Never look down on anybody unless you're helping him up
HEMOLYTIC ANAEMIAS:
Normal red cell life span = 120 days

Splenic reticuloendothelial cells

Degradation of Hb → bilirubin
HAEMOPOIETIC SYSTEM

Hemolysis $\rightarrow$ shortened red cell life span

Stimulated erythropoiesis $\rightarrow$ intra & extramedullary

$\uparrow$ Hb breakdown $\rightarrow$ $\uparrow$ bilirubin $\rightarrow$ jaundice $\rightarrow$ gall stones
Hemoglobin – Fe\(^{2+}\)

Heme + Globin → amino acids

Hematin Fe\(^{3+}\)

Fe\(^{3+}\) + Protoporphyrin

Biliverdin

Bilirubin

CO

Transferrin

Albumin

Fe\(^{3+}\) → Ferritin → hemosidrin → Apoferritin

Apoferritin → Fe\(^{3+}\) → Ferritin → heme synthesis

Liver cell Bilirubin diglucuronide

Expired CO

Amino acids → protein synthesis

Urea

Metabolism
### HAEMOPOIETIC SYSTEM

<table>
<thead>
<tr>
<th>Extravascular</th>
<th>Intravascular</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physiologic</strong></td>
<td><strong>Pathologic</strong></td>
</tr>
<tr>
<td><strong>RE cells spleen</strong></td>
<td><strong>In blood vessels</strong></td>
</tr>
<tr>
<td><strong>Fc receptor mediated</strong></td>
<td><strong>Complement mediated</strong></td>
</tr>
<tr>
<td><strong>Less deformable RBC</strong></td>
<td><strong>Mechanical injury</strong></td>
</tr>
<tr>
<td><strong>Splenomegaly ++</strong></td>
<td><strong>Splenomegaly +/-</strong></td>
</tr>
<tr>
<td><strong>Indirect hyperbilirubinemia</strong></td>
<td><strong>Hbaemia, Hburia, hemosidrinuria</strong></td>
</tr>
<tr>
<td><strong>Jandice ++</strong></td>
<td><strong>Jandice +</strong></td>
</tr>
<tr>
<td><strong>Normal</strong></td>
<td>↓ plasma Haptoglobin</td>
</tr>
</tbody>
</table>
HAEMOPOIETIC SYSTEM

Anaemia $\rightarrow$ ↑ EPO $\rightarrow$ erythroid hyperplasia $\rightarrow$

$\rightarrow$ Marrow expansion $\rightarrow$ reticulocytosis $\rightarrow$

$\rightarrow$ Leukoerythroblastic blood picture
$\rightarrow$ Gall stones
$\rightarrow$ haemosiderosis
HAEMOPOIETIC SYSTEM

HAEMOGLOBIN:
Heme + 4 Globin chains

HbA → 2a/2β
HbA2 → 2a/2δ
HbF → 2a/2γ

ξ and ζ embryonic chains
Hemoglobin Molecule

- red blood cell
- α chain
- iron
- heme group
- β chain
- helical shape of the polypeptide molecule
HAEMOPOIETIC SYSTEM

Synthesis of globin chains:

Haemopoietic GF
↓
Gene activation
↓
Transcription
↓
Translation
↓
Post translation stability
Transcription & Translation

1. DNA → RNA synthesis (transcription)
2. RNA → Intron 1 and Intron 2
3. Introns are removed (RNA splicing)
4. mRNA → Protein synthesis (translation)
Fe²⁺-binding elements → mRNA transcription → Glycine

ALA synthetase → d-Amino-levulinic acid (dALA)

Succinyl CoA

Protoporphyrinogen III

Protoporphyrin IX

Ferrochelatase

Heme

MITOCHONDRIUM

ALA dehydrogenase

Porphobilinogen

2x → Porphobilinogen

4x → PB deaminase

Hydroxymethyl bilane

Uroporphyrinogen III synthase

Uroporphyrinogen III

UP III decarboxylase

CO₂

Coproporphyrinogen III

CP-III oxidase

Heme

Cytoplasm

Hemoglobin

Globin chains
HAEMOPOIETIC SYSTEM

1.5 year girl
Failure to thrive
pallor and abdominal distension
Cousin died at 3 years with similar problems
Two transfusions in past

O/E pallor +++
Spleen 4 cm
Liver edge
### HAEMOPOIETIC SYSTEM

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLC</td>
<td>24.6</td>
</tr>
<tr>
<td>Hb</td>
<td>6.2</td>
</tr>
<tr>
<td>Plt</td>
<td>130</td>
</tr>
<tr>
<td>MCV</td>
<td>72</td>
</tr>
<tr>
<td>MCH</td>
<td>21</td>
</tr>
<tr>
<td>NRBC</td>
<td>43/100 WBC</td>
</tr>
</tbody>
</table>

Left shift in neutrophils
HbF : 97%

DIAGNOSIS:
Clinical, blood and electrophoresis findings are consistent with
\( \beta \)-thalassaemia major(\( \beta^o \))
THALASSAEMIAS:
Reduced or no synthesis of one or more globin chains of Hb.
Autosomal recessive
α chain deficiency $\rightarrow$ α thalassaemia
β chain deficiency $\rightarrow$ β thalassaemia
HAEMOPOIETIC SYSTEM

CLASSIFICATION:
Clinical
Genetic
Thalassaemia major
  homozygous $\beta + (\beta+/\beta+)$
  homozygous $\beta o (\beta o/\beta o)$
  $\beta / Hb$ Lepore
  $\beta / HbE$
HAEMOPOIETIC SYSTEM

Thalassaemia Intermedia:
- $\beta^+/\beta^+$
- $\beta$ with $\alpha$ thalassaemia
- HbH disease
- $\beta/\delta$ compound heterozygotes
- HbE/ $\beta$
HAEMOPOIETIC SYSTEM

Thalassaemia minor:
Silent carriers
\(\alpha^+\) thalassaemia trait
rare \(\beta\) thalassaemia trait
Mild anaemia
\(\alpha^0\) thalassaemia trait
\(\alpha^+\) thalassaemia
\(\beta^0\) trait
\(\beta^+\) trait
\(\delta\beta\) trait
HAEMOPOIETIC SYSTEM

BETA THALASSAEMIA:
Mutations in β globin gene
  Transcription
    promoter region mutations
    chain terminator mutations
Processing of mRNA
  splicing mutations
  splice site in exon
  IVS
  CAP site
Translation
    nonsense
    frameshift
    initiation site
Post translational stability
    Exon 3
overproduction of δ chain

increased Hb A2 in blood

selected survival of Hb F cells

increased level of HbF in blood

increased Hb oxygen affinity

increased erythropoietin production

skeletal changes

hyperuricemia

increased proliferation of erythroid cells

blocked β chain synthesis

underproduction of Hb A

precipitation of excess α chains

in blood

trapping in RES

hemolysis

ANEMIA

transfusion

iron overload

in bone marrow

ineffective erythropoiesis

cirrhosis

pancreatic failure

heart failure

folic acid deficiency

hypersplenism

extramedullary hematopoiesis

splenomegaly
HAEMOPOIETIC SYSTEM

DIAGNOSIS:
History
Examination
Blood film
Hb electrophoresis
PCR
Family studies
HAEMOPOIETIC SYSTEM

TREATMENT:
Regular blood transfusions
Iron chelation
  injectable
  oral
Supportive treatment
Bone marrow transplant
HAEMOPOIOIETIC SYSTEM

PREVENTION***
- genetic counseling
- antenatal diagnosis

COMPLICATIONS:
- growth retardation
- iron overload
- endocrine abnormalities
- CCF
- hepatic failure
- transfusion mediated infections (HBV, HCV)
"Sometimes the best helping hand you can get is a good, firm push"

This dog has failed.
5 years boy
Progressive pallor
Painful swelling of fingers & toes
Jaundice twice
O/E pallor ++
Jaundice +
Spleen +
Leg ulcers
Short right middle finger
HAEMOPOIETIC SYSTEM

Hb = 5.5 gm/dl
MCV = 74 fl
MCH = 26 l/l
TLC = 18.6
Plt = 110
Retics = 12%
Leucoerythroblastic blood picture
HAEMOPOIETIC SYSTEM

HAEMOGLOBIN ELECTROPHORESIS:

Band of HbS
ELECTROPHORESIS ON CELLULOSE ACETATE PAPER

A
AS
SS
AC
HAEMOPOIETIC SYSTEM

SICKLING TEST
HAEMOPOIETIC SYSTEM

SICKLE CELL DISEASE:
Autosomal recessive
Structural variant of Hb

6\textsuperscript{th} position $\beta$ globin chain
Valine $\rightarrow$ Glutamic acid $\rightarrow$ HbS
Deoxy Hb
↓
Crystallization/polymerization HbS
↓
Tactoid formation (reversible)
↓
Repeated sickling de-sickling
↓
Irreversibly sickled
↓
Vascular occlusion
Normal red blood cells are compact and flexible, enabling them to squeeze through small capillaries.

Sickled red blood cells are stiff and angular, causing them to become stuck in small capillaries.

Normal hemoglobin forms long, inflexible chains.
HAEMOPOIETIC SYSTEM

Membrane damage $\rightarrow$ $\uparrow$ Ca $\rightarrow$ $\downarrow$ K$^+$

$\downarrow$

Intracellular dehydration

$\downarrow$

Sticky RBCs

$\downarrow$

Vascular occlusion
HAEMOPOIETIC SYSTEM

Homozygous $\rightarrow$ SCD
Heterozygous $\rightarrow$ SC trait
HbF inhibits polymerization of HbS
Intracellular dehydration $\rightarrow$ $\uparrow$ MCHC $\rightarrow$ Sickling ++
$\downarrow$ pH $\rightarrow$ deoxy Hb $\rightarrow$ sickling
HAEMOPOIETIC SYSTEM

CLINICAL PRESENTATION:
Chronic hemolysis (extravascular)
Anaemia
Jaundice
Infections by encapsulated organisms
ön osteomyelitis (salmonella)
H-Influenza, Pneumococci
Leg ulcers
HAEMOPOIETIC SYSTEM

Vaso occlusive crisis ➔ painful crisis
  bones ➔ hand – foot syndrome
  lungs ➔ acute chest syndrome
  brain ➔ seizures / stroke
  liver ➔ hepatic sequestration ➔ pain
  spleen ➔ sequestration syndrome
  penis
HAEMOPOIETIC SYSTEM

Marrow expansion → hair on ends (x-ray skull)

Prominent cheek bones
Extramedullary haemopoiesis
Gall stones
Aplastic crisis (parvo virus)
Autosplenectomy
HAEMOPOIETIC SYSTEM

DIAGNOSIS:
History
Examination
Peripheral smear
  ISC
leucoerythroblastic blood picture
reticulocytosis
HAEMOPOIETIC SYSTEM

- Hb electrophoresis
- HbS band
- Sickling test
- PCR
HAEMOPOIETIC SYSTEM

MANAGEMENT:
Blood transfusion (RCC)
Prevention
Bone marrow transplant
A man who is "of sound mind" is one who keeps the inner madman under lock and key.
HAEMOPOIETIC SYSTEM

HEREDITARY SPHEROCYTOSIS:
Red Cell Cytoskeleton

glycophorin

lipid bilayer

4.2

band 3

ankyrin 2.1

β-spectrin

α-spectrin

actin
HAEMOPOIETIC SYSTEM

Autosomal dominant
Intrinsic membrane defect
Deformability of RBC due to cytoskeletal Proteins
Spectrin
Actin
Ankyrin
Band 4.2 & 3
HAEMOPOIETIC SYSTEM

Reduced membrane stability
Reduced deformability $\rightarrow$ spheroidal
Trapped in spleen $\rightarrow$ lactic acid ++
$\rightarrow$ Intracellular Na$^+$ $\uparrow$ $\rightarrow$ osmotic injury
Phagocytosis by RE cells
Splenomegaly
Splenic trauma or disease
HAEMOPOIETIC SYSTEM

Variable severity
Chronic hemolytic anaemia
Aplastic crisis
Hemolytic crisis
HAEMOPOIETIC SYSTEM

DIAGNOSIS:
History
Examination
Blood film
Osmotic Fragility test
HAEMOPOIETIC SYSTEM

GLUCOSE 6 PO4 DEHYDROGENASE DEFICIENCY
Red Blood Cell Metabolism

Glucose → ATP (via Glucokinase) → ADP

G-6-P (Glucose-6-Phosphate) → 70% Embden-Meyerhof Pathway → F-6-P (Fructose-6-Phosphate)

2 H₂O₂ (Hydrogen Peroxide) → Glutathione Peroxidase → GSH (Reduced Glutathione) → GSSG (Oxidized Glutathione)

NADP⁺ (Nicotinamide Adenine Dinucleotide Phosphate) → Glucose-6-Phosphate Dehydrogenase → 6-P-G (6-Phosphogluconate)

NADPH (Reduced Nicotinamide Adenine Dinucleotide Phosphate) → Pyruvic Acid + 2 ATP + 2H⁺

Glyceraldehyde-3-P + CO₂ + H⁺ + NADPH
HAEMOPOIETIC SYSTEM

X linked
Oxidant damage to RBCs →
Heinz bodies → Bite cells

Oxidant stress:
  Drugs (antimalarials, sulfonamides)
  Foods (Fava beans)
  Infections
HAEMOPOIETIC SYSTEM

Variants → G6PD-A (Mediterranean)
   → G6PD-B (commonest)
   → G6PD A- (African, mild)

Neonatal jaundice
Acute hemolysis
Chronic low grade hemolysis (CNSHA)

Intravascular hemolysis
Extravascular hemolysis
Heinz Bodies (G6PD Deficiency)
ACQUIRED HEMOLYTIC ANAEMIAS:
Immune hemolytic anaemia:
Autoimmune HA
  warm antibody type
  idiopathic
  autoimmune diseases
  LPD
  infections
  cancers
  drugs
HAEMOPOIETIC SYSTEM

cold antibody type
cold agglutinin syndrome
CHAD (idiopathic)
infections
LPD
PCH
HAEMOPOIETIC SYSTEM

Alloimmune HA transfusion reactions
HDN
allograft associated
drug induced
  macrophage mediated
  complement mediated
<table>
<thead>
<tr>
<th>Warm antibody HA</th>
<th>Cold antibody HA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commonest (45-70%)</td>
<td>15-30%</td>
</tr>
<tr>
<td>50% idiopathic</td>
<td>Secondary &gt;</td>
</tr>
<tr>
<td>IgG, IgA</td>
<td>IgM</td>
</tr>
<tr>
<td>Extravascular hemolysis</td>
<td>Intravascular ++</td>
</tr>
<tr>
<td></td>
<td>Extravascular &lt;</td>
</tr>
<tr>
<td>Fc receptor mediated macrophage</td>
<td>Complement activation, C3b macro</td>
</tr>
<tr>
<td>Spherocytosis</td>
<td>RBC agglutinates</td>
</tr>
<tr>
<td>---------------</td>
<td>--------------------------------</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>Raynauds phenomena</td>
</tr>
</tbody>
</table>
Paroxysmal Cold Haemoglobinuria:
Acute intermittent severe intravascular
Hemolysis
P blood group
Donath – Landsteiner antibody
IgG → biphasic antibody
Complement mediated
**Direct Coombs test / Direct antiglobulin test**

Blood sample from a patient with immune mediated haemolytic anaemia: antibodies are shown attached to antigens on the RBC surface.

The patient's washed RBCs are incubated with antihuman antibodies (Coombs reagent).

RBCs agglutinate: antihuman antibodies form links between RBCs by binding to the human antibodies on the RBCs.

**Legend**
- Antigens on the red blood cell's surface
- Human anti-RBC antibody
- Antihuman antibody (Coombs reagent)

**Indirect Coombs test / Indirect antiglobulin test**

Recipient's serum is obtained, containing antibodies (Ig's).

Donor's blood sample is added to the tube with serum.

Recipient's Ig's that target the donor's red blood cells form antibody-antigen complexes.

Anti-human Ig's (Coombs antibodies) are added to the solution.

Agglutination of red blood cells occurs, because human Ig's are attached to red blood cells.
APLASTIC ANAEMIA:
“Presence of pancytopenia in the peripheral blood & a hypocellular marrow in which normal haemopoietic marrow is replaced by fat cells.”
Haemopoietic stem cell defect
Defect in microenvironment
Cytotoxic T cell mediated suppression of Stem cells
IFN gamma, TNF
Absence of abnormal cells or fibrosis in Bone marrow
HAEMOPOIETIC SYSTEM

Causes:
Idiopathic
  primary stem cell defect
  immune mediated
Chemical agents
dose related
  alkylating agents & antimetabolites
  benzene, arsenic
  chloramphenicol
HAEMOPOIETIC SYSTEM

idiosyncratic
chloramphenicol
phenylbutazone
arsenic, streptomycin
insecticides & pesticides

Physical agents
radiation
HAEMOPOIETIC SYSTEM

Infections
  hepatitis
  CMV, EBV, herpes V
Inherited
  Fanconi’s anaemia
HAEMOPOIETIC SYSTEM

Clinical presentation:
Anaemia →
Thrombocytopenia →
Neutropenia →
HAEMOPOIETIC SYSTEM

Diagnosis:
History
Examination
Blood CP
Bone marrow aspiration & trephine
Ability is of little account without opportunity