

# Adrenogenital Syndromes

Adrenal androgen excess • Congenital adrenal hyperplasia •  
Clinicopathologic interpretation

Pathology lecture

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## Learning outcomes

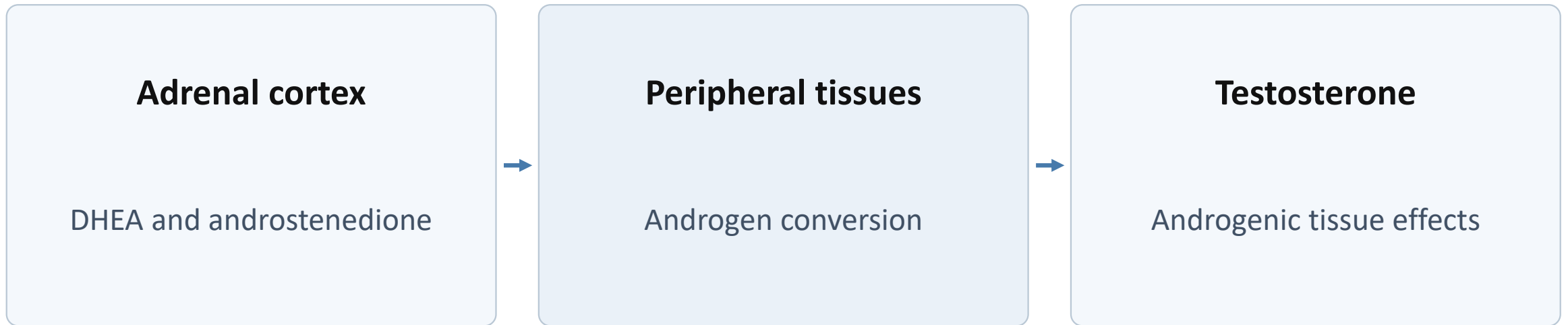
- Distinguish neoplastic adrenal androgen excess from congenital adrenal hyperplasia (CAH).
- Explain 21-hydroxylase deficiency through steroidogenesis and corticotropin feedback.
- Differentiate salt-wasting, simple virilizing, and nonclassic presentations.
- Relate biochemical defects to adrenal morphology, clinical features, and management.

## What is an adrenogenital syndrome?

- Excess adrenal sex steroid activity can produce virilization or related disturbances of sexual differentiation.
- Primary gonadal disorders can create similar phenotypes but represent a different etiologic source.
- Adrenal-derived androgen excess is encountered in tumors or congenital enzyme defects.

# Where do adrenal androgens come from?

Adrenal precursors can become more potent androgens outside the adrenal gland.



Original editable mechanism schematic

# Adrenal and gonadal androgen regulation

| Adrenal androgen production                      | Gonadal androgen production                               |
|--------------------------------------------------|-----------------------------------------------------------|
| Predominantly regulated by corticotropin (ACTH). | Regulated by the gonadal endocrine axis.                  |
| Can increase with persistent ACTH stimulation.   | A distinct source that may mimic adrenal androgen excess. |
| Important in CAH and some adrenal neoplasms.     | Must be distinguished clinically from adrenal disease.    |

# Two etiologic routes to adrenal androgen excess

Both routes can increase androgen effects, but their mechanisms differ.

## Adrenocortical neoplasm

Steroid-secreting tumor

May cause virilization

May co-secrete cortisol

## Congenital adrenal hyperplasia

Inherited enzyme deficiency

ACTH-driven adrenal enlargement

Androgen precursor diversion

## Virilizing adrenal tumors tend to be carcinomas

- Among androgen-producing cortical tumors, virilizing carcinomas are more likely than adenomas.
- The clinical hormonal phenotype does not establish tumor histologic subtype on its own.
- Adrenocortical neoplasm is a separate etiologic category from CAH.

## Neoplastic androgen excess may be a mixed syndrome

- Some virilizing tumors secrete glucocorticoids as well as androgens.
- The coexistence of androgen excess and hypercortisolism creates a mixed hormonal phenotype.
- A single adrenal neoplasm may account for apparently different endocrine syndromes.

## Hormonal behavior does not define tumor morphology

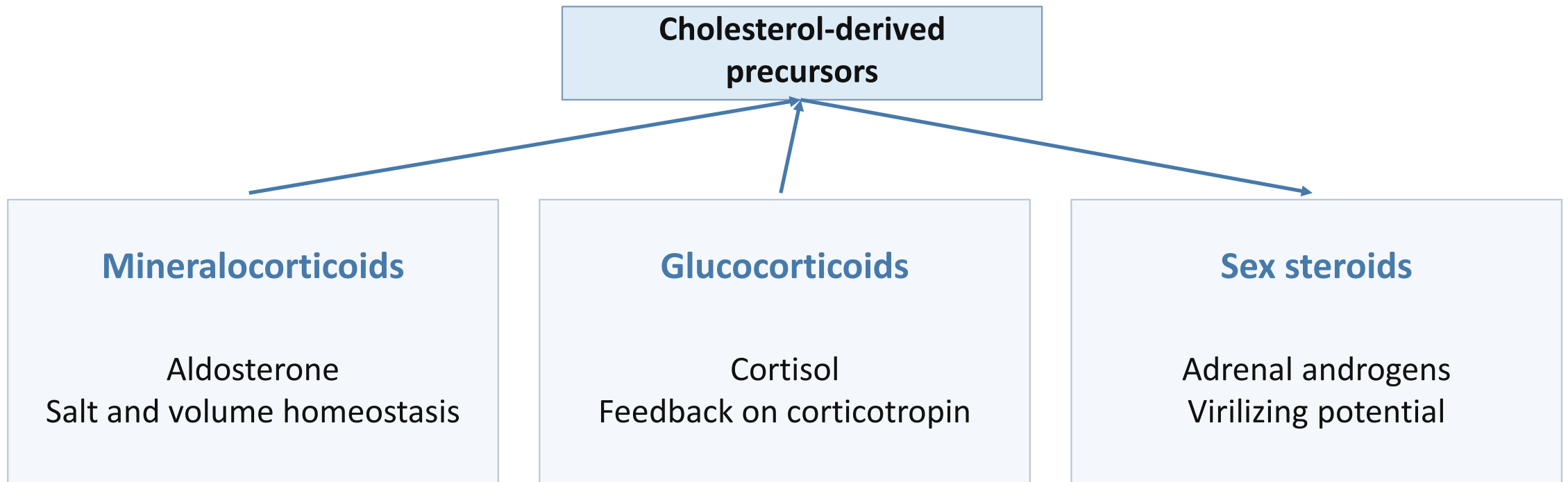
- Virilizing adrenal tumors as morphologically like other cortical neoplasms.
- Virilization is a functional secretion pattern rather than a unique histologic appearance.
- Definitive neoplastic morphology belongs to the broader adrenocortical tumor assessment.

## CAH is a group of inherited steroidogenic disorders

- CAH comprises several autosomal recessive metabolic disorders.
- Each involves deficiency of a steroid-biosynthetic enzyme, usually affecting cortisol production.
- Defects upstream in steroidogenesis change both hormone deficiency and precursor availability.

# Steroidogenesis has three major functional outputs

Simplified steroidogenic destinations



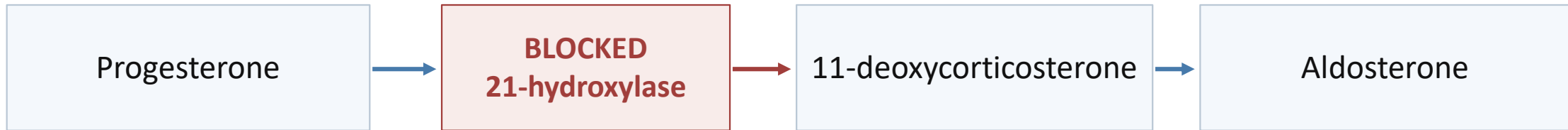
An enzymatic block can reduce one branch and divert precursors toward another.

## A biosynthetic block has two downstream effects

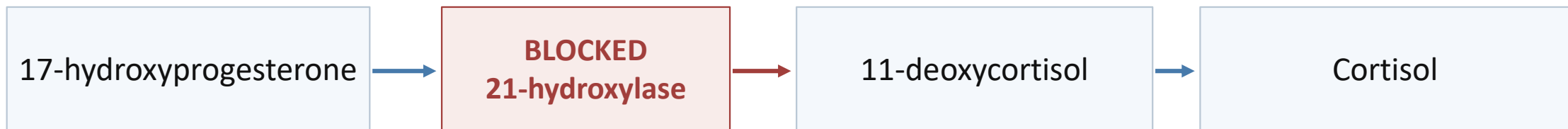
- Reduced synthesis of hormones beyond the affected enzyme step.
- Accumulation of steroid precursors upstream of that step.
- Diversion of intermediates toward pathways that remain functional.

# 21-hydroxylase participates in two hormone pathways

## Mineralocorticoid pathway



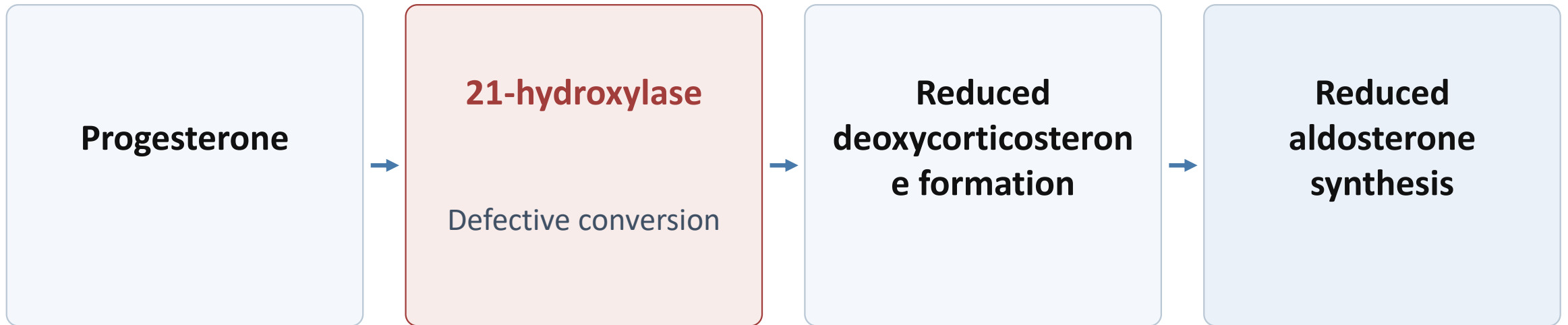
## Glucocorticoid pathway



Original schematic; “blocked” denotes defective conversion in 21-hydroxylase deficiency.

# Block in the mineralocorticoid arm

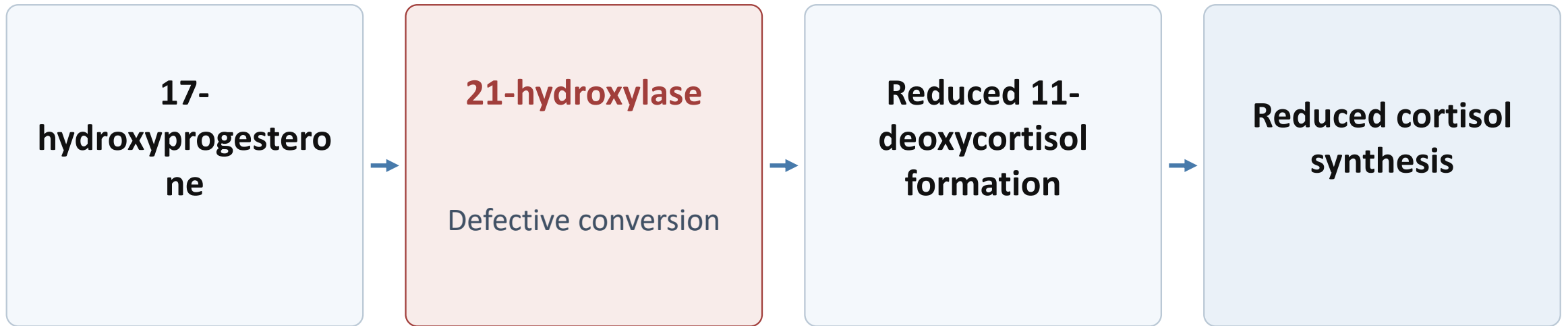
The extent of aldosterone deficiency determines the salt-wasting risk.



Original editable mechanism schematic

# Block in the glucocorticoid arm

Loss of cortisol feedback triggers compensatory ACTH secretion.



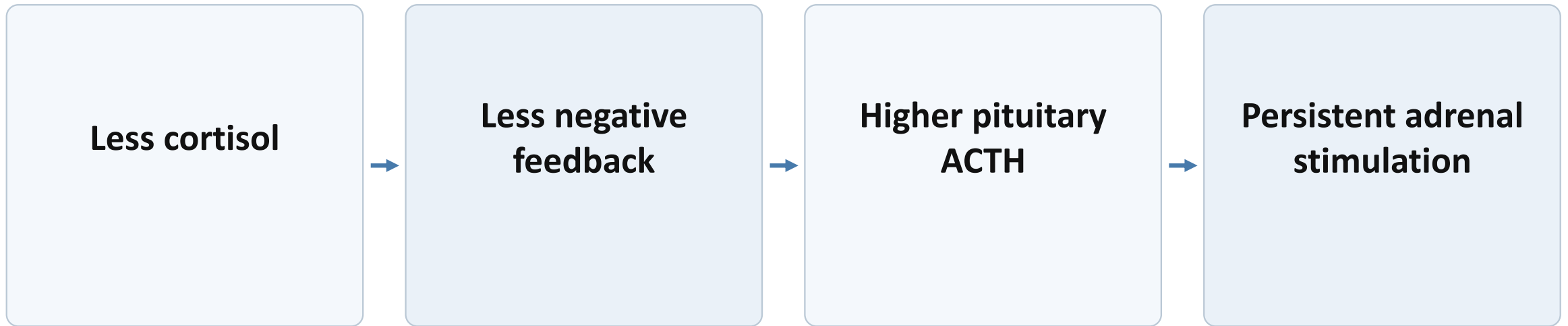
Original editable mechanism schematic

# The dual consequences of 21-hydroxylase deficiency

| Cortisol branch                           | Aldosterone branch                     | Androgen branch                        |
|-------------------------------------------|----------------------------------------|----------------------------------------|
| Impaired cortisol synthesis               | May have severely reduced aldosterone  | Precursors favor androgen formation    |
| Reduced negative feedback on ACTH         | Salt wasting when deficiency is severe | Virilization and hyperandrogenism      |
| ACTH elevation drives adrenal hyperplasia | Volume/electrolyte derangements        | Clinical effects vary with age and sex |

# Cortisol deficiency releases the feedback brake

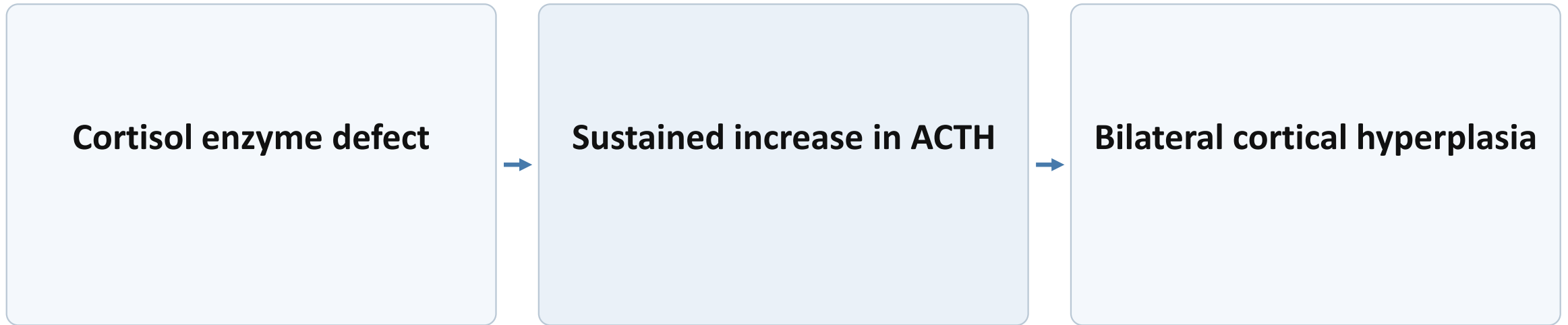
ACTH = corticotropin. This explains both enlargement and increased androgenic output.



Original editable mechanism schematic

# Why do the adrenal glands enlarge?

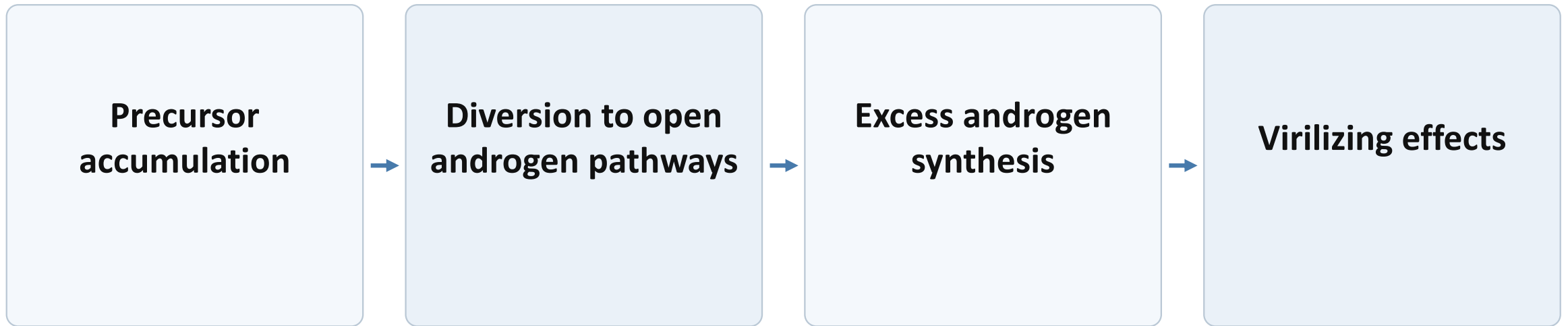
The trophic action of ACTH creates a characteristic structural response.



Original editable mechanism schematic

# Why are androgens increased in CAH?

The metabolic rerouting occurs in the setting of persistent ACTH stimulation.



Original editable mechanism schematic

## Hormonal deficit and hormonal excess coexist

| Deficiency                                                  | Excess                                           |
|-------------------------------------------------------------|--------------------------------------------------|
| Cortisol: Decreased feedback and impaired stress physiology | ACTH: Compensatory pituitary hypersecretion      |
| Aldosterone: Deficient in some enzyme defects               | Adrenal androgen output: Increased               |
| May cause hypotension and salt wasting                      | May cause genital or pubertal androgenic effects |

## Not every steroid enzyme defect behaves identically

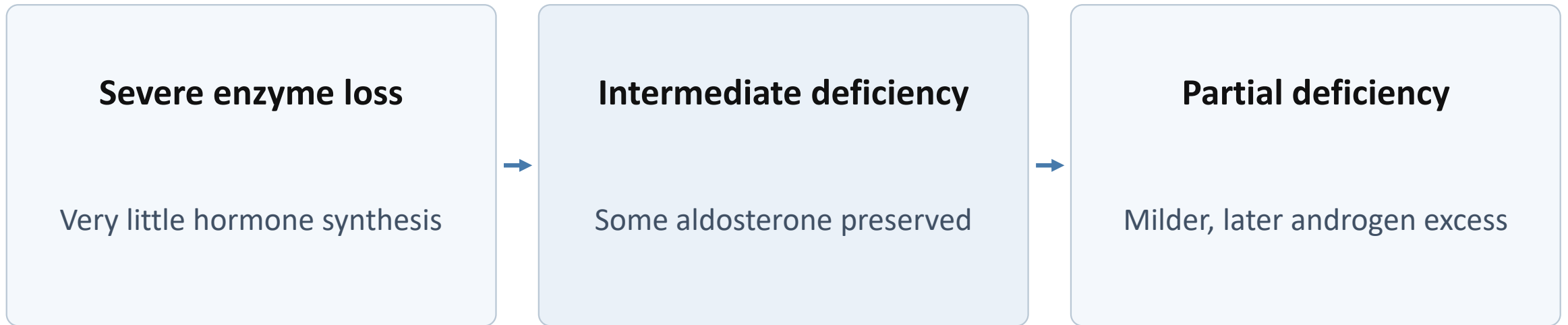
- Specific steroidogenic enzyme deficiencies alter different branches of the pathway.
- Some defects reduce mineralocorticoids as well as cortisol.
- Other defects may be incompatible with life or affect an isolated branch.

## CYP21A2 explains most congenital adrenal hyperplasia

- Mutations in CYP21A2 cause 21-hydroxylase deficiency.
- More than 90% of CAH cases to this enzyme defect.
- The residual activity of the defective enzyme influences the clinical phenotype.

# Residual enzyme function explains a severity spectrum

These patterns form a clinical spectrum rather than unrelated disorders.



Original editable mechanism schematic

# Three phenotypes of 21-hydroxylase deficiency

## Classic salt-wasting

Severe cortisol deficiency

Severe mineralocorticoid deficit

Potential neonatal crisis

## Simple virilizing

Reduced cortisol feedback

Mineralocorticoid sufficient to avert crisis

Progressive virilization

## Nonclassic

Partial enzyme deficiency

Later onset

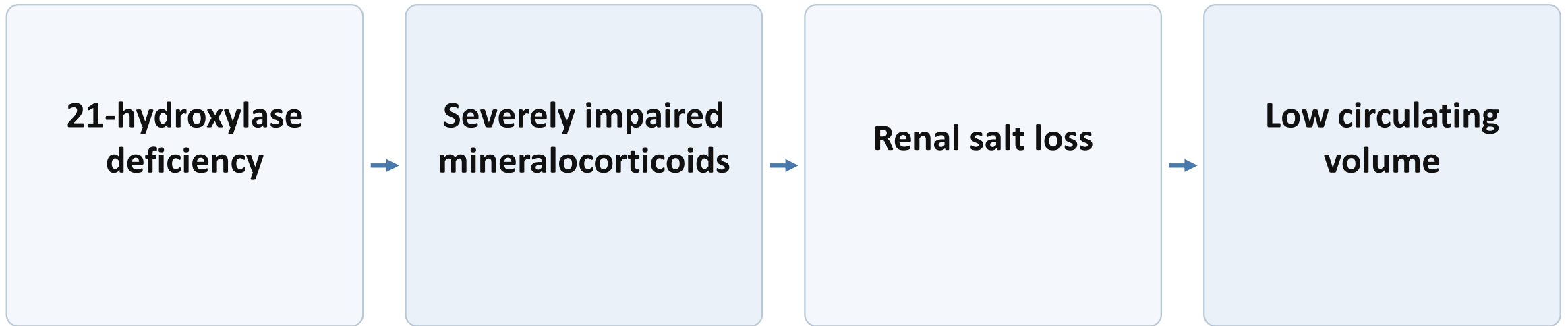
Milder androgenic features

## Classic salt-wasting CAH: Severe enzyme blockade

- Little or no functional 21-hydroxylase blocks both affected branches of steroidogenesis.
- Aldosterone and cortisol synthesis are profoundly impaired.
- Androgenic excess coexists with potentially life-threatening hormone deficiency.

# Salt-wasting CAH: Failure of aldosterone synthesis

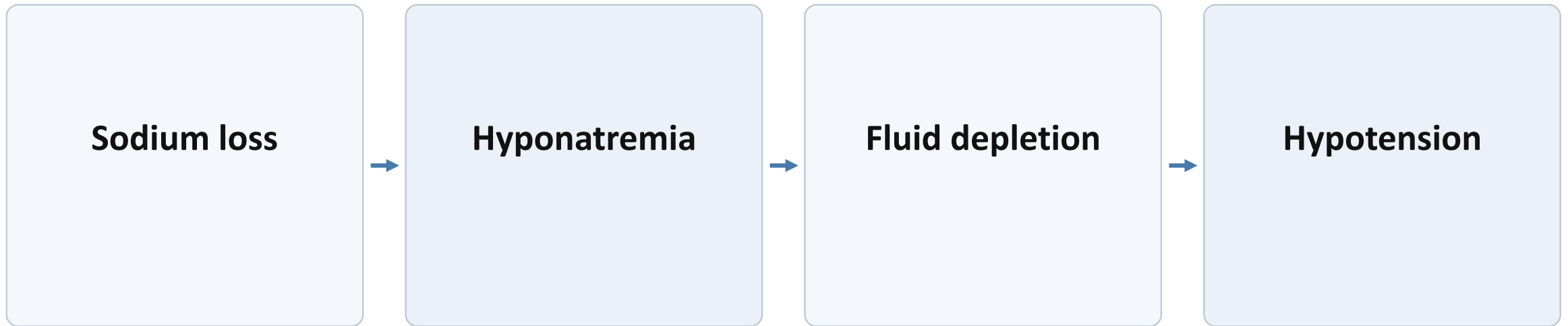
Mineralocorticoid deficiency explains fluid depletion rather than androgen excess.



Original editable mechanism schematic

# Salt-wasting CAH: Sodium and volume consequences

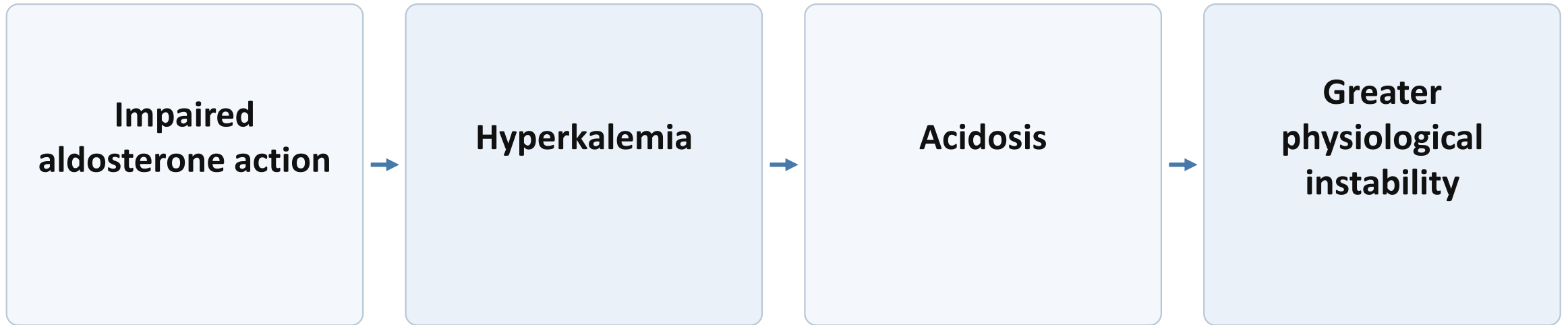
The ionic abnormality and hemodynamic compromise are causally linked.



Original editable mechanism schematic

# Salt-wasting CAH: Potassium and acid–base effects

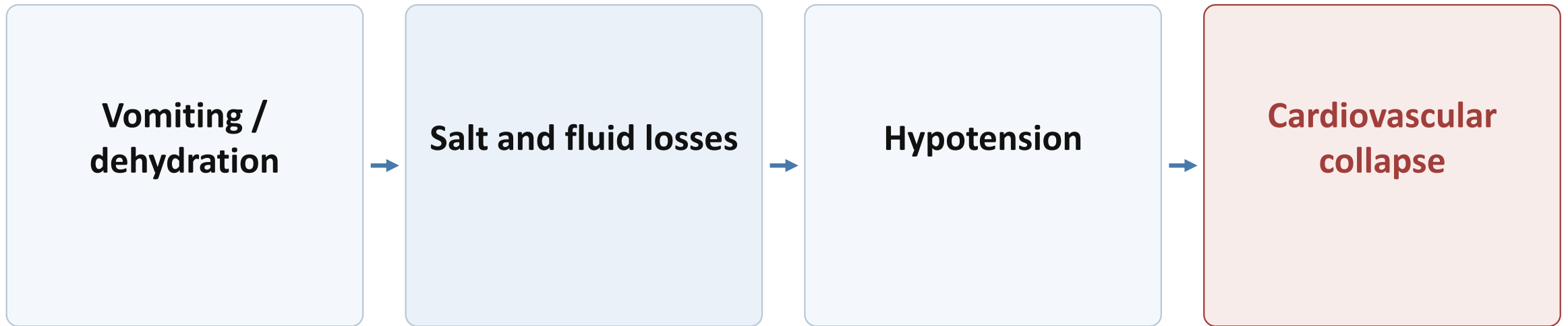
The severe classic form combines electrolyte and circulatory compromise.



Original editable mechanism schematic

# An untreated salt-wasting crisis can be fatal

Immediate recognition is clinically crucial; The chain represents the severe phenotype.



Original editable mechanism schematic

## Why can salt-wasting become apparent only after birth?

- Before delivery, maternal physiology maintains fetal electrolyte and fluid homeostasis.
- Postnatal independence exposes the infant's inadequate mineralocorticoid production.
- An initially inconspicuous newborn examination does not rule out severe CAH.

## Classic CAH in newborns with female genitalia

- Prenatal androgen excess can cause genital virilization evident at birth.
- Clitoral enlargement and differences in sexual development are described.
- External virilization may alert clinicians before severe salt loss appears.

## Classic CAH in newborns with male genitalia

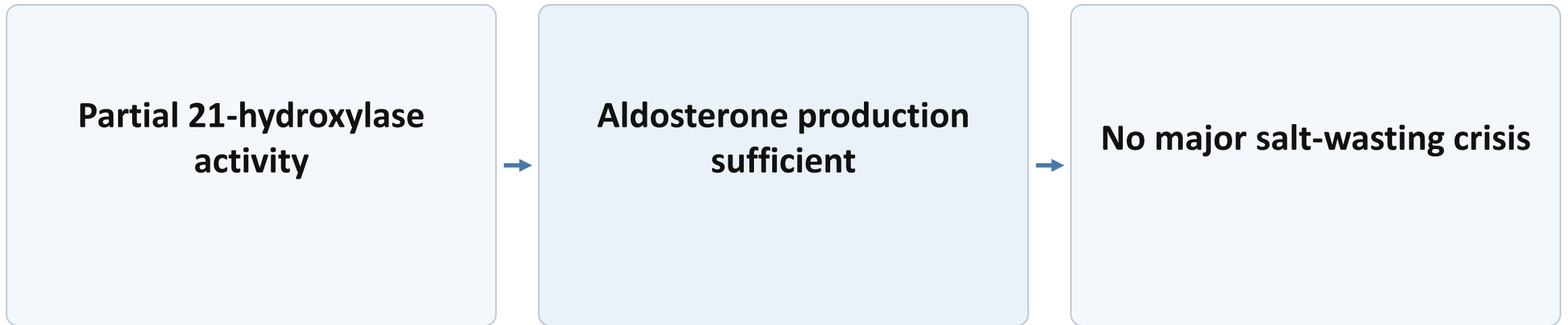
- The external genital examination may not identify the underlying enzyme defect.
- Presentation with salt loss and hypotension commonly at 5–15 days.
- An apparently typical genital examination must not delay assessment of dehydration and shock.

## Simple virilizing CAH preserves enough aldosterone

- Mineralocorticoid production remains sufficient to avert a salt-wasting crisis.
- Cortisol production is still inadequate to suppress ACTH appropriately.
- Androgen excess therefore persists despite the relative preservation of salt balance.

# Simple virilizing CAH: Preserved salt balance

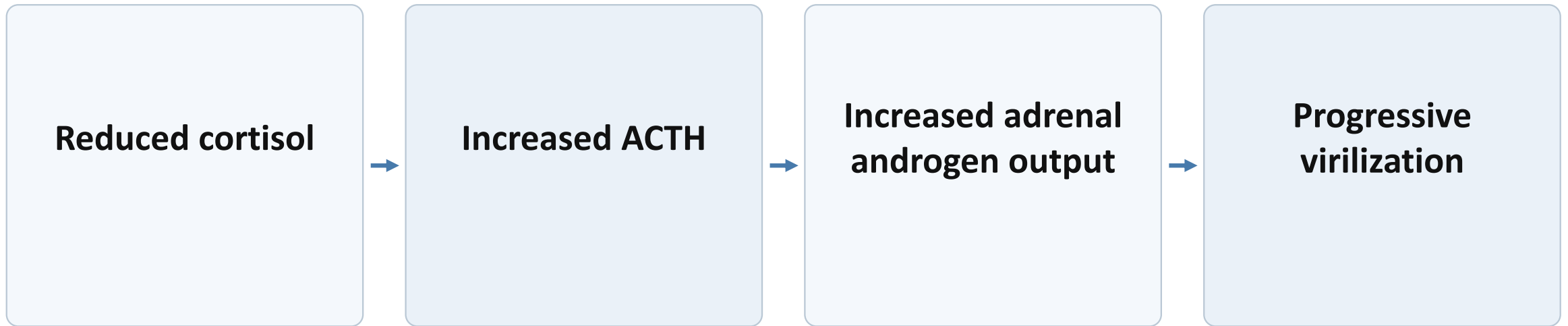
The term “simple virilizing” does not imply intact cortisol feedback.



Original editable mechanism schematic

# Simple virilizing CAH: Continued androgen excess

A normal volume state does not remove the androgenic phenotype.



Original editable mechanism schematic

## Virilization may be progressive in childhood

- The clinical phenotype reflects cumulative androgen exposure.
- Genital differences can be present from prenatal exposure.
- Continuing excess androgen secretion produces additional masculinizing effects over time.

## Nonclassic CAH reflects partial enzyme deficiency

- Residual 21-hydroxylase activity makes manifestations milder than in classic disease.
- Clinical signs may first emerge later in childhood or after puberty.
- Hyperandrogenism rather than neonatal adrenal crisis predominates.

## Nonclassic hyperandrogenism: Typical manifestations

- Hirsutism may be a presenting complaint.
- Acne reflects increased androgenic activity.
- Menstrual irregularity may be the clue to an underlying steroidogenic defect.

## Routine newborn screens do not reliably find nonclassic CAH

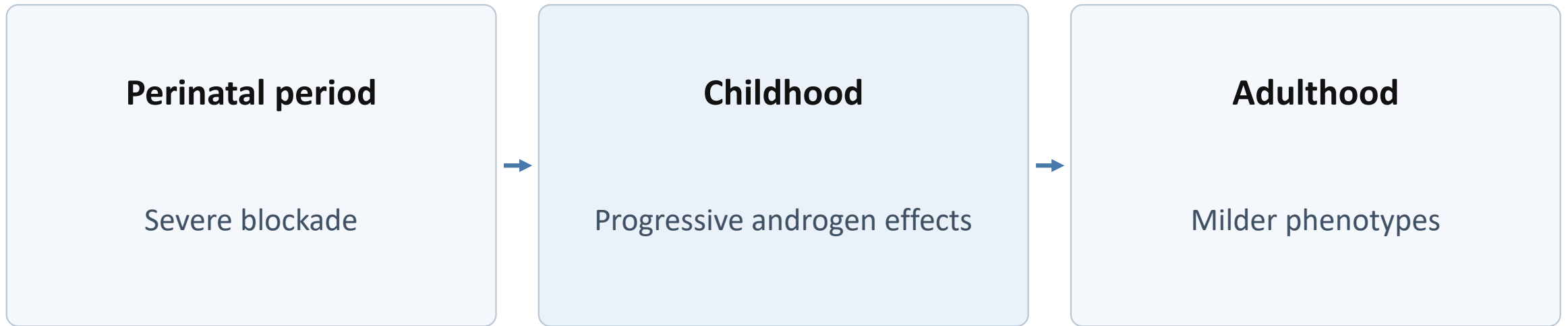
- That nonclassic cases are generally missed by routine neonatal CAH screening.
- Diagnosis is usually made later through investigation of steroid biosynthesis.
- A normal newborn screen does not exclude a mild enzyme defect.

## Clinical phenotypes: The decisive distinctions

| Feature                  | Salt-wasting classic    | Simple virilizing               | Nonclassic                      |
|--------------------------|-------------------------|---------------------------------|---------------------------------|
| Enzyme impairment        | Severe                  | Partial, clinically significant | Mild / partial                  |
| Mineralocorticoid effect | Insufficient; Salt loss | Enough to prevent crisis        | Severe salt loss usually absent |
| Predominant concern      | Neonatal collapse       | Progressive virilization        | Mild later hyperandrogenism     |
| Onset                    | Usually infancy         | Often early life                | Later childhood / adulthood     |

# Clinical onset varies with the severity of the defect

Timing is one axis of CAH severity; Manifestations also depend on the affected hormone.



Original editable mechanism schematic

## Androgen excess in infants with female genitalia

- Virilization may be present during fetal development.
- Clinical findings range from clitoral hypertrophy to other differences in sexual development.
- The degree of androgen exposure shapes the external phenotype.

## Androgen excess after puberty in females

- Oligomenorrhea and other menstrual irregularities may occur.
- Hirsutism and acne are frequent androgenic manifestations.
- A mild later presentation is compatible with nonclassic steroidogenic deficiency.

## Androgen excess in prepubertal males

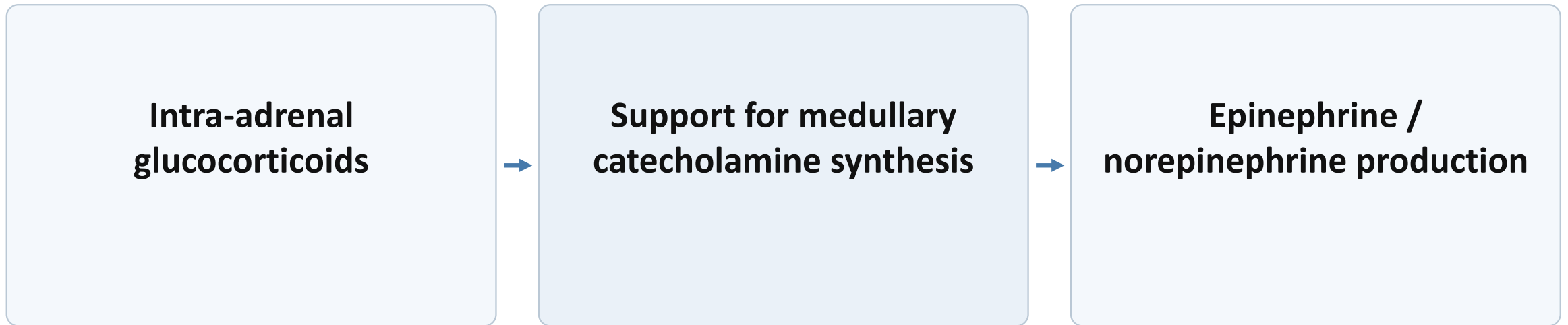
- Excess adrenal androgen can enlarge the external genitalia.
- Clinical features can mimic or cause signs of precocious puberty.
- The absence of neonatal genital ambiguity does not exclude CAH.

## Androgen excess in older males

- Oligospermia among possible manifestations.
- Androgen excess can disrupt reproductive physiology despite apparently masculinized features.
- Clinical expression changes with developmental stage.

# The adrenal cortex supports the medulla

Normal medullary function partly depends on adequate local glucocorticoid exposure.



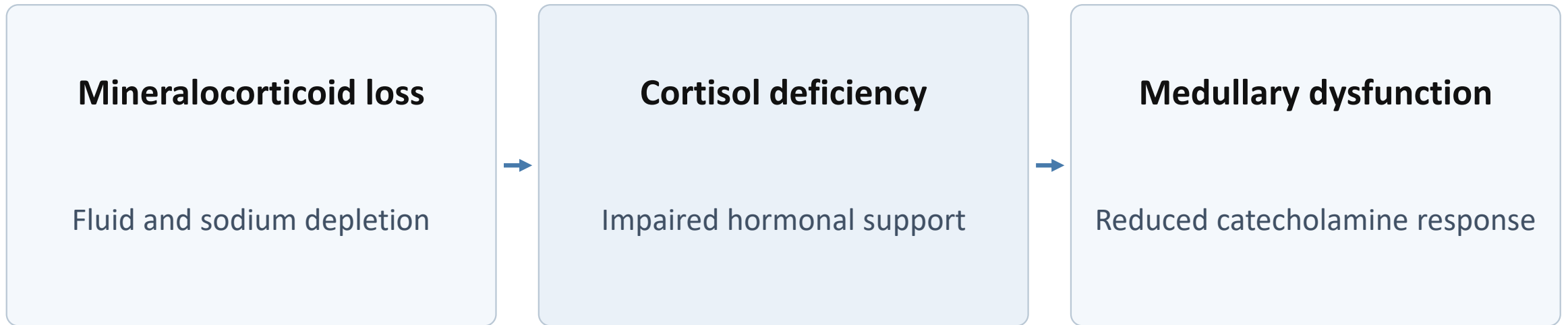
Original editable mechanism schematic

## Severe CAH may include adrenomedullary dysplasia

- Severe salt-wasting 21-hydroxylase deficiency can impair adrenal medullary development.
- Reduced intra-adrenal glucocorticoid exposure affects catecholamine secretion.
- The disorder can therefore compromise both cortical and medullary physiology.

# Why can severe disease magnify hypotension?

These converging mechanisms increase the risk of circulatory collapse.



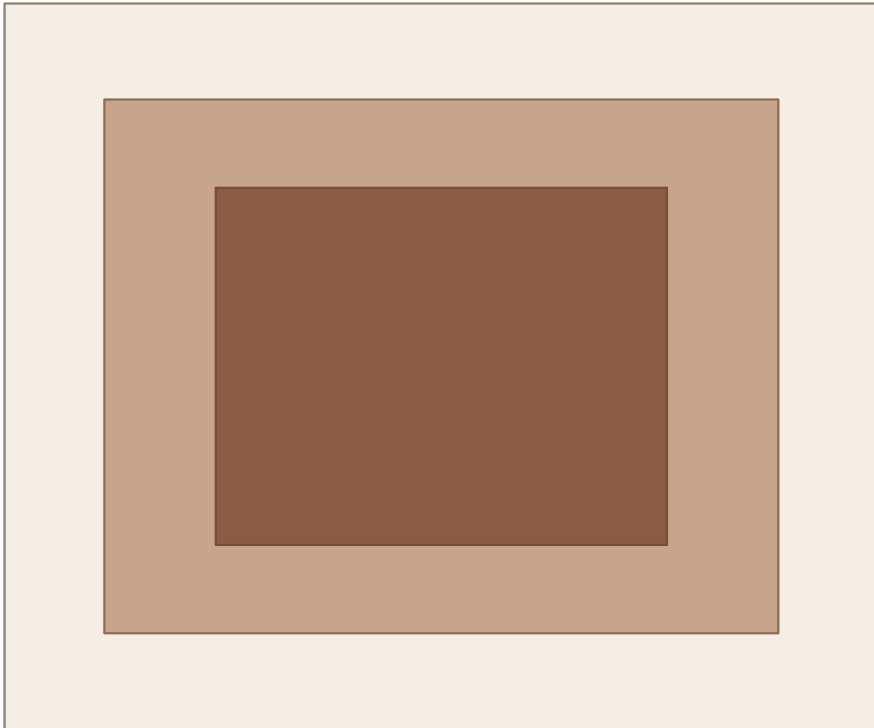
Original editable mechanism schematic

## Gross pathology: Bilateral adrenal enlargement

- Persistent ACTH stimulation leads to bilateral cortical hyperplasia.
- The glands may become markedly enlarged; Up to 10–15 times normal weight.
- Hyperplasia is a diffuse trophic response rather than an isolated androgen-producing tumor.

# Gross morphology: Thick, brown, nodular cortex

Schematic — not a gross pathology photograph



## **Thickened cortex**

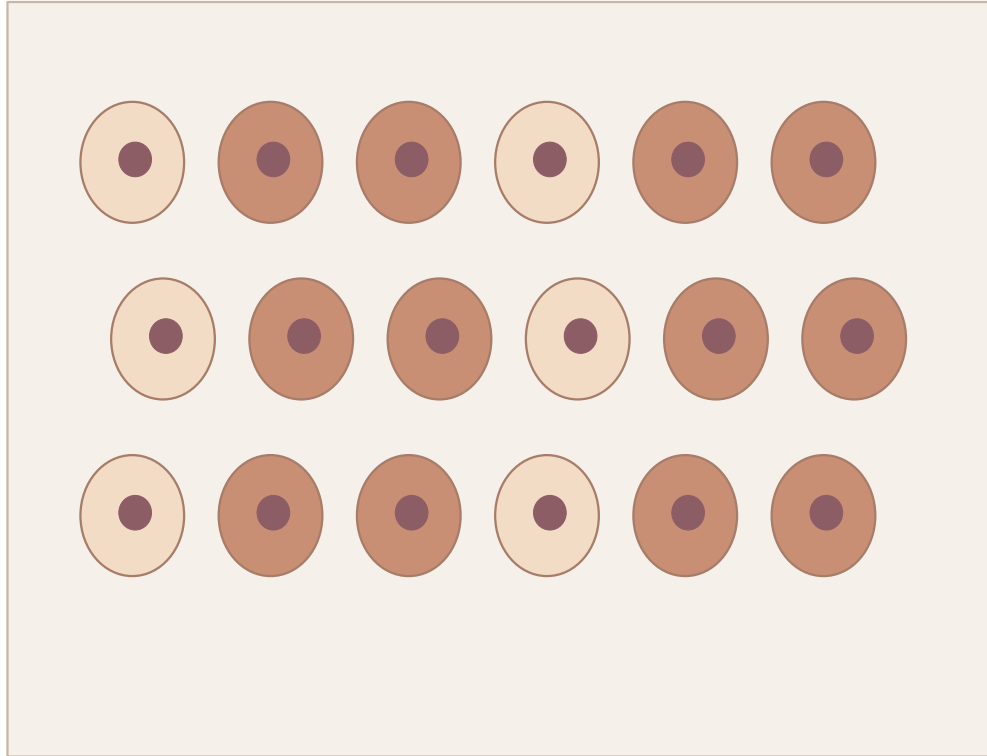
Bilateral cortical hyperplasia

Nodular brown cut surface

Brown color reflects lipid depletion.

# Microscopic morphology: Lipid-depleted compact cells

Schematic — not a histology micrograph



## Compact cells

Eosinophilic cytoplasm; Depleted lipid

## Intermixed clear cells

Residual lipid-containing cells

## Pituitary morphology is part of the feedback response

- Reduced circulating cortisol removes negative feedback from corticotroph cells.
- Most individuals with CAH show corticotroph hyperplasia in the anterior pituitary.
- The pituitary change parallels the sustained elevation in ACTH.

## Link the structure to the pathophysiology

| Morphological finding                       | Underlying mechanism                                       |
|---------------------------------------------|------------------------------------------------------------|
| Bilateral adrenal cortical enlargement      | Sustained trophic stimulation by ACTH                      |
| Brown, lipid-depleted cortex                | Increased steroidogenic activity with reduced lipid stores |
| Compact eosinophilic cortical cells         | Hyperplastic lipid-depleted population                     |
| Anterior pituitary corticotroph hyperplasia | Compensatory ACTH response to cortisol deficit             |

## Diagnostic warning: Ambiguous genitalia in a neonate

- Congenital adrenal hyperplasia is an important consideration in any neonate with genital ambiguity.
- The presentation may reflect prenatal adrenal androgen excess.
- Evaluate concurrently for evidence of glucocorticoid and mineralocorticoid deficiency.

## Diagnostic warning: The vomiting infant

- Vomiting, dehydration, and salt wasting may be the initial features of severe CAH.
- Hyponatremia, hyperkalemia, acidosis, and hypotension reinforce the salt-wasting pattern.
- Possible circulatory collapse makes this presentation a medical emergency.

## Diagnosis follows the steroidogenic defect

- The clinical pattern directs attention to the affected hormone pathways.
- Biochemical demonstration of abnormal steroidogenesis is central, particularly for nonclassic disease.
- CYP21A2-related molecular testing can confirm the inherited etiology when indicated.

## Newborn detection: A critical distinction

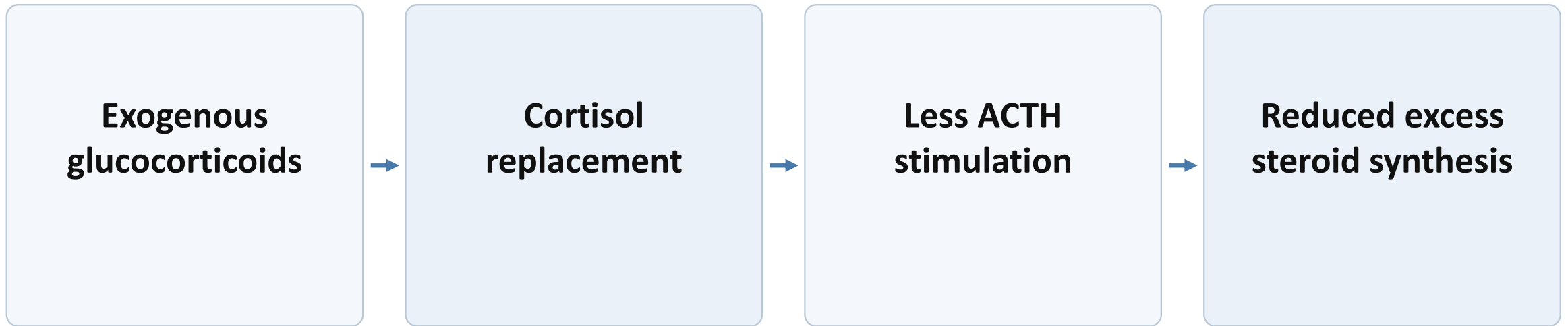
| Severe classic CAH                                                 | Nonclassic CAH                                             |
|--------------------------------------------------------------------|------------------------------------------------------------|
| May be detected through neonatal metabolic screening.              | Often escapes routine newborn screening.                   |
| Early identification can prevent severe salt-wasting consequences. | Evaluation usually follows symptoms of hyperandrogenism.   |
| A screening program does not replace clinical assessment.          | A normal neonatal result is not a lifetime exclusion test. |

## Molecular testing can detect CYP21A2 abnormalities

- CYP21A2 is the gene affected in common 21-hydroxylase deficiency.
- Feasibility of molecular testing for antenatal detection.
- Genetic identification complements—rather than replaces—the clinical and biochemical phenotype.

# Glucocorticoid therapy has two mechanistic effects

Providing glucocorticoids also suppresses the trophic drive behind androgen excess.



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## Salt-wasting CAH requires mineralocorticoid support

- Glucocorticoid replacement alone does not directly restore severely deficient aldosterone activity.
- Mineralocorticoid supplementation is needed in salt-wasting variants.
- Clinical assessment must address both steroid deficiencies and androgen excess.

## Why outcomes improve with early recognition

- Routine neonatal screening supports earlier identification of severe forms.
- Genetic testing can identify CYP21A2 defects before birth when indicated.
- Timely hormone replacement reduces the consequences of critical endocrine deficiency.

## Application case: Neonatal collapse

### Clinical vignette

A newborn with male external genitalia develops vomiting, severe dehydration, and hypotension near the end of the first postnatal week. Laboratory evaluation reveals low sodium and high potassium.

**Which CAH phenotype best explains the full presentation?**

## Case interpretation: Classic salt-wasting CAH

- The postnatal onset and electrolyte derangements point to severe mineralocorticoid deficiency.
- Low cortisol permits persistent ACTH drive, but androgenic signs may not be obvious at birth in males.
- The syndrome requires prompt recognition of life-threatening adrenal hormone deficiency.

# Application case: Delayed hyperandrogenism

## Clinical vignette

A postpubertal patient presents with hirsutism, acne, and menstrual irregularity. There is no history of neonatal salt-wasting crisis. Investigation indicates an adrenal steroid biosynthetic abnormality.

**Which end of the 21-hydroxylase deficiency spectrum is most consistent?**

## Case interpretation: Nonclassic CAH

- Later-onset, comparatively mild androgenic features favor nonclassic disease.
- Partial enzyme deficiency permits sufficient steroidogenesis to avoid severe neonatal salt loss.
- The biochemical steroidogenic abnormality helps distinguish this syndrome from other androgen excess causes.

## Differentiate CAH from an androgen-secreting tumor

| <b>Congenital adrenal hyperplasia</b>           | <b>Adrenocortical neoplasm</b>                       |
|-------------------------------------------------|------------------------------------------------------|
| Autosomal recessive inherited enzyme deficiency | Autonomous or neoplastic cortical steroid secretion  |
| Cortisol deficiency leads to sustained ACTH     | May co-produce cortisol and produce a mixed syndrome |
| Bilateral ACTH-driven cortical hyperplasia      | Morphology follows cortical neoplasm patterns        |
| Severe forms include salt-wasting physiology    | Virilizing neoplasms are more often carcinomas       |

# Integrated causal model

**21-hydroxylase defect → impaired cortisol synthesis → increased ACTH → bilateral adrenal hyperplasia.**

Blocked steroidogenic reactions → precursor diversion → androgen excess and virilization.

Severe aldosterone deficiency → salt loss, electrolyte disturbance, and possible neonatal collapse.

## Three clinical principles to retain

**Determine whether adrenal androgen excess is caused by CAH or a cortical neoplasm.**

Separate androgenic manifestations from cortisol and aldosterone deficiency.

Recognize that clinical onset and severity vary with residual steroidogenic enzyme activity.

# Primary reference and scope

Robbins, Cotran & Kumar: Pathologic Basis of Disease

11th edition (2026), endocrine system chapter

Section: Adrenogenital Syndromes

Original teaching schematics; no patient-derived or synthetic diagnostic specimens.