

Glucose-6-phosphate dehydrogenase deficiency

Oxidative injury, red-cell morphology, and episodic hemolysis

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Learning outcomes

- Explain how G6PD generates NADPH for antioxidant defense.
- Relate X-linked inheritance and enzyme stability to red-cell vulnerability.
- Trace oxidative damage to Heinz bodies, bite cells, and hemolysis.
- Interpret major triggers, timing, and the recovery pattern.

G6PD deficiency is an inherited enzymatic hemolytic disorder

Reduced G6PD activity compromises red-cell protection against oxidant stress.

- The defect is in the hexose monophosphate shunt.
- Hemolysis is commonly intermittent, following oxidant exposure.
- The affected circulating cell is the erythrocyte.

Where it sits among the hemolytic anemias

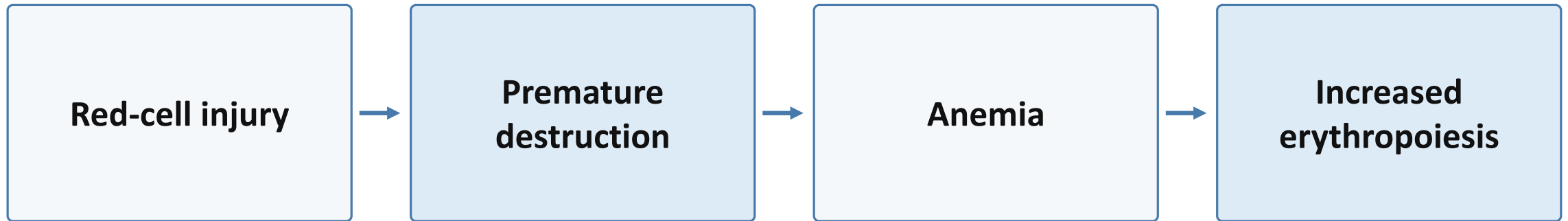
Underlying defect

- Inherited red-cell enzyme deficiency
- Impaired antioxidant capacity
- Intrinsic vulnerability of erythrocytes

Result

- Premature red-cell destruction
- Intravascular and extravascular pathways
- Compensatory erythropoiesis after injury

Hemolysis reduces the circulating red-cell life span



The general response to hemolysis explains why reticulocytosis appears during recovery.

Two locations of red-cell destruction

Intravascular

- Erythrocytes rupture in the circulation.
- Hemoglobin enters plasma.
- Hemoglobinuria may follow.

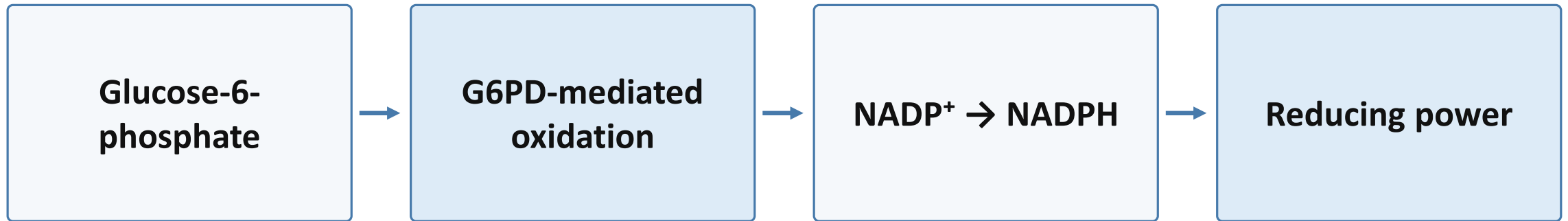
Extravascular

- Abnormal erythrocytes lose deformability.
- Splenic macrophages remove affected cells.
- Jaundice may reflect heme breakdown.

Why erythrocytes need oxidative defense

- Oxidants can injure hemoglobin and membrane proteins.
- Hydrogen peroxide is an important example of an oxidant.
- Reduced glutathione helps detoxify peroxide.
- NADPH is required to regenerate reduced glutathione.

G6PD initiates the protective NADPH supply



Glucose-6-phosphate oxidation is coupled to reduction of NADP⁺.

The hexose monophosphate shunt supports red-cell survival

The pathway is a source of the reducing equivalents required for glutathione recycling.

- G6PD occupies the first depicted step.
- The clinically consequential output is NADPH.
- Reduced NADPH availability lowers oxidant tolerance.

NADP⁺ and NADPH are distinct redox states

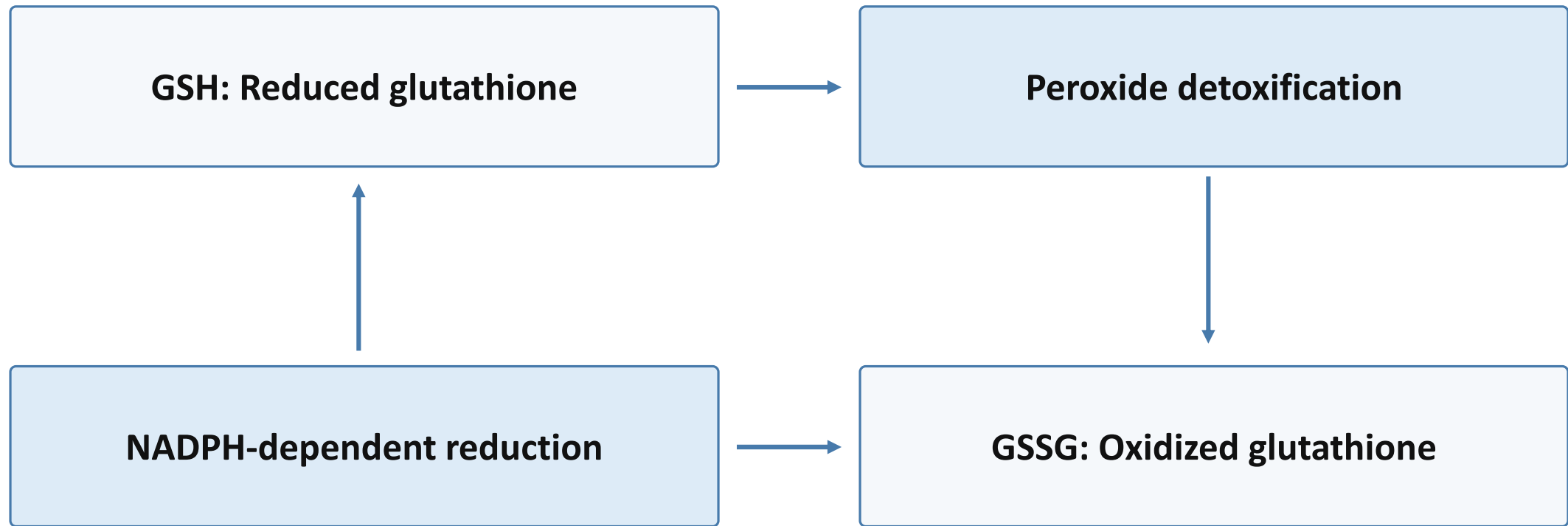
NADP⁺

- Oxidized electron acceptor
- Reduced during the G6PD-linked reaction
- Precursor to NADPH

NADPH

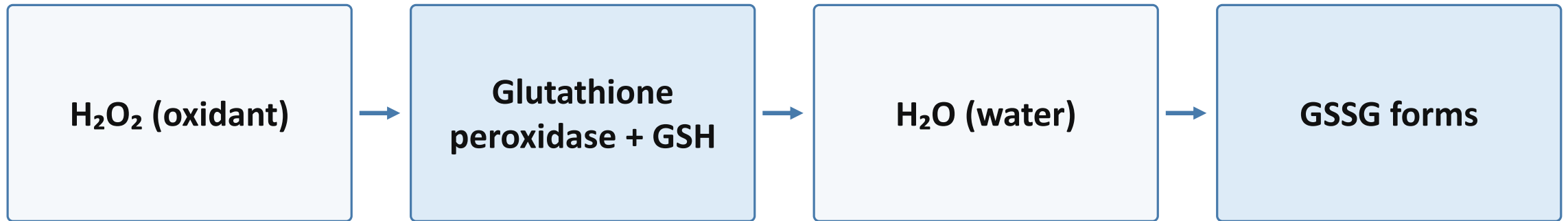
- Reduced electron donor
- Supplies reducing equivalents
- Enables reduced-glutathione regeneration

Glutathione cycles between reduced and oxidized forms



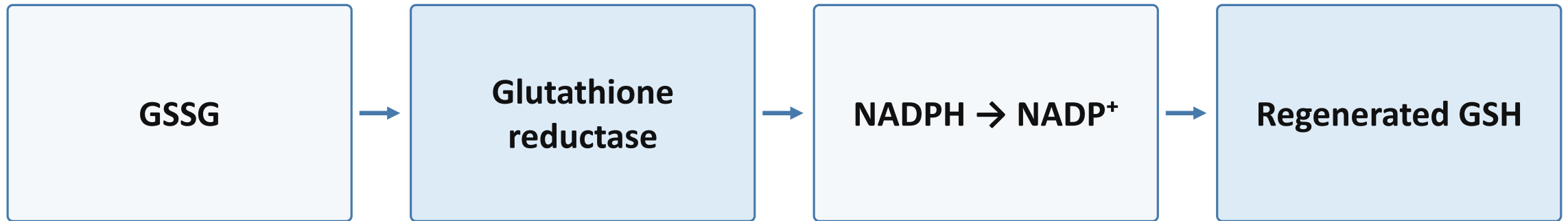
NADPH allows GSSG to return to the protective GSH pool.

Glutathione peroxidase consumes reduced glutathione



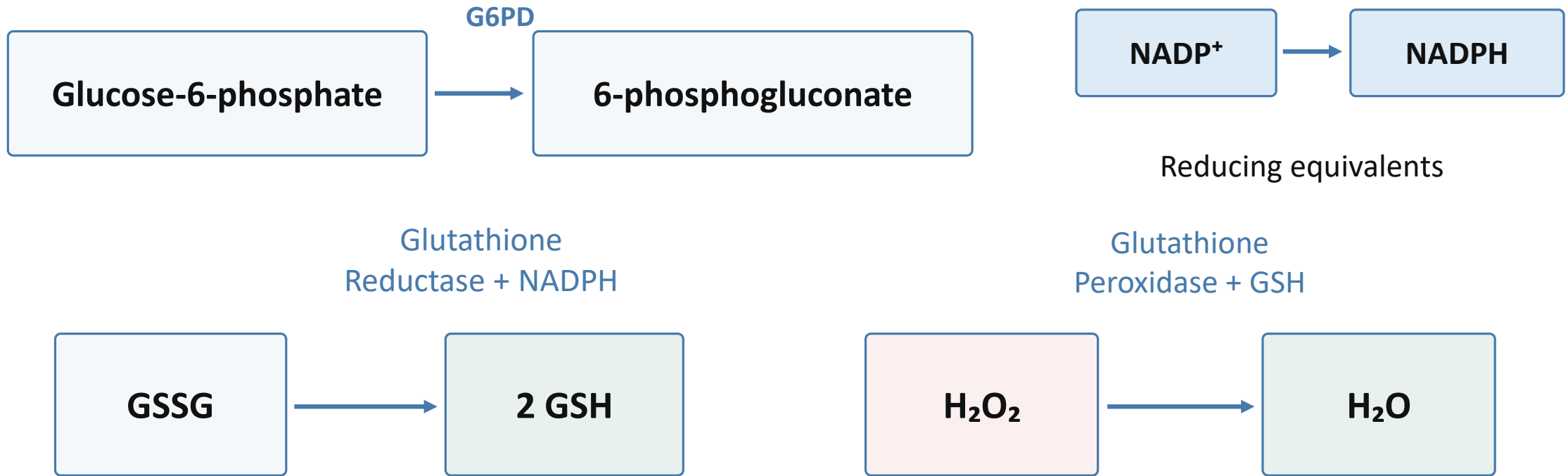
The peroxidase reaction neutralizes peroxide while oxidizing GSH.

Glutathione reductase restores the GSH pool



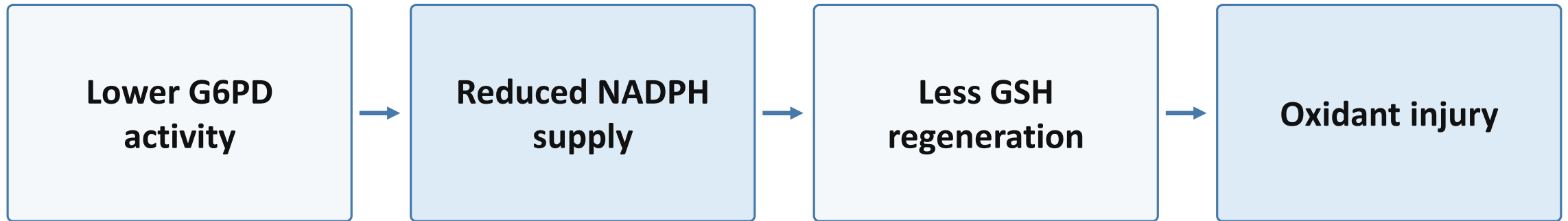
This regeneration is impaired when the NADPH supply is inadequate.

G6PD, reductase, and peroxidase form a defensive system



Conceptual coupling of NADPH generation to glutathione-dependent oxidant detoxification

G6PD deficiency weakens the entire defensive chain



The upstream enzyme deficiency compromises a downstream detoxification pathway.

Mature red cells cannot replace unstable enzyme

- Circulating mature erythrocytes cannot synthesize new proteins.
- Some clinically important G6PD variants undergo rapid degradation.
- The enzyme reserve therefore decreases as red cells age.
- Older cells become especially sensitive to oxidative stress.

G6PD deficiency follows X-linked inheritance

Gene transmission

- Recessive X-linked trait
- Males have a single X chromosome
- One deficient allele can confer susceptibility

Clinical consequence

- Symptomatic deficiency is more common in males
- Inheritance informs family-history interpretation
- Not all variant carriers have equal hemolytic severity

Variant diversity does not imply equal clinical severity

- Several hundred G6PD genetic variants.
- Two historically important hemolysis-associated examples are A- and Mediterranean.
- The major mechanism discussed is decreased protein stability.
- Variant-dependent enzyme half-life influences red-cell vulnerability.

G6PD B is the textbook comparator

G6PD B is used as the common normal reference variant.

- Other variants are compared by residual enzyme persistence.
- Shorter protein half-life causes activity to decline with red-cell aging.
- Do not infer a patient-specific severity from a name alone.

G6PD A– shows moderately reduced enzyme persistence

Biochemical behavior

- Protein is less stable than G6PD B.
- Activity decreases during red-cell aging.

Functional result

- Old red cells are especially susceptible.
- Younger cells retain more protective enzyme activity.

G6PD Mediterranean has more marked instability

Biochemical behavior

- Enzyme half-life is markedly decreased.
- Aging rapidly reduces activity.

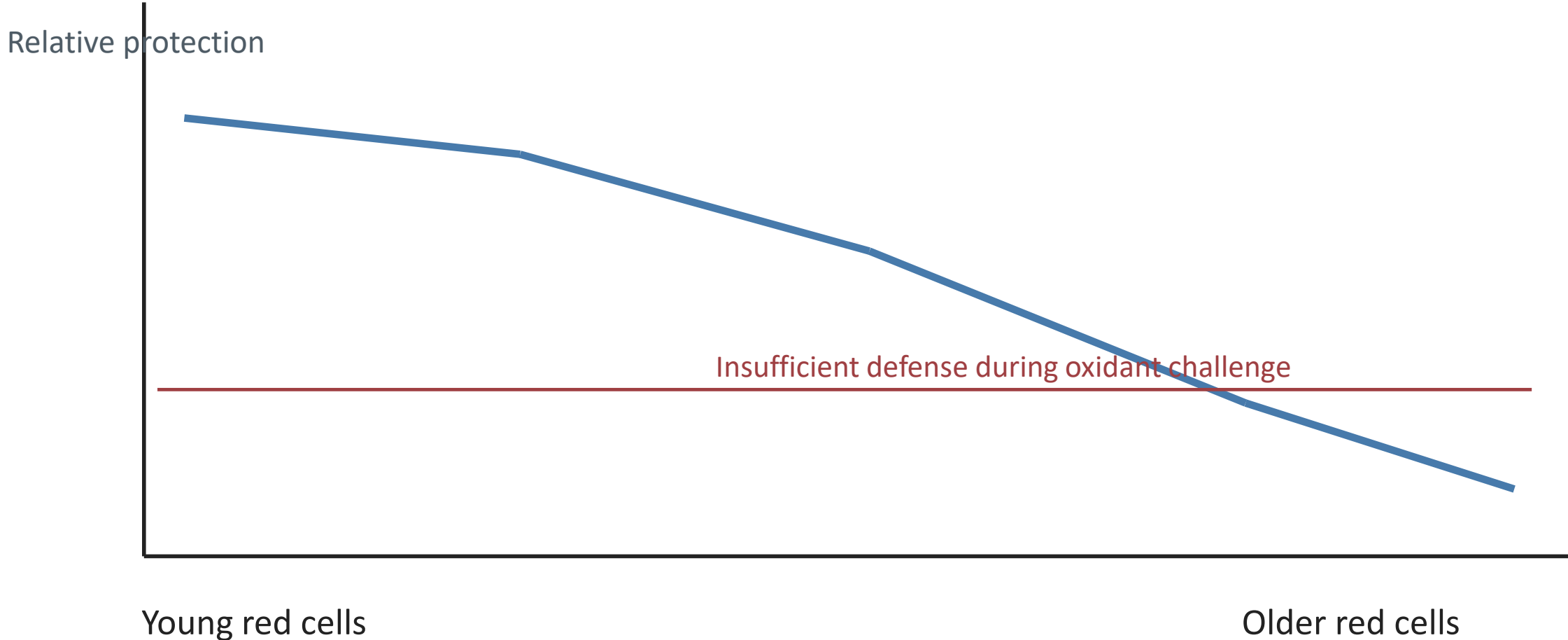
Functional result

- Older erythrocytes become poorly protected.
- Certain oxidant exposures may produce more severe hemolysis.

Variant stability predicts age-dependent susceptibility

Variant	Relative enzyme persistence	Physiologic implication
G6PD B	Normal comparator	Antioxidant capacity maintained
G6PD A-	Moderately reduced half-life	Greater injury in older cells
G6PD Mediterranean	Markedly reduced half-life	Marked age-related vulnerability

The age of the erythrocyte matters



Qualitative schematic — no quantitative G6PD activity data are represented

Hemolysis requires a disturbance in oxidant balance

Everyday state

- Oxidant burden can remain manageable.
- Residual protection may be sufficient.
- A person may appear clinically well.

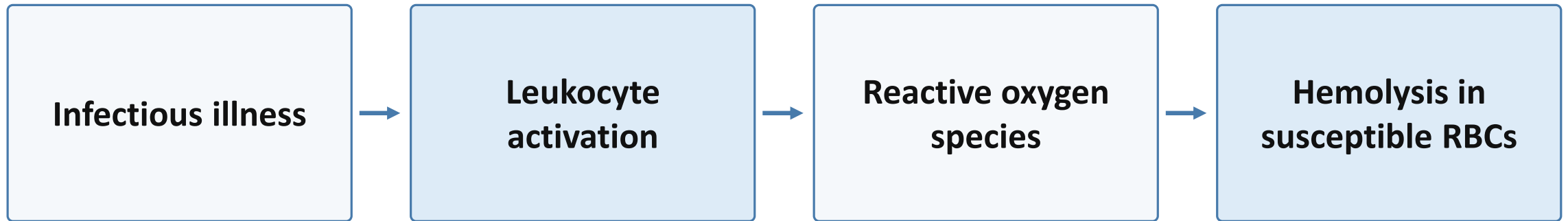
Trigger exposure

- Free-radical burden rises.
- Reduced NADPH becomes limiting.
- Red-cell injury crosses a functional threshold.

Infections commonly precipitate hemolytic episodes

- Activated leukocytes generate oxygen-derived free radicals.
- This increases the oxidative challenge to vulnerable red cells.
- Viral hepatitis, pneumonia, and typhoid fever as examples.
- The infectious illness acts as a precipitant, not the inherited defect.

An infection links immunity to erythrocyte injury



Host inflammatory oxidants can act on red cells with limited antioxidant reserve.

Certain medicines can create oxidant stress

- Primaquine and chloroquine among historical examples.
- It also mentions sulfonamides and nitrofurantoin.
- Risk varies with the drug, exposure, and G6PD variant.
- A textbook example is not a comprehensive current prescribing restriction list.

Drug susceptibility is not uniform across variants

Exposure

- Oxidant-generating medicinal agent
- Potential increase in reactive intermediates
- Dose and agent influence the burden

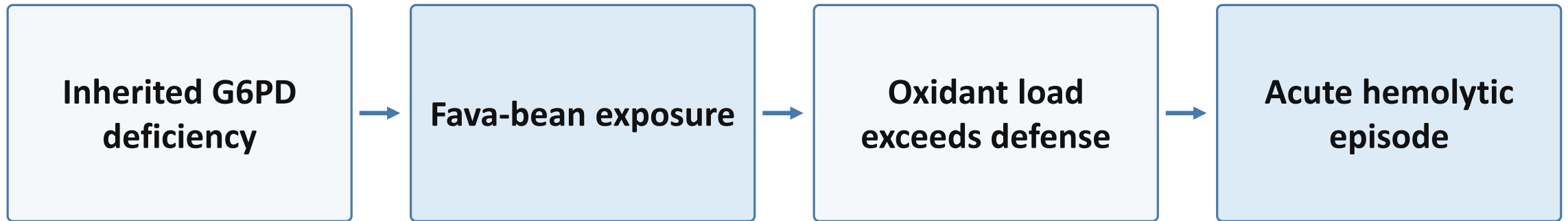
Host susceptibility

- Residual enzyme activity matters
- Variant stability differs
- Older erythrocytes may be preferentially lost

Fava beans are a classic dietary precipitant

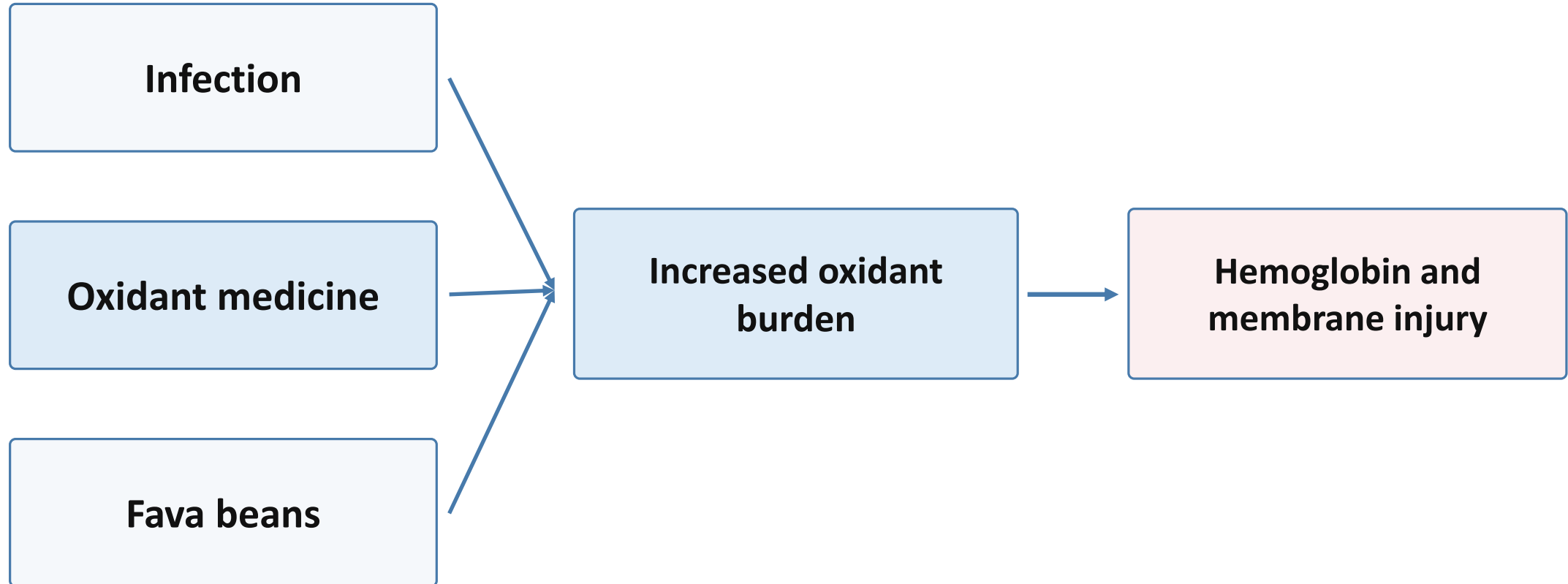
- Fava-bean metabolism produces oxidant substances.
- Susceptible erythrocytes cannot fully neutralize the resulting stress.
- The clinical syndrome after exposure is termed favism.
- Mediterranean, Middle Eastern, and African settings.

Favism illustrates gene–environment interaction

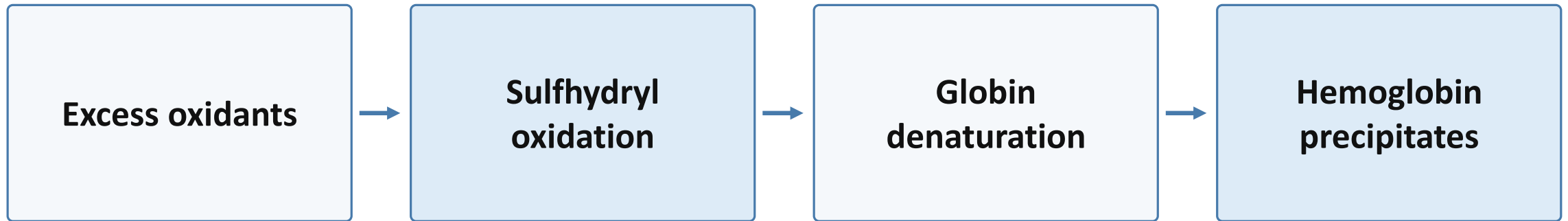


The inherited susceptibility may remain silent until an environmental trigger occurs.

Distinct triggers converge on the same redox problem



Oxidants cross-link reactive globin sulfhydryl groups



Denaturation and precipitation are the structural basis of Heinz-body formation.

Heinz bodies are precipitated denatured hemoglobin

Heinz bodies are membrane-associated precipitates of oxidatively damaged globin.

- They arise after strong oxidant stress.
- They are distinct from normal hemoglobin distribution.
- They can themselves compromise membrane integrity.

Heinz bodies require an appropriate staining method

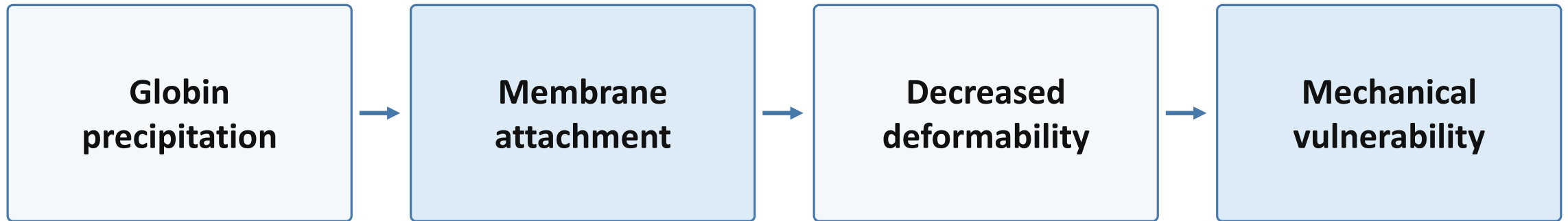
Crystal violet preparation

- Dark inclusions.
- The inclusions represent denatured globin.
- This is a special stain finding.

Routine morphology

- Bite cells are a downstream clue.
- Inclusion removal changes cell contour.
- Do not label a routine smear as a Heinz-body stain.

Oxidative globin damage affects the red-cell membrane



Membrane-associated inclusions can impair red-cell survival.

Severe and less severe injury lead to different fates

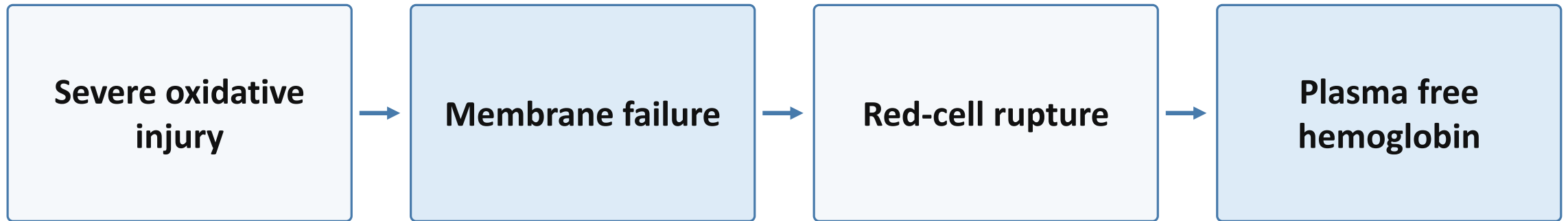
Severe membrane injury

- Major loss of integrity
- Cell may rupture in circulation
- Intravascular hemolysis

Less severe membrane injury

- Cell remains intact but rigid
- Splenic macrophages remove inclusions
- Extravascular hemolysis

Direct lysis produces intravascular hemolysis

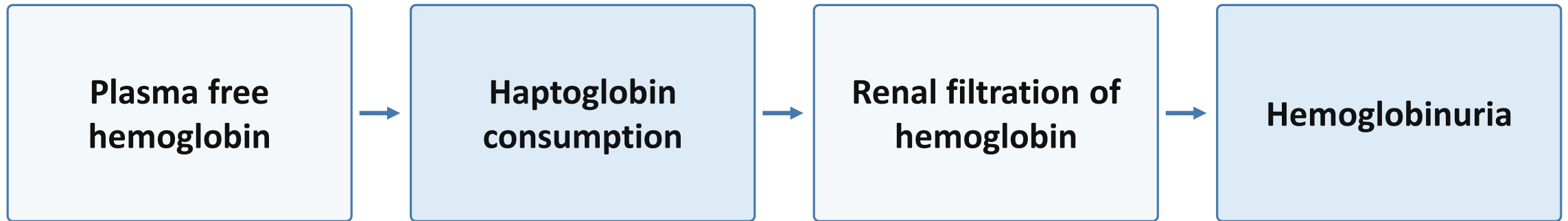


Circulating free hemoglobin provides the basis for hemoglobinemia and hemoglobinuria.

Hemoglobinemia reflects release of red-cell contents

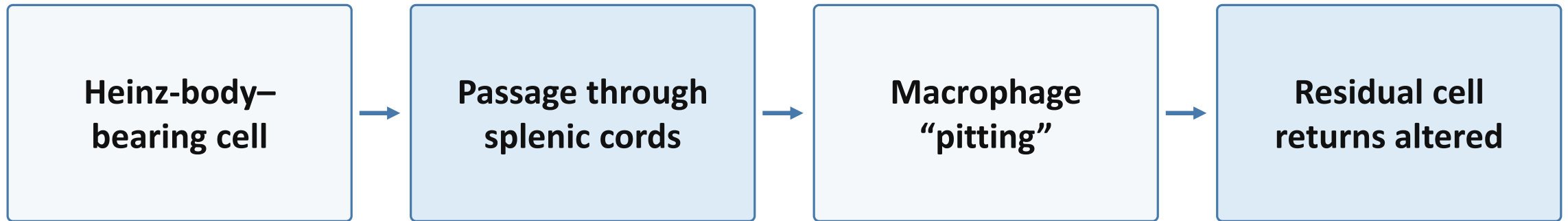
- Intravascular destruction releases hemoglobin directly into plasma.
- Haptoglobin normally binds free hemoglobin.
- Hemoglobinemia appears when the burden of circulating hemoglobin rises.
- This pathway distinguishes intravascular from solely splenic destruction.

Hemoglobinuria follows extensive intravascular lysis



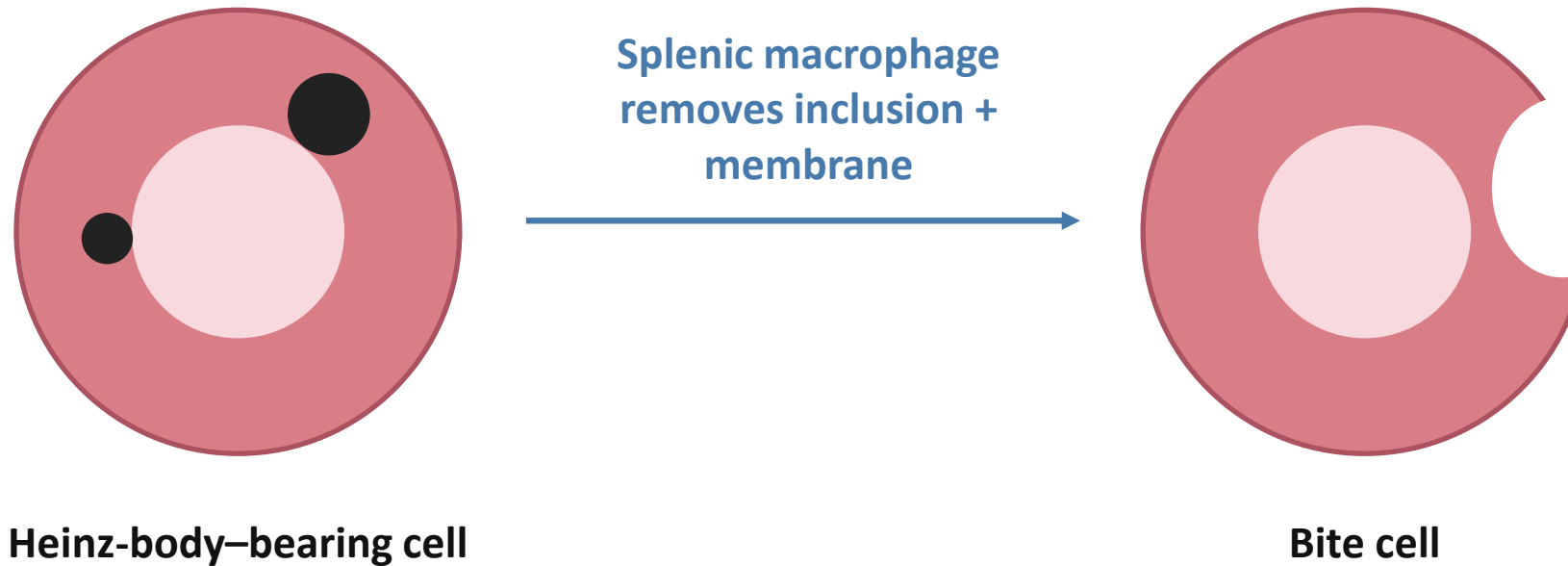
The parent hemolytic-anemia section describes red-brown urine from filtered hemoglobin.

The spleen removes Heinz-body inclusions



The process removes both the inclusion and a portion of membrane.

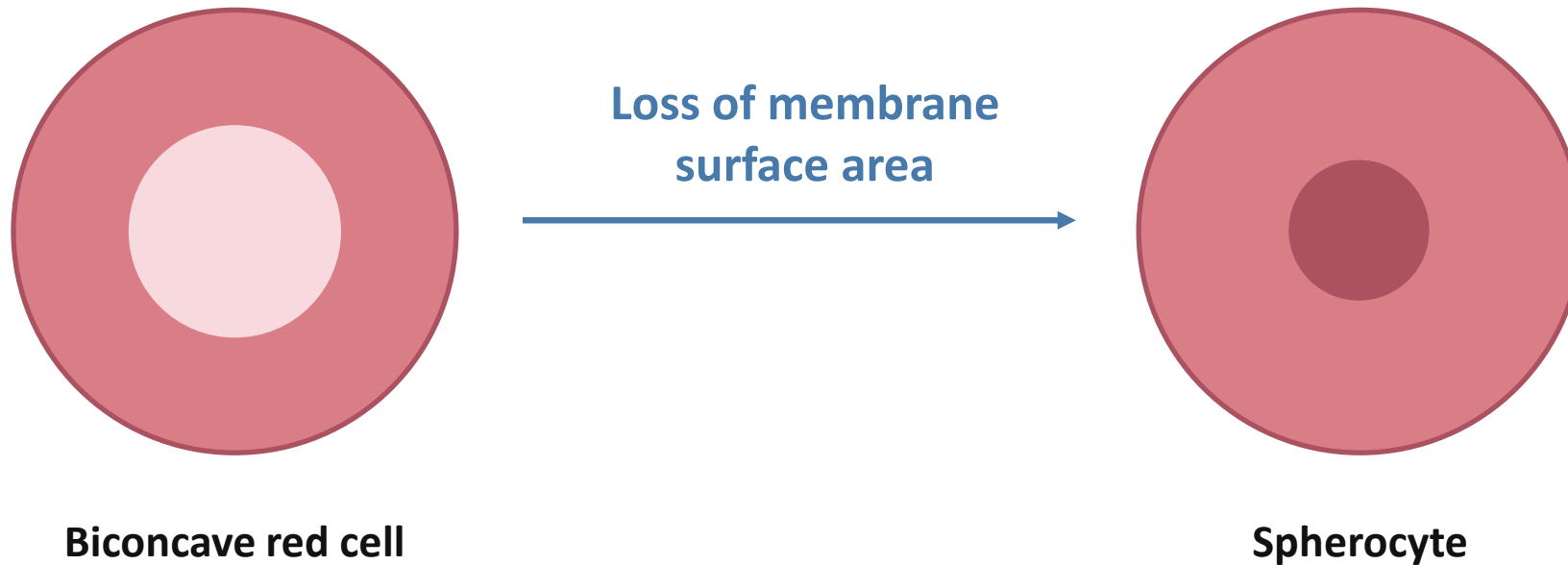
Pitting explains the characteristic bite cell



The macrophage removes Heinz-body material and adjacent membrane, leaving a crescent-like indentation.

Schematic morphology — editable teaching shapes, not a microscopic specimen

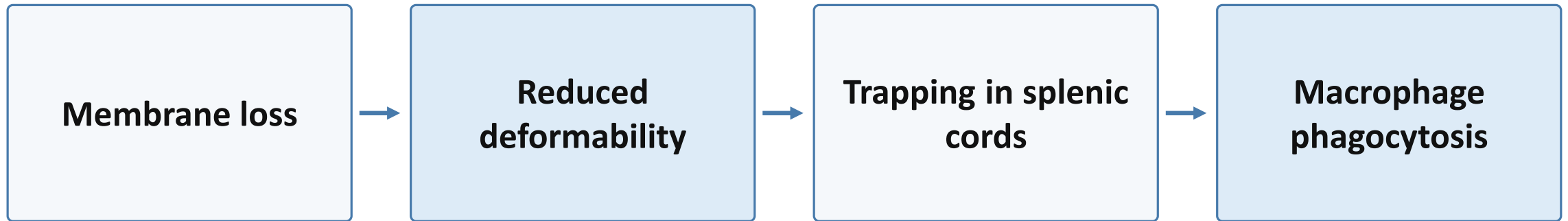
Membrane loss can also produce a spherocyte



A smaller membrane surface area alters red-cell shape; Spherocytes are not specific to G6PD deficiency.

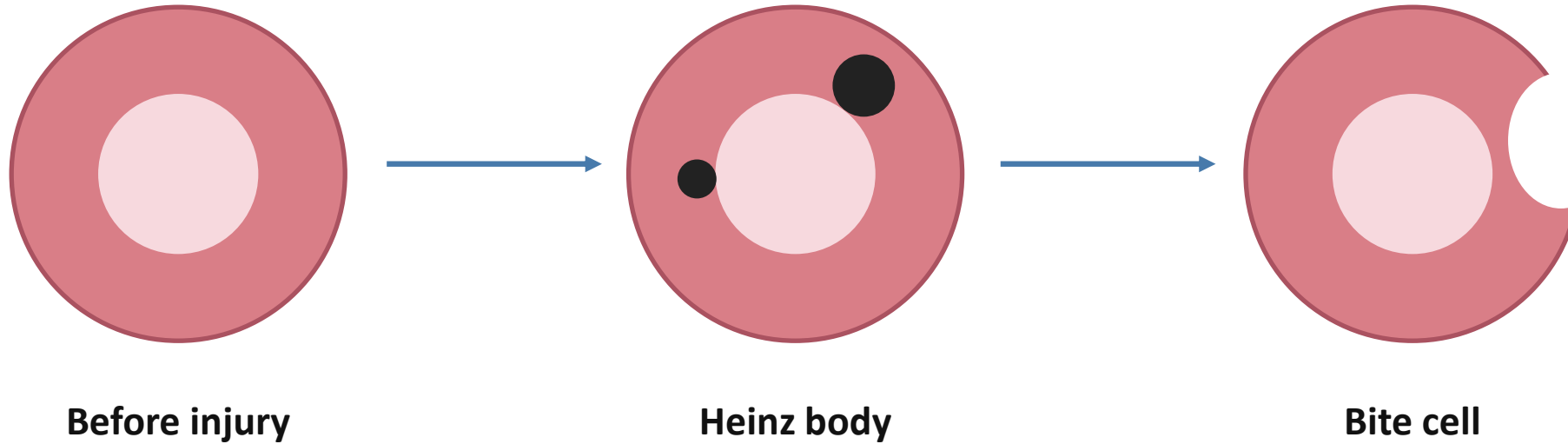
Schematic morphology — editable teaching shapes, not a microscopic specimen

Both bite cells and spherocytes can be cleared



These are extravascular components of an oxidant-mediated hemolytic process.

Three red-cell appearances reflect successive events



Simplified native-vector morphology; Not a clinical photomicrograph.

A bite cell is a consequence—not the initial lesion

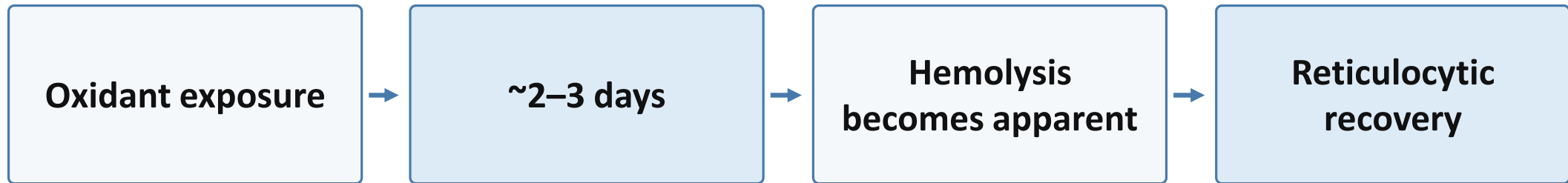
Upstream event

- Insufficient antioxidant reserve
- Denatured hemoglobin precipitates
- Heinz-body formation

Downstream appearance

- Splenic macrophage removes inclusion
- Membrane contour becomes indented
- Bite cells may circulate temporarily

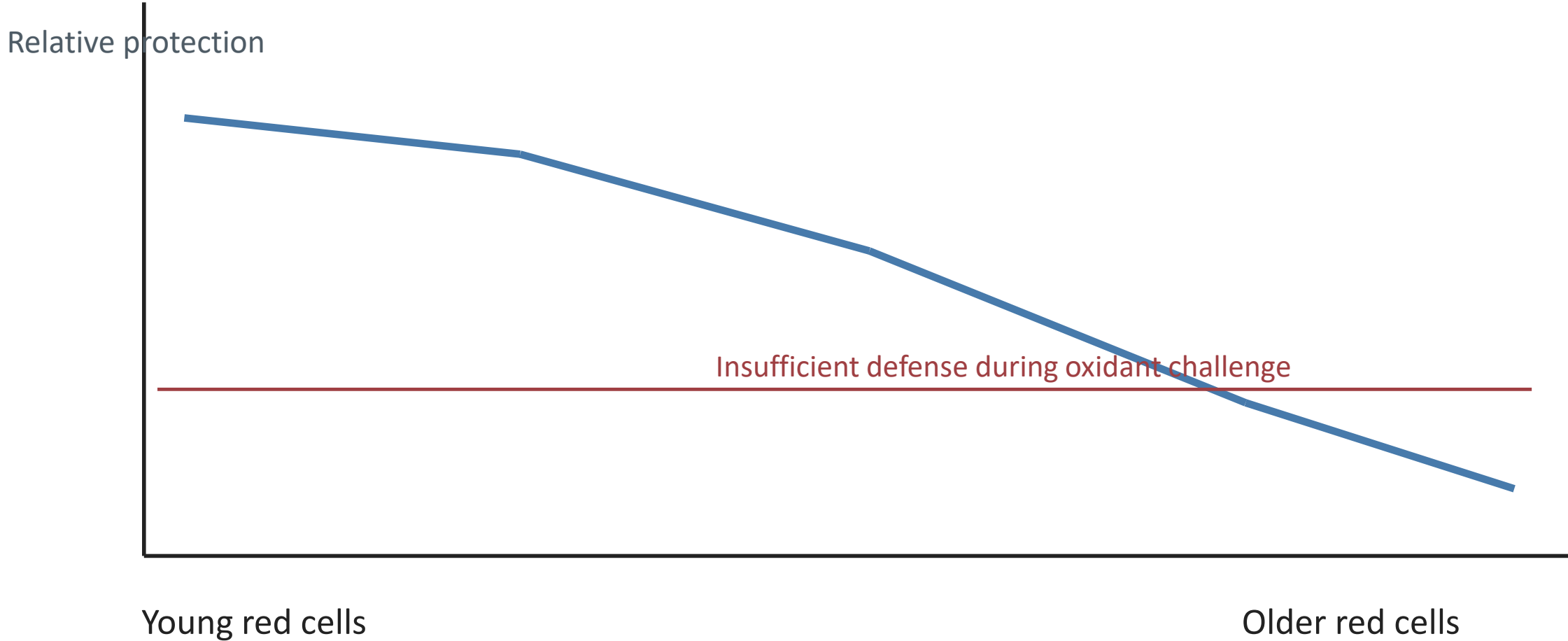
Acute hemolysis usually follows exposure by days



Typical onset 2–3 days after environmental triggers.

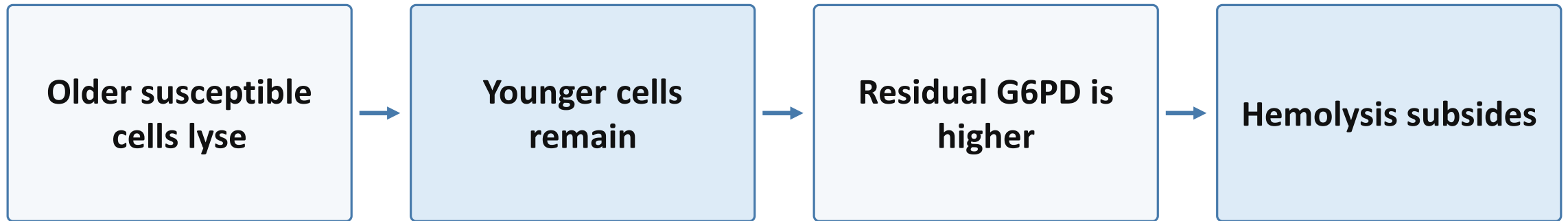
Timing is characteristic but does not replace individual clinical assessment.

Older cells are depleted first



Qualitative schematic — no quantitative G6PD activity data are represented

The hemolytic episode often terminates spontaneously



A self-limited episode can occur even while the exposure persists; This does not make continued exposure safe.

Reticulocytosis marks hematologic recovery

- The marrow responds to anemia by increasing red-cell production.
- Reticulocytes are newly released erythroid cells.
- Their appearance helps identify recovery after a hemolytic episode.
- Reticulocytosis is a response to hemolysis, not its initiating cause.

The episodic course limits chronic hemolytic sequelae

Typical episodic G6PD deficiency

- Attacks occur intermittently
- Periods of relative normality
- Chronic splenomegaly and gallstones usually absent

Persistent hemolysis generally

- Repeated hemoglobin breakdown
- Pigment-gallstone risk over time
- Splenic enlargement when clearance is sustained

Neonatal jaundice is an uncommon presentation

- Robbins recognizes neonatal jaundice as a less frequent presentation.
- Its existence shows that an obvious drug or food trigger is not obligatory.
- Neonatal jaundice warrants clinical evaluation for multiple causes.
- Do not assume all jaundice in a G6PD-deficient infant has one mechanism.

Chronic low-grade hemolysis occurs in some variants

- A minority of patients can have hemolysis without a recognized exposure.
- Chronic low-grade anemia differs from the usual episodic course.
- Severity reflects the functional behavior of the enzyme variant.
- The absence of a trigger does not exclude G6PD-related hemolysis.

G6PD deficiency and hereditary spherocytosis differ

Finding	G6PD deficiency	Hereditary spherocytosis
Primary defect	Oxidant defense enzyme	Membrane skeleton
Typical pattern	Trigger-associated episodic	Often chronic hemolysis
Bite cells	Can follow splenic pitting	Not characteristic
Spherocytes	May develop secondarily	Characteristic morphology
Splenomegaly	Usually absent in episodic disease	Common in clinically evident disease

Interpreting a hemolytic episode

Clinical clues

- Recent illness, medicine, or fava beans
- Onset over the following days
- Anemia, jaundice, or dark urine

Mechanistic clues

- Heinz bodies with special stain
- Bite cells or spherocytes
- Later reticulocytosis

Case 1: Hemolysis after a respiratory infection

Teaching vignette: A boy with inherited G6PD deficiency develops jaundice and dark urine after pneumonia.

What links the infection to red-cell destruction?

Activated leukocytes generate oxidants that overwhelm the limited NADPH–glutathione defense.

Hypothetical teaching vignette; Not a patient record

Case 2: An oxidant medicine precedes anemia

Teaching vignette: A patient with a susceptible G6PD variant becomes anemic several days after an oxidant-generating medicine.

Why is the delay compatible with the mechanism?

Oxidative injury accumulates in vulnerable older red cells; Onset commonly after 2–3 days.

Hypothetical teaching vignette; Not a patient record

Case 3: Why can an attack subside?

Teaching vignette: A brief hemolytic episode is followed by rising reticulocytes and cessation of red-cell destruction.

Which circulating cells now predominate?

Younger erythrocytes with higher residual enzyme activity, which tolerate the same oxidant burden better.

Hypothetical teaching vignette; Not a patient record

Case 4: Identifying the morphological sequence

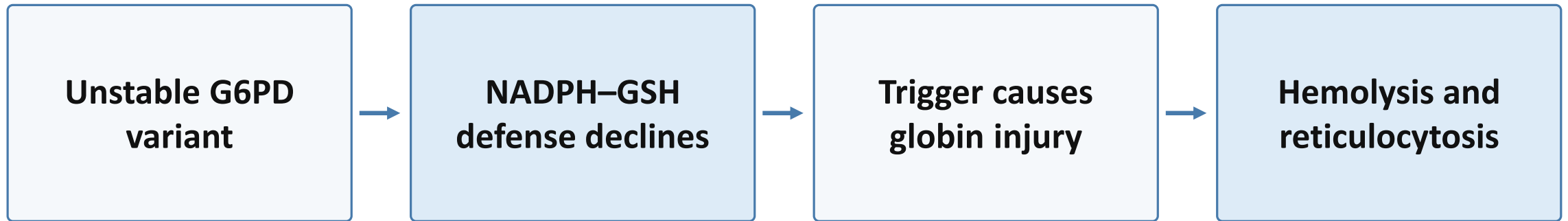
Teaching vignette: An inclusion is visible with crystal violet; Later, a notched erythrocyte is seen on a smear.

Which splenic event connects the two findings?

Macrophage removal of the Heinz body and adjacent membrane (“pitting”) produces a bite cell.

Hypothetical teaching vignette; Not a patient record

An integrated mechanism: Gene to clinical episode



Gene, environment, membrane morphology, and clinical recovery are linked parts of one mechanism.

Core points to retain

- G6PD supplies NADPH to recycle glutathione and neutralize oxidants.
- Unstable enzyme variants leave aging red cells especially vulnerable.
- Infections, certain medicines, and fava beans can initiate attacks.
- Heinz bodies, bite cells, and both hemolytic routes follow oxidative damage.
- Typical attacks begin after exposure and recover with reticulocytosis.

Primary references

Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th ed. (2026). Chapter 14, pp. 579–582.

Source topic: “Glucose-6-Phosphate Dehydrogenase Deficiency,” pp. 581–582.

Context: “Hemolytic Anemias,” pp. 579–580.

Original teaching diagrams and case vignettes are interpretive educational reconstructions.