

Hypercortisolism

Cushing syndrome

Etiology • Pathogenesis • Morphology • Clinical correlation

An adrenal pathology lecture

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Cortisol excess: The defining abnormality

Cushing syndrome denotes the clinical consequences of sustained glucocorticoid excess.

Exogenous corticosteroid exposure and endogenous cortisol overproduction cause a similar systemic phenotype.

Determining the source of hormone excess explains the observed adrenal morphology.

The adrenal cortex has functionally distinct zones

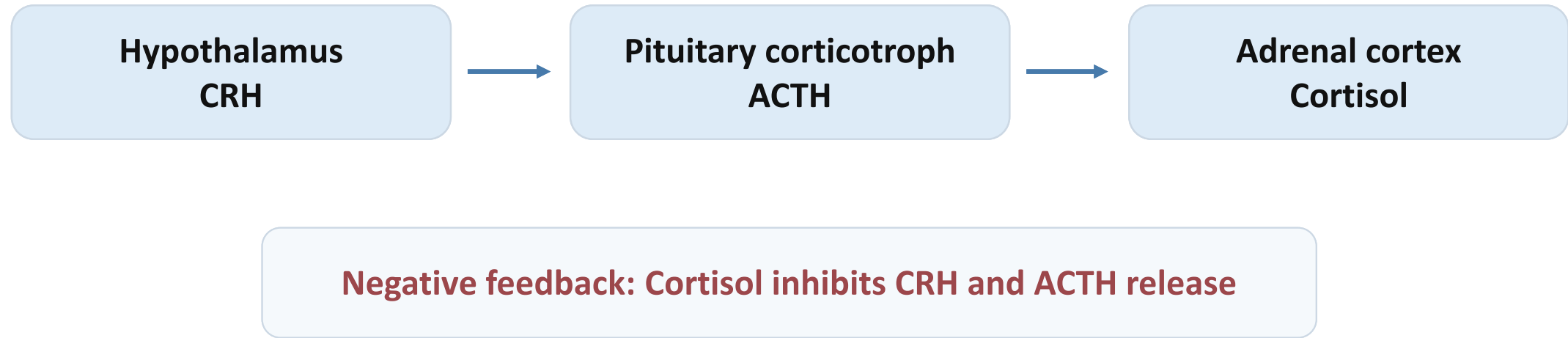


Zona fasciculata is the principal source of cortisol.

Zona reticularis contributes to glucocorticoid production and secretes sex steroids.

Zona glomerulosa primarily makes aldosterone and is relatively ACTH independent.

The hypothalamic–pituitary–adrenal axis



CRH drives pituitary ACTH; ACTH stimulates the adrenal cortisol-producing cortex.
Circulating cortisol restrains upstream secretion through negative feedback.

Negative feedback predicts the ACTH result



Low ACTH points toward an ACTH-independent adrenal source or exogenous exposure.

In ACTH-dependent disease, the driver persists despite high cortisol.

Etiologic classification starts with steroid exposure

Exogenous

Therapeutic glucocorticoid exposure

Most frequent overall source

Suppression of native ACTH

Endogenous

Internally produced cortisol excess

Requires ACTH-based etiologic
subdivision

Pituitary, ectopic, or adrenal source

The commonest cause of the syndrome is iatrogenic glucocorticoid administration.

Endogenous Cushing syndrome: Two mechanistic groups

ACTH dependent

Pituitary ACTH-producing neoplasm

Ectopic tumor-associated ACTH or
CRH

Usually bilateral adrenal hyperplasia

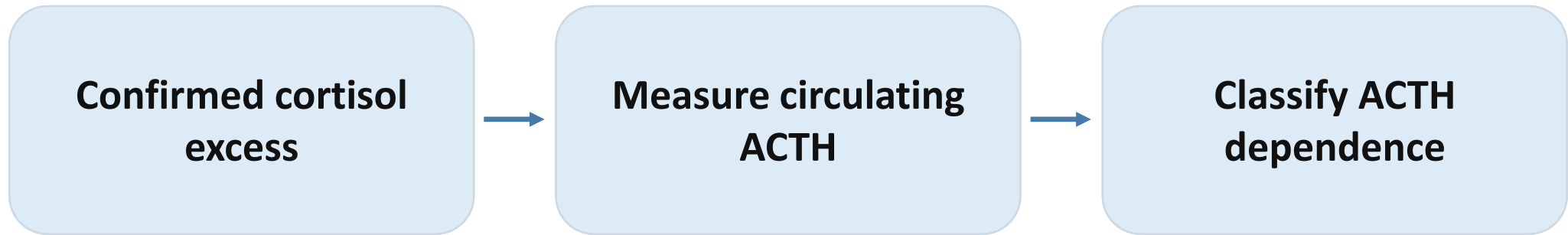
ACTH independent

Cortisol-secreting adrenal neoplasm

Primary bilateral nodular hyperplasia

Suppressed ACTH; Lesion-driven
cortisol

ACTH level is a mechanistic discriminator



Low ACTH favors adrenal autonomy or exogenous suppression.

Normal or increased ACTH in the face of hypercortisolism is inappropriate and suggests ACTH dependence.

Exogenous glucocorticoids: The dominant cause

Iatrogenic Cushing syndrome results from the administration of glucocorticoids.

Steroid exposure can reproduce the systemic effects of endogenous hypercortisolism.

Suppression of pituitary ACTH explains the accompanying adrenal cortical atrophy.

A medication history is integral to the etiologic assessment.

Iatrogenic hypercortisolism suppresses native ACTH

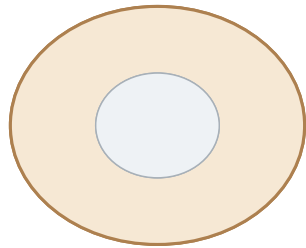


Decreased ACTH trophic stimulation affects the zona fasciculata and zona reticularis.

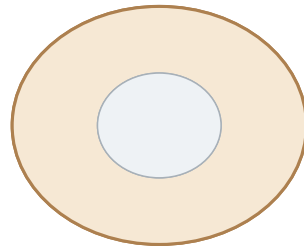
Zona glomerulosa is generally preserved because its control is largely ACTH independent.

Cortical atrophy in steroid-induced disease

Paired adrenal glands



Left adrenal



Right adrenal

Both adrenal cortices become thin when ACTH is chronically suppressed.

The fasciculata and reticularis lose trophic support.

The glomerulosa retains near-normal thickness.

Schematic anatomy — not a gross specimen

Endogenous causes follow a distinct hierarchy

Cause	Control mechanism	Typical adrenal effect
Pituitary corticotroph tumor	ACTH dependent	Bilateral cortical hyperplasia
Ectopic ACTH/CRH production	ACTH dependent	Bilateral cortical hyperplasia
Cortisol-producing adrenal tumor	ACTH independent	Tumor + suppressed nonneoplastic cortex
Primary bilateral nodular hyperplasia	ACTH independent	Bilateral macronodules or micronodules

Cushing disease is specifically pituitary ACTH excess

Cushing disease refers to hypercortisolism caused by pituitary corticotroph ACTH production.

An ACTH-secreting pituitary neuroendocrine tumor accounts for most pituitary cases.

Persistent ACTH stimulation drives bilateral adrenal cortical growth and cortisol release.

Pituitary disease dominates endogenous cases

Pituitary corticotroph neoplasms account for approximately 60%–70% of endogenous hypercortisolism description.

Cushing disease is reported more frequently in females, often in young adulthood.

These epidemiologic patterns provide context but do not replace biochemical testing.

Textbook proportion is source-specific; Not presented as a current population registry estimate.

Pituitary cellular pathology is not uniform

Most cases

Discrete ACTH-producing pituitary
neuroendocrine tumor

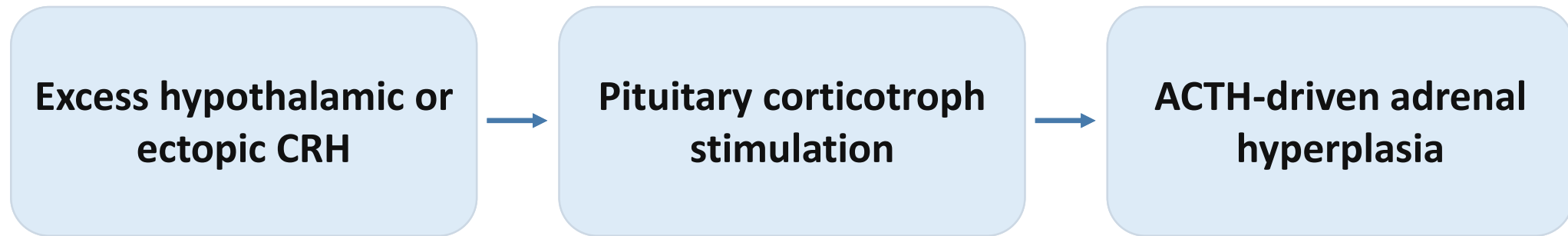
Typically a small adenoma

Less common

Pituitary macroadenoma

Rare corticotroph hyperplasia without
a discrete tumor

Corticotroph hyperplasia may follow CRH excess

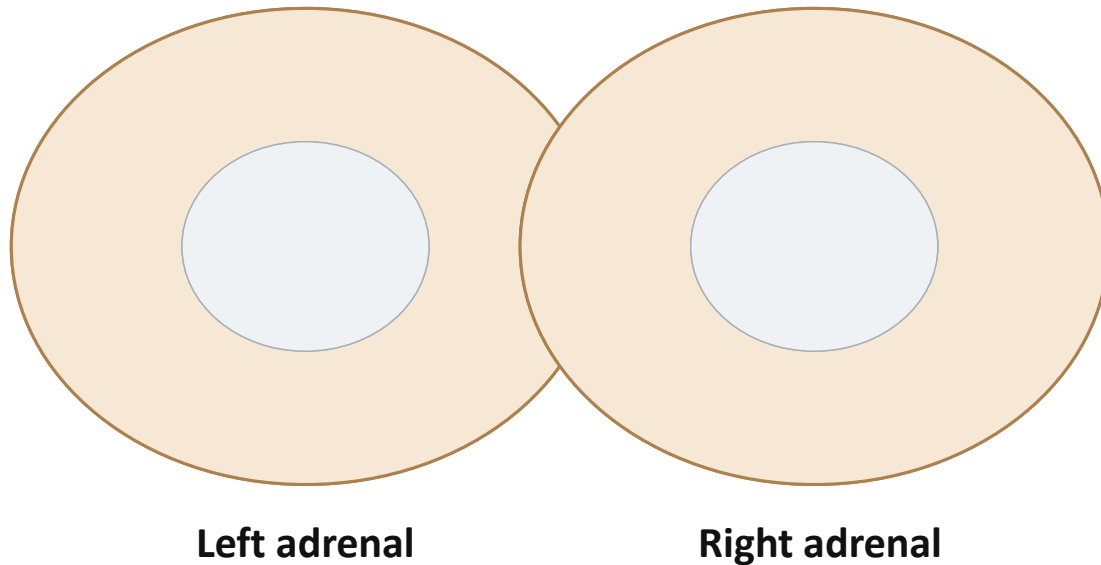


Corticotroph hyperplasia may arise primarily or from excessive CRH drive.

A CRH-producing lesion can therefore indirectly produce an ACTH-dependent Cushing phenotype.

ACTH drives a bilateral adrenal response

Paired adrenal glands



Long-standing ACTH stimulation thickens the adrenal cortex.

Both glands typically enlarge rather than a unilateral tumor becoming dominant.

This tissue response generates excess cortisol.

Schematic anatomy — not a gross specimen

Cushing syndrome and Cushing disease are not synonyms

Cushing syndrome

All causes of glucocorticoid excess

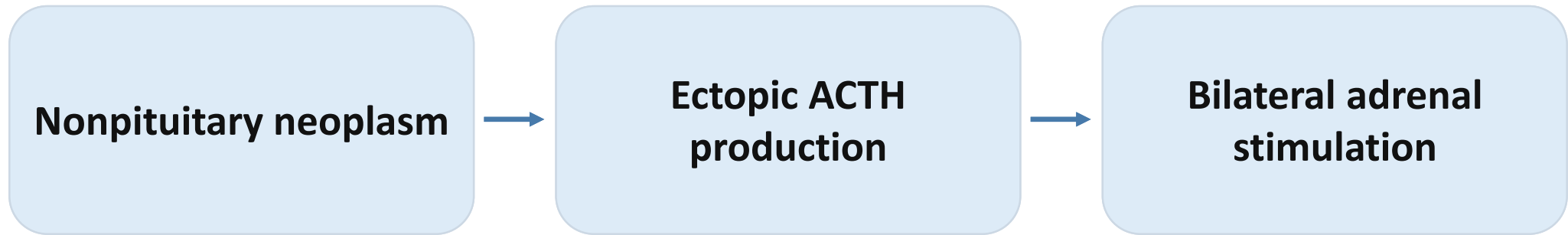
Can be iatrogenic, ACTH dependent or independent

Cushing disease

Specific pituitary ACTH-driven etiology

A subset of endogenous Cushing syndrome

Ectopic ACTH is a tumor-associated source



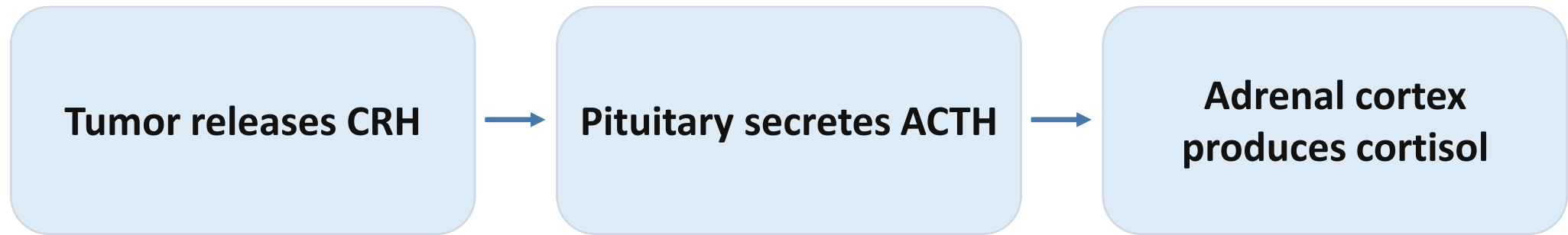
The source lies outside the pituitary.

The adrenal glands are secondarily hyperplastic rather than the primary autonomous driver.

Neoplasms implicated in ectopic ACTH production

Neoplasm	Textbook association
Small-cell carcinoma of lung	Frequently responsible
Carcinoid / neuroendocrine tumor	Recognized source
Medullary thyroid carcinoma	Reported association
Pancreatic neuroendocrine neoplasm	Reported association

Ectopic CRH can also produce hypercortisolism



The ectopic tumor supplies CRH rather than necessarily supplying ACTH.

ACTH remains the immediate pituitary-to-adrenal signal.

Pituitary and ectopic ACTH share an adrenal pattern

Pituitary ACTH

Pituitary lesion is primary

Bilateral cortical hyperplasia

May evolve gradually

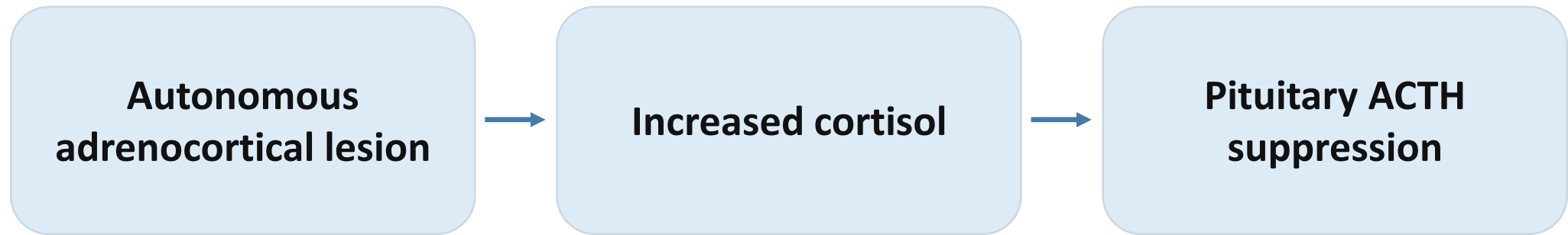
Ectopic ACTH

Nonpituitary neoplasm is primary

Bilateral cortical hyperplasia

Rapid tumor course may limit enlargement

Adrenal neoplasms generate ACTH-independent cortisol



Adenomas and carcinomas are the principal tumor causes.

Contralateral and adjacent nonneoplastic cortex lose ACTH trophic stimulation.

ACTH-independent syndrome has a biochemical hallmark

High cortisol occurs together with low circulating ACTH.

The inappropriate cortisol secretion originates in the adrenal cortex.

The hormone pattern should be interpreted together with exposure history and morphology.

Cortisol-producing adenoma versus carcinoma

Adrenocortical adenoma

Generally small and well circumscribed

Yellow appearance; Cells resemble fasciculata

Can be hormonally functional

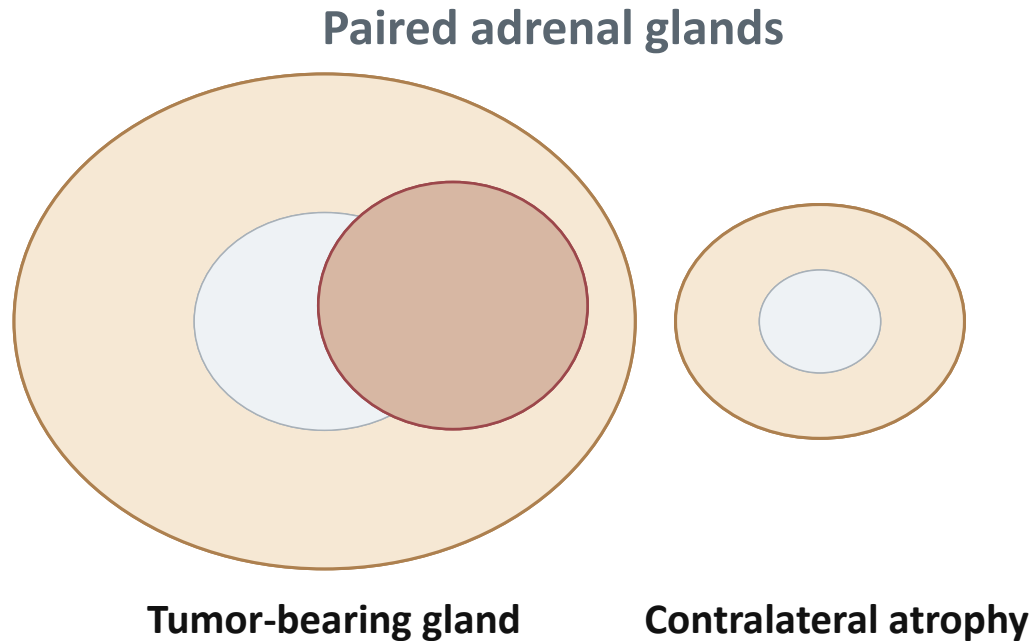
Adrenocortical carcinoma

Generally larger and unencapsulated

Anaplastic malignant morphology

Can produce marked hypercortisolism

Feedback suppression surrounds a functional adrenal tumor



Schematic anatomy — not a gross specimen

A functional tumor releases cortisol without normal ACTH control.

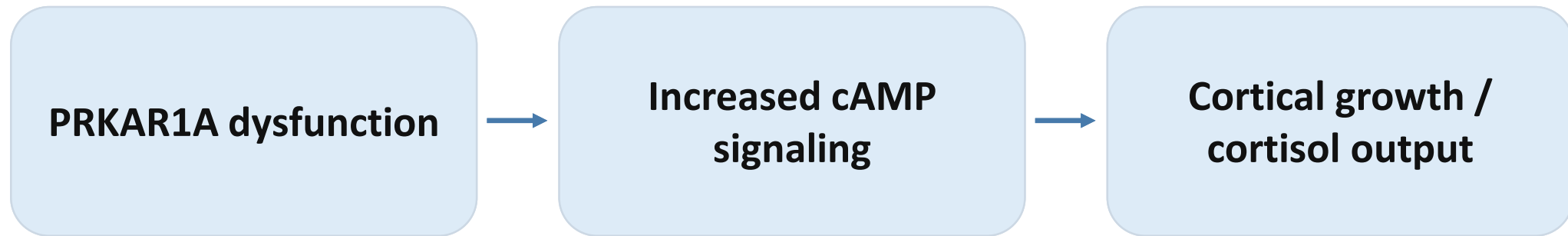
ACTH suppression atrophies the adjacent nonneoplastic cortex.

The contralateral gland also becomes atrophic.

Genetic alterations in adrenocortical carcinoma

Gene	Alteration described in source
CTNNB1	Recurrent activating mutations
TP53	Recurrent inactivating mutations
MEN1	Recurrent inactivating mutations
PRKAR1A	Recurrent inactivating mutations

PRKAR1A links cortisol-producing lesions through cAMP



Alterations are described in adenomas, carcinomas and micronodular hyperplasia.

A shared signaling mechanism does not imply that these lesions have identical morphology or behavior.

Primary adrenal hyperplasia can be ACTH independent

Macronodular

Prominent bilateral nodules

Usually >10 mm diameter

May involve aberrant hormone
receptor signaling

Micronodular

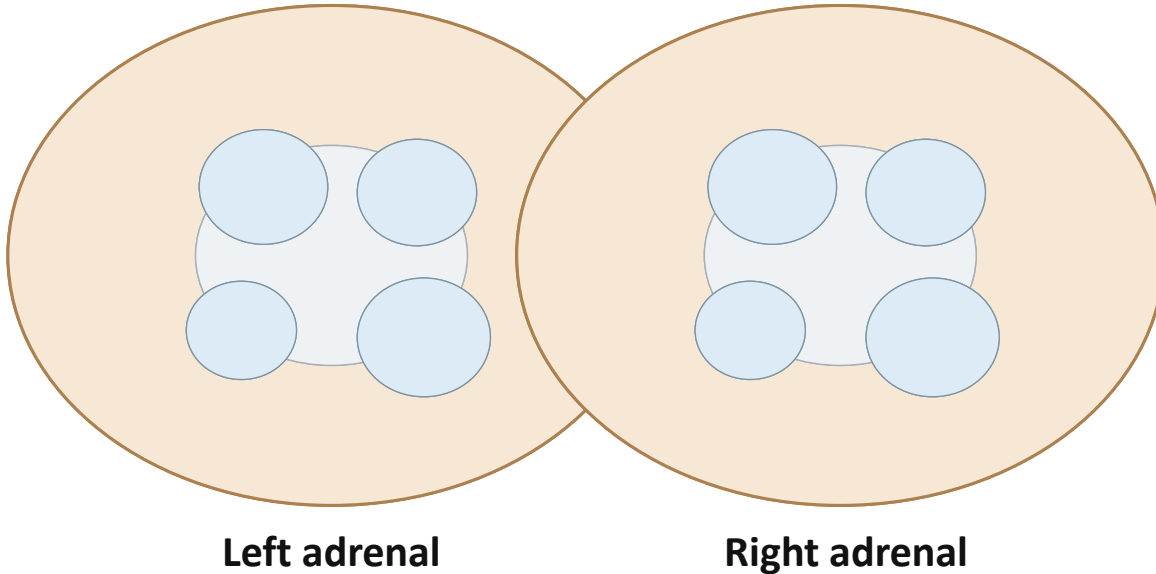
Small nodules, typically <10 mm

May be darkly pigmented

Often linked to PRKAR1A-pathway
disease

Bilateral macronodular adrenal hyperplasia

Paired adrenal glands



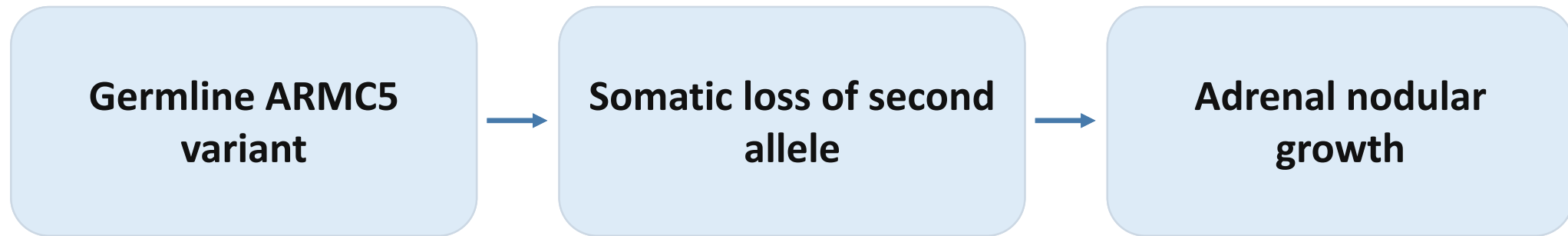
Schematic anatomy — not a gross specimen

The cortex is remodeled by prominent nodules of variable size, often 10–30 mm.

Between gross nodules, microscopic nodularity may persist.

Lipid-rich and lipid-poor cells can coexist within nodules.

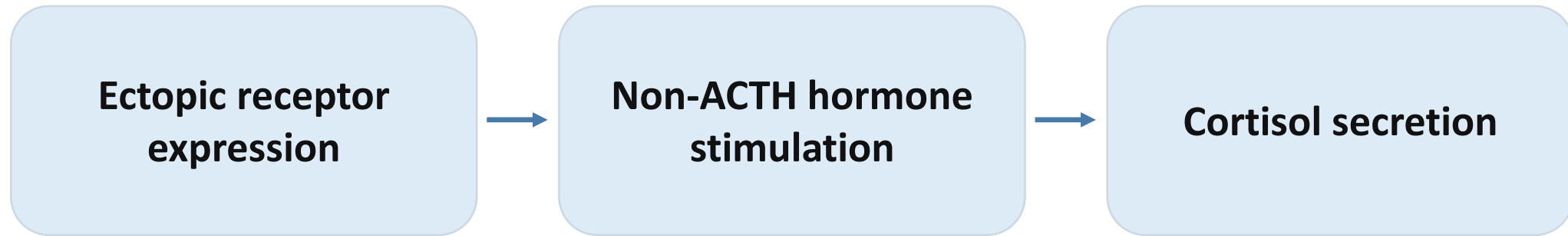
ARMC5: A two-hit mechanism in some BMAH



Familial BMAH can show ARMC5 tumor-suppressor disruption.

The textbook also reports germline variants in some apparently sporadic cases.

Aberrant G-protein-coupled receptors in BMAH

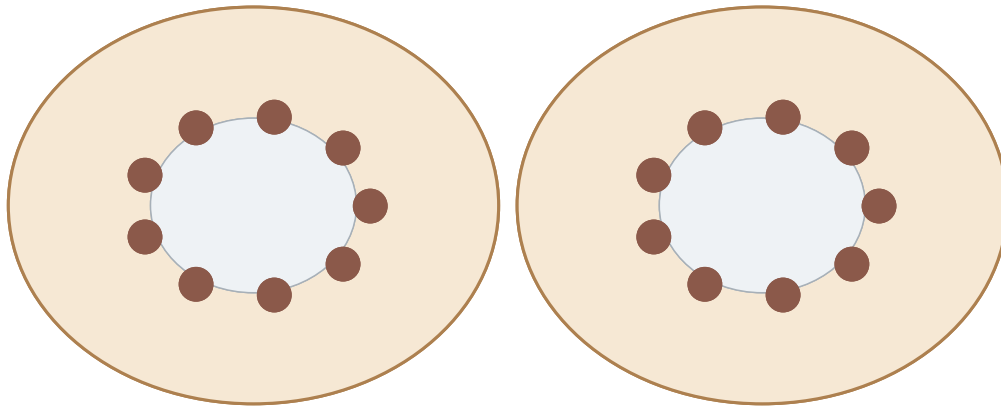


Examples described include gastric inhibitory polypeptide, LH and vasopressin.

Such lesions need not be entirely autonomous from hormonal signals.

Micronodular cortical hyperplasia is often pigmented

Paired adrenal glands



Left adrenal

Right adrenal

Schematic anatomy — not a gross specimen

Small cortical nodules are commonly brown-black because of lipofuscin pigment.

Intervening cortex may be atrophic.

Pigmented nodules are not interchangeable with macronodular hyperplasia.

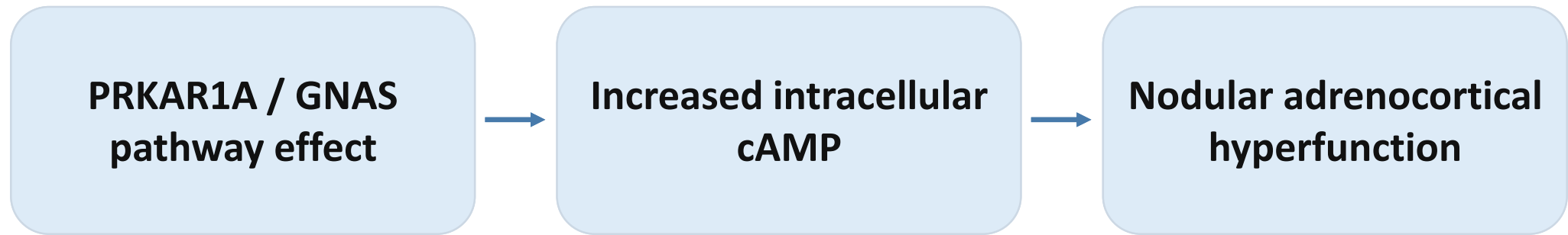
Pigmented nodular disease and Carney complex

Primary pigmented nodular adrenocortical disease may occur independently.

It can also occur within Carney complex, a multisystem syndrome with endocrine and nonendocrine neoplasms.

Both settings are commonly associated with PRKAR1A alterations.

CAMP-pathway activation: Shared signal, different lesions



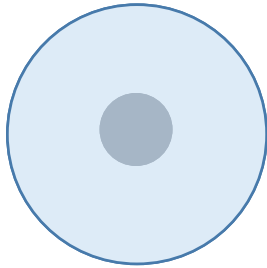
The source links PRKAR1A inactivation and activating GNAS alterations to increased cAMP signaling.

Genotype and phenotype are not one-to-one; Do not infer a mutation solely from histology.

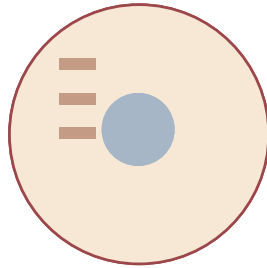
Bilateral nodular hyperplasia: Pathologic comparison

Feature	Macronodular	Micronodular
Nodule size	Usually >10 mm; often 10–30 mm	Often 1–3 mm; typically <10 mm
Gross pattern	Numerous prominent nodules	Multiple small brown-black nodules
Intervening tissue	May show microscopic nodules	Often atrophic
Pigmentation	Not defining	Lipofuscin often prominent

Crooke hyaline change in pituitary corticotrophs



Typical corticotroph



Crooke hyaline change

A common pituitary response to prolonged glucocorticoid excess.

Corticotroph cytoplasm becomes pale and homogeneous rather than normally granular-basophilic.

Accumulation of intermediate keratin filaments produces the change.

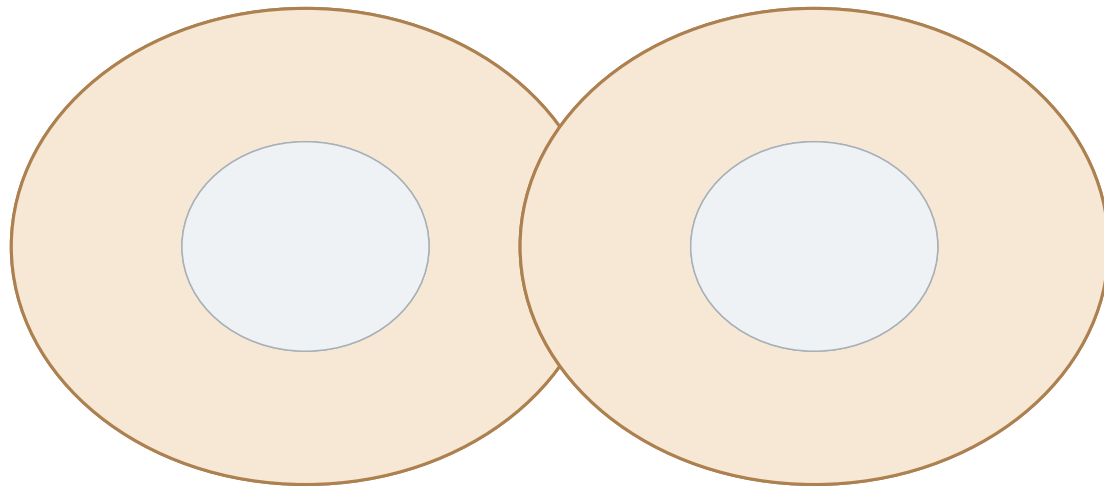
Schematic — not a histologic specimen

Adrenal morphology encodes the underlying source

Driving mechanism	Expected adrenal finding
Exogenous glucocorticoids	Bilateral cortical atrophy
Pituitary / ectopic ACTH	Bilateral diffuse cortical hyperplasia
Primary nodular hyperplasia	Bilateral macro- or micronodules
Functional adrenal neoplasm	Cortical tumor; nonneoplastic cortex atrophic

Diffuse cortical hyperplasia: Gross pattern

Paired adrenal glands



Left adrenal

Right adrenal

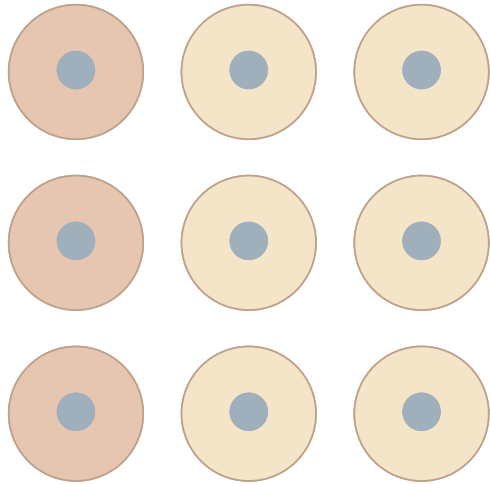
Schematic anatomy — not a gross specimen

Both glands are enlarged, sometimes subtly.

Yellow cortical thickening may show mild nodularity.

This differs from prominent large-nodule macronodular disease.

Diffuse hyperplasia: Lipid-poor and lipid-rich zones



Simplified cellular schematic

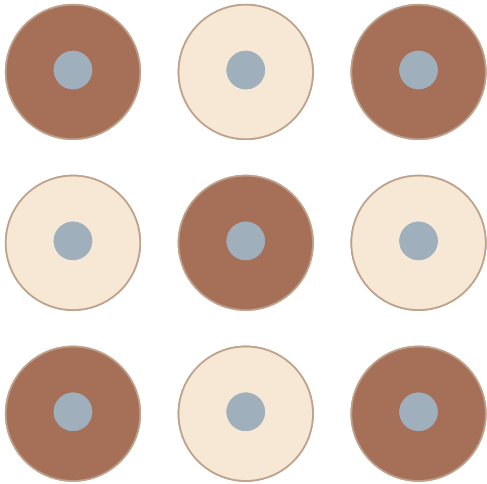
Schematic — not a histologic specimen

Expanded inner lipid-poor zona reticularis has compact eosinophilic cells.

An outer lipid-rich zone contains vacuolated cells resembling zona fasciculata.

Vacuolated nodules contribute to the yellow gross appearance.

Micronodular disease: Pigmented cortical nodules



Simplified cellular schematic

Schematic — not a histologic specimen

Dark micronodules can contain lipofuscin pigment.

Nodules are surrounded by relatively atrophic nonnodular cortex.

A cellular schematic illustrates pigment distribution; It is not H&E evidence.

Functional adenomas resemble nonfunctioning adenomas

Grossly, adenomas are generally yellow and encapsulated or well circumscribed.

Their cells resemble normal zona fasciculata cells.

Function cannot be established from routine architecture alone.

Most adenomas weigh less than 30 g; Do not use mass alone as a malignancy criterion.

Adrenocortical carcinoma: Malignant morphology

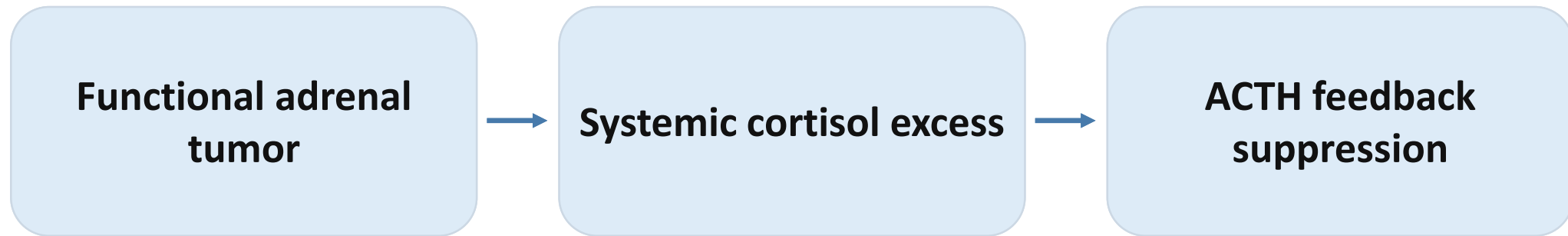
Carcinomas tend to be much larger than adenomas and often lack a capsule.

They exhibit malignant cytologic and architectural features rather than a unique cortisol-secreting morphology.

Cortisol production may be particularly marked in some carcinomas.

Masses frequently exceeding 200–300 g, without making weight a standalone diagnostic test.

Why nonneoplastic cortex atrophies beside a tumor



The adjacent cortex and the contralateral gland receive less ACTH.

This is a hormone-feedback effect, not necessarily direct destruction of surrounding tissue.

Distinct patterns can be read as a morphology map

Adrenal image pattern	Most relevant etiologic inference	Important qualification
Bilateral small glands	Exogenous suppression	Integrate medication history
Bilateral diffuse enlargement	ACTH-driven cortisol excess	Pituitary and ectopic ACTH overlap
Bilateral discrete nodules	Primary nodular disease	Macro-/micronodular subtyping
Unilateral cortical neoplasm	Adrenal autonomy	Assess adjacent/contralateral atrophy

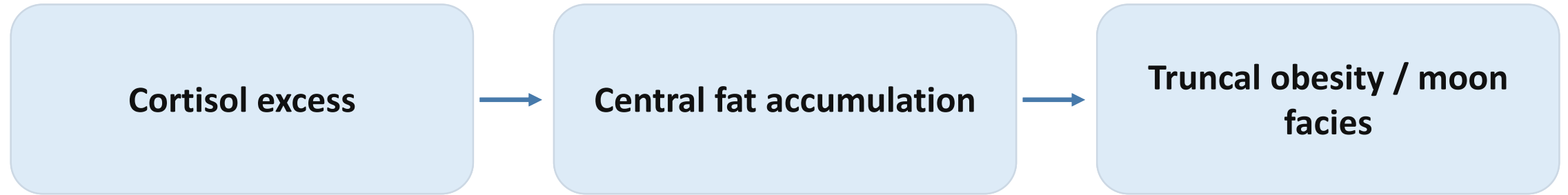
Clinical syndrome develops gradually

Onset may be insidious, and early findings are relatively nonspecific.

Weight gain and hypertension may precede the full constellation of signs.

Sustained cortisol excess produces the characteristic multisystem phenotype over time.

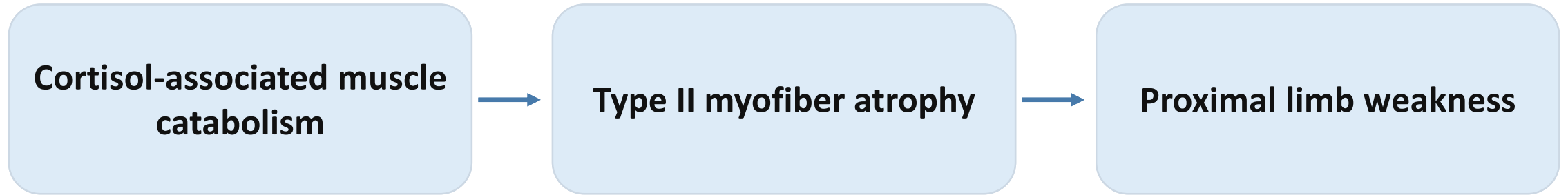
Redistribution of adipose tissue produces a pattern



Posterior cervical and upper-back fat deposition contributes to the “buffalo hump.”

Regional adipose changes are more informative as a constellation than as isolated findings.

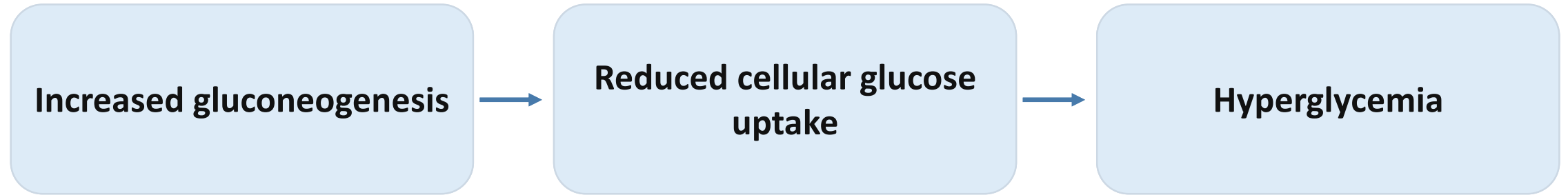
Selective type II myofiber atrophy causes weakness



Muscle mass declines despite central weight gain.

Proximal weakness is an important functional consequence of chronic glucocorticoid excess.

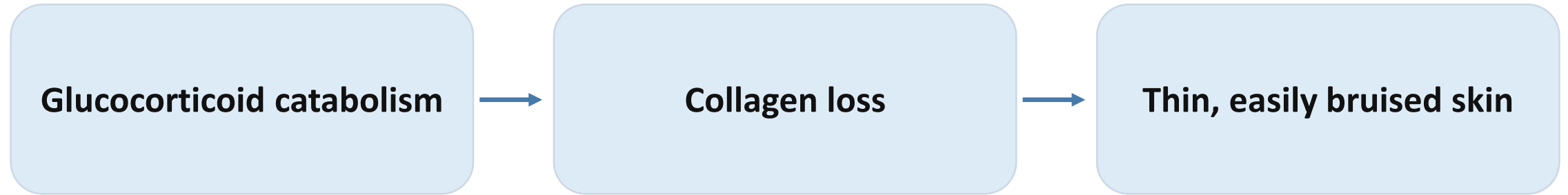
Glucose dysregulation follows metabolic hormone action



Secondary diabetes and glucosuria may develop.

Polydipsia can reflect the metabolic consequences of increased circulating glucose.

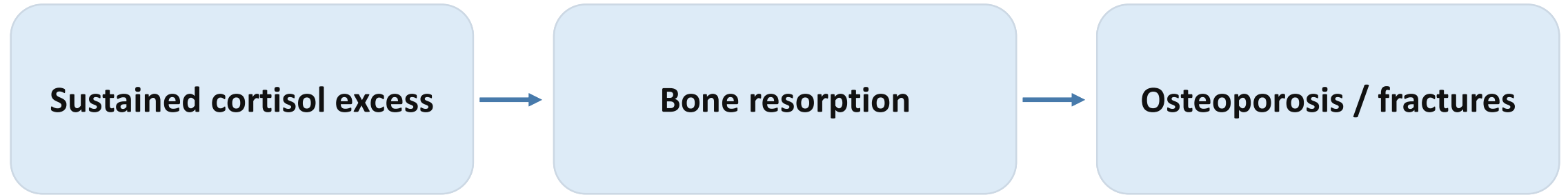
Skin fragility reflects impaired structural maintenance



Poor wound healing and conspicuous abdominal striae reflect matrix and tissue fragility.

These changes connect superficial clinical signs with collagen metabolism.

Bone resorption explains osteoporotic complications



Skeletal weakening can produce back pain.

Fracture susceptibility is an important consequence of chronic disease.

Glucocorticoids impair antimicrobial defense



The clinical susceptibility follows pharmacologic and endogenous glucocorticoid immunosuppression.

The presence of infection does not specify which mechanism produced the excess cortisol.

Neuropsychiatric and reproductive effects

Neuropsychiatric

Mood instability

Depressive symptoms

Potential severe psychotic features

Reproductive / androgenic

Menstrual irregularity

Hirsutism

Changes in libido

Clinical feature frequencies: Selected source examples

Finding	Frequency reported in textbook table
Weight gain / obesity	95%
Facial plethora	90%
Hypertension	75%
Easy bruising	65%
Glucose intolerance	60%
Weakness	60%
Historical source estimates; Not sensitivities or a contemporary population prevalence study.	

Clinical signs require biochemical corroboration

Obesity, hypertension and hyperglycemia individually have many possible causes.

Concordant findings spanning skin, muscle, fat distribution and bone increase clinical suspicion.

Clinical recognition initiates biochemical evaluation; It does not establish etiology.

Twenty-four-hour urinary free cortisol

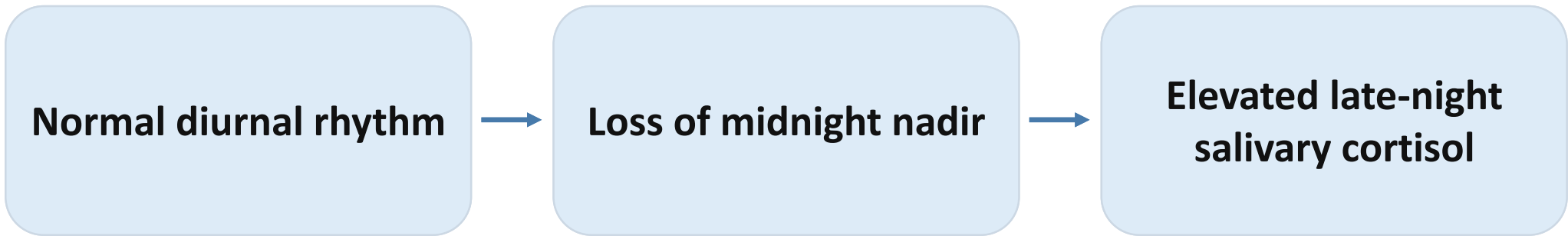
Increased urinary free cortisol is one biochemical indication of hypercortisolism.

The collection integrates free cortisol excretion across a full day.

Interpret biochemical testing in clinical context rather than from appearance alone.

Urinary free cortisol among the central tests for syndrome recognition.

Loss of cortisol circadian regulation



Cushing syndrome disturbs the normal diurnal pattern.

Late-night salivary cortisol is used to detect this characteristic loss of suppression.

Low-dose dexamethasone suppression test



An exogenous glucocorticoid should suppress cortisol through feedback in a normal regulatory axis.

The 1-mg test as a method to identify hypercortisolism.

The biochemical sequence separates two questions

Does hypercortisolism exist?

24-hour urinary free cortisol

Late-night salivary cortisol

Low-dose dexamethasone test

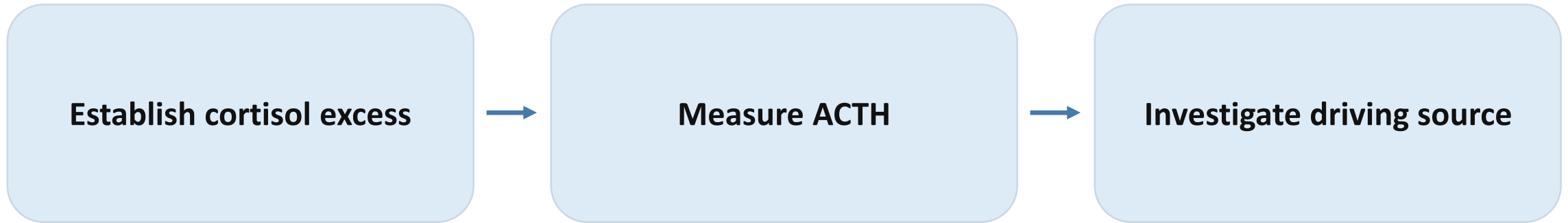
What causes it?

Medication exposure history

Serum ACTH level

Further investigation of pituitary,
ectopic or adrenal source

Serum ACTH guides etiologic evaluation



Low ACTH: Adrenal source or exogenous suppression.

Inappropriately normal/high ACTH: Pituitary or ectopic ACTH/CRH pathway.

High-dose dexamethasone: Utility and limits

Pituitary source

Often suppresses cortisol at higher dexamethasone dose

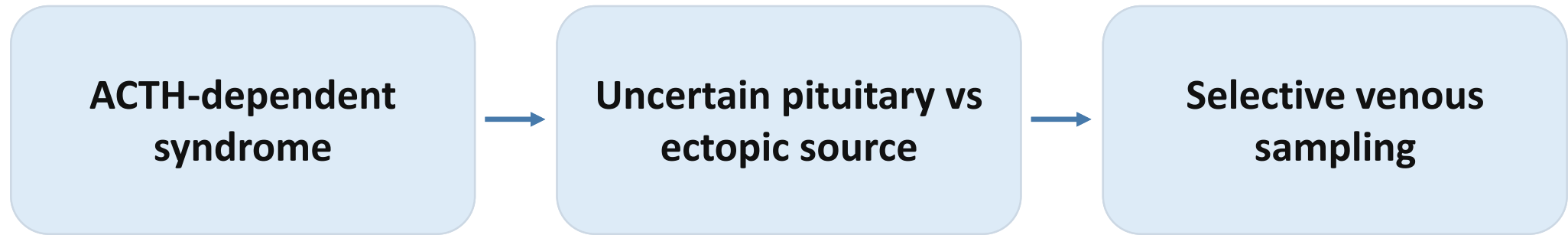
Interpret as a tendency, not an absolute rule

Ectopic ACTH source

Often lacks suppression with higher dose

Some overlap and failures of discrimination occur

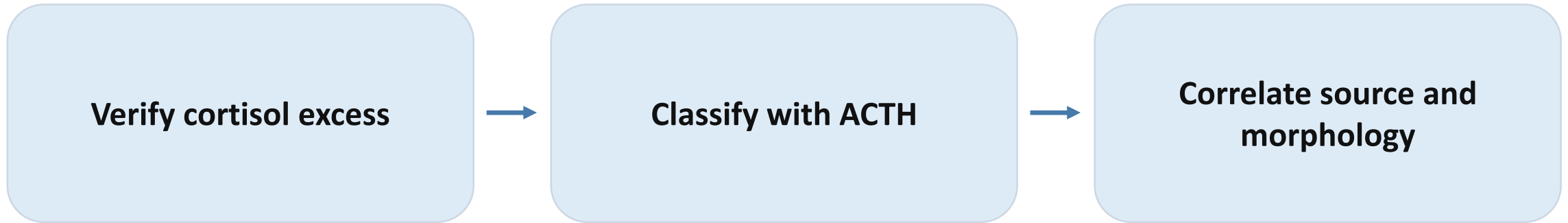
Inferior petrosal sinus sampling resolves ambiguity



Some ambiguous cases require inferior petrosal sinus sampling.

High-dose dexamethasone alone is not definitive.

The diagnostic map integrates mechanism and morphology



Exposure history precedes attribution to endogenous disease.

The expected adrenal pattern is an independent pathophysiologic consistency check.

Case: Iatrogenic hypercortisolism

Teaching vignette (hypothetical)

An adult treated with prolonged systemic glucocorticoids develops truncal obesity, easy bruising and proximal weakness. The endogenous pituitary–adrenal axis is suppressed.

Clinicopathologic interpretation

Etiology: Exogenous steroid-associated Cushing syndrome.

Expected ACTH: Suppressed.

Expected adrenal morphology: Bilateral cortical atrophy.

Case: Pituitary ACTH-dependent disease

Teaching vignette (hypothetical)

A young adult has progressive centripetal weight gain, proximal weakness and biochemical cortisol excess. ACTH is not suppressed, and a pituitary corticotroph tumor is identified.

Clinicopathologic interpretation

Etiology: Cushing disease.

Pituitary ACTH stimulates both adrenal cortices.

Expected adrenal pattern: Bilateral diffuse hyperplasia.

Case: Autonomous adrenal tumor

Teaching vignette (hypothetical)

A patient has hypercortisolism with suppressed ACTH. A unilateral cortical tumor is identified; The opposite adrenal is small.

Clinicopathologic interpretation

Mechanism: ACTH-independent cortisol production.

Adjacent and contralateral cortical atrophy follow ACTH suppression.

Histologic assessment is needed to distinguish benign from malignant tumor.

Case: Ectopic ACTH production

Teaching vignette (hypothetical)

A patient with a lung neuroendocrine malignancy develops rapidly progressive clinical hypercortisolism. ACTH is inappropriately increased.

Clinicopathologic interpretation

Consider ectopic ACTH production from the malignancy.

Expected adrenal response: Bilateral cortical hyperplasia.

Pituitary and ectopic ACTH sources can require further discrimination.

Morphology–biochemistry integration

Syndrome driver	ACTH	Adrenals
Exogenous steroid	Low	Bilateral atrophy
Pituitary corticotroph	Normal/high relative to cortisol	Bilateral hyperplasia
Ectopic ACTH/CRH	Normal/high relative to cortisol	Bilateral hyperplasia
Adrenal cortisol-producing tumor	Low	Unilateral neoplasm; residual atrophy
Primary nodular hyperplasia	Low	Bilateral nodules

Integrated clinicopathologic synthesis

The most common overall cause is exogenous glucocorticoid administration.

Endogenous sources are classified by ACTH dependence and can be inferred from biochemical feedback.

Adrenal atrophy, diffuse hyperplasia, nodular hyperplasia and neoplasia reflect different hormonal mechanisms.

Clinical recognition and biochemical testing must be integrated with the etiologic diagnosis.

References and interpretation limits

Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th edition (2026), Chapter 24, pp. 1012–1015.

Clinical-frequency examples are drawn from Table 24.8, adapted in the textbook from Newell-Price et al., Lancet (2006).

This lecture presents the supplied textbook account; contemporary guideline validation and chapter-PDF figure verification were not performed.