

Adrenal Cortex

Structure, hormone physiology, hyperfunction, insufficiency, and neoplasia

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Learning objectives

- Map the cortical zones to their predominant steroid hormones.
- Explain hormone excess and deficiency through feedback physiology.
- Distinguish causes, morphology, and clinical patterns of major cortical disorders.
- Interpret adrenal lesions using morphology, hormone activity, and clinical context.

The adrenal gland houses two endocrine systems

- The cortex and medulla differ in developmental origin, organization, and secretory products.
- Cortical cells synthesize steroid hormones; Medullary chromaffin cells release catecholamines.
- Cortical pathology may cause excess hormone production, hormone failure, or a mass lesion.
- The cortex is the focus of this lecture; Medullary neoplasms form a separate topic.

Normal adrenal cortex: Zonal organization

Capsule	Fibrous covering
Zona glomerulosa	Aldosterone
Zona fasciculata	Predominant cortical volume; Cortisol
Zona reticularis	Androgens; Some glucocorticoids
Medulla	Catecholamines

Schematic orientation from capsular surface toward the adrenal medulla

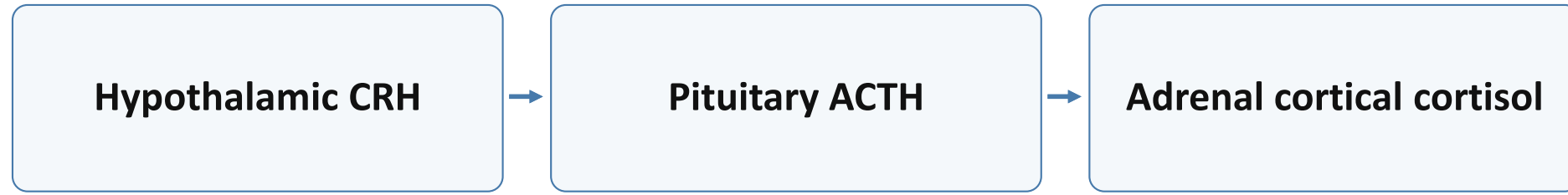
Adrenal zones and predominant outputs

Cortical zone	Principal hormones	Key regulatory linkage
Glomerulosa	Mineralocorticoids (aldosterone)	Renin–angiotensin and potassium
Fasciculata	Glucocorticoids (cortisol)	Pituitary corticotropin (ACTH)
Reticularis	Adrenal androgens; some cortisol	Predominantly corticotropin (ACTH)

Architecture predicts cortical responses to injury

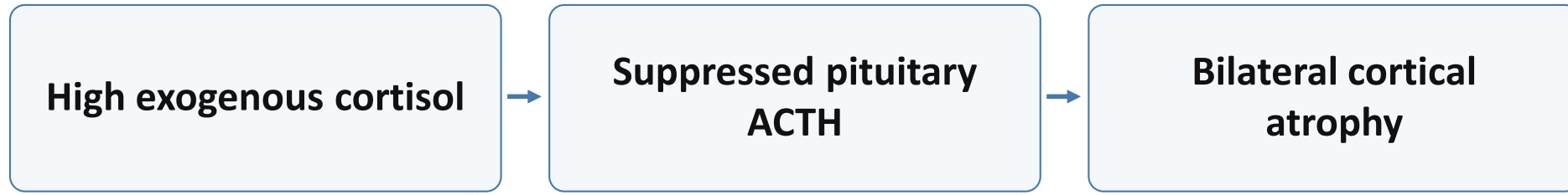
- The zona fasciculata is the broadest zone, comprising roughly three quarters of the cortex.
- Glomerulosa lies beneath the capsule; Reticularis borders the medulla.
- Chronic corticotropin drive produces enlargement of ACTH-responsive cortical compartments.
- ACTH suppression preferentially atrophies fasciculata and reticularis while sparing glomerulosa.

The hypothalamic–pituitary–adrenal axis



- Glucocorticoid output rises in response to corticotropin.
- Cortisol feedback suppresses hypothalamic and pituitary stimulation.
- Failure or escape at different levels changes both ACTH and adrenal morphology.

Feedback explains adrenal atrophy and hyperplasia



- Glucocorticoid medication may suppress endogenous ACTH.
- Without trophic ACTH, fasciculata and reticularis regress.
- Conversely, sustained ACTH excess drives bilateral cortical hyperplasia.

Three steroid systems: Principal effects

Steroid class	Major physiologic roles	Characteristic excess
Glucocorticoids	Metabolism; immune suppression; stress response	Cushing syndrome
Mineralocorticoids	Renal Na ⁺ retention and K ⁺ excretion	Hyperaldosteronism
Adrenal androgens	Sex-steroid precursor contribution	Virilizing syndromes

A useful first division: Function versus lesion

- Hyperfunction: Cortisol, aldosterone, or androgen excess dominates the phenotype.
- Hypofunction: Cortical hormone deficiency can be primary or secondary.
- Structural pathology: Diffuse or nodular hyperplasia, adenoma, carcinoma, hemorrhage, or infiltration.
- The appearance of a cortical mass alone does not establish its hormonal functionality.

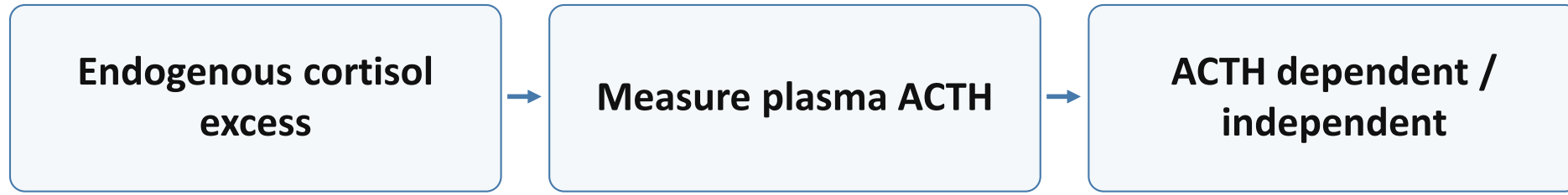
Hormone pattern guides the diagnostic question

Dominant abnormality	Clinical cue	Pathologic question
Cortisol excess	Central adiposity, catabolism, hyperglycemia	ACTH dependent or independent?
Aldosterone excess	Hypertension $\pm$ hypokalemia	Autonomous adrenal or renin driven?
Androgen excess	Virilization or precocious puberty	CAH or cortical neoplasm?
Cortisol deficiency	Weakness, hypotension, crisis	Primary adrenal or pituitary?

Cushing syndrome means sustained glucocorticoid excess

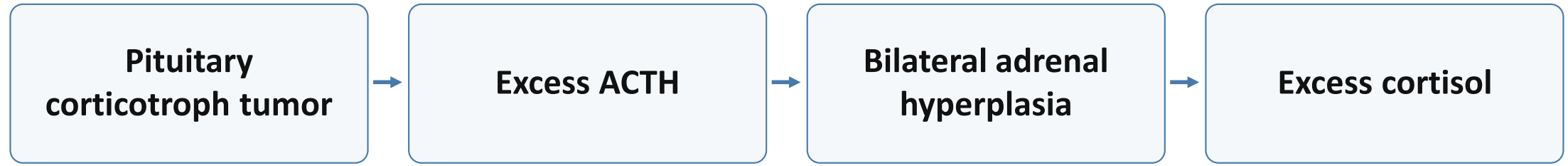
- Exogenous glucocorticoid administration is the most common overall cause.
- Endogenous hypercortisolism arises from ACTH-dependent or ACTH-independent mechanisms.
- Cushing disease specifically denotes pituitary ACTH-producing tumor-associated Cushing syndrome.
- The adrenal morphology varies with the source of cortisol excess.

Classifying endogenous Cushing syndrome



- ACTH-dependent causes include pituitary tumors and ectopic ACTH secretion.
- ACTH-independent causes include cortisol-producing adrenal lesions.
- The classification predicts whether both glands are stimulated or ACTH is suppressed.

Pituitary Cushing disease: Causal sequence

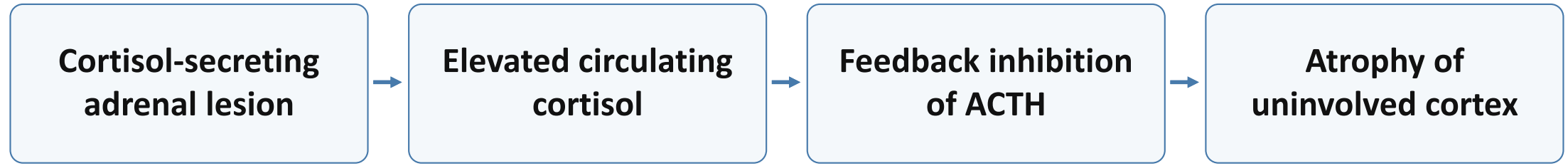


- Sustained ACTH stimulation expands steroid-producing cortical cells.
- The adrenal glands are effectors, not the autonomous source of the signal.
- A corticotroph neoplasm may be small despite substantial systemic consequences.

Ectopic ACTH: Endocrine effects of nonpituitary tumors

- Certain neuroendocrine cancers secrete ACTH outside the pituitary.
- Small-cell carcinoma of the lung is a prominent example.
- Ectopic CRH secretion can also stimulate pituitary ACTH in rare settings.
- High ACTH can produce bilateral adrenal cortical hyperplasia and hypercortisolism.

Autonomous adrenal cortisol: Suppressed ACTH



- An adenoma, carcinoma, or primary bilateral hyperplasia may produce ACTH-independent cortisol excess.
- Both adjacent and contralateral normal cortex can atrophy in unilateral cortisol-secreting tumors.

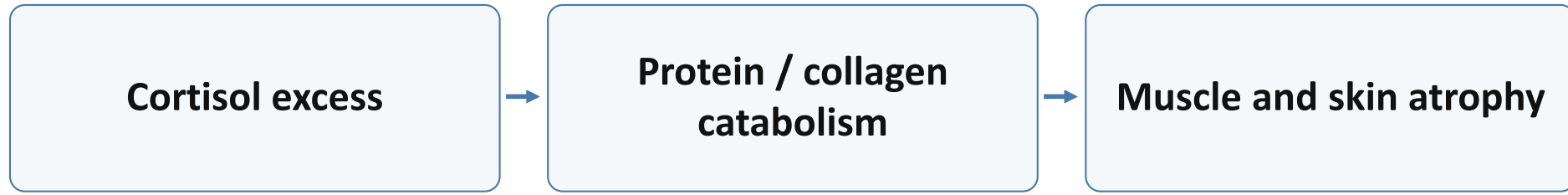
Bilateral macronodular adrenal hyperplasia

- Primary bilateral macronodular hyperplasia is usually ACTH independent.
- Macroscopic nodules are generally greater than 10 mm and can replace much of the cortex.
- Some familial and apparently sporadic cases involve germline ARMC5 alterations.
- Aberrant hormone receptors can drive cortisol secretion independently of pituitary ACTH.

Pigmented micronodules and Carney complex

- Micronodular cortical lesions are typically below 10 mm and may appear darkly pigmented.
- Pigment corresponds to intracytoplasmic lipofuscin in compact cortical cells.
- Primary pigmented nodular disease may be sporadic or part of Carney complex.
- PRKAR1A pathway defects promote inappropriate cAMP-dependent signaling.

Cortisol effects explain the clinical phenotype



- Glucocorticoids also favor hepatic glucose production and impair peripheral glucose uptake.
- The net phenotype combines fat redistribution, hypertension, hyperglycemia, and tissue fragility.

Cushing syndrome: Change in body composition

- Truncal obesity develops with rounded facial contours (“moon facies”).
- Fat may accumulate in the posterior neck and upper back.
- Muscle mass falls because glucocorticoids promote protein catabolism.
- Proximal weakness reflects preferential atrophy of type II myofibers.

Cushing syndrome: Skin and skeletal pathology

- Collagen loss produces thin skin, easy bruising, and poor wound repair.
- Abdominal striae reflect structural weakening during tissue expansion.
- Bone resorption contributes to osteoporosis and fragility fractures.
- Findings are mechanistically linked to prolonged glucocorticoid exposure.

Cushing syndrome: Metabolic and immune effects

- Hyperglycemia follows increased gluconeogenesis and reduced cellular glucose uptake.
- Hypertension can be an early, nonspecific presenting feature.
- Immune suppression increases susceptibility to infection.
- Mood disturbance, menstrual changes, and hirsutism broaden the clinical spectrum.

Cushing syndrome: Morphology by pathogenesis

Cause	Adrenal appearance	Explanation
Exogenous glucocorticoids	Bilateral cortical atrophy	Pituitary ACTH suppression
Pituitary / ectopic ACTH	Bilateral diffuse cortical hyperplasia	Sustained trophic stimulation
Primary bilateral nodular disorder	Macro- or micronodular hyperplasia	Autonomous steroidogenic signaling
Cortisol-secreting tumor	Unilateral lesion; residual cortex atrophic	Tumor cortisol suppresses ACTH

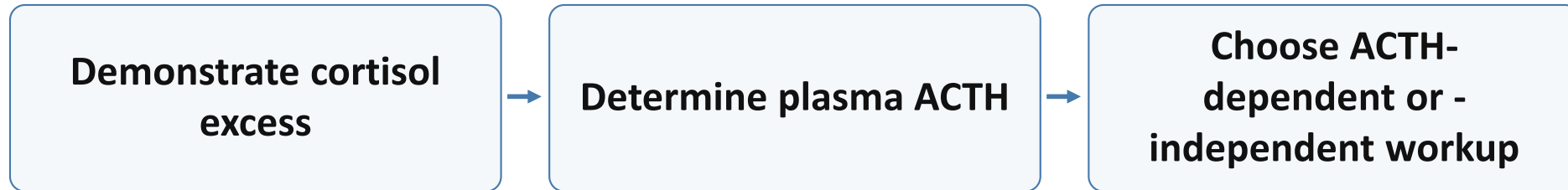
Adrenal hyperplasia has recognizable patterns

- Diffuse ACTH-dependent enlargement creates a broadened cortex, sometimes with subtle nodularity.
- Macronodular hyperplasia contains prominent cortical nodules of variable sizes.
- Micronodular hyperplasia may show dark lipofuscin-containing nodules with atrophic intervening tissue.
- These patterns should not be equated simply because all can cause excess cortisol.

Biochemical evidence precedes localization

- A 24-hour urinary free cortisol increase supports hypercortisolism.
- Loss of late-night cortisol nadir may be demonstrated with midnight salivary cortisol.
- A low-dose dexamethasone suppression test may document failure to suppress.
- Testing must be interpreted in clinical context before selecting adrenal or pituitary imaging.

After confirming hypercortisolism: Use ACTH



- Suppressed ACTH favors autonomous adrenal cortisol production or exogenous steroid exposure.
- Nonsuppressed ACTH requires localization of pituitary versus ectopic secretion.
- Suppression tests alone may be imperfect; Additional sampling may sometimes be needed.

Cushing disease versus ectopic ACTH secretion

Pituitary source

- Pituitary corticotroph neoplasm
- ACTH-dependent cortisol excess
- Bilateral adrenocortical hyperplasia
- May suppress with higher-dose dexamethasone

Ectopic source

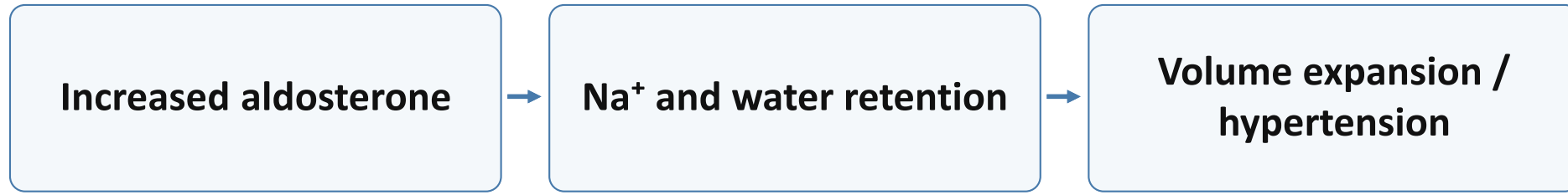
- Nonpituitary ACTH-producing tumor
- ACTH-dependent cortisol excess
- Bilateral adrenocortical hyperplasia
- Often resists high-dose dexamethasone suppression

High-dose suppression is not a definitive standalone discriminator.

Hyperaldosteronism: Two fundamentally different mechanisms

- Primary: Autonomous adrenal aldosterone secretion suppresses renin.
- Secondary: Increased renin–angiotensin stimulation drives aldosterone release.
- Both can cause sodium retention, volume expansion, and hypertension.
- Distinguishing primary from secondary disease prevents erroneous etiologic classification.

Renal consequences of aldosterone excess



- Aldosterone stimulates mineralocorticoid receptor-mediated tubular sodium reabsorption.
- Enhanced potassium excretion can produce hypokalemia.
- Hypokalemia is not obligatory; Normal potassium does not exclude primary aldosteronism.

Primary aldosteronism: Major source categories

Category	Defining pathologic setting	Important distinction
Bilateral idiopathic disease	Bilateral glomerulosa-type hyperplasia	Commonest source in the textbook
Aldosterone-producing adenoma	Usually solitary, small cortical adenoma	Conn syndrome
Familial forms	Inherited alterations to steroidogenesis	Multiple genetic subtypes
Adrenocortical carcinoma	Malignant autonomous production	Rare cause

Conn syndrome: Aldosterone-producing adenoma

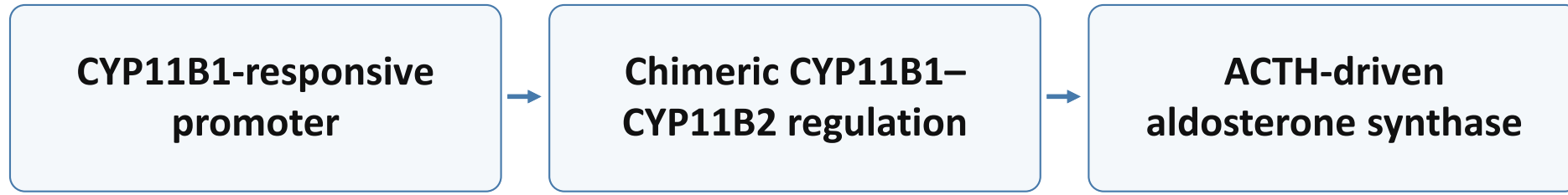
- Typically a small, solitary, circumscribed bright-yellow cortical tumor.
- Microscopy often resembles lipid-rich zona fasciculata rather than native glomerulosa.
- ACTH secretion is usually not suppressed, so surrounding cortex is not typically atrophic.
- A lesion's size and cytology cannot independently establish its secretory status.

KCNJ5 alterations: An aldosterone-producing mechanism



- Recurrent somatic KCNJ5 mutations in aldosterone-producing adenomas.
- The effect is sustained aldosterone biosynthesis rather than simple trophic proliferation.

Familial hyperaldosteronism type I



- Glucocorticoid-remediable aldosteronism links aldosterone synthesis to pituitary ACTH.
- Promoter rearrangement—not cortical destruction—creates aberrant hormone regulation.

Primary and secondary hyperaldosteronism

Primary: Adrenal autonomy

- Aldosterone elevated
- Renin suppressed
- Adrenal adenoma or bilateral hyperplasia
- Hypertension; K⁺ may be normal

Secondary: Renin-angiotensin drive

- Aldosterone elevated
- Renin elevated / activated
- Renal hypoperfusion, edema states, or related stimuli
- Correction of underlying driver is central

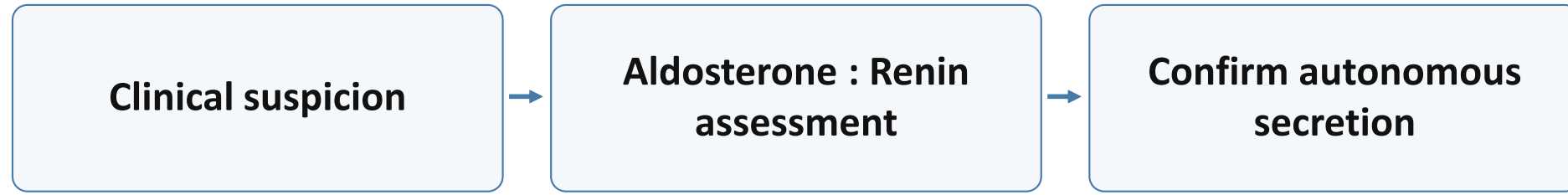
Morphology: Bilateral glomerulosa hyperplasia

- The cortex may show subtle bilateral enlargement rather than a dominant mass.
- Glomerulosa-like cells expand in diffuse and focal patterns.
- Wedge-shaped hyperplastic foci may extend inward from the gland periphery.
- The microscopic differential includes a discrete aldosterone-producing adenoma.

Hyperaldosteronism: Cardiovascular consequences

- Persistent aldosterone-mediated volume expansion elevates blood pressure.
- The textbook links the syndrome with cardiac hypertrophy and cardiovascular events.
- Renal potassium wasting can cause weakness, paresthesias, or arrhythmic risk.
- Severity of hypertension and potassium concentration alone do not reliably identify the cause.

Evaluating suspected primary hyperaldosteronism



- Elevated aldosterone relative to suppressed renin is a central biochemical clue.
- Positive screening generally requires appropriate confirmation and subtype evaluation.
- Preanalytic, physiologic, and medication-related confounding can influence testing.

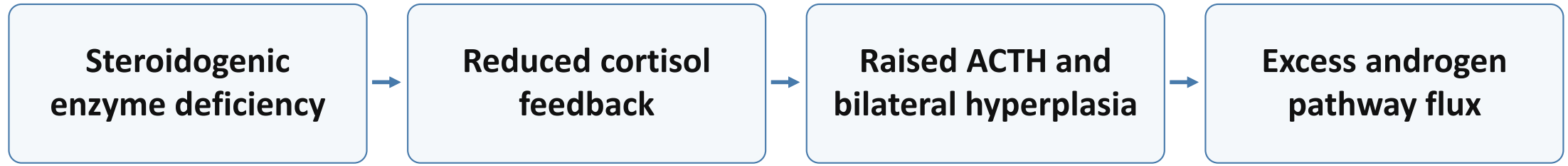
The adrenal cortex is a source of androgen precursors

- Zona reticularis generates dehydroepiandrosterone and androstenedione.
- Peripheral conversion contributes biologically active androgens.
- ACTH regulates adrenal androgen output.
- Marked virilization may indicate congenital steroidogenic defects or an androgen-producing neoplasm.

Androgen-secreting neoplasms: Interpret the phenotype

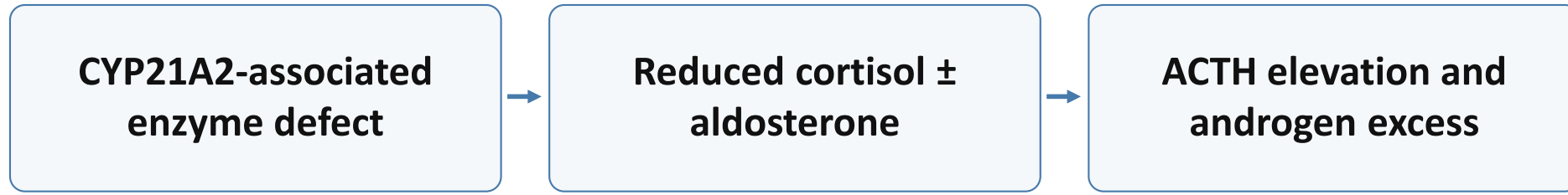
- Adrenocortical tumors can produce virilization, occasionally with cortisol excess.
- A virilizing adrenal neoplasm is more likely to be carcinoma than adenoma.
- Hormone production must be established biochemically, not deduced from appearance alone.
- Morphology is evaluated separately for evidence of malignant growth.

Congenital adrenal hyperplasia: Feedback mechanism



- CAH encompasses inherited steroid biosynthetic disorders.
- Mineralocorticoid deficiency occurs in some, not all, enzyme defects.
- The clinical outcome depends on residual enzyme activity and affected pathways.

21-hydroxylase deficiency: Two blocked outputs



- 21-hydroxylase is required in the glucocorticoid and mineralocorticoid pathways.
- Residual activity determines whether salt wasting accompanies virilization.
- This as the predominant genetic cause of CAH.

21-hydroxylase deficiency: Clinical phenotypes

Phenotype	Cortisol / aldosterone effect	Typical presentation
Classic salt-wasting	Marked deficiency of both hormones	Neonatal dehydration, hypotension, hyperkalemia
Classic simple-virilizing	Cortisol deficient; mineralocorticoid function sufficient	Genital virilization without salt crisis
Nonclassic	Partial enzyme deficiency	Later hirsutism, acne, menstrual changes

Salt-wasting CAH is a neonatal emergency

- Severe mineralocorticoid deficiency produces sodium loss and hyperkalemia.
- Volume depletion can progress to hypotension, acidosis, and circulatory collapse.
- Affected newborns may appear stable initially because placental and maternal physiology maintained fluid balance.
- Cortisol insufficiency and androgen excess coexist.

Simple-virilizing CAH: Cortisol feedback failure

- Residual mineralocorticoid synthesis prevents the classic salt-wasting crisis.
- Deficient cortisol feedback sustains excess ACTH secretion.
- Androgen overproduction can produce genital virilization or precocious pubertal changes.
- Absence of salt wasting does not mean the cortisol axis is normal.

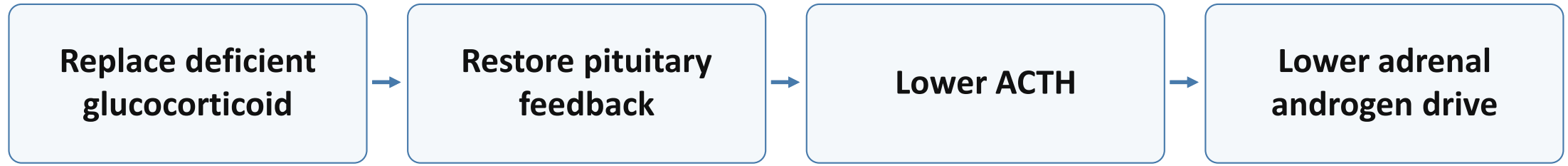
Nonclassic CAH: Partial steroidogenic impairment

- A partial 21-hydroxylase deficiency may present beyond infancy.
- Hirsutism, acne, oligomenorrhea, and menstrual irregularities are typical clues.
- Presentation overlaps with common alternative causes of hyperandrogenism.
- The diagnosis requires evaluation of steroid biosynthesis rather than appearance alone.

CAH morphology follows chronic ACTH stimulation

- Both adrenal glands may be markedly enlarged and nodular.
- A lipid-depleted, brown expanded cortex is described in severe disease.
- Compact eosinophilic cells mingle with lipid-containing cortical cells.
- Anterior pituitary corticotroph hyperplasia can accompany chronic low cortisol feedback.

Why glucocorticoid replacement reduces virilization

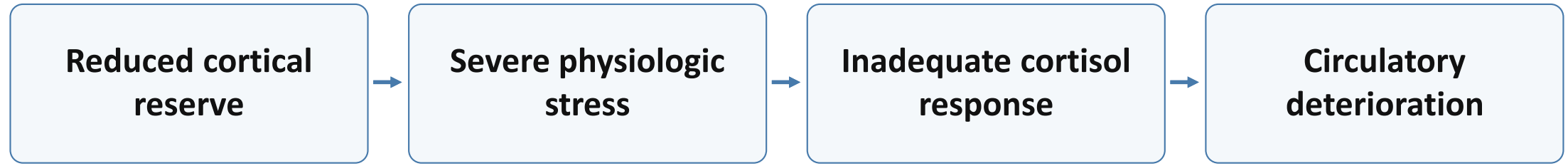


- Replacement treats cortisol deficiency and limits inappropriate ACTH-mediated stimulation.
- Salt-wasting forms also require mineralocorticoid replacement.
- The therapeutic logic directly follows the endocrine feedback defect.

Adrenocortical insufficiency: Classify by level

- Primary insufficiency arises from cortical loss or failure of steroid biosynthesis.
- Secondary insufficiency reflects inadequate pituitary ACTH output.
- Primary disease can present acutely as a crisis or chronically as Addison disease.
- Aldosterone preservation in secondary disease has important diagnostic implications.

Acute adrenal crisis: Stress exceeds reserve



- Acute decompensation may complicate established chronic adrenal insufficiency.
- Rapid steroid withdrawal can precipitate crisis in ACTH-suppressed patients.
- Bilateral hemorrhagic destruction is another potentially catastrophic mechanism.

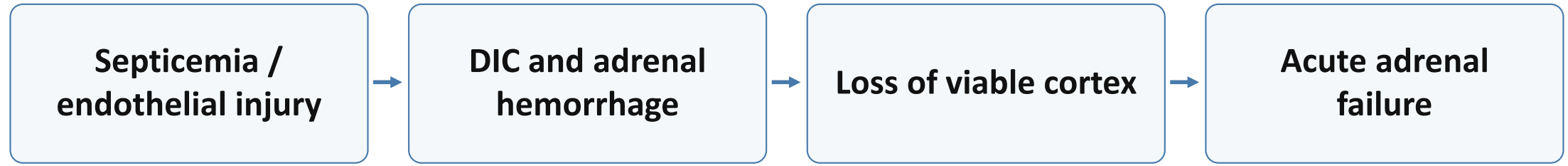
Primary acute insufficiency: Common precipitating settings

- Unrecognized chronic cortisol deficiency stressed by infection or illness.
- Abrupt discontinuation of long-term exogenous glucocorticoids.
- Bilateral adrenal hemorrhage, including DIC-associated injury or severe infection.
- Immune-checkpoint therapy may injure adrenal or pituitary tissue.

Waterhouse–Friderichsen syndrome

- A fulminant infection classically associated with meningococcal septicemia.
- Rapid shock and DIC accompany extensive purpura.
- Massive bilateral adrenal hemorrhage destroys steroidogenic reserve.
- It is a clinicopathologic emergency; Delayed recognition may be fatal.

Waterhouse–Friderichsen: Tissue injury sequence

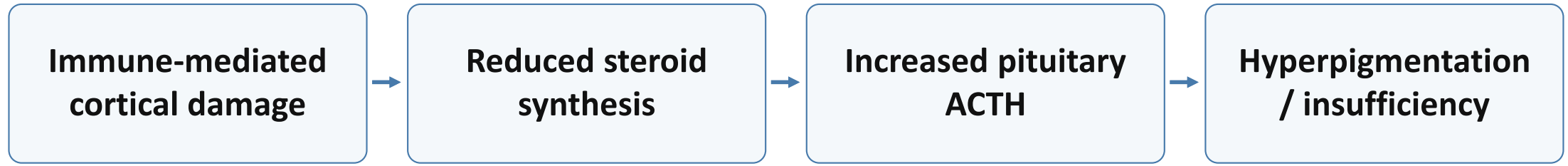


- Hemorrhage can begin near the medullary venous sinusoids and extend into the cortex.
- Gross glands may be largely replaced by clotted blood with little preserved architecture.

Addison disease: Progressive primary cortical loss

- Chronic adrenal insufficiency follows progressive destruction of the cortex.
- Substantial functional tissue may be lost before the clinical syndrome becomes evident.
- Etiologies include autoimmunity, infection, infiltration, hemorrhage, and metastatic disease.
- Primary hormone deficits produce high compensatory ACTH and may affect aldosterone.

Autoimmune adrenalitis: Loss of steroidogenic cells



- Antibodies to steroidogenic enzymes, including 21-hydroxylase, may support an autoimmune process.
- Autoimmune adrenalitis can be isolated or accompany polyendocrine autoimmunity.

APS-1 links adrenal autoimmunity to central tolerance

- The syndrome is associated with defects in the AIRE gene.
- Defective thymic expression of tissue antigens impairs deletion of autoreactive T cells.
- Adrenalitis can coexist with hypoparathyroidism and mucocutaneous candidiasis.
- The source explains candidiasis by impaired Th17-related antifungal immunity.

Autoimmune polyendocrine syndromes

APS-1

- AIRE-related central tolerance defect
- Adrenalitis and hypoparathyroidism may occur
- Chronic mucocutaneous candidiasis
- Ectodermal abnormalities can be present

APS-2

- Adrenalitis with autoimmune thyroid disease
- Type 1 diabetes may coexist
- More frequent than APS-1
- No defining candidiasis or ectodermal dysplasia

Other causes of primary chronic adrenal loss

- Tuberculosis and fungal infection may destroy both glands.
- Opportunistic infections are especially relevant in immunocompromised patients.
- Metastatic carcinoma can extensively replace adrenal parenchyma.
- Amyloid, granulomatous disease, iron deposition, and inherited disorders form additional mechanisms.

Primary Addison disease: Phenotype from hormone loss

- Weakness, fatigue, gastrointestinal disturbance, and hypotension are common.
- ACTH elevation produces hyperpigmentation in primary disease.
- Mineralocorticoid deficiency can contribute to salt loss and hyperkalemia.
- Clinical severity depends on the extent and tempo of cortical destruction.

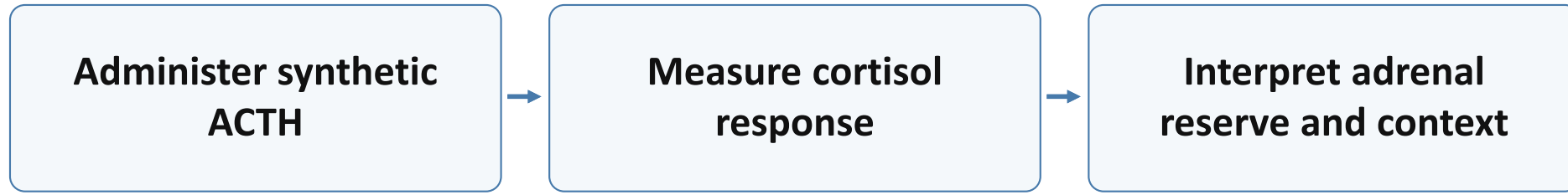
Secondary adrenal insufficiency: Inadequate ACTH

- Pituitary or hypothalamic injury reduces ACTH drive to the cortex.
- Long-term exogenous glucocorticoids can suppress endogenous ACTH.
- Cortisol and adrenal androgen output fall, but aldosterone is usually preserved.
- The absence of hyperpigmentation and marked hyperkalemia helps distinguish secondary disease.

Primary versus secondary adrenal insufficiency

Feature	Primary cortical failure	Secondary ACTH deficiency
ACTH	High (loss of cortisol feedback)	Low or inappropriately normal
Cortisol	Reduced	Reduced
Aldosterone	Often reduced	Usually normal / near normal
Hyperpigmentation	May be present	Not characteristic
Hyperkalemia	May occur	Not characteristic

Cosyntropin response tests cortical reserve



- Primary cortical destruction reduces cortisol responsiveness.
- Long-standing secondary ACTH deficiency can also blunt the response through adrenal atrophy.
- Recent-onset secondary deficiency may retain an initially normal response.

Morphology of secondary insufficiency

- Loss of sustained ACTH stimulation shrinks cortisol-producing cortical compartments.
- The gland can be small and flattened while retaining yellow cortical tissue.
- Zona glomerulosa is relatively preserved because aldosterone does not depend primarily on ACTH.
- A normal-size gland does not exclude recent-onset secondary dysfunction.

Adrenocortical neoplasms: A functional spectrum

- Many cortical adenomas are nonfunctional and incidentally detected.
- Functioning lesions may cause cortisol or aldosterone excess.
- Pronounced virilization raises concern for adrenocortical carcinoma.
- A diagnosis of functionality requires clinical and biochemical evidence.

Adrenocortical adenoma: Core morphologic features

- A circumscribed yellow to yellow-brown nodule often resembles normal steroidogenic cortex.
- Lipid-rich cells can have pale, vacuolated cytoplasm.
- Limited nuclear pleomorphism can be present without establishing malignancy.
- Mitotic activity is generally low; Hormone function is not determined by H&E appearance.

Carcinoma: Destructive growth changes the diagnosis

- Adrenocortical carcinoma is often a large, infiltrative tumor effacing the gland.
- Cut surfaces may be variegated with hemorrhage, necrosis, and cystic change.
- Venous, lymphatic, and distant invasion are important malignant behaviors.
- Smaller or better-differentiated carcinomas may be morphologically challenging.

Cortical adenoma versus carcinoma: Overview

Criterion	Adenoma (typical)	Carcinoma (typical)
Gross border	Well circumscribed	Often infiltrative / poorly demarcated
Gross cut surface	Yellow, lipid rich	Variegated necrosis or hemorrhage
Cytologic variability	Mild atypia possible	May be markedly atypical or deceptively bland
Biologic behavior	Noninvasive	Can invade veins and metastasize

Carcinoma genetics: Separate susceptibility from diagnosis

- Li–Fraumeni syndrome predisposes to carcinoma through germline TP53 alterations.
- Beckwith–Wiedemann syndrome links adrenal tumor susceptibility to IGF2 imprinting biology.
- Somatic TP53 changes and elevated IGF2 expression may also occur in sporadic tumors.
- Genetic associations are not substitutes for integrated morphologic and clinical assessment.

Cortical lineage versus adrenal metastasis

- Metastases to the adrenal are more frequent than primary adrenocortical carcinomas.
- Cortical tumors may express steroidogenic factor 1 (SF-1) and inhibin- α .
- Immunohistochemical results should be interpreted within a differential, not in isolation.
- Clinical imaging and evidence of an extra-adrenal primary are crucial for classification.

Adrenal incidentaloma is a clinical discovery pattern

- Imaging performed for unrelated complaints can reveal a silent adrenal mass.
- Many incidental lesions are small, nonsecretory cortical adenomas.
- A subset produces cortisol without overt classic Cushing features: Mild autonomous cortisol secretion.
- Risk appraisal combines hormone evaluation with radiologic and pathologic assessment.

Adrenal myelolipoma and cysts: Relevant mimics

- Myelolipoma is a benign admixture of mature adipose and hematopoietic tissue.
- Some myelolipomas become large but are frequently incidentally discovered.
- Cysts and cystic tumor degeneration can present as apparently nonfunctional masses.
- Not all adrenal masses are steroid-producing cortical neoplasms.

An integrated adrenal pathology checklist

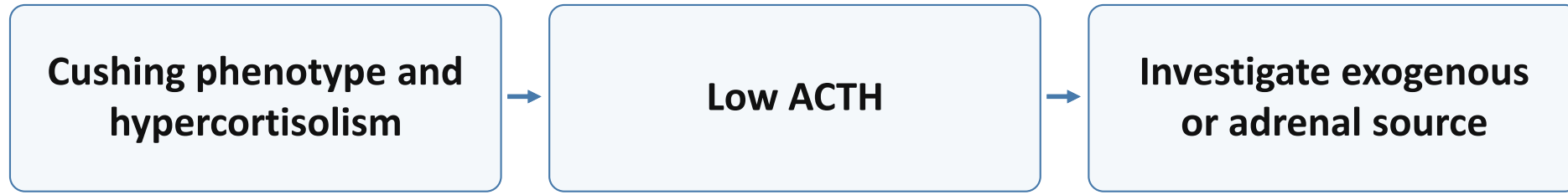
Question	Interpretation	Next intellectual step
What is produced?	Cortisol, aldosterone, androgen, or none	Document biochemical functionality
What drives production?	ACTH, renin–angiotensin, or autonomous lesion	Interpret endocrine feedback
What is the tissue response?	Atrophy, diffuse/nodular hyperplasia, mass	Describe native morphology
Is it malignant?	Invasion and integrated tumor features	Evaluate carcinoma versus metastasis

Case integration: Hypertension and low renin



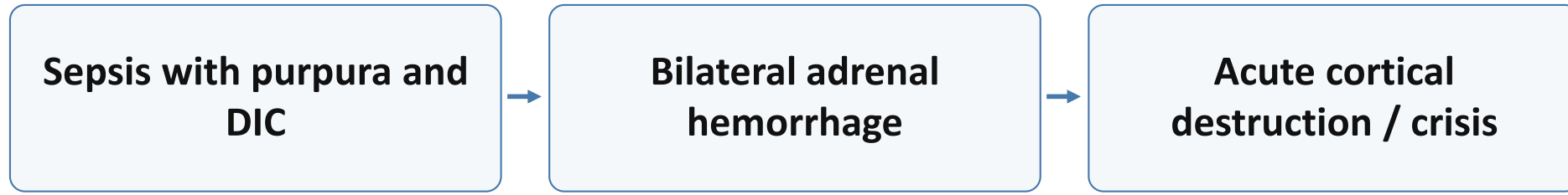
- An adenoma and bilateral glomerulosa hyperplasia are different pathologic subtypes.
- Normal potassium does not exclude the syndrome.
- Biochemical subtype localization must precede causal attribution to an imaging nodule.

Case integration: Cortisol excess with low ACTH



- A cortisol-producing adrenal neoplasm may suppress the contralateral cortex.
- By contrast, exogenous glucocorticoids may produce bilateral ACTH-dependent atrophy.
- A mass is not automatically the cause without biochemical correlation.

Case integration: Shock and adrenal hemorrhage



- Waterhouse–Friderichsen syndrome is an urgent clinical-pathologic diagnosis.
- Massive hemorrhage can obliterate the usual adrenal architecture.
- Its mechanism is not the chronic autoimmune destruction of Addison disease.

Integrated principles of adrenal cortical pathology

- Zone-specific steroid production predicts the functional syndrome.
- Pituitary ACTH explains both hyperplasia during stimulation and atrophy during suppression.
- Primary versus secondary failure differs in ACTH, aldosterone, and pigmentation patterns.
- Adrenal neoplasm classification requires morphology plus hormonal and clinical evidence.

Primary reference and scope

- Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th edition (2026).
- Chapter 24, The Endocrine System: Adrenal glands and adrenal cortex, printed pp. 1012–1023.
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