

Primary Chronic Adrenocortical Insufficiency (Addison Disease)

Etiology • mechanisms • morphology • clinicopathologic interpretation

Pathology teaching lecture

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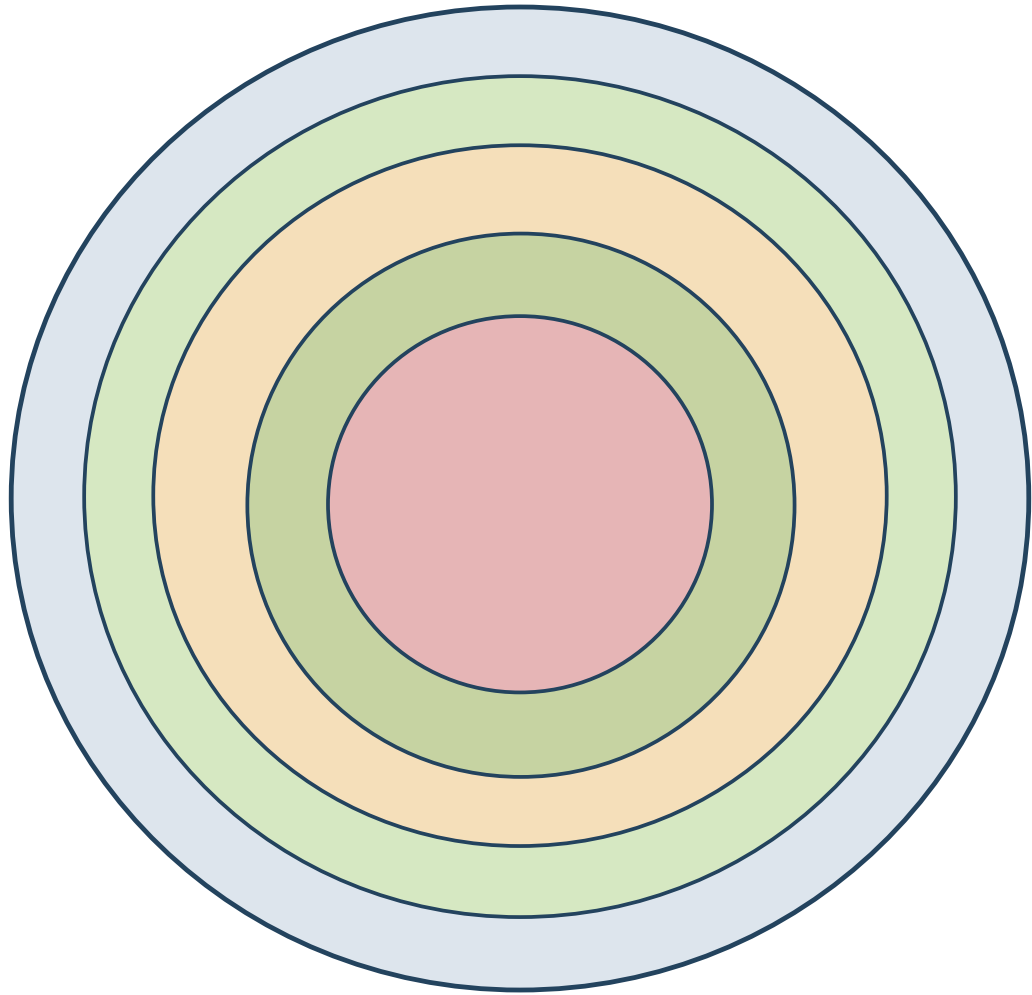
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Learning objectives

- Distinguish primary chronic adrenal failure from acute and secondary hypoadrenalism.
- Explain autoimmune, infectious, metastatic, and genetic causes.
- Recognize characteristic gland morphology and connect hormone loss with clinical findings.
- Interpret adrenal crisis and the diagnostic value of corticotropin responses.

Adrenal anatomy: Cortex and medulla



Capsule

Fibrous covering

Zona glomerulosa

Mineralocorticoids:
Aldosterone

Zona fasciculata

Glucocorticoids:
Cortisol

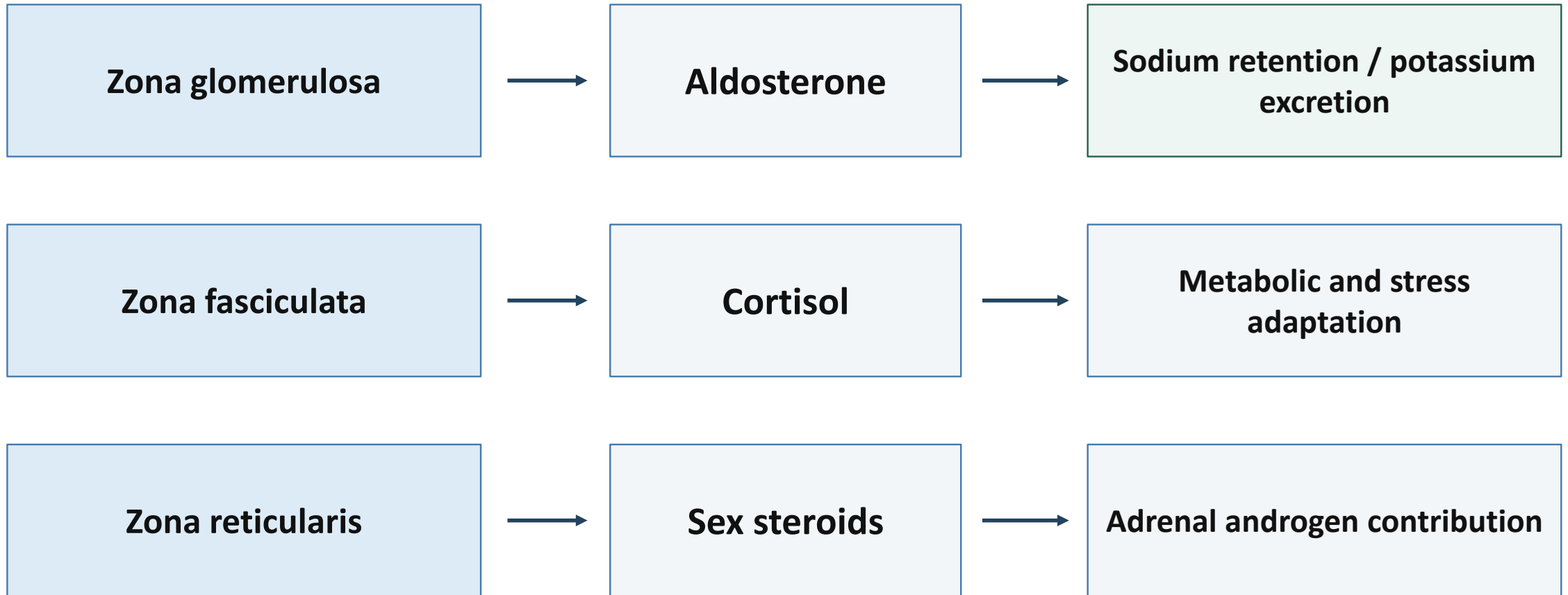
Zona reticularis

Adrenal sex steroids

Medulla

Catecholamines;
Distinct from cortex

The adrenal cortex synthesizes distinct hormone classes



Conceptual relationship, not a steroid-synthesis pathway

Addison disease: Definition and basic lesion

- Uncommon disorder caused by progressive destruction of the adrenal cortex.
- Loss of steroidogenic cells compromises glucocorticoid and mineralocorticoid output.
- Its manifestations appear insidiously as the functioning cortical reserve is depleted.

The three patterns of adrenal insufficiency

Primary acute



Abrupt adrenal failure; Crisis

Primary chronic (Addison disease)



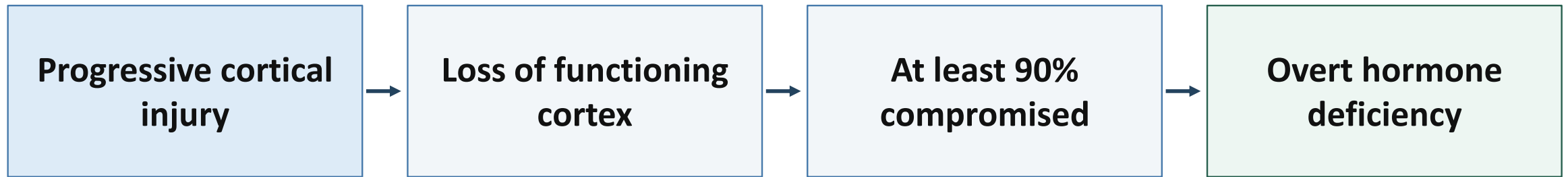
Progressive cortical destruction

Secondary



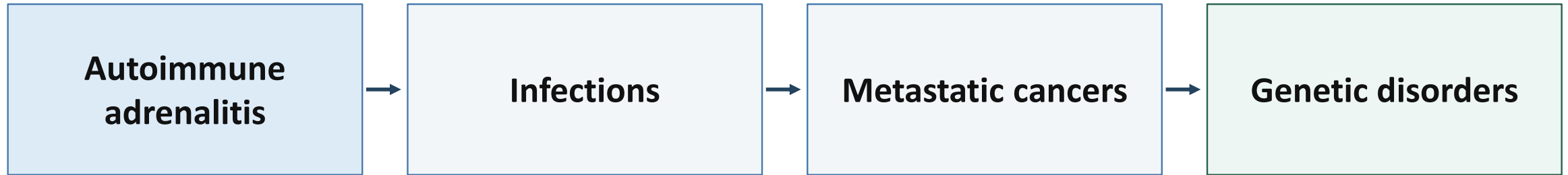
Insufficient pituitary corticotropin

Large cortical reserve delays clinical recognition



- Symptoms generally emerge only after extensive cortical compromise.
- The pace and morphology of destruction depend on etiology.

Etiologic groups: Several routes to cortical destruction



- Additional infiltrative and hemorrhagic processes are described in the broader insufficiency differential.
- All four principal groups can impair adrenal function, but their morphologic signatures differ.

Cause distribution depends on clinical setting

- Autoimmune adrenalitis accounts for 80%–90% of primary insufficiency in high-income countries.
- Tuberculosis remains important in low-resource settings and with active disease elsewhere.
- The textbook attributes over 90% of cases to autoimmune adrenalitis, tuberculosis, AIDS, or metastatic cancer.

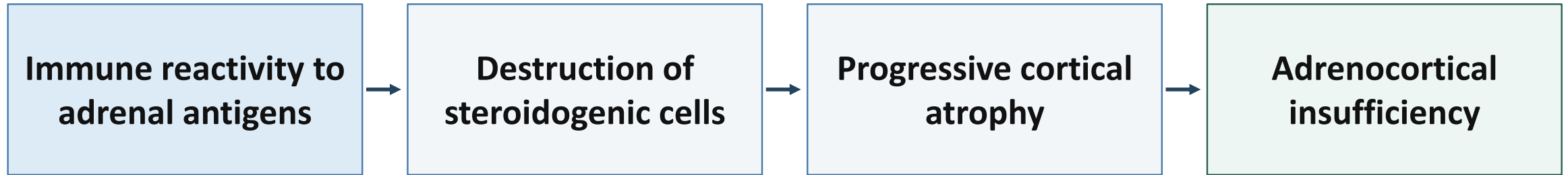
Interpret denominators

80%–90%:

Primary cases in high-income countries

Not a global estimate

Autoimmune adrenalitis: Pathogenesis



- Autoimmune injury may occur alone or in autoimmune polyendocrinopathy.
- Autoimmune inflammation is not necessarily prominent in every histologic section.

Autoantibodies implicate steroidogenic targets

- Autoantibodies to 21-hydroxylase are detected in many patients with autoimmune adrenalitis.
- The textbook also identifies reactivity against 17-hydroxylase.
- These antibodies support the autoimmune nature of the disease; They do not themselves demonstrate functional reserve.

Autoimmune adrenalitis: Isolated versus syndromic

Isolated adrenalitis

- Reported as 40% of autoimmune cases.
- Clinical process is centered on adrenal insufficiency.
- Evaluate the endocrine context rather than assuming other organs are affected.

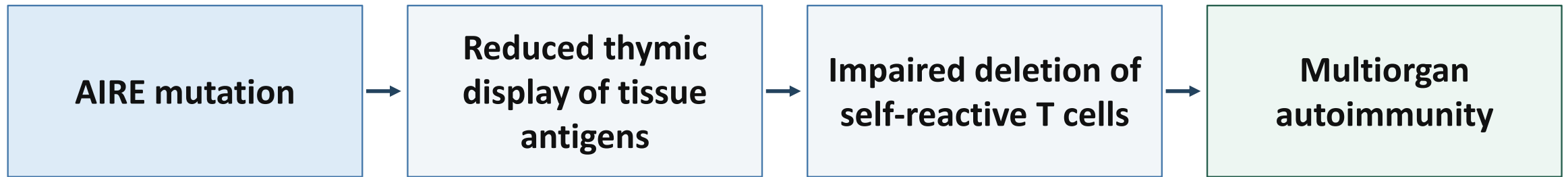
Polyendocrinopathy

- Reported as 60% of autoimmune cases.
- Adrenal disease coexists with other autoimmune disorders.
- Patterns are grouped into APS-1, APS-2, and APS-4.

APS-1: Autoimmune disease across multiple organs

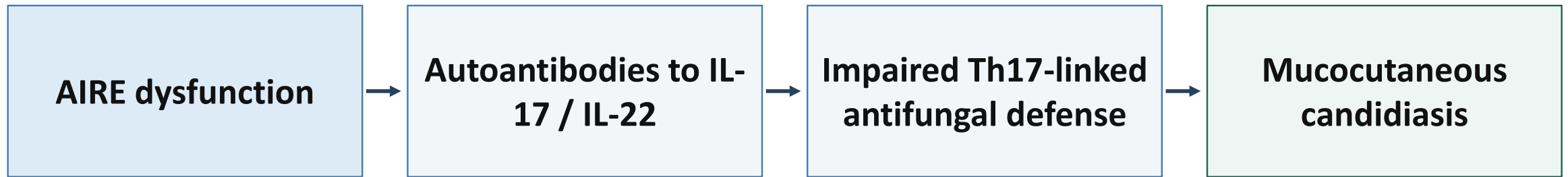
- Characterized by organ-specific autoimmunity affecting the adrenals and other endocrine targets.
- Associated examples: Hypoparathyroidism, idiopathic hypogonadism, and pernicious anemia.
- Mucocutaneous candidiasis and ectodermal abnormalities are distinctive additional features.

APS-1: AIRE and loss of central immune tolerance



- AIRE encodes an autoimmune regulator transcription factor.
- The source locates AIRE on chromosome 21q22.

Why candidiasis accompanies APS-1



- IL-17 and IL-22 are effector cytokines important in protection from fungal infection.
- This phenotype illustrates that autoimmunity may compromise host defense.

APS-2: Adrenalitis with thyroid and pancreatic autoimmunity

- Usually presents in the fourth decade of life in the source description.
- Combines adrenal insufficiency with autoimmune thyroiditis, with or without type 1 diabetes.
- Unlike APS-1, mucocutaneous candidiasis, ectodermal dysplasia, and autoimmune hypoparathyroidism do not develop.

APS-1 versus APS-2: Clinically discriminating pattern

Feature	APS-1	APS-2
Underlying basis	AIRE mutation	Pathogenesis not understood in source
Typical cluster	Adrenal and other autoimmune targets	Adrenalitis + thyroiditis ± type 1 diabetes
Candidiasis	Characteristic	Absent as APS feature
Ectodermal change	Can occur	Not typical
Frequency	Less prevalent	More prevalent

APS-4: Autoimmune overlap outside APS-1 and APS-2

- Rare syndrome characterized by adrenalitis with other autoimmune manifestations.
- Examples include gastritis, vitiligo, alopecia, and pernicious anemia.
- By definition here, associated thyroiditis and type 1 diabetes are absent.

Polyendocrinopathy syndromes: Rapid classification

Syndrome	Characteristic association	Important separator
APS-1	AIRE-related organ-specific autoimmunity	Candidiasis / ectodermal changes
APS-2	Addison disease + autoimmune thyroiditis $\pm$ T1D	No APS-1 ectodermal / candidal pattern
APS-4	Adrenalitis + other autoimmunity	Neither thyroiditis nor T1D

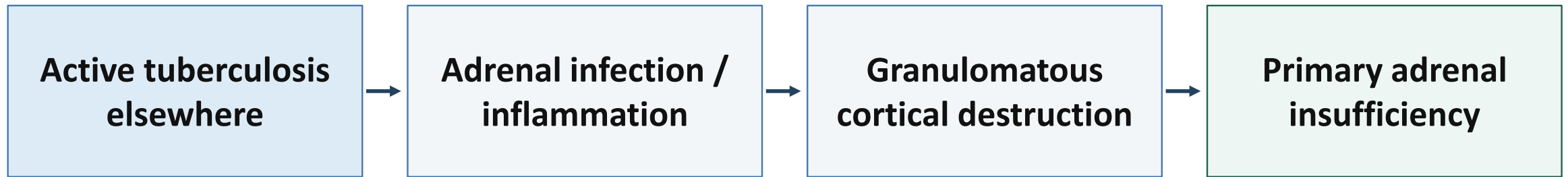
Cancer immunotherapy can induce adrenalitis

- Immune checkpoint blockade may cause primary adrenal insufficiency through autoimmune adrenalitis.
- It can also cause secondary insufficiency through hypophysitis.
- This distinction matters because primary and secondary states differ in aldosterone function and corticotropin levels.

Tuberculous adrenalitis remains an important etiology

- Tuberculosis was historically a major cause of Addison disease.
- Its contribution declined with antimycobacterial therapy but remains relevant in certain settings.
- Granulomatous inflammation may destroy enough cortex to cause chronic deficiency.

Tuberculous Addison disease often has an extraglandular clue



- When present, adrenal tuberculosis is usually associated with infection in lungs or genitourinary tract.
- Interpret adrenal findings in conjunction with the broader infectious context.

Disseminated fungi can cause adrenal insufficiency

- *Histoplasma capsulatum* can involve the adrenal glands in disseminated fungal disease.
- *Coccidioides immitis* is another source-listed cause.
- Fungal adrenalitis may efface normal architecture through granulomatous inflammation.

AIDS broadens the adrenal disease differential

- Patients with AIDS may develop adrenal insufficiency through opportunistic infections.
- Examples named: Cytomegalovirus and Mycobacterium avium-intracellulare.
- Kaposi sarcoma is a noninfectious AIDS-associated adrenal lesion implicated in insufficiency.

Infectious causes: Associate organism with context

Category	Representative causes	Pathologic implication
Tuberculosis	Mycobacterium tuberculosis	Granulomatous effacement
Systemic fungi	Histoplasma; Coccidioides	Granulomatous adrenalitis
AIDS-related infection	CMV; M. Avium-intracellulare	Infectious cortical injury

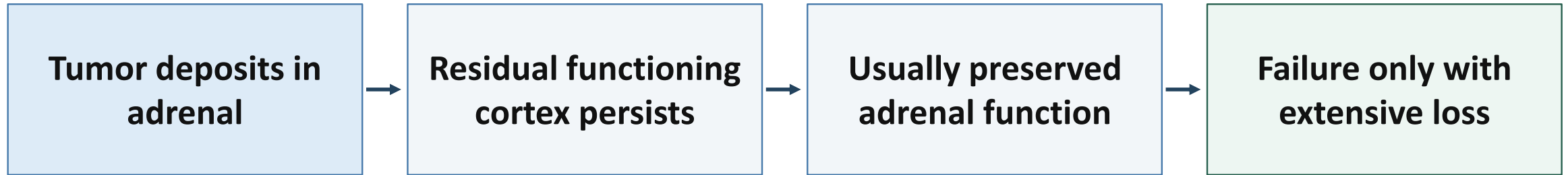
Adrenal metastases: Frequent deposits, unusual failure

- The adrenal glands are relatively common metastatic sites in disseminated cancer.
- Adrenal hormone function is preserved in most patients despite metastatic deposits.
- Clinical Addison disease develops only when enough cortex is replaced or destroyed.

Primary tumors commonly implicated in adrenal metastases

- Lung and breast carcinomas account for most adrenal metastases discussion.
- Gastrointestinal carcinomas and malignant melanoma may also involve the adrenals.
- Hematopoietic neoplasms are additional potential adrenal infiltrators.

Metastasis does not automatically mean Addison disease



- Distinguish radiologic adrenal involvement from physiologic adrenocortical insufficiency.
- Metastatic lesions often enlarge the gland and obscure its native architecture.

Genetic categories of primary adrenal insufficiency

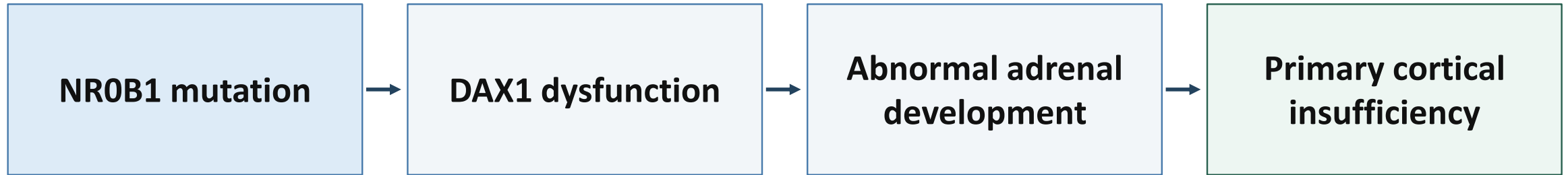
Congenital adrenal hypoplasia

- Rare X-linked disorder.
- Mutations of NR0B1.
- DAX1 transcription factor is implicated in adrenal development.

Adrenoleukodystrophy

- Caused by ABCD1 mutations.
- Listed among genetic causes of primary insufficiency.
- Neurologic details are outside this textbook unit.

NR0B1-related adrenal hypoplasia: Developmental mechanism



- Congenital adrenal hypoplasia differs mechanistically from acquired destruction by inflammation.

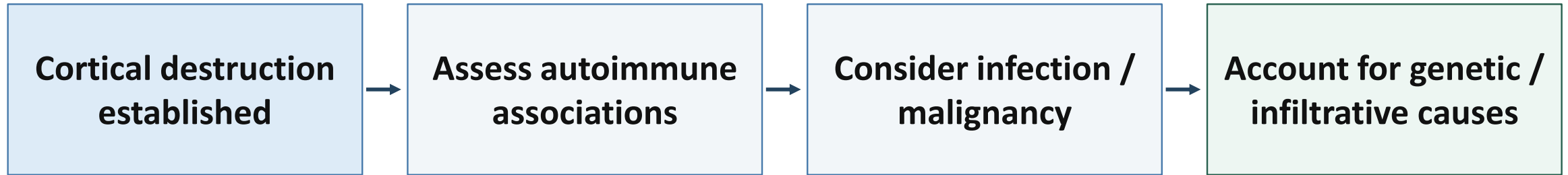
ABCD1-associated adrenoleukodystrophy

- Adrenoleukodystrophy is identified as a genetic cause of adrenal insufficiency.
- It is associated with mutations in the ABCD1 gene.
- The disorder further in the nervous-system chapter; The present unit establishes its adrenal association.

Less common destructive and infiltrative causes

- Lymphoma and amyloidosis are among additional processes involving the adrenal cortex.
- Sarcoidosis and hemochromatosis can also compromise adrenal tissue.
- Adrenal hemorrhage is included in the broader etiology, especially for acute presentations.

Etiologic reasoning starts with the type of gland lesion



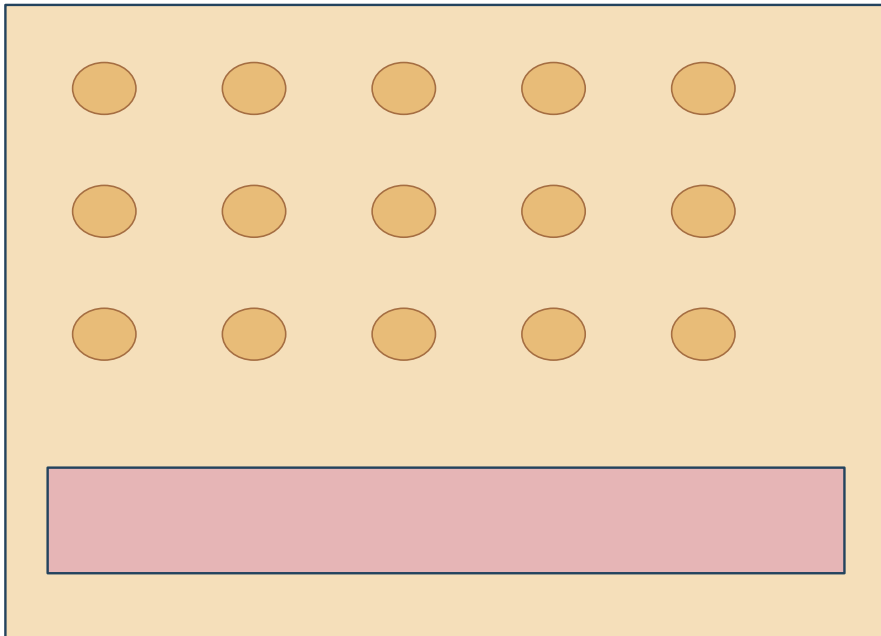
- The sequence is an educational checklist, not a validated diagnostic guideline.
- Clinical setting and morphology direct the differential.

Autoimmune adrenalitis: Gross appearance

- Glands are irregularly shrunken.
- Atrophy may make them difficult to identify in suprarenal adipose tissue.
- The gross pattern reflects extensive, long-standing loss of cortical parenchyma.

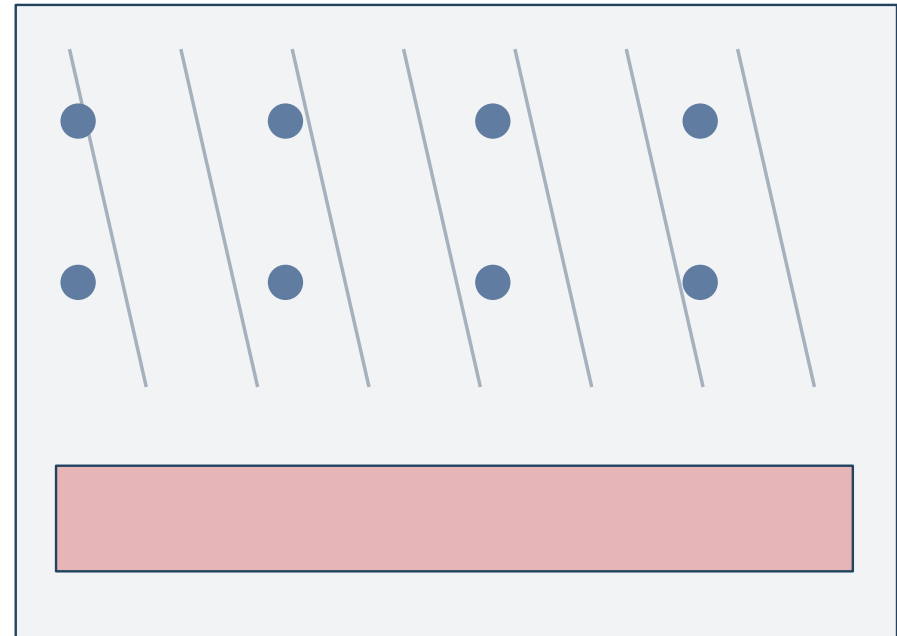
Autoimmune adrenalitis: Architectural loss

Normal adrenal cortex



Intact cortex above medulla

Autoimmune adrenalitis



Collapsed, fibrotic cortex; Medulla spared

Autoimmune adrenalitis: Microscopic pattern

- Only scattered residual cortical cells remain.
- Cortical architecture is replaced by a collapsed connective-tissue network.
- Variable lymphoid infiltrates may be present.

Medulla sparing helps localize autoimmune injury

- Lymphocytes may extend from the cortex into adjacent medulla.
- Despite this, the medulla is otherwise generally preserved.
- Loss of cortical steroid secretion is the defining functional consequence.

Different lesions produce different adrenal anatomy

Infectious granulomatous adrenalitis

- Tuberculous or fungal inflammation.
- Granulomatous reaction obscures normal gland architecture.
- Appearance reflects infection-driven inflammatory injury.

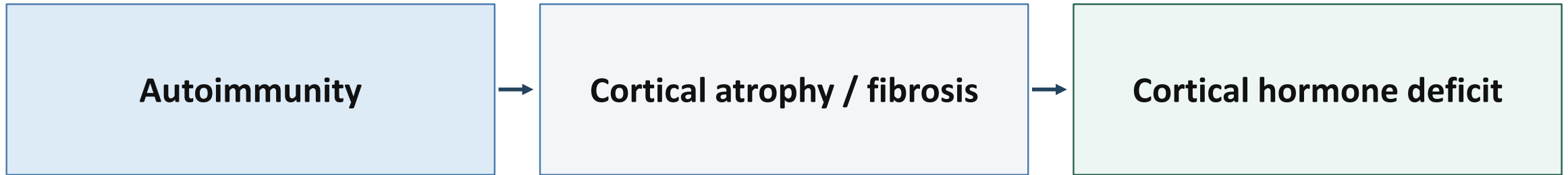
Metastatic carcinoma

- Adrenals may be enlarged.
- Tumor infiltrates and replaces native architecture.
- Appearance reflects space-occupying neoplastic infiltration.

Morphology by etiology: Gross and microscopic distinctions

Cause	Gross pattern	Microscopic explanation
Autoimmune	Irregularly shrunken glands	Atrophic cortex; Connective tissue; Variable lymphocytes
Tuberculous / fungal	Architecture effaced	Granulomatous inflammatory destruction
Metastatic carcinoma	Often enlarged glands	Infiltrating tumor obscures cortex

Morphology is a clue to the mechanism



- Infection and neoplasia produce other distinct morphologies.
- Recognize the lesion before inferring its likely cause.

Addison disease usually evolves insidiously

- Long asymptomatic period reflects substantial adrenal functional reserve.
- Symptoms emerge once glucocorticoid and mineralocorticoid concentrations decline substantially.
- Early manifestations may be mistaken for nonspecific constitutional illness.

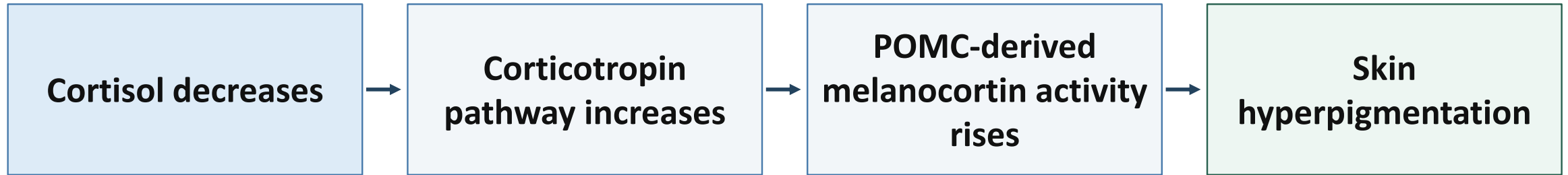
Weakness and easy fatigability are common early complaints

- Progressive weakness is a characteristic first manifestation.
- Easy fatigability can initially be dismissed as nonspecific.
- The clinical significance increases when accompanied by pigmentation or signs of salt loss.

Gastrointestinal symptoms broaden the presentation

- Anorexia and weight loss are frequent components of the syndrome.
- Nausea and vomiting are also common.
- Diarrhea can occur and may contribute to symptomatic volume depletion.

Hyperpigmentation reflects pituitary feedback response



- POMC is the shared precursor of corticotropin and melanocyte-stimulating hormone.
- This association differentiates primary from pituitary or hypothalamic insufficiency.

Hyperpigmentation: Characteristic distribution

- Pigmentation may be conspicuous in sun-exposed areas.
- Pressure points such as neck, elbows, knees, and knuckles are emphasized.
- Its absence does not by itself exclude primary disease, but its presence is a valuable discriminator.

High versus low corticotropin: Why pigmentation differs

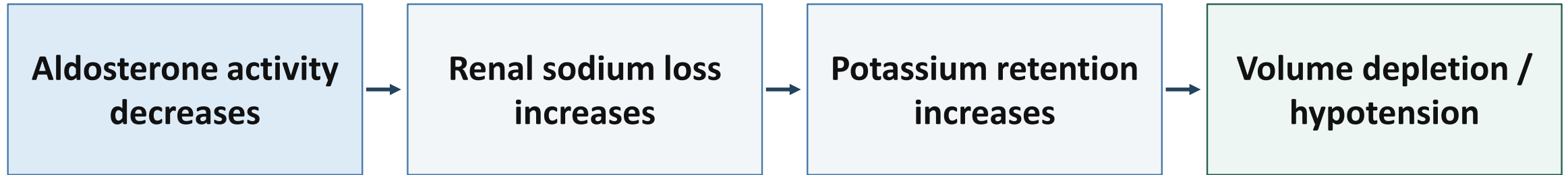
Primary adrenal disease

- Adrenal cortex cannot provide adequate cortisol.
- Pituitary corticotropin increases.
- POMC-related pigmentation can occur.

Pituitary / hypothalamic disease

- Corticotropin output is deficient.
- The stimulus for the pigmentation pathway is lacking.
- Characteristic Addison hyperpigmentation is absent.

Mineralocorticoid deficiency produces salt loss



- The predicted serum pattern includes hyponatremia and hyperkalemia.
- Renin–angiotensin–aldosterone function is typically preserved in secondary disease.

Biochemical pattern: Trace abnormalities to hormone loss

Finding	Hormonal basis	Clinical implication
Hyponatremia	Reduced mineralocorticoid effect → sodium loss	Contributes to extracellular fluid depletion
Hyperkalemia	Reduced renal potassium excretion	Suggests primary over secondary failure
Hypotension	Salt / water depletion	Hemodynamic vulnerability
Occasional hypoglycemia	Deficient cortisol → reduced gluconeogenesis	Limited metabolic stress response

Volume depletion and hypotension are central consequences

- Aldosterone normally supports sodium retention and potassium excretion.
- With mineralocorticoid failure, sodium and water losses reduce circulating volume.
- Hypotension may worsen rapidly if a stressor precipitates crisis.

Cortisol deficiency impairs glucose homeostasis

- Cortisol participates in gluconeogenesis.
- Deficiency diminishes this metabolic support.
- Hypoglycemia may occasionally occur, particularly when metabolic demands rise.

Match hormone deficiency to clinical phenotype

Hormone / pathway	Characteristic change	Observed phenotype
Cortisol	Reduced gluconeogenic / stress support	Weakness; Occasional hypoglycemia
Aldosterone	Sodium loss; Potassium retention	Hypotension; Hyponatremia; Hyperkalemia
Elevated POMC / ACTH	Increased melanocortin activity	Cutaneous hyperpigmentation

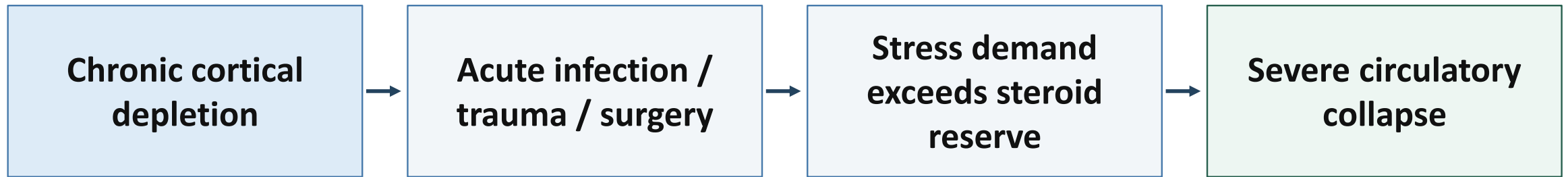
Stress can reveal a critically limited adrenal reserve

- Infection may precipitate acute decompensation.
- Trauma and surgical procedures are other textbook examples.
- The already damaged cortex cannot augment steroid secretion sufficiently for increased demand.

Adrenal crisis: Recognize the high-risk phenotype

- Intractable vomiting and abdominal pain may dominate the presentation.
- Marked hypotension and circulatory collapse can follow.
- Altered consciousness or coma may occur.
- Prompt corticosteroid therapy is lifesaving; Untreated collapse can be rapidly fatal.

Chronic Addison disease can deteriorate into acute crisis



- A potentially compensated chronic state becomes a medical emergency.
- The threshold for crisis is driven by limited adrenal reserve and increased demand.

Acute adrenal crisis is not synonymous with Addison disease

Addison-associated crisis

- Chronic, progressive loss of adrenal cortex.
- An acute stressor precipitates decompensation.
- Pre-existing pigmentation and salt-loss findings may be clues.

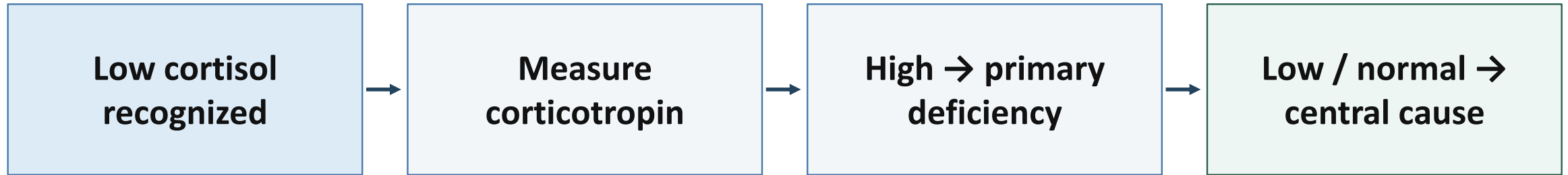
Hemorrhagic acute failure

- Massive bilateral adrenal hemorrhage.
- May accompany sepsis or disseminated intravascular coagulation.
- Waterhouse–Friderichsen is the classic infective syndrome.

Primary versus secondary insufficiency: Core distinctions

Feature	Primary (Addison)	Secondary (pituitary)
Anatomic defect	Adrenal cortex	Deficient corticotropin
Cortisol	Low	Low
Aldosterone	Usually deficient	Preserved / near-normal
Corticotropin	Elevated	Low or inappropriately normal
Skin pigment	May increase	No Addison pattern
Hyperkalemia	Possible / characteristic	Generally absent

Corticotropin provides a mechanistic diagnostic distinction



- A normal corticotropin concentration can be inappropriate when cortisol is deficient.
- Use hormone results in clinical context, not as isolated signs.

Cosyntropin tests adrenal cortical responsiveness

- Synthetic corticotropin (1–24), or cosyntropin, stimulates the adrenal cortex.
- In established primary failure, cortical destruction blunts cortisol response.
- In long-standing secondary failure, chronically understimulated glands can also respond poorly.

Cosyntropin: Interpret time course, not just response

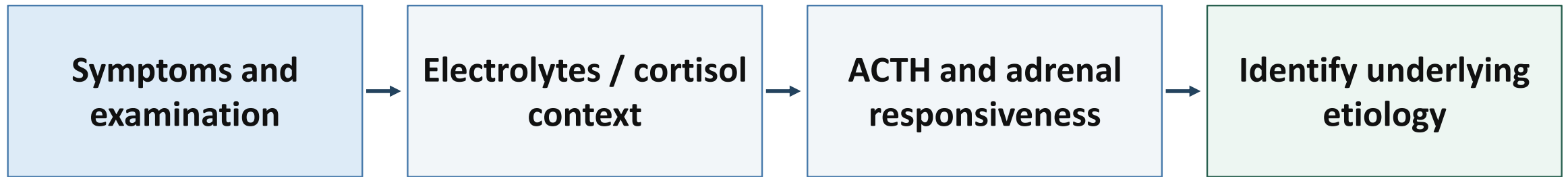
Established primary failure

- Cortex is destroyed.
- Response to exogenous corticotropin is reduced.
- Baseline endogenous corticotropin is elevated.

Secondary insufficiency

- Long-standing disease can also blunt response.
- Recent-onset secondary disease may retain a normal cortisol response.
- Baseline corticotropin is low or inappropriately normal.

Clinicopathologic synthesis of suspected Addison disease



- Primary failure is suggested by hyperpigmentation plus aldosterone-deficiency findings.
- This is a teaching synthesis, not a formal diagnostic guideline or testing protocol.

Clinical exercise: Autoimmune polyendocrinopathy

Hypothetical teaching case

A patient with progressive weakness, weight loss, skin darkening, and hypotension also has a history of autoimmune thyroiditis.

- Which adrenal compartment is failing?
- Which autoimmune syndrome is suggested?
- What electrolyte pattern would support primary failure?

Case interpretation: Adrenalitis with thyroid autoimmunity

- The combination is compatible with primary adrenal insufficiency in APS-2.
- Aldosterone deficiency makes hyponatremia and hyperkalemia plausible.
- Pigmentation supports an adrenal rather than pituitary source of cortisol deficiency.

Clinical exercise: Granulomatous adrenal destruction

Hypothetical teaching case

A patient being treated for active pulmonary tuberculosis develops fatigue, weight loss, low blood pressure, and diffuse skin darkening.

- Which disease process could link lung and adrenal findings?
- What adrenal histologic reaction is expected?
- Why would primary adrenal function fail?

Case interpretation: Tuberculous Addison disease

- Tuberculous adrenalitis can accompany infection at other sites, particularly lungs.
- Granulomatous inflammation can efface adrenal architecture.
- Functional failure requires sufficiently extensive destruction of cortex.

Clinical exercise: Bilateral adrenal metastases

Hypothetical teaching case

A patient with disseminated lung carcinoma has bilateral adrenal masses on imaging but no clear evidence of hormone deficiency.

- Does metastatic adrenal involvement establish Addison disease?
- What functional threshold must be crossed?
- What morphologic pattern would suggest metastasis?

Case interpretation: Anatomy and function differ

- The adrenal glands are common metastatic sites, but functional reserve is usually retained.
- Addison disease develops only if adequate cortical tissue is lost.
- Neoplastic infiltration typically enlarges glands and obscures native architecture.

Integrated pathogenesis–morphology–clinical matrix

Etiology	Main mechanism	Morphology	Clinical clue
Autoimmune	Steroidogenic cell injury	Small, fibrotic cortex	Other autoimmune diseases
Tuberculous / fungal	Infectious granulomatous damage	Granulomatous effacement	Infection at another site
Metastatic neoplasm	Replacement by tumor	Often enlarged / infiltrated	Disseminated cancer
Genetic	Adrenal development or ABCD1-linked disease	Not specified for all variants	Relevant inherited context

Most discriminating clinicopathologic lessons

- Addison disease reflects extensive destruction of adrenal cortex with combined glucocorticoid and mineralocorticoid deficiency.
- Autoimmune adrenalitis predominates among primary cases in high-income countries; Infections and metastases remain important alternatives.
- Cortical atrophy, granulomatous effacement, and tumor infiltration point toward different causes.
- Hyperpigmentation, salt loss, elevated corticotropin, and impaired stress response localize disease to the adrenal cortex.

Primary reference

- Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th edition (2026).
- The Endocrine System: adrenal glands, adrenocortical insufficiency, and Addison disease.
- Figures and diagnostic tissue photographs from the textbook are not reproduced; conceptual mechanisms and morphology are redrawn as editable schematics.