

Primary Hyperaldosteronism

Adrenal pathology • mechanisms, morphology, and clinical correlation

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Learning objectives

- Distinguish autonomous aldosterone secretion from renin-driven excess.
- Recognize the major causes and characteristic adrenal morphology.
- Link mineralocorticoid action to hypertension and variable hypokalemia.
- Explain diagnostic sequence and cause-directed management.

Adrenal cortex: Functional zones

Capsule

Zona glomerulosa — aldosterone

Zona fasciculata — cortisol

Zona reticularis — sex steroids

Medulla — catecholamines

Zona glomerulosa is the normal aldosterone source

- The narrow subcapsular zona glomerulosa generates mineralocorticoids.
- The wider zona fasciculata produces mainly glucocorticoids.
- Zona reticularis contributes to adrenal sex steroid production.
- Different cortical disorders reflect excessive secretion of different hormone classes.

Hyperaldosteronism: The unifying definition

- Chronic excess secretion of the mineralocorticoid aldosterone.
- The category includes primary adrenal and secondary extra-adrenal causes.
- Interpretation requires considering aldosterone together with the renin response.

Primary versus secondary excess

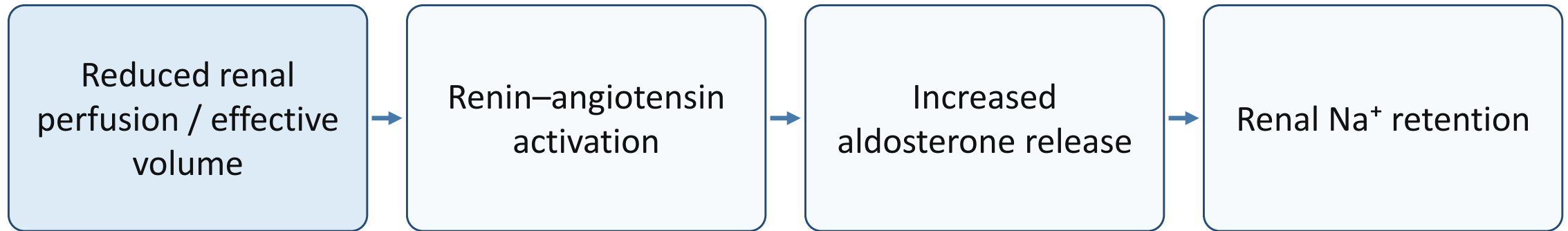
Primary (adrenal autonomous)

- Aldosterone production escapes normal regulation.
- Renin–angiotensin activity is suppressed.
- Hypertension is a typical downstream result.

Secondary (renin driven)

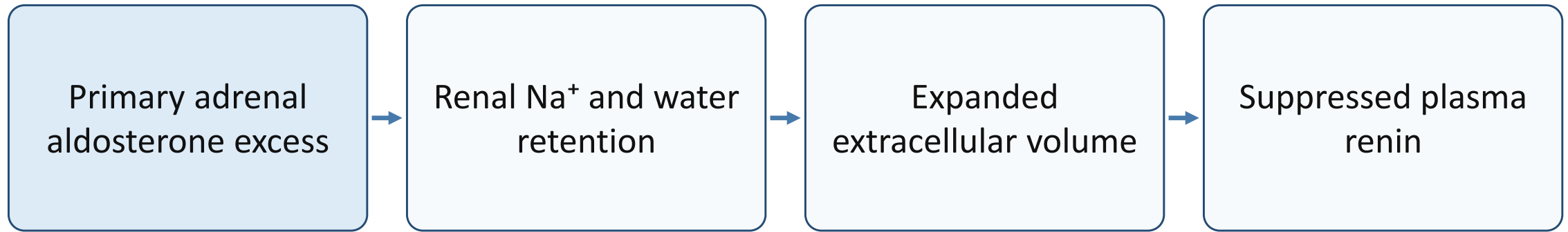
- Aldosterone is secreted after RAAS stimulation.
- Plasma renin is increased.
- Renal perfusion or effective volume often provides the trigger.

Normal renin-driven aldosterone response



Physiologic compensation is initiated outside the adrenal gland.

Autonomous secretion breaks feedback control



An elevated aldosterone-to-renin relationship follows from excess hormone despite renin suppression.

Three major causes of primary disease

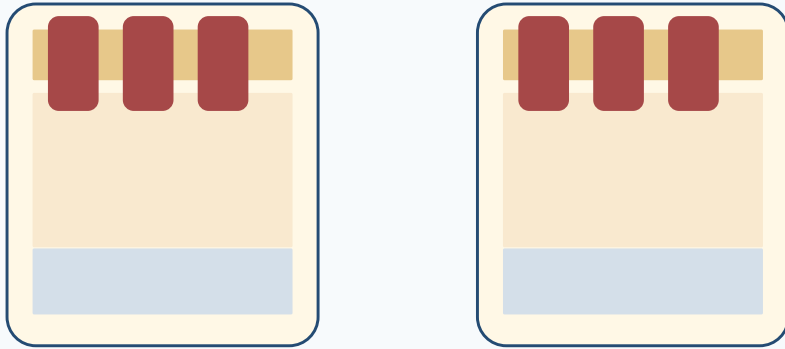
Cause	Approximate textbook share	Key lesion
Bilateral idiopathic hyperaldosteronism	~60%	Bilateral glomerulosa hyperplasia
Aldosterone-producing adenoma	~35%	Solitary functioning cortical neoplasm
Familial hyperaldosteronism	<5%	Inherited regulatory abnormalities
Adrenocortical carcinoma	Rare	Malignant cortical neoplasm

Bilateral idiopathic disease predominates

- About 60% of primary hyperaldosteronism in the cited textbook.
- Usually sporadic rather than familial.
- Involves hyperplasia of aldosterone-secreting zona glomerulosa cells.
- Both adrenal glands are affected.

Bilateral disease is not a single adenoma

Bilateral zona glomerulosa hyperplasia



Diffuse + focal glomerulosa
expansion

Simplified schematic — not actual gross or microscopic pathology

Clinical tendency in bilateral disease

- Affected individuals tend to be older than patients with adenomas.
- Hypertension may be less severe than in primary adrenal neoplasms.
- These are group-level tendencies, not reliable individual diagnostic criteria.

Hyperplasia: Diffuse and focal expansion

- Proliferating cells resemble those of normal zona glomerulosa.
- Both diffuse and focal cortical hyperplasia may be present.
- The degree of gland enlargement can be subtle.

Wedge-shaped cortical hyperplasia

Subcapsular zona glomerulosa



Wedge-shaped expansion
toward cortex center



May create only subtle
enlargement

Pathology must exclude a discrete aldosterone-producing adenoma before labeling hyperplasia.

Aldosterone-producing adenoma: Conn syndrome

- A solitary aldosterone-secreting adrenocortical adenoma causes Conn syndrome.
- It accounts for approximately 35% of primary cases in the source.
- Adrenocortical carcinoma is an uncommon alternative neoplastic cause.

Adenoma: Who typically presents?

- Most often observed in mid-adult life.
- The morphology discussion places most patients in their 30s and 40s.
- The source describes a female-to-male ratio of approximately 2:1.
- Demographic clues support context but do not establish a diagnosis.

Gross appearance of aldosterone-producing adenoma

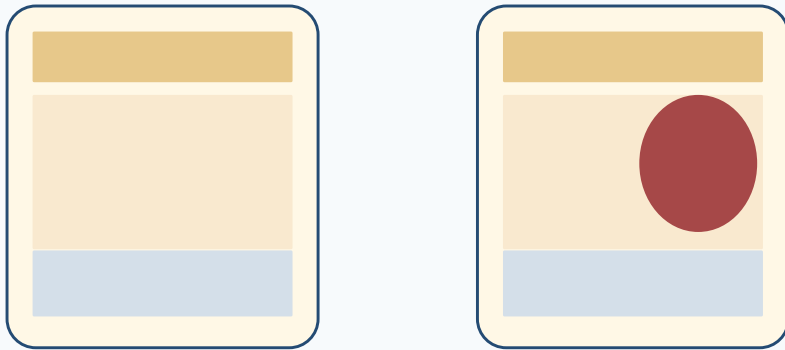
- Usually solitary and well circumscribed.
- Typically small, with a diameter under 2 cm.
- Bright yellow cut surface corresponds to lipid-rich cortical cells.

Small lesions can be hard to localize

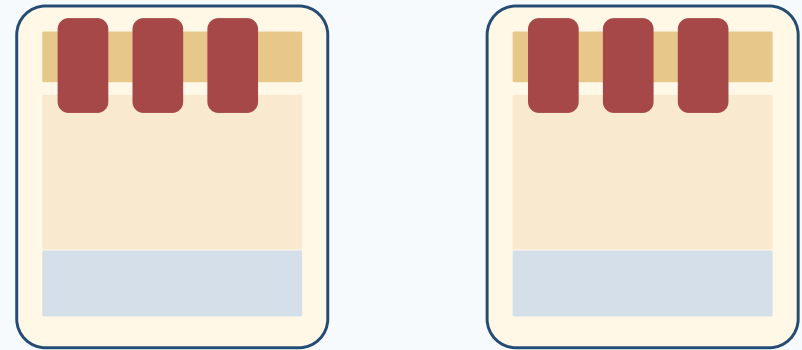
- Adenomas may be buried within adrenal parenchyma.
- The gland may not be visibly enlarged.
- Small dimensions and intraglandular position complicate imaging localization.
- The source reports a left-sided predominance.

Focal adenoma versus bilateral cortical change

Aldosterone-producing adenoma



Bilateral zona glomerulosa hyperplasia



Simplified schematic — not actual gross or microscopic pathology

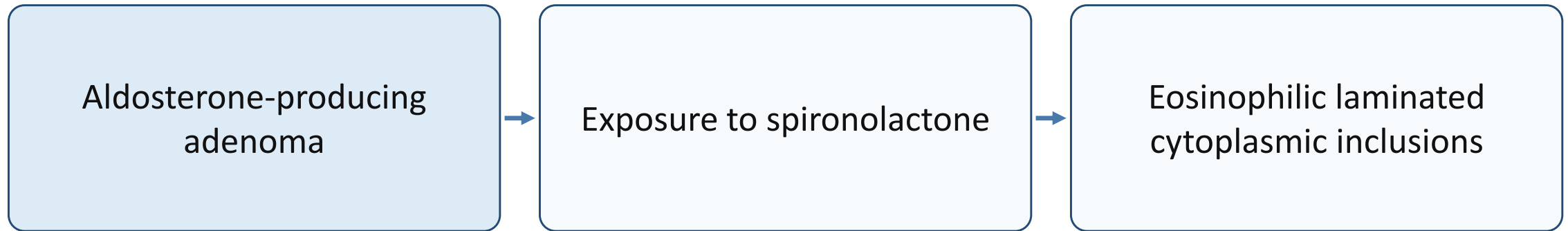
Adenoma cells are lipid rich

- Microscopy typically shows uniform cortical cells with abundant lipid.
- Their morphology resembles zona fasciculata cells.
- This is noteworthy because normal aldosterone arises from zona glomerulosa.

Nuclear atypia in a benign adenoma

- Most neoplastic cells are uniform in size and shape.
- Modest nuclear or cellular pleomorphism can occur.
- These limited cytologic changes should not be interpreted as carcinoma on their own.

Spironolactone bodies: Treatment-related finding

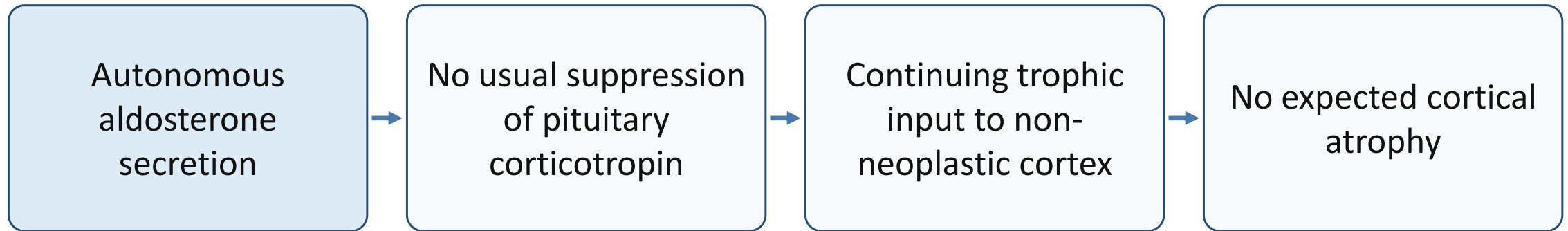


Spironolactone bodies are described in treated adenomas; They are not an untreated-lesion requirement.

Adjacent cortex is generally preserved

- Aldosterone-producing adenomas usually do not suppress corticotropin secretion.
- Therefore, the nearby adrenal cortex is not characteristically atrophic.
- The opposite adrenal cortex also is not typically atrophic.

Functional reason for preserved adrenal cortex



Contrast conceptually with ACTH suppression in cortisol-producing cortical lesions.

Morphology-based differential

Feature	Adenoma / Conn syndrome	Bilateral idiopathic hyperplasia
Distribution	Solitary focal lesion	Bilateral diffuse/focal change
Gross pattern	Small, circumscribed, yellow nodule	Often only subtly enlarged
Dominant cells	Lipid-rich cells resembling fasciculata	Cells resembling glomerulosa
Surrounding cortex	No typical atrophy	Hyperplastic glomerulosa

Neoplasia is not always benign

- Most neoplastic primary hyperaldosteronism reflects an adenoma.
- Rare cases arise from adrenocortical carcinoma.
- Neoplasia and bilateral idiopathic hyperplasia are distinct etiologic categories.

Genetic findings in aldosterone-producing adenomas

- Somatic mutations define a molecular subset of aldosterone-producing adenomas.
- KCNJ5 mutations in up to 50% of adenomas.
- The mechanism links ion-channel dysfunction to autonomous hormone synthesis.

KCNJ5 encodes the GIRK4 channel

- KCNJ5 codes for a potassium ion-channel protein known as GIRK4.
- The channel is expressed in cells of the zona glomerulosa.
- Mutations can alter channel ion selectivity.

Normal channel versus mutated channel

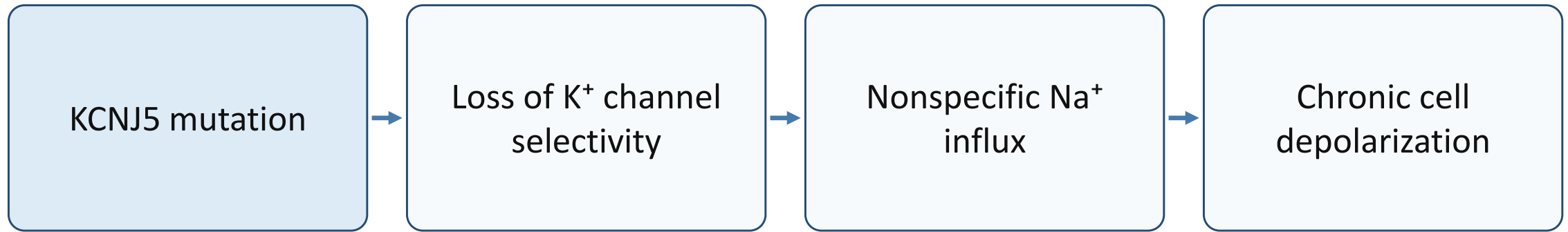
Normal GIRK4/KCNJ5 channel

- Potassium-selective channel
- Maintains normal ionic selectivity

Mutated GIRK4/KCNJ5

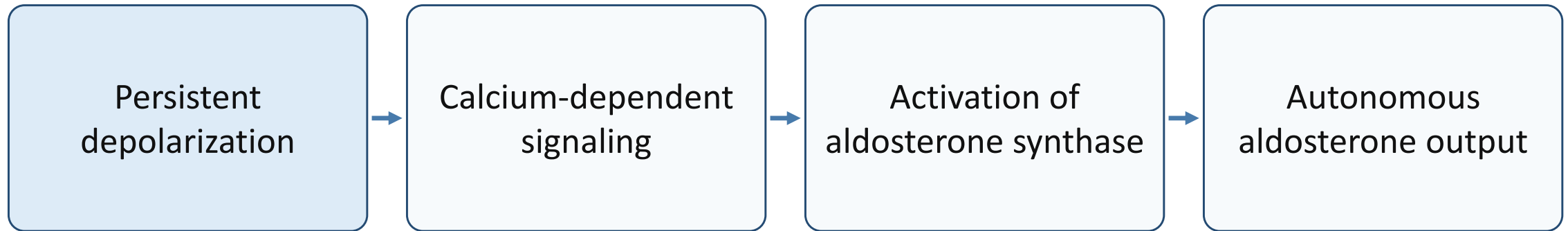
- Loss of K⁺ selectivity
- Na⁺ influx → persistent depolarization

Mutation permits abnormal sodium influx



Abnormal cation flux provides a cell-autonomous stimulus in the aldosterone-producing neoplasm.

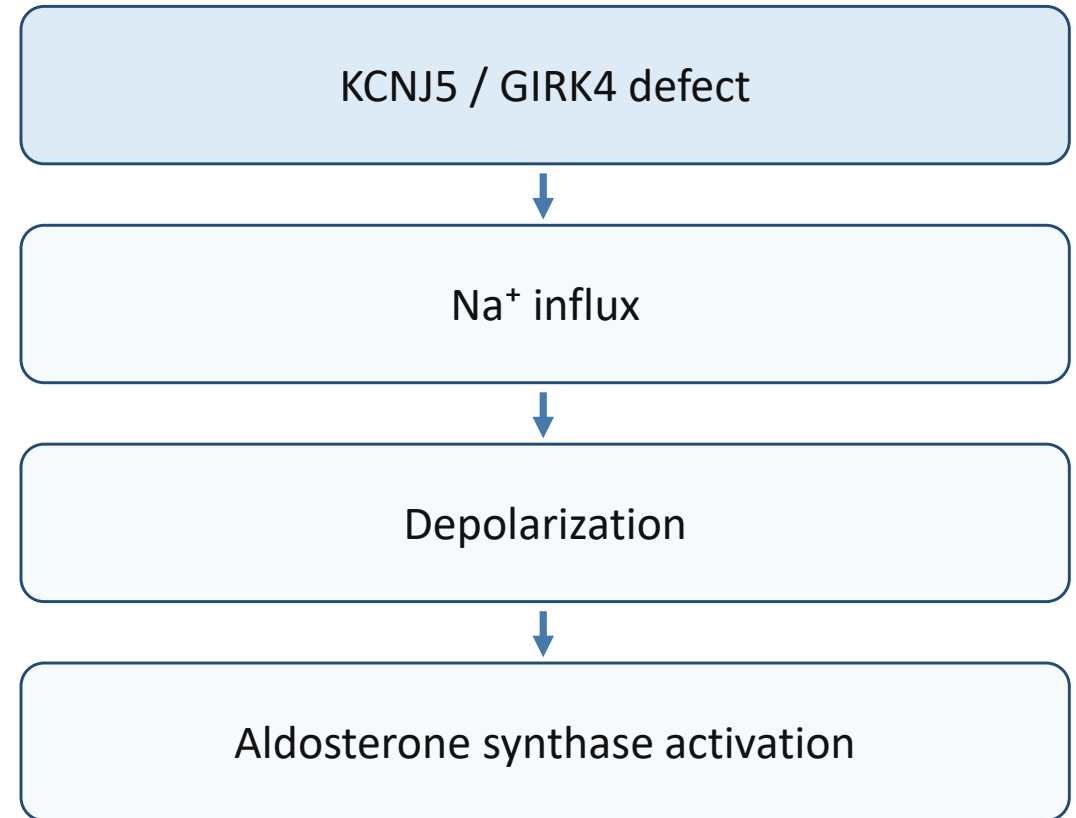
Depolarization activates aldosterone synthesis



The described calcium-linked mechanism explains secretion despite suppressed systemic renin.

Integrating the adenoma molecular pathway

- Mutant GIRK4 is not simply an overactive normal potassium channel.
- The important defect is loss of potassium selectivity.
- Ion influx and membrane voltage changes drive synthesis.



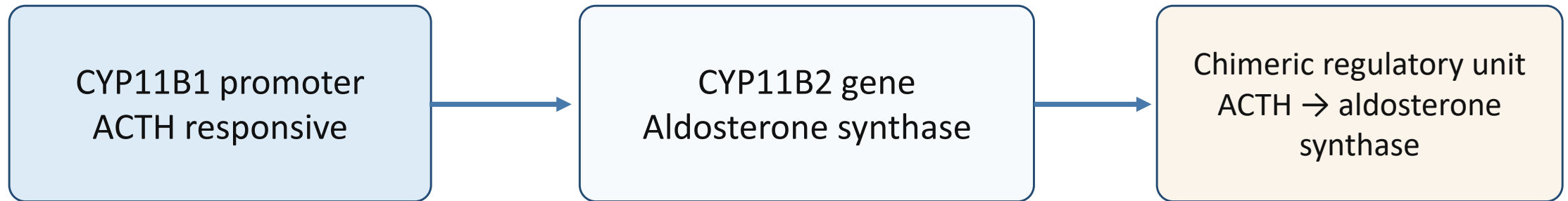
Familial primary hyperaldosteronism is uncommon

- Familial forms account for fewer than 5% of cases.
- Four distinct subtypes, FH-I through FH-IV, are described.
- FH-I is the most common familial subtype in this textbook.

FH-I is glucocorticoid-remediable aldosteronism

- FH-I reflects altered regulatory control of aldosterone synthesis.
- Corticotropin becomes a major stimulus for aldosterone synthase expression.
- The molecular defect differs from the somatic KCNJ5 mechanism.

FH-I: A chimeric regulatory arrangement



FH-I: Chromosome 8 rearrangement

Schematic gene regulatory arrangement; Not a genomic breakpoint map

CYP11B1 and CYP11B2 have different roles

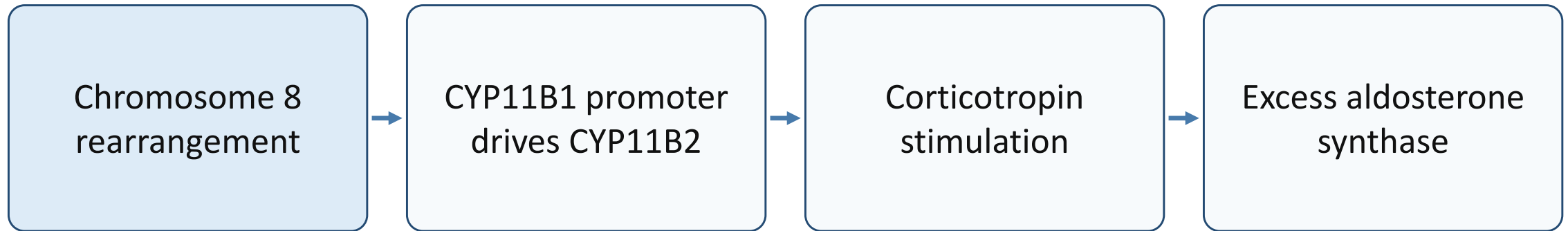
CYP11B1 promoter

- Provides a corticotropin-responsive regulatory element.
- Abnormally controls CYP11B2 after the rearrangement.

CYP11B2 coding region

- Encodes aldosterone synthase.
- Catalyzes the final step of aldosterone biosynthesis.

FH-I mechanism links ACTH to aldosterone



The gene rearrangement changes regulation, not the identity of aldosterone as the secreted steroid.

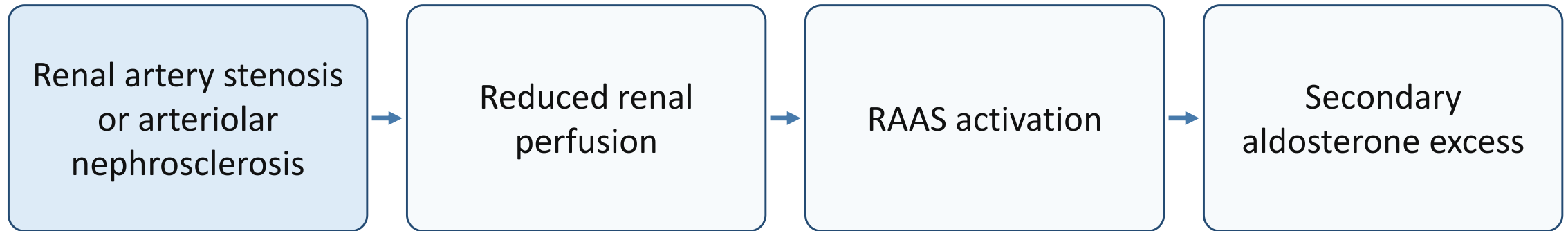
Sporadic adenoma versus FH-I

Dimension	Aldosterone-producing adenoma	Familial hyperaldosteronism I
Principal lesion	Solitary functional neoplasm	Hereditary regulatory disorder
Molecular model highlighted	Somatic KCNJ5 channel mutation in a subset	CYP11B1/CYP11B2 chimeric gene
Proximal signal	Abnormal cation flux / depolarization	Corticotropin-responsive promoter

Secondary hyperaldosteronism: Renin rises

- Adrenal secretion occurs after physiologic renin–angiotensin activation.
- Plasma renin is elevated rather than suppressed.
- The initiating problem is outside the adrenal gland.

Reduced renal perfusion can stimulate RAAS

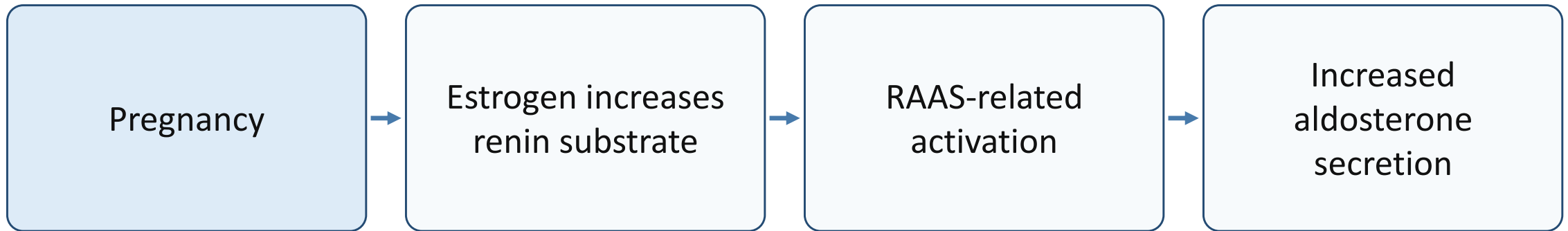


These are examples of secondary rather than autonomous adrenal hypersecretion.

Edema states can increase aldosterone

- Congestive heart failure is one textbook example.
- Cirrhosis and nephrotic syndrome are additional examples.
- The relevant signal is arterial underfilling or hypovolemia associated with edema.

Pregnancy is another secondary setting



A pregnancy-associated aldosterone rise does not itself imply primary adrenal autonomy.

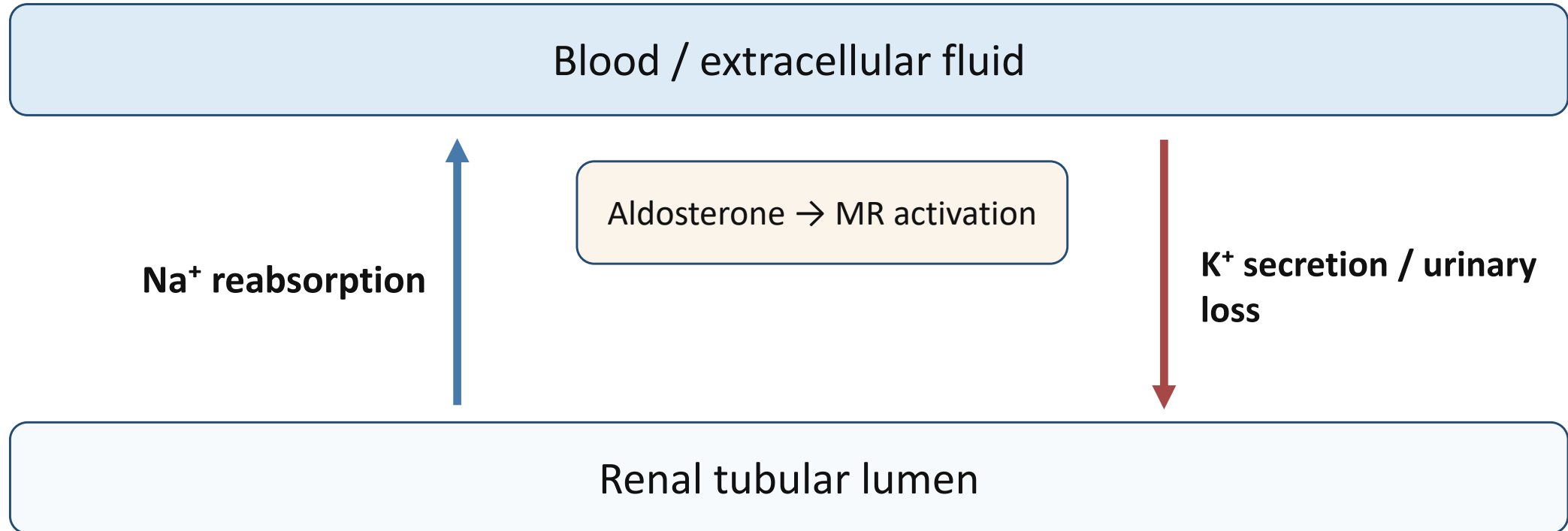
Primary versus secondary: Laboratory logic

Finding	Primary hyperaldosteronism	Secondary hyperaldosteronism
Aldosterone	Increased	Increased
Plasma renin	Suppressed / low	Increased
Dominant mechanism	Autonomous adrenal secretion	Physiologic RAAS drive
Illustrative source	Adenoma or bilateral hyperplasia	Renal hypoperfusion or effective volume loss

Renal mineralocorticoid receptor mediates effects

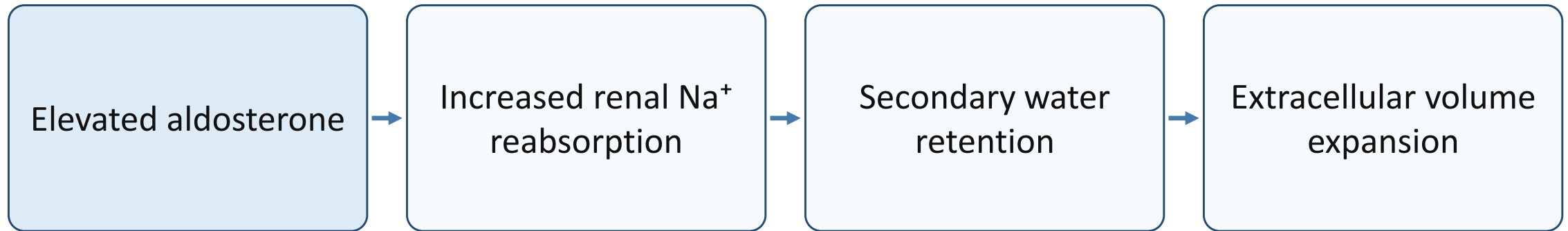
- Excess aldosterone acts on renal mineralocorticoid receptors.
- The principal relevant effects involve sodium reabsorption and potassium excretion.
- Extracellular water follows retained sodium.

Direction of renal ion transport



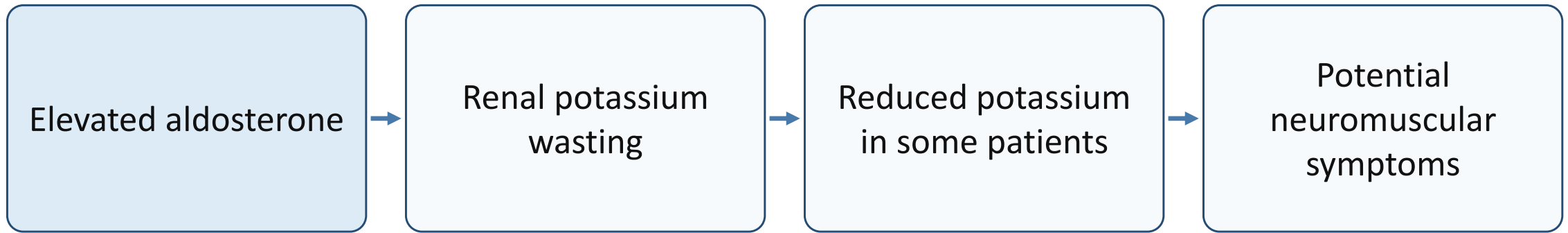
Schematic transport directions — not a renal micrograph

Sodium retention expands extracellular volume



The textbook links volume expansion to higher cardiac output and hypertension.

Potassium is lost into urine



Hypokalemia is variable: Its absence must not be used to exclude primary hyperaldosteronism.

One hormone, two renal consequences

Sodium / water axis

- Increased sodium reclamation.
- Water retention expands extracellular volume.
- Promotes raised blood pressure.

Potassium axis

- Increased potassium secretion into urine.
- May cause hypokalemia.
- Weakness and paresthesias are possible.

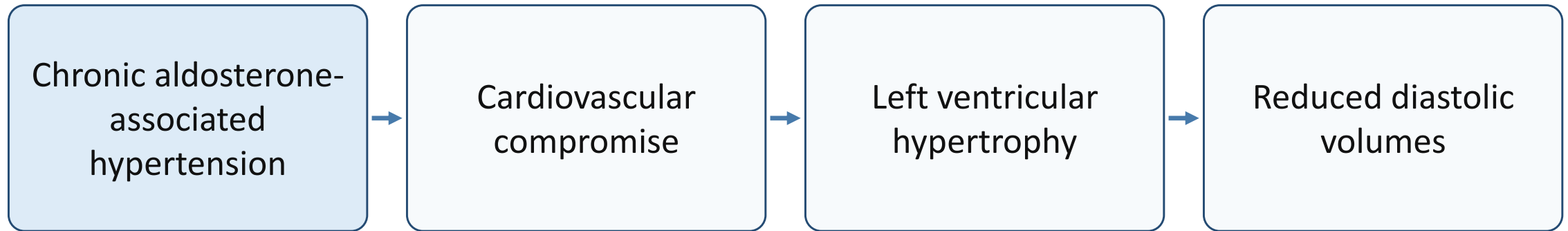
Primary hyperaldosteronism and hypertension

- Identified by Robbins as the most common cause of secondary hypertension.
- Elevated blood pressure is a consequence of renal volume expansion.
- The condition is potentially identifiable among patients with difficult hypertension.

Resistant hypertension enriches prevalence

- Prevalence increases with the severity of hypertension.
- Some cited studies report 20% or more among treatment-resistant hypertension.
- This is a context-specific textbook estimate, not a universal prevalence.

Long-term pressure burden affects the heart



The syndrome has consequences beyond a single abnormal blood pressure measurement.

Clinical complications extend beyond the heart

- Increased adverse cardiovascular events.
- Stroke is among the associated adverse outcomes.
- Myocardial infarction is another noted outcome.
- Early recognition provides an opportunity to target the hormonal cause.

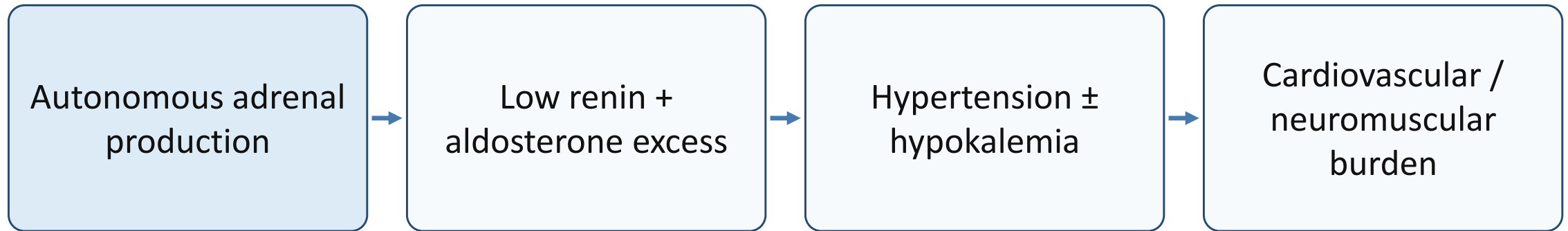
Hypokalemia is not obligatory

- Some patients have primary hyperaldosteronism without low serum potassium.
- Renin suppression and inappropriate aldosterone are more fundamental to the syndrome.
- Using hypokalemia as a mandatory entry criterion would miss cases.

When potassium falls: Clinical effects

- Neuromuscular weakness can occur.
- Paresthesias are a characteristic reported manifestation.
- Visual disturbances are also listed in the source.
- Symptoms are not exclusive to this disorder.

Clinical pattern: Connect the abnormalities



A single laboratory measurement should be interpreted in its physiological and clinical setting.

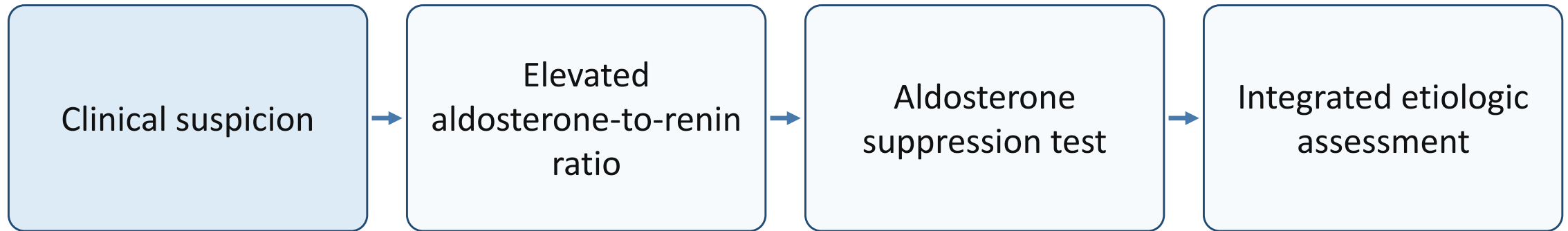
Aldosterone-to-renin ratio: Screening principle

- Compare the plasma aldosterone concentration with plasma renin activity.
- The ratio is elevated in typical primary hyperaldosteronism.
- The relationship is informative because renin is suppressed despite excessive aldosterone.

Why a positive ratio is not definitive

- Other disorders and circumstances can alter aldosterone and renin measurements.
- A positive screening ratio requires clinical interpretation.
- Confirmatory suppression testing after positive screening.

Aldosterone suppression as confirmation

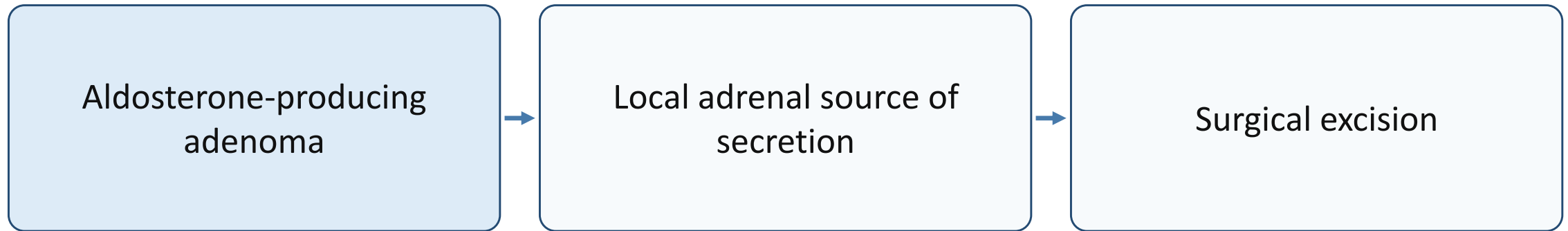


Shown here is the textbook conceptual sequence; Assay-specific cutoffs and protocols are not provided.

Etiology matters after biochemical recognition

- Bilateral glomerulosa hyperplasia and a functional adenoma have different treatments.
- A small, buried adenoma may not produce obvious adrenal enlargement.
- Morphology and hormone physiology should be interpreted together.

Management of aldosterone-producing adenoma



The therapeutic approach targets a discrete functional cortical lesion.

Management of bilateral hyperplasia

- Surgical removal of a single focal adenoma does not address bilateral hyperplasia.
- The source favors medical treatment with mineralocorticoid receptor antagonists.
- Spironolactone and eplerenone are named examples.
- Potassium-sparing diuretics have also been used.

Treat the underlying cause in secondary disease

- Secondary hyperaldosteronism reflects heightened RAAS activity.
- Management therefore targets the driving disorder rather than an autonomous adrenal lesion.
- Examples include renal perfusion deficits and edematous systemic states.

Treatment follows etiologic classification

Etiology	Pathologic mechanism	Textbook treatment principle
Solitary aldosterone-producing adenoma	Autonomous focal cortical secretion	Surgical excision
Bilateral idiopathic hyperplasia	Bilateral aldosterone-secreting hyperplasia	Mineralocorticoid receptor blockade
Secondary hyperaldosteronism	Extra-adrenal RAAS activation	Treat underlying disorder

Case 1: Hypertension without hypokalemia

A patient has persistent hypertension and a non-low potassium concentration. Plasma aldosterone is inappropriately elevated while plasma renin is suppressed. Does normal potassium exclude primary hyperaldosteronism?

Explain the likely pathological mechanism.

Case 1: Interpretation

- No: The source explicitly states that hypokalemia is not mandatory.
- The renin-suppressed hormonal pattern supports autonomous aldosterone excess.
- Aldosterone-to-renin screening and appropriate subsequent evaluation are indicated conceptually.

Case 2: Small yellow adrenal nodule

A solitary, small, well-circumscribed yellow cortical lesion is found in a patient with autonomous aldosterone excess. Microscopy shows uniform lipid-rich cells resembling fasciculata. Which primary etiologic subtype best fits?

Explain the likely pathological mechanism.

Case 2: Interpretation

- Aldosterone-producing adenoma (Conn syndrome) fits the combined morphology and hormonal setting.
- Gross yellow color reflects abundant cortical cell lipid.
- Nearby cortical atrophy is not a typical expectation for this adenoma.

Case 3: Aldosterone and renin both rise

A patient with decreased renal perfusion has increased plasma renin activity and increased aldosterone secretion. Is the abnormality consistent with primary adrenal autonomy?

Explain the likely pathological mechanism.

Case 3: Interpretation

- The pattern is more consistent with secondary hyperaldosteronism.
- Renin–angiotensin stimulation is the proposed physiological driver.
- The initiating cause is extra-adrenal and management targets that cause.

Integrated diagnostic distinctions

Question	Typical primary answer	Typical secondary answer
What initiates aldosterone excess?	Adrenal autonomous secretion	Extra-adrenal renin stimulus
What happens to renin?	Suppressed	Increased
What lesion might be present?	Adenoma / bilateral hyperplasia	No necessary autonomous adrenal lesion
How is treatment directed?	Adrenal subtype	Underlying RAAS trigger

Core messages to retain

- Primary hyperaldosteronism couples aldosterone excess with suppressed renin.
- Bilateral hyperplasia is more frequent than a solitary adenoma.
- Adenomas and bilateral hyperplasia differ in morphology and treatment.
- KCNJ5 and CYP11B1/CYP11B2 illustrate distinct molecular routes.
- Hypertension is central; Hypokalemia is optional.

Reference and scope

Robbins, Cotran & Kumar: Pathologic Basis of Disease

11th edition (2026) · Chapter 24, The Endocrine System
“Primary Hyperaldosteronism,” pp. 1015–1017

Lecture content follows the supplied textbook extraction; diagnostic protocols and current guideline-specific cutoffs are not reproduced.