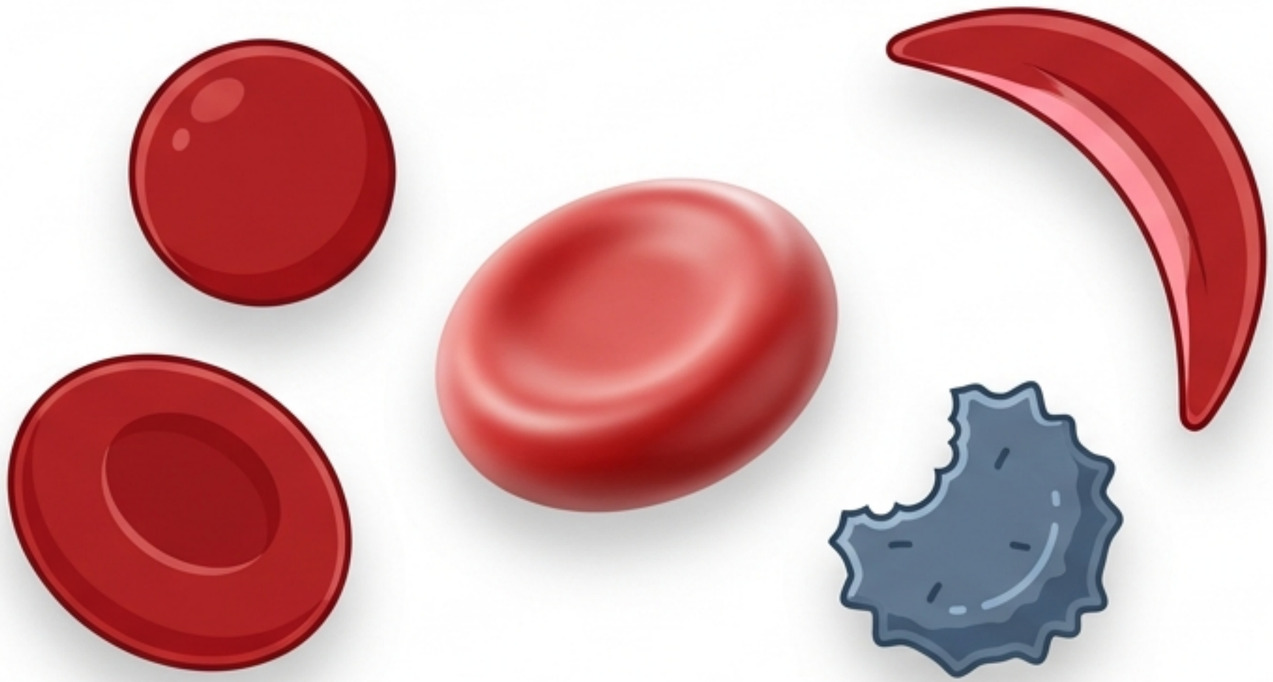
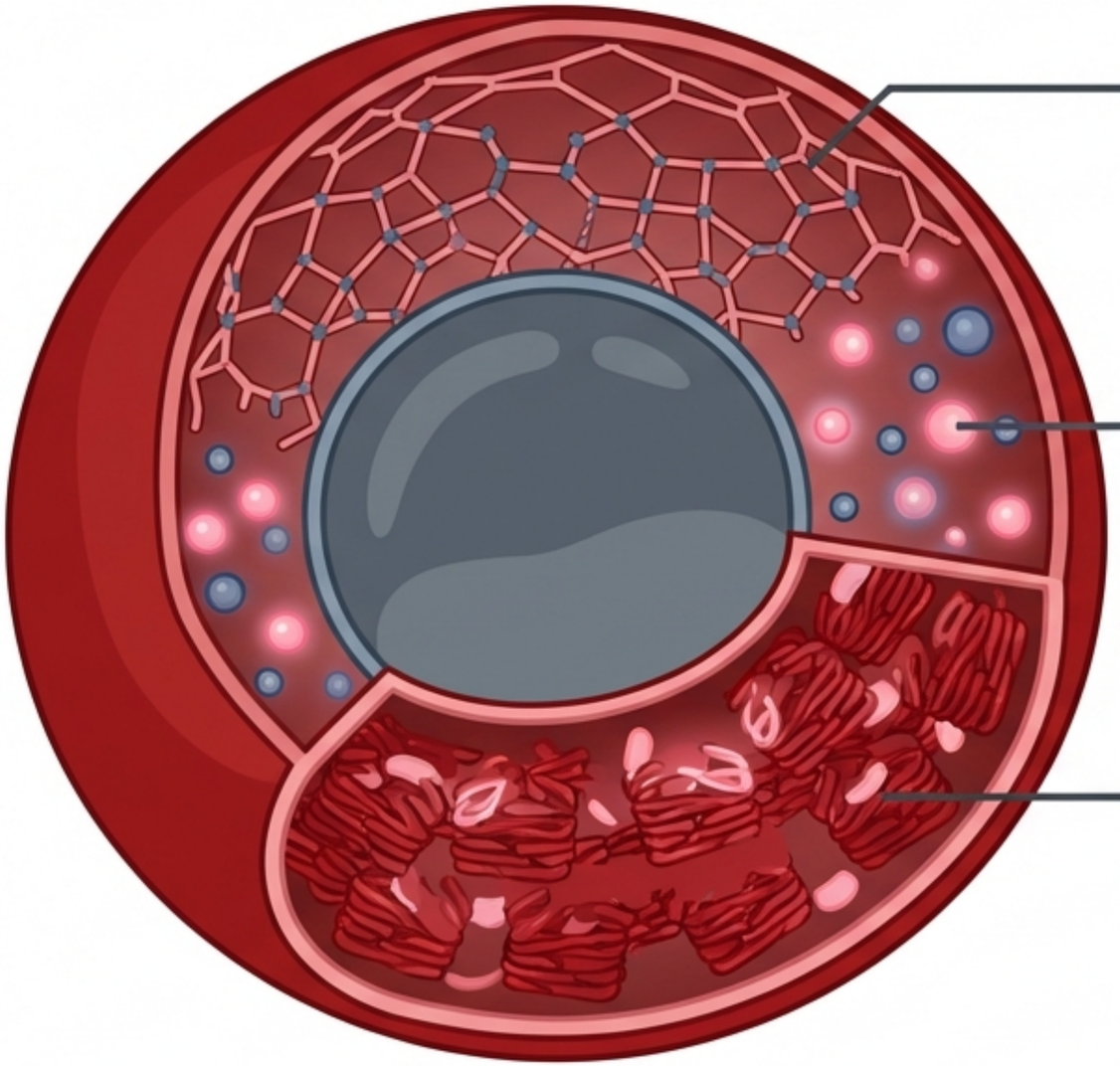
Hereditary Hemolytic Anemia



A Structural Deconstruction: From The Perfect Machine to Clinical Management

[Presenter Name/Organization]

The RBC: A Specialized Vessel for Cargo and Flexibility



1. The Skeleton (Chassis)
Spectrin/Ankyrin network. Provides durability and deformability.

2. The Engine (Protection)
Metabolic enzymes (G6PD, Pyruvate Kinase). Provides energy and anti-oxidant defense.

3. The Cargo (Payload)
Hemoglobin (Hgb). Sacrifices nucleus/organelles to maximize O2 transport.

The Trade-Off

To survive the 120-day journey through microcirculation, the RBC is stripped of its "brain" (Nucleus) and "factories" (Ribosomes/ Mitochondria). It relies entirely on this pre-built Triad of Stability.

Classification of Hereditary Defects: Where the Machine Breaks

1. Membrane Defects
(The Chassis)

Defect: Structural proteins (Spectrin, Ankyrin, Band 3).
Result: Loss of surface area & shape.
Key Disease: Hereditary Spherocytosis (HS).

2. Enzymopathies
(The Protection)

Defect: Metabolic energy or oxidative defense.
Result: Vulnerability to stress.
Key Disease: G6PD Deficiency.

3. Hemoglobinopathies
(The Cargo)

Defect: Globin chain synthesis.
Result: Quantity imbalance (Thal) or Quality failure (Sickle).
Key Diseases: Thalassemia, Sickle Cell Disease.

Hereditary Spherocytosis: The Trap of the Rigid Sphere

1. Genetic Defect

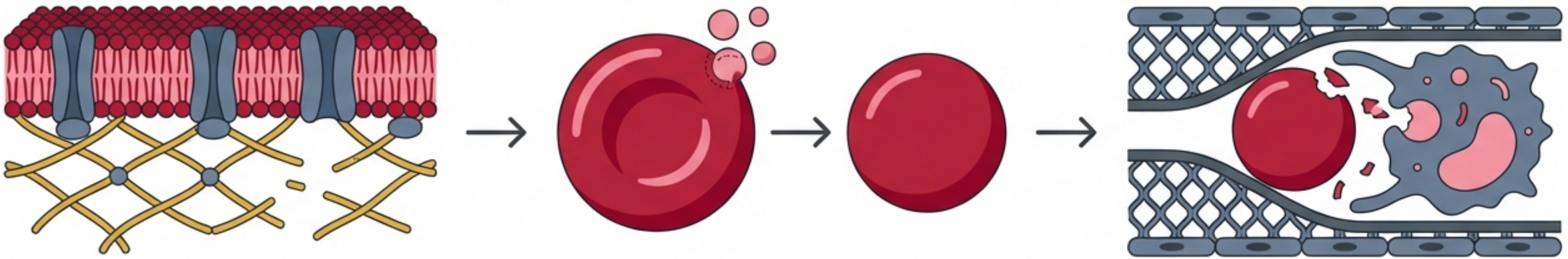
Mutation in Spectrin, Ankyrin, or Band 3 destabilizes the lipid bilayer.

2. Morphological Change

Membrane shedding leads to surface area loss. The cell is forced into a sphere (lowest surface-to-volume ratio).

3. Splenic Conditioning

Rigid spherocytes cannot pass through splenic sinusoids. Macrophages nip the membrane (conditioning), causing further volume loss until destruction (Extravascular Hemolysis).



Diagnosing HS: Case of the 33-Year-Old Male

Diagnostic Dashboard: A comprehensive view from presentation to confirmation.

Clinical Context

Patient: 33-year-old male.

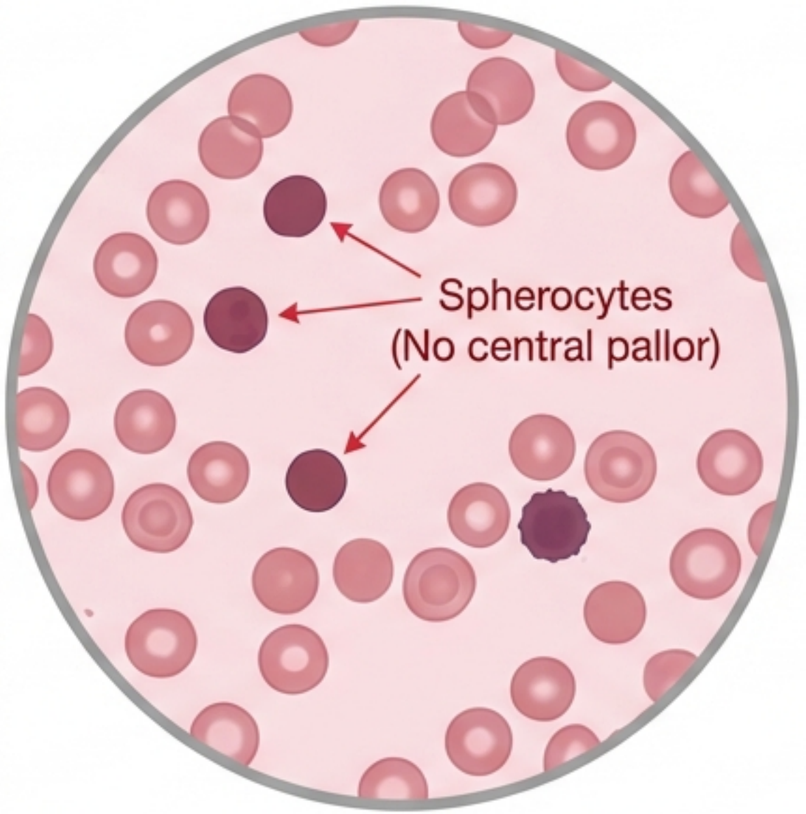
Presentation: Jaundice, Splenomegaly.

Family Hx: Anemia.

Key Labs: High Bilirubin, High LDH, Negative Coombs.

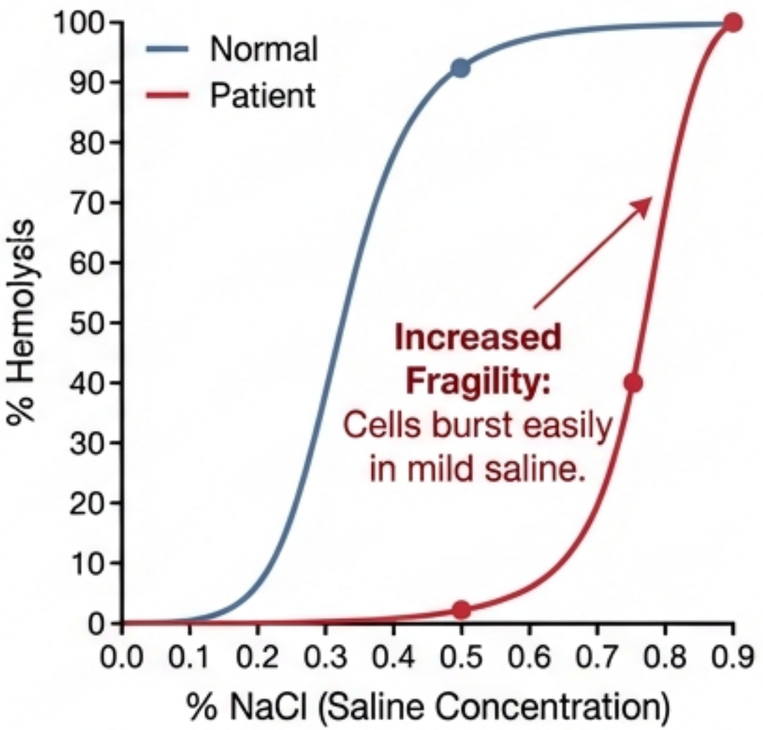
Test	Result	Units	Ref. Range
HGB	15.3	g/dL	[g/dL]
MCHC	37.0	g/dL	[g/dL]
RET%	8.51	%	[%]
RDW-CV	17.5	%	[%]

The Smear



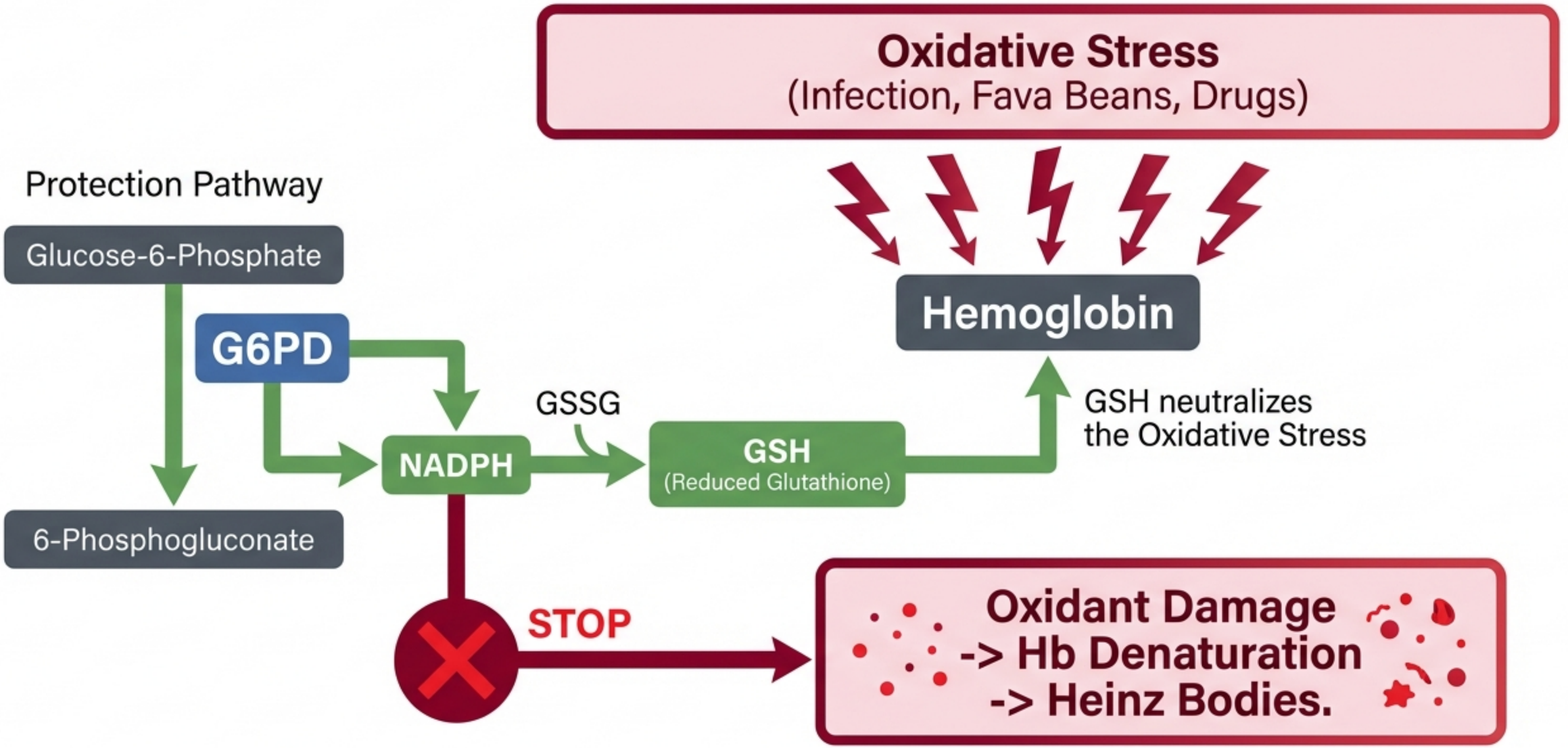
Confirmatory Testing

Osmotic Fragility Test



EMA Binding: Decreased fluorescence (Gold Standard).

Enzymopathies: When Oxidative Defense Fails (G6PD)



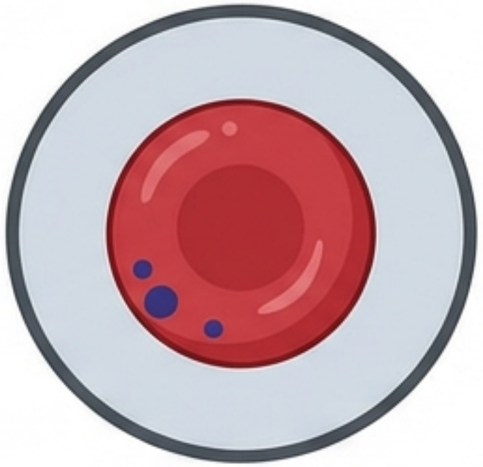
G6PD Deficiency: Triggers and Morphology

The Triggers

* **Diet:** Fava Beans (Favism)
* **Infection:** DKA, Acute Illness (Most common trigger)
* **Drugs:** Antimalarials (Primaquine), Sulfonamides (Bactrim), Nitrofurantoin

Morphology Gallery

Heinz Bodies

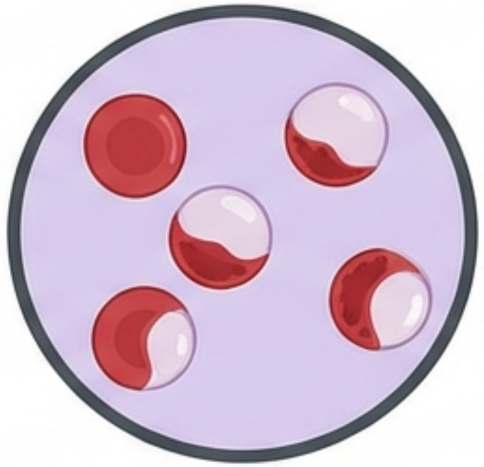


Precipitated Hemoglobin (Supravital stain).

Bite Cells

Result of splenic macrophages removing rigid inclusions.

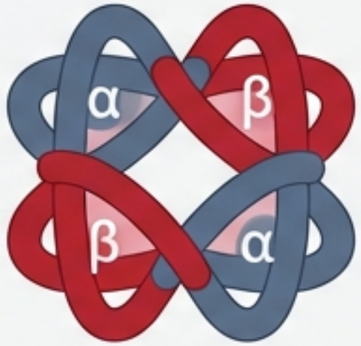
Blister Cells



Result of splenic macrophages removing rigid inclusions.

Clinical Note: X-Linked Recessive. Hemolysis is Episodic and Intravascular.

Hemoglobinopathies: Defects of Cargo



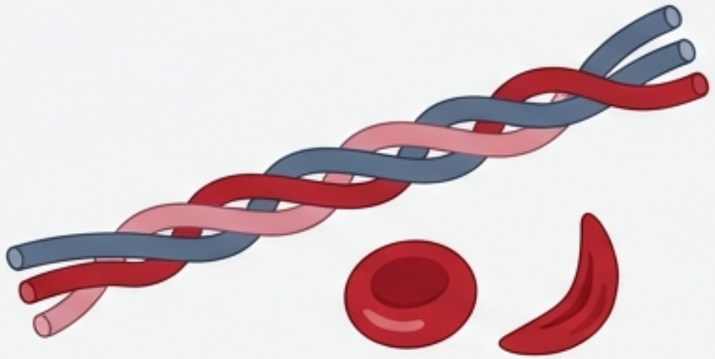
Normal HbA
(2 Alpha + 2 Beta chains)

Thalassemia
(The Quantity Problem)

Defect: Decreased synthesis of globin chains.

Result: Chain Imbalance. Excess free chains precipitate, causing precursor death (Ineffective Erythropoiesis).

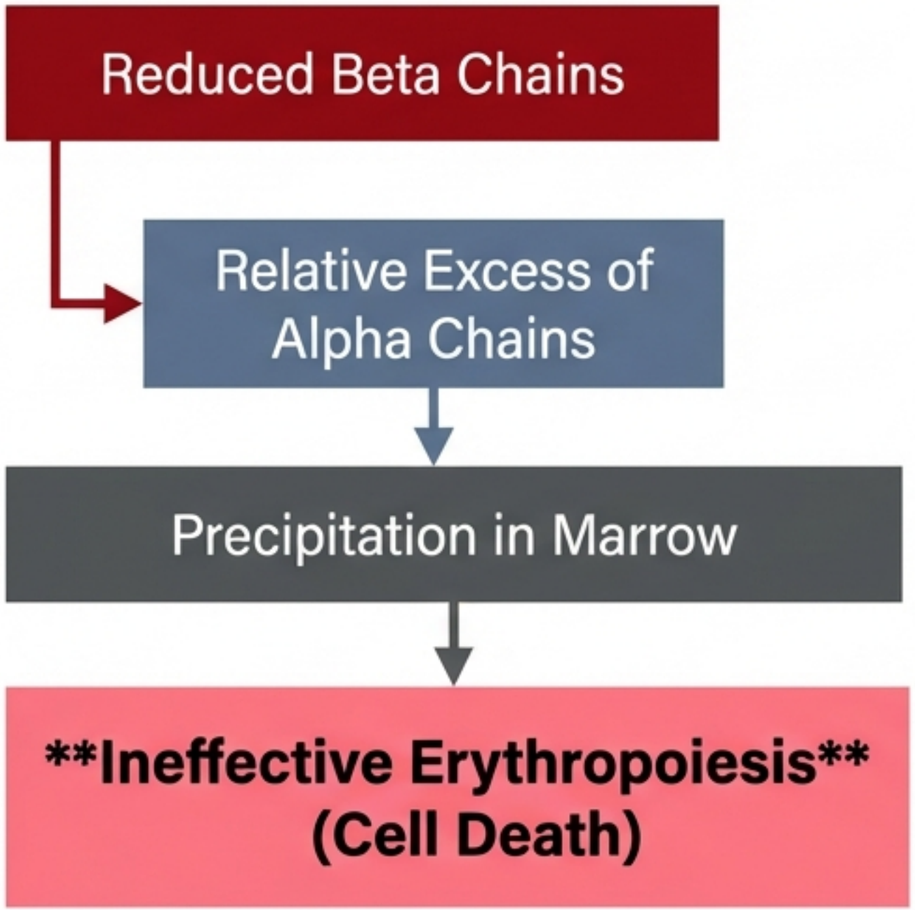
Sickle Cell Disease
(The Quality Problem)



Defect: Point mutation (Glu -> Val) in Beta-globin.

Result: Structural Failure. Hb polymerizes under stress, deforming the cell.

Beta-Thalassemia: The Spectrum of Beta-Globin Loss



Beta-Thal Minor (Trait)

- Genetics: Heterozygous.
- Clinical: Asymptomatic, mild microcytosis.
- Key Lab: **HbA2 > 3.5%**

Beta-Thal Major (Cooley's Anemia)

- Genetics: Homozygous (Beta-Zero).
- Clinical: Severe anemia, Transfusion Dependent, "Chipmunk Facies" (Marrow expansion).
- Risk: Iron Overload.

Alpha-Thalassemia: The Gene Deletion Spectrum

1 Deletion (Silent Carrier)

Asymptomatic.

2 Deletions (Alpha-Thal Trait)

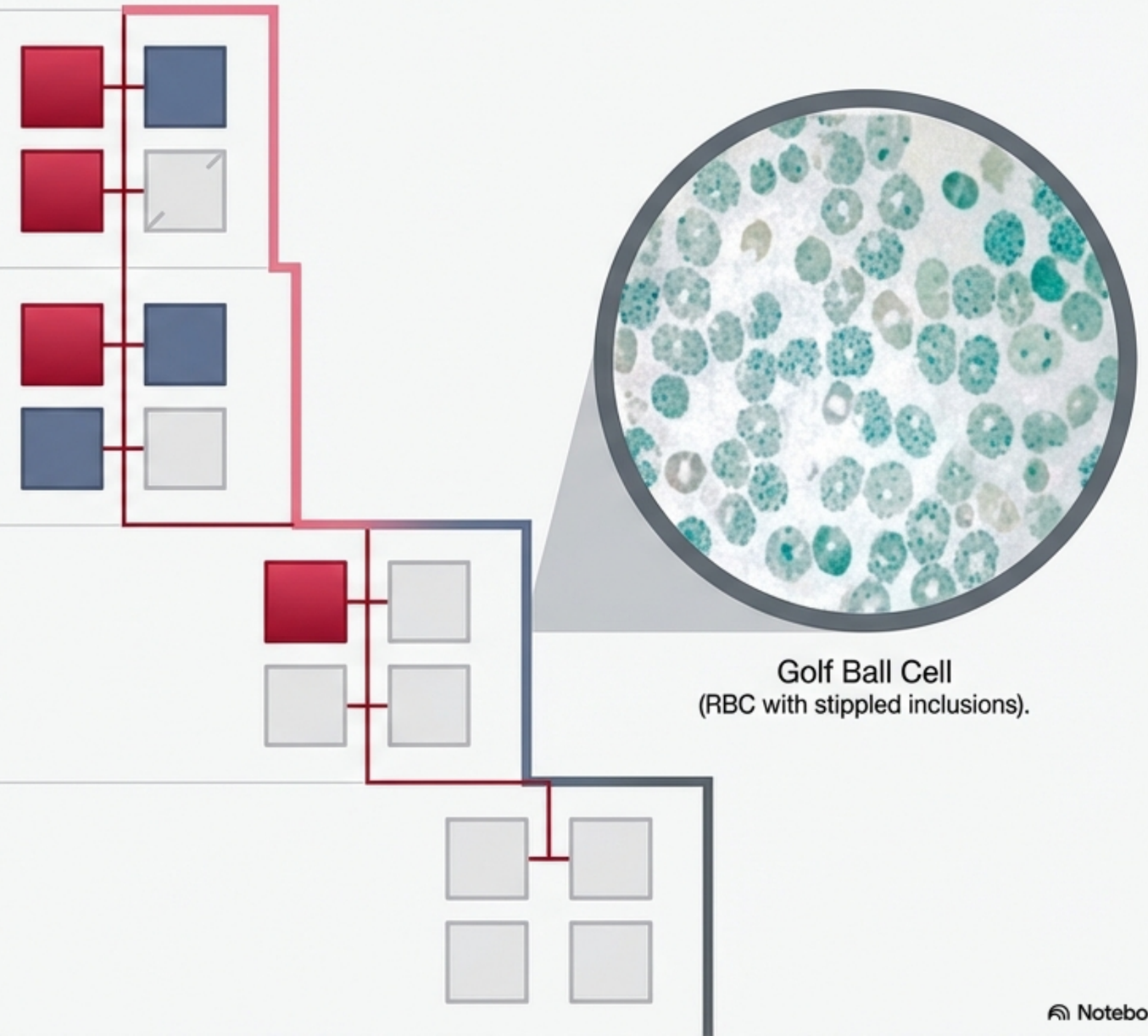
Mild microcytosis. Cis vs Trans deletions.

3 Deletions (Hb H Disease)

Excess Beta-chains form Beta-4 Tetramers.

4 Deletions (Hydrops Fetalis)

Incompatible with life. Hb Barts (Gamma-4).



Golf Ball Cell
(RBC with stippled inclusions).

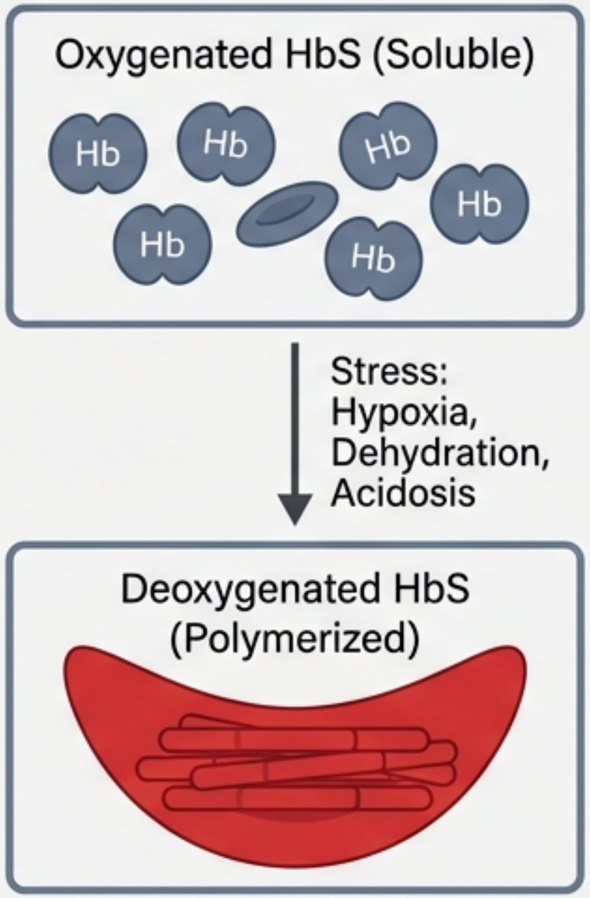
Sickle Cell Disease: A Single Point Mutation

Molecular Defect

Mutation: Glutamic Acid -> Valine at position 6 of Beta-globin.

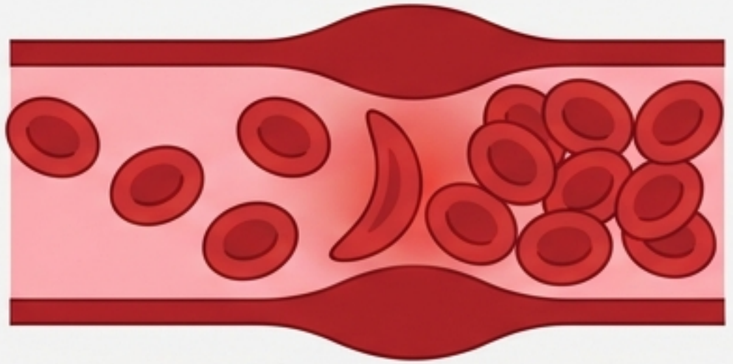
Genetics: Autosomal Recessive.

Polymerization Cycle



The Result

Vaso-Occlusion → Ischemia → Pain



Case Context: 20yo male with MSK pain and splenomegaly.

SCD Management: The Two-Front War

Acute Vaso-Occlusive Crisis

- **Pain Crisis:** Bones, Chest, Extremities.
- **Acute Chest Syndrome:** New infiltrate + Fever. Leading cause of mortality.
- **Splenic Sequestration:** Rapid enlargement, Hb drop.

Chronic Sequelae

- **Autosplenectomy:** Fibrosis leads to immune deficiency (Encapsulated bacteria risk).
- **Renal Failure & Avascular Necrosis.**

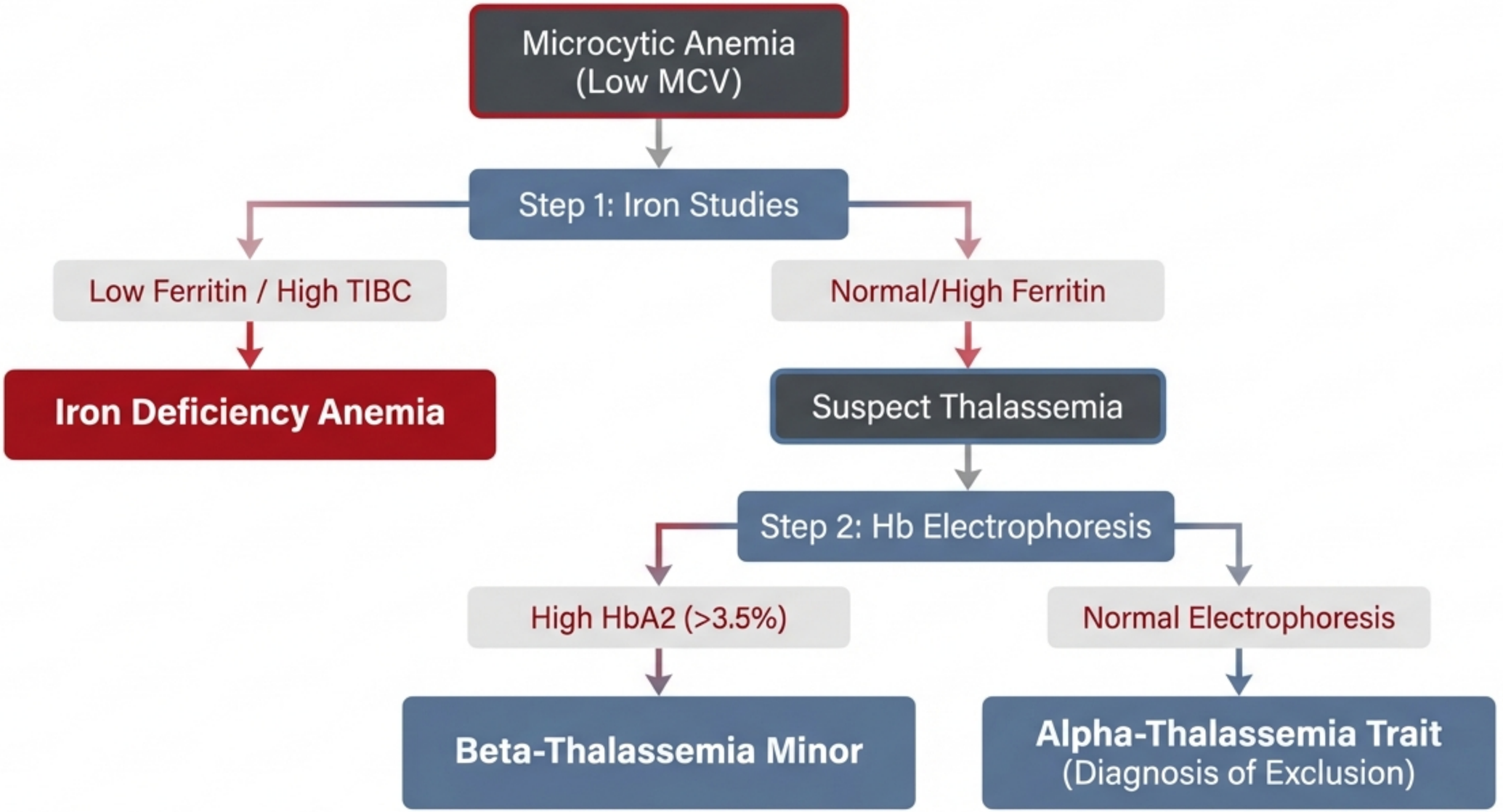
Diagnosis

Smear: Sickle Cells present.

Confirmatory: **Hb Electrophoresis** (HbS > 90%, No HbA).

	Hb conc.	Hb A	Hb A2	Hb F	Hb S
Hemoglobinopathy	Low	0%	↔	↔	>95%
Hemoglobinopathy SS	Low	0%	↔	↔	>95%
Sickle SS	Low	0%	↔	↔	>95%
Sickleglobin S	Low	0%	↔	↔	>95%
Catalon SS	Low	0%	↔	↔	>95%
Hemoglobiny F	Low	0%	↔	↔	>95%

The Microcytic Anemia Detective



The Hemolytic Anemia Detective: Clues in the Blood

The Diagnostic Approach

1

Confirm Hemolysis

- High Reticulocytes
- High LDH
- High Indirect Bilirubin
- Low Haptoglobin

2

The Fork in the Road: Coombs Test (DAT)

- **Autoimmune Hemolytic Anemia** (⊕)
- **Hereditary Cause** (Look at the Smear!) (⊖)

3

Morphology Decoding

Osmotic Fragility	Enzyme Assay	Electrophoresis	Electrophoresis
HS	**G6PD**	**SCD**	**Thalassemia**

Clinical Pearls & Takeaways

1 Architecture is Destiny.

The specific structural failure (Membrane, Enzyme, or Cargo) dictates the shape of the cell and the clinical presentation.

2 Rule Out the Common First.

Microcytic Anemia? Rule out Iron Deficiency. Spherocytes? Rule out Autoimmune (Coombs) before diagnosing HS.

3 Management Divergence.

G6PD is about avoidance (triggers). HS, Thalassemia, and SCD are about managing chronic organ damage (iron overload, stones, infection).

4 The Smear is the Story.

Visual inspection of the peripheral smear is the most powerful, cost-effective initial diagnostic tool.