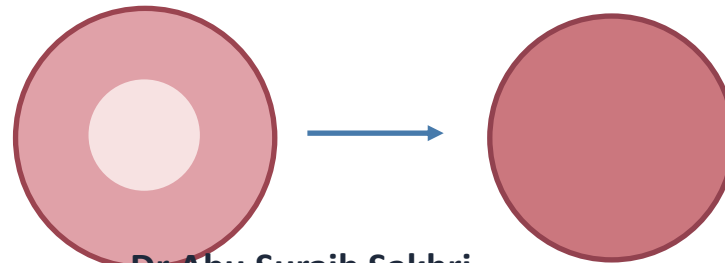

Hereditary Spherocytosis

Red cell membrane skeleton, splenic hemolysis and clinical expression



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Learning objectives

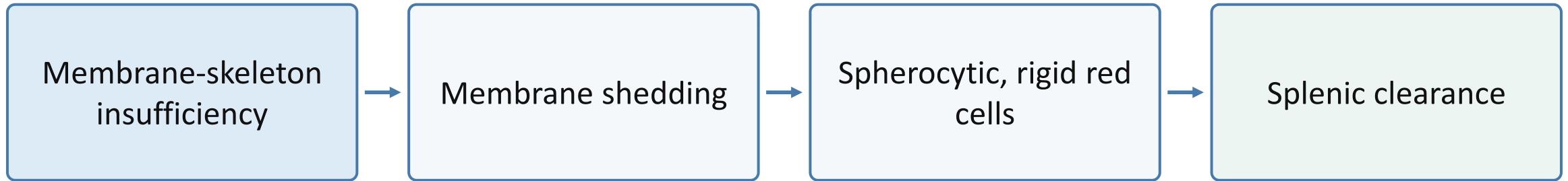
- Explain how membrane-skeleton proteins maintain red cell deformability.
- Trace membrane loss to spherocyte formation and splenic destruction.
- Connect the laboratory findings with the underlying mechanisms.
- Interpret clinical severity, crises, and the effect of splenectomy.

Definition and core lesion

- Inherited abnormality of the red cell membrane skeleton.
- Progressive membrane loss converts red cells from disks toward spheres.
- Reduced deformability predisposes cells to splenic sequestration.
- Premature removal by macrophages produces extravascular hemolysis.

The primary defect is intrinsic to the red cell; The spleen is the chief site of destruction.

Hereditary spherocytosis in one mechanism



A structural membrane abnormality becomes a clinical hemolytic anemia.

Hemolysis: Essential parent context

Extravascular hemolysis

- Premature removal within phagocytes
- Often linked to impaired red cell deformability
- Can produce splenomegaly and jaundice

Intravascular hemolysis

- Red cell rupture within the circulation
- Can produce hemoglobinemia and hemoglobinuria
- Mechanistically distinct from typical HS

Hereditary spherocytosis is a model of extravascular hemolysis.

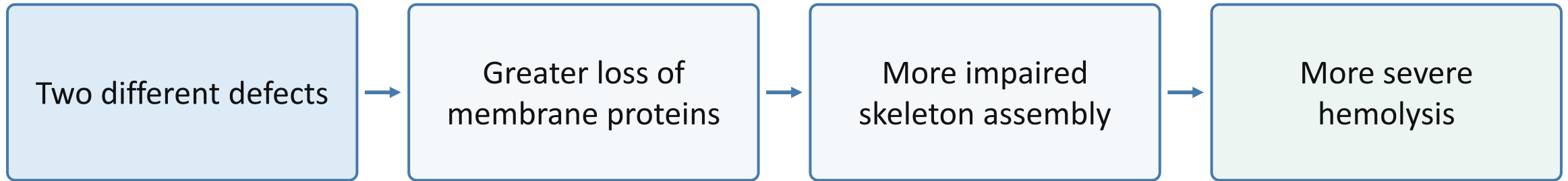
Geographic occurrence

- Hereditary spherocytosis occurs worldwide.
- The supplied Robbins text reports its highest prevalence in northern Europe.
- The reported northern European prevalence is approximately 1 in 5,000.
- Prevalence and inheritance are context, not standalone diagnostic tests.

Inheritance patterns

- Approximately 75% of cases show an autosomal dominant pattern.
- Other patients may have a more severe phenotype associated with two different defects.
- Inheritance of two different deleterious alleles is termed compound heterozygosity.
- Family history supports suspicion, but clinical severity varies.

Why two defective alleles can produce severe disease



Compound heterozygosity with deeper structural deficiency and, generally, greater severity.

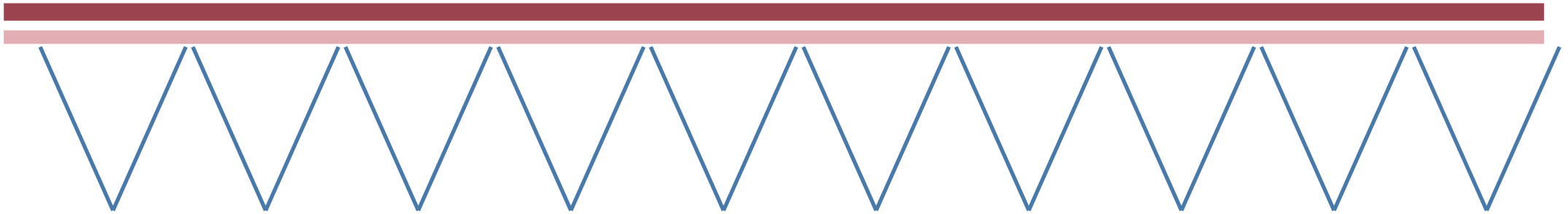
The normal red cell must be deformable

- The biconcave red cell can change shape in narrow microvascular passages.
- Its specialized membrane skeleton supplies flexibility and durability.
- The skeleton lies directly beneath the plasma membrane.
- The spleen makes exceptional demands on red cell deformability.

Membrane mechanics are central to red cell survival.

Normal red cell: Two coupled layers

Lipid bilayer



Submembranous protein lattice

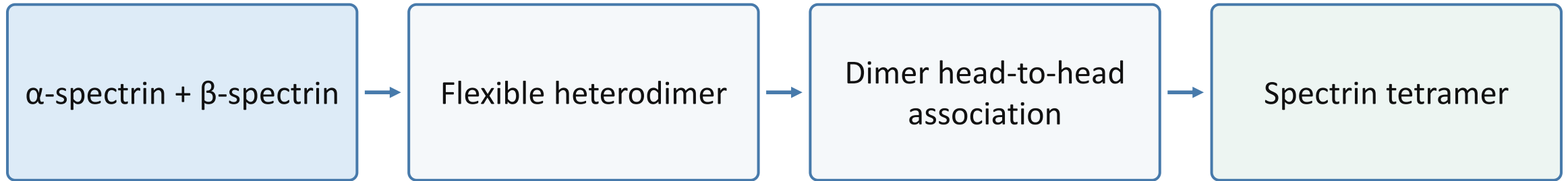
Native schematic: The membrane and skeletal meshwork function as a coupled mechanical system.

Schematic — not to molecular scale

Spectrin: The principal scaffold

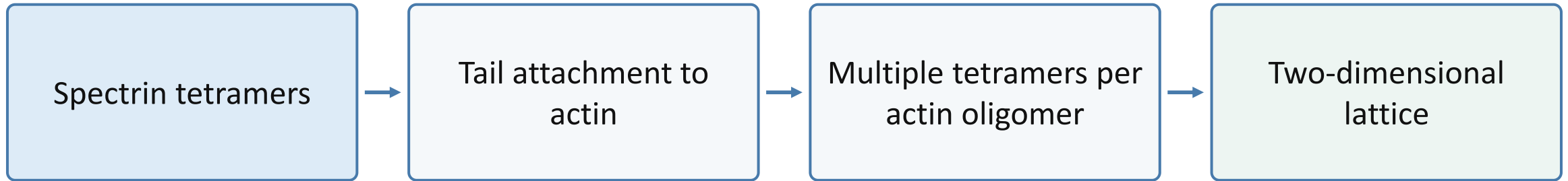
- Spectrin is the chief structural protein of the red cell skeleton.
- Its α - and β -polypeptide chains form flexible helical heterodimers.
- Spectrin dimers connect to other units to form a resilient mesh.
- Defects that diminish spectrin compromise the skeleton as a whole.

From spectrin dimer to tetramer



The association of spectrin units permits an extended network beneath the membrane.

How the spectrin–actin network forms



The network can stretch and recoil while the red cell deforms.

Two attachment systems connect skeleton to bilayer

Membrane tether: Ankyrin pathway

Band 3 (transmembrane)



Ankyrin + band 4.2



Spectrin

Membrane tether: Protein 4.1 pathway

Glycophorin A (membrane)



Protein 4.1



Spectrin / actin junction

Two specific anchoring relationships stabilize the overlying bilayer.

Ankyrin–band 3 anchoring pathway

- Band 3 is a transmembrane ion transporter.
- Ankyrin and band 4.2 connect spectrin to band 3.
- This interaction tethers the skeleton to the lipid bilayer.
- Mutations disrupting this route favor membrane instability.

Protein 4.1–glycophorin pathway

- Protein 4.1 contributes a second membrane-skeleton connection.
- It couples the tail region of spectrin to glycophorin A.
- This connection acts alongside ankyrin–band 3 tethering.
- A mechanically integrated bilayer and skeleton are required for normal red cells.

Principal proteins implicated in HS

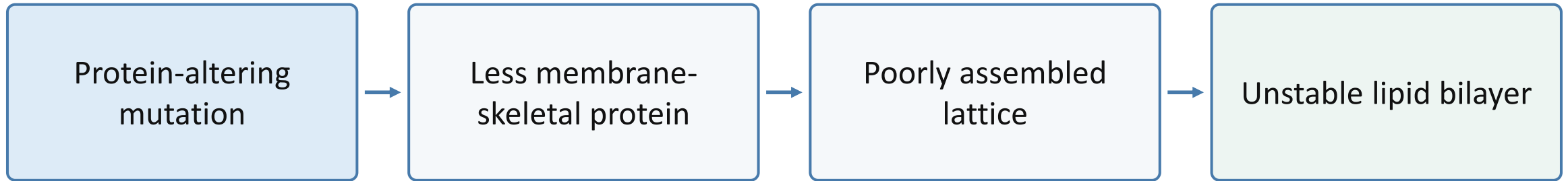
Protein	Normal role	Pathogenic consequence
Ankyrin	Linker in band 3 tether	Weakened membrane attachment
Band 3	Transmembrane anchor / transporter	Impaired bilayer–skeleton coupling
Spectrin (α or β)	Flexible cytoskeletal scaffold	Defective skeletal lattice
Band 4.2	Stabilizes ankyrin–band 3 complex	Less stable skeleton anchorage

Protein functions and mutation targets are drawn; This is not a complete genetic variant catalogue.

A common genetic consequence: Missing protein

- Many HS mutations as frameshifts or premature stop codons.
- A mutant allele may fail to make the corresponding protein.
- Insufficiency of one component limits assembly of the wider skeleton.
- The membrane then becomes vulnerable to loss during circulation.

Gene defect to cytoskeletal insufficiency

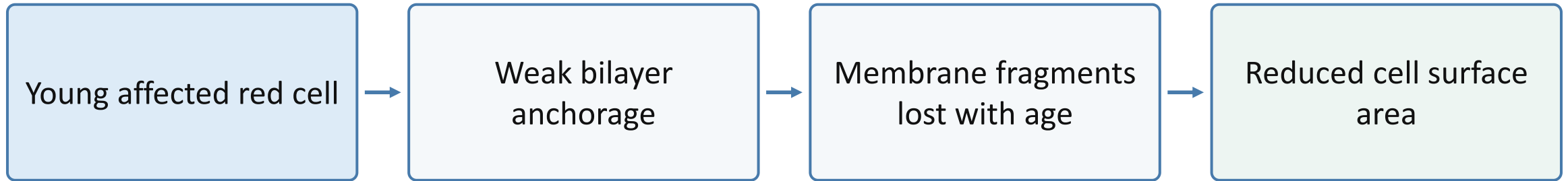


The effect is not confined to one protein; Insufficiency can destabilize the integrated network.

Why young HS red cells may look normal

- Young hereditary spherocytosis red cells may retain normal shape.
- Membrane instability is expressed progressively as red cells circulate.
- Repeated passage and aging allow cumulative loss of membrane fragments.
- Spherocytes thus represent the evolving consequence of a structural defect.

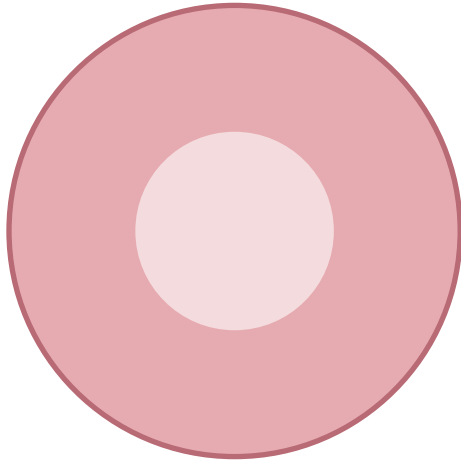
Progressive membrane shedding



Progressive membrane loss, rather than initial red cell production as a sphere, explains the characteristic shape.

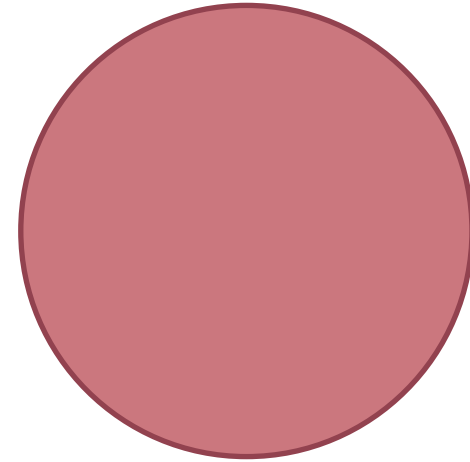
A disk becomes a sphere

Normal biconcave erythrocyte



Relatively large surface area for its volume;
Central pallor in a planar view.

Spherocytic erythrocyte



Reduced membrane area relative to contents;
Dense, round appearance.

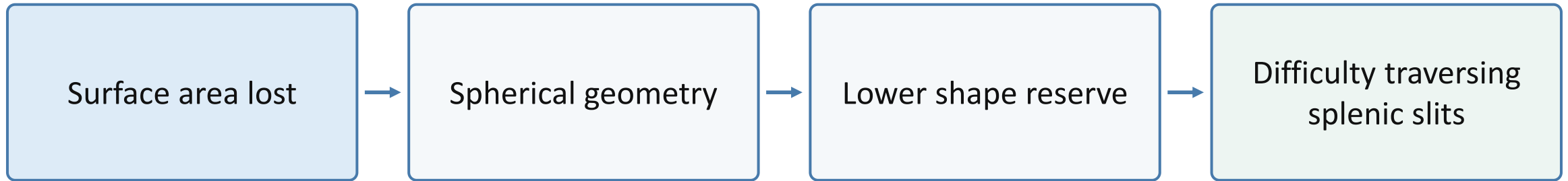
Schematic — not a photomicrograph

Original diagram based on the described shape change; Not a clinical smear.

Geometry: Falling surface-area-to-volume ratio

- Membrane vesiculation decreases surface area relative to cell contents.
- The cell becomes progressively less able to retain a biconcave outline.
- A sphere uses the least surface area for a given volume.
- Shape change is the visible expression of lost membrane.

Why a spherocyte has poor deformability

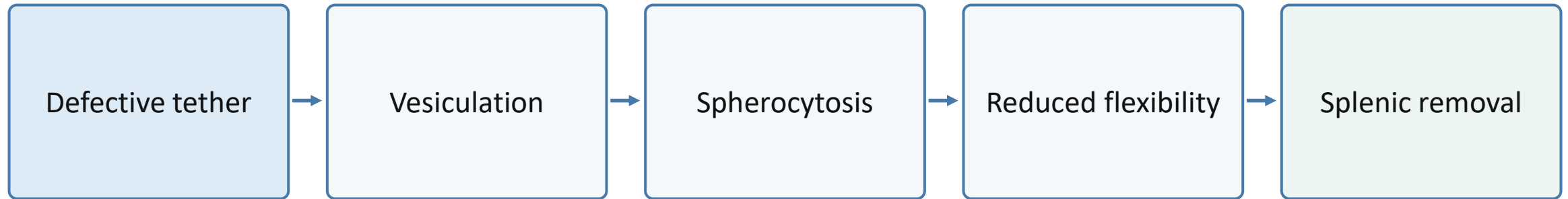


Spherocytes cannot make the extreme contour changes demanded by splenic circulation.

The potassium-and-water contribution

- Splenic exposure can intensify membrane loss from HS red cells.
- Affected red cells may lose K^+ ions and H_2O .
- Cellular dehydration contributes to increased mean cell hemoglobin concentration.
- The result compounds impaired cell geometry and splenic retention.

Complete pathogenic chain



A single pathway connects gene-level lesions with anemia, splenomegaly and jaundice.

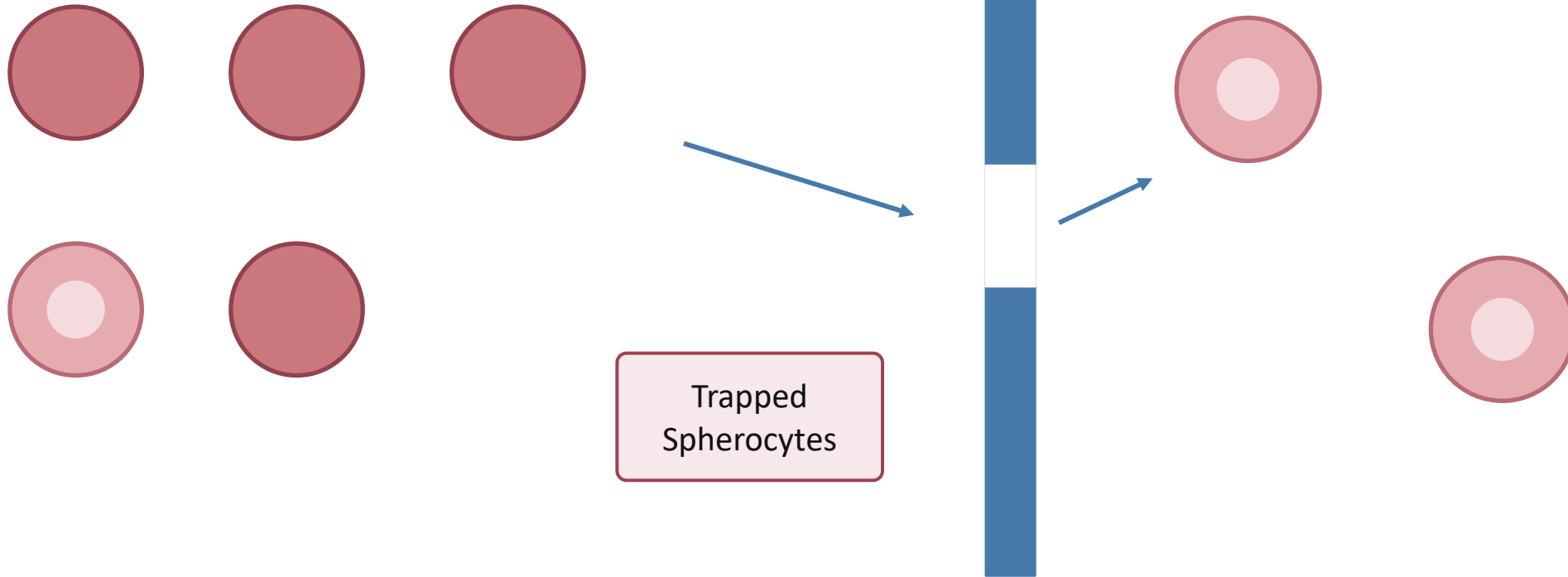
Why the spleen is the decisive organ

- Normal erythrocytes traverse the splenic red-pulp cords to reach venous sinusoids.
- This transition requires pronounced mechanical deformation.
- Spherocytes are poorly suited to that passage.
- Retention creates prolonged contact with resident phagocytes.

Splenic red-pulp filtration

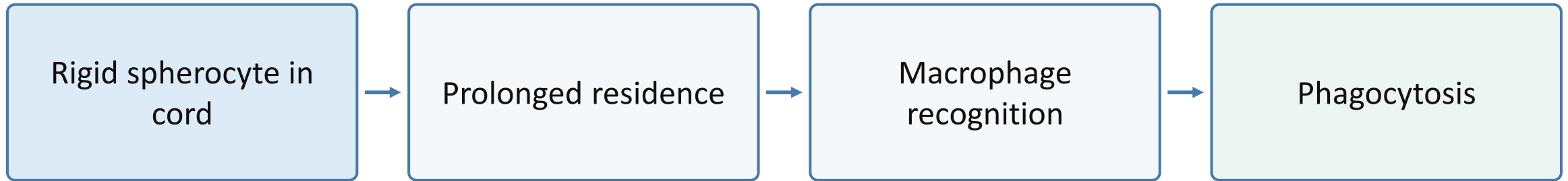
Splenic red-pulp cords

Sinusoid



Less deformable spherocytes accumulate in cords; More deformable cells can pass to sinusoids.

From mechanical retention to destruction



Splenic destruction is predominantly extravascular; It need not involve red cell rupture in plasma.

Local splenic conditions worsen red cell injury

- Prolonged erythrostasis exposes spherocytes to metabolically demanding conditions.
- Glucose depletion and reduced pH as proposed contributors.
- Membrane loss and loss of K^+ and H_2O may intensify during sequestration.
- These influences amplify the underlying membrane-skeleton lesion.

Splenectomy reveals the mechanism

- Removal of the spleen markedly reduces premature red cell removal.
- Anemia can be corrected even though the inherited membrane lesion remains.
- Spherocytes therefore persist after splenectomy.
- The intervention separates cell shape from the organ-specific site of clearance.

A hematologic response to splenectomy does not mean the genetic membrane defect has disappeared.

Red cell survival is markedly shortened

Red cell lifespan in days

Normal red

120 days

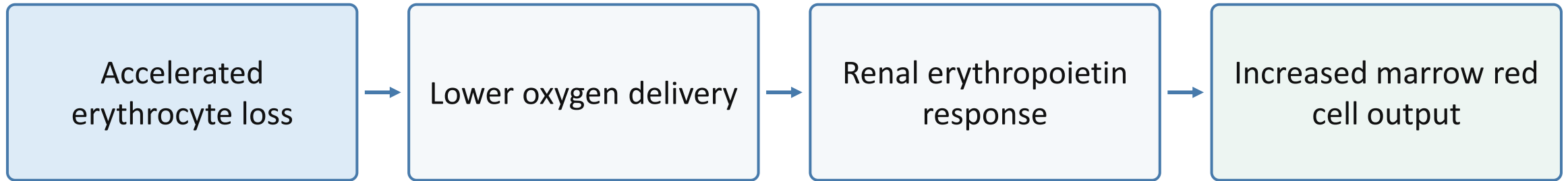


HS red cell

10–20

Robbins gives an average affected-cell lifespan of 10–20 days, compared with about 120 days normally.

Compensatory erythropoiesis



Marrow compensation can be sufficient in mild HS or inadequate when hemolysis is greater.

Bone marrow response

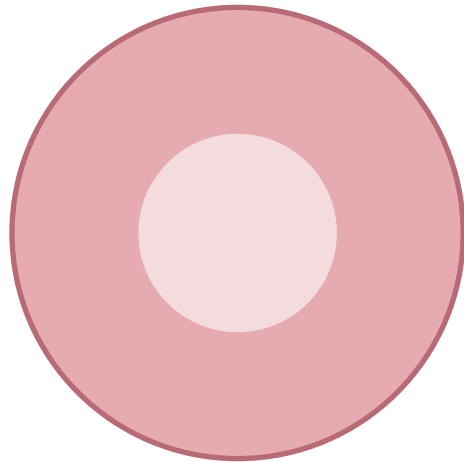
- Enhanced erythropoietin drive stimulates erythroid precursors in the marrow.
- Erythroid hyperplasia is a general consequence of sustained hemolytic anemia.
- An expanded erythroid compartment attempts to replace prematurely lost cells.
- The magnitude of marrow compensation influences clinical severity.

Reticulocytosis: The blood counterpart of compensation

- Increased marrow output releases more reticulocytes into the circulation.
- Reticulocytes are larger, RNA-containing recently released red cells.
- Peripheral reticulocytosis reflects an active erythropoietic response.
- An abrupt loss of reticulocyte production is central to an aplastic crisis.

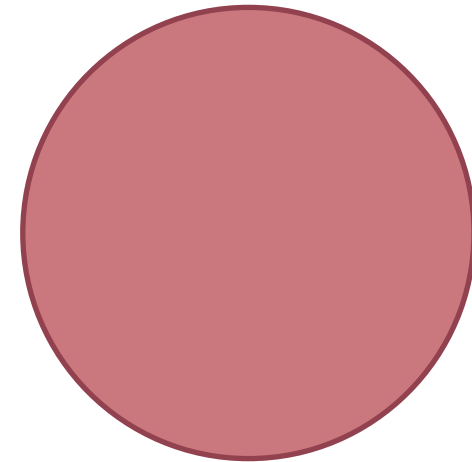
Peripheral morphology: Identify the pattern

Red cell with central pallor



Biconcavity gives a pale center in the conceptual planar projection.

Spherocyte



Round, compact red cell lacking the typical central pallor.

Schematic — not a photomicrograph

Schematic — genuine blood film not available in the provided source files.

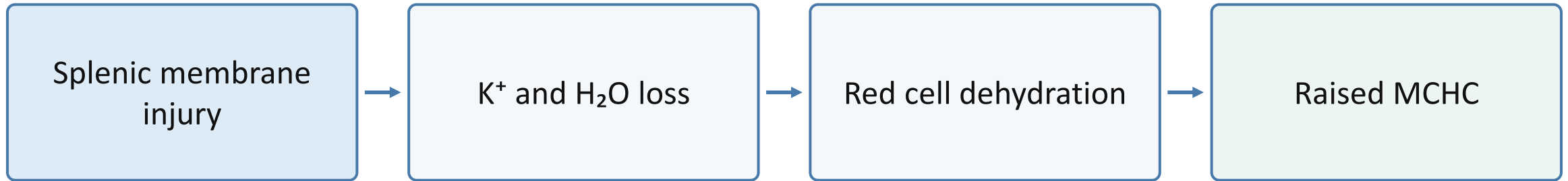
What morphology establishes—and what it does not

- A spherocytic shape supports a red cell membrane or clearance abnormality.
- Morphology should be interpreted with the clinical and inherited pattern.
- The underlying membrane protein defect cannot be identified from shape alone.
- Diagnostic testing must be integrated rather than inferred from an isolated cell.

Raised mean cell hemoglobin concentration

- An increased mean cell hemoglobin concentration in HS.
- The change reflects dehydration as red cells lose K^+ and H_2O .
- Membrane loss is the cause of spherocytic geometry; Dehydration modifies cell concentration.
- A blood-count index is supportive rather than molecularly specific.

Mechanism of increased MCHC

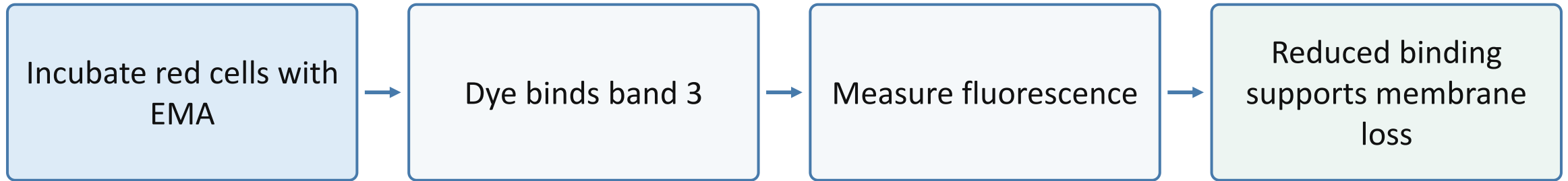


MCHC = mean cell hemoglobin concentration; It is not synonymous with total hemoglobin concentration.

Eosin-5-maleimide test: Basic principle

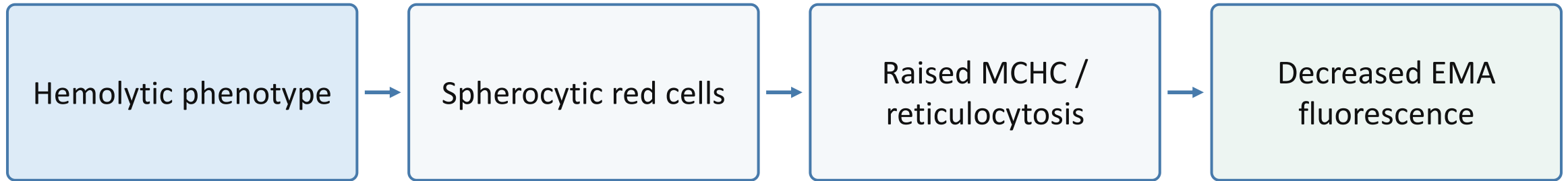
- Eosin-5-maleimide (EMA) is a fluorescent dye used in confirmatory testing.
- It binds selectively to the band 3 membrane protein.
- Disorders such as HS with reduced membrane material show decreased fluorescence.
- The signal is an indicator of membrane abnormality, not direct allele sequencing.

EMA binding assay: Interpretation



EMA fluorescence as a useful confirmatory test; Interpretation requires clinical context.

Pathology-centered diagnostic reasoning



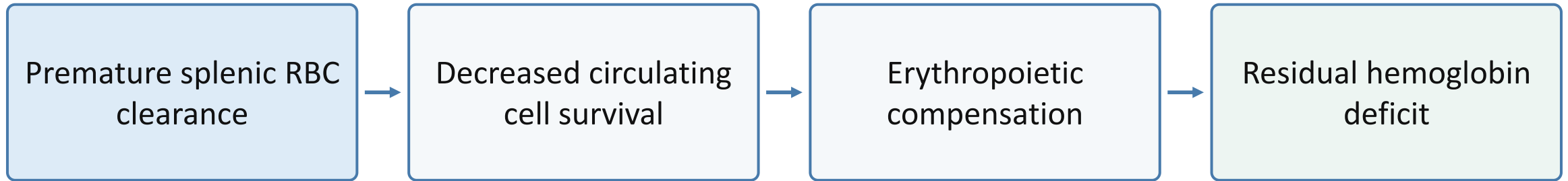
Concordance between mechanism, morphology and laboratory findings is more informative than any one feature.

The characteristic clinical triad

- Anemia: Red cell destruction outstrips replacement.
- Splenomegaly: Sustained red cell sequestration and macrophage activity.
- Jaundice: Increased bilirubin generation during heme catabolism.
- The degree of each finding varies considerably among affected patients.

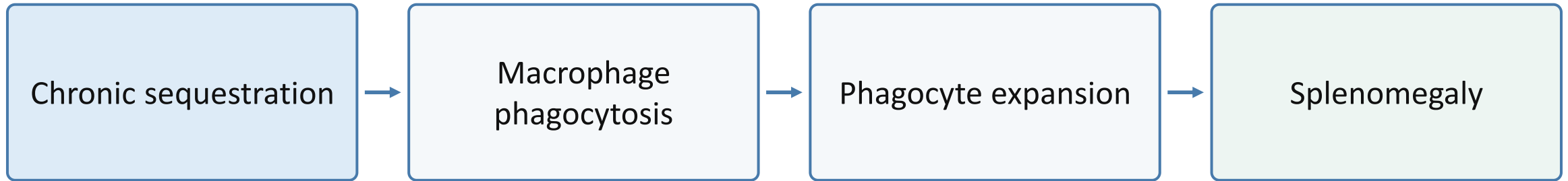
Anemia + splenomegaly + jaundice reflects the physiology of extravascular hemolysis.

Why anemia develops



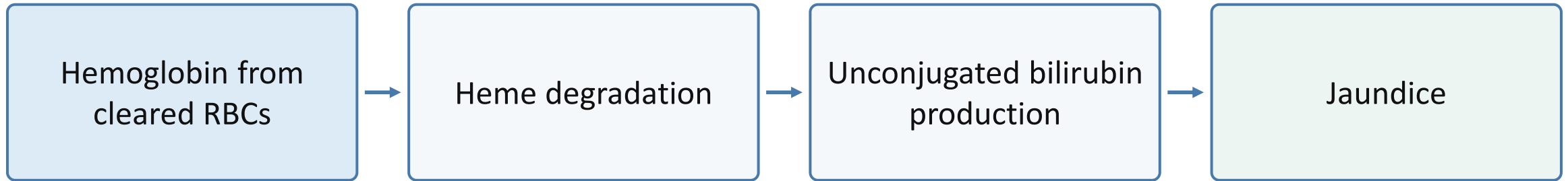
Clinical anemia emerges when compensatory production cannot keep pace with red cell loss.

Why the spleen enlarges



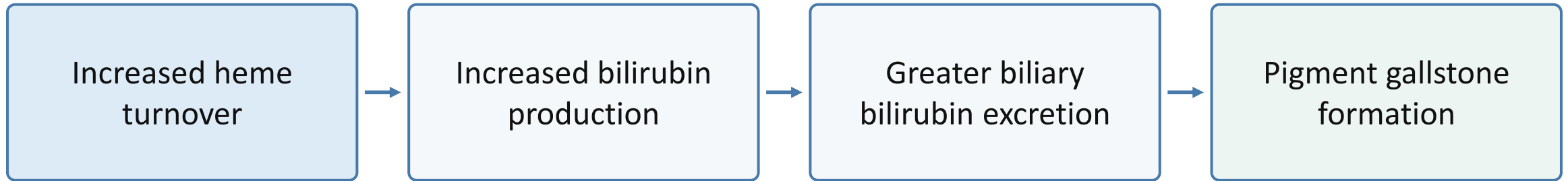
Splenic enlargement is a pathologic consequence of sustained extravascular destruction.

Why jaundice develops



The parent hemolytic-anemia section specifies unconjugated hyperbilirubinemia in uncomplicated hemolysis.

From chronic hemolysis to pigment stones



Cholelithiasis can produce an additional symptomatic burden independent of the anemia.

Mild or compensated disease

- In approximately 20%–30%, increased erythropoiesis fully compensates for reduced survival.
- These patients may have few symptoms or remain nearly asymptomatic.
- A minimal hemoglobin deficit does not imply normal red cell survival.
- Clinical findings reflect the balance between destruction and production.

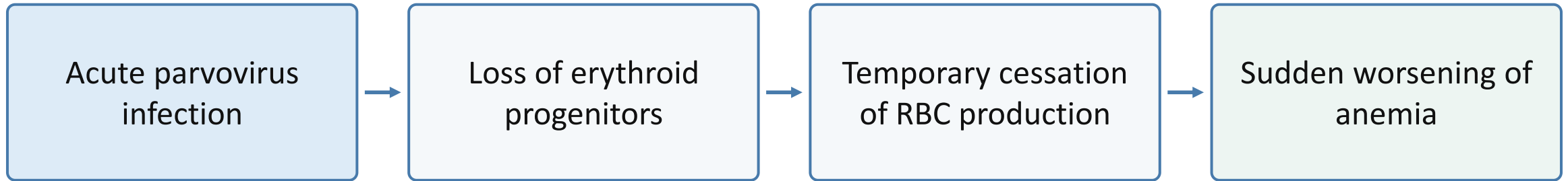
Typical chronic disease

- For most affected patients, compensation does not entirely match hemolysis.
- The resulting anemia is usually mild to moderate and chronic.
- Splenomegaly and jaundice reflect continuous extravascular clearance.
- A relatively stable baseline may still be disrupted by acute events.

Severe disease in the newborn

- A small minority present at birth with marked jaundice.
- Severe neonatal presentation is especially associated with compound heterozygosity.
- Exchange transfusion may be necessary.
- Early presentation reflects high hemolytic burden relative to compensation.

Aplastic crisis: The interruption of supply

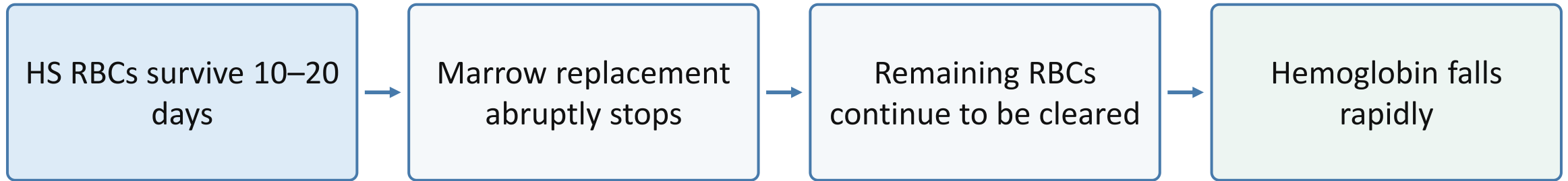


Because red cell survival is already short, even brief suppression of replacement is consequential.

Parvovirus-associated marrow suppression

- Parvovirus can infect and kill erythroid progenitors.
- During the infection, new red cell production may temporarily cease.
- Recovery after immune clearance, generally within 1–2 weeks.
- Transfusion support may be required during the acute period.

Why a short production pause is dangerous



An aplastic crisis is a failure of production superimposed on accelerated clearance.

Hemolytic crisis: Accelerated clearance

- A hemolytic crisis reflects a transient increase in red cell destruction.
- Robbins gives infectious mononucleosis with increased spleen size as an example.
- The underlying membrane lesion is unchanged during the intercurrent event.
- , hemolytic crises are generally less significant than aplastic crises.

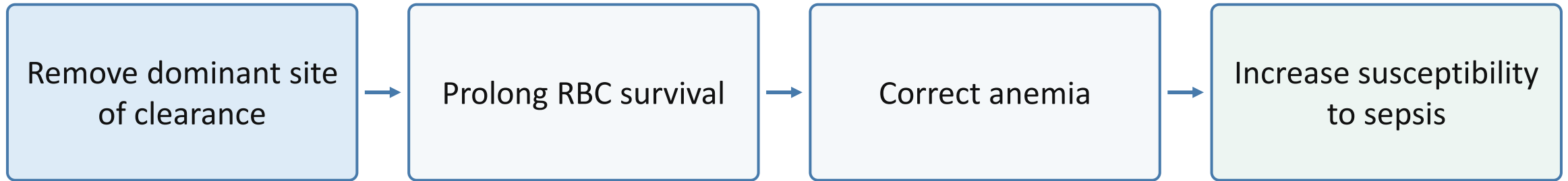
Aplastic crisis versus hemolytic crisis

Feature	Aplastic crisis	Hemolytic crisis
Dominant process	Red cell production falls	Splenic red cell destruction rises
Example trigger	Parvovirus infection	Intercurrent infection / splenic enlargement
Immediate mechanism	Erythroid progenitor injury	Increased clearance of rigid red cells
Major risk	Rapid anemia worsening as cells age out	Additional hemolytic anemia
Robbins emphasis	Potential need for transfusion	Usually less consequential

Clinical complications arise from distinct mechanisms

- Chronic hemolysis produces anemia and bilirubin overload.
- Pigment gallstones reflect sustained heme turnover.
- Aplastic crisis represents interruption of erythropoiesis.
- Hemolytic crisis represents increased destruction under additional splenic stress.

Splenectomy: Benefit and cost



The spleen is an important filter of blood-borne bacteria.

Before and after splenectomy

Before splenectomy

- Splenic sequestration is prominent
- Spherocytes have shortened survival
- Hemolytic anemia may persist

After splenectomy

- Spherocytes still circulate
- Red cell loss is diminished
- Anemia improves; Sepsis risk rises

Splenectomy treats the consequence of membrane pathology, not the inherited molecular cause.

Why sepsis risk matters after splenectomy

- The spleen normally filters blood-borne microorganisms.
- Its removal reduces an important host-defense mechanism.
- The resulting increased risk of serious infection must be weighed against anemia control.
- The Robbins passage does not supply a regimen for prophylaxis or vaccination.

Case: Chronic anemia with splenomegaly

Clinical vignette

A patient has a long-standing hemolytic anemia, jaundice and an enlarged spleen. The peripheral blood includes numerous small, densely stained round erythrocytes.

Teaching question

How does a membrane-skeleton defect produce the clinical triad?

Answer: Membrane shedding → spherocytes → splenic phagocytosis → anemia, splenomegaly and bilirubin excess.

Case: Sudden worsening after viral illness

Clinical vignette

A patient with stable hereditary spherocytosis develops a pronounced fall in hemoglobin during an acute illness, with markedly reduced erythroid output.

Teaching question

Which mechanism best explains this abrupt deterioration?

Answer: Transient suppression of red cell production—consider a parvovirus-associated aplastic crisis.

Case: Anemia improves, spherocytes remain

Clinical vignette

A person with hereditary spherocytosis undergoes splenectomy. The anemia improves, but spherocytes are still seen on the blood film.

Teaching question

Does persistent spherocytosis mean splenectomy failed?

Answer: No. The spleen was removed as a site of clearance; The intrinsic membrane lesion persists.

Conceptual differential: Site of hemolysis

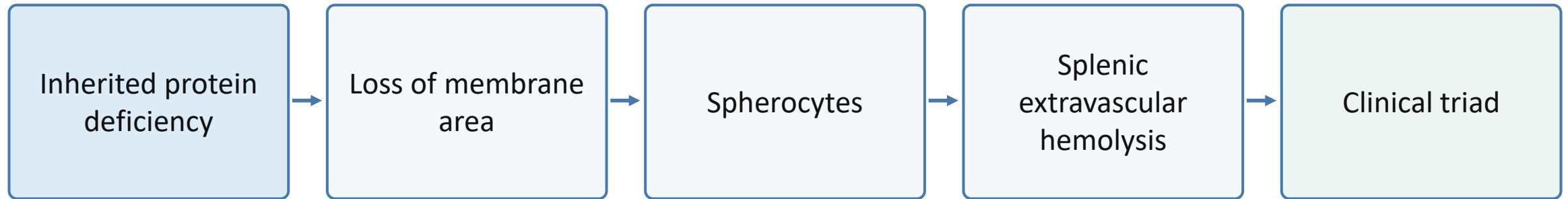
Observation	Typical HS (extravascular)	Intravascular hemolysis
Dominant process	Macrophage removal of intact RBCs	Red cell disruption in circulation
Anatomic emphasis	Splenic red pulp	Blood plasma / vasculature
Splenomegaly	Expected in many patients	Not typical per Robbins
Urinary hemoglobin	Not a defining feature	Can be present
Shared biology	Accelerated heme degradation	Accelerated heme degradation

This contrast is restricted to the general hemolytic-anemia framework.

Important interpretive distinctions

- Membrane skeleton insufficiency is the primary lesion; Hemolysis is its consequence.
- Spherocytes can remain after splenectomy because the shape defect persists.
- Elevated MCHC relates to dehydration; Reduced surface area explains spherical shape.
- Aplastic and hemolytic crises differ in production versus destruction.

Mechanism consolidated



Genotype → membrane mechanics → cellular geometry → organ-level clearance → clinical phenotype.

Clinical synthesis

- Severity depends on whether marrow compensation keeps pace with shortened cell survival.
- Chronic bilirubin excess may lead to symptomatic pigment gallstones.
- Parvovirus-mediated cessation of production explains severe aplastic crises.
- Splenectomy improves anemia but increases infection susceptibility.

References and source boundaries

Primary source

Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th edition (2026). Chapter 14: Red Blood Cell and Bleeding Disorders, pp. 579–581.

Source scope

Hereditary Spherocytosis, with limited parent-section context from Hemolytic Anemias. All mechanism diagrams and cell drawings are original editable schematics.

No genuine blood-smear image or textbook figure is reproduced in this deck.