

# **HYPOTHYROIDISM**

Mechanisms, causes, morphology and clinicopathologic diagnosis

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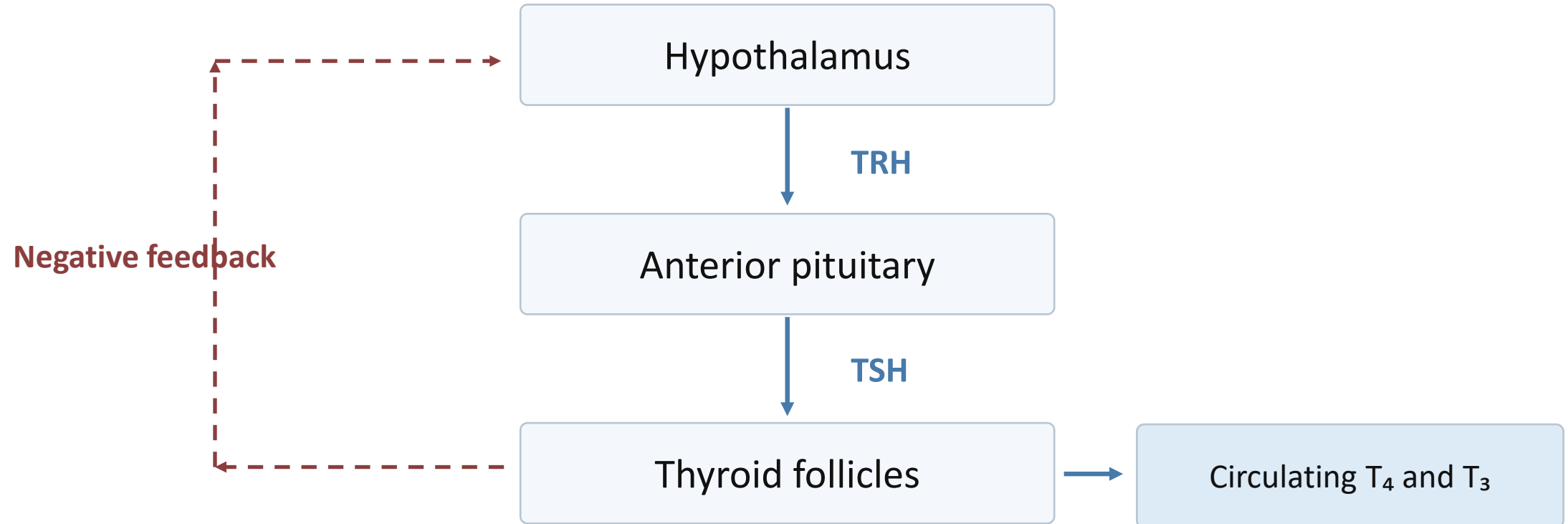
## Learning outcomes

- Localize hormone deficiency to the thyroid or the central axis.
- Distinguish congenital, autoimmune, iatrogenic and central causes.
- Explain systemic findings through loss of thyroid-hormone action.
- Interpret the TSH–free T<sub>4</sub> patterns of overt and subclinical disease.

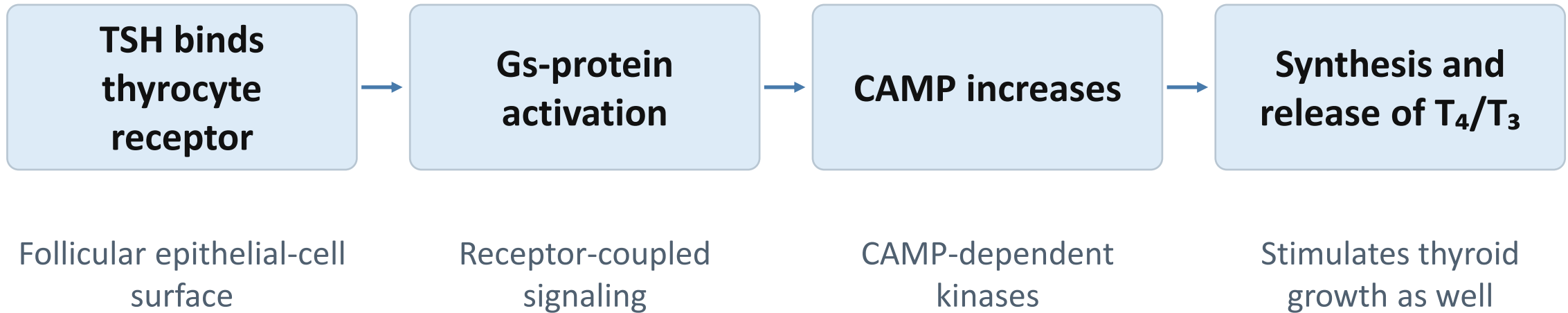
## **Definition: Deficient thyroid-hormone production**

- Structural or functional disturbance reduces thyroid-hormone output.
- Deficiency may originate in the thyroid, pituitary or hypothalamus.
- The common clinical endpoint is insufficient hormone action at tissues.

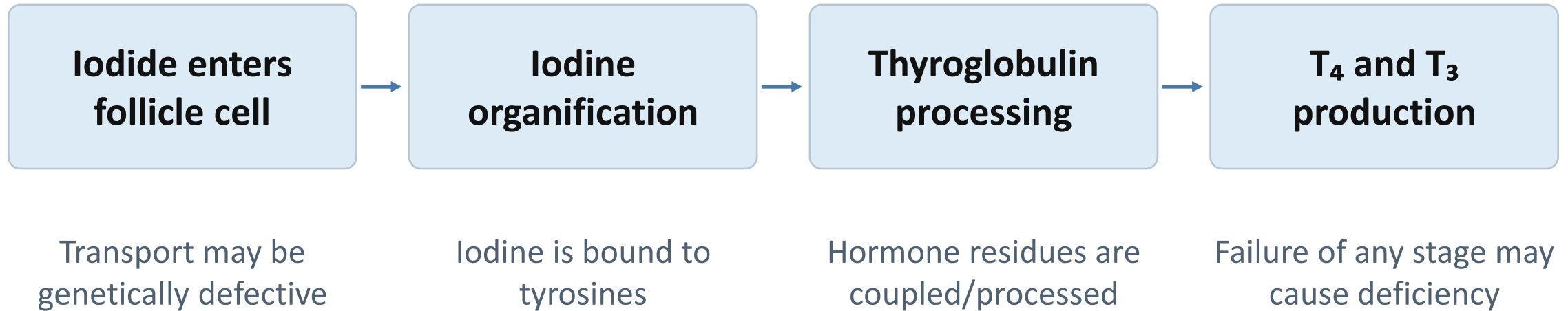
# Hypothalamic–pituitary–thyroid axis



# How TSH drives thyroid function



# Steps required for thyroid-hormone synthesis



## Transport and peripheral hormone activation

- Most circulating  $T_4$  and  $T_3$  bind reversibly to plasma proteins.
- Free hormone concentrations determine available cellular exposure.
- Peripheral deiodination converts much of free  $T_4$  into  $T_3$ .
- $T_3$  binds thyroid-hormone nuclear receptors with greater affinity.

# Why deficiency has multisystem effects

## Normal hormone action

- Stimulates cellular catabolism and protein synthesis.
- Increases basal metabolic rate.
- Is essential to fetal and neonatal brain development.

## Hormone deficiency

- Reduced metabolic and autonomic activity.
- Slower mental and physical performance.
- Developmental vulnerability early in life.

## Disease classification by site of defect

| Category  | Primary site  | Physiologic deficiency             |
|-----------|---------------|------------------------------------|
| Primary   | Thyroid gland | T <sub>4</sub> production impaired |
| Secondary | Pituitary     | TSH deficiency                     |
| Tertiary  | Hypothalamus  | TRH deficiency                     |

## Distribution of hypothyroidism

- Primary disease accounts for most hypothyroid cases.
- By estimates reported, overt disease affects about 0.3%.
- Subclinical disease exceeds 4% in those estimates.
- The figures are illustrative source estimates, not universal rates.

## Demographic pattern

- Prevalence rises with age.
- Hypothyroidism is markedly more frequent in females.
- An approximately tenfold female predominance is reported.
- Demographic likelihood supplements, but cannot replace, biochemical assessment.

# The four major etiologic pathways

## **Congenital**

Deficient gland or synthetic machinery

## **Autoimmune**

Progressive follicular destruction

## **Iatrogenic**

Therapeutic or drug-related suppression

## **Central**

Pituitary/hypothalamic failure

## **Congenital hypothyroidism: Causal categories**

- Dietary iodine deficiency is an important global cause.
- Dyshormonogenetic disease interrupts one or more synthesis steps.
- Thyroid agenesis or hypoplasia reduces functional follicular tissue.
- These mechanisms converge on inadequate hormone availability from birth.

# Iodine supply and thyroid synthesis

## Iodine available

- Iodide transport permits substrate entry.
- Organification enables hormone synthesis.
- T<sub>3</sub>/T<sub>4</sub> production supports development.

## Dietary iodine deficiency

- Insufficient substrate limits biosynthesis.
- Compensatory TSH drive may enlarge the gland.
- Neurologic consequences depend on developmental timing.

# Dyshormonogenesis: Sites of failure

**Iodide transport**



**Organification**



**Hormone-forming  
processing**

Failure to move iodide into  
thyrocytes

Failure to bind iodine to  
thyroglobulin tyrosines

Failure of synthesis/processing  
toward active hormone

## **Iodide transport: A critical first step**

- Thyrocytes must import iodide to synthesize iodinated hormones.
- An inherited transport defect can impair this entry step.
- The downstream synthetic pathway becomes substrate-limited.
- This is one recognized mechanism of dyshormonogenetic goiter.

## **Iodine organification: A second vulnerable step**

- Organification attaches iodine covalently to tyrosine residues in thyroglobulin.
- An inherited defect prevents normal formation of iodinated intermediates.
- Iodide availability alone cannot overcome a block in organification.

## Later hormone-processing defects

- Hormone synthesis requires additional processing beyond organification.
- Inherited defects at these downstream steps reduce functional  $T_3$  and  $T_4$ .
- Each biosynthetic lesion can yield the same phenotype: Hormone deficiency.

# Thyroid dysgenesis

## Agenesis

- Thyroid parenchyma is absent.
- Primary hormone output is profoundly limited.
- A developmental rather than autoimmune defect.

## Hypoplasia

- Functional parenchyma is greatly reduced.
- Germline developmental-gene defects may be responsible.
- PAX8, FOXE1 and TSH-receptor mutations.

## Congenital etiologies: Mechanistic contrasts

| Etiology           | What is missing or defective         | Goiter possible?              |
|--------------------|--------------------------------------|-------------------------------|
| Iodine deficiency  | Hormone-synthesis substrate          | Yes, with sustained TSH drive |
| Dyshormonogenesis  | Hormone-production pathway           | Yes                           |
| Agensis/hypoplasia | Development of follicular parenchyma | Not a defining feature        |

## Why some hypothyroid glands enlarge

- Reduced thyroid hormone weakens feedback inhibition.
- Pituitary TSH secretion rises in primary hypothyroidism.
- Persistent TSH stimulation can produce hyperplastic enlargement.
- A goiter is possible in iodine deficiency, biosynthetic defects and Hashimoto thyroiditis.

## **Autoimmune hypothyroidism: Principal acquired cause**

- The leading cause in iodine-sufficient regions is autoimmune thyroid disease.
- Most autoimmune cases are associated with Hashimoto thyroiditis.
- Progressive follicular destruction gradually compromises hormone production.
- Thyroid enlargement may accompany the autoimmune process.

## **Hashimoto thyroiditis: Loss of self-tolerance**

- Autoimmunity targets antigens expressed by thyroid follicles.
- Lymphocytic infiltration accompanies progressive tissue injury.
- Destruction of thyroid epithelial cells leads to functional failure.
- The precise initiating event remains unresolved.

# Thyroid autoantibodies and their interpretation

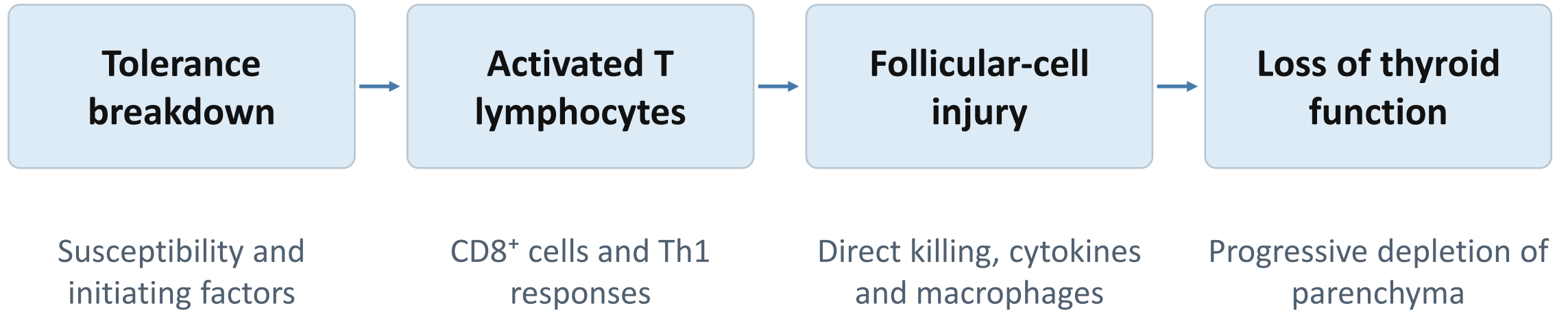
## Anti-TPO

- Antibodies against thyroid peroxidase occur commonly.
- Formerly termed antimicrosomal antibodies.
- Support an autoimmune etiology.

## Anti-thyroglobulin

- Also occurs in Hashimoto thyroiditis.
- Reflects autoimmunity against thyroid components.
- Antibody positivity alone does not establish the injury mechanism.

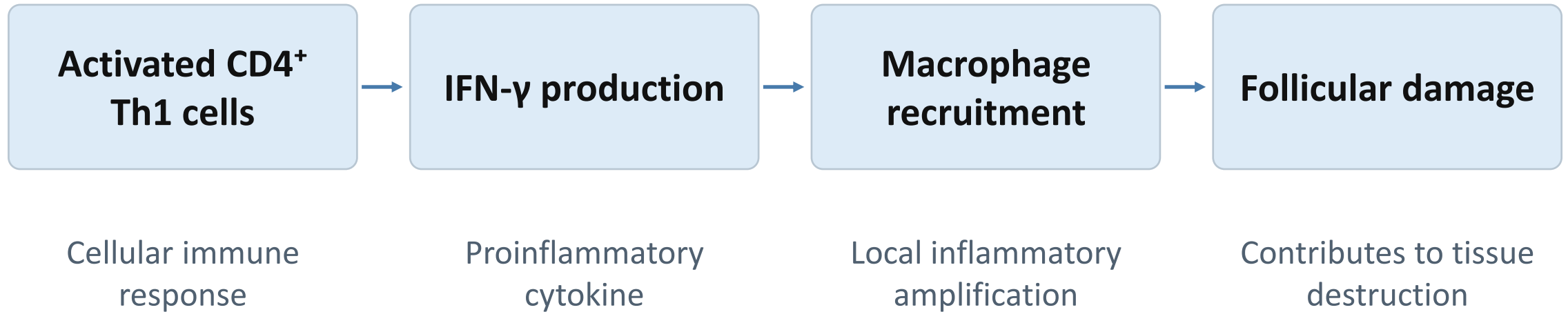
# Immune mechanisms injuring thyroid follicles



## **CD8<sup>+</sup> cytotoxic T cells: Direct injury**

- Activated cytotoxic T cells can recognize thyroid follicular targets.
- Cell-mediated cytotoxicity contributes to epithelial-cell destruction.
- Cumulative tissue loss reduces the gland's synthetic reserve.

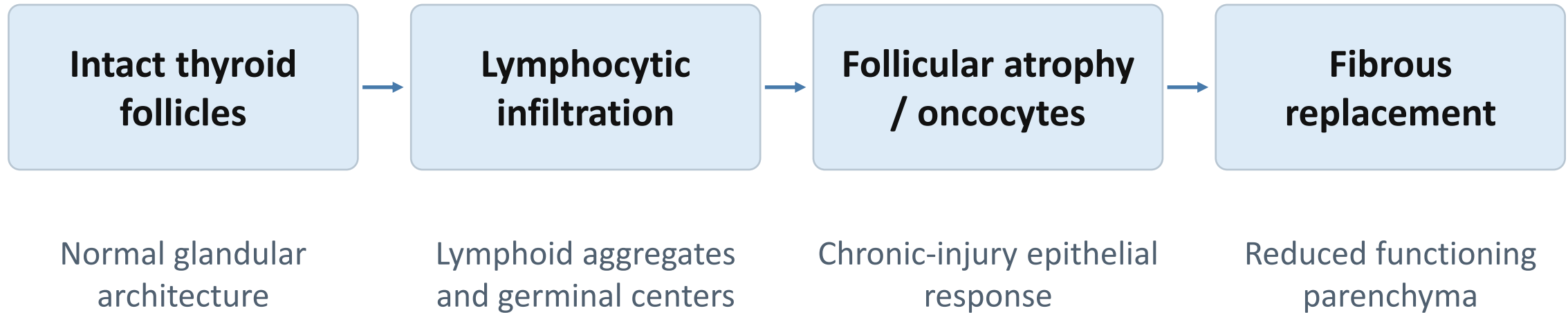
# Th1-driven inflammatory injury



## **Caution: Antithyroid antibodies are not a proven sole cause**

- Antibodies against TPO and thyroglobulin are prevalent in Hashimoto disease.
- Complement-mediated or antibody-dependent injury is biologically plausible.
- Their causal contribution to tissue injury remains uncertain.
- Morphologic inflammation reflects several interacting immune mechanisms.

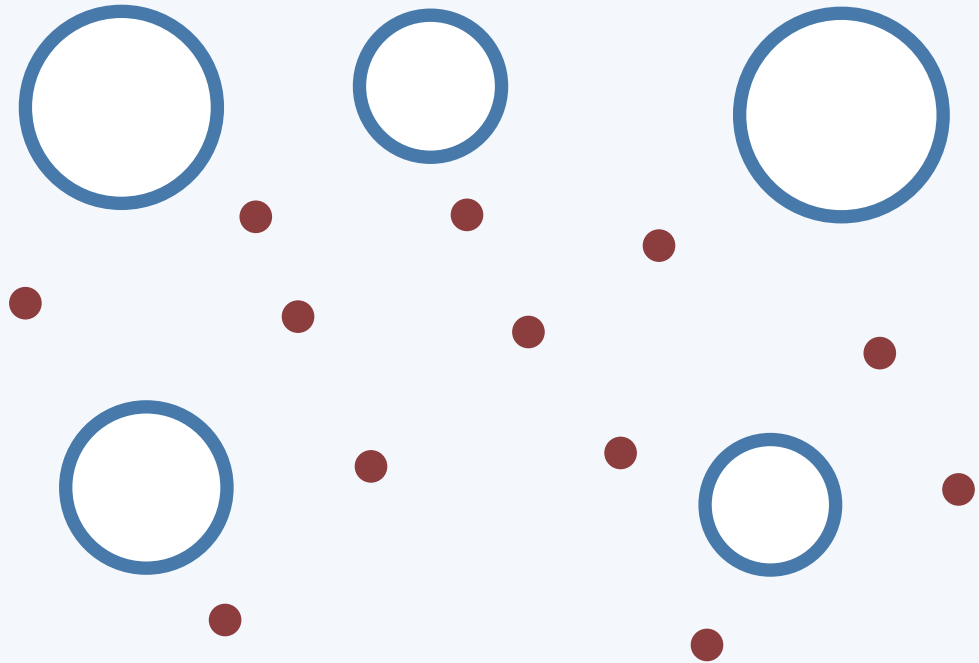
# Histologic progression in Hashimoto thyroiditis



## **Macroscopic morphology in Hashimoto disease**

- The thyroid is often diffusely enlarged and well demarcated.
- Cut surfaces may appear pale, yellow-tan, firm and somewhat nodular.
- The goiter may be symmetrical or occasionally localized enough to resemble a mass.

# Microscopic pattern: Schematic, not a specimen



SCHEMATIC

## Hallmarks

- Dense lymphocytes; Germinal centers
- Atrophic residual follicles
- Oncocytic (Hürthle) cells
- Variable interstitial fibrosis

# **Oncocytic transformation is a chronic-injury response**

- Residual follicular epithelial cells may acquire abundant eosinophilic granular cytoplasm.
- These oncocytes were formerly called Hürthle cells.
- An oncocyte-rich aspirate with heterogeneous lymphocytes supports Hashimoto thyroiditis.
- The finding must be interpreted in its full cytologic context.

## Hashimoto disease: Clinical trajectory

- Painless thyroid enlargement often precedes or accompanies dysfunction.
- Hypothyroidism usually develops gradually.
- A transient thyrotoxic phase may occur when damaged follicles release stored hormones.
- This destructive phase is distinct from sustained hormone overproduction.

## **Associated autoimmune and other disorders**

- Hashimoto disease may coexist with type 1 diabetes or autoimmune adrenalitis.
- Nonendocrine autoimmune associations include Sjögren syndrome and systemic lupus erythematosus.
- There is an increased risk of thyroid extranodal marginal-zone B-cell lymphoma, although rare.
- A proposed association with papillary thyroid carcinoma remains controversial.

## **Autoimmune polyendocrine context**

- Autoimmune hypothyroidism can occur in isolation.
- Robbins also describes association with autoimmune polyendocrine syndrome types 1 and 2.
- Coexisting glandular failure changes clinical assessment and the interpretation of symptoms.

# Iatrogenic etiologies: Interventions and agents

| Exposure                        | Relationship to hypothyroidism          |
|---------------------------------|-----------------------------------------|
| Thyroid surgery                 | Loss of hormone-producing parenchyma    |
| Radioiodine treatment           | Ablation of functional thyroid tissue   |
| External neck irradiation       | Radiation-associated thyroid injury     |
| Thionamides                     | Suppression of new hormone synthesis    |
| Lithium / p-aminosalicylic acid | Drug-associated acquired hypothyroidism |
| Amiodarone                      | May cause hypo- or hyperthyroidism      |

## Postoperative hypothyroidism

- Resection of substantial thyroid tissue can reduce total hormone-production capacity.
- Thyroid surgery for hyperthyroidism or neoplasia is a recognized cause.
- The mechanism is postablative loss of functioning follicles.

# Radiation-associated hypothyroidism

## Radioiodine

- Used to ablate thyroid tissue in hyperthyroidism.
- Loss of functioning follicles may cause persistent deficiency.

## External neck irradiation

- Radiation exposure can damage the thyroid.
- This is a recognized iatrogenic cause distinct from radioiodine.

# Antithyroid drug–associated deficiency

**Thionamide exposure**

Examples: Methimazole,  
propylthiouracil

**Thyroid-hormone  
synthesis falls**

The intended pharmacologic  
action can become excessive

**Circulating T<sub>4</sub>/T<sub>3</sub> declines**

Physiologic consequence is  
hypothyroidism

## Other drug-associated causes

- Lithium may be associated with acquired hypothyroidism.
- P-Aminosalicylic acid is another listed drug association.
- The key etiologic clue is a temporal relationship to medication exposure.
- No drug-specific incidence or dose threshold is provided by the source.

# Amiodarone: A bidirectional thyroid disturbance

## Hypothyroidism

- Amiodarone exposure may be associated with reduced thyroid function.
- Symptoms and hormone studies determine functional state.

## Hyperthyroidism

- The same agent may also be associated with hormone excess.
- Drug exposure alone does not specify the biochemical diagnosis.

## **Central hypothyroidism: The driving signal is deficient**

- Pituitary TSH deficiency produces secondary hypothyroidism.
- Hypothalamic TRH deficiency produces tertiary hypothyroidism.
- Robbins groups the two as central hypothyroidism.
- A damaged thyroid gland is not required for this phenotype.

## **Pituitary causes of central hypothyroidism**

- Pituitary tumors may impair thyrotroph function.
- Postpartum pituitary necrosis is an established cause of hypopituitarism.
- Trauma and nonpituitary tumors may similarly disrupt pituitary function.
- Deficient TSH stimulation ultimately lowers thyroid output.

## **Hypothalamic causes of central hypothyroidism**

- Hypothalamic tumors can compromise TRH release.
- Traumatic injury, radiation and infiltrative disorders are additional causes.
- The resulting pituitary TSH drive is insufficient for normal thyroid output.

# Different laboratory consequences of feedback failure

Primary thyroid failure

Thyroid  $T_4$  ↓



Feedback restraint ↓



TSH ↑

Central-axis failure

TRH/TSH stimulation ↓



Thyroid  $T_4$  ↓



TSH not appropriately ↑

# Primary versus central disease

| Feature                              | Primary hypothyroidism  | Central hypothyroidism           |
|--------------------------------------|-------------------------|----------------------------------|
| Affected level                       | Thyroid follicles       | Pituitary or hypothalamus        |
| TSH pattern                          | Usually raised          | Low or inappropriately normal    |
| Free T <sub>4</sub> in overt disease | Decreased               | Decreased                        |
| Examples                             | Hashimoto; postablation | Pituitary or hypothalamic lesion |

## **Why adult hypothyroidism can be overlooked**

- Onset is often gradual and insidious.
- Patients may experience symptoms for years before a specific endocrine cause is suspected.
- Early complaints are nonspecific, including fatigue and mental slowing.
- Biochemical evaluation is therefore central to accurate diagnosis.

## **Early neurobehavioral manifestations**

- Generalized fatigue and apathy may be prominent early complaints.
- Mental sluggishness may resemble a depressive syndrome.
- Advanced hormone deficiency can slow speech and intellectual functioning.
- Clinical assessment alone cannot reliably establish the etiology.

# Thermoregulation and metabolic activity

## Cold intolerance

- Reduced thyroid-hormone action diminishes basal metabolic activity.
- Patients may feel cold even in ordinary surroundings.

## Changes in weight

- Weight gain may accompany reduced metabolic activity.
- Weight gain alone is neither sensitive nor specific for hypothyroidism.

## **Autonomic and gastrointestinal manifestations**

- Reduced sympathetic activity contributes to constipation.
- Decreased sweating is another characteristic manifestation.
- These features accompany generalized slowing of body functions.

## **Skin findings reflect reduced peripheral flow**

- Skin often becomes cool and pale.
- These findings partly to reduced cutaneous blood flow.
- Distinct nonpitting edema arises from tissue-matrix accumulation rather than ordinary fluid retention.

## Cardiovascular consequences

- Thyroid deficiency can reduce cardiac output.
- Patients may develop breathlessness and diminished exercise capacity.
- Functional effects reflect altered hormone-dependent transcription in cardiomyocytes.

# Molecular basis of reduced cardiac performance

**Reduced thyroid hormones**

Deficient nuclear-receptor signaling



**Altered sarcolemmal gene transcription**

Examples: Calcium ATPases and  $\beta$ -adrenergic receptor



**Lower cardiac output**

Contributes to exercise intolerance and dyspnea

# Lipid effects link hypothyroidism to vascular risk

**Reduced thyroid-hormone action**



**Total cholesterol / LDL rise**



**Proatherogenic milieu**

Changes in lipid metabolism

Pattern

Contributes to cardiovascular morbidity and mortality

## **Myxedema: Extracellular matrix accumulation**

- Glycosaminoglycans and hyaluronic acid accumulate in tissues.
- The matrix change involves skin, subcutis and some visceral sites.
- Tissue expansion produces a characteristic nonpitting edema.
- This morphologic substrate explains several recognizable clinical signs.

# The phenotype of tissue myxedema

## Facial and mucosal changes

- Facial features become broader and coarser.
- The tongue may enlarge.
- The voice may deepen.

## Tissue mechanism

- Matrix substances accumulate in interstitium.
- Expansion is not simply dependent edema.
- The swelling is characteristically nonpitting.

## **Severe hypothyroidism and myxedema coma**

- Myxedema is historically associated with profound hypothyroidism.
- The term is commonly used clinically for severe disease and myxedema coma.
- This represents the extreme clinical end of thyroid-hormone deficiency.
- The term denotes severe clinical decompensation, not a separate etiologic category.

## **Developmental timing determines vulnerability**

- Thyroid hormone is essential for fetal and neonatal brain development.
- Profound deficiency early in development risks severe neurocognitive injury.
- The congenital iodine-deficiency discussion links severity to timing during pregnancy.
- Developmental disease cannot be interpreted as merely adult myxedema in miniature.

# Age of onset shapes the clinical pattern

| Domain                  | Congenital / early life                  | Adult onset                             |
|-------------------------|------------------------------------------|-----------------------------------------|
| Principal vulnerability | Brain and somatic development            | Metabolic and functional slowing        |
| Characteristic features | Growth and neurodevelopmental impairment | Fatigue, cold intolerance, constipation |
| Shared substrate        | Insufficient thyroid-hormone action      | Insufficient thyroid-hormone action     |

## **Why laboratory testing is essential**

- Clinical symptoms are common and nonspecific.
- Biochemical testing distinguishes overt disease from compensated states.
- Weight gain or otherwise unexplained hypercholesterolemia can prompt thyroid assessment.
- Clinical context determines whether central disease is plausible.

## **Serum TSH in primary hypothyroidism**

- TSH is the most sensitive screening measure for primary disease.
- Falling thyroid hormone releases hypothalamic–pituitary feedback restraint.
- The pituitary consequently raises TSH secretion.
- The magnitude of TSH elevation should not be mistaken for proof of a specific etiology.

## **Free T<sub>4</sub> identifies overt hormone deficiency**

- Overt hypothyroidism is accompanied by reduced T<sub>4</sub>.
- A low free T<sub>4</sub> occurs in overt primary or central disease.
- Interpreting free T<sub>4</sub> with TSH helps localize the dysfunction.
- An isolated TSH result may miss central hypothyroidism.

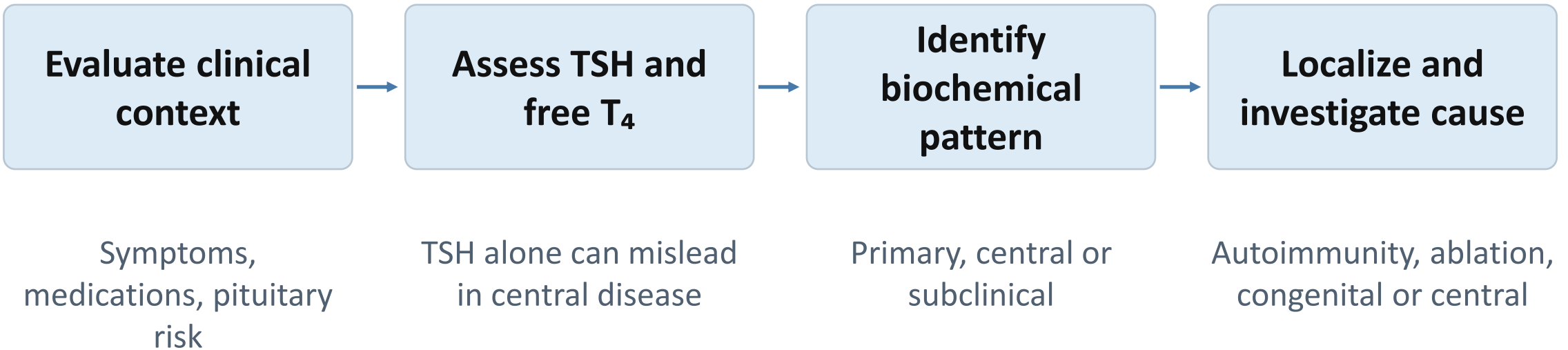
## **Subclinical hypothyroidism: Compensatory phase**

- TSH is elevated while free T<sub>4</sub> remains normal.
- T<sub>3</sub> remains normal in the subclinical phase described here.
- This typically represents an early primary form, not central hypothyroidism.
- Symptoms may be absent or nonspecific.

## Core biochemical patterns

| State               | TSH                            | Free T <sub>4</sub> |
|---------------------|--------------------------------|---------------------|
| Primary overt       | Elevated                       | Low                 |
| Central overt       | Low or inappropriately normal  | Low                 |
| Subclinical primary | Elevated                       | Normal              |
| Euthyroid           | Appropriate for feedback state | Normal              |

# Reasoning from TSH and free T<sub>4</sub>



## Diagnostic pitfalls

- Nonspecific fatigue and slowed cognition may mimic nonendocrine disease.
- Normal or low TSH does not exclude a central cause when free T<sub>4</sub> is low.
- Goiter can occur in several etiologies and is not itself a diagnosis.
- Anti-TPO positivity indicates autoimmunity, not a proven sole injury mechanism.

# Case 1: Progressive fatigue and goiter

## CLINICAL PRESENTATION

A middle-aged adult develops insidious fatigue, constipation and painless diffuse thyroid enlargement. TSH is elevated, free T<sub>4</sub> is low, and anti-TPO antibodies are detected.

**Which etiologic and functional diagnoses best fit?**

## Case 1: Explanation

### Overt primary hypothyroidism, likely Hashimoto thyroiditis

- Low free T<sub>4</sub> with compensatory high TSH localizes disease to the thyroid.
- Autoantibodies and painless diffuse goiter support autoimmune thyroiditis.
- The antibodies support etiology; Cell-mediated injury remains central.

## **Case 2: Low free T<sub>4</sub> without a TSH rise**

### **CLINICAL PRESENTATION**

A patient with a known pituitary mass develops fatigue and cold intolerance. Free T<sub>4</sub> is low but serum TSH is not elevated.

**Why is this not reassuringly normal thyroid function?**

## Case 2: Explanation

### Suspect central hypothyroidism

- A pituitary lesion may impair TSH secretion.
- TSH is inappropriately normal relative to deficient circulating T<sub>4</sub>.
- The low free T<sub>4</sub> is the crucial evidence of overt hormone deficiency.

## Case 3: An incidental biochemical abnormality

### CLINICAL PRESENTATION

A person evaluated for an unrelated concern has elevated TSH with free T<sub>4</sub> in the reference interval and no distinct hypothyroid syndrome.

**How should this biochemical state be classified?**

## **Case 3: Explanation**

### **Subclinical primary hypothyroidism**

- The pituitary compensates for declining thyroid reserve by increasing TSH.
- Circulating free T<sub>4</sub> remains normal at this stage.
- This pattern does not, by itself, specify the underlying etiology.

# **Etiology → mechanism → observed pattern**

Iodine / enzyme defect



Synthesis limited



Primary pattern

Hashimoto thyroiditis



Follicular destruction



Primary pattern

Postablation



Loss of functioning tissue



Primary pattern

Pituitary / hypothalamus



Low TSH/TRH drive



Central pattern

## Core clinicopathologic synthesis

- Hypothyroidism describes deficient hormone production, not a single thyroid lesion.
- Primary disease is common and raises TSH through loss of negative feedback.
- Autoimmune destruction, congenital disorders and iatrogenic injury have distinct mechanisms.
- Central disease is recognized by low free T<sub>4</sub> without an appropriate TSH response.
- Systemic findings follow loss of metabolic, cardiovascular and tissue-matrix regulation.

# Reference

## **Robbins, Cotran & Kumar**

Pathologic Basis of Disease, 11th edition (2026)

Chapter 24 · The Endocrine System

Hypothyroidism and directly related thyroid sections