

Hemolytic Anemias

Red-cell destruction, compensatory erythropoiesis, and clinicopathologic mechanisms

Mechanisms · morphology · clinical correlation

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Learning objectives

- Explain the fundamental features shared by hemolytic anemias.
- Distinguish intravascular from extravascular hemolysis mechanistically.
- Relate hemolysis to marrow, splenic, hepatic, and renal findings.
- Classify major inherited and acquired causes by underlying mechanism.

Hemolysis: Destruction exceeds normal turnover

**Premature red-cell
destruction**



Shortened circulating red-cell
lifespan

**Compensatory
erythropoietic response**

Anemia results when erythropoietic compensation does not maintain red-cell mass.

Three unifying features of hemolytic anemia

Reduced survival

Circulating red cells survive for less than the usual 120 days.

Marrow adaptation

Elevated erythropoietin increases erythroid production.

Catabolic products

Hemoglobin degradation products accumulate.

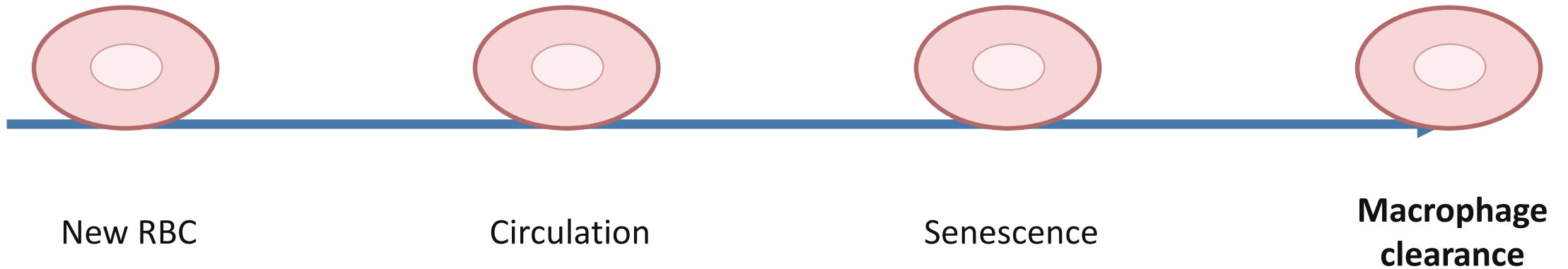
Variable compensation

Production may partially offset destruction.

These features apply despite markedly different initiating diseases.

Normal red-cell lifespan provides the benchmark

Normal circulating red cells survive for approximately 120 days.

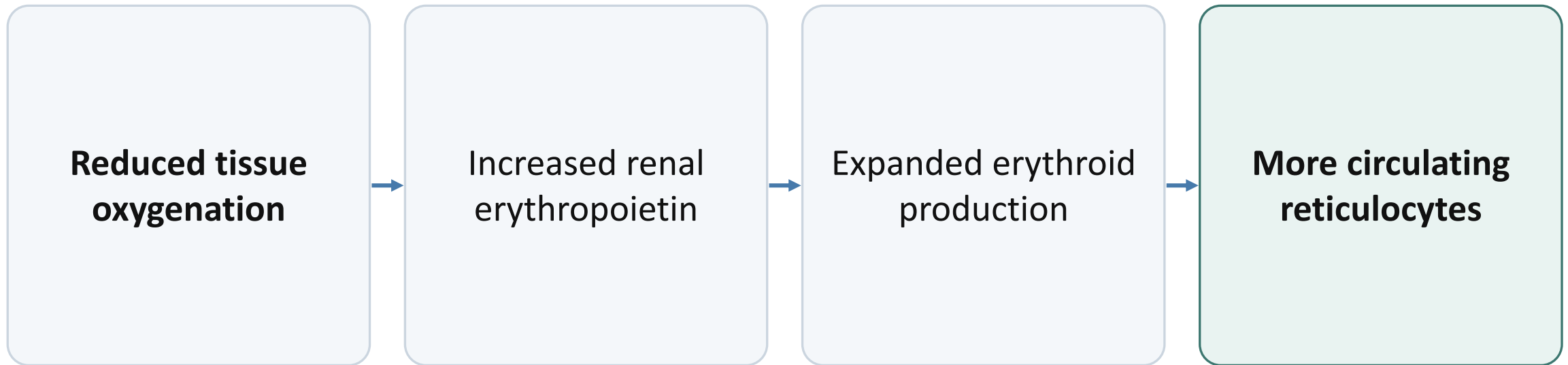


Typical lifespan: ~120 days

Schematic — original editable PowerPoint shapes

Hemolysis concerns shortened survival, not a specific mean corpuscular volume.

Oxygen delivery links anemia to the kidney



Reticulocytosis is an expected compensatory finding when marrow responsiveness is preserved.

Two major sites of premature red-cell removal

Extravascular

Macrophages ingest red cells, especially in the spleen.

Intravascular

Red cells rupture in the bloodstream.

Mixed mechanisms

The same etiologic disorder may involve more than one process.

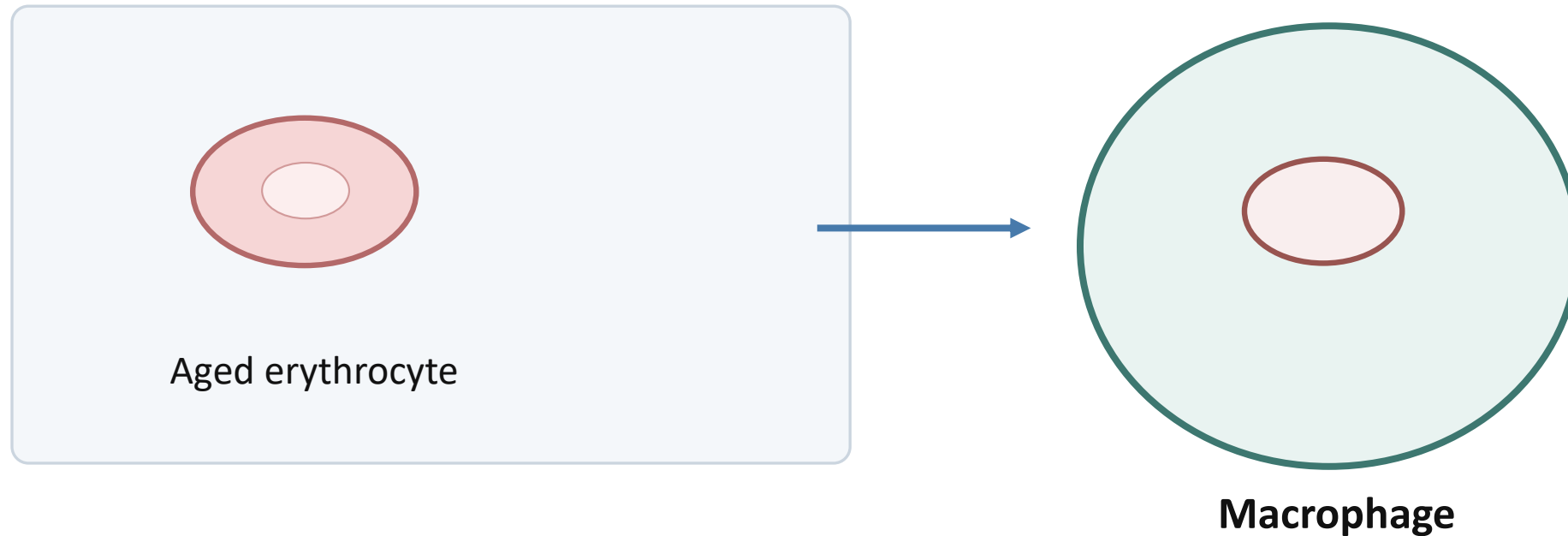
Shared endpoint

Hemoglobin degradation and marrow compensation follow both.

Site of destruction predicts useful clinicopathologic clues.

Physiologic clearance of senescent red cells

Macrophages in the spleen, liver, and marrow normally remove aged erythrocytes.



Schematic — original editable PowerPoint shapes

Premature macrophage clearance uses the same disposal system at excessive rates.

Aging red cells become recognizable to phagocytes

Age-related red-cell surface change



Recognition by phagocytic cells

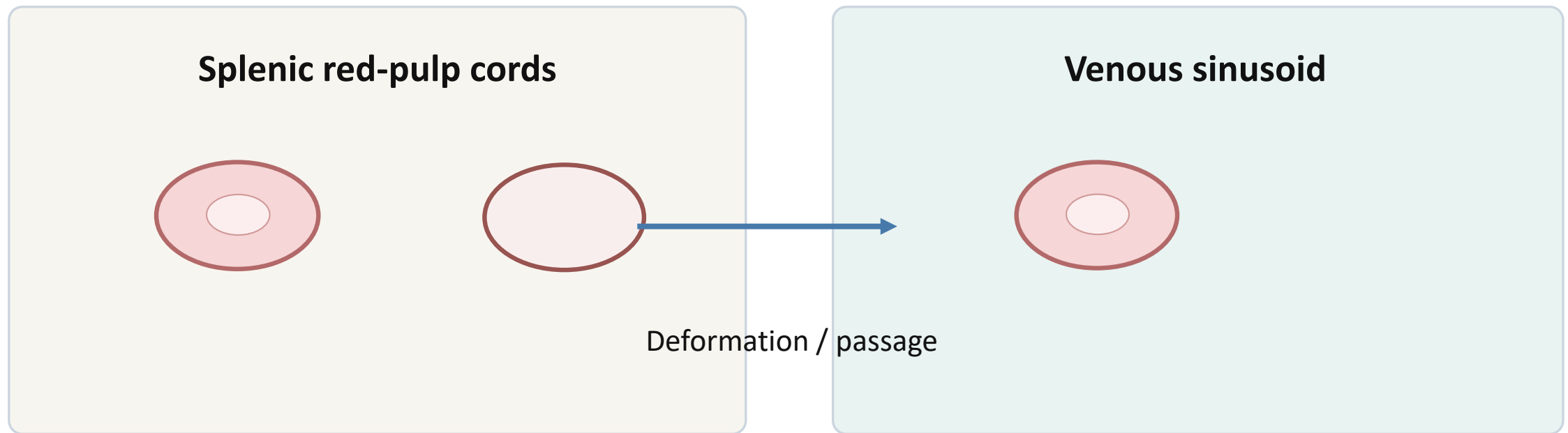


Removal within macrophages

The underlying aging signal is as involving surface-protein changes.

Red-cell deformability determines splenic passage

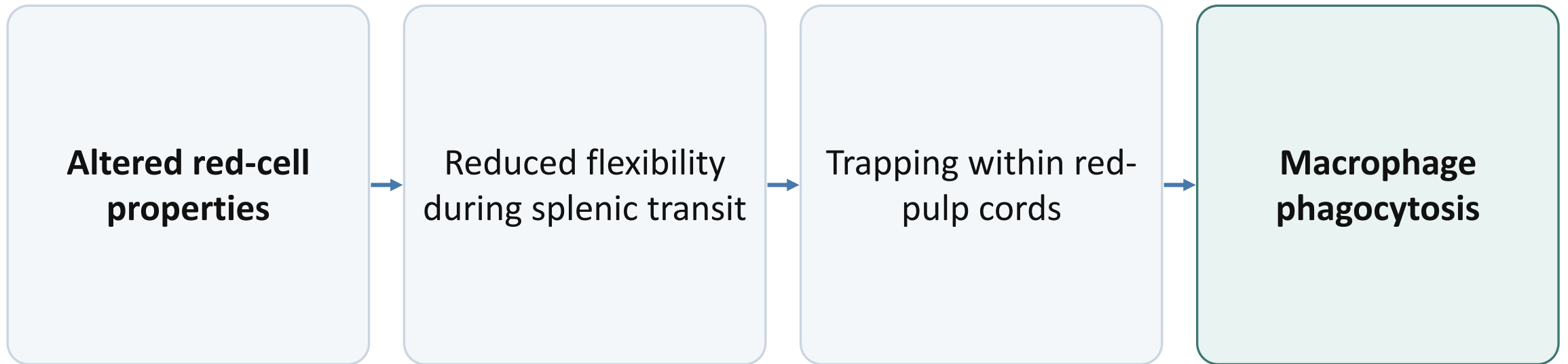
Red cells must deform substantially to travel from red-pulp cords into splenic sinusoids.



Poorly deformable cells are trapped

Reduced deformability increases sequestration and macrophage removal.

Extravascular hemolysis begins with impaired deformability



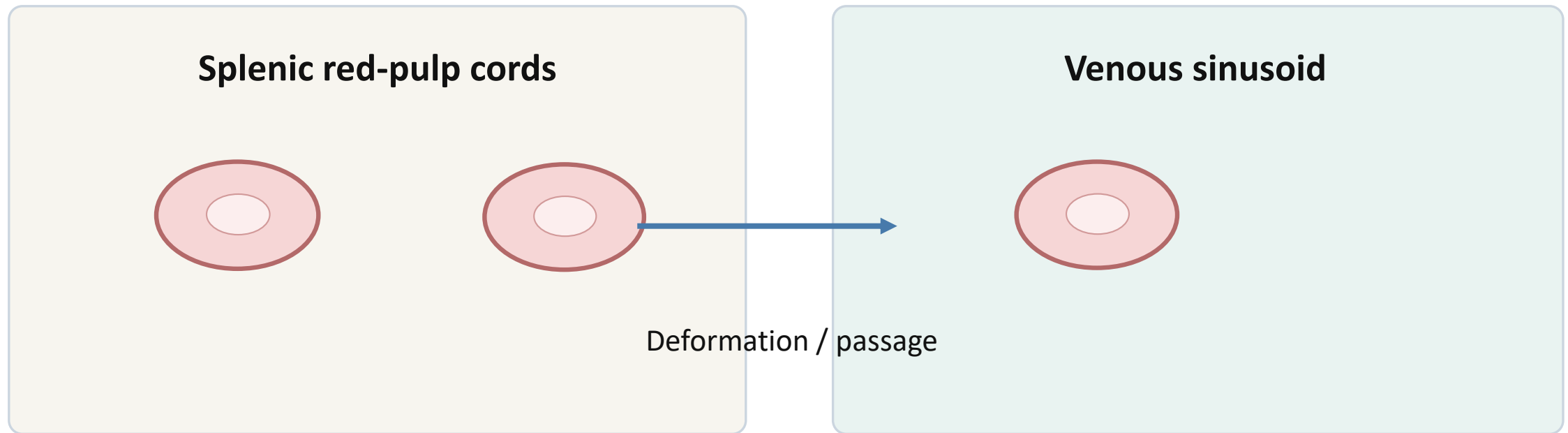
Location of cell destruction explains the dominant splenic manifestations.

Extravascular hemolysis is usually macrophage mediated

- The spleen is the principal clinically relevant site in many disorders.
- Liver and marrow macrophages also participate in erythrocyte clearance.
- Cell removal is premature, even though the phagocytic process resembles normal senescence.

Splenic sequestration amplifies phagocytic activity

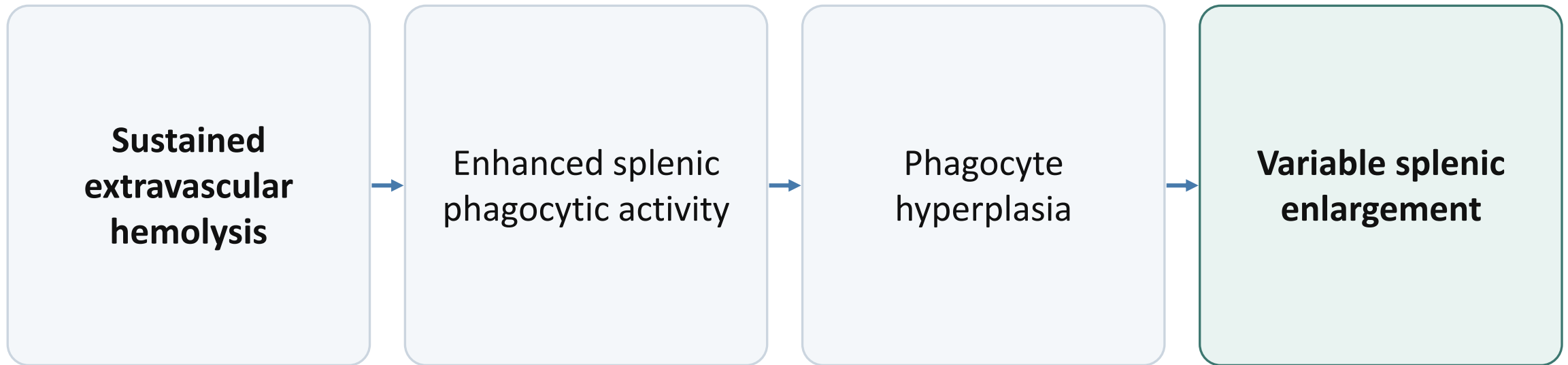
Trapped, poorly deformable erythrocytes are removed in splenic red-pulp cords.



Phagocytes remove retained cells

Repeated removal increases macrophage workload and red-pulp cellularity.

Macrophage hyperplasia produces splenomegaly



Splenomegaly is an anatomic consequence of a persistent clearance burden.

The classic extravascular clinical triad

Anemia

Premature red-cell removal may exceed replacement.

Splenomegaly

Increased splenic clearance enlarges the organ.

Jaundice

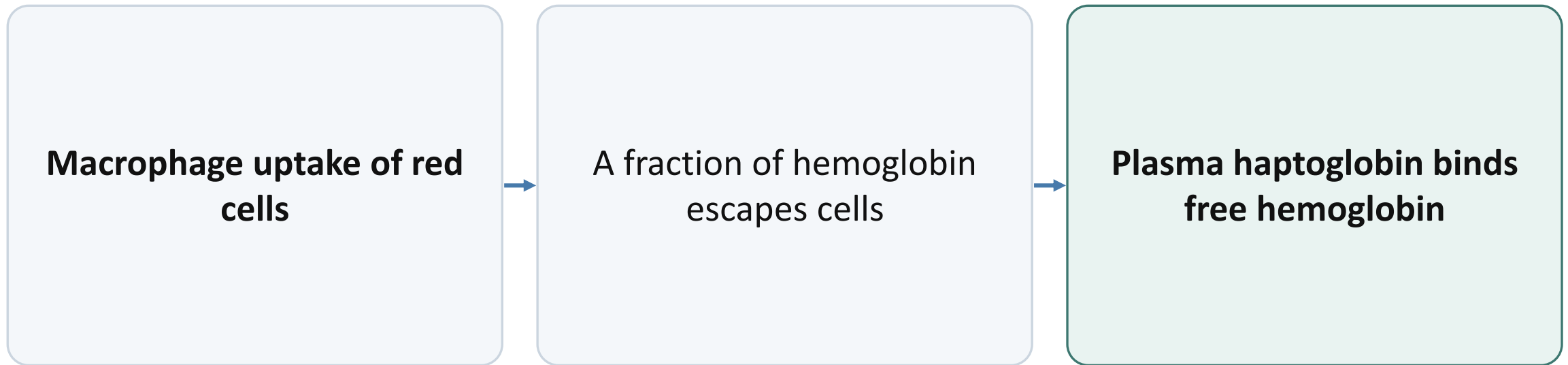
Increased heme catabolism raises bilirubin generation.

Interpret together

The triad favors extravascular destruction; It does not specify a unique etiology.

Symptoms and organ changes must be connected to their mechanism.

Extravascular destruction and circulating haptoglobin



Haptoglobin can be reduced in extravascular hemolysis, but the fall is variable.

Why splenectomy may benefit extravascular hemolysis

- Removing a major site of premature red-cell destruction can improve anemia.
- The effect is mechanistically most relevant when splenic sequestration is central.
- This principle does not imply that splenectomy is appropriate for every cause of hemolysis.

Intravascular hemolysis: Four initiating routes

Mechanical injury

Shearing or trauma physically disrupts erythrocytes.

Complement-mediated injury

Antibody recognition can trigger complement fixation.

Intraerythrocytic infection

Certain parasites injure infected red cells.

Exogenous toxins

Microbial and chemical factors can damage membranes.

Bloodstream rupture is less common than macrophage-mediated destruction in the Robbins framework.

Abnormal cardiac valves can damage red cells

**Passage across a
traumatizing valve**



Mechanical injury to
circulating RBCs



Intravascular hemolysis

The pathological process is mechanical, not necessarily immunologic.

Microvascular narrowing causes mechanical fragmentation

**Thrombi or tumor cells
narrow the microcirculation**



RBCs traverse injured or
restricted vessels



**Mechanical intravascular
red-cell injury**

Microangiopathic hemolysis is a mechanism with multiple possible underlying diseases.

Repetitive mechanical trauma is another route

Endurance activity

Prolonged physical impact can injure red cells.

Percussive hand trauma

Repetitive bongo drumming is a textbook example.

High-impact activity

Repeated trauma may cause intravascular destruction.

Principle

External repetitive force can be translated into red-cell injury.

Repetitive trauma is an example category, not a common cause of all hemolytic anemia.

Complement-mediated injury follows antigen recognition

Antibody binds a red-cell antigen



Complement fixation occurs



Membrane injury can cause intravascular lysis

Antibody-mediated hemolytic disorders are treated in detail in a separate unit.

Intraerythrocytic parasites can trigger lysis

Parasite infects red cell



Infected RBC is injured or
destroyed



**Intravascular hemolysis may
occur**

Falciparum malaria is the example named in the general Robbins section.

Clostridial sepsis illustrates direct toxic injury

**Clostridial infection
produces damaging enzymes**



Red-cell membranes are
digested

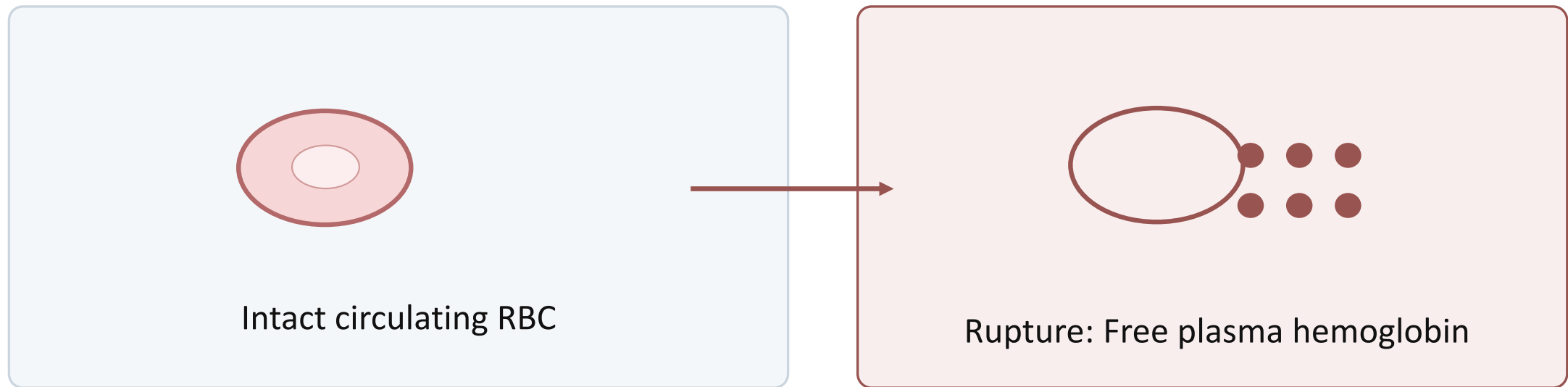


Intravascular hemolysis

The relevant mechanism is membrane injury from exogenous microbial products.

Intravascular hemolysis releases hemoglobin into plasma

Rupture in the circulation places hemoglobin directly into the plasma compartment.



Schematic — original editable PowerPoint shapes

Downstream findings depend partly on the capacity of the haptoglobin clearance system.

Haptoglobin scavenges liberated hemoglobin



This system reduces the amount of free hemoglobin available for renal filtration.

Haptoglobin depletion permits free hemoglobin accumulation

Ongoing intravascular hemolysis



Consumption of available haptoglobin



More unbound circulating hemoglobin

Marked depletion is a useful mechanistic signature of substantial bloodstream lysis.

Free hemoglobin may oxidize to methemoglobin

**Unbound plasma
hemoglobin**



Oxidation to methemoglobin

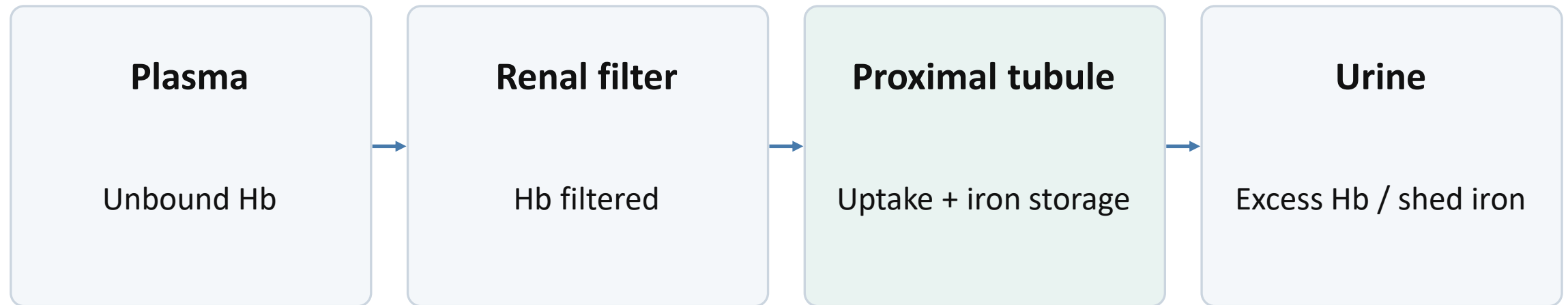


**Brown pigment in the
plasma/urine pathway**

The reddish-brown urinary appearance has a biochemical explanation.

Kidney handling of filtered hemoglobin

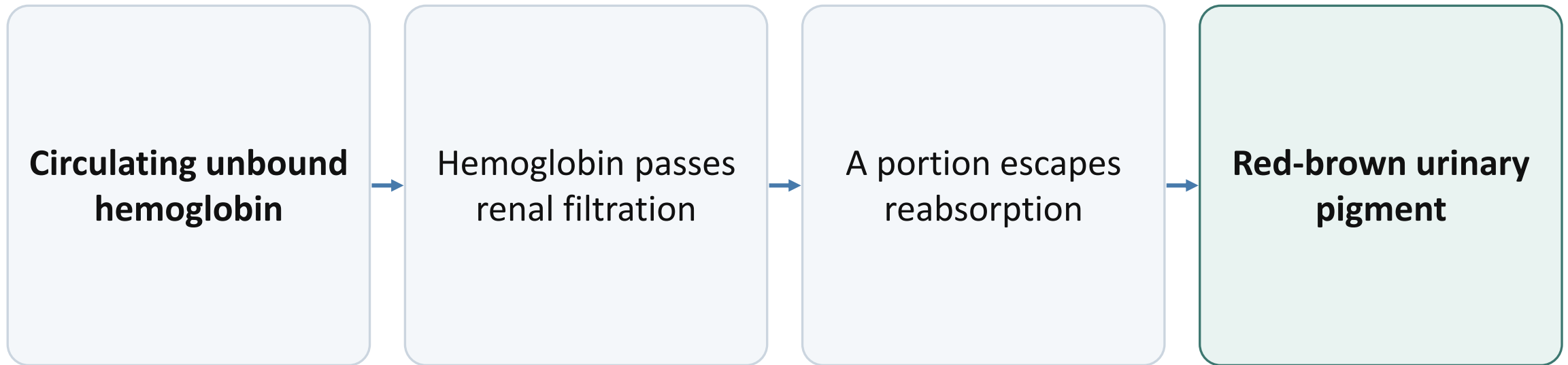
Filtered hemoglobin is reabsorbed and catabolized by proximal tubular cells.



Schematic — original editable PowerPoint shapes

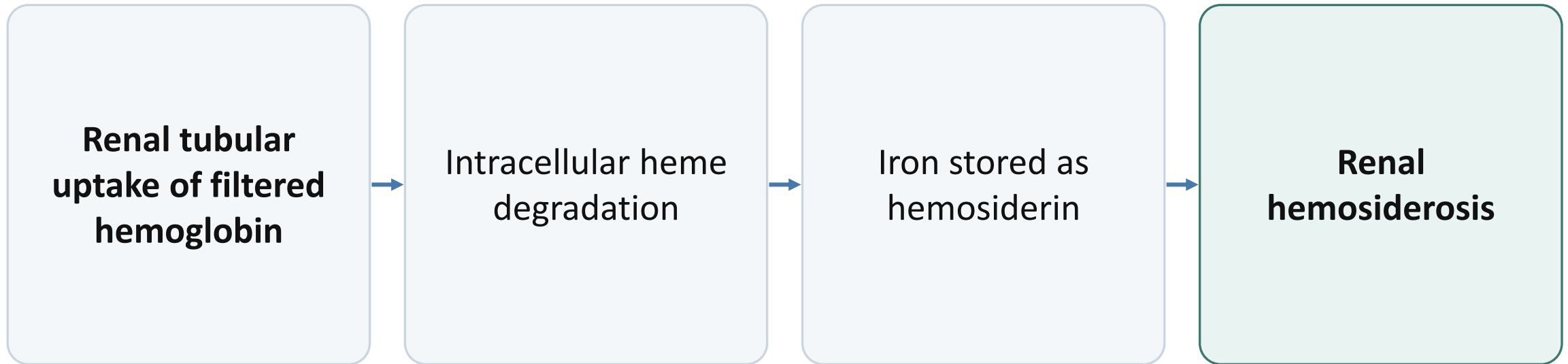
The proximal tubule is central to both renal iron deposition and urinary pigment.

Hemoglobinuria reflects overflow of renal handling



Hemoglobinuria is a consequence of intravascular release, not of splenic erythrophagocytosis alone.

Proximal tubules accumulate hemoglobin-derived iron



Iron deposition reflects tissue processing of the filtered pigment load.

Hemosiderinuria is linked to tubular-cell shedding

Hemosiderin accumulates in proximal tubular cells



Iron-containing tubular cells desquamate



Hemosiderin appears in urine

Hemosiderinuria and hemoglobinuria reflect different steps of the renal pathway.

Chronic intravascular loss may deplete iron

- Urinary hemoglobin contains iron that can leave the body.
- Iron also exits in sloughed, hemosiderin-containing tubular cells.
- Persistent urinary iron loss may ultimately cause iron deficiency.

The characteristic intravascular pattern

Anemia

Loss of circulating erythrocytes.

Hemoglobinemia

Free plasma hemoglobin after red-cell rupture.

Pigmenturia

Hemoglobinuria and/or hemosiderinuria.

Jaundice

Heme breakdown ultimately raises bilirubin production.

A plasma–renal pigment signature distinguishes intravascular from isolated splenic hemolysis.

Splenomegaly is not a defining feature of intravascular lysis

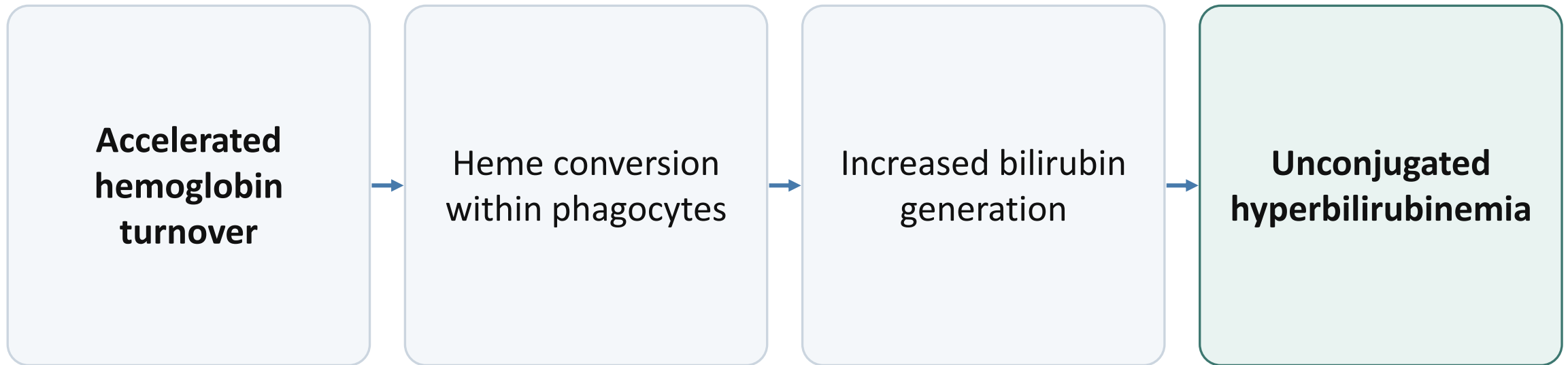
- RBC destruction occurs in blood rather than predominantly within splenic cords.
- The general Robbins pattern contrasts intravascular hemolysis with splenic enlargement.
- Coexisting disease processes can alter this pattern; Interpret organ findings clinically.

Extravascular versus intravascular hemolysis

Feature	Extravascular	Intravascular
Primary site	Macrophages, especially spleen	Bloodstream
Key injury	Poor deformability / clearance	Membrane rupture or traumatic injury
Spleen	Enlargement common	Not a typical direct result
Plasma/urine	Variable haptoglobin decrease	Hemoglobinemia, pigmenturia
Shared	Anemia; indirect bilirubin rise	Anemia; indirect bilirubin rise

Patterns describe dominant mechanisms; Mixed hemolysis is possible.

Heme catabolism links both pathways to bilirubin



Uncomplicated hemolysis produces an excess of unconjugated bilirubin.

The bilirubin response depends on two competing rates

Hemolytic flux

How much heme is supplied by RBC destruction.

Liver function

How efficiently the liver processes bilirubin.

Clinical result

Visible jaundice reflects the balance between both.

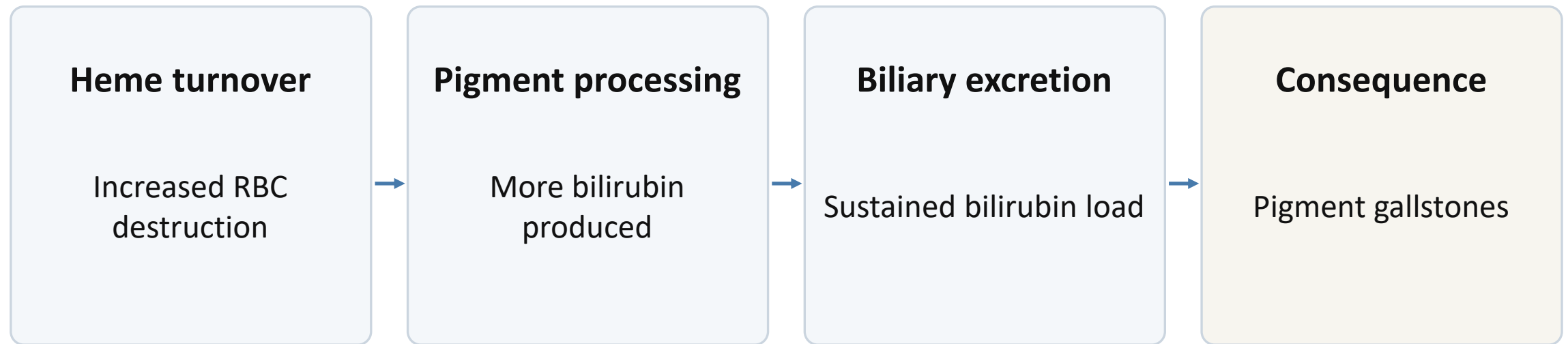
Interpretive caution

A severe appearance is not inevitable in every hemolytic patient.

Jaundice is rarely severe when hepatic function is normal.

Chronic hemolysis predisposes to pigment gallstones

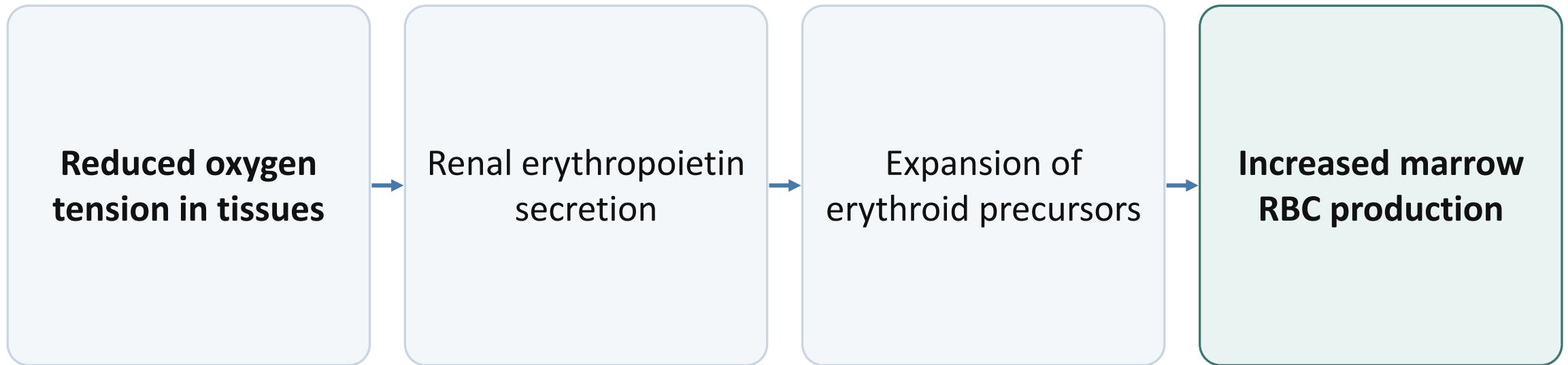
Increased bilirubin excretion into bile favors pigment stone formation.



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Cholelithiasis is a cumulative complication of persistent heme turnover.

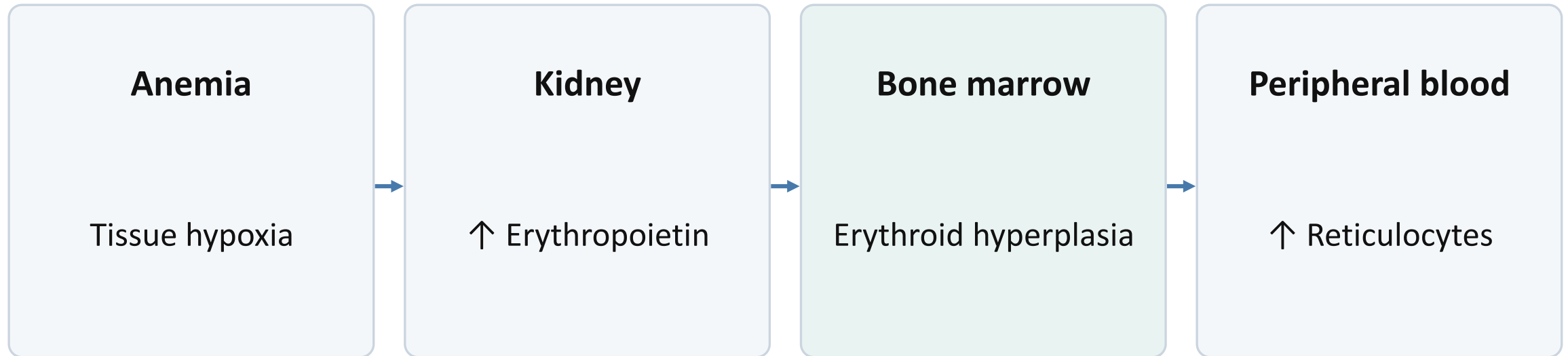
Marrow compensation requires an erythropoietin signal



The compensatory response is tied to hypoxic signaling, rather than to the destruction site.

Erythroid hyperplasia alters marrow cellularity

The number of maturing erythroid precursors (normoblasts) increases.



Schematic — original editable PowerPoint shapes

This is a marrow response and not the primary mechanism of RBC loss.

Increased marrow output produces reticulocytosis

**Erythroid precursor
expansion**



Enhanced delivery of newly
formed RBCs



**More reticulocytes in
circulating blood**

Reticulocytosis links peripheral hemolysis to compensatory marrow function.

Reticulocytes are evidence of regeneration

- Reticulocytes represent recently released immature red cells.
- Increased circulating reticulocytes are expected with effective compensation.
- Interpret reticulocyte findings together with the degree of anemia.

Morphologic consequences beyond the blood

Marrow

Increased erythroid precursors / erythroid hyperplasia.

Mononuclear phagocytes

Iron-containing pigment accumulates after phagocytosis.

Liver and spleen

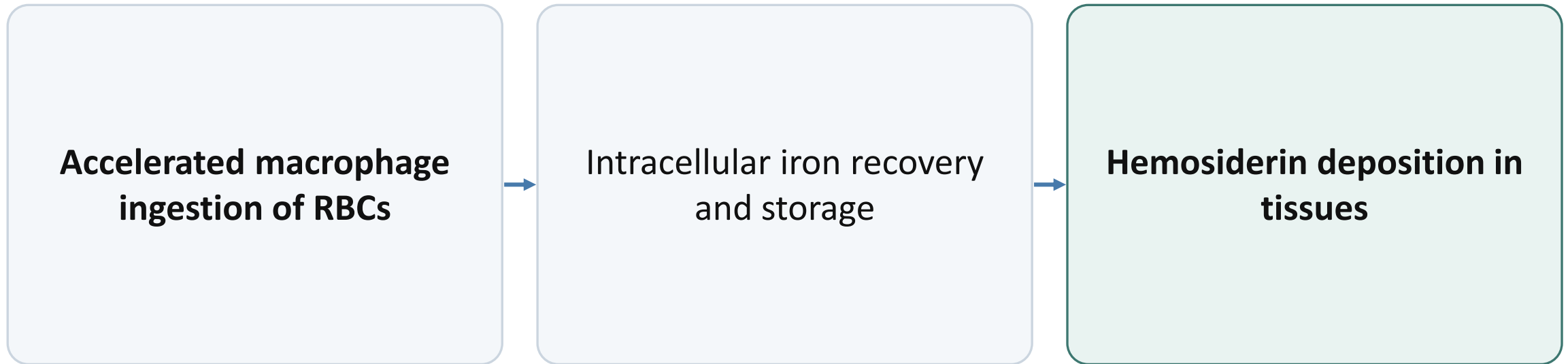
Pigment deposition can accompany chronic turnover.

Severe anemia

Additional hematopoietic sites may become active.

The response spans hematopoietic and phagocytic compartments.

Phagocytosis can produce systemic hemosiderosis



Robbins specifically names spleen, liver, and marrow as prominent sites.

Severe hemolysis may recruit extramedullary hematopoiesis

**Marked erythropoietic
demand**



Insufficient marrow
replacement alone



**Hematopoiesis outside
marrow**

Potential sites include liver, spleen, and lymph nodes.

Anemia-related symptoms reflect reduced oxygen delivery

- Weakness, easy fatigability, and dyspnea on exertion are manifestations of anemia.
- Myocardial hypoxia may produce ischemic symptoms in susceptible individuals.
- Headache, visual dimming, or faintness may accompany cerebral hypoxia.

Hemolysis has both systemic and site-specific consequences

Systemic oxygen deficit

Anemia and exercise intolerance.

Reticuloendothelial response

Splenic enlargement and pigment deposition.

Hepatobiliary system

Jaundice and pigment gallstones.

Renal pathway

Hemoglobinuria, hemosiderosis, and urinary iron loss in intravascular hemolysis.

Interpret symptoms and laboratory patterns through the affected organ pathway.

Classification: Inherited intrinsic red-cell defects

Mechanism	Representative disorders
Membrane defects	Hereditary spherocytosis; hereditary elliptocytosis
Protective enzyme defects	G6PD deficiency; glutathione synthetase deficiency
Glycolytic enzyme defects	Pyruvate kinase; hexokinase deficiencies
Reduced globin synthesis	Thalassemia syndromes
Abnormal globin structure	Sickle cell disease; unstable hemoglobins

Mechanism-based classification precedes disease-specific teaching.

Membrane disorders impair red-cell mechanical fitness

Inherited membrane protein abnormality



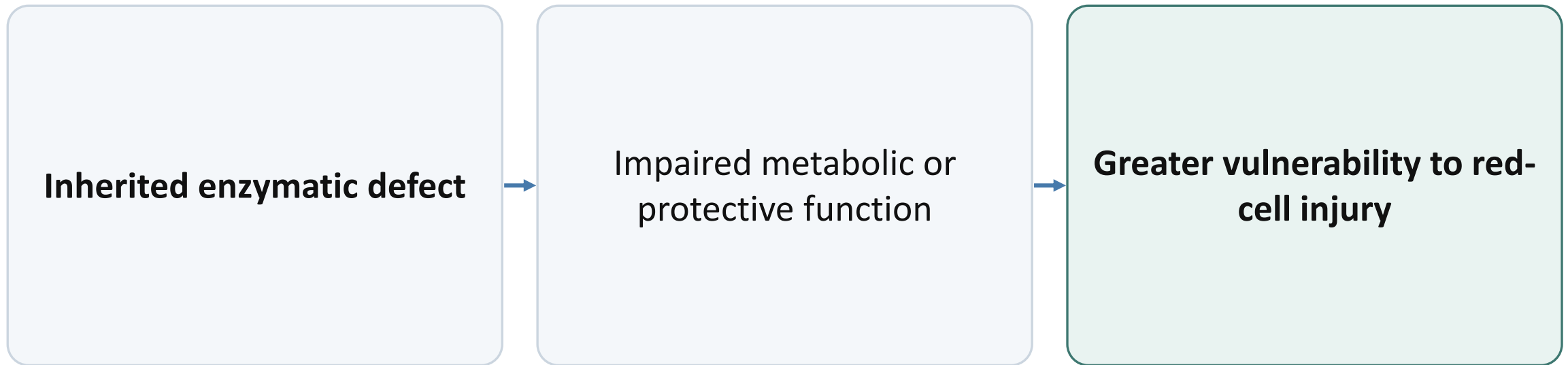
Loss of normal stability or deformability



Premature removal or hemolysis

Hereditary spherocytosis and elliptocytosis are examples, not interchangeable diagnoses.

Enzyme defects may compromise erythrocyte survival



The source lists both hexose monophosphate shunt and glycolytic enzyme defects.

Hemoglobin abnormalities form two distinct categories

Deficient globin synthesis

Thalassemia syndromes.

Abnormal globin structure

Sickle cell disease and unstable hemoglobins.

Shared classification

Both involve hemoglobin itself.

Important distinction

Quantity of globin and structure of globin are different defect classes.

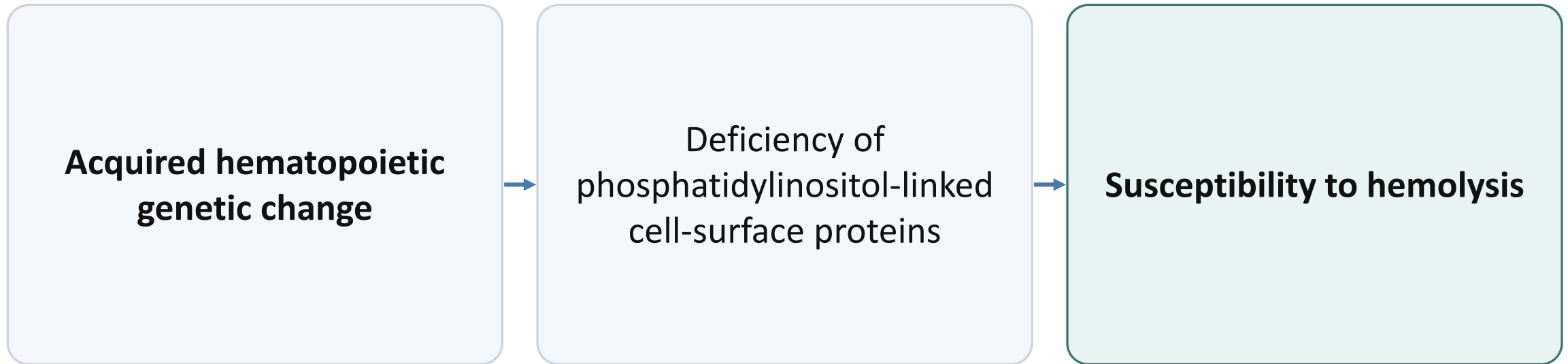
Mechanism categories should not be collapsed into a generic “abnormal hemoglobin” label.

Classification: Acquired mechanisms

Mechanism	Representative examples
Acquired genetic membrane-protein defect	Paroxysmal nocturnal hemoglobinuria
Antibody-mediated injury	Rh disease; transfusion reactions; drug induced; autoimmune
Mechanical trauma	Microangiopathy; defective cardiac valves
Intraerythrocytic infection	Malaria; babesiosis
Toxic injury / sequestration	Clostridial sepsis; venom; hypersplenism

Examples derive from the general anemia classification Table 14.1.

An acquired genetic lesion can initiate hemolysis



Paroxysmal nocturnal hemoglobinuria is listed as an acquired genetic cause.

Antibody-mediated hemolysis is an etiologic group

- Antibodies may cause destruction in transfusion reactions and autoimmune states.
- Maternal–fetal incompatibility and drug-related processes are additional examples.
- Complement fixation is one possible route to intravascular injury.

Microangiopathic hemolysis: Representative settings

Named setting	Mechanistic context
Thrombotic thrombocytopenic purpura	Microvascular pathology can mechanically injure RBCs
Hemolytic uremic syndrome	Microangiopathic cause of red-cell trauma
Disseminated intravascular coagulation	Thrombi can narrow the red-cell passage
Tumor-related microvascular obstruction	Cells may be injured traversing restricted vessels

The listed syndromes should not be inferred from schistocytes alone without clinical context.

Other acquired settings for hemolysis

Infection

Malaria and babesiosis are listed erythrocyte infections.

Toxins

Snake venom, clostridial sepsis, and lead injury are examples.

Abnormal membrane lipids

Abetalipoproteinemia and severe hepatocellular disease.

Sequestration

Hypersplenism can increase erythrocyte removal.

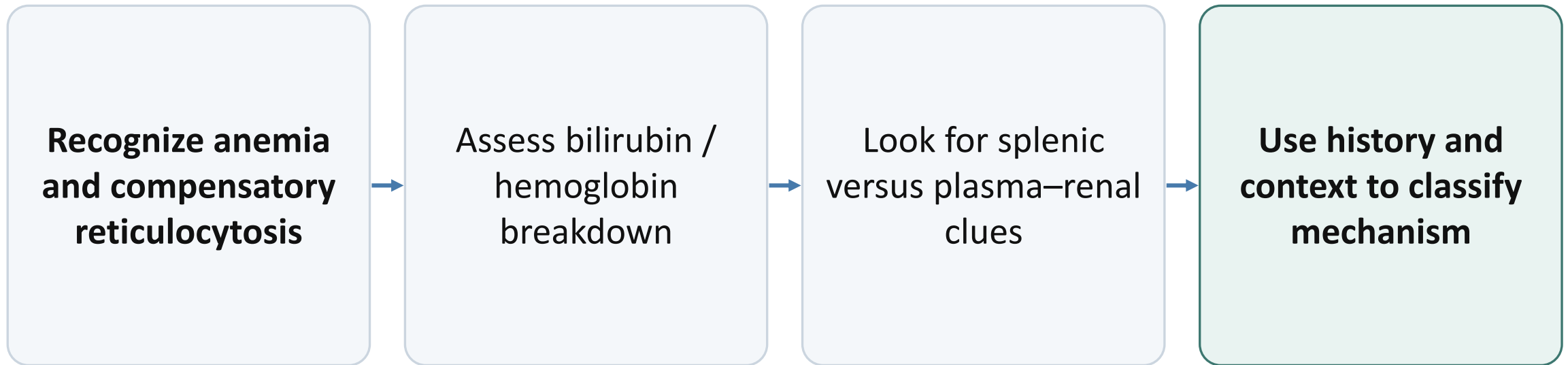
A mechanism-based taxonomy helps interpret very different etiologic exposures.

Two classification axes must be kept separate

Question	Possible answers
Where are RBCs destroyed?	Extravascular / intravascular
Why are RBCs destroyed?	Membrane, enzyme, hemoglobin, antibody, trauma, toxin, infection, sequestration
Is the initiating defect inherited?	Inherited / acquired
Are processes mutually exclusive?	No; mixed site-specific destruction may occur

An etiologic category does not specify one universal anatomical site of hemolysis.

Integrating the findings in a hemolysis workup



This is a source-derived conceptual sequence, not a complete modern laboratory guideline.

Clinical exercise: Predominant extravascular destruction

Clinical pattern

A patient has chronic anemia, increased reticulocytes, splenomegaly, and unconjugated jaundice. No hemoglobinuria is described.

Which mechanism best accounts for the spleen enlargement and jaundice?

Discussion and interpretation follow on the next slide

Clinical exercise: Mechanistic interpretation

Splenomegaly

Repeated phagocytic clearance can expand the splenic macrophage population.

Anemia

Red-cell removal exceeds replacement.

Reticulocytosis

The marrow increases erythrocyte production.

Unconjugated jaundice

Macrophage heme catabolism increases bilirubin formation.

The pattern narrows the destruction site but does not uniquely diagnose hereditary spherocytosis.

Clinical exercise: Predominant intravascular lysis

Clinical pattern

A patient develops anemia and red-brown urine following a hemolytic event. Plasma free hemoglobin rises and haptoglobin becomes depleted.

Trace how circulating hemoglobin causes the urinary finding.

Discussion and interpretation follow on the next slide

Clinical exercise: Renal consequences

Free Hb

Intravascular rupture increases circulating hemoglobin.

Scavenger system

Haptoglobin is consumed during binding and clearance.

Tubular handling

Filtered hemoglobin is partly reabsorbed by proximal cells.

Urinary loss

Persistent overflow or cell shedding causes pigment/iron loss.

With chronicity, renal hemosiderosis and iron deficiency may become relevant.

Mechanism-to-finding summary

Mechanism	Expected consequence
Splenic macrophage clearance	Variable splenomegaly; reticuloendothelial iron loading
Circulating RBC rupture	Plasma free Hb; reduced haptoglobin; pigmenturia
Compensatory erythropoiesis	Marrow erythroid hyperplasia; reticulocytosis
Accelerated heme turnover	Unconjugated hyperbilirubinemia; pigment gallstones
Marked erythropoietic demand	Possible extramedullary hematopoiesis

Different findings represent different steps in the pathophysiologic sequence.

Central conclusions

- Hemolytic anemia means shortened erythrocyte survival with a variable compensatory response.
- Extravascular hemolysis is characterized by macrophage clearance and frequently splenomegaly.
- Intravascular lysis adds plasma-hemoglobin and renal-pigment consequences.
- Bilirubin production, marrow hyperplasia, and chronic pigment-related complications cross etiologies.

Reference and scope

Primary reference

Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th edition (2026).
Section: Hemolytic Anemias; etiologic classification from the same chapter.

Detailed inherited and acquired disorders are addressed in their separate teaching units.