

Sickle Cell Nephropathy

Vascular, medullary, and glomerular injury in HbS-associated disease

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Learning objectives

- Explain why the renal medulla favors sickling of HbS-containing erythrocytes.
- Link sickling to hematuria, hyposthenuria, papillary necrosis, and proteinuria.
- Distinguish renal manifestations of sickle cell trait from sickle cell disease.
- Relate renal morphology to functional impairment and clinical interpretation.

A syndrome of renal structural and functional alterations

Sickle cell nephropathy

An umbrella term for renal alterations occurring in people with sickle cell disease or sickle cell trait.

Kidney injury is not confined to individuals with homozygous HbS.

Two genotypic settings: Disease and trait

Sickle cell disease

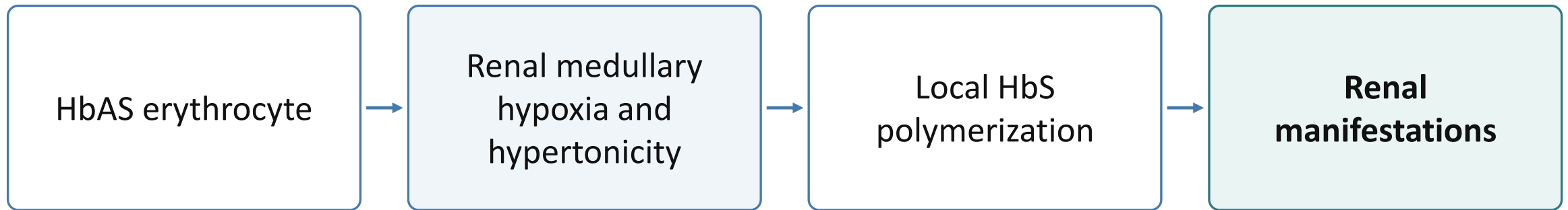
- Homozygous HbS description.
- Most hemoglobin is HbS.
- Systemic sickling and vascular injury are prominent.

Sickle cell trait

- Heterozygous HbAS description.
- HbA inhibits HbS polymerization.
- Renal medullary stress can still induce sickling.

Renal involvement does not require generalized sickling

A locally stressful environment can unmask risk in sickle cell trait.



A mechanism-to-lesion framework

Red cell

HbS polymerization and dehydration

Medullary vessels

Sickling under hypertonic, hypoxic conditions

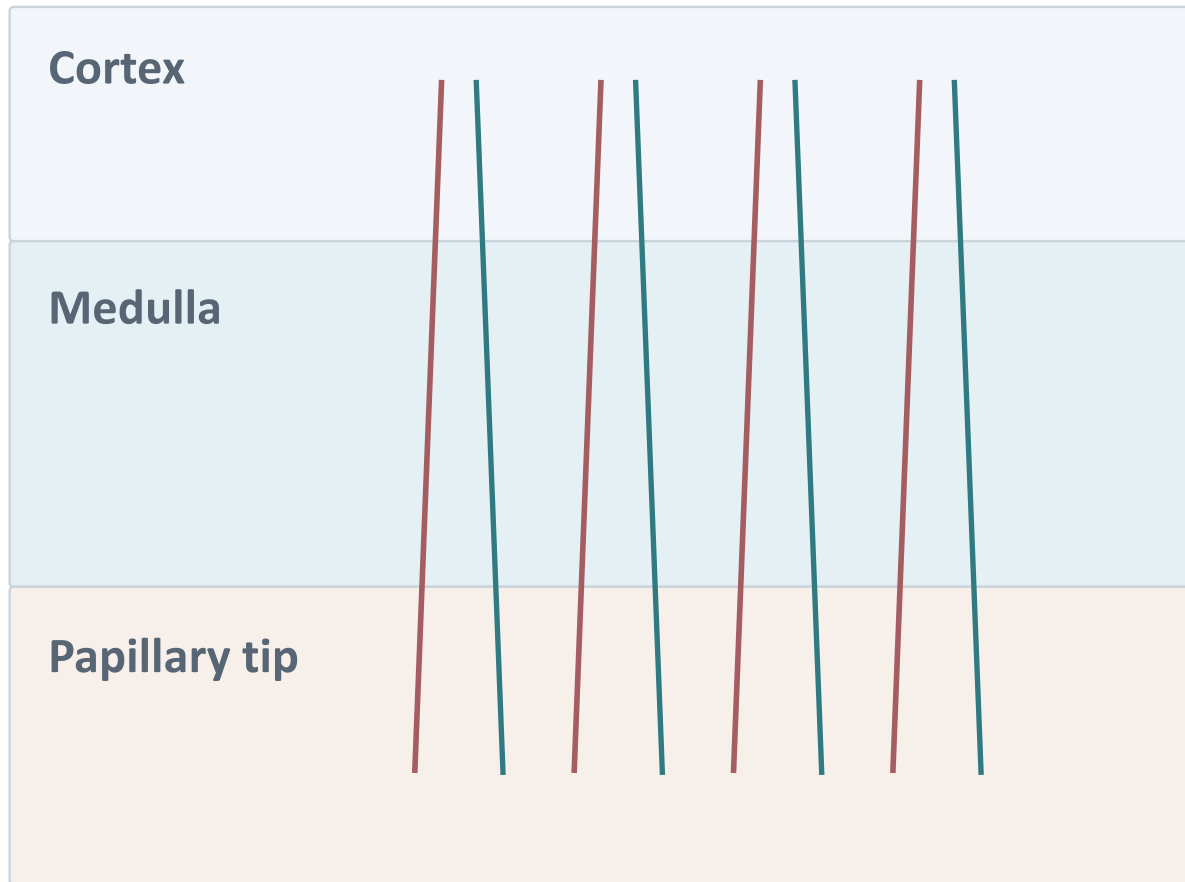
Kidney

Concentrating defect, bleeding, papillary injury

Glomerulus

Proteinuria with possible sclerosis

Renal cortex, medulla, and papillary tip



- Glomeruli lie in the cortex.
- The medulla supports urine concentration.
- The papillary tip is a recognized site of necrotic injury.

Schematic—not a histologic section

Why the renal medulla is uniquely vulnerable

Low oxygen tension

Promotes HbS deoxygenation

Hypertonicity

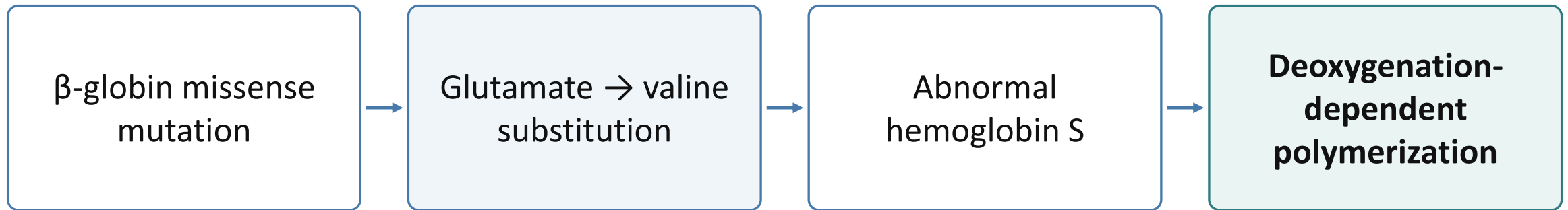
Draws water from
erythrocytes

Microcirculatory transit

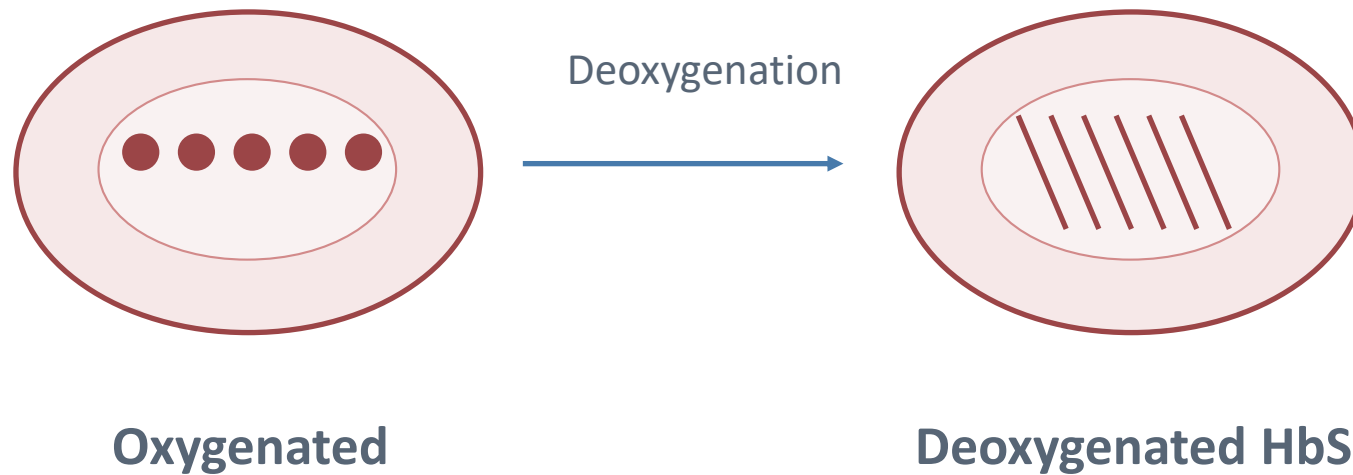
Allows time for sickling in
vulnerable beds

The molecular origin: β -globin missense mutation

A single amino-acid replacement changes the physical behavior of hemoglobin.



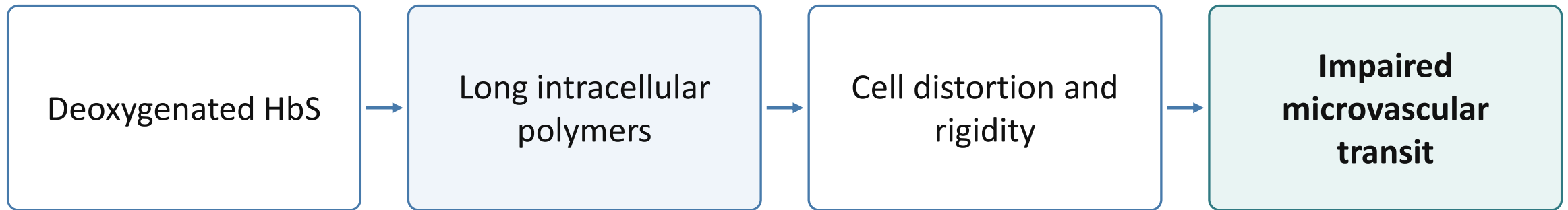
Deoxygenation converts HbS into polymers



The relevant event is HbS polymer assembly—not an intrinsic inability to bind oxygen.

Original schematic

Polymer formation changes red-cell mechanics



Vaso-occlusion is favored when polymerization develops during capillary passage.

Sickling begins as a reversible deformation

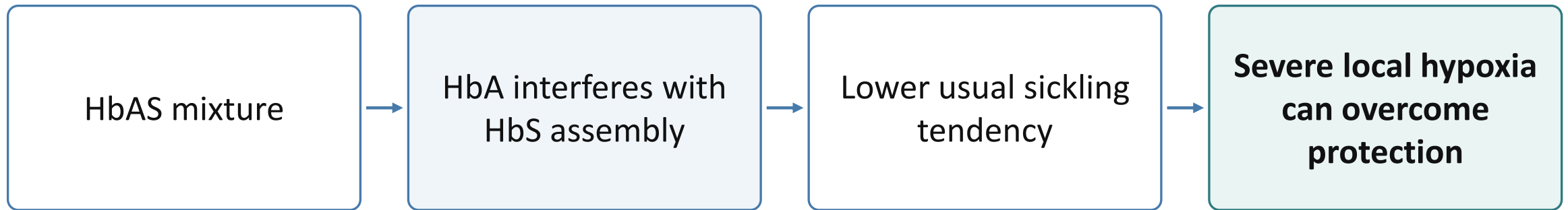
Earlier episodes

- Polymer formation after deoxygenation.
- Shape distortion can reverse on reoxygenation.
- Membrane damage may accumulate with repeated cycles.

Repeated episodes

- Cells become dehydrated and rigid.
- Some red cells become irreversibly sickled.
- Mechanical fragility and removal increase.

HbA limits polymerization in sickle cell trait



HbF also counteracts HbS polymerization

HbS

Polymerizes when
deoxygenated

HbA

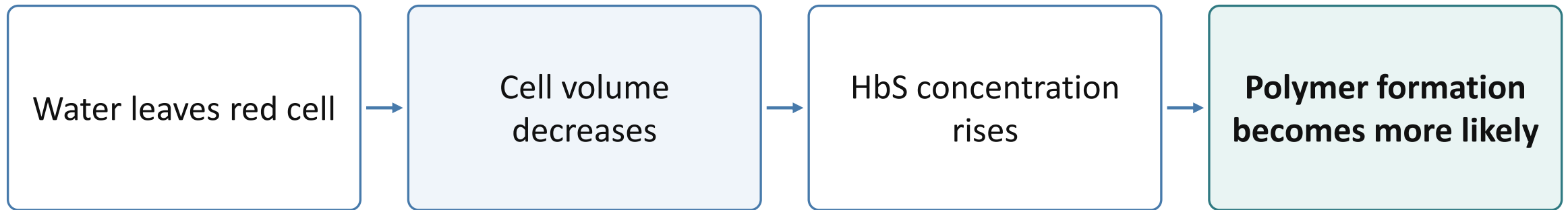
Interferes with HbS
polymerization

HbF

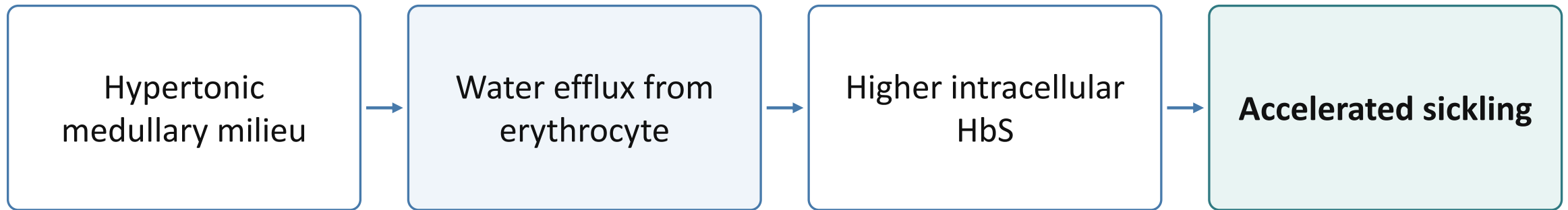
Inhibits HbS polymerization
more strongly than HbA

Intracellular HbS concentration is a key variable

Concentrating HbS within the erythrocyte accelerates sickling.



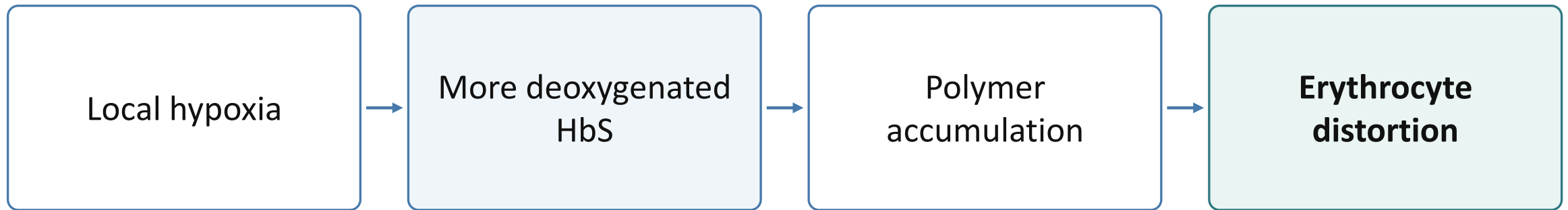
Hypertonicity dehydrates medullary erythrocytes



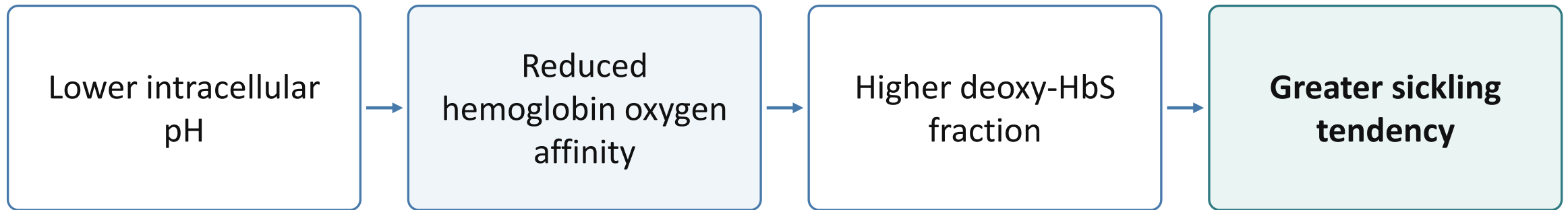
This is the mechanism highlighted for both disease and trait.

Low oxygen tension promotes HbS assembly

Oxygen availability directly modulates the fraction of HbS that can polymerize.



Intracellular acidity amplifies sickling



General sickle cell pathogenesis; Not quantified for medullary renal injury here.

Transit time matters in microvascular beds

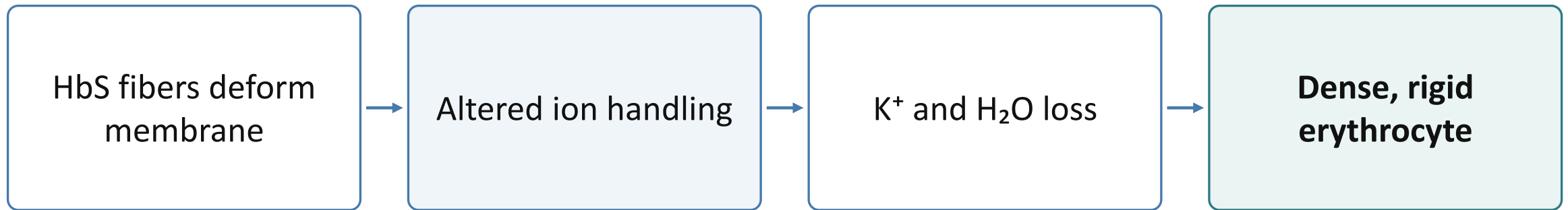
Rapid transit

- Limited time for substantial polymerization.
- Less chance of intravascular cell distortion.
- Illustrates the role of exposure duration.

Prolonged transit

- Deoxygenated HbS persists longer.
- Sickling becomes more probable.
- Stasis may intensify vascular obstruction.

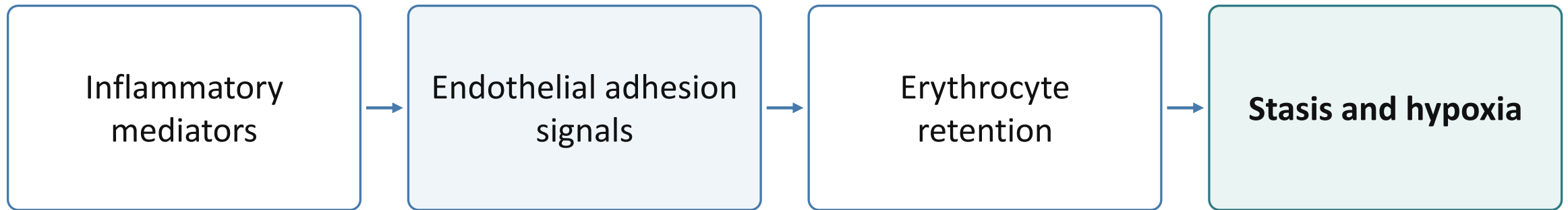
Repeated sickling damages the red-cell membrane



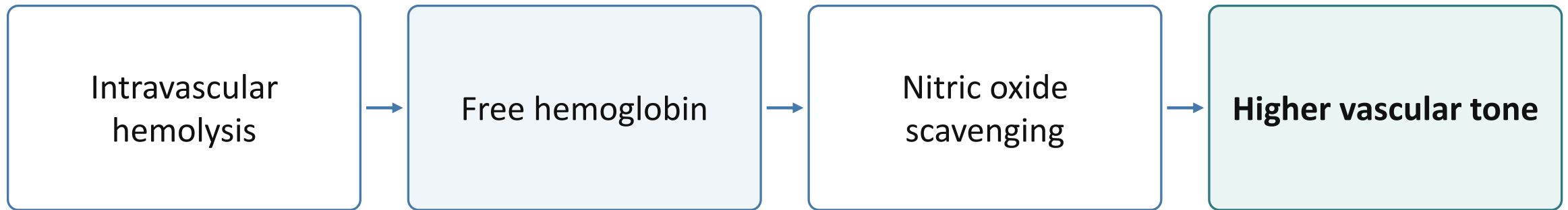
Membrane injury links repeated sickling to increased cellular dehydration.

Inflammation can enhance sickle-cell adhesion

The broader vasculopathy helps explain why local microvascular conditions matter.

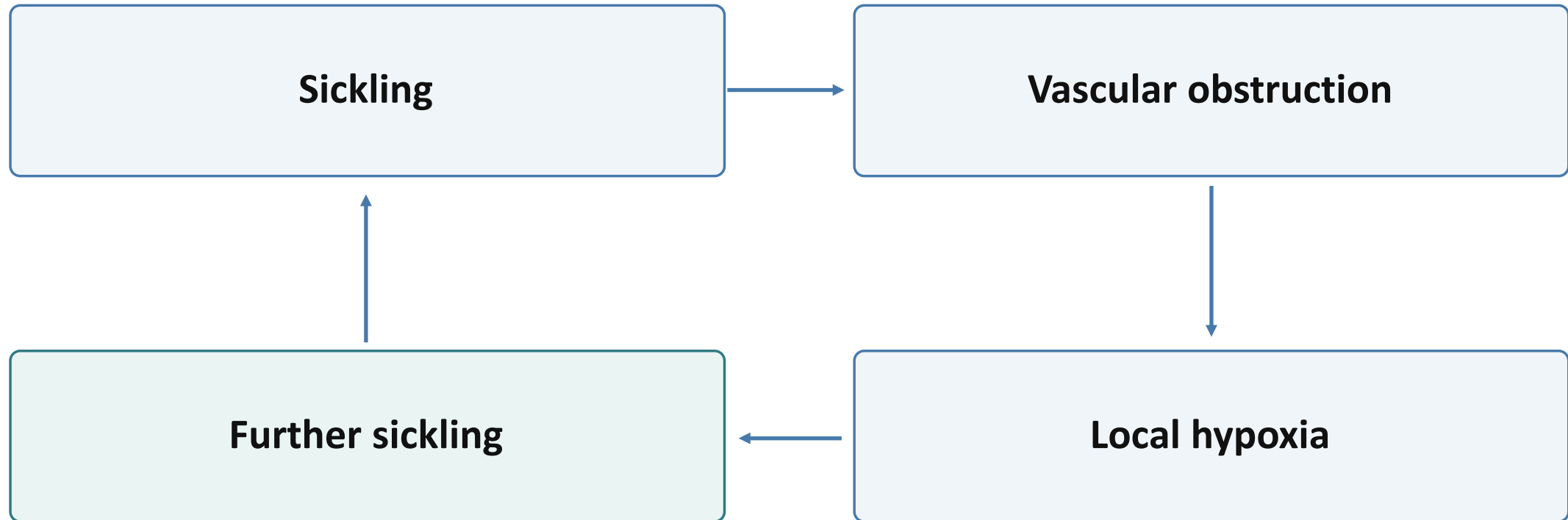


Hemolysis may decrease bioavailable nitric oxide



This as a possible contributor to vaso-occlusion, not its sole cause.

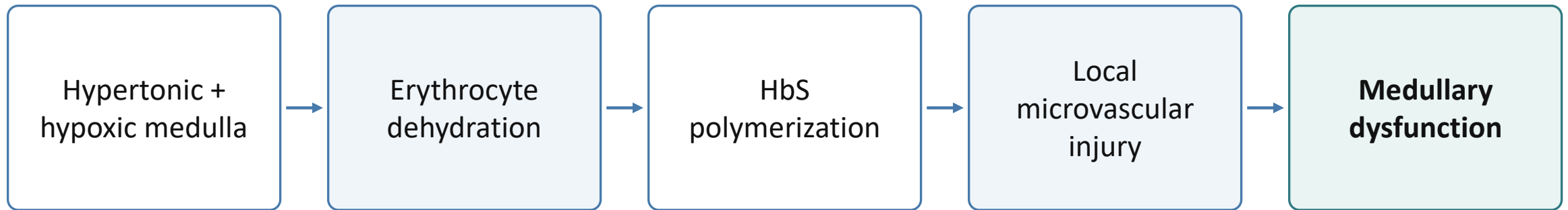
Sickling and hypoxia can reinforce one another



Reinforcing cycle (schematic)

A renal medullary injury cascade

Mechanism integrates the renal and hematologic Robbins sections.



Why heterozygous HbAS is not completely protected

Systemic circulation

- HbA interferes with polymerization.
- Trait is largely asymptomatic in everyday conditions.
- Short transit often limits HbS assembly.

Renal medulla

- Low oxygen and hypertonicity coexist.
- Erythrocytes become locally dehydrated.
- Renal findings can occur even in trait.

Clinical renal findings form two major clusters

Medullary–papillary

Hematuria · hyposthenuria · papillary necrosis

Glomerular

Proteinuria · glomerular sclerosis · occasional
nephrotic syndrome

Hematuria is a common renal manifestation

Hematuria

One of the two most common abnormalities grouped under sickle cell nephropathy.

Occurs in the context of HbS-associated renal injury; Other causes are not excluded.

Hematuria indicates urinary red-cell loss

Clinical signal

Blood or erythrocytes
detected in urine

Pathologic context

Medullary and papillary
vulnerability in HbS states

Interpretation

Hematuria alone does not
identify a specific renal lesion

Hyposthenuria is impaired urine concentration

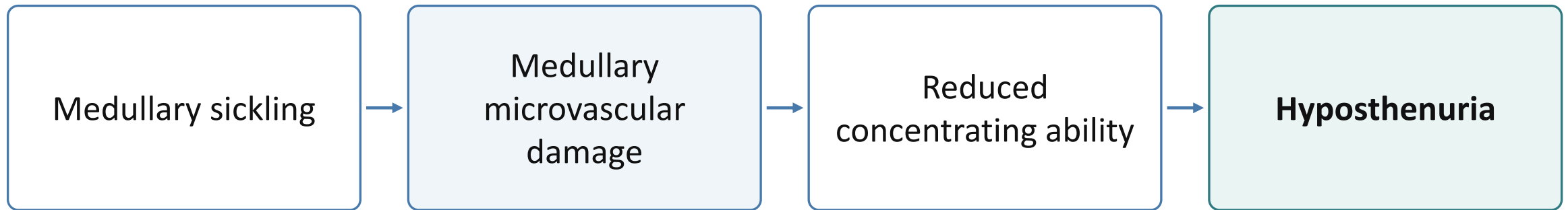
Hyposthenuria

A reduction in the kidney's ability to concentrate urine.

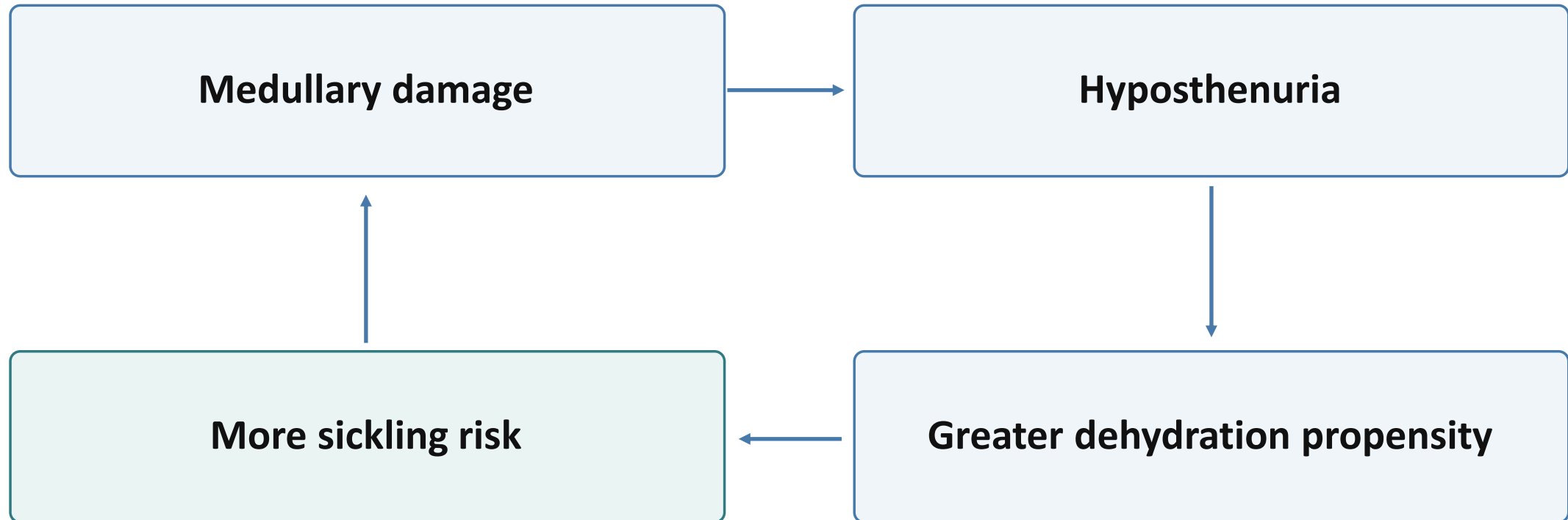
It, alongside hematuria, as a common renal abnormality.

Medullary injury undermines concentrating function

The renal concentrating apparatus is vulnerable to ischemic injury.



Hyposthenuria can aggravate dehydration risk



Reinforcing cycle (schematic)

Distinguish solute concentration from urine volume

Hyposthenuria

- Primary concept: Impaired urine concentration.
- A renal functional abnormality.
- Described explicitly in sickle cell disease and trait.

Dehydration risk

- A clinical consequence of poor concentrating ability.
- May worsen the milieu favoring sickling.
- Do not infer a measured urine output from the term alone.

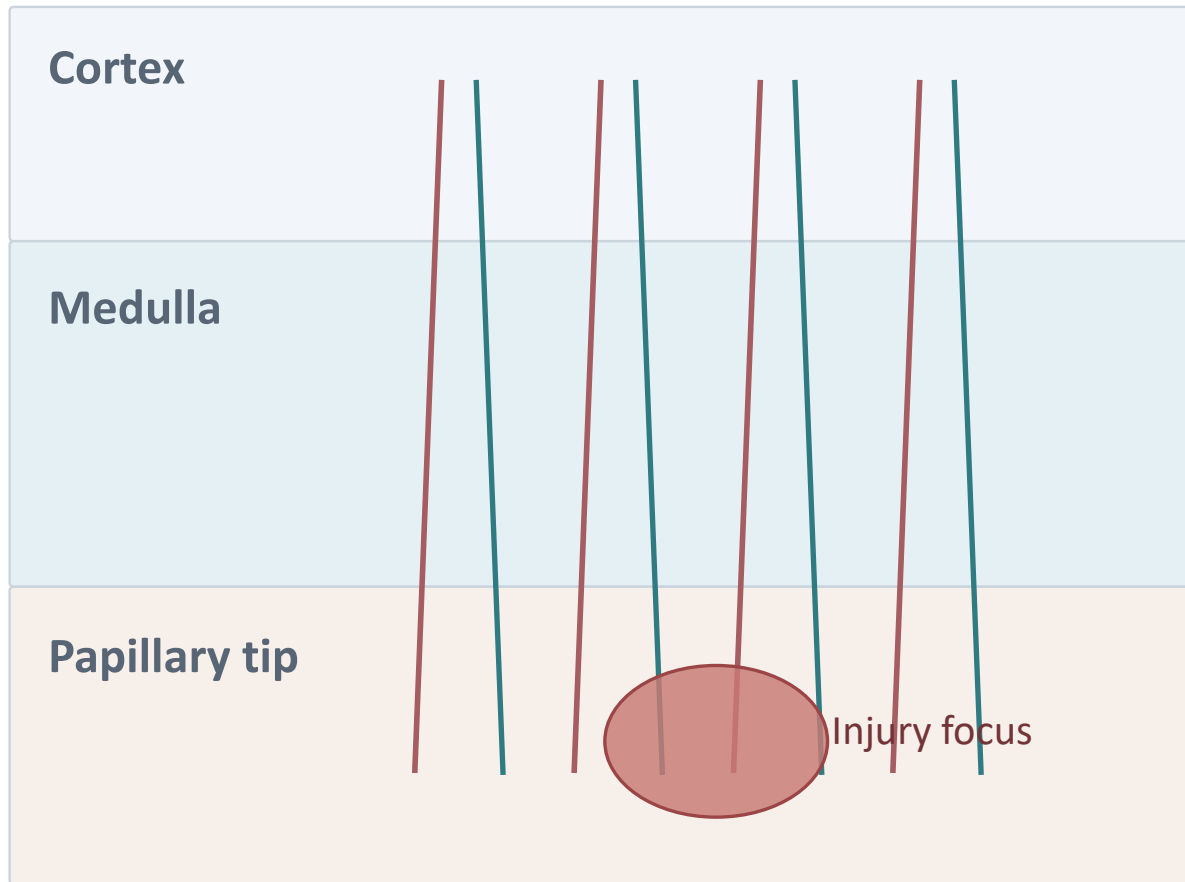
Papillary necrosis is a focal ischemic lesion

Patchy papillary necrosis

May occur in either homozygous sickle cell disease or heterozygous sickle cell trait.

The renal papilla is the anatomic focus; An entire cortical infarct is a different lesion.

Localize papillary necrosis anatomically



- Injury centers on papillary / pyramidal tissue.
- Patchy papillary necrosis.
- A schematic is used here; No genuine photomicrograph supplied.

Schematic—not a histologic section

Gross pattern of papillary necrosis

Site

Tips or distal parts of renal
pyramids

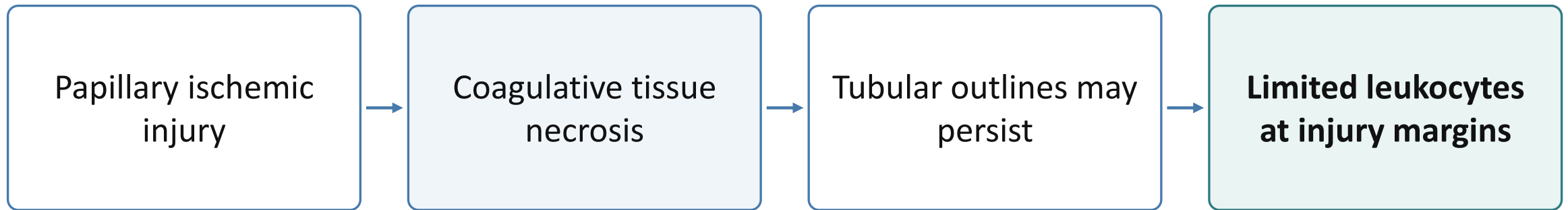
Gross appearance

Gray-white to yellow necrotic
areas

Extent

One or multiple papillae;
Unilateral or bilateral

Microscopic correlate: Ischemic coagulative necrosis



General papillary necrosis morphology from the renal chapter; Schematic relationship only.

Papillary injury can vary in distribution

Patchy involvement

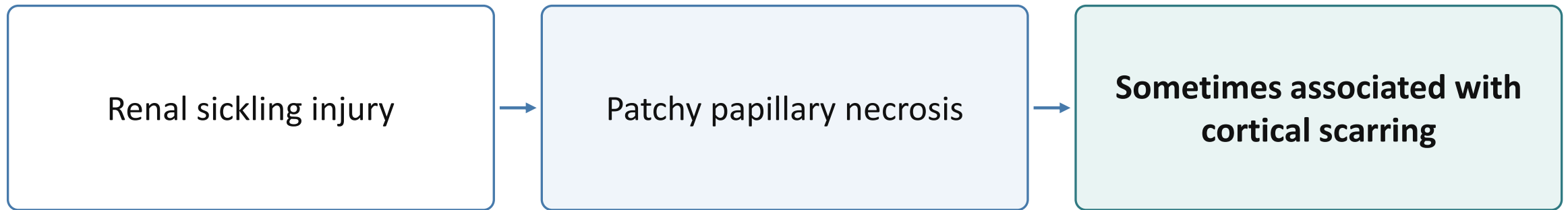
- Necrosis is not necessarily uniform.
- Individual papillae may be affected.
- Robbins specifically uses “patchy.”

More extensive injury

- Several papillary regions may be involved.
- Associated ischemic damage can be more widespread.
- Do not assume a fixed extent in every case.

Cortical scarring may accompany papillary necrosis

Association is stated in the source; A single causal route is not established.



Papillary necrosis has multiple clinical contexts

Context	Robbins relationship
Sickle cell disease / trait	Papillary necrosis can occur.
Diabetes mellitus	Recognized associated condition.
Urinary tract obstruction	Recognized associated condition.
Acute pyelonephritis	May have superimposed papillary necrosis.

Proteinuria is frequent in sickle cell disease

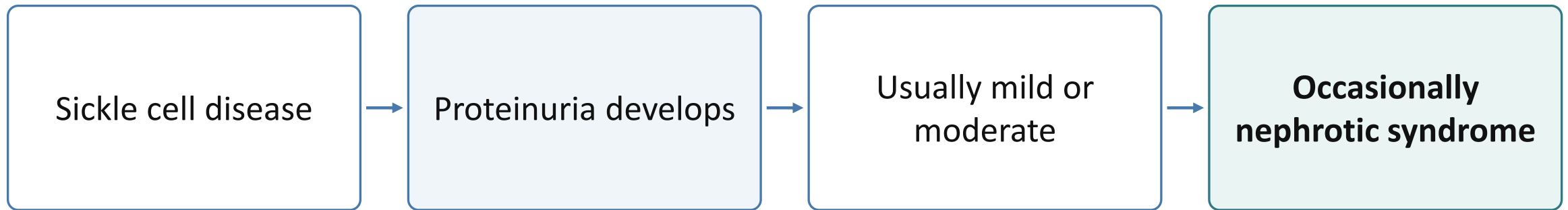
About 30%

Proteinuria in approximately 30% of patients with sickle cell disease.

This is a textbook estimate; It is not presented as an updated population-specific prevalence.

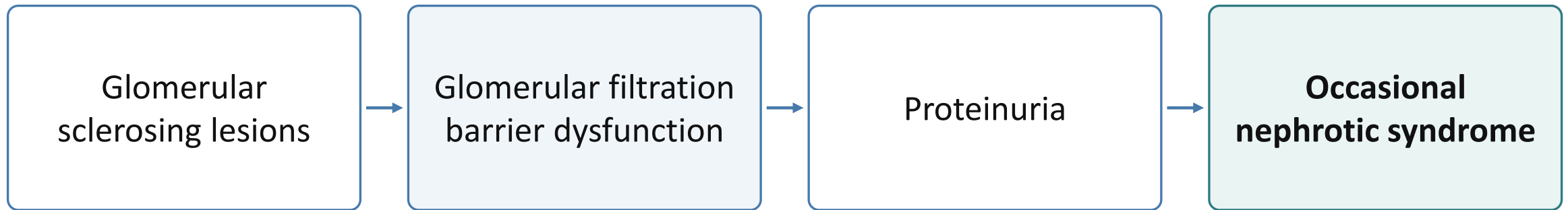
Proteinuria is usually mild to moderate

Protein loss has a broad clinical severity spectrum.



Sclerosing glomerular lesions explain severe protein loss

Overt nephrotic syndrome with sclerosing glomerular lesions.



Nephrotic syndrome is not the typical presentation

Usual proteinuric finding

- Proteinuria may be present.
- Usually mild to moderate.
- Does not by itself establish nephrotic syndrome.

Occasional severe presentation

- Overt nephrotic syndrome can arise.
- Associated with glomerular sclerosis.
- A distinct manifestation within a broad spectrum.

Glomerular injury and medullary injury are distinct

Medullary / papillary

- Hypertonic and hypoxic milieu.
- Hyposthenuria and hematuria.
- Patchy papillary necrosis.

Glomerular

- Proteinuria is a major signal.
- Sclerosing lesions may be present.
- Occasional nephrotic syndrome.

Link renal structure to the clinical phenotype

Site / lesion	Functional or clinical correlate
Medullary concentrating region	Hyposthenuria
Medullary / papillary injury	Hematuria
Papillary tissue necrosis	Patchy papillary necrosis
Sclerosing glomerular lesions	Proteinuria; Sometimes nephrotic syndrome

The disease–trait comparison is lesion-specific

Manifestation	Sickle cell disease	Sickle cell trait
Renal involvement	Possible	Possible
Hyposthenuria	Highlighted in renal passage	Explained by local medullary sickling
Papillary necrosis	Explicitly described	Explicitly described
Proteinuria ~30%	Estimate applies here	No frequency stated in source

Do not conflate papillary necrosis and renal infarction

Papillary necrosis

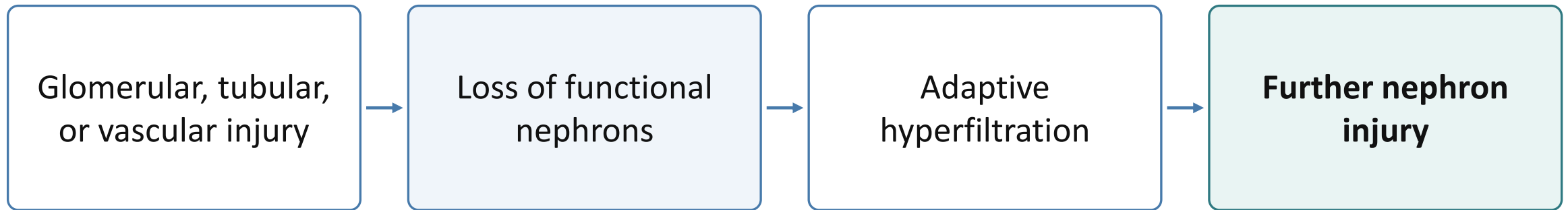
- Localized in renal papillae / pyramids.
- Patchy lesions occur with HbS states.
- Ischemic coagulative necrosis is possible.

Renal infarction

- Often embolic in the renal chapter.
- Classically wedge-shaped cortical lesions.
- May heal as depressed cortical scars.

Kidney injury can progress through nephron loss

General CKD mechanism from the adjacent Robbins section; Not a measured trajectory in this lecture.



Chronic kidney disease has convergent morphology

Glomeruli

Glomerulosclerosis

Tubules

Tubular atrophy

Interstitial

Interstitial fibrosis

Vessels

Arteriosclerosis

Avoid over-attributing urinary abnormalities to HbS

Hematuria

A clinical sign, not a specific morphologic diagnosis

Concentrating defect

Implies medullary functional impairment

Proteinuria

Warrants consideration of glomerular injury

Renal scarring

Requires interpretation in the full pathologic context

Clinical vignette: Hematuria in HbAS trait

Constructed teaching vignette

An individual known to have sickle cell trait presents with hematuria. There is no established systemic vaso-occlusive syndrome in the vignette.

Can HbAS be relevant to the renal presentation?

- Yes. The medullary milieu can promote local sickling even in trait.
- Hematuria remains nonspecific; Other causes must still be considered.

Clinical vignette: Interpretation of hyposthenuria

Constructed teaching vignette

A patient with sickle cell disease has a documented inability to concentrate urine appropriately.

Which renal region is central to the textbook mechanism?

- The hypoxic, hypertonic renal medulla.
- The local tendency for HbS-containing erythrocytes to sickle.

Clinical vignette: Proteinuria in sickle cell disease

Constructed teaching vignette

A patient with sickle cell disease has persistent proteinuria, now considerably more pronounced than previously documented.

Which lesion category is linked to the severe proteinuric phenotype?

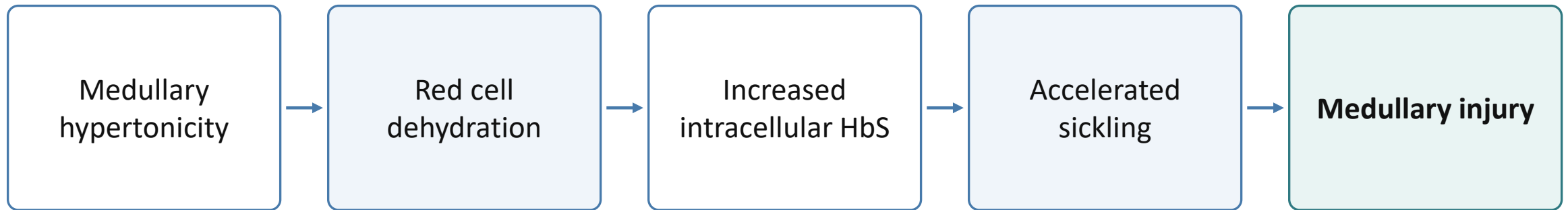
- Sclerosing glomerular lesions.
- Overt nephrotic syndrome is possible but not the usual severity.

Morphology challenge: Identify the compartment

Finding	Most relevant compartment
Poor urine concentration	Renal medulla
Patchy papillary necrosis	Renal papilla
Proteinuria with sclerosis	Glomerulus
Possible cortical scar	Cortex (associated finding)

Mechanism challenge: Order the causal steps

A mechanistic sequence supported directly by the renal text.



Diagnostic reasoning: What the source does not establish

- Hematuria alone does not establish papillary necrosis.
- No biopsy-defined grading or staging system is provided for sickle cell nephropathy.
- The approximately 30% proteinuria estimate applies to sickle cell disease in the source.
- No source-specific testing thresholds or treatment algorithm is supplied.

Integrated renal injury model

Triggering milieu

Medullary hypoxia and hypertonicity

Cell response

HbS polymerization and red-cell sickling

Regional damage

Concentrating defect and papillary necrosis

Glomerular phenotype

Proteinuria; Possible sclerosis and nephrotic syndrome

Five clinicopathologic conclusions

- Both sickle cell disease and trait may affect the kidney.
- Medullary hypertonicity and hypoxia favor HbS sickling.
- Hematuria and hyposthenuria are common renal abnormalities.
- Papillary necrosis may be patchy and may coexist with cortical scarring.
- Proteinuria is common in disease; Occasional nephrotic syndrome accompanies glomerular sclerosis.

Source materials and scope

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th edition (2026).
- Chapter 20: The Kidney — Sickle Cell Nephropathy; renal papillary necrosis; chronic kidney disease; renal infarcts.
- Chapter 14: Red Blood Cell and Bleeding Disorders — Sickle Cell Disease.
- Original visual diagrams and constructed vignettes created for this lecture; no textbook micrographs reproduced.