

Hypoparathyroidism

Mechanisms, clinicopathologic manifestations, and endocrine differentials

Pathology lecture

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Learning objectives

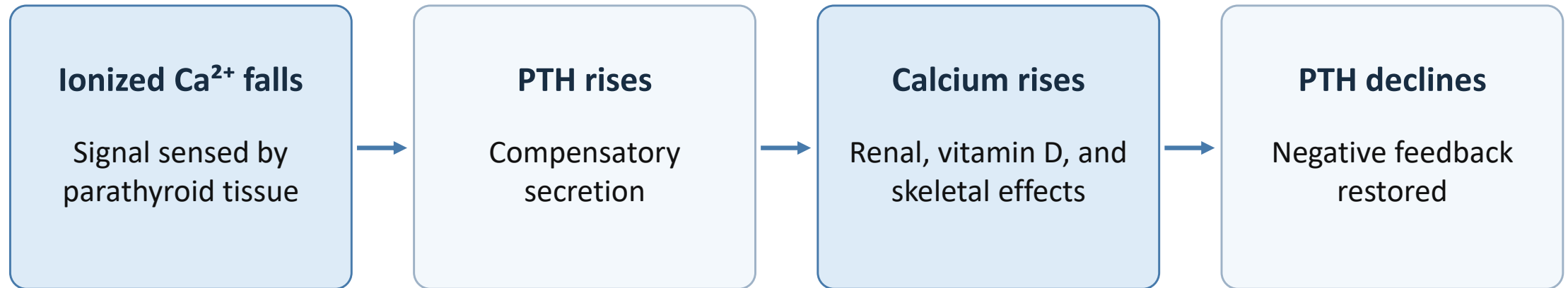
- Explain normal PTH feedback regulation and target-organ actions.
- Differentiate surgical, autoimmune, inherited, and developmental causes.
- Link hypocalcemia to neurologic, cardiac, ocular, and dental manifestations.
- Distinguish PTH deficiency from PTH resistance.

Core definition: Insufficient PTH action

Hypoparathyroidism is a state of deficient parathyroid hormone secretion or availability.

- PTH normally increases ionized calcium through kidney, intestine, and bone.
- Deficient hormone action leads to a tendency toward hypocalcemia.
- PTH resistance produces a similar biochemical effect but is a distinct disorder.

Normal feedback responds to a fall in calcium



The direction of the loop explains why absent PTH secretion is inappropriate during hypocalcemia.

Parathyroid glands: Anatomy relevant to surgery

- Usually four glands lie near the superior and inferior poles of the thyroid.
- Developmental descent can leave ectopic glands along the migration pathway.
- Documented ectopic sites include carotid sheath, thymus, and anterior mediastinum.
- Anatomical variability helps explain inadvertent removal during cervical surgery.

Normal parathyroid cell populations

Chief cells

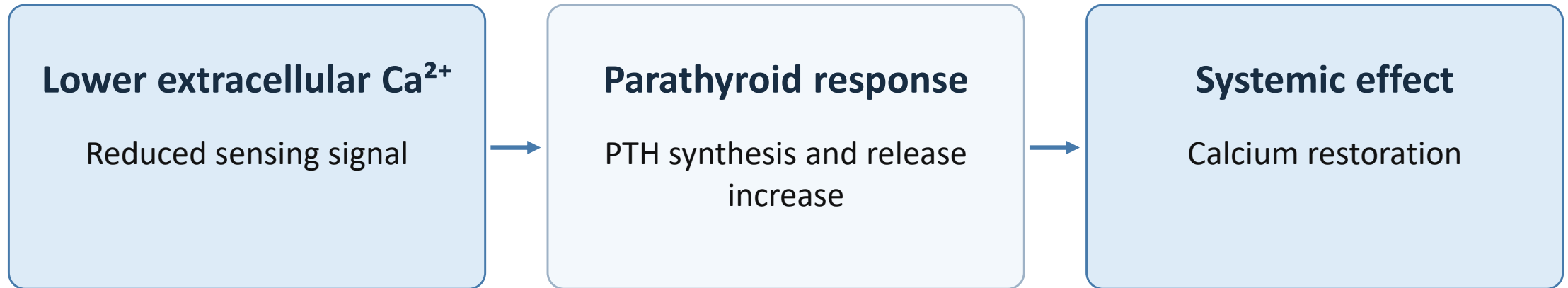
- Predominant cell type
- PTH-containing secretory granules
- Small polygonal cells with rounded nuclei

Oxyphil cells

- Larger eosinophilic cells
- Abundant mitochondria
- Few or absent secretory granules

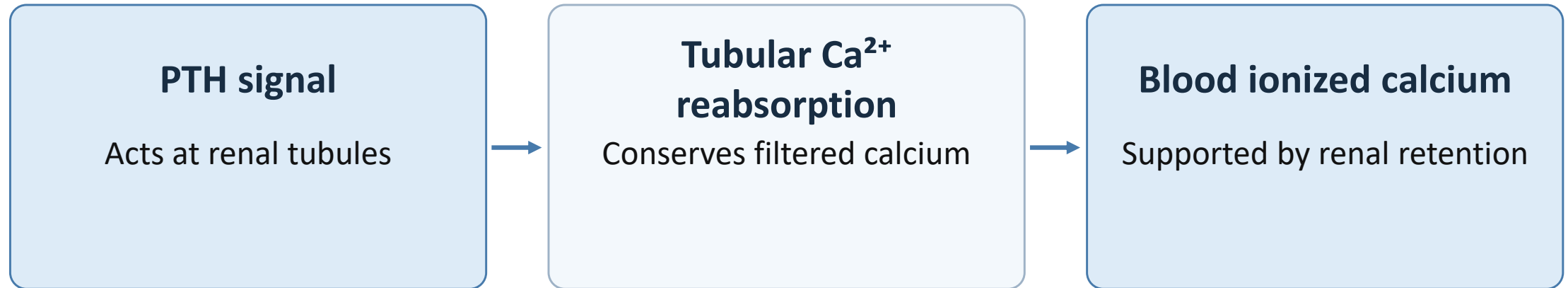
Schematic cellular comparison; Not a histologic photomicrograph.

Calcium sensing controls PTH output



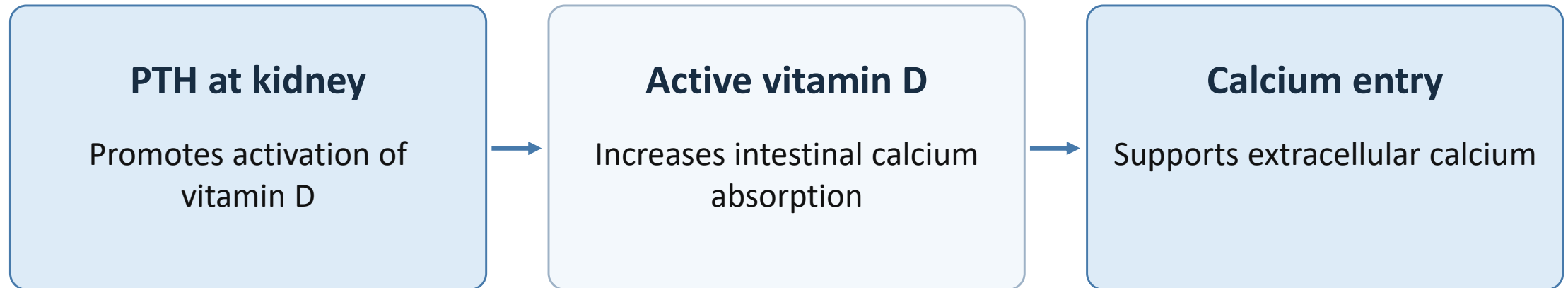
Calcium-sensing receptor behavior becomes a disease mechanism in activating CASR mutations.

PTH conserves calcium in the kidney



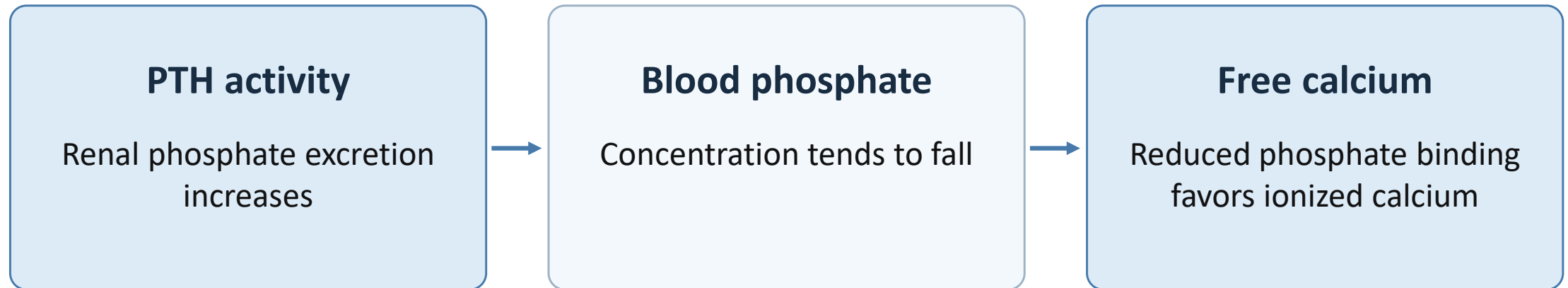
Loss of PTH removes this calcium-conserving endocrine signal.

PTH links kidney vitamin D to intestinal calcium



PTH deficiency impairs the normal stimulation of this calcium-absorptive pathway.

PTH promotes urinary phosphate excretion



Reduced PTH activity may permit phosphate retention; This relationship is central to tissue calcification.

Skeletal contribution to PTH action



PTH acts on calcium homeostasis in multiple organs, not only on bone.

Three coordinated effects increase ionized calcium

Renal calcium

Tubular reabsorption
conserves circulating
calcium.

Active vitamin D

Intestinal calcium absorption
increases.

Skeletal mineral

Osteoclast-mediated
resorption releases calcium.

Renal phosphate excretion provides an additional calcium-favoring effect.

Normal compensation versus hypoparathyroidism

Normal response to low Ca^{2+}

- PTH secretion increases
- Renal calcium retention increases
- Vitamin D activation increases
- Phosphate excretion increases

Insufficient PTH

- PTH response is inadequate
- Calcium-conserving signals diminish
- Intestinal support is reduced
- Phosphate may accumulate

Clinical severity depends on calcium deficit

The manifestations of hypoparathyroidism reflect the severity and chronicity of hypocalcemia.

- Early neuromuscular excitability may be clinically striking.
- Persistent biochemical disturbance is associated with organ-specific changes.
- A patient's phenotype reflects both intensity and duration of the deficit.

Etiologic groups of hypoparathyroidism

Acquired

Inadvertent loss of parathyroid tissue after surgery.

Immune-mediated

APS-1 associated with AIRE pathway dysfunction.

Inherited/developmental

CASR, PTH, GCM2, or congenital gland absence.

Each route converges on insufficient effective PTH production.

Surgery is the dominant acquired association

- Acquired hypoparathyroidism as almost always an inadvertent consequence of surgery.
- Loss of viable parathyroid tissue can follow surgery on the thyroid or neck.
- Excessive removal of parathyroid tissue is another described setting.
- Cause is loss of endocrine tissue rather than a PTH-secreting tumor.

Three described surgical routes

Thyroidectomy

- Accidental removal of all glands
- Anatomical proximity creates the risk

Radical neck dissection

- Glands may be mistaken for lymph nodes
- Parathyroid tissue removed with neck specimen

Parathyroid surgery

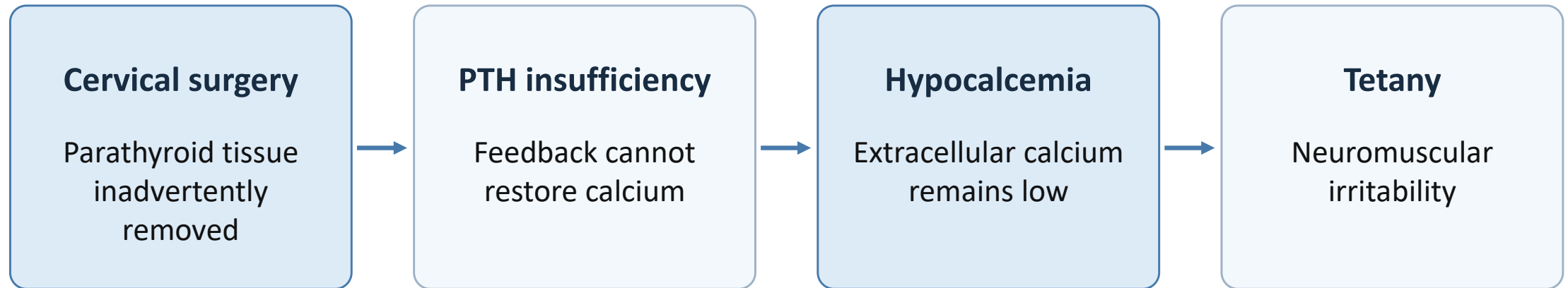
- Too much tissue excised
- Can follow treatment of primary hyperparathyroidism

Post-thyroidectomy hypocalcemia: Mechanism

Removal of parathyroid tissue prevents the normal compensatory PTH response.

- Reduced PTH-dependent calcium retention and vitamin D activation follow.
- Calcium falls despite the normal stimulus for PTH secretion.
- The surgical context is a major etiologic clue.

From gland loss to neuromuscular symptoms



A clinical sequence explains why prior surgery should be sought in the history.

Operative context helps localize the risk

Thyroid operation

- Parathyroid glands adjacent to thyroid poles
- Removal can occur during thyroidectomy
- Consider postoperative calcium disturbance

Neck tumor operation

- Parathyroid may resemble a node
- Removal can occur in radical dissection
- Consider the full operative field

APS-1: Characteristic clinical constellation

Candidiasis

Chronic mucocutaneous
fungal infection.

Hypoparathyroidism

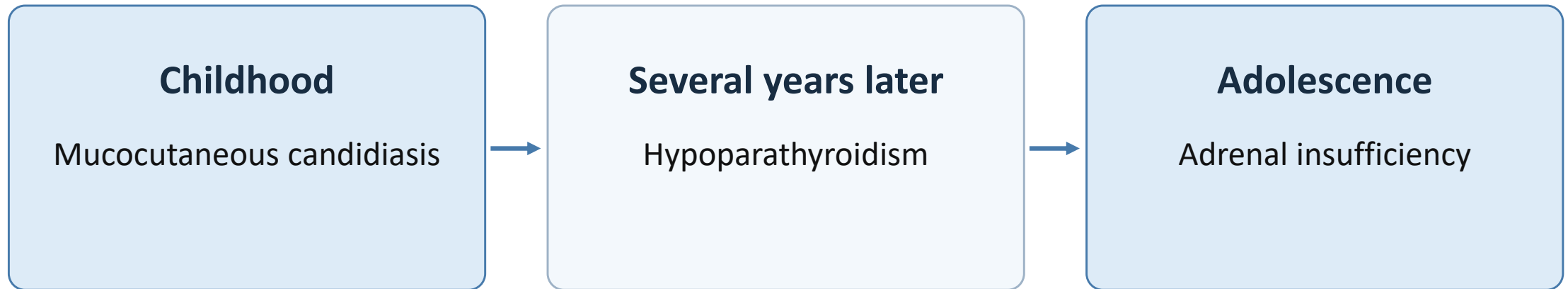
Autoimmune damage with
hypocalcemia.

Adrenal insufficiency

Primary adrenal cortical
insufficiency.

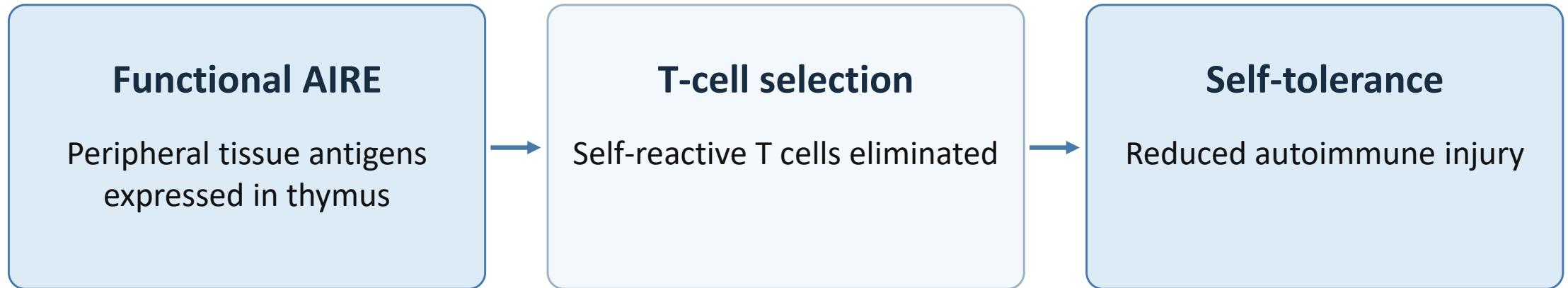
APS-1 is a syndromic cause: An isolated calcium result is not the full phenotype.

APS-1: Typical clinical sequence



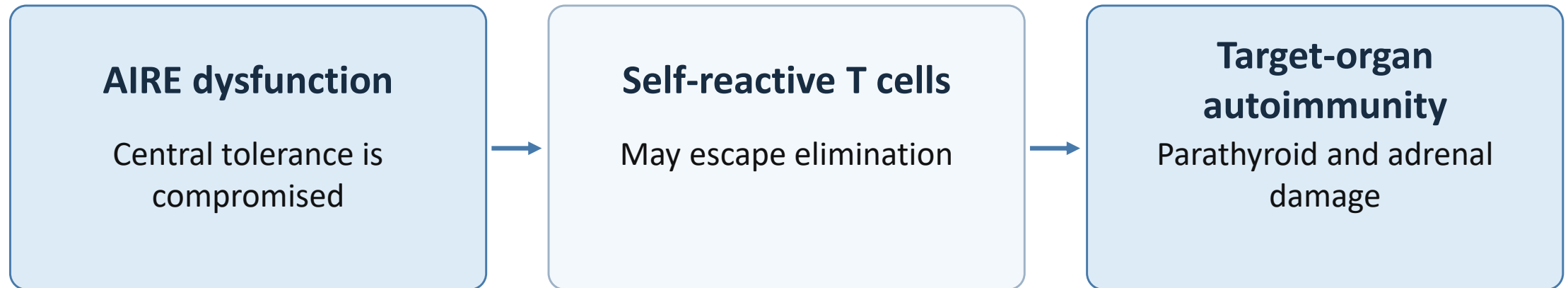
The sequence is typical, not a strict rule applying to every affected individual.

AIRE preserves central T-cell tolerance



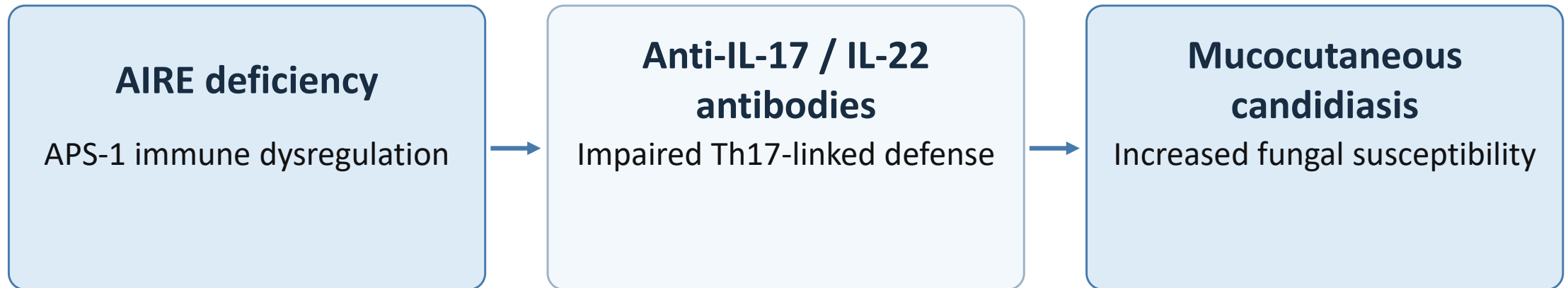
AIRE loss impairs central tolerance and predisposes to multiorgan autoimmune disease.

AIRE loss permits autoimmune gland injury



Loss of immune tolerance provides the mechanistic connection between the APS-1 components.

APS-1 candidiasis: Cytokine explanation



Antibodies to IL-17 and IL-22 as a link to candidiasis.

APS-1 versus APS-2: Clinically important distinction

APS-1

- AIRE-associated syndrome
- Hypoparathyroidism may occur
- Mucocutaneous candidiasis
- Primary adrenal insufficiency

APS-2

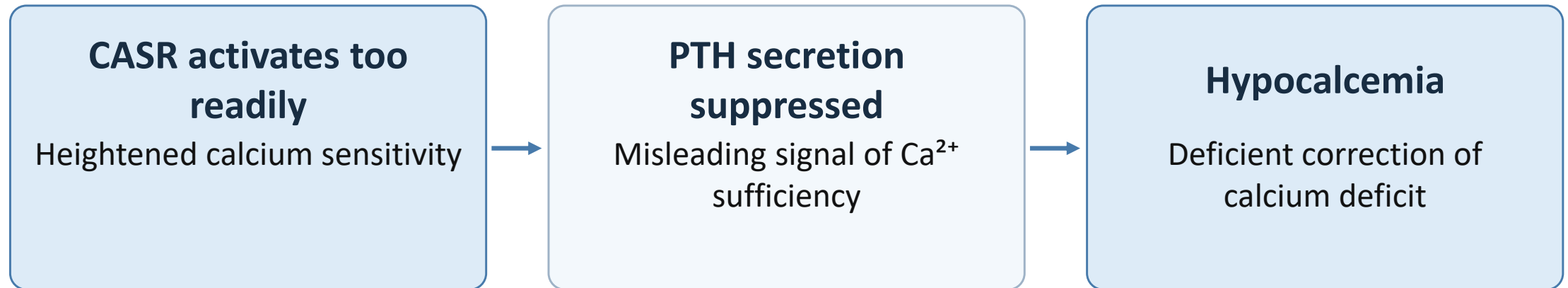
- Adrenal insufficiency + autoimmune thyroiditis
- May include type 1 diabetes
- Not characterized by autoimmune hypoparathyroidism
- Not characterized by candidiasis

Activating CASR mutations alter the calcium set point

A gain-of-function CASR mutation makes parathyroid cells behave as though calcium is higher than it is.

- The receptor responds excessively to extracellular calcium.
- PTH secretion becomes inappropriately suppressed.
- Patients develop hypocalcemia despite a low-calcium stimulus.

CASR gain of function: Excessive calcium sensing



Inherited activating CASR variants are a cause of autosomal dominant hypoparathyroidism.

CASR activation and urinary calcium

Parathyroid effect

- Heightened calcium sensing
- PTH output decreases
- Hypocalcemia develops

Renal phenotype

- Hypercalciuria accompanies hypocalcemia
- The combination is a clue to CASR activation
- Do not assume every hypocalcemia implies low urine calcium

CASR allelic effects are direction-dependent

Gain of function

- Autosomal dominant hypoparathyroidism
- Suppressed PTH
- Hypocalcemia + hypercalciuria

Heterozygous loss of function

- Familial hypocalciuric hypercalcemia
- Reduced sensing of ambient calcium
- Hypercalcemic phenotype

Homozygous loss of function

- Severe neonatal primary hyperparathyroidism
- Markedly defective sensing
- Opposite functional direction from activating mutation

Familial isolated hypoparathyroidism: Inheritance

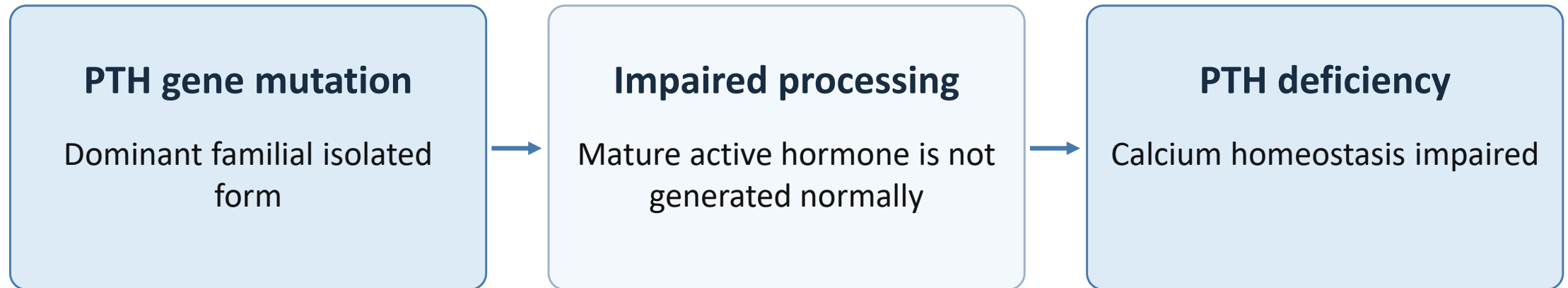
Autosomal dominant FIH

- Mutation of PTH gene
- Impaired maturation of PTH peptide
- Functionally inadequate active hormone

Autosomal recessive FIH

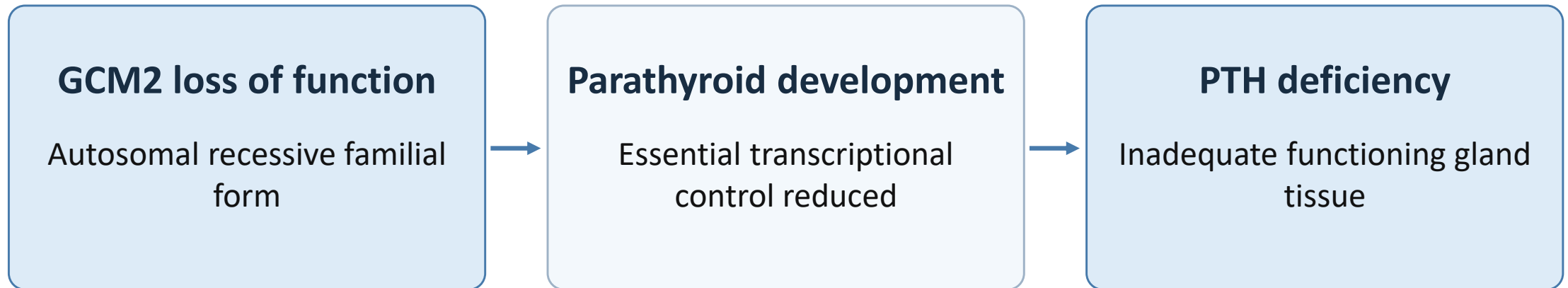
- Loss of GCM2 function
- Parathyroid developmental program impaired
- Insufficient parathyroid gland development

PTH gene variant blocks mature hormone generation



This mechanism concerns hormone processing, not tissue loss at surgery.

GCM2 loss impairs gland development



GCM2 and PTH gene variants produce deficiency through different biological levels.

Different genetic lesions affect different levels

CASR

- Calcium sensing defect
- Excess suppression of secretion
- Hypocalcemia with hypercalciuria

PTH

- Hormone processing defect
- Mature PTH impaired
- Autosomal dominant FIH

GCM2

- Developmental transcription factor
- Parathyroid development impaired
- Autosomal recessive FIH

Congenital absence: A linked developmental pattern

Parathyroid absence

Defective gland development causes PTH deficiency.

Thymic defect

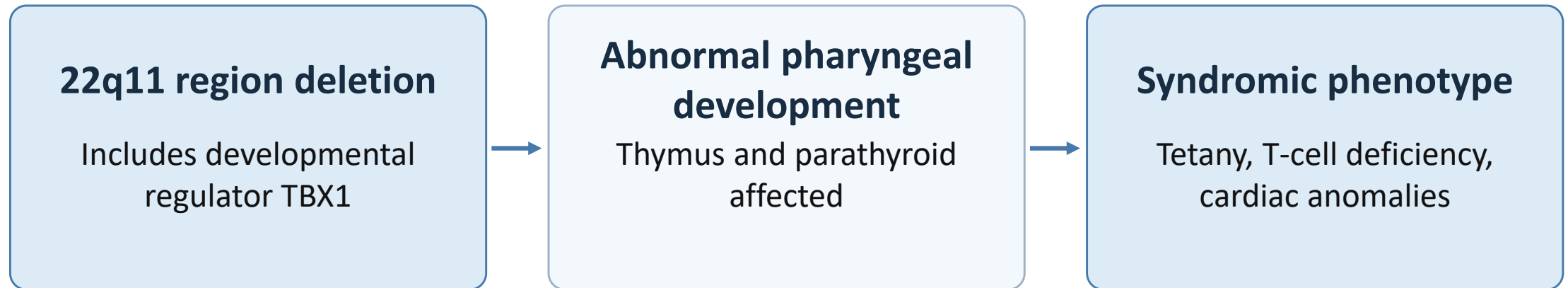
Thymic aplasia or hypoplasia may coexist.

Cardiac anomalies

Defects of the heart and great vessels may coexist.

The shared pharyngeal-pouch origin explains the organ constellation.

22q11 deletion disrupts pharyngeal development



DiGeorge syndrome denotes the 22q11-related pattern when thymic defects are present.

Congenital hypoparathyroidism: Clinical clues

Parathyroid involvement

- Hypocalcemia
- Tetany
- May be apparent early in life

Associated malformations

- Thymic aplasia or hypoplasia
- Cardiovascular defects
- Supports syndromic congenital cause

Hypocalcemia causes neuromuscular irritability

Tetany is the hallmark clinical manifestation of hypocalcemia.

- Symptoms begin with sensory complaints or muscle spasms.
- More severe disturbance can involve airway and cerebral function.
- Neuromuscular symptoms should trigger a search for calcium disturbance.

Tetany presents on a severity continuum

Sensory

Circumoral numbness and distal paresthesias.

Motor

Carpopedal spasm and involuntary muscle contraction.

Severe

Laryngospasm or generalized seizures.

Severity is not inferred from one symptom alone.

Paresthesias: Earliest recognizable clues

- Circumoral numbness is a characteristic sensory symptom.
- Tingling of distal extremities reflects neuromuscular irritability.
- These symptoms may precede overt sustained muscle spasm.
- The clinical context determines whether PTH deficiency is plausible.

Carpopedal spasm is a motor expression of tetany

Sustained involuntary contraction may involve the hands and feet.

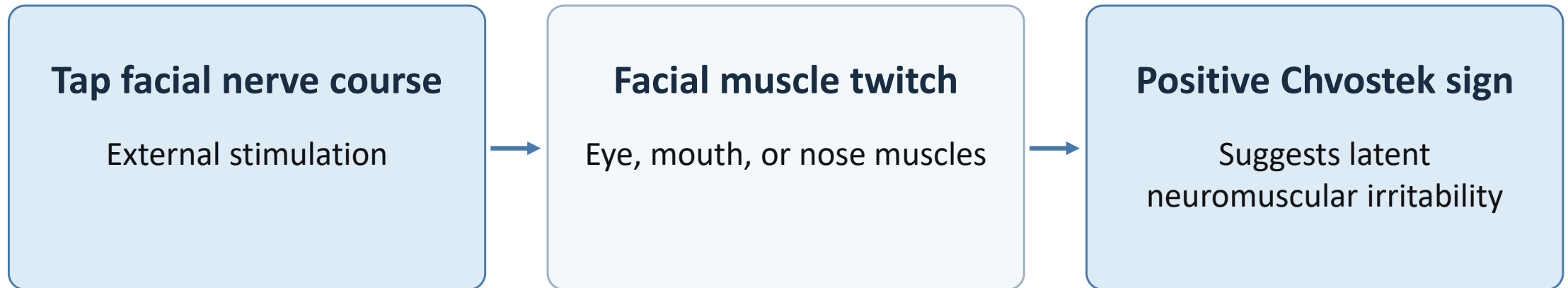
- It is a manifestation of low extracellular calcium.
- The same motor irritability underlies the Trousseau maneuver.
- A positive sign supports hypocalcemia but does not identify its cause.

Severe tetany may become life-threatening

Laryngospasm and generalized seizures are severe manifestations of hypocalcemia.

- Laryngospasm threatens airway patency.
- Generalized seizures represent severe cerebral excitability.
- These findings warrant urgent clinical assessment rather than routine follow-up.

Chvostek sign: Facial nerve irritability



The sign may be elicited in subclinical disease; It does not determine the underlying etiology.

Trousseau sign: Ischemic provocation of spasm



The demonstration is a clinical sign of hypocalcemic neuromuscular excitability.

Chvostek and Trousseau: Distinguish the maneuvers

Chvostek sign

- Tap along facial nerve
- Observe facial contraction
- Eye / mouth / nose muscles

Trousseau sign

- Inflate blood pressure cuff
- Maintain several minutes
- Observe carpal spasm

Psychiatric and cognitive manifestations

Affective

Emotional instability, anxiety,
or depression.

Cognitive

Confusion or behavioral
change.

Severe

Hallucinations or frank
psychosis.

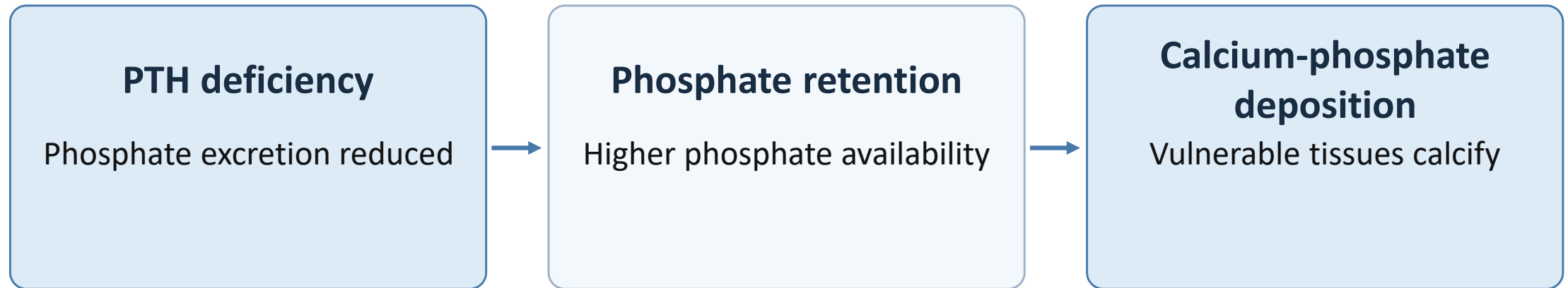
Neuropsychiatric signs are associated with the systemic calcium disturbance.

Basal ganglia calcification can accompany low calcium

Intracranial calcium deposition is described in chronic hypoparathyroidism.

- Basal ganglia are specifically identified as a susceptible site.
- Movement disorders resembling parkinsonism can coexist.
- Tissue mineral deposition is not equivalent to circulating hypercalcemia.

The apparent paradox: Hypocalcemia and calcification



Robbins frames phosphate-mediated deposition as a possible explanation, not a proven unique mechanism.

Hypoparathyroidism may resemble parkinsonian disease

Basal ganglia involvement may produce parkinsonian-like movement disorders.

- The clinical phenomenon is an extrapyramidal motor phenotype.
- It should be interpreted with the broader electrolyte and endocrine picture.
- Intracranial calcification is a reported association, not a universal feature.

Raised intracranial pressure is another neurologic association

Hypoparathyroidism can be associated with increased intracranial pressure and papilledema.

- Papilledema is a funduscopy consequence of raised intracranial pressure.
- This differs from the acute excitability mechanism of tetany.
- Chronically affected patients may have multiple neurologic manifestations.

Ocular changes: Lens calcification and cataract

Chronic hypoparathyroidism can produce calcification of the lens and cataract formation.

- The change is an ocular tissue manifestation, not merely transient paresthesia.
- Chronicity is relevant when interpreting lens abnormalities.
- Ocular and intracranial calcification share a mineral-deposition theme.

Cardiac conduction: A prolonged QT interval

Hypocalcemia causes a characteristic QT-interval prolongation on ECG.

- The electrophysiologic abnormality reflects disturbed calcium physiology.
- It is a systemic manifestation of PTH-related hypocalcemia.
- Do not confuse a conduction manifestation with an etiologic diagnosis.

Dental abnormalities record early-life hypocalcemia

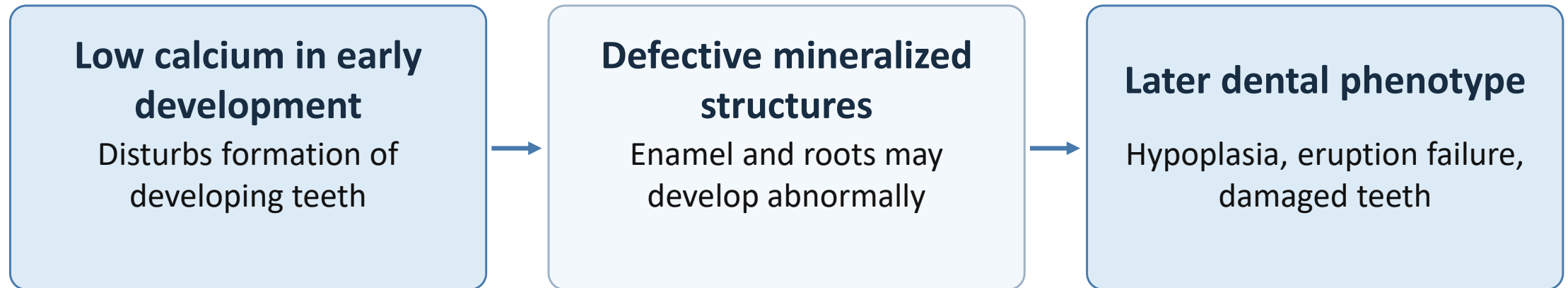
Tooth development

- Dental hypoplasia
- Defective enamel formation
- Defective root formation

Eruption and tooth integrity

- Failure of eruption
- Abraded teeth
- Carious teeth

Why timing matters for dental abnormalities



Dentition provides a clue to the developmental timing of calcium deficiency.

Acute versus chronic emphasis

Immediate excitability

- Circumoral paresthesias
- Carpopedal tetany
- Laryngospasm / seizures
- QT prolongation

Longer-standing associations

- Basal ganglia calcifications
- Movement disorders
- Lens calcification / cataracts
- Dental defects if onset is early

Teaching grouping reflects manifestations and chronicity, not rigid temporal diagnostic criteria.

Three clinical domains to screen conceptually

Neurologic

Tetany, seizures, psychiatric symptoms, and basal ganglia changes.

Cardio-ocular

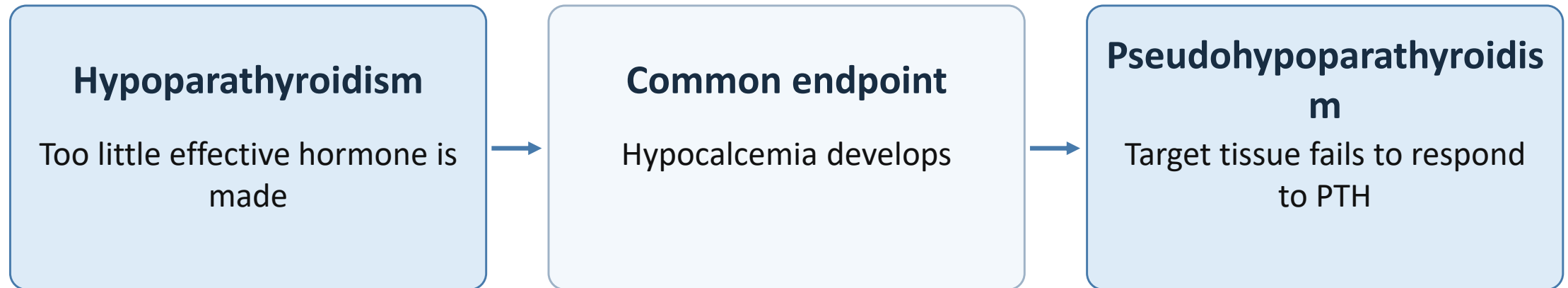
Prolonged QT; Lens calcification and cataract.

Developmental

Abnormal dental development after early hypocalcemia.

Organ involvement follows calcium imbalance rather than a mass-producing gland lesion.

PTH deficiency versus PTH resistance



Similar calcium results require different endocrine interpretation of circulating PTH.

Interpret calcium together with circulating PTH

True hypoparathyroidism

- Calcium low
- PTH insufficient / inappropriately low
- Hormone deficiency mechanism
- Phosphate tends to be retained

Pseudohypoparathyroidism

- Calcium low
- PTH normal or elevated
- End-organ PTH resistance
- Hyperphosphatemia described

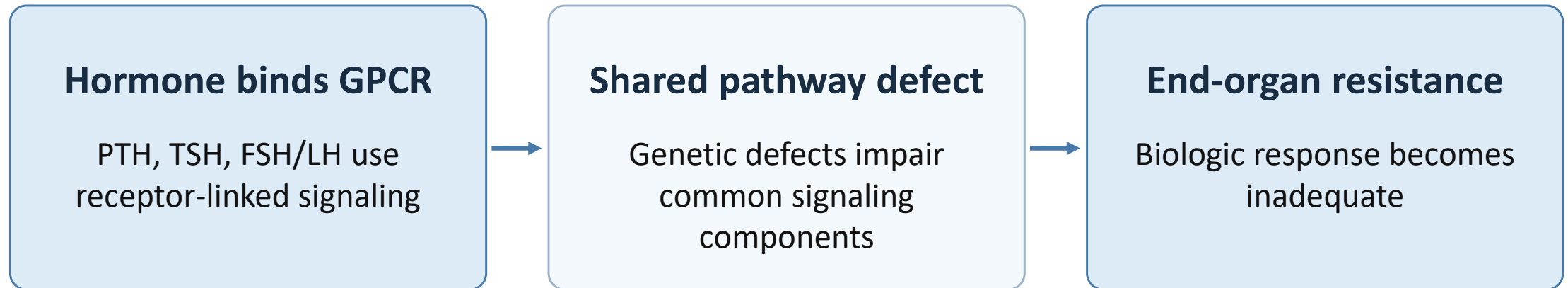
No numeric reference cutoffs are asserted; Biochemical descriptors are qualitative.

Pseudohypoparathyroidism: PTH is present but ineffective

The defining lesion is end-organ resistance to PTH.

- Circulating PTH is normal or elevated, unlike deficient secretion.
- The classic pattern is hypocalcemia and hyperphosphatemia.
- Clinical PTH resistance can coexist with resistance to other hormones.

Post-receptor signaling explains multihormone resistance



Some pseudohypoparathyroidism forms to shared G-protein–coupled signaling defects.

Pseudohypoparathyroidism can involve three endocrine axes

PTH

Most obvious resistance;
Low calcium and high
phosphate.

TSH

Resistance is generally mild.

FSH/LH

Female hypergonadotropic
hypogonadism can occur.

Multihormone resistance is described in one form—not all forms.

PTH deficiency versus receptor-pathway resistance

Hormone deficiency

- Surgical or genetic causes of low PTH
- Secretion or gland development impaired
- Hypocalcemic manifestations
- PTH itself is inadequate

PTH resistance

- End-organ signal transduction impaired
- PTH may be elevated
- Hypocalcemia + hyperphosphatemia
- Other GPCR hormones sometimes affected

Etiologic diagnosis: Three high-yield clues

Operative history

Thyroid, radical neck, or parathyroid surgery.

Syndromic history

Candidiasis/adrenal disease or thymic/cardiac defects.

Inheritance pattern

CASR activation, PTH processing, or GCM2 developmental disorder.

Case application: Post-thyroidectomy tetany

Clinical vignette

A patient develops circumoral tingling and carpopedal spasm after thyroidectomy.

Reason through the mechanism

Which endocrine tissue may have been removed? How does this cause the symptoms?

Case application: Childhood candidiasis and tetany

Clinical vignette

A child has recurrent mucocutaneous candidiasis and later develops symptoms of hypocalcemia.

Reason through the mechanism

Which inherited autoimmune syndrome is suggested? Which later endocrine disorder is classically associated?

Case application: Low calcium with high urinary calcium

Clinical vignette

A person with familial hypocalcemia also has hypercalciuria and an inappropriately suppressed PTH response.

Reason through the mechanism

Which calcium-sensing receptor change best explains the combined phenotype?

Case application: Hypocalcemia plus thymic defects

Clinical vignette

An infant develops tetany and has a congenital cardiovascular anomaly and thymic hypoplasia.

Reason through the mechanism

Which shared developmental defect should be considered? What broad chromosomal syndrome is associated?

Case application: Hypocalcemia despite elevated PTH

Clinical vignette

A patient has low calcium, high phosphate, and elevated circulating PTH. Mild TSH resistance is also suspected.

Reason through the mechanism

Is hormone deficiency or end-organ resistance the better model? Which signaling class is implicated?

Hypocalcemia: Final etiologic comparison

Low PTH output

- Postsurgical loss
- APS-1 associated autoimmunity
- PTH / GCM2 genetic defect
- CASR gain of function

PTH resistance

- PTH normal or elevated
- Target-organ hormone signaling impaired
- Low calcium / high phosphate
- Additional hormone resistance in some forms

Clinical synthesis: four mechanisms, one key phenotype

Hypocalcemia is the common consequence; etiology is determined by the failed step.

- Loss of tissue: surgery or developmental absence.
- Immune injury: APS-1 with AIRE dysfunction.
- Altered gene function: CASR, PTH, or GCM2.
- Target resistance: pseudohypoparathyroidism with PTH present.