

Primary Hyperparathyroidism

Pathogenesis · morphology · clinicopathologic correlations

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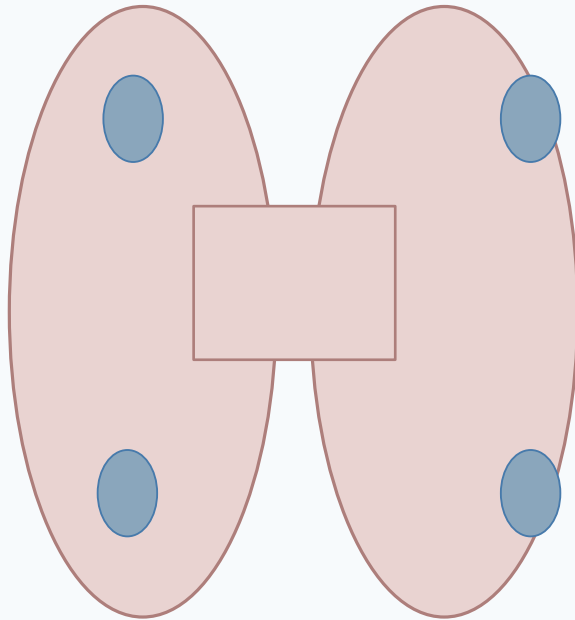
Learning objectives

- Explain how autonomous PTH secretion produces hypercalcemia and phosphate loss.
- Distinguish adenoma, primary hyperplasia, atypical neoplasm and carcinoma.
- Relate genetic alterations to parathyroid lesions and familial syndromes.
- Connect skeletal, renal and systemic pathology to biochemical findings.

A pathology-focused, mechanism-to-morphology lecture

Four glands, variable locations

Schematic positions

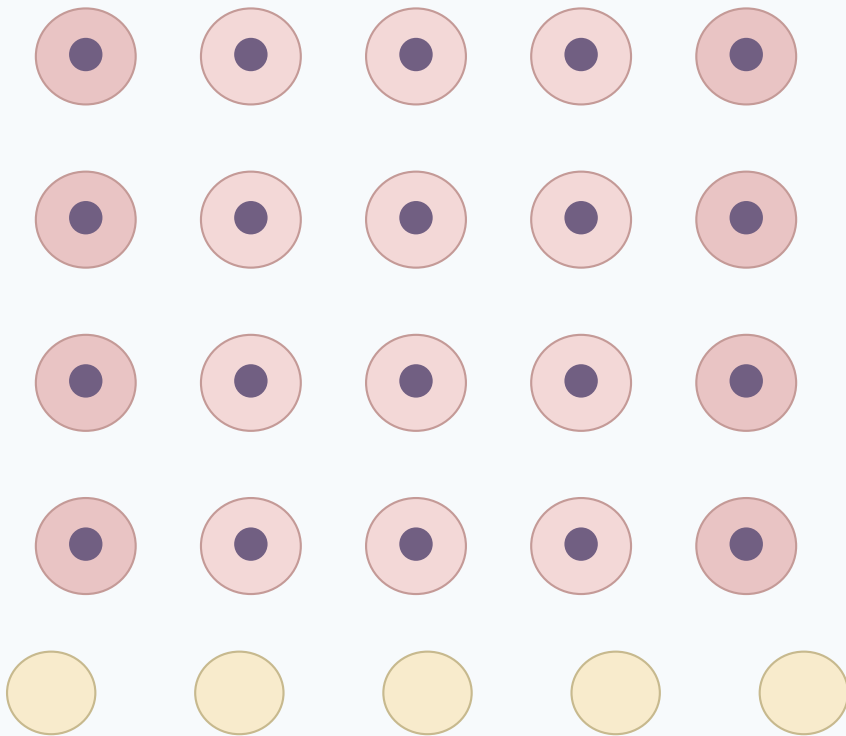


- Most glands lie near superior and inferior poles of each thyroid lobe.
- Developmental descent permits ectopic glands, including thymic or mediastinal locations.
- A functional parathyroid neoplasm may lie outside the usual cervical sites.

Anatomical variation matters when a lesion is being localized.

Chief and oxyphil cells

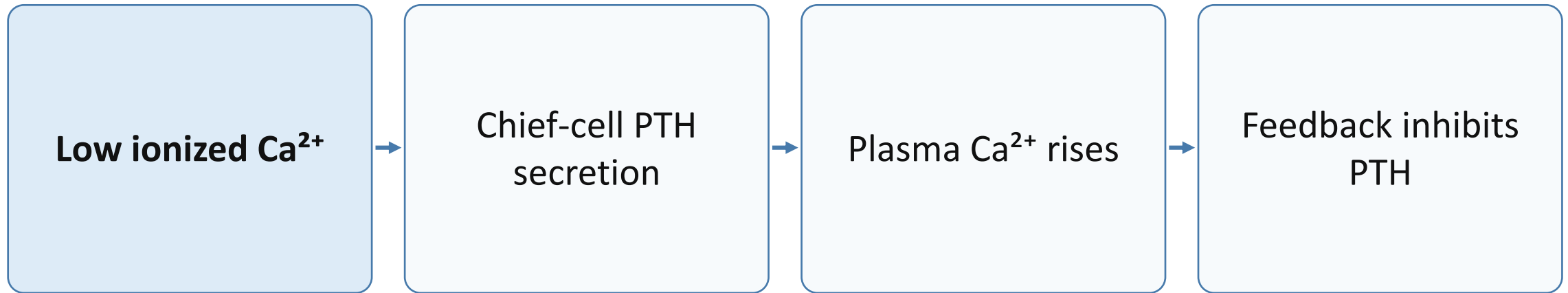
Chief cells and stromal fat (schematic)



- Chief cells predominate and contain secretory granules with PTH.
- Oxyphil cells are larger, mitochondria-rich and conspicuously eosinophilic.
- Normal adult parathyroid contains appreciable stromal adipose tissue.

Cell identity and stromal fat provide context for tumor morphology.

Ionized calcium controls PTH



Normal calcium feedback restrains parathyroid activity.

Four actions of PTH

Kidney

Conserves calcium by increasing tubular reabsorption

Kidney / vitamin D

Promotes generation of active vitamin D

Urine / phosphate

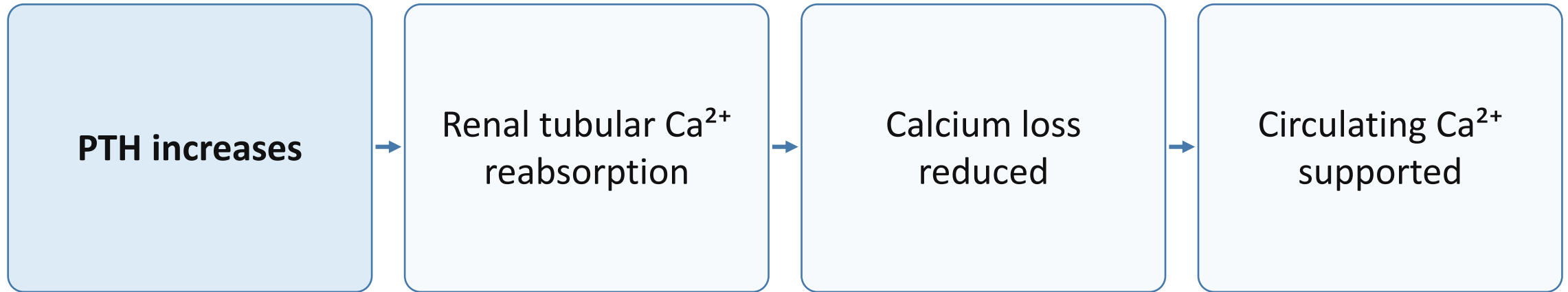
Enhances phosphate excretion

Skeleton

Increases osteoclast-mediated resorption

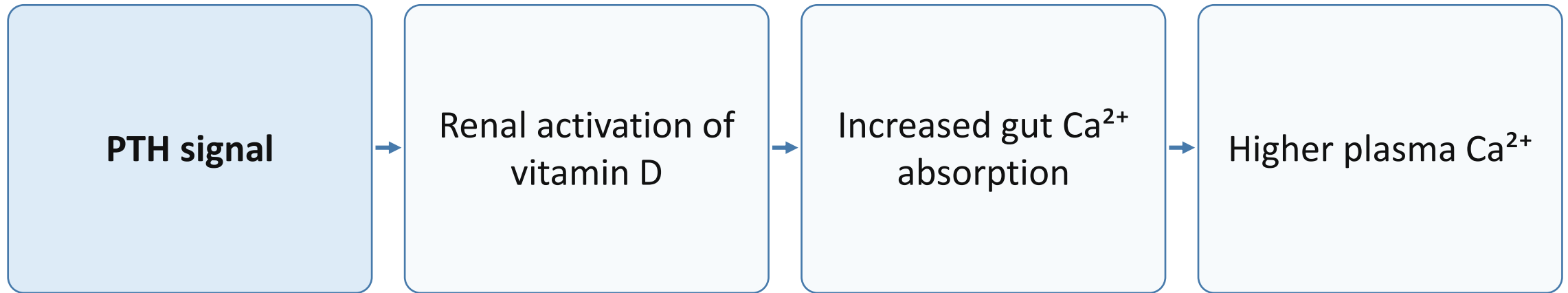
The net effect is increased circulating ionized calcium.

Renal calcium conservation



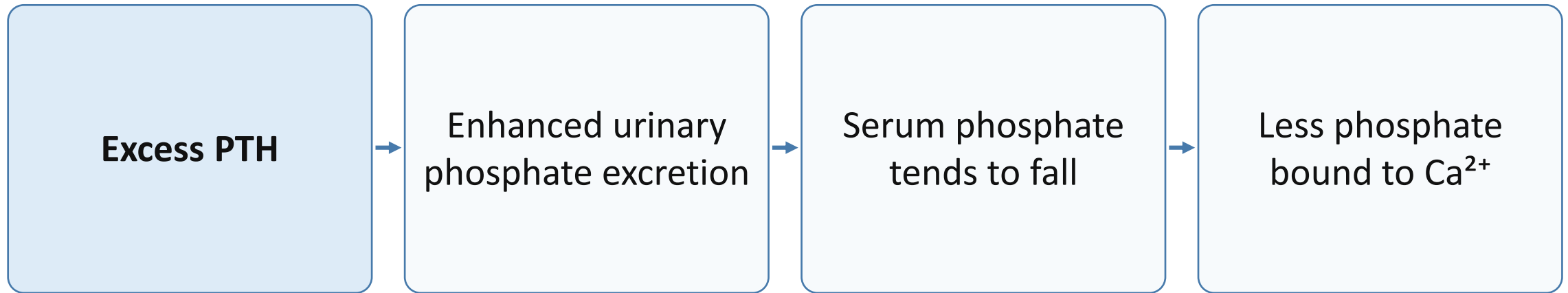
PTH affects renal calcium handling before downstream tissue complications.

Vitamin D amplifies calcium absorption



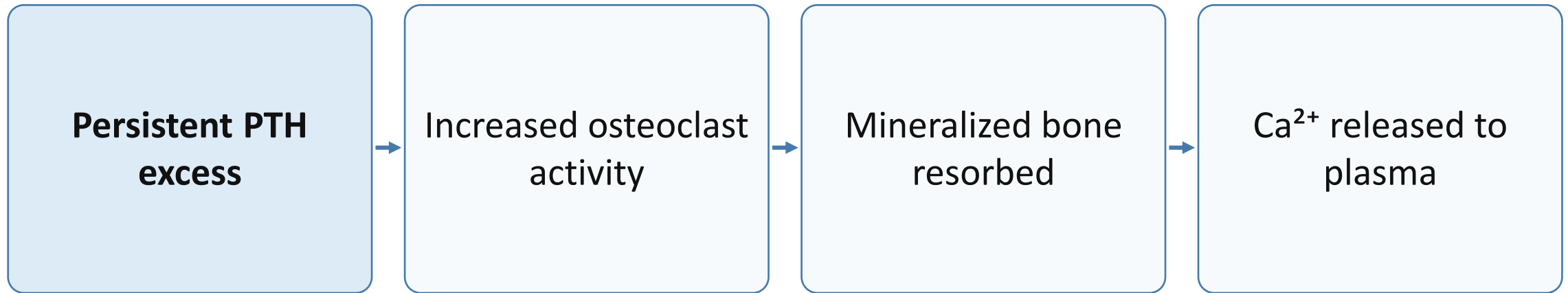
The intestine is affected indirectly through renal vitamin D activation.

Phosphate loss is part of the PTH signature



Renal insufficiency may alter the expected phosphate concentration.

Bone resorption raises blood calcium



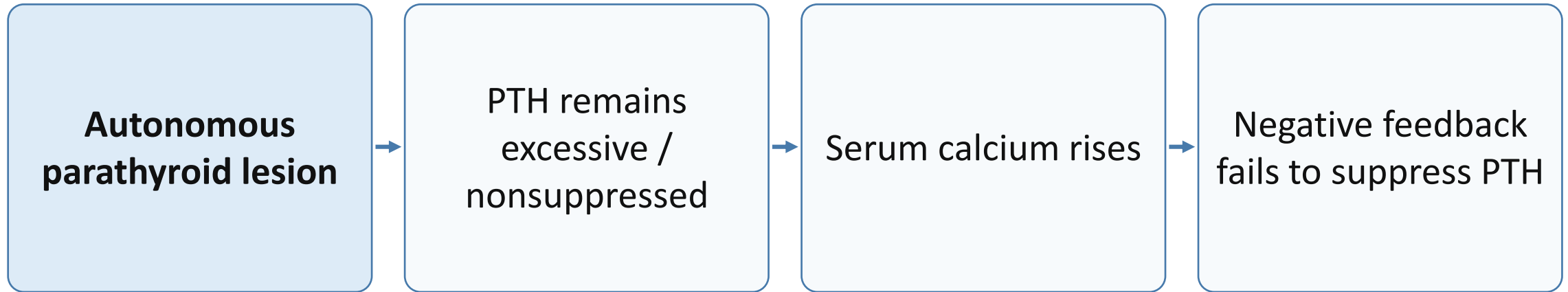
Long-standing signaling causes structural skeletal injury.

Primary, secondary and tertiary hyperparathyroidism

Feature	Primary	Secondary	Tertiary
Driver	Autonomous PTH secretion	Compensatory PTH secretion	Autonomy after long-standing secondary disease
Typical setting	Parathyroid adenoma / hyperplasia	Renal disease or vitamin D deficiency	Prolonged secondary hyperparathyroidism
Pathophysiologic concept	Excess hormone despite high calcium	Response to persistent calcium-related stimulus	Acquired autonomy

Mechanism, rather than gland size alone, defines the category.

Primary disease breaks normal feedback



Inappropriately normal PTH during hypercalcemia is not physiologically normal.

Clinical epidemiology

Typical age

Most cases occur in adults aged 50 years or older

Sex distribution

Female predominance; Nearly 4:1

Reported incidence

Approximately 25 per 100,000 annually in the cited US/Europe data

Detection

Up to 80% found incidentally in outpatient laboratory tests

These are textbook estimates, not independently updated population statistics.

Distribution of underlying parathyroid lesions

Adenoma

85–95% of cases

Primary hyperplasia

5–10% of cases

Carcinoma

Less than 1% of cases

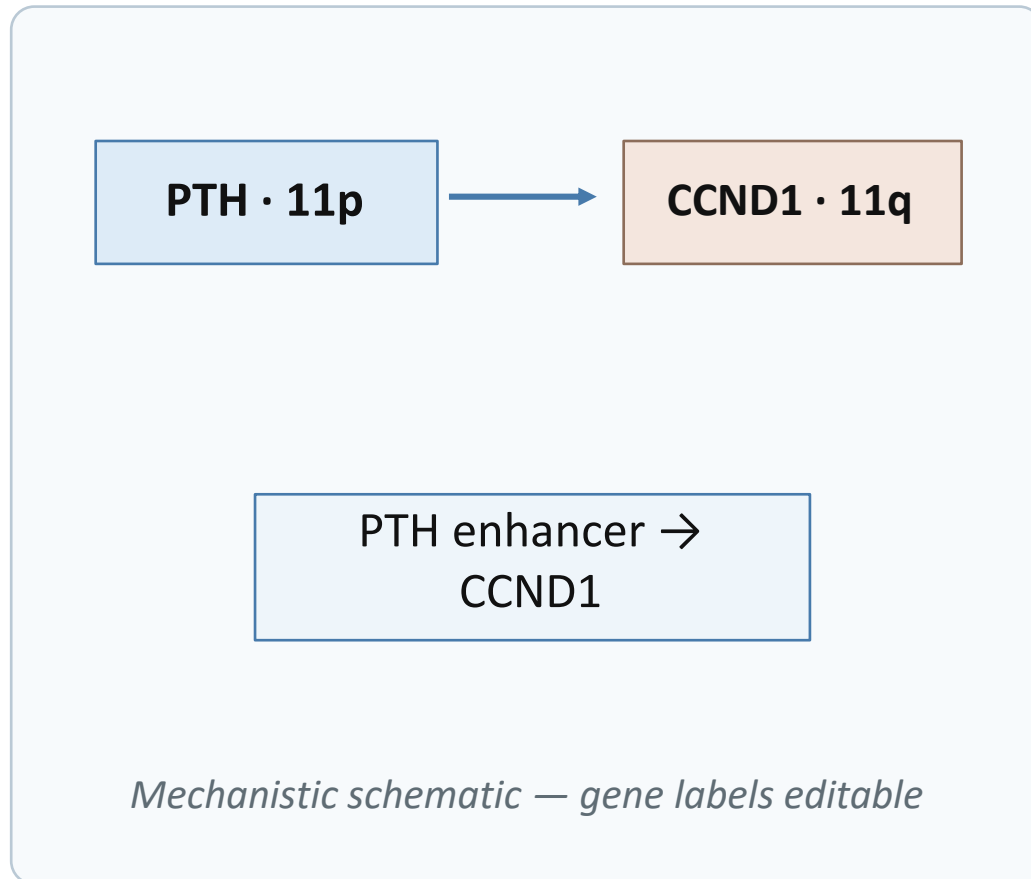
Solitary sporadic adenoma is the dominant substrate.

Adenomas are typically monoclonal

- Most sporadic parathyroid adenomas are clonal neoplasms.
- Autonomous growth and hormone production distinguish them from normal feedback-controlled tissue.
- The two established recurrent adenoma pathways in the source are CCND1 dysregulation and MEN1 inactivation.

Clonality supports neoplasia; It does not by itself imply malignancy.

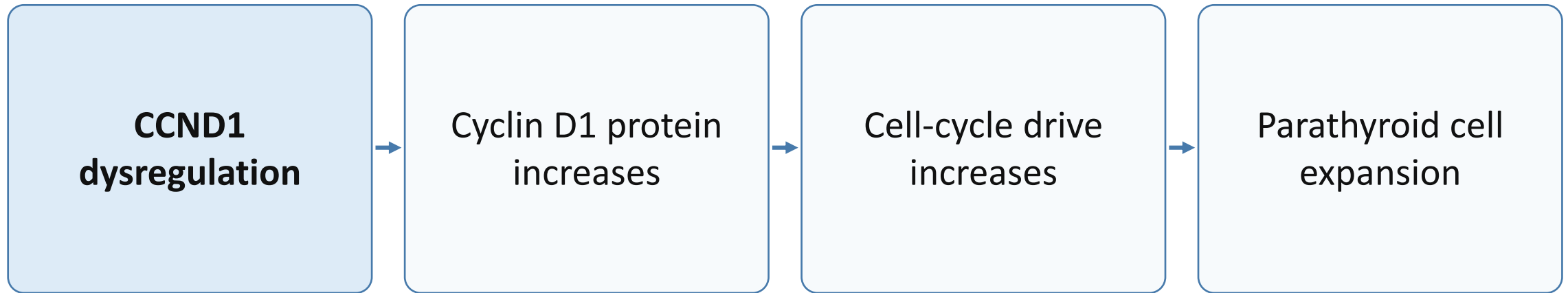
CCND1 inversion places a growth gene near PTH control



- Pericentromeric chromosome 11 inversion juxtaposes CCND1 with a PTH regulatory element.
- CCND1 is normally at 11q; The PTH locus is at 11p.
- The altered transcriptional context drives cyclin D1 overexpression.

This is an enhancer-position effect, not a PTH coding sequence change.

Cyclin D1 overexpression promotes proliferation



Cyclin D1 overexpression can also occur without the inversion.

Cyclin D1 dysregulation is not limited to inversion

- Up to 40% of adenomas without CCND1 rearrangement overexpress cyclin D1.
- Therefore, multiple upstream routes can converge on the same cell-cycle effector.
- Finding cyclin D1 elevation alone does not demonstrate a specific chromosome inversion.

Distinguish a pathway readout from the underlying genomic lesion.

MEN1 is a tumor-suppressor pathway

MEN1 · 11q13



Mutation + allelic loss

Mechanistic schematic — gene labels editable

- About 15% of sporadic parathyroid tumors harbor somatic MEN1 alterations.
- The MEN1 tumor-suppressor locus lies at chromosome 11q13.
- Loss of heterozygosity of the second allele is described.

Germline MEN1 disease and sporadic somatic MEN1 alterations are different contexts.

Two distinct sporadic adenoma mechanisms

Feature	CCND1 pathway	MEN1 pathway
Primary alteration	Gene juxtaposition / excess expression	Tumor-suppressor mutation and allelic loss
Protein-level consequence	Cyclin D1 upregulated	MEN1 tumor-suppressor function disrupted
Oncogenic logic	Growth drive increased	Growth restraint reduced

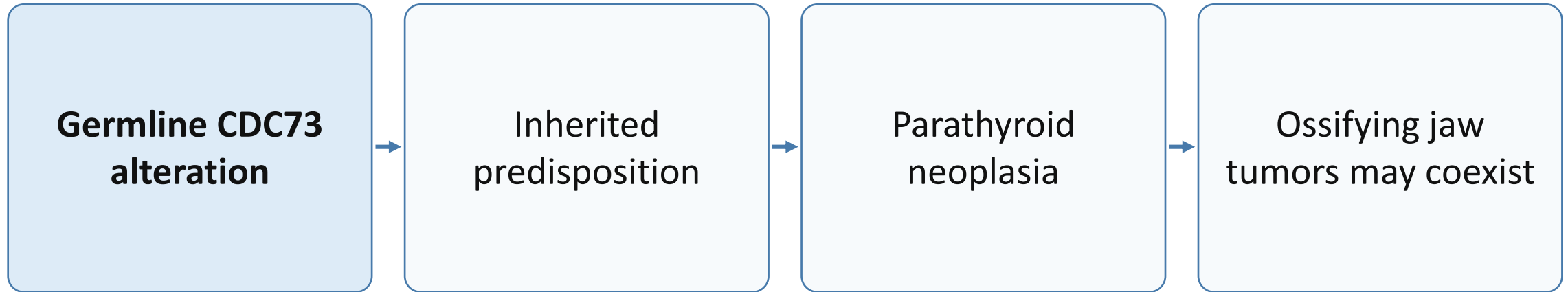
Both mechanisms can yield clonal parathyroid expansion.

CDC73 links adenoma and carcinoma biology

- CDC73 encodes parafibromin, a protein implicated in transcriptional regulation.
- The source describes CDC73 alterations as frequent in sporadic parathyroid carcinomas.
- CDC73 changes may also occur in some adenomas.
- A molecular association is not equivalent to a standalone histologic malignancy criterion.

Retain the distinction between genetic risk and invasive behavior.

Hyperparathyroidism–jaw tumor syndrome



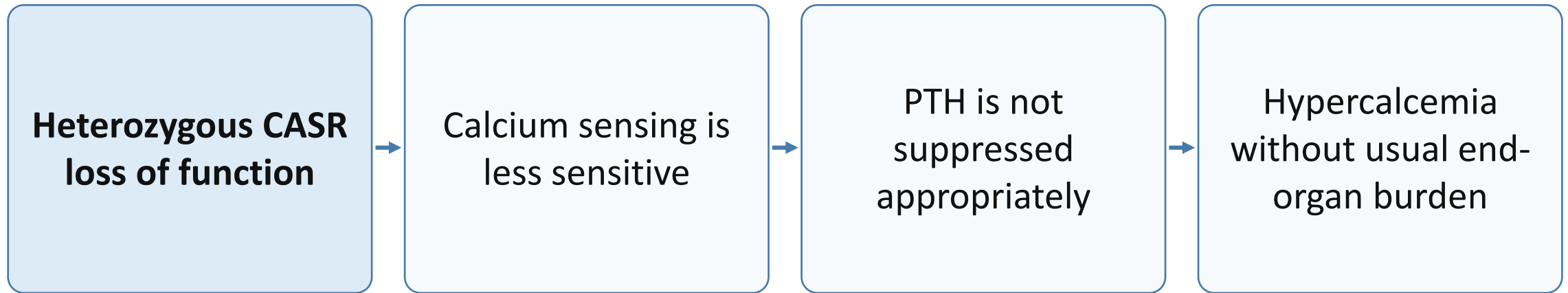
The syndrome includes a spectrum in which parathyroid carcinoma can occur.

Familial syndromes occur less often than sporadic adenoma

- The source identifies MEN-1, MEN-2 and MEN-4 in the familial setting.
- Family history and other endocrine tumors can alter the diagnostic context.
- Familial disease warrants a different interpretation from an isolated sporadic gland lesion.

The familial syndromes are noted here, not expanded beyond the source section.

Familial hypocalciuric hypercalcemia: A mimic



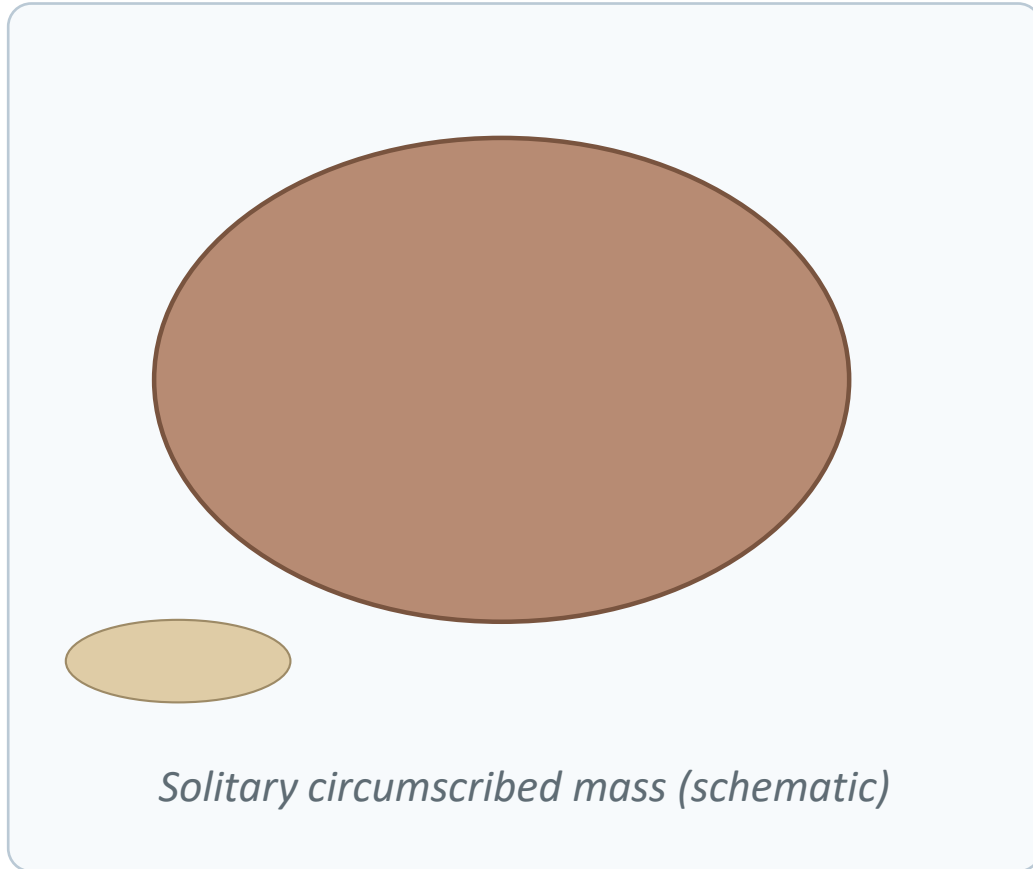
FHH is a differential diagnosis, not simply another adenoma.

Primary hyperparathyroidism versus FHH

Feature	Primary hyperparathyroidism	Familial hypocalciuric hypercalcemia
Origin	Autonomous PTH-producing lesion	Altered calcium sensing (often CASR)
PTH during high calcium	High or inappropriately normal	Nonsuppressed
Skeletal / renal effects	May be clinically significant	Usually lacks typical downstream burden
Interpretive point	Evaluate parathyroid pathology	Avoid reflex assumption of tumor

The textbook excerpt does not supply a urinary calcium ratio cutoff.

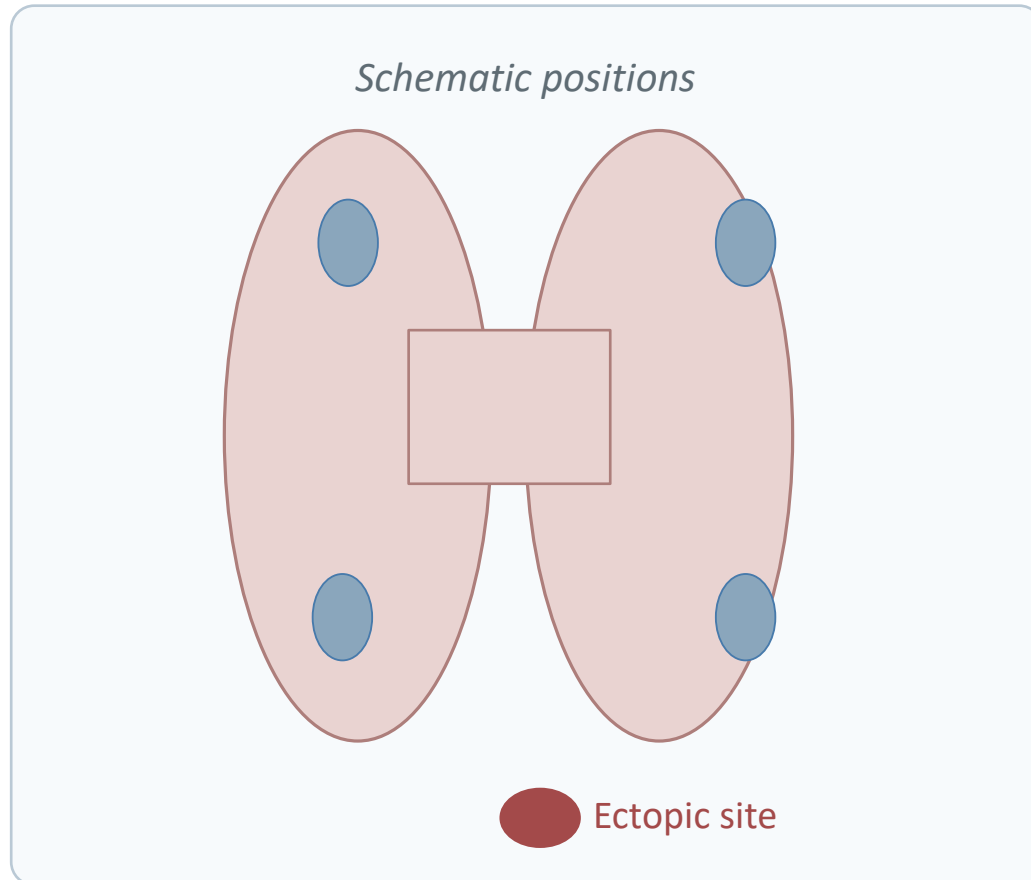
Adenoma: Macroscopic morphology



- Usually one well-circumscribed, soft nodule.
- Tan to reddish-brown cut surface; Typical reported weight 0.5–5 g.
- Other parathyroid glands are often normal sized or reduced.

Gross circumscription and solitary distribution support adenoma.

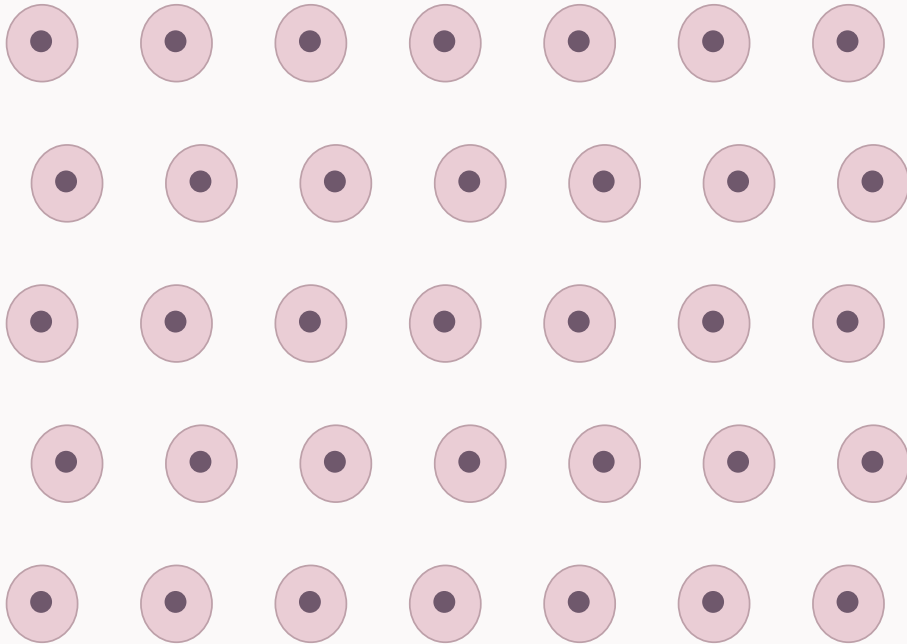
Adenoma may be ectopic



- Adenomas can arise near the thyroid or at an ectopic site.
- Anterior mediastinum is a documented ectopic location.
- Failure to identify a cervical lesion does not exclude functioning parathyroid tumor.

Anatomic and functional localization should be interpreted together.

Chief-cell adenoma: Uniform cellular sheets

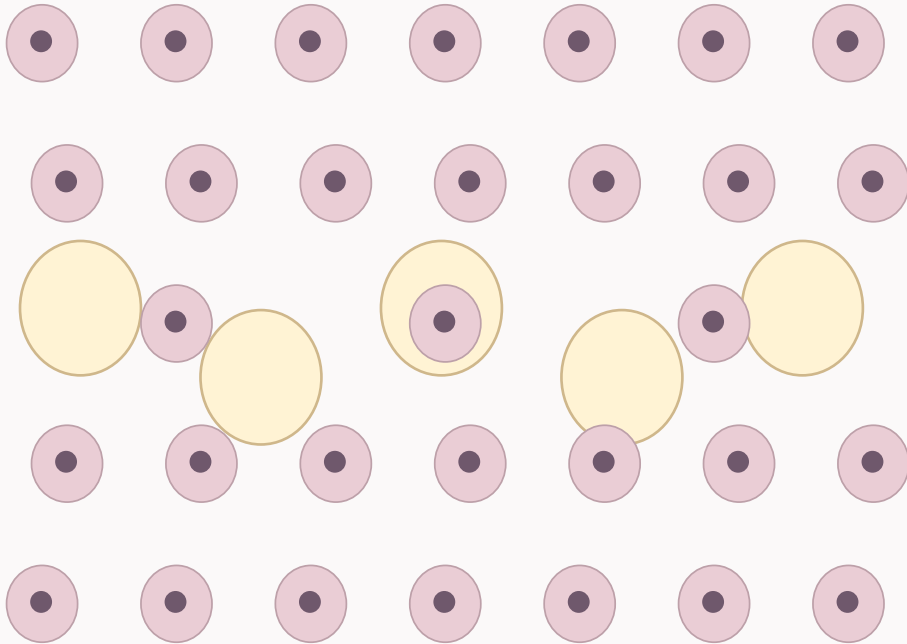


Native schematic — not a photomicrograph

- Sheets of polygonal chief cells with centrally placed nuclei.
- Uniform architecture; Mitotic figures uncommon.
- An edge of compressed nonneoplastic gland can be present.

Schematic of cellular relationships; Not a photomicrograph.

Adenoma usually lacks obvious stromal fat



Native schematic — not a photomicrograph

- Normal adult parathyroid commonly contains interspersed adipocytes.
- In adenoma, stromal fat is inconspicuous.
- A small remnant of compressed normal gland may retain fat.

Fat distribution is supportive, not a stand-alone determination.

Adenoma: Uncommon cytologic variants

Chief-cell

Dominant conventional cell population

Oxyphil adenoma

Predominantly eosinophilic oxyphil cells

Water-clear adenoma

Predominantly clear cells

Chief-cell sheets remain the usual pattern.

Endocrine atypia is not carcinoma

- Occasionally, adenomas contain bizarre or pleomorphic nuclei.
- This phenomenon is described as endocrine atypia.
- Cytologic atypia alone does not establish invasive malignancy.
- Confirm destructive invasion or metastasis before labeling carcinoma.

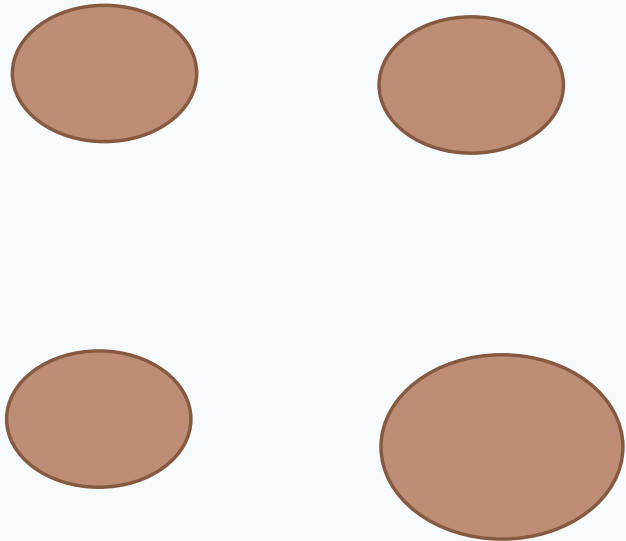
A high-value diagnostic pitfall in endocrine pathology.

Normal gland versus adenoma

Observation	Normal parathyroid	Adenoma
Cellularity	Chief and oxyphil cells with stromal fat	Cellular chief-cell sheets
Stromal fat	Conspicuous in typical adult tissue	Often markedly reduced
Distribution	Four glands regulate calcium	Usually one discrete expanded nodule
Periphery	No tumor compression	Compressed normal rim may be present

These are patterns; Clinical and operative context remain essential.

Primary hyperplasia: Often multiglandular



Multigland process (schematic)

- Diffuse or nodular enlargement often affects all four glands.
- Degree of enlargement can be asymmetric.
- Combined gland weight rarely exceeds 1 g description.

Do not infer single-gland disease purely from asymmetry.

Asymmetry complicates gland-level classification

Pattern A

Several glands enlarged:
Hyperplasia favored

Pattern B

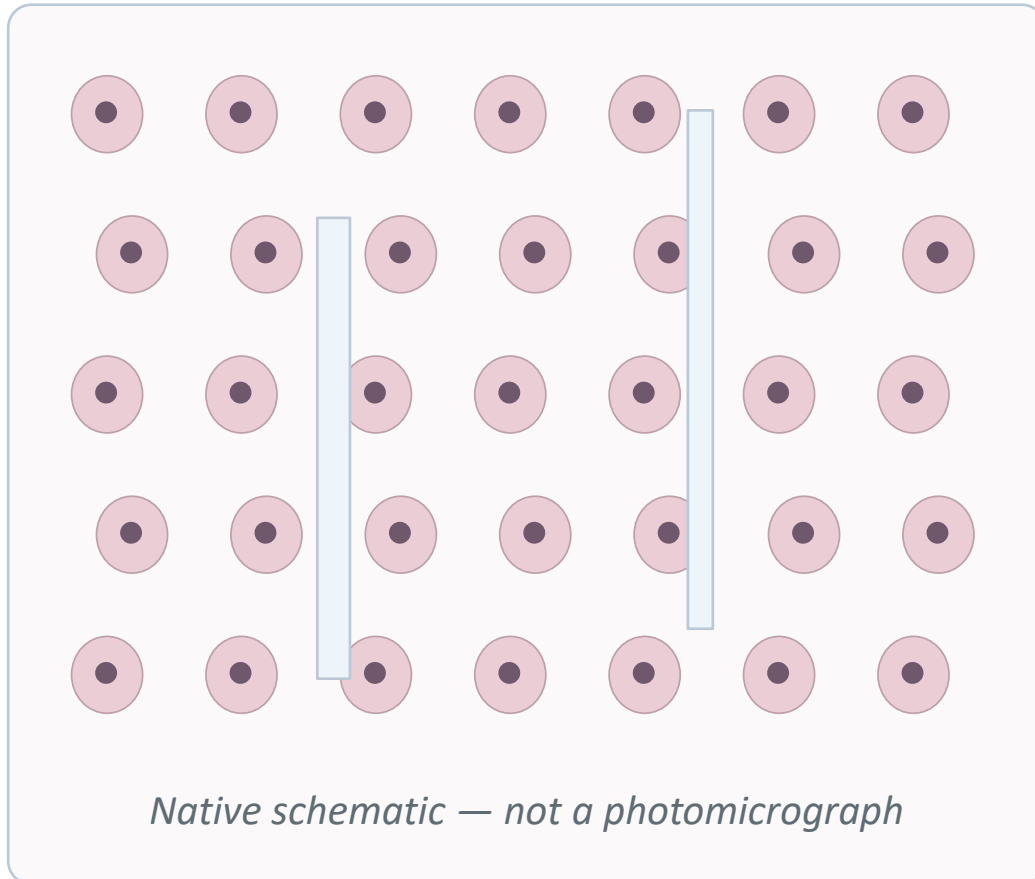
One gland much larger than
others: Could still be
asymmetric hyperplasia

Pattern C

One solitary adenoma with
suppressed remaining glands:
Adenoma favored

Morphologic overlap can require correlation with gland distribution.

Primary hyperplasia: Cellular patterns



- Chief-cell hyperplasia is the common microscopic pattern.
- Growth may be diffuse or multinodular.
- Water-clear cells and oxyphil islands are recognized; Fat is reduced.

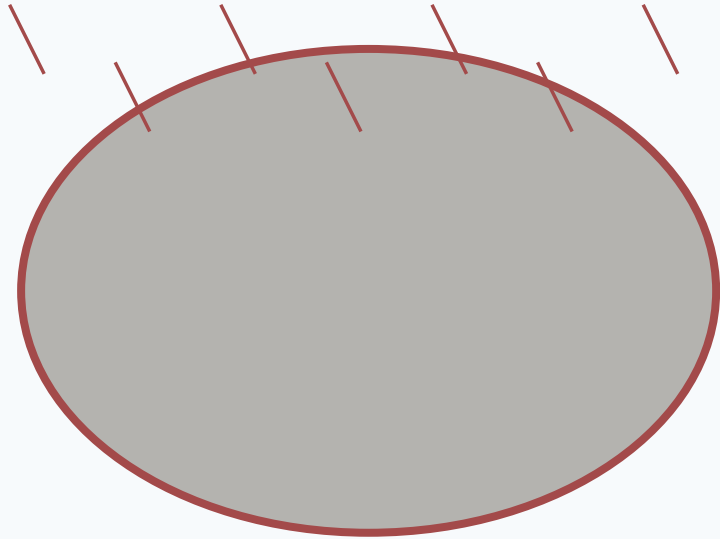
Native schematic illustrates pattern, not authentic histology.

Adenoma and hyperplasia can overlap histologically

Feature	Adenoma	Primary hyperplasia
Typical gland count	Single gland	Multiple glands, sometimes asymmetric
Growth pattern	Well-circumscribed mass	Diffuse or multinodular
Stromal fat	Scarce	Scarce
Key pitfall	Single mass may dominate	An apparently spared gland does not rule it out

The number and behavior of glands can be more informative than cell appearance.

Parathyroid carcinoma: Gross warning features

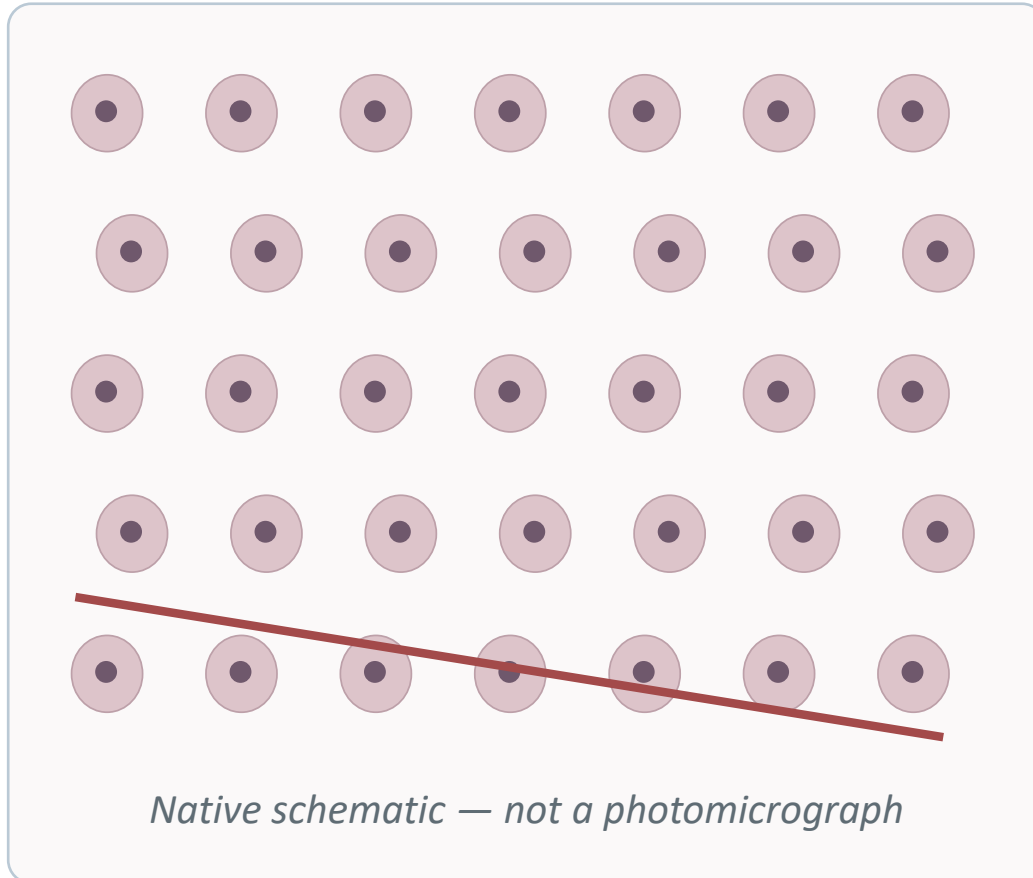


Irregular tumor (schematic)

- Commonly one affected gland forming irregular gray-white mass.
- Some lesions exceed 10 g description.
- An infiltrative interface requires meticulous examination.

Large size and irregularity raise suspicion; Invasion confirms carcinoma.

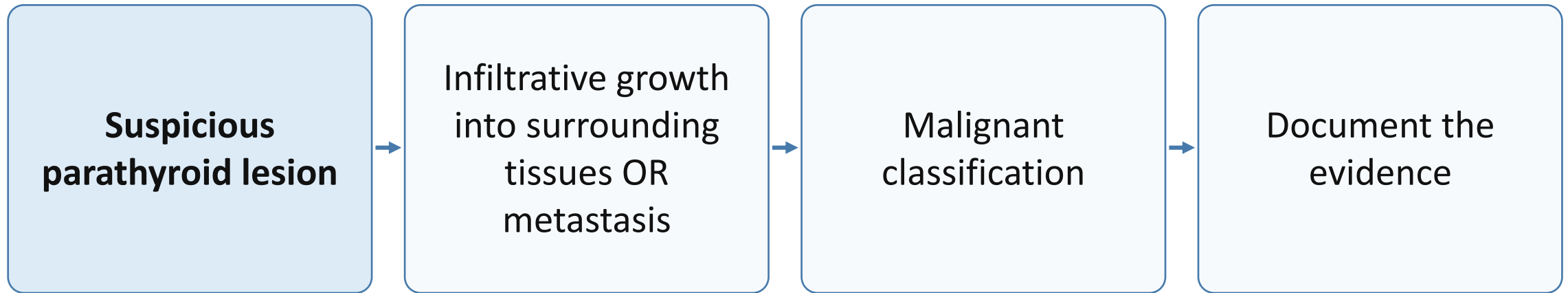
Carcinoma cytology often looks deceptively bland



- Tumor cells can be cytologically uniform and resemble normal cells.
- Growth can be nodular or trabecular.
- Cytologic detail by itself is unreliable for defining carcinoma.

Architectural invasion outweighs nuclear appearance.

Defining carcinoma: Invasion or metastasis



This is the defining criterion given, not pleomorphism alone.

Pitfalls in diagnosing parathyroid malignancy

Not independently diagnostic	Strongly diagnostic in source
Large gland size	Invasion into surrounding structures
Cytologic pleomorphism	Demonstrated metastasis
Bizarre nuclei / endocrine atypia	Invasive growth pattern
Nodular architecture	Tumor spread beyond the primary site

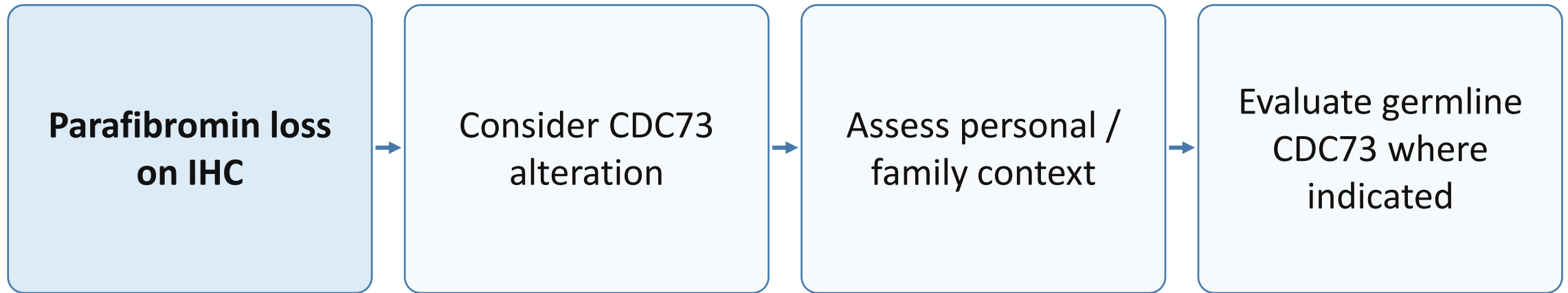
The distinction prevents overdiagnosis of adenomas with endocrine atypia.

Atypical parathyroid neoplasm

- A category for neoplasms with worrisome, non-definitive features.
- Fibrosis, cystic alteration and macronucleoli are examples given.
- Such changes cannot substitute for documented invasion or metastasis.
- The label preserves diagnostic uncertainty.

Suspicion is a different conclusion from proven carcinoma.

Parafibromin loss and inherited predisposition



Robbins calls for germline screening in parafibromin-deficient neoplasms or carcinoma.

Four parathyroid lesions: Diagnostic logic

Lesion	Most useful distinguishing feature
Adenoma	Usually circumscribed solitary tumor
Primary hyperplasia	Usually multiglandular, diffuse or nodular
Atypical neoplasm	Worrisome features without definite invasion
Carcinoma	Invasive growth and/or metastasis

Histologic labels should correspond to evidence, not presumed biologic potential.

Skeletal and renal injury explain the syndrome

Skeleton

Osteoclastic resorption → fragility and reparative lesions

Renal collecting system

Hypercalcemia favors urinary calculi

Renal parenchyma

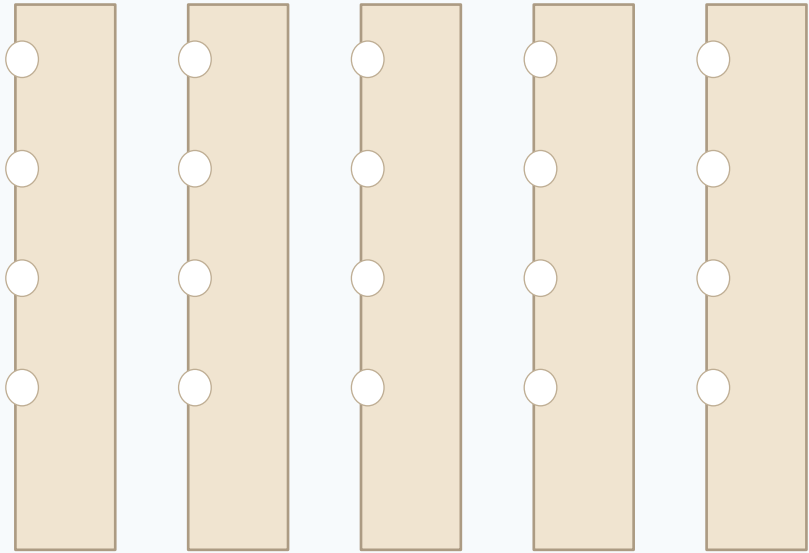
Calcium deposition injures tubules and interstitium

Other organs

Severe hypercalcemia may cause metastatic calcification

Target-organ pathology reflects sustained PTH excess and hypercalcemia.

Cortical bone bears major injury

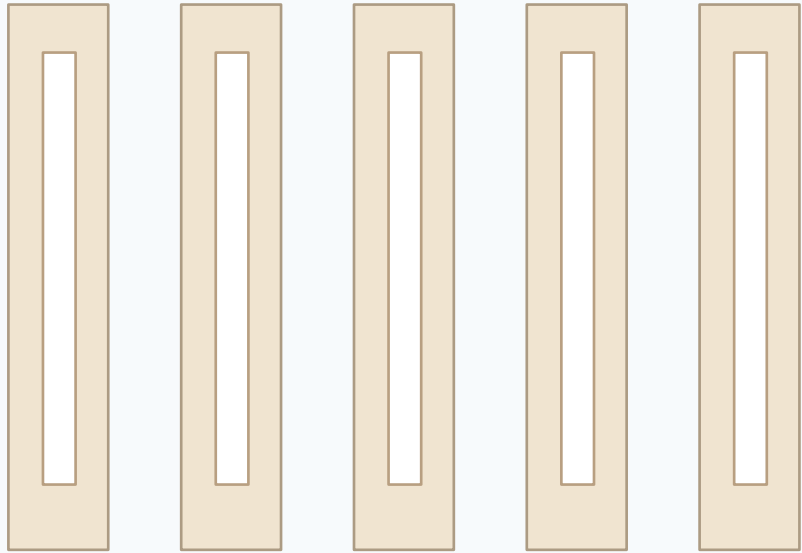


Cortical / endosteal resorption (schematic)

- Osteoclastic resorption predominantly affects cortical surfaces.
- Subperiosteal and endosteal bone are particularly involved.
- Bone mass falls, increasing susceptibility to fractures.

The reported cortical predominance is a feature of skeletal involvement.

Dissecting osteitis: Resorption tunnels

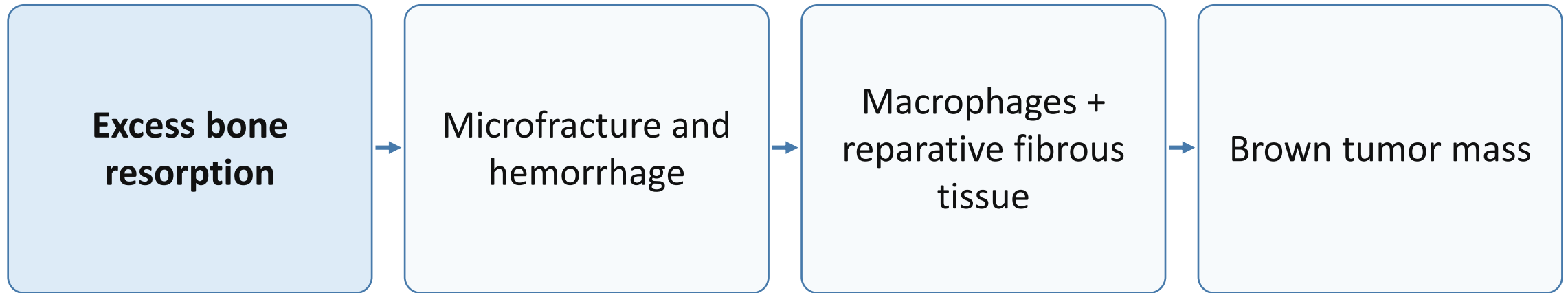


Longitudinal trabecular tunnels (schematic)

- Osteoclasts tunnel longitudinally through medullary trabeculae.
- The resulting tracks may resemble railroad rails.
- Surrounding marrow spaces develop fibrovascular tissue.

Schematic rendering of the described destructive process.

Brown tumors are reactive, not epithelial cancer



Hemosiderin, hemorrhage and vascularity explain the brown color.

Osteitis fibrosa cystica is a composite lesion

Bone resorption

Increased osteoclast action

Peritrabecular response

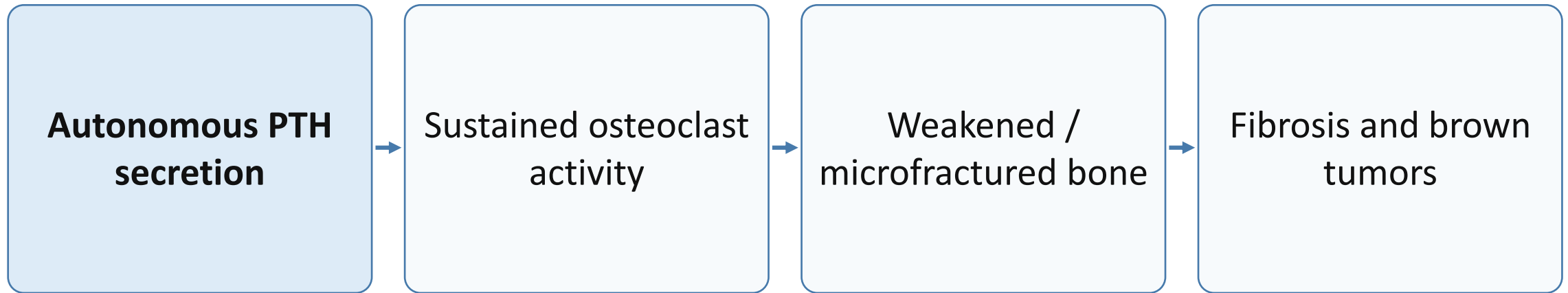
Fibrous stromal replacement

Cystic / hemorrhagic lesions

Brown tumors may undergo cystic change

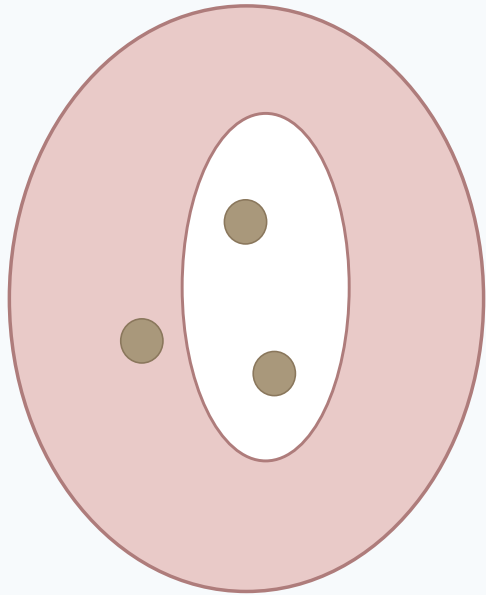
Severe, untreated disease combines all three processes.

Mechanism-to-lesion sequence in bone



The same pathway links biochemical abnormality to morphologic damage.

Nephrolithiasis reflects high calcium burden

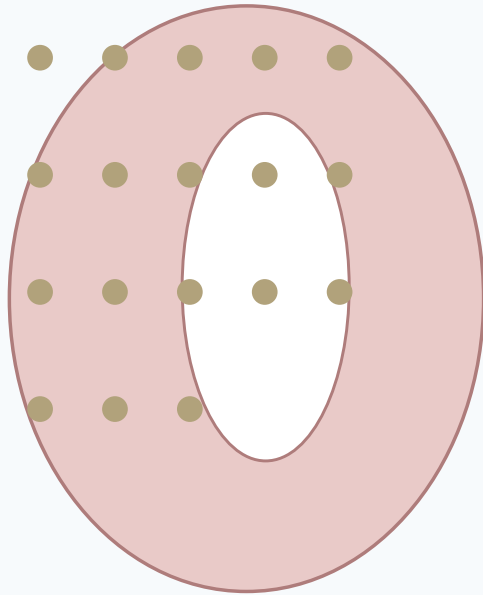


Discrete urinary stones (schematic)

- PTH-driven hypercalcemia promotes renal tract stone formation.
- Stones can cause pain and obstructive uropathy.
- Chronic renal injury can complicate prolonged disease.

Renal stones are an end-organ manifestation, not the cause of primary autonomy.

Nephrocalcinosis is distinct from stones



Parenchymal deposits (schematic)

- Calcium deposition may involve renal interstitium and tubules.
- Unlike a discrete urinary calculus, this is parenchymal calcification.
- Kidney injury can alter phosphate handling and clinical manifestations.

Separate parenchymal mineralization from collecting-system calculi.

Metastatic calcification can involve multiple organs

Stomach

Visceral calcium deposits in severe disease

Lung

Pulmonary tissue may accumulate calcium

Heart

Myocardial and valvular abnormalities may occur

Blood vessels

Vascular mineralization can occur

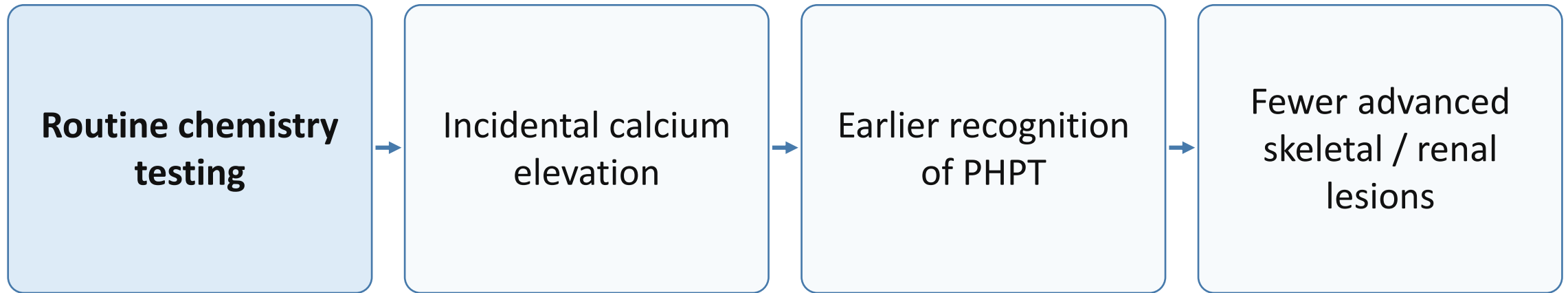
Here “metastatic calcification” denotes calcium deposition, not tumor metastasis.

Two modes of presentation

Feature	Asymptomatic detection	Symptomatic disease
Recognition	Incidental elevated serum calcium	Clinical effects of high calcium / PTH
Morphologic burden	Often no severe bone / renal lesions	May include stones, skeletal disease, organ calcification
Diagnostic implication	Biochemical evaluation is decisive	Exclude nonparathyroid causes of hypercalcemia

Biochemical screening shifted detection away from advanced manifestations.

Why classical lesions are now less frequent



That osteitis fibrosa cystica and brown tumors are less commonly encountered today.

Painful bones, renal stones, abdominal groans...

Bones

Pain and fractures from loss of skeletal integrity

Stones

Nephrolithiasis and obstruction

Abdomen

Constipation, nausea and other GI complaints

Psychic moans

Mood, consciousness and CNS symptoms

The mnemonic compresses several pathophysiologic pathways.

Gastrointestinal and neuromuscular manifestations

Feature	Gastrointestinal	Neuromuscular
Common in source	Constipation, nausea	Fatigue and weakness
Also described	Peptic ulcers, pancreatitis, gallstones	Reduced functional capacity
Link to disease	Systemic effect of excess PTH / calcium	Systemic effect of hypercalcemia

Symptoms are clinically relevant but nonspecific in isolation.

Neurologic and cardiovascular involvement

Neuropsychiatric

Depression and lethargy

Severe CNS involvement

Seizures can occur in advanced manifestations

Cardiac / valvular

Aortic or mitral valvular calcification

Clinical synthesis

Hypercalcemia can produce multisystem disease

Symptom severity does not identify the underlying gland lesion by itself.

Malignancy: Major competing cause of hypercalcemia

- Malignancy is described as the leading cause of symptomatic hypercalcemia in adults.
- Solid tumors and hematologic malignancies may produce hypercalcemia.
- PTH-related peptide-mediated bone resorption is a major mechanism in solid-tumor settings.
- Nonparathyroid hypercalcemia usually suppresses endogenous PTH.

Do not diagnose PHPT from high calcium alone.

Biochemistry separates PTH-dependent causes

Interpret circulating PTH during hypercalcemia



Elevated or inappropriately normal PTH

Supports a PTH-dependent process

Consider PHPT and mimics such as FHH

Low or undetectable PTH

Supports PTH-independent hypercalcemia

Evaluate malignancy and other etiologies

During hypercalcemia, PTH should be physiologically suppressed.

Typical biochemical pattern of PHPT

Serum calcium

Increased

PTH

Elevated or inappropriately normal

Phosphate

Often decreased from phosphaturia

Urine

Calcium and phosphate excretion increased in the source description

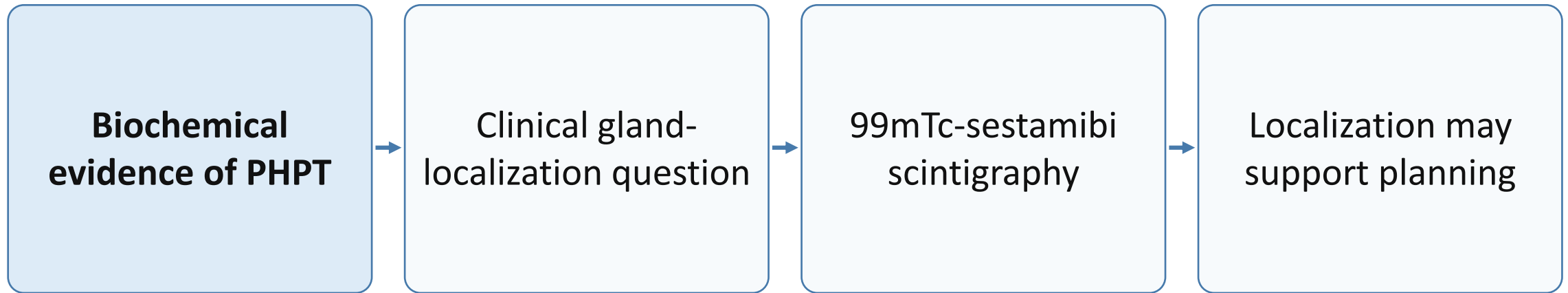
Renal disease can obscure the anticipated low serum phosphate.

Hypercalcemia: A mechanism-based differential

Feature	PTH not suppressed	PTH suppressed
Typical categories	Primary / tertiary hyperparathyroidism; FHH	Malignancy; Vitamin D excess
Other examples	Assess disease context	Granulomatous disease; Immobilization
Additional medication context	Interpret thiazide exposure clinically	Medication effects need clinical correlation

Table is a conceptual regrouping of Robbins Table 24.5; No laboratory cutoffs supplied.

Localization is not the biochemical diagnosis



Robbins Fig. 24.24 illustrates uptake in a left inferior adenoma.

Application case: Incidental hypercalcemia

An otherwise well adult has elevated calcium on routine blood chemistry. Intact PTH is not suppressed.

Interpretive questions

- Why is a nonsuppressed PTH abnormal in this biochemical context?
- What parathyroid lesion is most probable?
- Which mimic should be considered before assuming a surgically removable tumor?

Case interpretation: Autonomy versus altered sensing

Feedback logic

Calcium elevation normally suppresses PTH

Most likely morphology

A solitary sporadic adenoma is the commonest cause

Important mimic

FHH can produce calcium elevation with nonsuppressed PTH

A lesion diagnosis needs the correct clinical and biochemical context.

Application case: A suspicious parathyroid tumor

A resected parathyroid mass contains relatively bland, uniform cells, focal fibrosis and prominent nuclei. No invasion or metastasis is documented.

Interpretive questions

- Can cytologic blandness exclude carcinoma?
- Do fibrosis and macronucleoli alone prove malignancy?
- Which evidence would be required for a definitive carcinoma diagnosis?

Case interpretation: Prove invasion

Bland nuclei

Compatible with carcinoma;
Not exclusionary

Fibrosis and macronucleoli

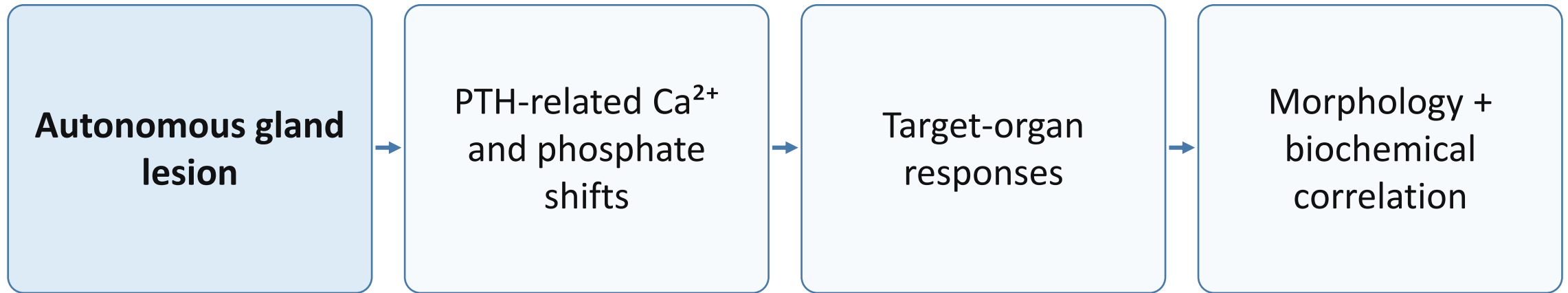
May support an atypical
neoplasm label

Definitive evidence

Invasion into surrounding
tissue and/or metastasis

Document the demonstrated criterion rather than infer malignant behavior.

Integrated pathologic interpretation



A credible diagnosis connects mechanism, lesion type and clinical consequences.

Core conclusions

- Solitary adenoma accounts for most primary hyperparathyroidism.
- CCND1 and MEN1 drive sporadic adenoma biology; CDC73 is important in carcinoma-associated risk.
- Invasion or metastasis—not endocrine nuclear atypia—defines carcinoma.
- Skeletal resorption, urinary stones and tissue calcification explain the systemic phenotype.
- PTH during hypercalcemia anchors the biochemical differential.

Interpret morphology together with feedback physiology and disease context.

Principal reference

Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. Elsevier; 2026.

Chapter 24: The Endocrine System — Parathyroid Glands and Primary Hyperparathyroidism, pp. 993–996.

The source text was available as an extracted Markdown conversion. Original textbook figure panels and chapter PDF were not supplied; all illustrations here are native schematics.