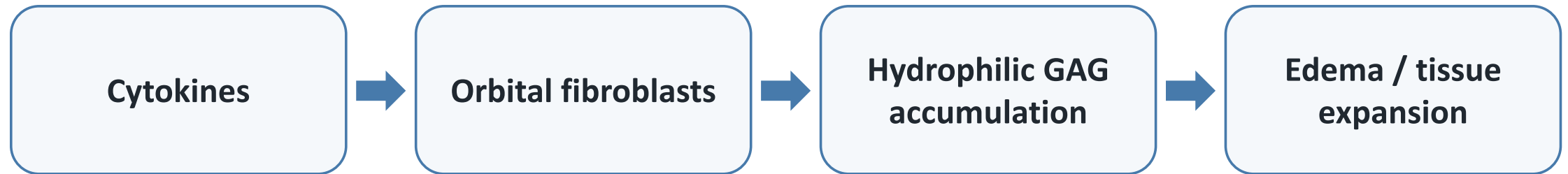
Orbitopathy involves a distinct immune tissue response

- Activated CD4⁺ helper T cells contribute to retro-orbital inflammation.
- Secreted cytokines stimulate fibroblast proliferation and matrix synthesis.
- The resulting change occurs outside the thyroid gland.



Fibroblast matrix synthesis drives orbital swelling

- Stimulated fibroblasts increase extracellular matrix glycosaminoglycans.
- Hyaluronic acid and chondroitin sulfate bind water.
- Hydrophilic matrix expansion contributes to edema and tissue volume increase.



Four contributors to increased orbital volume

- Mononuclear inflammatory-cell infiltration, principally T cells.
- Extraocular-muscle inflammation and edema.
- Hydrophilic glycosaminoglycan accumulation in connective tissue.
- An increase in retro-orbital adipocytes.

**Immune
infiltration**

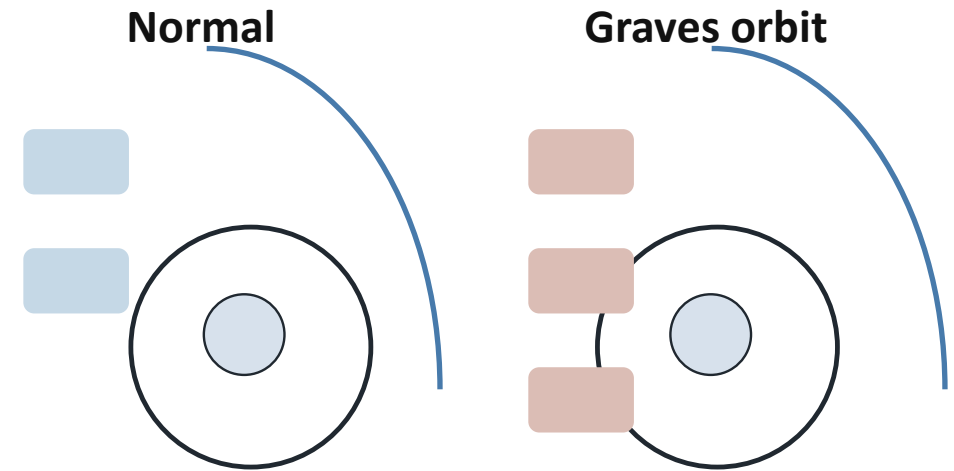
Muscle edema

GAG accumulation

Adipose expansion

Exophthalmos reflects restricted orbital space

- Retro-orbital connective tissue and extraocular muscles expand.
- Orbital contents displace the globe anteriorly.
- The same process may compromise extraocular-muscle function.

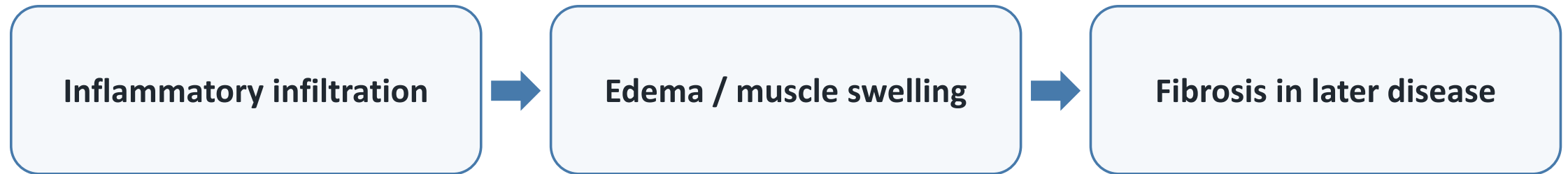


Expanding tissue → globe displacement

Schematic — not a specimen

Orbital inflammation may evolve into fibrosis

- Early orbital muscles and connective tissue are edematous.
- Continued inflammation may lead to fibrosis of involved muscle.
- Late structural change helps explain persistent ocular dysfunction.

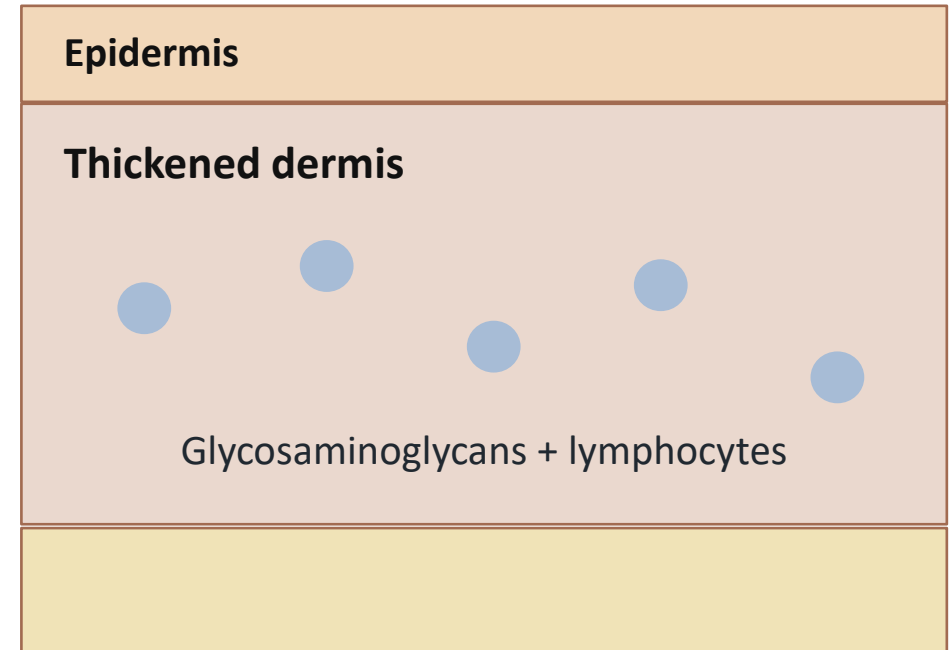


Exophthalmos and lid lag are not equivalent

Finding	Underlying basis
Exophthalmos	Infiltrative orbital tissue expansion
Lid lag	Sympathetic stimulation of eyelid elevation
Staring gaze	Sympathetic overactivity

Pretibial myxedema is an infiltrative dermatopathy

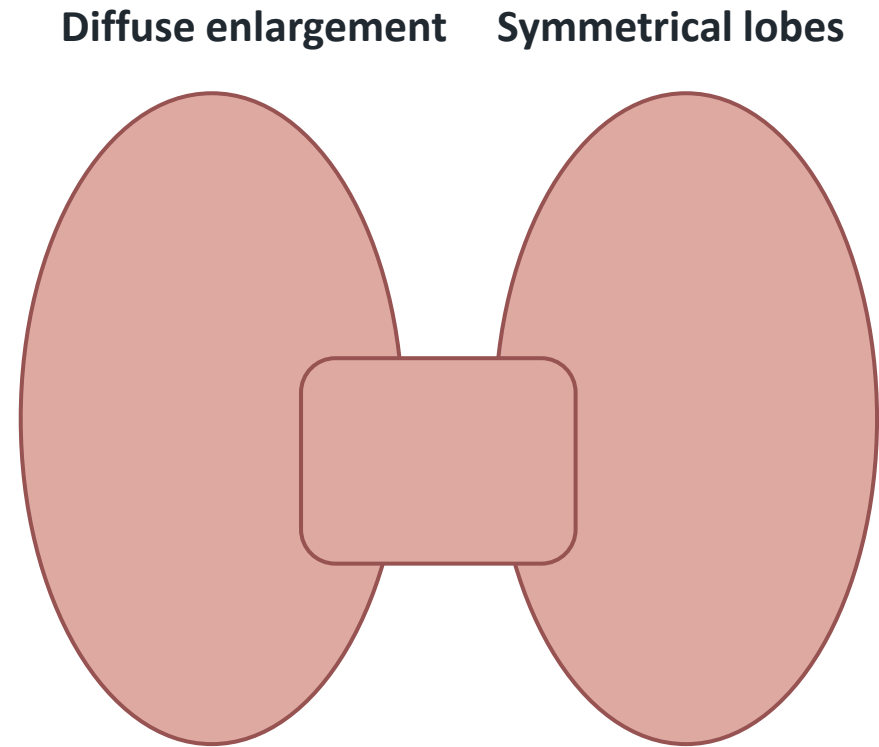
- Dermal fibroblast-associated matrix accumulation thickens the skin.
- Glycosaminoglycan deposition and lymphocyte infiltration underlie the lesion.
- Clinical involvement occurs in a minority of Graves patients.



Schematic — not a specimen

Gross thyroid morphology: Diffuse and symmetrical

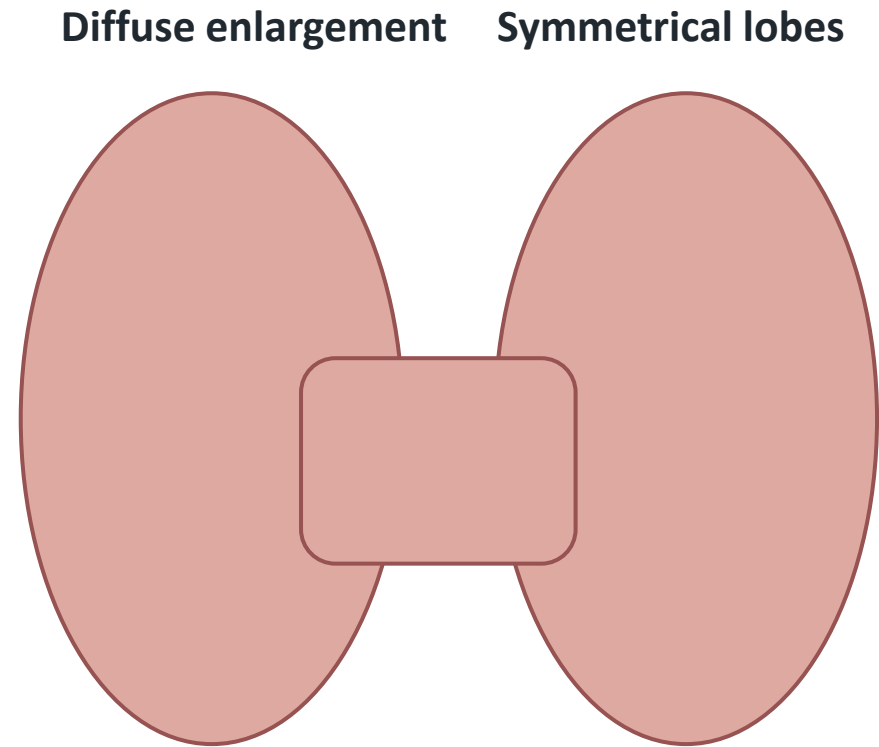
- The thyroid is usually diffusely enlarged and symmetric.
- Diffuse follicular epithelial hypertrophy and hyperplasia increase gland mass.
- Weights over 80 g are not uncommon.



Schematic — not a specimen

Gross cut surface in Graves disease

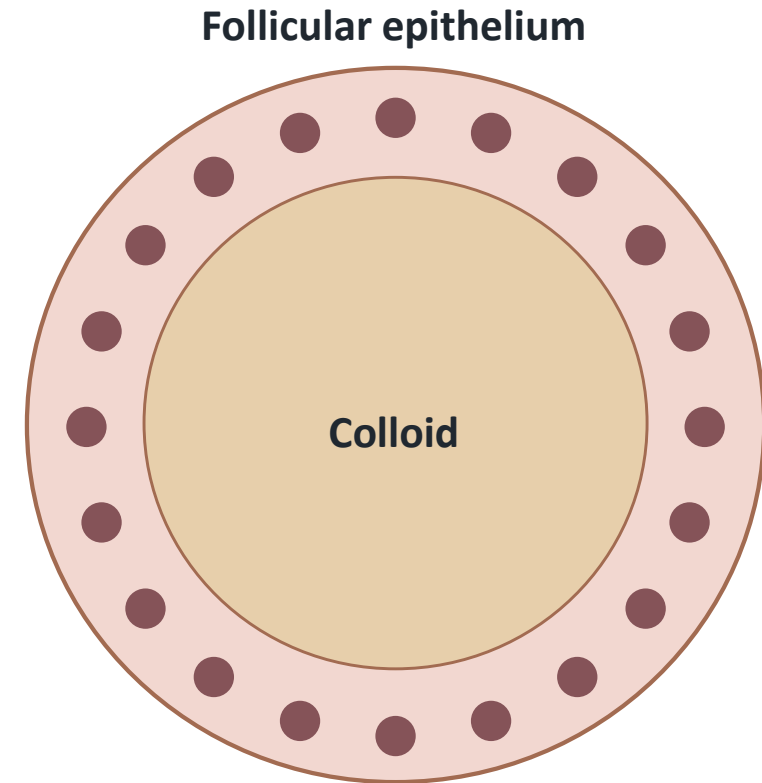
- Parenchyma is classically soft and brown-red.
- The gland may appear beefy deep red on gross examination.
- This diffuse pattern contrasts with nodular and heterogeneous goiters.



Schematic — not a specimen

Follicles respond to chronic receptor stimulation

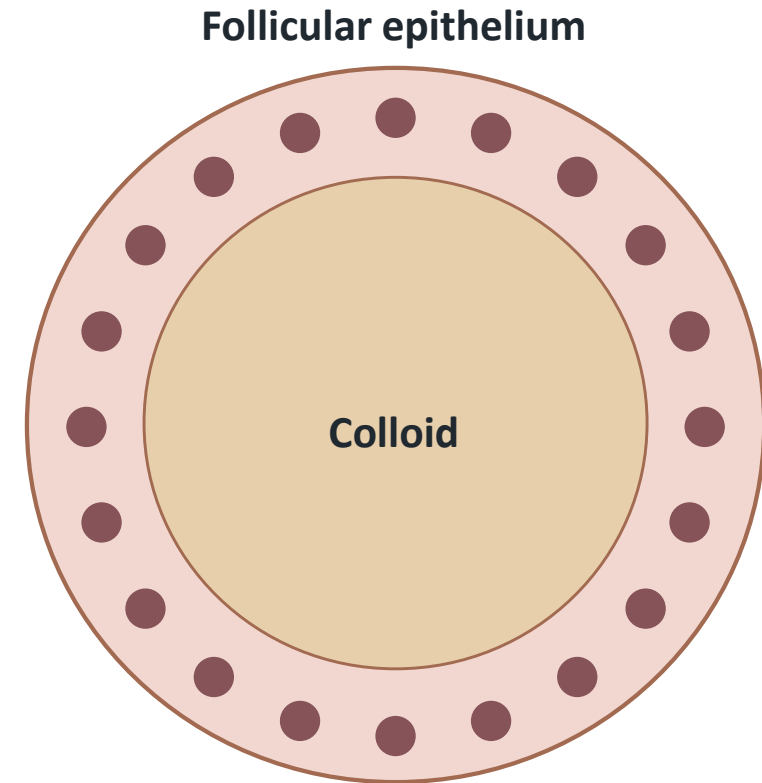
- The epithelial lining becomes taller and more cellular.
- Crowded cells narrow the space available for luminal colloid.
- The picture reflects active hormone production and resorption.



Schematic — not a specimen

Untreated Graves: Tall columnar follicular cells

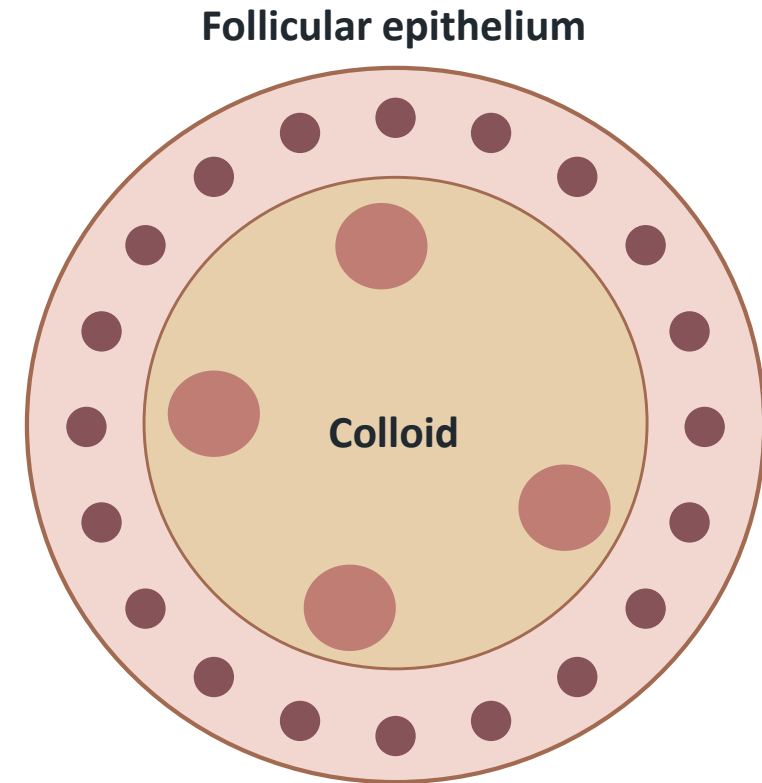
- Follicular epithelial cells are typically tall rather than flat.
- Increased cell height and crowding are distributed diffusely.
- The appearance is best assessed with untreated-tissue context.



Schematic — not a specimen

Intraluminal epithelial projections

- Crowded follicular epithelium forms small projections into follicle lumens.
- Some hyperplastic folds encroach substantially on luminal colloid.
- The projections are an epithelial response to trophic stimulation.



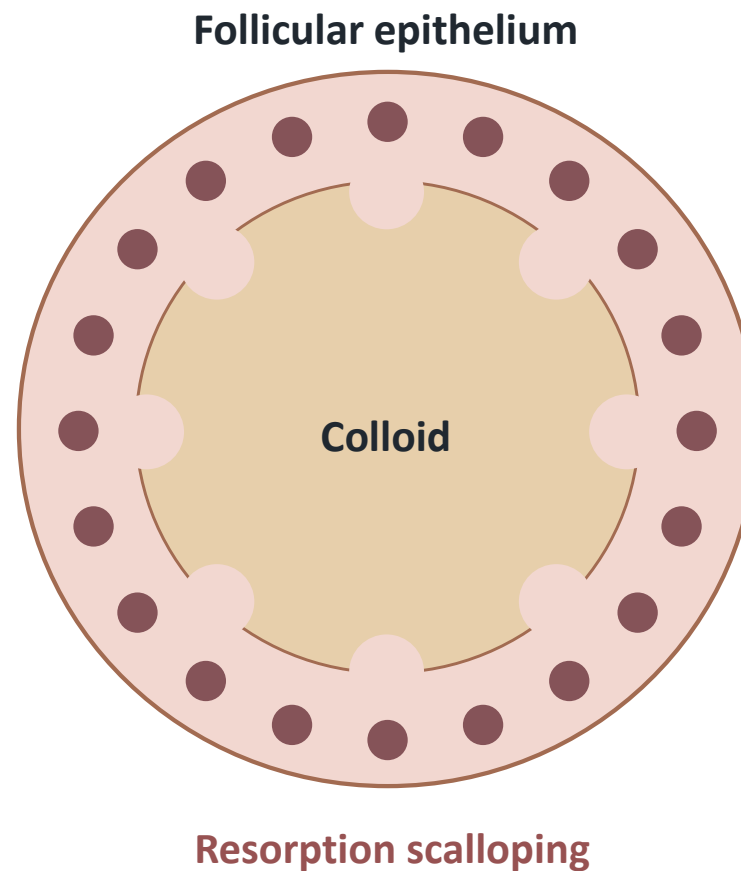
Schematic — not a specimen

Graves micropapillae lack fibrovascular cores

Feature	Graves epithelial fold	True papilla
Core	No fibrovascular core	Fibrovascular core present
Context	Diffuse follicular hyperplasia	Requires broader tumor assessment

Scalloped colloid signals active resorption

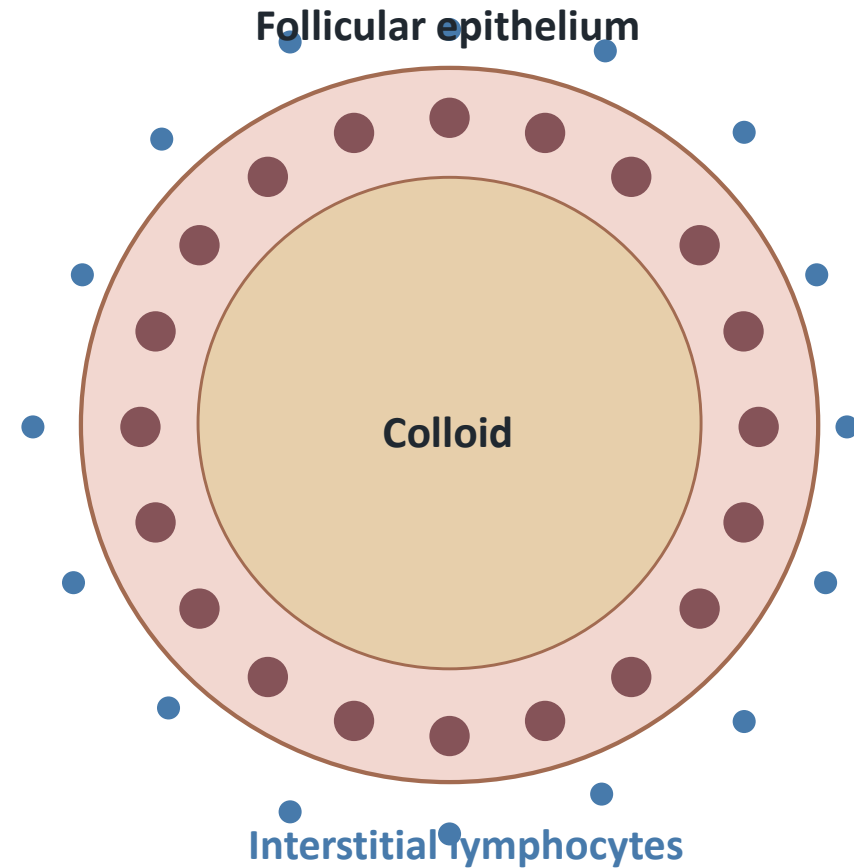
- Follicular cells actively resorb thyroglobulin-rich colloid.
- Luminal colloid becomes pale with irregular scalloped edges.
- Scalloping should be interpreted together with epithelial hyperplasia.



Schematic — not a specimen

Interstitialium contains lymphoid inflammation

- Predominantly T-cell lymphocytes occur between follicles.
- Scattered B cells and mature plasma cells also occur.
- The inflammatory infiltrate reinforces the autoimmune pathogenesis.



Schematic — not a specimen

Germinal centers may be conspicuous

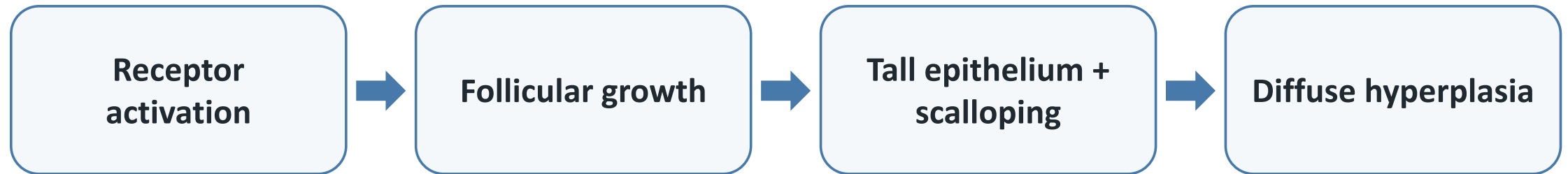
- Lymphoid aggregates may develop germinal centers.
- Germinal centers are common in Graves thyroid tissue.
- They are not exclusive to Graves: Correlation with endocrine function matters.

Clinical / pathologic inference

Autoimmune thyroid histology must be integrated with the gland's functional state.

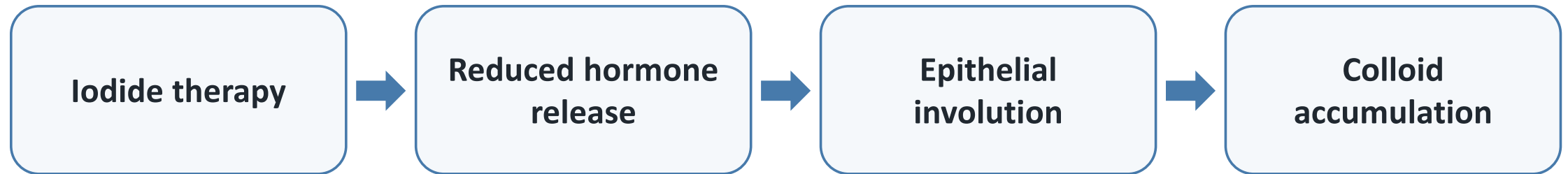
Morphologic sequence: Signal to follicle

- TSH-receptor stimulation promotes growth and endocrine activity.
- Follicles develop crowded tall epithelium and resorption vacuoles.
- The integrated finding is diffuse hyperplastic activity.



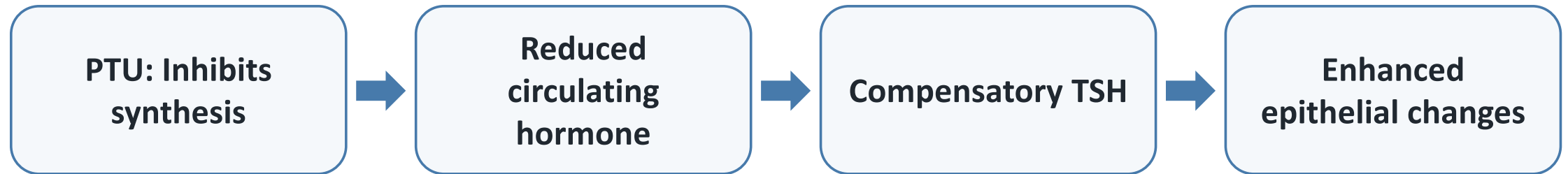
Iodine treatment alters the histologic pattern

- Preoperative iodide can cause involution of stimulated follicular epithelium.
- Colloid accumulates as thyroglobulin release is blocked.
- Pretreatment may therefore partially obscure untreated morphology.



Propylthiouracil can accentuate hyperplasia

- Exaggerated epithelial hypertrophy and hyperplasia after PTU.
- Reduced hormone synthesis can induce compensatory trophic signaling.
- Medication history is essential when interpreting thyroidectomy morphology.



Histology depends on treatment context

Setting	Epithelial appearance	Colloid
Untreated	Tall / crowded	Scalloped
Iodide treated	Involution	Accumulated
PTU treated	Hyperplasia may increase	Variable

Generalized lymphoid tissue can respond

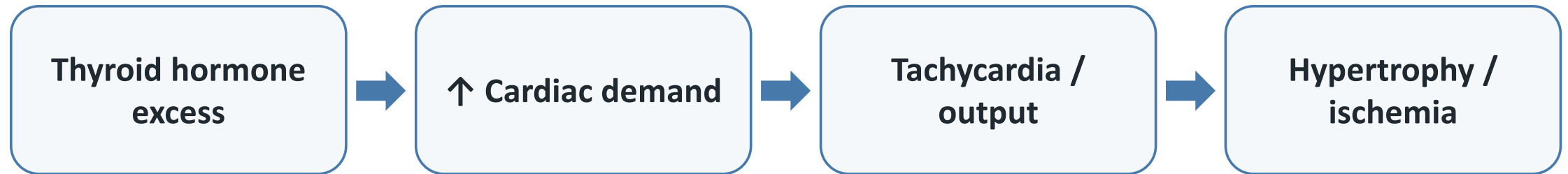
- Graves disease may cause lymphoid hyperplasia beyond the thyroid.
- Thymic enlargement is especially described in younger patients.
- This reflects systemic immune activation rather than a thyroid malignancy.

Clinical / pathologic inference

Thymic enlargement can accompany autoimmune hyperthyroidism in younger patients.

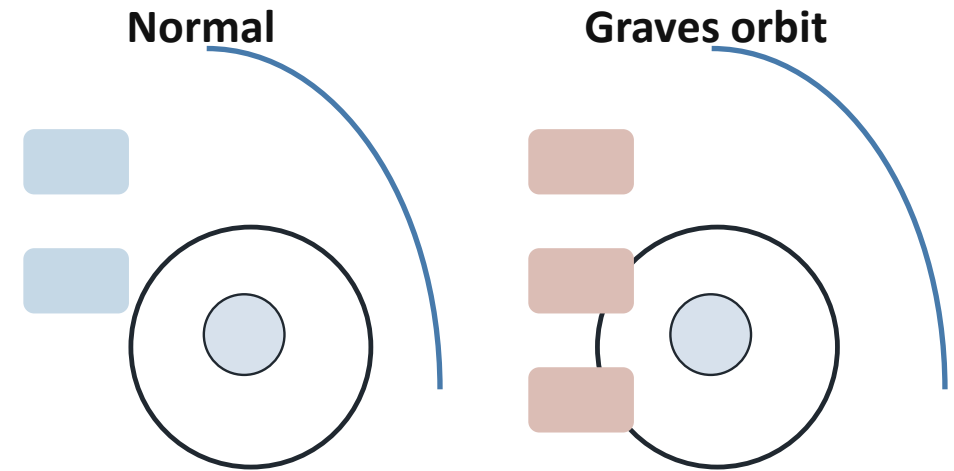
Cardiac pathology is clinically important

- Sustained thyrotoxicosis increases cardiac workload.
- Cardiac hypertrophy may develop with long-standing disease.
- Ischemic changes are especially relevant with preexisting coronary artery disease.



Histologic substrate of orbital disease

- Edema and hydrophilic matrix are present in orbital connective tissue.
- Lymphocytes infiltrate the expanded retro-orbital tissue.
- Extraocular muscle fibrosis can appear in later disease.

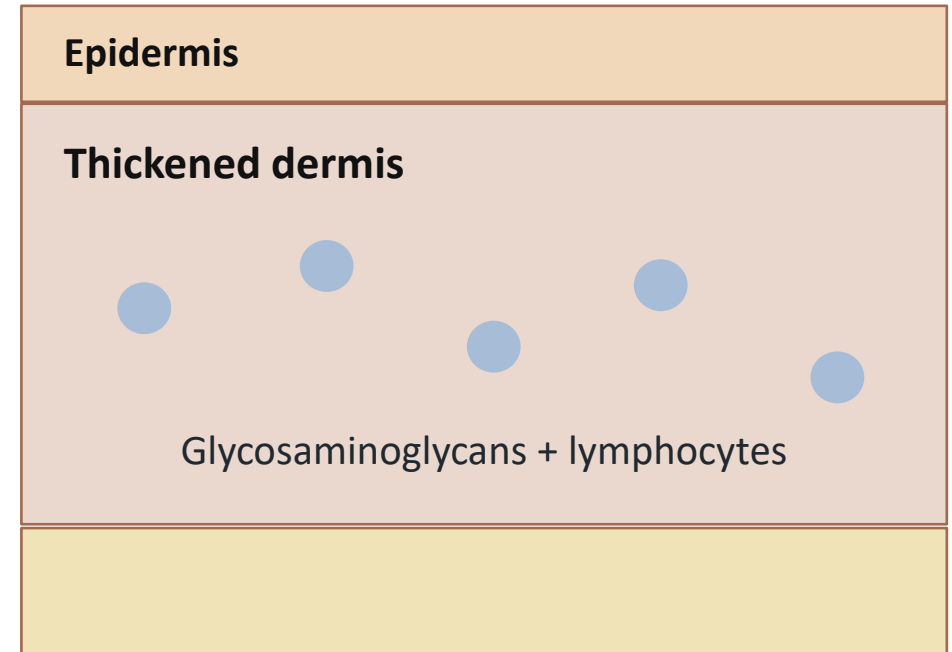


Expanding tissue → globe displacement

Schematic — not a specimen

Skin pathology: Dermal glycosaminoglycans

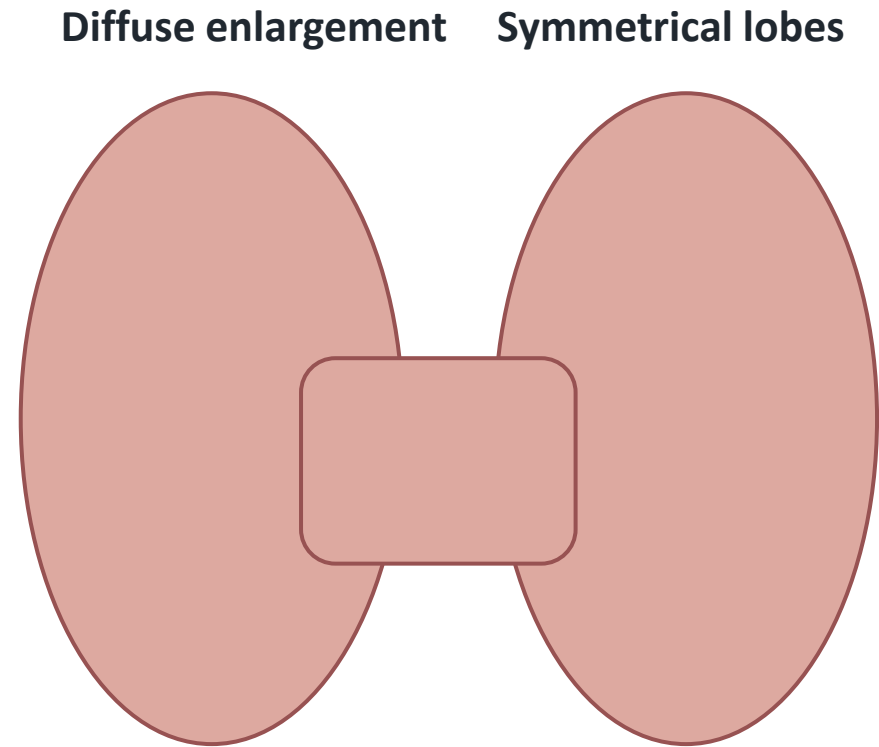
- Infiltrative dermatopathy produces dermal thickening.
- Glycosaminoglycans accumulate among connective-tissue elements.
- Lymphocytic infiltration is also observed.



Schematic — not a specimen

Diffuse goiter may produce a bruit

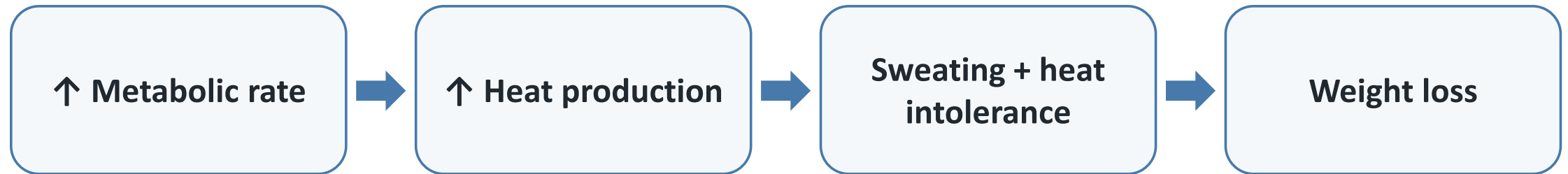
- Thyroid enlargement is generally diffuse rather than nodular.
- Marked gland hyperactivity increases thyroid blood flow.
- In some patients, vascular flow is sufficient to produce an audible bruit.



Schematic — not a specimen

Metabolic consequences of excess thyroid hormone

- Increased basal metabolic rate causes heat intolerance and sweating.
- Weight loss may occur despite increased appetite.
- Peripheral vasodilation gives the skin a warm, flushed quality.



Cardiovascular presentation of thyrotoxicosis

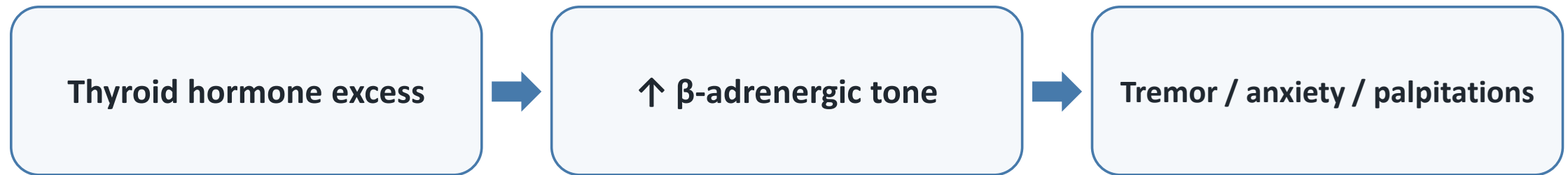
- Tachycardia and palpitations may occur early.
- Increased output and cardiac contractility contribute to physiologic strain.
- Atrial fibrillation and heart failure particularly affect vulnerable older adults.

Clinical / pathologic inference

Cardiovascular findings can be the presenting clue to thyroid hormone excess.

Adrenergic overactivity drives neurobehavioral signs

- Tremor, anxiety, insomnia, and emotional lability are characteristic.
- Restlessness and impaired concentration can be prominent.
- These effects are often controlled rapidly by β -adrenergic blockade.



Muscle, gut, and skeletal consequences

- Proximal muscle weakness and reduced muscle mass may occur.
- Intestinal hypermotility can cause increased stool frequency.
- Increased bone resorption raises the risk of osteoporosis and fractures.

**Proximal
weakness**

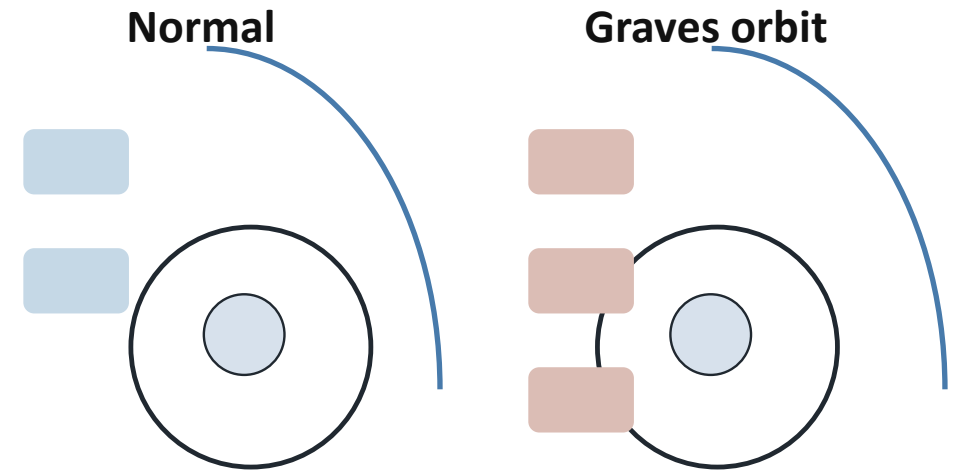
Hypermotility

Bone resorption

Catabolic effects

Ocular complications can persist after control

- Exophthalmos may persist or progress despite treatment of thyrotoxicosis.
- Extraocular muscle dysfunction may affect eye movements.
- Severe exposure can damage the corneal surface.

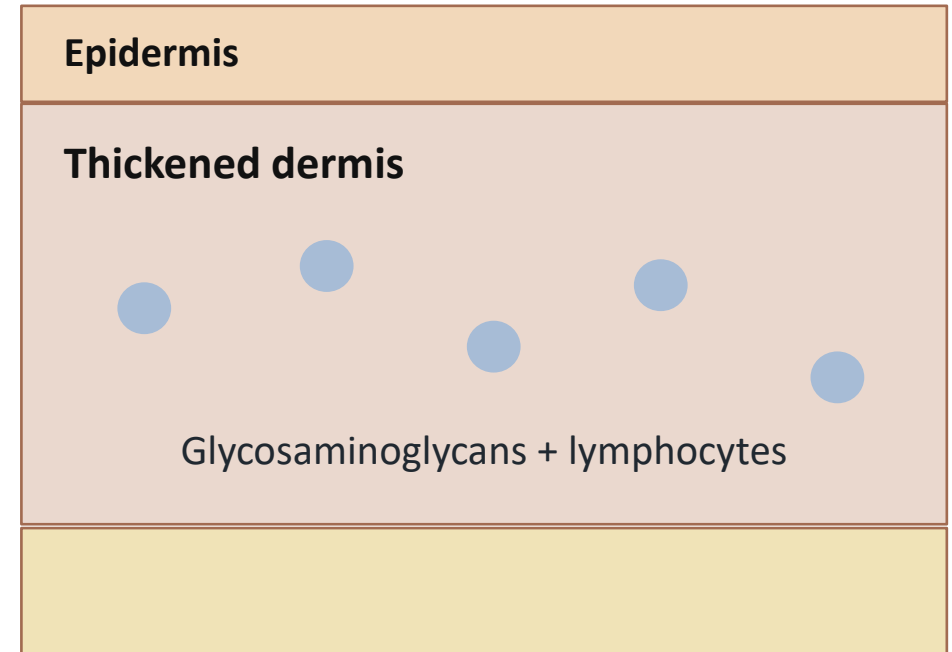


Expanding tissue → globe displacement

Schematic — not a specimen

Typical pretibial clinical findings

- Dermopathy occurs in only a minority of Graves patients.
- Skin over the shins becomes thickened, indurated, and sometimes scaly.
- The lesion is mechanistically distinct from ordinary hypermetabolic skin warmth.



Schematic — not a specimen

Associated autoimmune disorders

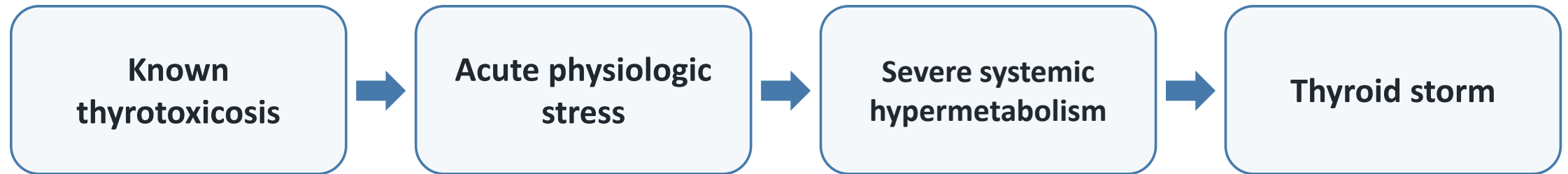
- Graves patients have an increased risk of other autoimmune conditions.
- Pernicious anemia, type 1 diabetes, Addison disease, and systemic lupus erythematosus.
- Autoimmune clustering is consistent with shared immune susceptibility.

Clinical / pathologic inference

The coexistence of another autoimmune disease does not alter the mechanism of Graves hyperthyroidism.

Thyroid storm: Acute decompensation

- A sudden severe thyrotoxic state may arise in Graves disease.
- Potential triggers include infection, surgery, drug cessation, and other stress.
- Fever and disproportionate tachycardia indicate a medical emergency.



Apathetic hyperthyroidism in older adults

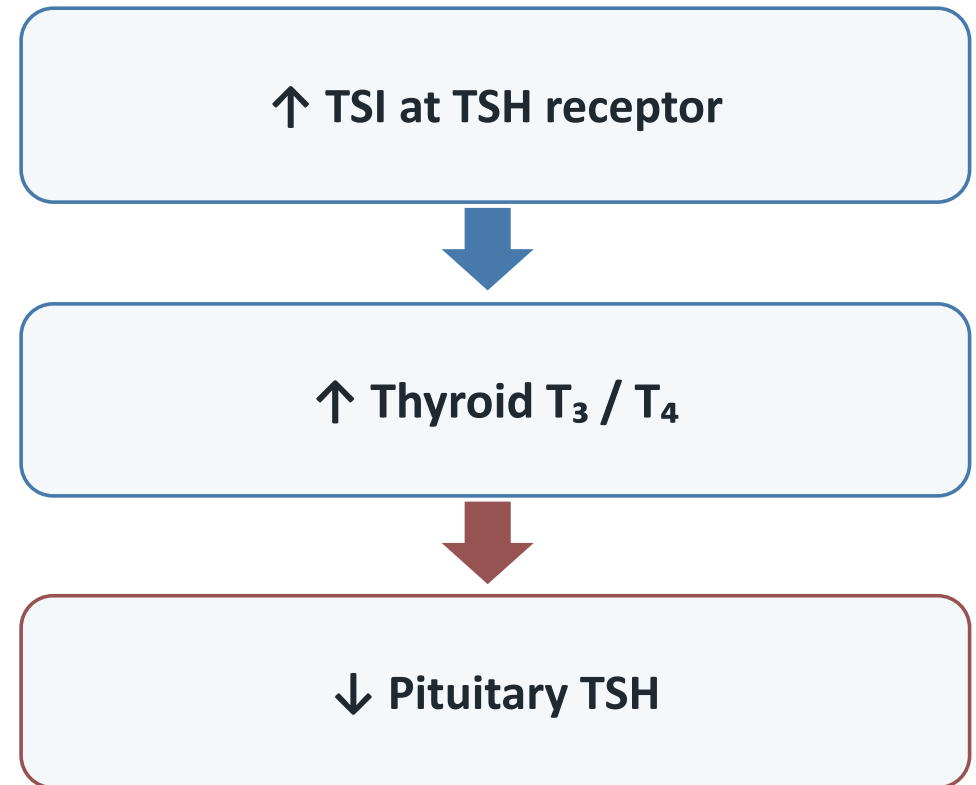
- The expected hyperadrenergic manifestations can be blunted.
- Unexplained weight loss or worsening cardiac disease may dominate.
- A suppressed TSH may reveal the disorder despite few classic symptoms.

Clinical / pathologic inference

The absence of obvious tremor or agitation does not exclude thyrotoxicosis in older patients.

Biochemical pattern of primary Graves disease

- Serum TSH is typically decreased due to negative feedback.
- Free T₄ and/or T₃ are elevated during overt thyrotoxicosis.
- The low TSH level does not imply that the thyroid gland is unstimulated.



Autoantibody stimulation persists

T₃-predominant thyrotoxicosis

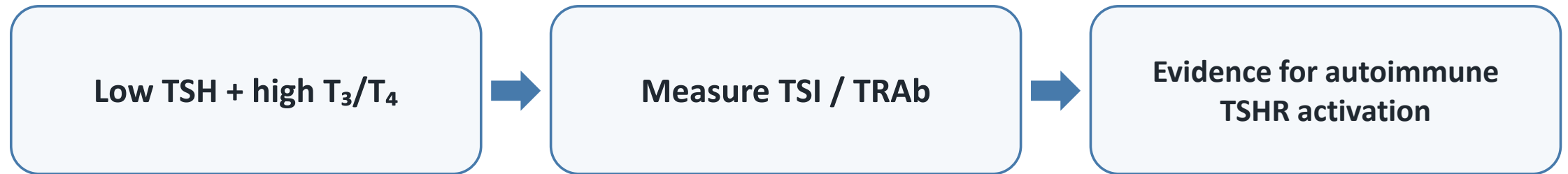
- Some hyperthyroid patients show predominantly increased circulating T₃.
- Free T₄ may not be elevated in that setting.
- Measuring T₃ can clarify low-TSH presentations with nondiagnostic free T₄.

Clinical / pathologic inference

TSH screening should be followed by the appropriate free-hormone measurements.

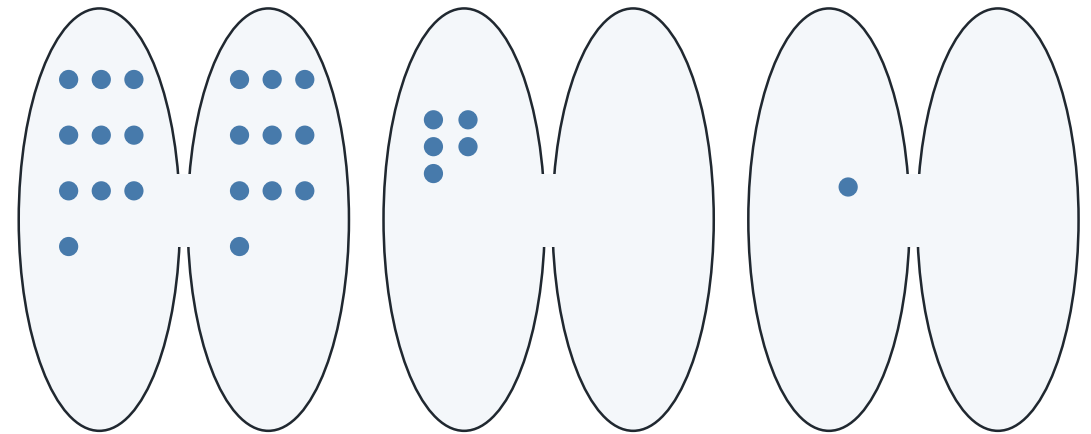
TSI and TSH-receptor antibody testing

- TSI detects stimulating receptor-directed immunoglobulin activity.
- TSH-receptor antibody assays provide etiologic evidence for Graves disease.
- Antibody type and functional effect are important conceptual distinctions.



Radioiodine uptake: Diffusely increased in Graves

- Persistent receptor activation increases iodine trapping throughout the gland.
- Radioiodine studies show a diffuse increase in uptake.
- The distribution helps separate Graves from focal toxic nodules and thyroiditis.



Diffuse Graves

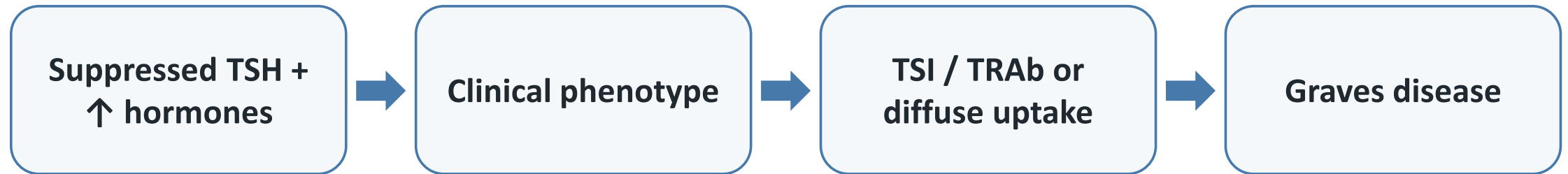
Focal nodule

Thyroiditis

Conceptual patterns; Not radionuclide scans

Integrated diagnostic reasoning

- Establish thyrotoxicosis biochemically with TSH and free thyroid hormones.
- Identify a diffuse, hypervascular goiter and any characteristic extrathyroidal features.
- Support etiology with receptor antibodies or a diffuse uptake pattern.



Major causes of primary thyrotoxicosis

Disease	Gland pattern	Functional driver
Graves	Diffuse symmetric	TSHR autoantibodies
Toxic adenoma	Solitary hot nodule	Autonomous nodule
Toxic MNG	Multinodular	Autonomous nodules

Graves versus diffuse nontoxic goiter

Feature	Graves	Diffuse nontoxic goiter
Typical function	Hyperthyroid	Usually euthyroid
Growth stimulus	Stimulating TSHR antibody	Compensatory TSH
Colloid	Often scalloped	Often abundant in involution

Graves versus Hashimoto thyroiditis

Feature	Graves	Hashimoto
Mechanism	Receptor stimulation	Follicular destruction
Epithelium	Tall / hyperplastic	Oncocytic change
Function	Usually hyperthyroid	Usually hypothyroid

Graves versus destructive thyroiditis

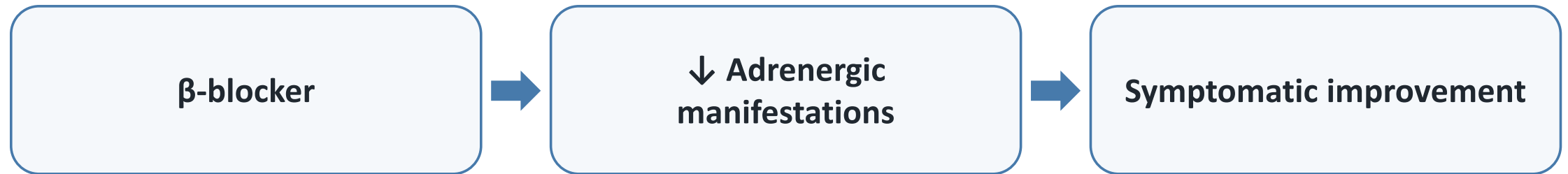
Feature	Graves	Destructive thyroiditis
Source of hormone	Increased production	Leakage of stored hormone
Radioiodine uptake	Diffusely increased	Decreased
TSHR autoantibody	Supports diagnosis	Not the causal mechanism

Therapeutic mechanisms address different targets

Intervention	Immediate target
β -blocker	Adrenergic symptoms
Methimazole / PTU	Thyroid hormone synthesis
Radioiodine / surgery	Functional thyroid tissue

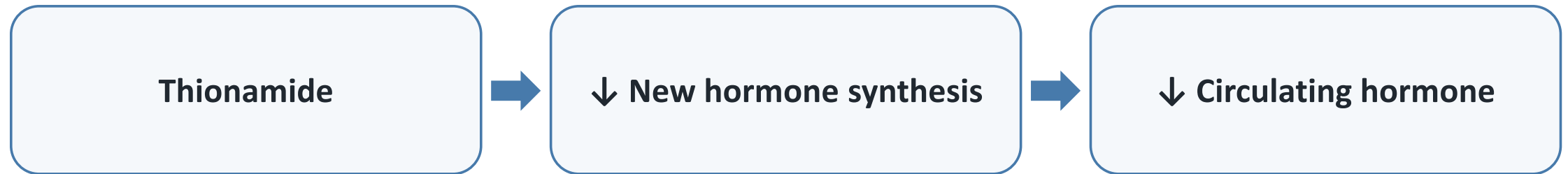
Symptom control is not suppression of autoimmunity

- β -blockade improves palpitations, tachycardia, tremor, and anxiety.
- It does not neutralize TSH-receptor autoantibodies.
- Hormone synthesis or functional gland mass must also be addressed.



Antithyroid drugs act on hormone synthesis

- Methimazole and propylthiouracil inhibit thyroid hormone biosynthesis.
- Propylthiouracil also impedes peripheral T_4 -to- T_3 conversion.
- Therapy may change the histology subsequently observed in resection specimens.

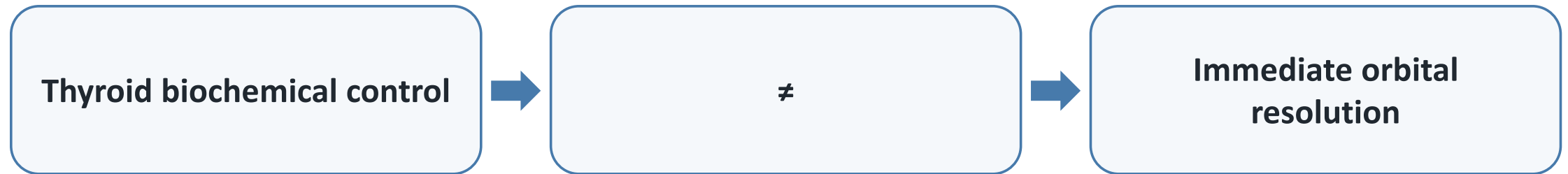


Definitive options target the gland

Option	Core effect
Radioiodine	Destroys functional thyroid cells
Thyroidectomy	Removes thyroid tissue
Clinical choice	Requires individual assessment

Orbitopathy may not track hormone normalization

- The orbit has a locally sustained immune and matrix-remodeling component.
- Controlling thyroid hormone does not always reverse established structural changes.
- Clinical assessment must separately consider thyroid function and eye involvement.



Case 1: Interpret the biochemical phenotype

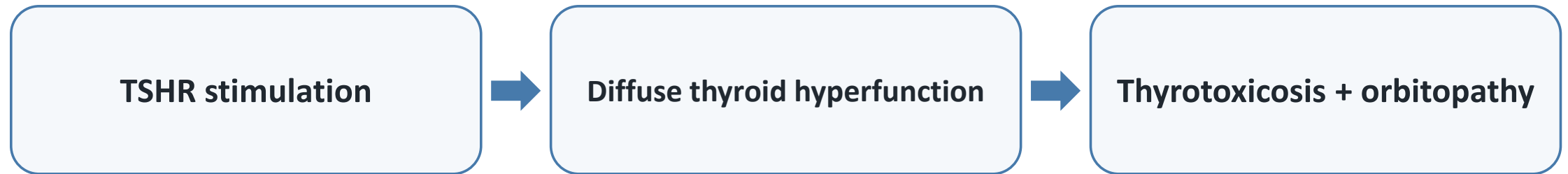
- A 31-year-old patient has weight loss, tremor, palpitations, and diffuse thyroid enlargement.
- TSH is suppressed; Free thyroid hormone concentrations are increased.
- A vascular goiter and exophthalmos are noted. What mechanism best unifies these findings?

Discussion question

Identify the driver of gland hyperfunction and the separate basis of exophthalmos.

Case 1: Mechanism-based answer

- Stimulating immunoglobulins bind the TSH receptor and activate follicular cells.
- Diffusely increased thyroid synthesis produces a low-TSH, high-hormone state.
- Orbital tissue inflammation and glycosaminoglycans account for exophthalmos.



Case 2: Recognize a treated thyroid specimen

- A thyroidectomy specimen shows diffuse enlargement with hyperplastic follicles.
- Epithelial cells are tall and crowded; Colloid has scalloped margins.
- What additional history can substantially modify these morphologic clues?

Discussion question

Describe two medication-related changes before interpreting the specimen.

Case 2: Treatment history changes morphology

Exposure	Morphologic influence
Iodide	Epithelial involution; more colloid
Propylthiouracil	May intensify epithelial hyperplasia

Integrated pathology summary

- Cause: Activating TSH-receptor autoantibodies produce diffuse thyroid hyperfunction.
- Thyroid: Symmetric enlargement, tall epithelial cells, scalloped colloid, lymphoid infiltrates.
- Outside gland: Immune-associated orbital and dermal glycosaminoglycan accumulation.
- Diagnosis: Low TSH, elevated free hormones, receptor antibodies, and diffuse uptake.

Primary reading and source context

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th edition (2026).
- Chapter 24, The Endocrine System: thyroid physiology, hyperthyroidism, Graves disease.
- Graves disease section, printed pages 984–985; contextual material on pages 979–986.