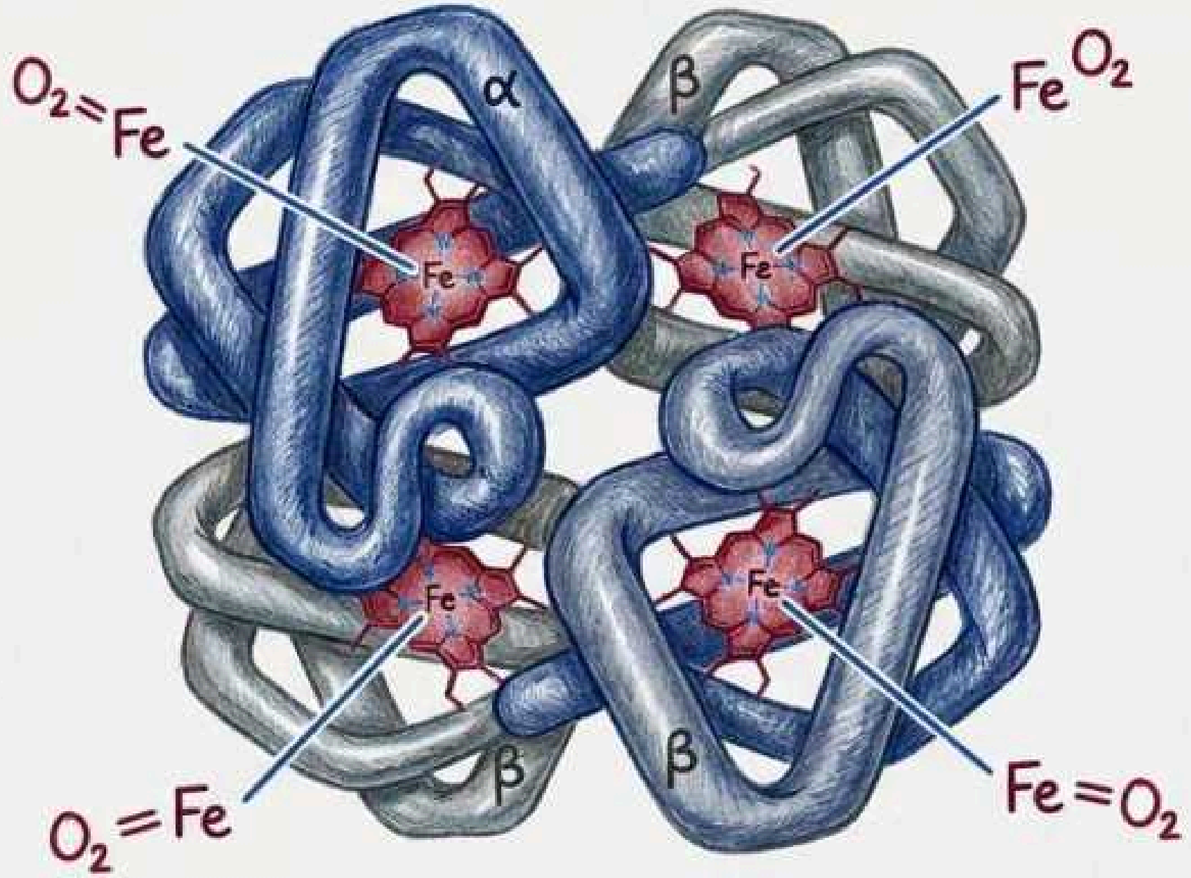
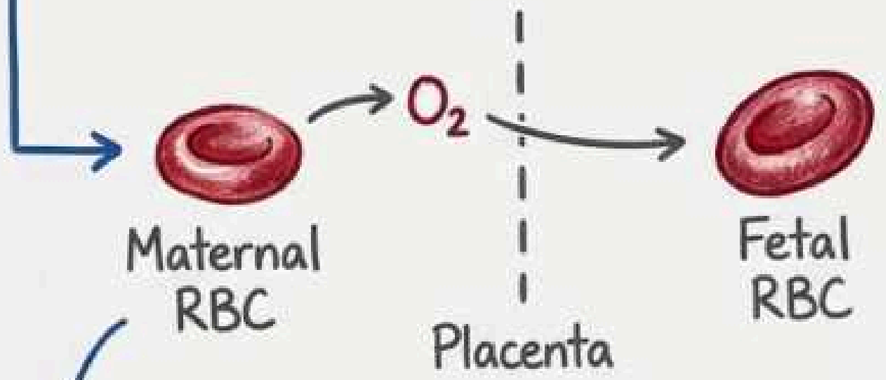
The Molecular Architecture of Haemoglobin

¶ 3.1



Adult Haemoglobin (HbA):	2α + 2β chains
Fetal Haemoglobin (HbF):	2α + 2γ chains

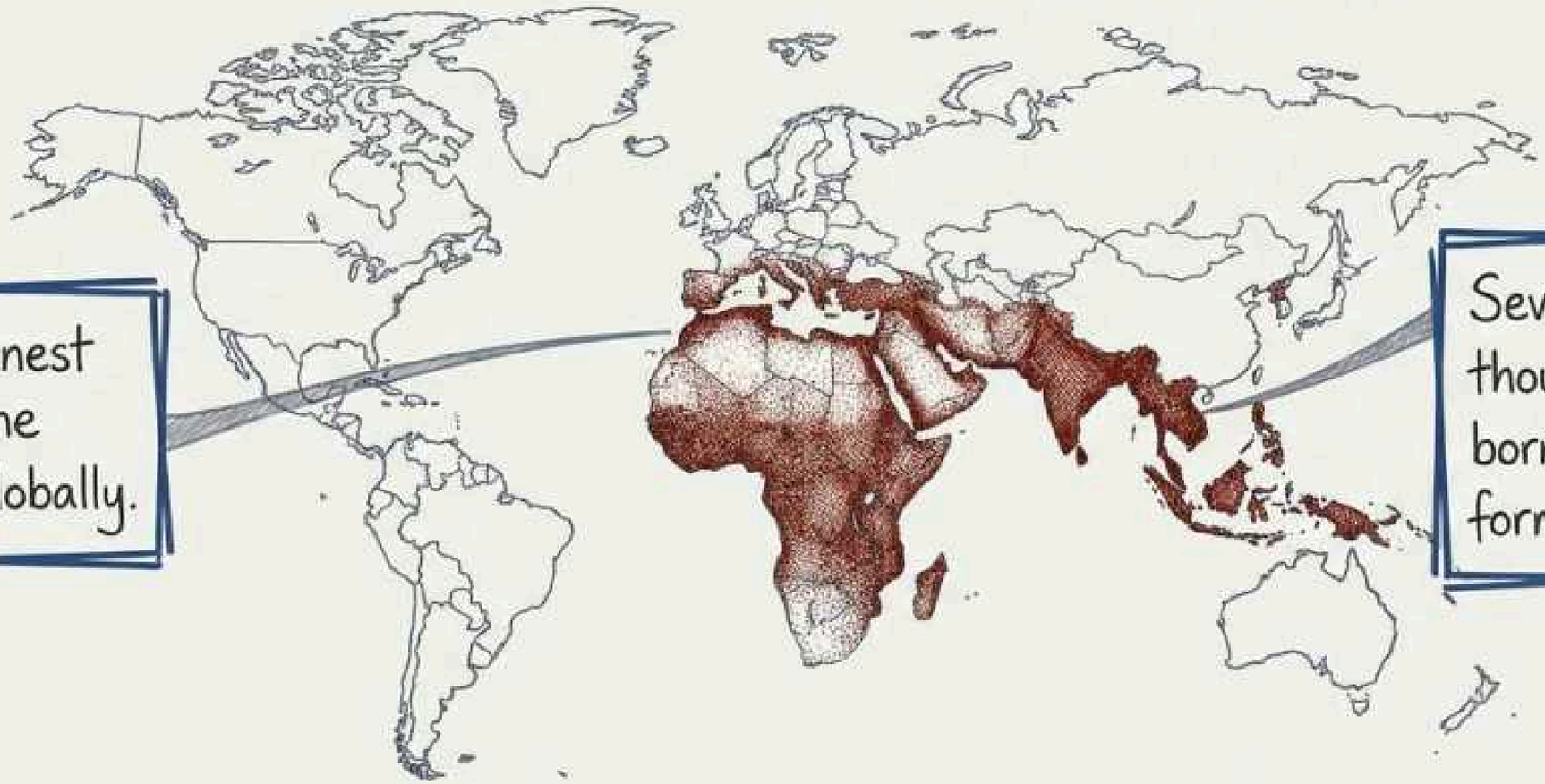


Higher O_2 affinity draws oxygen across the placenta.

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The Global Epidemiology of Haemoglobin Disorders

¶ 3.2



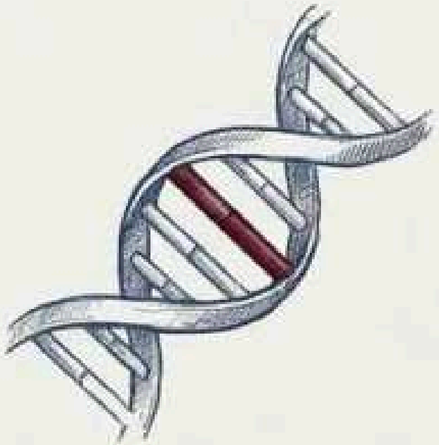
The commonest single-gene disorders globally.

Several hundred thousand babies born with serious forms annually.

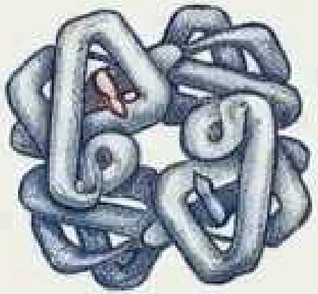
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Sickle Cell Disease: A Molecular Pathology

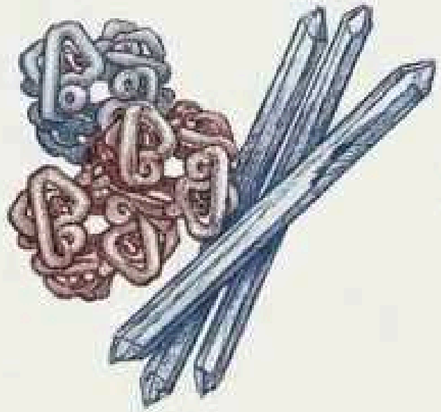
¶ 3.3



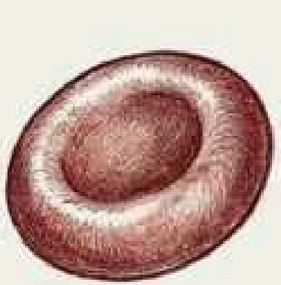
Mutation: β-chain alteration of a single amino acid.



Protein: Haemoglobin S (HbS).



Polymerization: HbS forms rigid fibres upon deoxygenation.





Healthy RBC Sickle Cell

Cellular Deformation: Rigid sickle shape.

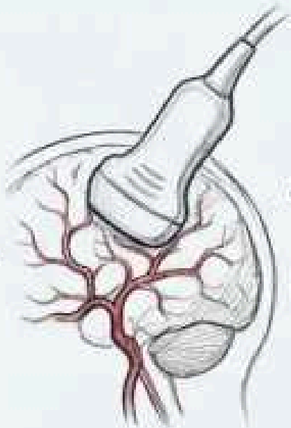
1949: Linus Pauling identifies the first disease understood entirely at the molecular level.

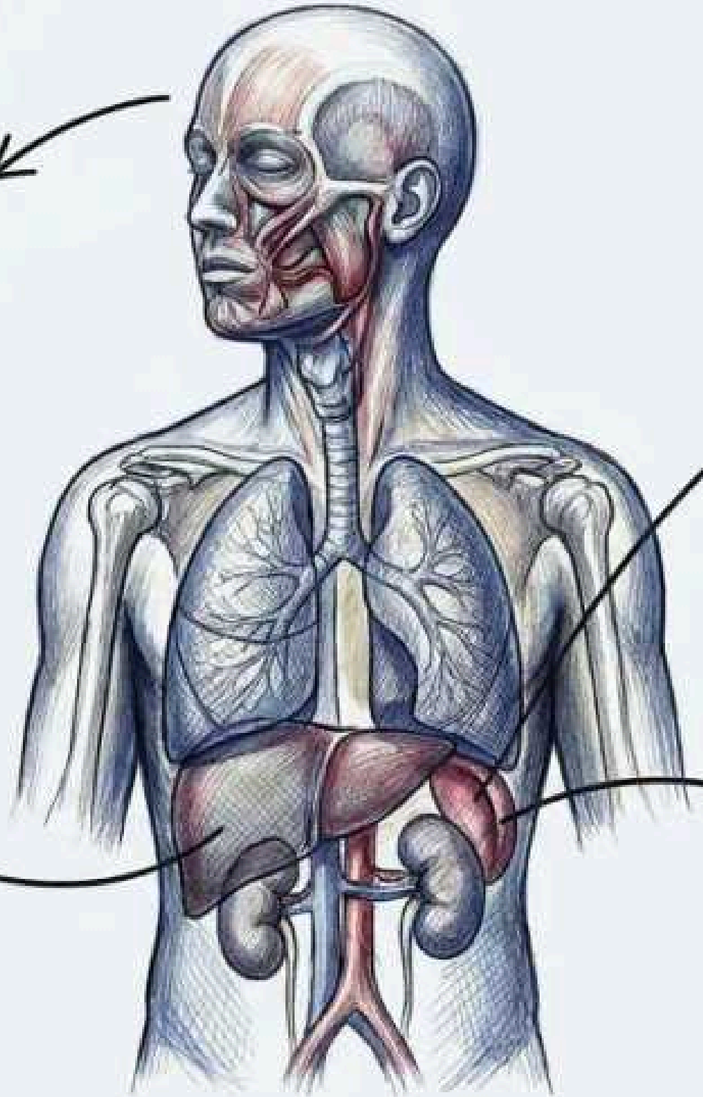
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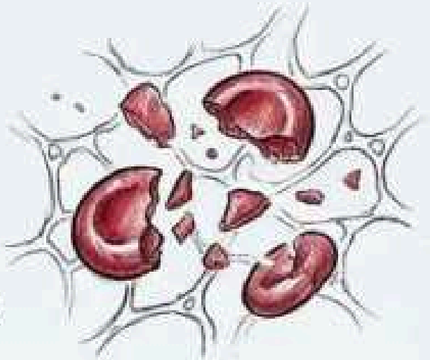
Systemic Consequences of Cellular Sickling

¶ 3.4

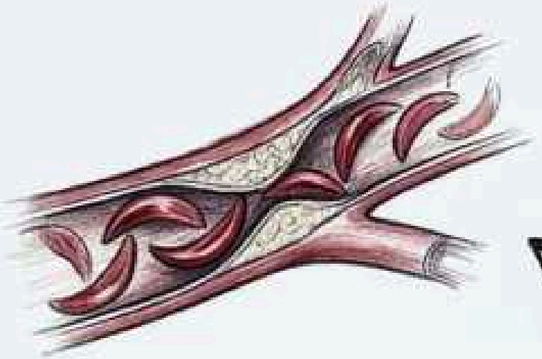
Pediatric Stroke Risk: Preventable through transcranial ultrasound screening and targeted treatment.







Early destruction of fragile cells → Anaemia.



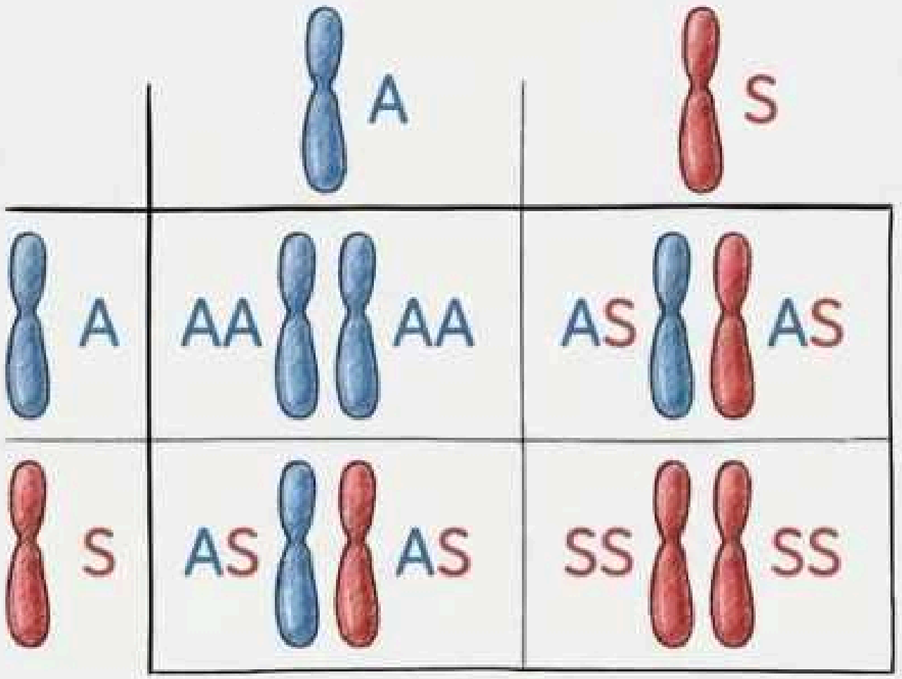
Stiff cells block flow → Severe pain crises.

Chronic damage to lungs, kidneys, spleen, and bones.

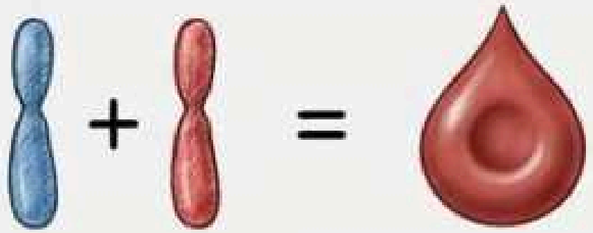
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Mendelian Inheritance of the Sickle Gene

¶ 3.5

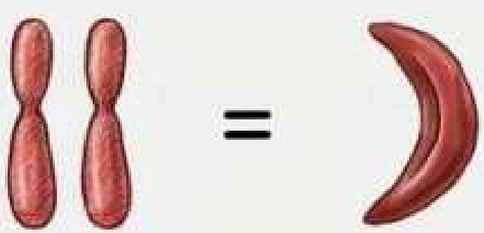


Carrier State (Sickle Cell Trait)



Usually asymptomatic.

Disease State (Sickle Cell Disease)



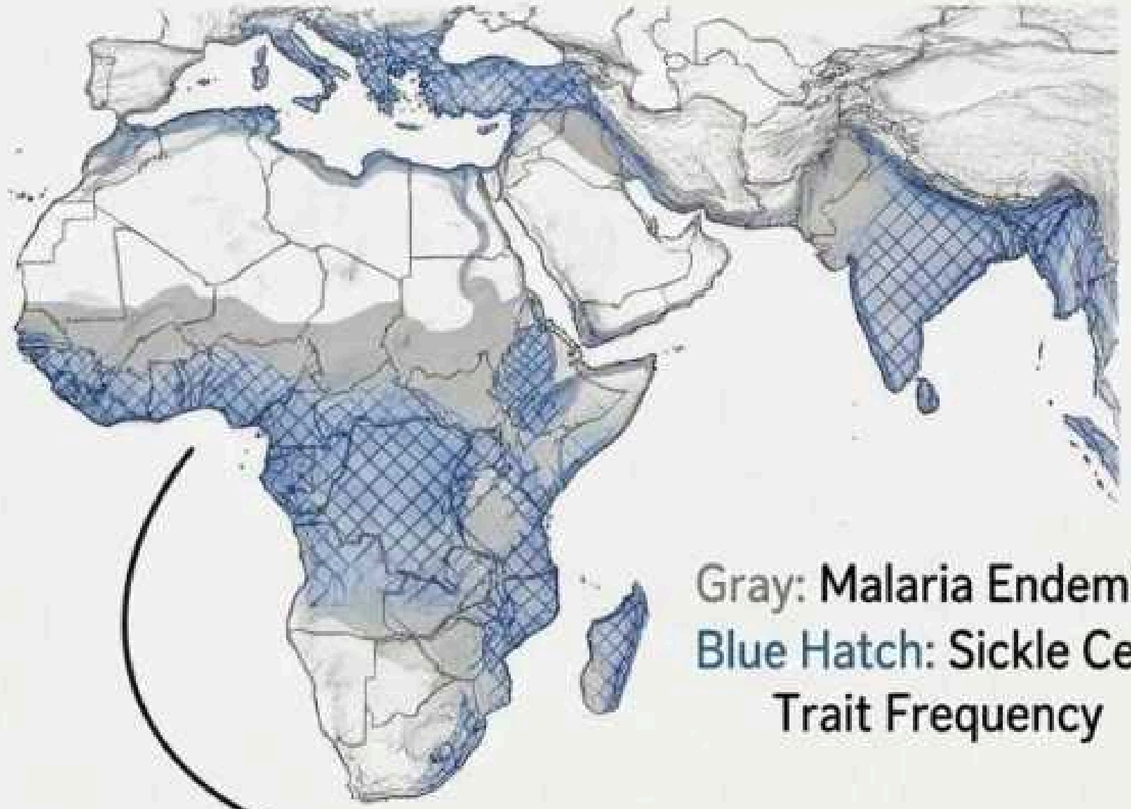
Clinical disease.

Follows classic autosomal recessive inheritance patterns (Ref: Medicine 503 B).

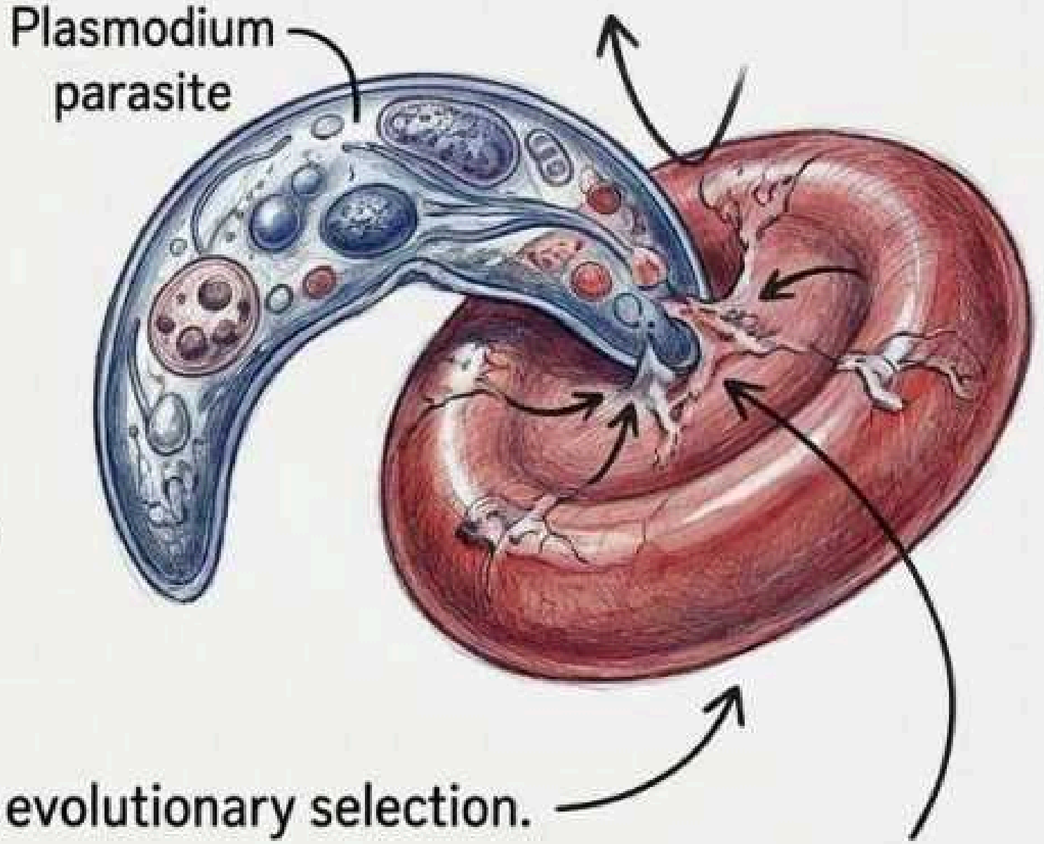
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Evolutionary Biology: The Heterozygote Advantage

¶ 3.6



Gray: Malaria Endemicity
Blue Hatch: Sickle Cell Trait Frequency



2 Copies (Disease) = Negative evolutionary selection.

1 Copy (Trait) = Partial protection against severe malaria = Positive evolutionary selection.

Classic Natural Selection: The trait persists in the population because carrying a single copy confers a survival advantage.

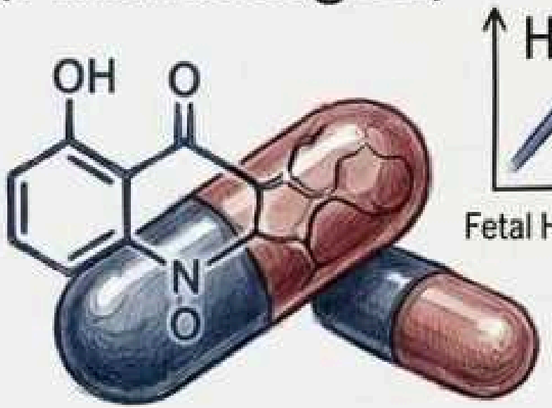
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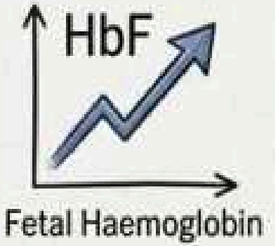
Standard Clinical Pathways for Sickle Cell Management

¶ 3.7

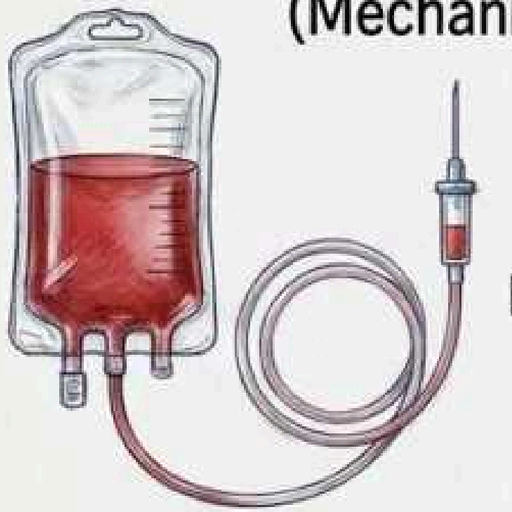
(Pharmacological)

Hydroxyurea: Raises Fetal Haemoglobin (HbF), reduces crises, prolongs life.





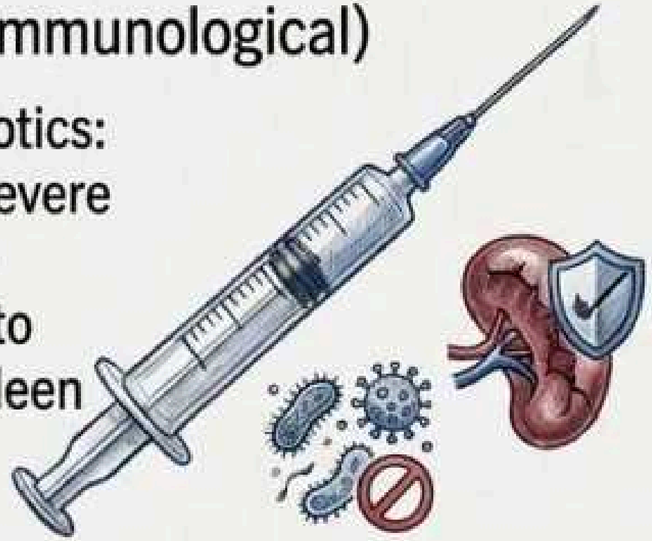
(Mechanical)



Blood Transfusions: Prophylactic stroke prevention in high-risk pediatric patients.

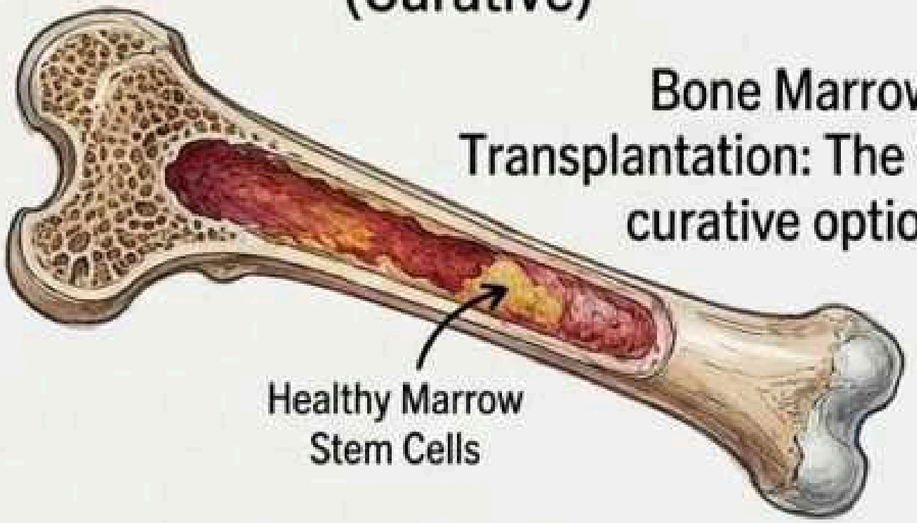
(Immunological)

Vaccines & Antibiotics: Protects against severe funtions due infections due to compromised spleen function.



(Curative)

Bone Marrow Transplantation: The traditional curative option.

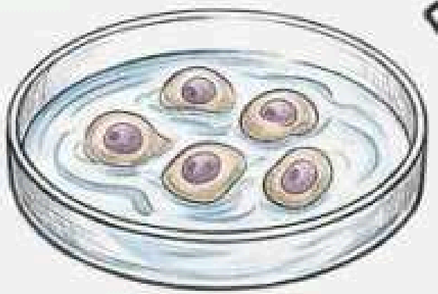


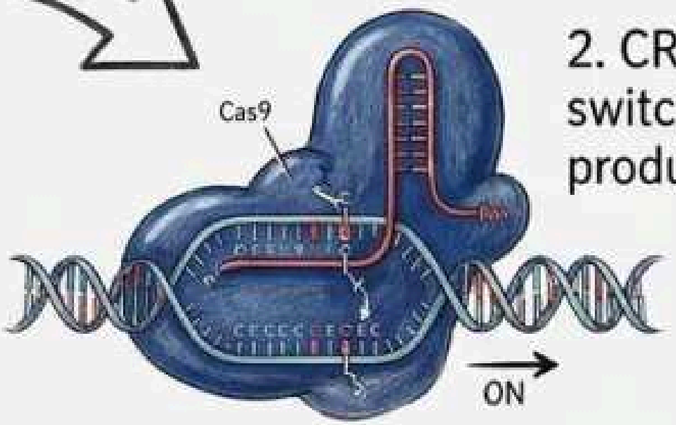
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The Genetic Revolution: 2023 Breakthroughs

¶ 3.8

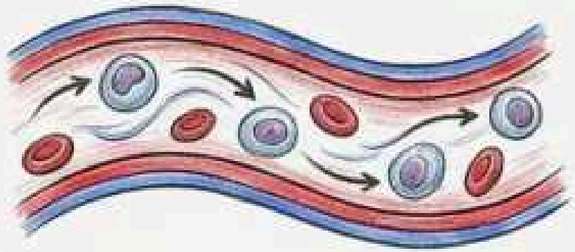
1. Stem cells extracted from patient.





2. CRISPR edits DNA to switch fetal haemoglobin production back ON.

3. Modified cells returned to the patient.



Approved in US & UK (2023). Transformative curative potential, but currently constrained by high complexity and exceptional cost.

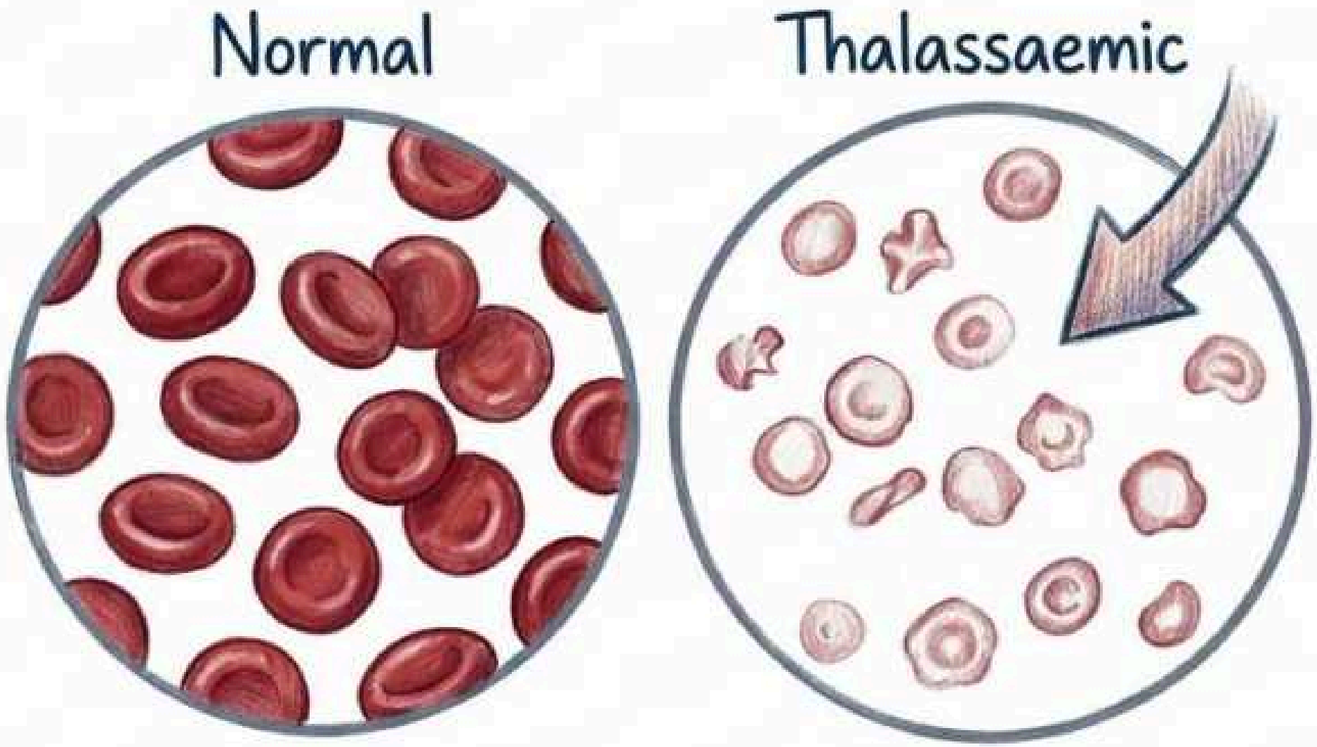
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The Thalassaemias: Quantitative Chain Defects

¶ 3.9

α-Thalassaemia = ↓ production of α chains.

β-Thalassaemia = ↓ production of β chains.



Unbalanced chains destroy red cell precursors. Clinically, this presentation must be carefully distinguished from standard iron deficiency anaemia.

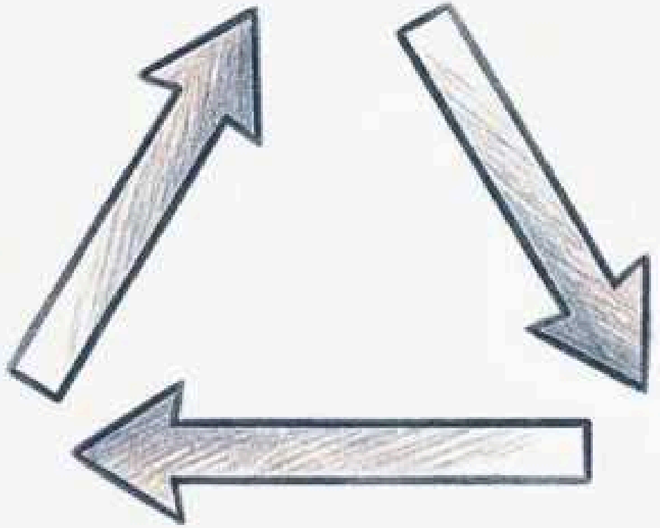
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Managing Severe β-Thalassaemia (Thalassaemia Major)

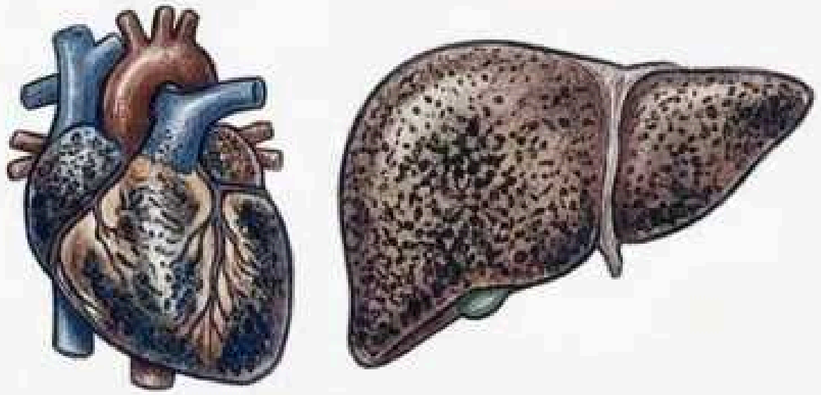
¶ 3.10

Severe **Anaemia** requires regular blood transfusions from early childhood.





Repeated transfusions trigger massive **Iron Overload.**



Organ damage mandates **Chelators** (drugs that bind and remove excess iron).



Curative avenues: Bone marrow transplantation and emerging gene therapies.

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Public Health Intervention: The Power of Population Screening

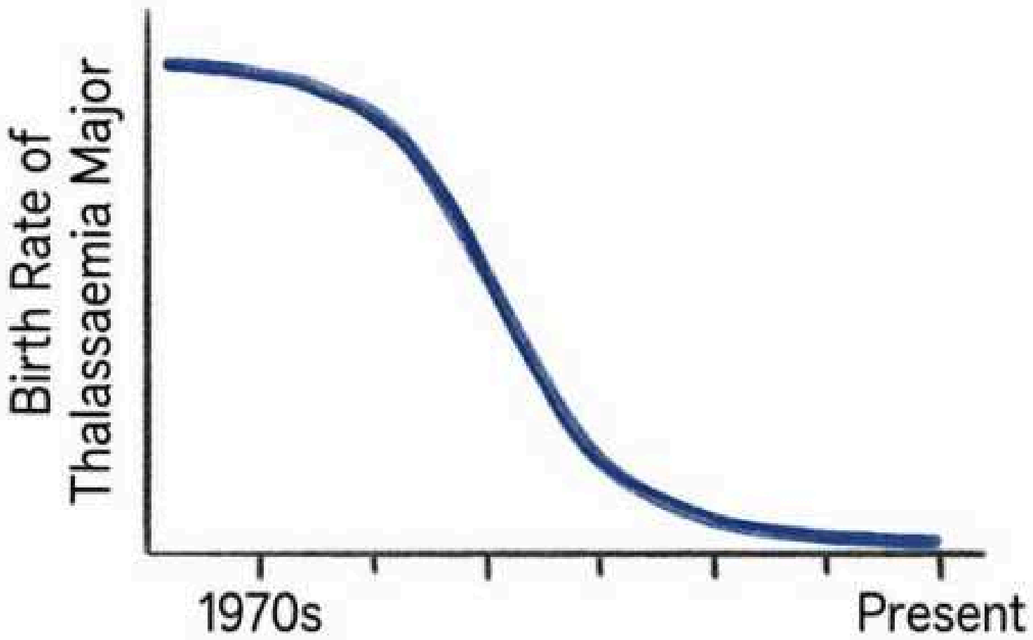
¶ 3.11

The Pathways

Screening Protocols

- Newborn Screening → Identifies affected infants immediately for early clinical intervention.
- Carrier Screening → Offered to couples pre-pregnancy to enable informed reproductive choices.

Cyprus Case Study



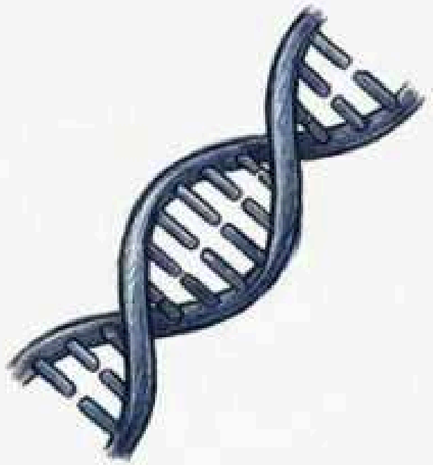
Cyprus effectively eliminated new cases of Thalassaemia Major through systematic carrier screening initiated in the 1970s.

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Synthesis: From Nucleotide to Cure

¶ 3.12

Pathology



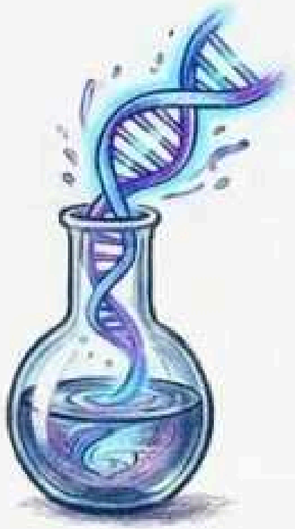
A microscopic genetic alteration dictates devastating, system-wide disease.

Evolution



Natural selection ruthlessly maintains deleterious genes when they offer localized survival advantages.

Medicine



A paradigm shift: moving from chronic symptom management to definitive molecular cures.

Next Lecture: The opposite physiological challenge—The Control of Bleeding.

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