

Secondary Adrenocortical Insufficiency

Mechanisms · morphology · clinicopathologic reasoning

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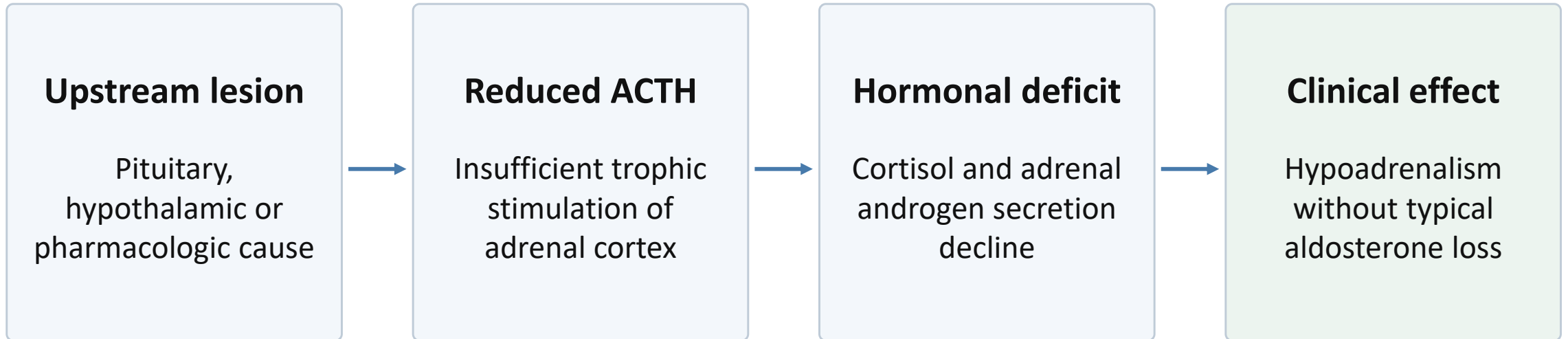
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What this lecture should enable

- Localize hypoadrenalism along the hypothalamic–pituitary–adrenal axis.
- Explain cortisol deficiency with preservation of aldosterone.
- Predict adrenal morphology after sustained ACTH deprivation.
- Interpret plasma ACTH and the timing of cosyntropin responses.
- Separate secondary insufficiency from primary Addison disease.

Secondary insufficiency: A failure of trophic drive



The primary abnormality is reduced ACTH drive—not initial destruction of the adrenal cortex.

Two broad mechanisms of adrenal hypofunction

Primary insufficiency

- Adrenal cortical cells are destroyed or dysfunctional.
- ACTH rises in response to inadequate cortisol.
- Mineralocorticoid deficiency is often important.

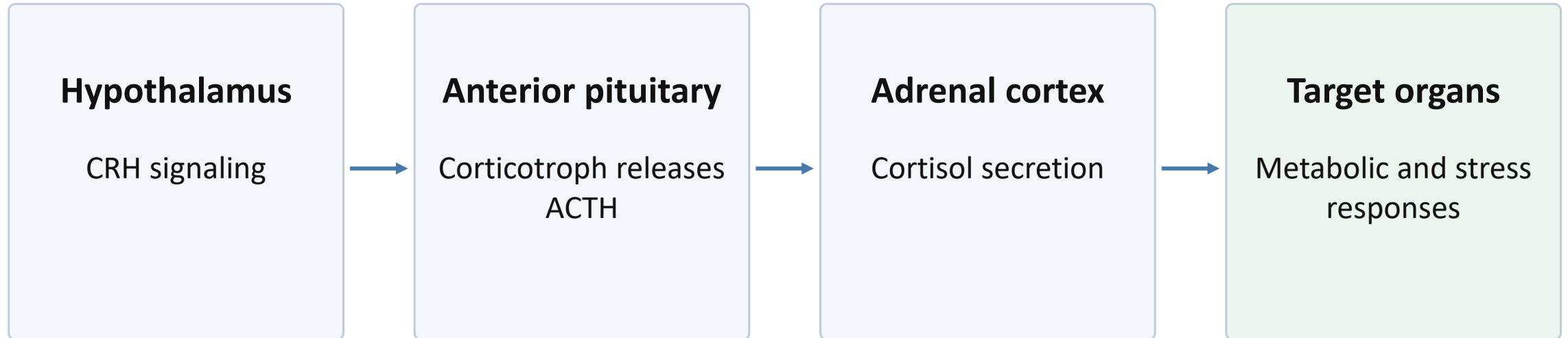
Secondary insufficiency

- ACTH output is deficient or suppressed.
- Cortical tissue loses trophic stimulation.
- Aldosterone remains normal or near normal.

Localization

Similar symptoms can arise from anatomically different lesions.

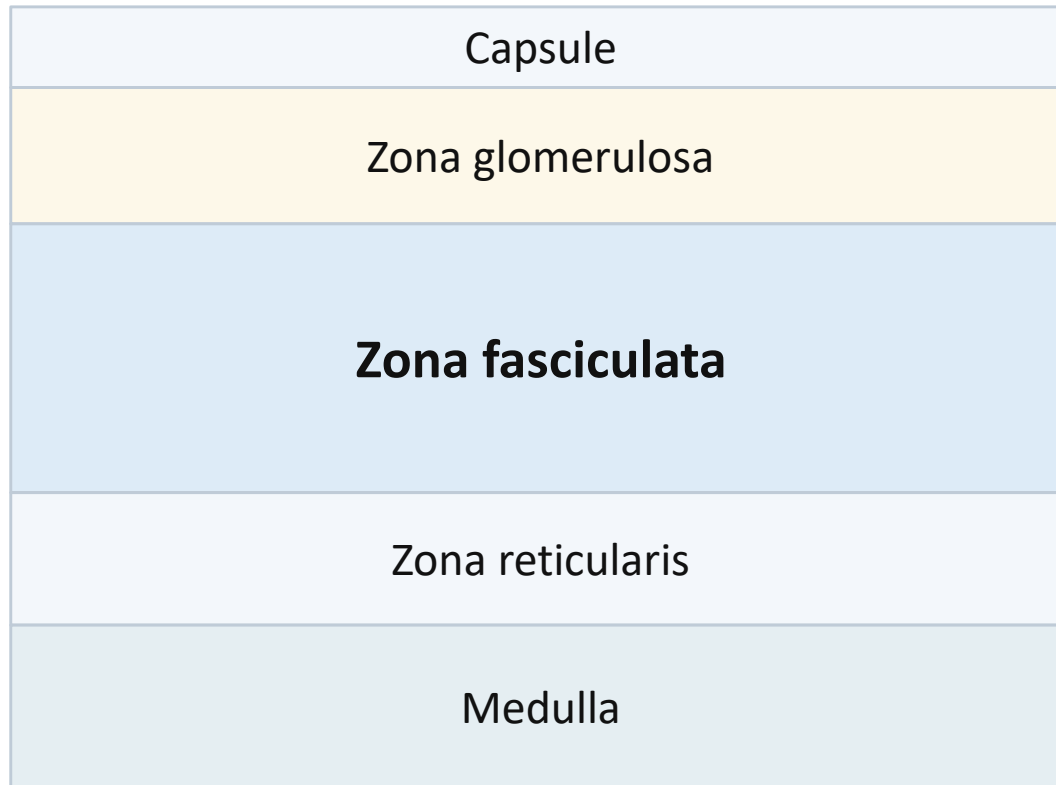
Hypothalamic–pituitary–adrenal regulation



Cortisol provides negative feedback to the hypothalamic–pituitary axis (physiologic context).

Anatomical compartments of the adrenal gland

Adrenal cortex · schematic



Schematic · not a clinical or histologic specimen

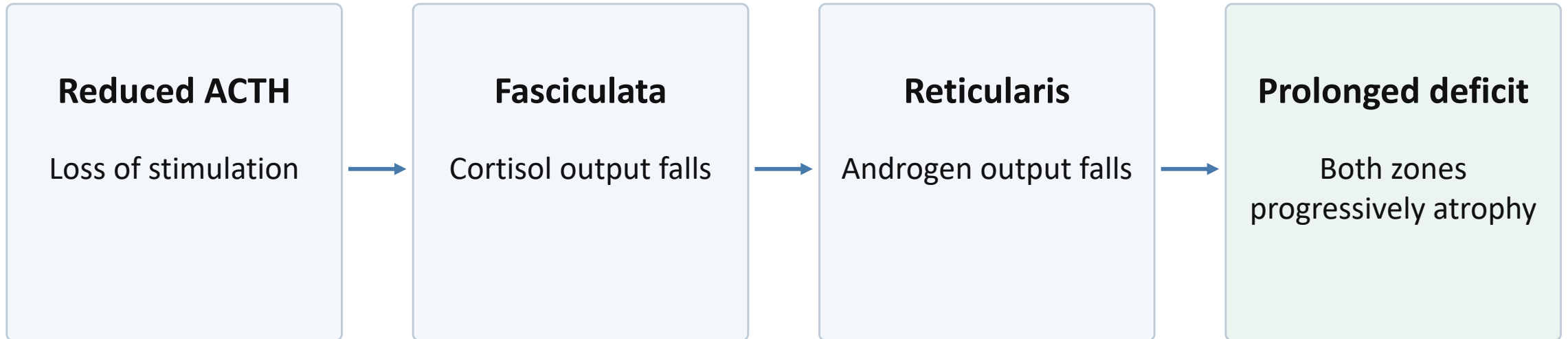
ACTH-responsive cortical zones

- Zona fasciculata: Principal cortisol source
- Zona reticularis: Major androgen source
- Zona glomerulosa: Aldosterone; RAAS-regulated
- Medulla: Catecholamines; Not cortical tissue

Which cortical zones make which hormones?

Compartment	Major endocrine output	Principal control relevant here
Zona glomerulosa	Aldosterone	Renin–angiotensin–aldosterone system
Zona fasciculata	Cortisol	ACTH trophic drive
Zona reticularis	Adrenal androgens	ACTH trophic drive
Adrenal medulla	Catecholamines	Separate medullary regulation

Why ACTH deficiency affects two cortical zones



Aldosterone synthesis is relatively spared because glomerulosa function is largely ACTH-independent.

Secondary versus tertiary terminology

Pituitary (secondary)

- Corticotroph dysfunction decreases ACTH directly.
- ACTH level is low or inappropriately normal.
- Other anterior pituitary deficits may coexist.

Hypothalamic (tertiary)

- Deficient releasing input can reduce ACTH.
- Biochemical adrenal consequences overlap.
- Robbins groups upstream hypoadrenalism together in places.

Vocabulary

The anatomic level should be stated explicitly when known.

Where loss of ACTH originates

- Intrinsic pituitary damage can eliminate corticotroph output.
- Hypothalamic lesions may reduce the signals driving corticotrophs.
- Exogenous glucocorticoids suppress endogenous corticotropin secretion.
- Any of these routes may culminate in insufficient cortisol synthesis.

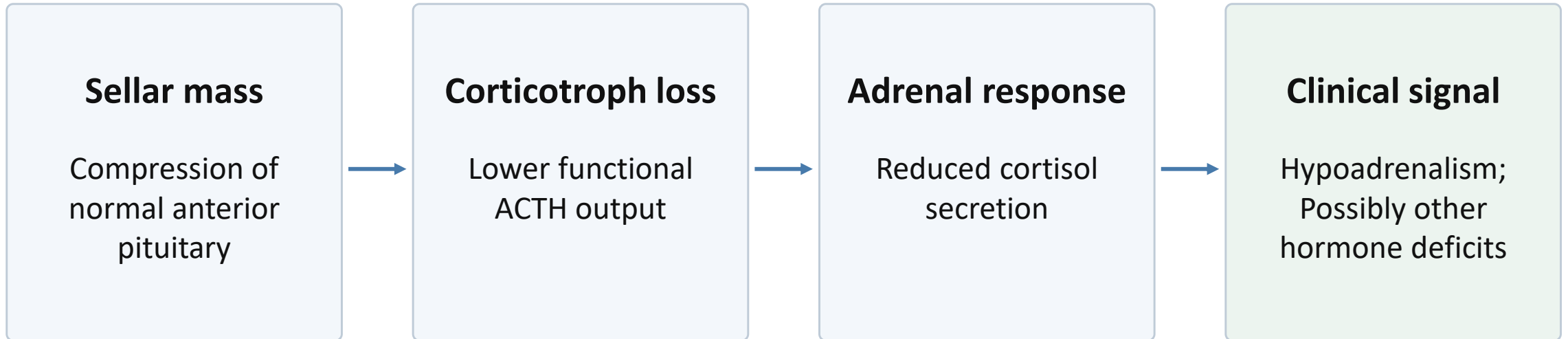
Unifying concept

Distinct upstream causes converge on reduced adrenal trophic stimulation.

Etiologic families

Mechanism	Representative settings	Final common effect
Mass or infiltrative injury	Metastatic cancer; Other sellar masses	Loss of functional pituitary tissue
Inflammatory / infectious injury	Infection; Immune checkpoint hypophysitis	Corticotroph dysfunction
Ischemic injury	Infarction; Pituitary apoplexy	Abrupt or evolving hormone loss
Iatrogenic injury	Irradiation; Pituitary surgery	Damage to remaining gland
Hormonal suppression	Long-term exogenous glucocorticoids	Reduced endogenous ACTH

Pituitary mass lesions: Tissue loss and hormone deficit



Pituitary tumors and metastases can produce hypopituitarism by damaging non-neoplastic cells.

Hypothalamic lesions: A different anatomical entry point

Hypothalamic injury

- Tumors or metastases may affect releasing signals.
- Irradiation can injure hypothalamic structures.
- Inflammatory disorders may involve the region.

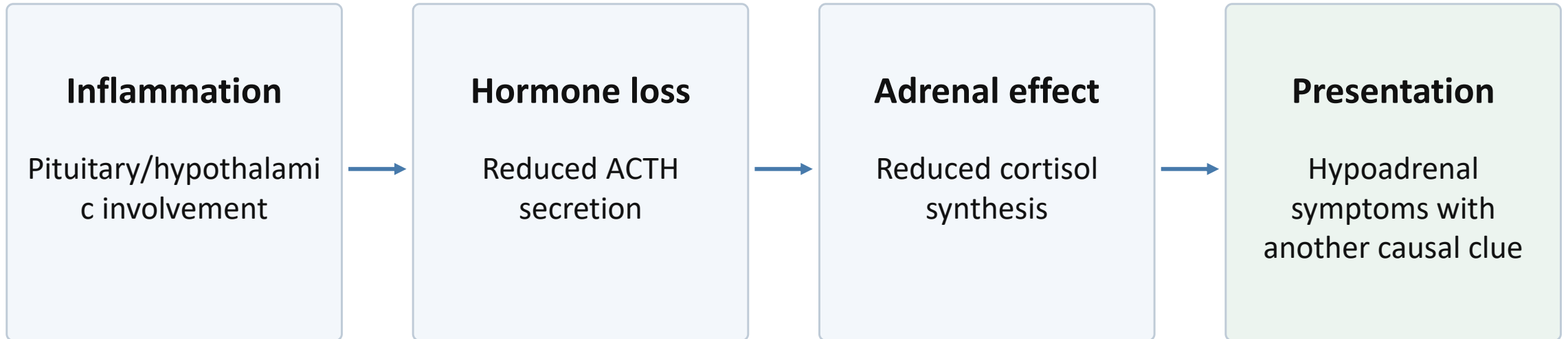
Endocrine consequence

- Corticotrophs receive inadequate stimulation.
- ACTH deficiency causes cortisol deficiency.
- Concurrent posterior pituitary abnormalities may coexist.

Caution

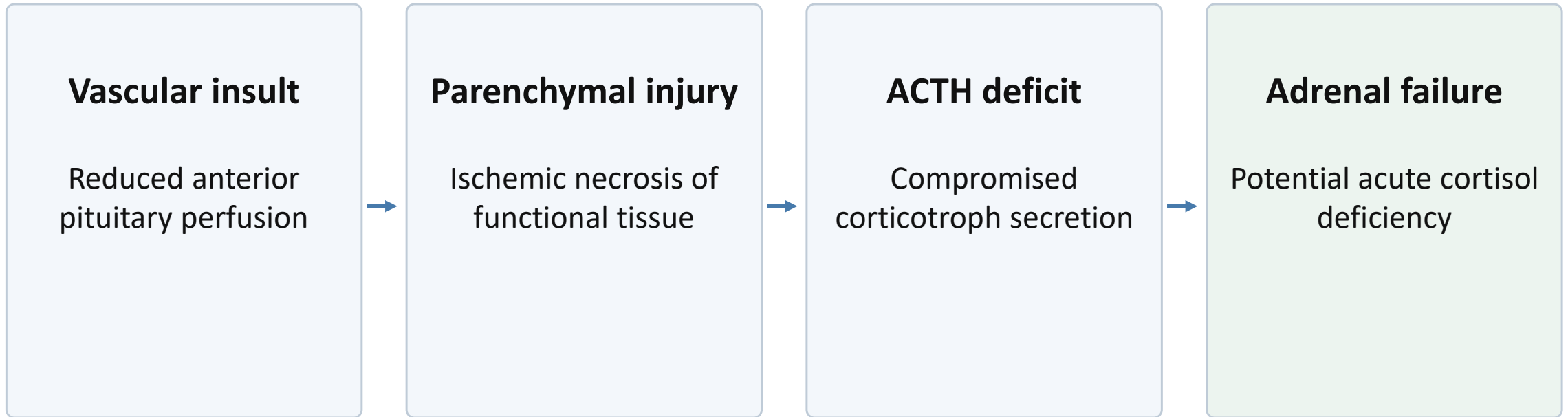
Hypothalamic and pituitary lesions require an anatomical differential.

Infections and inflammation can interrupt the axis



Examples include infectious and granulomatous disorders involving the axis.

Pituitary infarction: From vascular event to endocrine loss



Interpretation

Clinical severity depends on the degree and timing of pituitary tissue loss.

Pituitary apoplexy can cause an acute endocrine emergency

Pathologic event

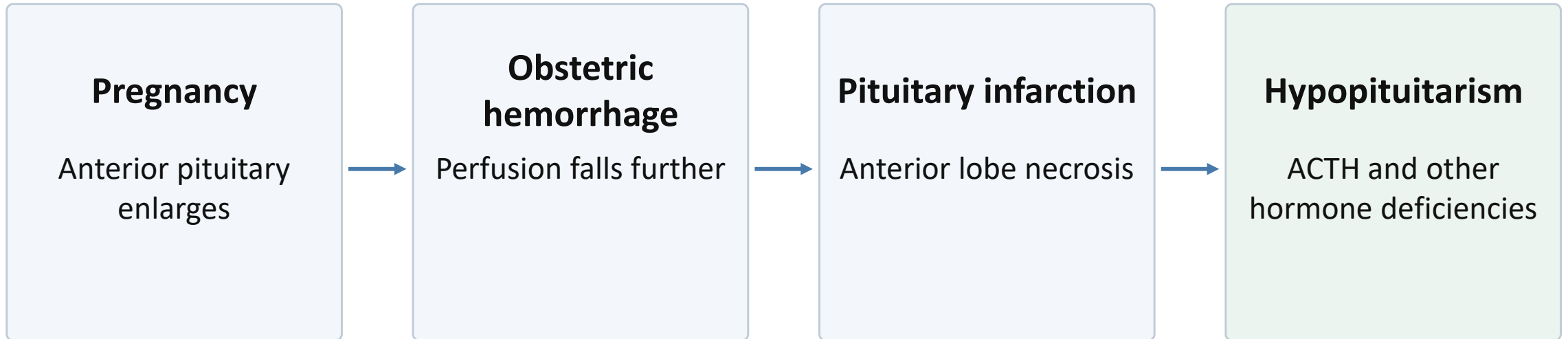
- Sudden hemorrhage into pituitary tissue, often a PitNET.
- Headache and ophthalmic symptoms may dominate initially.

ACTH-related consequence

- Rapid loss of corticotroph function.
- Hypotension, cardiovascular collapse or altered consciousness may follow.

Emergency feature An acute pituitary event can lead to acute adrenal insufficiency.

Sheehan syndrome: A postpartum causal sequence



The posterior pituitary is relatively spared because its blood supply differs.

Irradiation and surgery: Two iatrogenic pathways

Irradiation

- Radiation can damage residual non-neoplastic pituitary cells.
- Hypothalamic injury can also impair endocrine signaling.

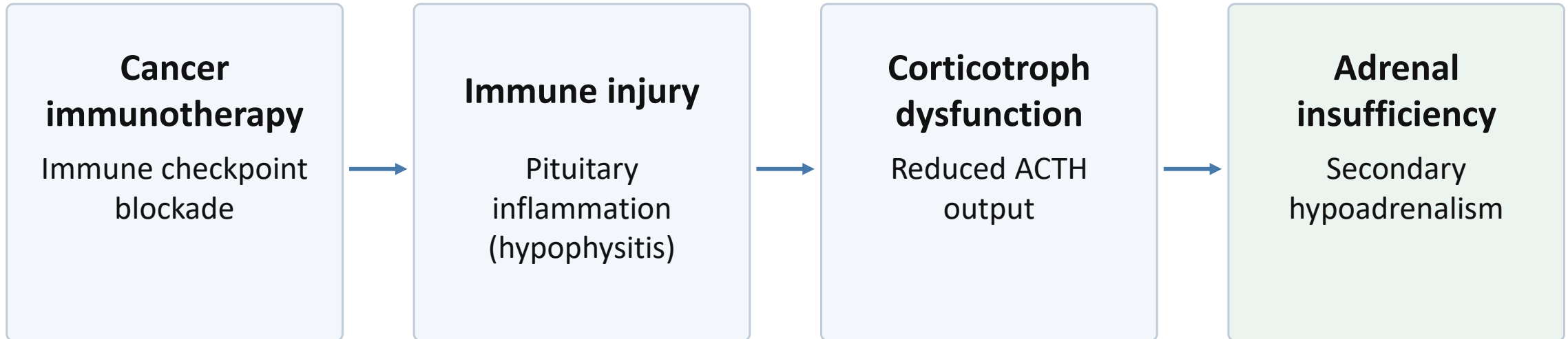
Pituitary surgery

- Excision may remove functioning pituitary with the lesion.
- Secondary hypoadrenalism can follow insufficient corticotroph reserve.

Mechanism

Treatment of intracranial disease can create a new endocrine deficiency.

Immune checkpoint blockade: Hypophysitis pathway



Robbins also notes that checkpoint blockade can cause primary adrenalitis: The site of injury matters.

Checkpoint-related endocrine disease has two routes

Primary adrenalitis

- Immune injury targets adrenal cortex.
- Cortisol loss is due to primary gland dysfunction.
- ACTH generally rises after cortisol falls.

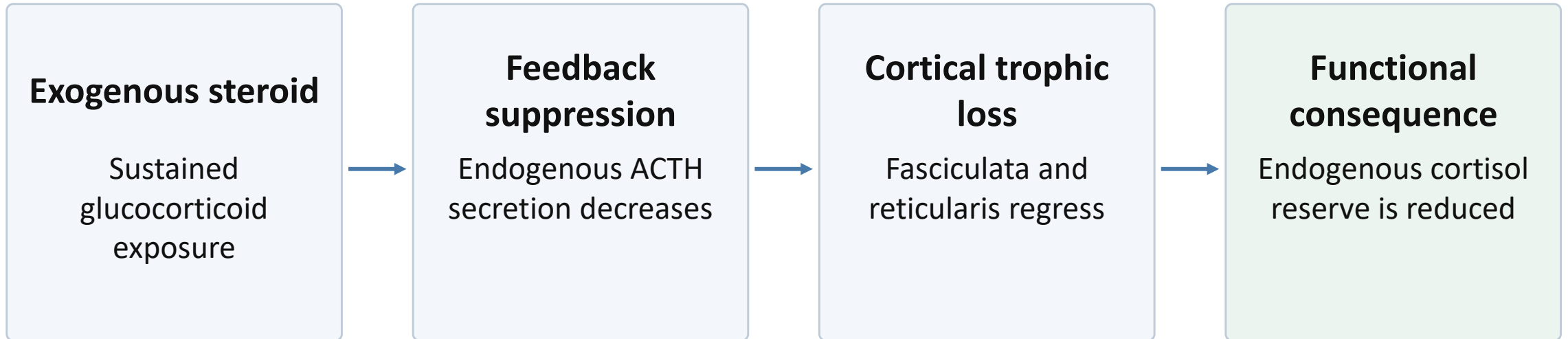
Secondary hypophysitis

- Immune injury targets pituitary function.
- ACTH is deficient or inappropriately normal.
- Aldosterone usually remains preserved.

Distinguish

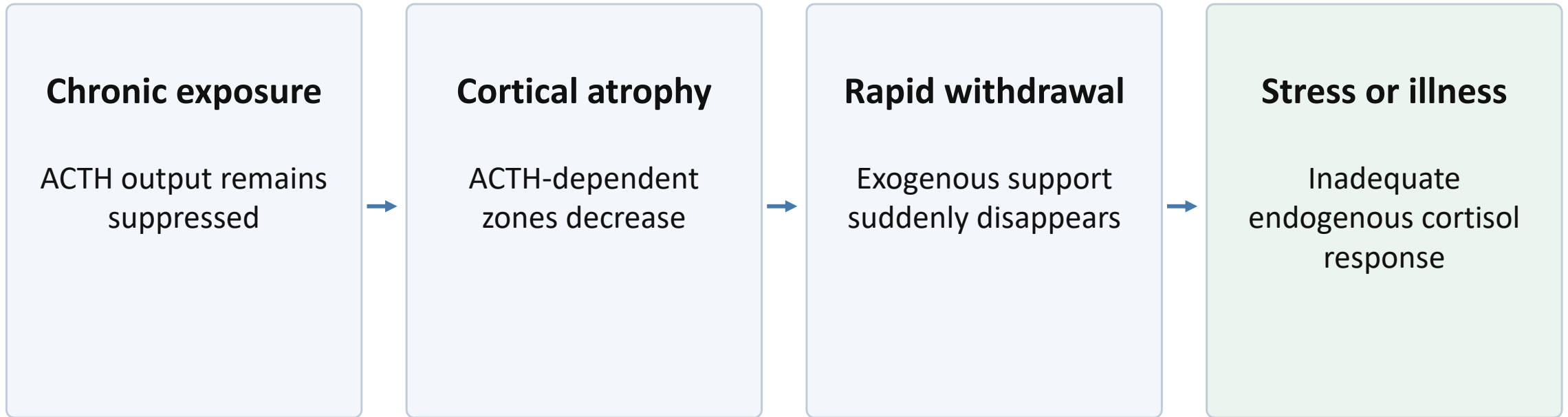
Do not equate all checkpoint-associated hypoadrenalism with primary gland damage.

Chronic glucocorticoids suppress endogenous ACTH



Long-term treatment can produce functional insufficiency even without a structural pituitary lesion.

Steroid withdrawal: Why timing matters



Interpretation

Abrupt withdrawal or failure to increase coverage during stress as crisis triggers.

Isolated ACTH deficiency or panhypopituitarism?

- Corticotropin deficiency can be isolated.
- A broader lesion may reduce several anterior pituitary tropic hormones.
- Coexisting TSH or gonadotropin deficiency can change clinical presentation.
- The pattern of associated deficits can help localize the source lesion.

Diagnostic implication

Do not restrict pituitary evaluation to ACTH when broader dysfunction is suggested.

Companion findings in broader anterior pituitary failure

Pituitary axis	Possible associated manifestation
ACTH	Hypoadrenalism
TSH	Central hypothyroid manifestations
LH / FSH	Amenorrhea, infertility, low libido
GH	Growth failure in children; Body-composition changes in adults
Prolactin	Failure of postpartum lactation

Adrenal gland size reflects chronic trophic input

- Sustained loss of corticotropin leads to reduced adrenal cortical mass.
- The degree of shrinkage varies with duration and severity of deficiency.
- Glands may become small and flattened yet remain yellow.
- Residual lipid accounts for persistence of yellow coloration.

Morphologic clue Atrophy is a downstream response to hormonal deprivation.

Normal cortex versus ACTH-deficient cortex

Normal gland

Capsule
Zona glomerulosa
Zona fasciculata
Zona reticularis
Medulla

Reduced corticotropin drive

Capsule
Zona glomerulosa
Atrophic fasciculata
Atrophic reticularis
Medulla

Relative glomerulosa and medulla
preservation

Schematic · not a clinical or histologic specimen

What is preserved despite cortical shrinkage?

Relatively preserved

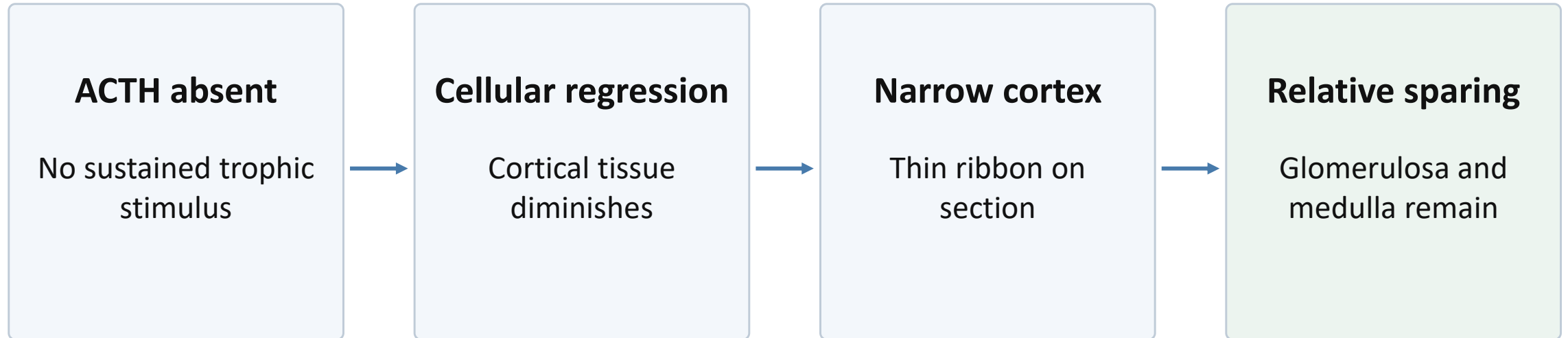
- Zona glomerulosa, maintained by RAAS.
- Adrenal medulla, a distinct endocrine compartment.

Progressively diminished

- Zona fasciculata: Cortisol-producing tissue.
- Zona reticularis: Adrenal androgen-producing tissue.

Pathology principle Selective zonal atrophy mirrors dependence on ACTH.

The morphologic mechanism is selective cortical atrophy



Markedly reduced glands with a residual cortical ribbon composed largely of glomerulosa.

Primary autoimmune destruction looks different

Primary autoimmune adrenalitis

- Primary damage to steroidogenic cortical cells.
- Cortex replaced by connective tissue in advanced cases.
- Lymphoid infiltrates may be present.

Secondary ACTH deficiency

- Small flattened glands, with residual lipid.
- Atrophic ACTH-responsive cortical layers.
- Medulla spared; Relative glomerulosa retention.

Do not conflate

Destruction of cortex $\neq$ atrophy from loss of trophic stimulation.

Anatomic pattern offers etiologic clues

Process	Typical adrenal pattern	Reason
Secondary ACTH deficiency	Small, thin cortex; Medulla preserved	Loss of trophic stimulation
Autoimmune Addison disease	Cortical destruction; Residual scar/inflammation	Direct immune injury
Adrenal metastasis	Architecture obscured by neoplasm	Infiltrating tumor
Waterhouse–Friderichsen	Bilateral hemorrhagic destruction	Hemorrhage in severe sepsis

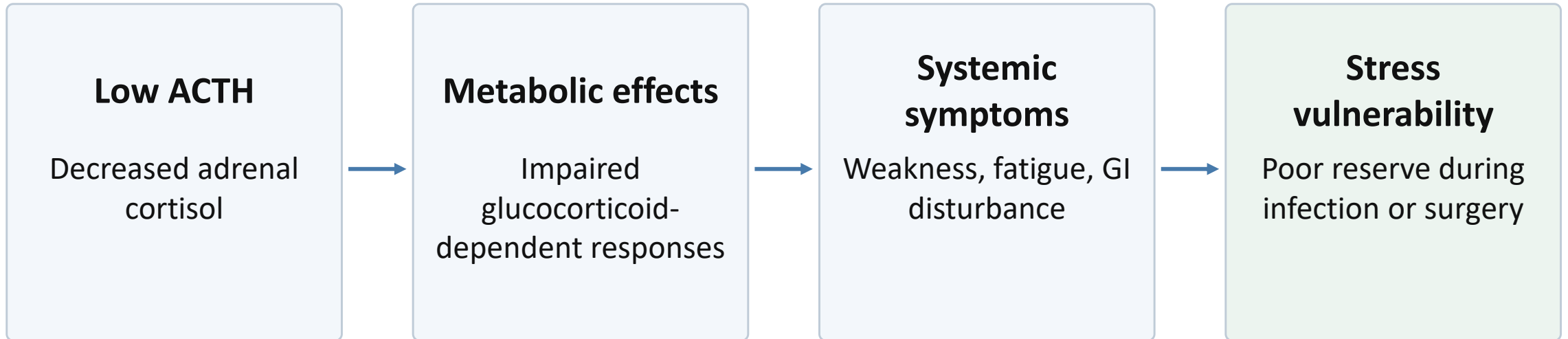
Gross morphology is not a stand-alone diagnosis

- Small adrenal glands are consistent with chronic reduced trophic drive.
- Gross gland size does not establish the pituitary cause.
- Endocrine testing and upstream clinical history are required.
- Microscopy and hormone data should be interpreted together.

Interpretive limit

Morphology supports a mechanism; It does not uniquely localize the lesion.

Clinical features begin with cortisol deficiency



Secondary and primary insufficiency share many symptoms because both reduce cortisol availability.

Nonspecific early symptoms can delay recognition

- Progressive weakness and easy fatigability may precede diagnosis.
- Anorexia, nausea, vomiting and weight loss can occur.
- Symptoms overlap with many nonendocrine conditions.
- Prior pituitary disease or long-term steroid use increases suspicion.

Clinical reasoning A nonspecific symptom cluster becomes meaningful in the right endocrine context.

Hypoglycemia links cortisol loss to metabolism

Physiologic loss

- Glucocorticoid availability is reduced.
- Hepatic gluconeogenic support is impaired.

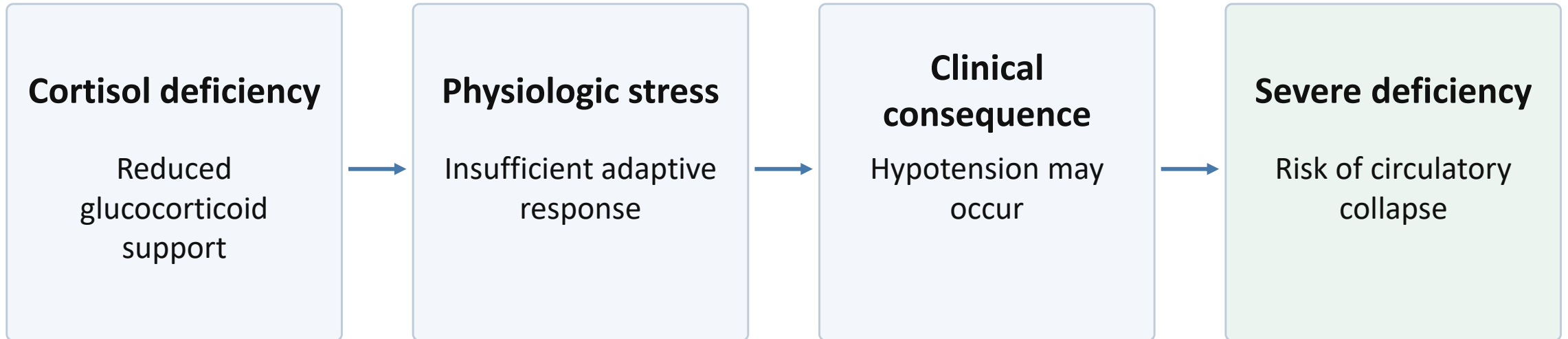
Clinical consequence

- Hypoglycemia may occur.
- Metabolic manifestations need not be present in every patient.

Mechanism

Cortisol deficiency can impair glucose homeostasis.

Why hypotension remains possible with intact aldosterone



Preserved aldosterone reduces salt-wasting physiology, but does not eliminate crisis risk.

Aldosterone is usually spared in central insufficiency

ACTH-deficient zones

- Cortisol output decreases.
- Adrenal androgen output decreases.
- Fasciculata and reticularis atrophy over time.

Aldosterone pathway

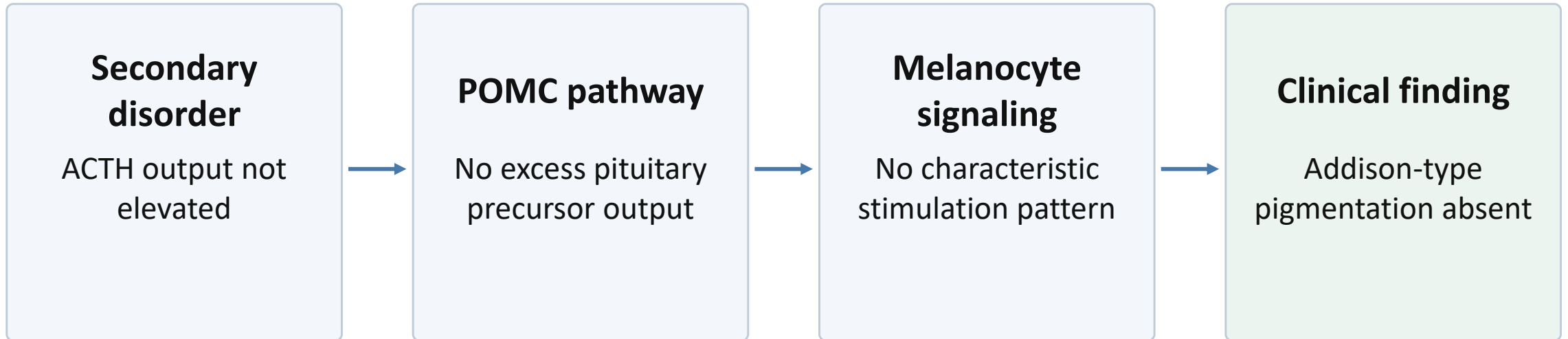
- RAAS signaling remains intact.
- Glomerulosa function is normal or near normal.
- Prominent hyperkalemia is therefore not expected.

Pattern recognition Normal potassium supports—but cannot independently establish—central insufficiency.

Why potassium differs between primary and secondary disease

Feature	Primary adrenal failure	Secondary ACTH deficiency
Aldosterone	Frequently reduced	Usually preserved
Sodium handling	Salt wasting may be prominent	Less primary mineralocorticoid loss
Potassium	Hyperkalemia may occur	Hyperkalemia generally absent
Underlying reason	Glomerulosa damage	RAAS remains functional

Why hyperpigmentation is absent



In primary insufficiency, increased POMC/ACTH is linked to increased melanocyte-stimulating activity.

Pigmentation as a localisation clue

Primary Addison disease

- Loss of cortisol feedback raises ACTH/POMC.
- Characteristic pigmentation may appear at pressure points and exposed skin.

Central insufficiency

- ACTH is low or inappropriately normal.
- Characteristic Addisonian hyperpigmentation is absent.

Important caveat Absence of pigmentation alone is not sufficient to classify an individual patient.

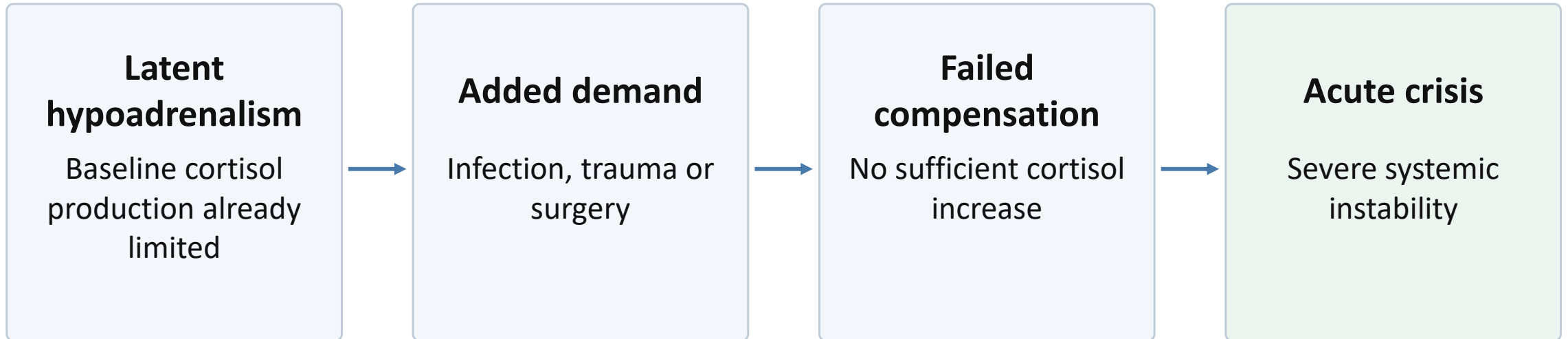
Adrenal androgen output also decreases

- ACTH supports zona reticularis steroidogenesis.
- Reduced trophic stimulation lowers adrenal androgen production.
- This deficit can accompany cortisol deficiency.
- It helps explain why central disease is not simply isolated loss of cortisol.

Clinical pattern

Robbins characterizes secondary hypoadrenalism by deficient cortisol and androgen output.

Intercurrent stress can unmask inadequate reserve



An acute adrenal crisis can supervene even when the initial disorder was insidious.

Adrenal crisis is a clinical emergency

Warning manifestations

- Intractable vomiting or abdominal pain.
- Marked hypotension or vascular collapse.
- Altered consciousness or coma.

Pathophysiologic setting

- Stress-related cortisol demand exceeds reserve.
- Corticotropin-deficient patients may be unable to respond.
- Prompt corticosteroid therapy is lifesaving.

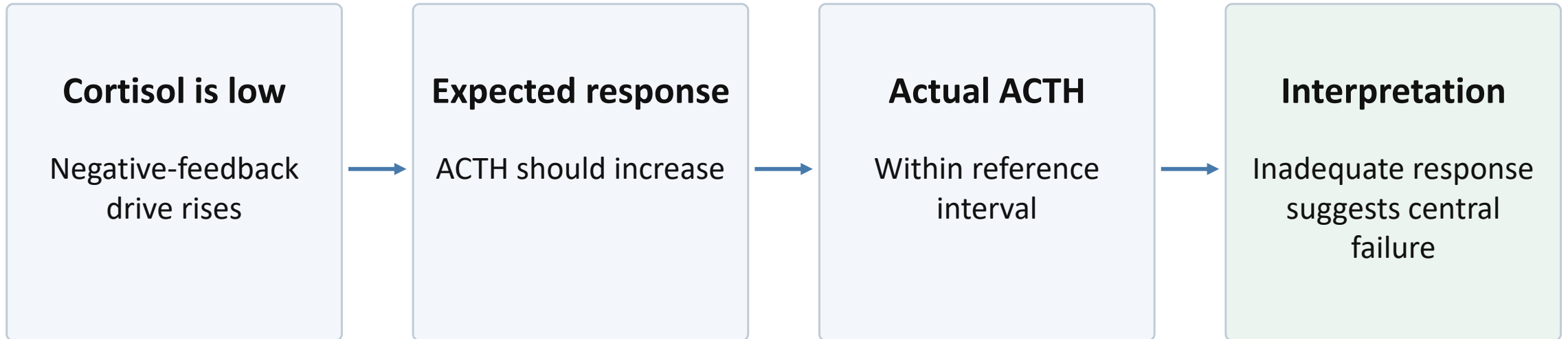
Emergency

Do not delay urgent treatment of suspected adrenal crisis for an elective diagnostic pathway.

Laboratory localization: Cortisol plus ACTH

Observed pattern	Interpretation	Mechanistic explanation
Low cortisol + high ACTH	Suggests primary adrenal failure	Pituitary attempts to drive damaged cortex
Low cortisol + low ACTH	Suggests central insufficiency	Deficient corticotroph output
Low cortisol + “normal” ACTH	May indicate central insufficiency	ACTH is inappropriately normal for low cortisol
Potassium preserved	Compatible with central disorder	Aldosterone often preserved

“Inappropriately normal” ACTH is not normal physiology



A reference-range ACTH value can be abnormal in the context of low cortisol.

Why a single cortisol value does not localize the lesion

What it establishes

- Deficient circulating cortisol may be suspected.
- Symptoms and other endocrine findings establish clinical relevance.

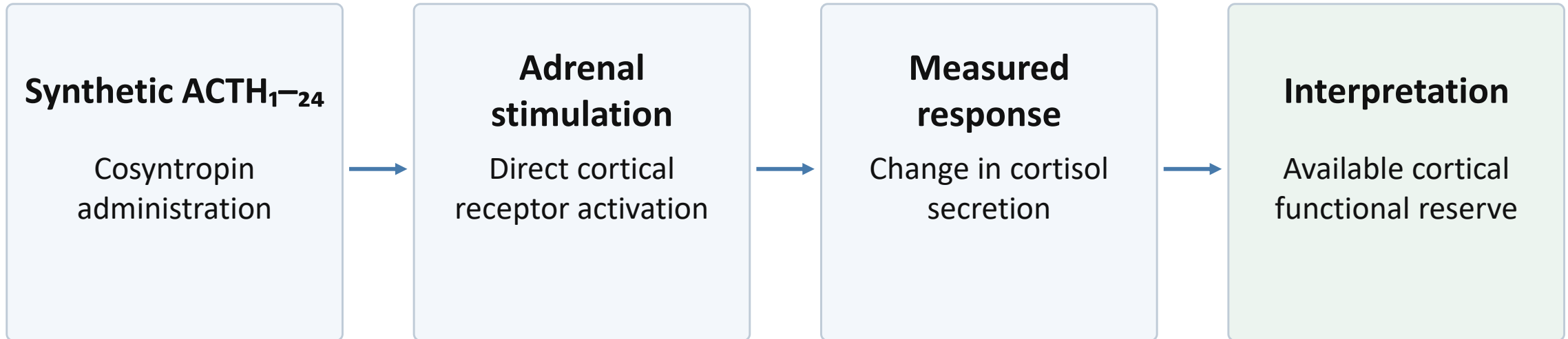
What is still needed

- Concurrent ACTH to assess source of failure.
- History of pituitary injury or glucocorticoid exposure.
- Dynamic testing when clinically appropriate.

Core rule

The hormone deficit and the site of causation are different diagnostic questions.

Cosyntropin challenges the adrenal cortex directly

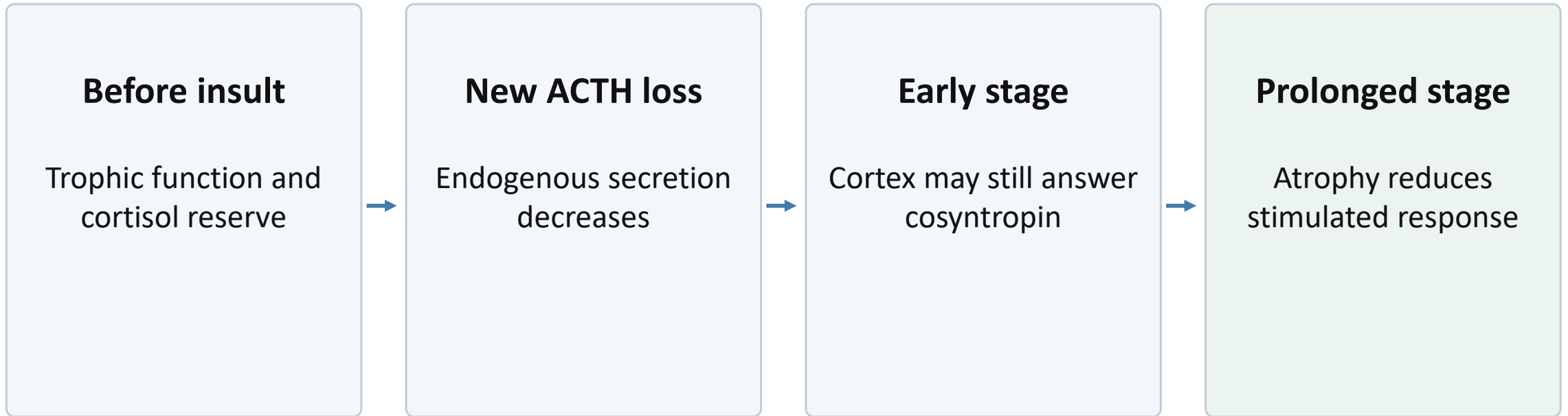


Testing interrogates adrenal responsiveness—not the ability of the pituitary to make ACTH.

Cosyntropin response depends on disease mechanism and duration

Clinical setting	Expected response	Why
Primary adrenal destruction	Reduced cortisol response	Functional cortical tissue destroyed
Long-standing central deficiency	May be reduced	Prolonged ACTH loss produces atrophy
Recent-onset central deficiency	May remain normal	Cortex retains responsiveness initially

Temporal evolution changes cosyntropin findings



Interpretation

A preserved response does not rule out recent central ACTH deficiency.

A normal early stimulation test can be misleading

- Cosyntropin bypasses upstream ACTH production.
- Recently ACTH-deprived cortical cells may still respond normally.
- A single adequate stimulated cortisol therefore cannot exclude recent central failure.
- Interpret testing alongside chronology, ACTH and clinical context.

Diagnostic pitfall

Do not use recent-onset central disease and long-standing central disease interchangeably.

Long-standing central disease can mimic primary failure on testing

Primary lesion

- The adrenal cortex is intrinsically destroyed.
- Exogenous ACTH cannot restore lost tissue.
- Stimulated cortisol response is diminished.

Chronic secondary lesion

- An initially intact cortex becomes atrophic.
- Cosyntropin response also diminishes.
- Concurrent endogenous ACTH helps distinguish mechanisms.

Discriminator

Interpret the basal ACTH level and history, not the stimulation result alone.

Integrating three independent observations

Observation	Question answered	Potential limitation
Plasma cortisol	Is cortisol availability inadequate?	Does not alone identify source
Plasma ACTH	Is corticotroph response appropriate?	Must be interpreted with cortisol
Cosyntropin response	Can cortex respond to ACTH?	May be normal early in central disease
Other pituitary axes	Is there broader hypopituitarism?	May vary with lesion extent

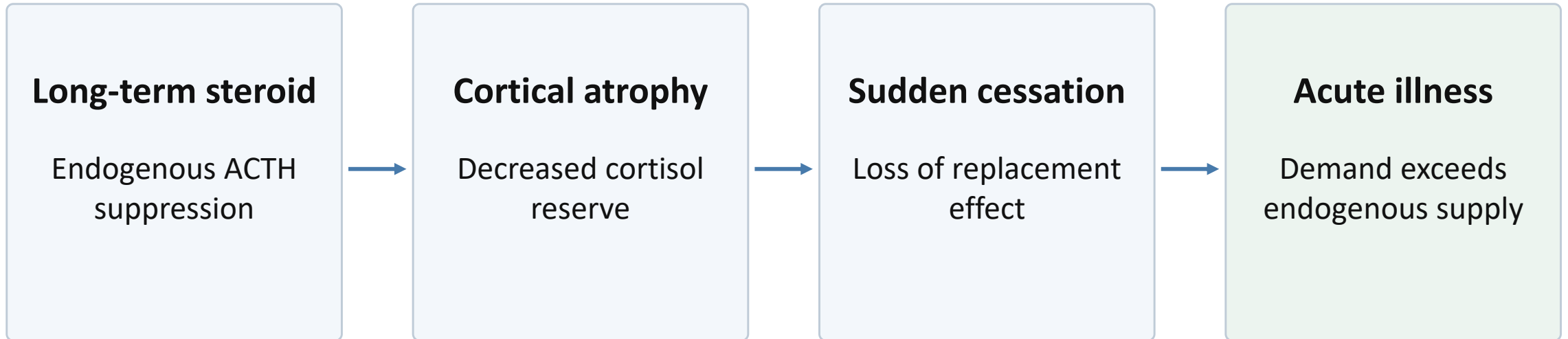
Case 1 · abrupt glucocorticoid cessation

Clinical vignette

A patient with prolonged glucocorticoid exposure stops treatment abruptly, then develops weakness, vomiting and hypotension during an intercurrent infection.

What links the medication history to impaired endogenous cortisol reserve?

Case 1 · feedback suppression explains the failure



Primary pathology is suppression of the axis with secondary cortical atrophy.

Case 2 · immune therapy and cortisol deficiency

Clinical vignette

During immune checkpoint blockade, a patient develops fatigue and hypotension. Cortisol is low, and ACTH is not appropriately elevated.

Which site of immune-related endocrine injury best fits this hormone pattern?

Case 2 · use ACTH to distinguish immune targets

Hypophysitis — favored

- Pituitary corticotroph impairment.
- ACTH is low or inappropriately normal.
- Low cortisol reflects central failure.

Adrenalitis — alternative

- Direct cortical injury.
- Low cortisol should provoke increased ACTH.
- Potential mineralocorticoid involvement.

Answer

The hormone pattern favors central insufficiency due to hypophysitis.

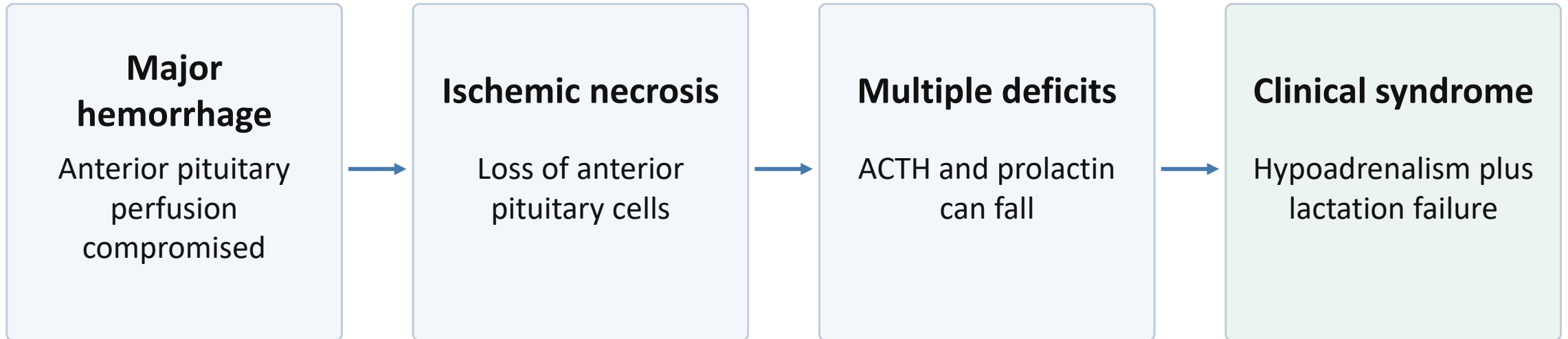
Case 3 · postpartum vascular injury

Clinical vignette

A patient experiences severe obstetric hemorrhage. Later, inability to lactate and symptoms of glucocorticoid deficiency raise concern for multiple anterior pituitary deficits.

Which pathologic process can connect these endocrine findings?

Case 3 · pituitary infarction connects the deficits



Sheehan syndrome is postpartum necrosis of the anterior pituitary.

Case 4 · normal cosyntropin after acute pituitary injury

Clinical vignette

Soon after pituitary apoplexy, cortisol is low with inadequate ACTH. A cosyntropin test nevertheless shows an apparently retained adrenal response.

Why is recent central insufficiency still a concern?

Case 4 · functional reserve precedes atrophy

Early central lesion

- Pituitary ACTH secretion can fail suddenly.
- Adrenal cortex has not yet undergone major atrophy.

Test response

- Injected ACTH can still stimulate intact cells.
- Normal early response does not exclude the upstream lesion.

Answer

Test interpretation must incorporate duration since ACTH loss.

Six integrated clinicopathologic distinctions

- 01** Central deficiency begins upstream of the adrenal cortex.
- 02** Reduced ACTH causes cortisol and adrenal androgen deficits.
- 03** Aldosterone is usually preserved through RAAS control.
- 04** Loss of pigmentation reflects lack of ACTH/POMC excess.
- 05** Long-standing disease causes selective cortical atrophy.
- 06** Low or inappropriately normal ACTH localizes the defect.

High-yield comparison: Primary versus central failure

Dimension	Primary Addison disease	Central insufficiency
Causal location	Adrenal cortex	Pituitary / hypothalamic axis
ACTH	Elevated	Low or inappropriately normal
Cortisol	Low	Low
Aldosterone	Frequently low	Normal or near normal
Hyperkalemia	May be present	Generally absent
Hyperpigmentation	Characteristic possible	Not characteristic

Applied interpretation: Three endocrine profiles

- Profile A: Low cortisol + elevated ACTH + hyperkalemia → favors primary adrenal failure.
- Profile B: Low cortisol + inadequate ACTH + preserved potassium → favors central failure.
- Profile C: Low cortisol + inadequate ACTH + early normal cosyntropin response → central failure remains possible.

Interpretive principle Read biochemical relationships, not isolated “normal” or “abnormal” flags.

Final clinical reasoning sequence

- Recognize symptoms or a stress-related adrenal crisis.
- Identify predisposing pituitary, hypothalamic, immune-therapy or steroid exposures.
- Interpret cortisol together with endogenous ACTH.
- Account for chronicity before interpreting cosyntropin responses.
- Assess additional pituitary deficits when clinically indicated.

Synthesis

Mechanism, morphology and hormone relationships should agree.

Primary textbook reference

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. (2026). Chapter 24: The Endocrine System.
- Central topic: Secondary Adrenocortical Insufficiency; mechanism, hormones, morphology, and diagnostic tests.
- Context: Hypopituitarism, adrenal anatomy, chronic primary hypoadrenalism, and acute adrenal crisis.