HAEMOPOIETIC SYSTEM
Objectives

At the end of lectures the learners would be able to:

1. Have an understanding of hemopoiesis
2. Classify anemias
3. Have an understanding of causes, pathogenesis, diagnosis & management of iron deficiency, megaloblastic, aplastic & hemolytic anemias.
4. Know Thalassemias in detail
Objectives (contd)

5. Classify bleeding disorders
6. Have an understanding of the etiology, pathogenesis, diagnosis and treatment of ITP and hemophilia
HAEMOPOIETIC SYSTEM

BLOOD

Plasma

  Coagulation factors

Cells

  White blood cells/Leukocytes (WBCs)
  Red blood cells/Erythrocytes (RBCs)
  Platelets/Thrombocytes
HAEMOPOIETIC SYSTEM

Haemopoiesis

yolk sac

Liver

Spleen

Bone marrow

long bones (children)

Axial skeleton (adults)
Embryonic/Foetal Life (months)
<table>
<thead>
<tr>
<th>Type of growth factor</th>
<th>Responding hematopoietic cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythropoietin (EPO)</td>
<td>Erythroid progenitors</td>
</tr>
<tr>
<td>Granulocyte colony-stimulating factor (G-CSF)</td>
<td>Granulocytes</td>
</tr>
<tr>
<td>Interleukin-4</td>
<td>B cells, T cells</td>
</tr>
<tr>
<td>Interleukin-7</td>
<td>Lymphoid stem cells</td>
</tr>
<tr>
<td>Interleukin-3</td>
<td>Pluripotent precursor cells, megakaryocytes</td>
</tr>
<tr>
<td>Granulocyte-macrophage colony-stimulating factor (GM-CSF)</td>
<td>Pluripotent precursor cells, megakaryocytes</td>
</tr>
<tr>
<td>Interleukin-5</td>
<td>B cells, eosinophils</td>
</tr>
<tr>
<td>Interleukin-2</td>
<td>T cells</td>
</tr>
<tr>
<td>Interleukin-6</td>
<td>T cells, activated B cells, monocytes</td>
</tr>
<tr>
<td>Thrombopoietin</td>
<td>Megakaryocytes</td>
</tr>
<tr>
<td>Macrophage colony-stimulating factor (M-CSF)</td>
<td>Macrophages, granulocytes</td>
</tr>
</tbody>
</table>
DISEASES OF HAEMOPOIETIC SYSTEM

Cytopenia

↓ production

↑ destruction / pooling

Cytosis

reactive

malignant
HAEMOPOIETIC SYSTEM

- RBCs → Anaemias
- WBCs → Leukaemias
  - myeloproliferative disorders
  - Lymphomas
  - plasma cell disorders
- Platelets → Thrombocytopenia
  - function defects
- Coagulation disorders → factor deficiency
ANAEMIA:
Reduction below the normal limits of the total circulating red cell mass.

Reduction in Hb, HCT/PCV below the normal limit for that age, sex and environment
ERYTHROPOIESIS:
Formation of RBCs
Erythropoietin
Minerals, vitamins etc:
  iron, Mn, Co
  vit B12, folic acid, B6, vit C, E, B1
  amino acids
  hormones
Erythropoiesis

Pronormoblast

Basophilic normoblast

Polychromatophilic normoblast

Orthochromatic normoblast

Reticulocyte

Erythrocyte
HAEMOPOIETIC SYSTEM

CLASSIFICATION OF ANAEMIAS:
Morphological
  Size
  Shape
  Colour
Pathogenetic
  blood loss
  Reduced production
  increased destruction
Morphological classification:

1. Normocytic Normochromic
   - acute blood loss
   - aplastic anaemia
   - ACD
   - hemolytic anaemia
HAEMOPOIETIC SYSTEM

2. Microcytic Hypochromic
   Iron deficiency anaemia
   Thalassaemias
   Sidroblastic anaemia
   ACD
HAEMOPOIETIC SYSTEM

3. Macrocytic
   Megaloblastic anaemia
   hemolytic anaemia
HAEMOPOIETIC SYSTEM

Pathogenetic classification:

1. Blood loss
   - Acute
   - Chronic

2. Increased destruction (hemolytic)
   - Hereditary
     - membrane defects
     - Spherocytosis
     - Elliptocytosis
HAEMOPOIETIC SYSTEM

- Metabolic defects
  - G6PD deficiency
  - PK deficiency
- Hb defects
  - Quantitative defects
  - Thalassaemias
  - Qualitative defects
  - Sickle cell anaemia
  - HbC, D, E
  - Unstable Hb
Acquired
  Immune hemolytic anaemias
  Non immune
    MAHAs (mechanical)
    PNH
    malaria & other infections
    mechanical trauma
  Hypersplenism
  DIC
  Drugs
HAEMOPOIETIC SYSTEM

3. Impaired production:
   Nutritional deficiencies
       megaloblastic anaemia
       iron deficiency anaemia
   Aplastic anaemia
   Pure red cell aplasia
   sideroblastic anaemia
   anaemia of chronic disease
## HAEMOPOIETIC SYSTEM

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb</td>
<td>15+/-2 gm/dl</td>
<td>13+/-1.5</td>
</tr>
<tr>
<td>RBC count</td>
<td>5+/-0.5x10^{12}/l</td>
<td>4.5+/-0.5</td>
</tr>
<tr>
<td>PCV</td>
<td>0.45+/- 0.05l/l</td>
<td>0.4+/- 0.5 l/l</td>
</tr>
<tr>
<td>MCV</td>
<td>92 +/- 9 fl</td>
<td></td>
</tr>
<tr>
<td>MCH</td>
<td>29.5 +/- 2.5 pg</td>
<td></td>
</tr>
<tr>
<td>MCHC</td>
<td>33 +/- 1.5 g/dl</td>
<td></td>
</tr>
<tr>
<td>Cell diameter</td>
<td>6.7 – 7.7 um</td>
<td></td>
</tr>
<tr>
<td>Reticulocyte count</td>
<td>0.5-2.5%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>50 – 100x10^{12}/l</td>
<td></td>
</tr>
</tbody>
</table>
HAEMOPOIETIC SYSTEM

35 yrs female
Mother of 5 children (LCB 1.5 yrs)
H/O menorrhagia 1 year
Increasing weakness & fatiguability
Husband is a labourer
HAEMOPOIETIC SYSTEM

Blood CP:

Hb : 7.6 gm/dl
TLC : 6.5
Plt : 460
MCV : 66
MCH : 19
DLC : normal
Retics : 1.0 %
HAEMOPOIETIC SYSTEM

Serum iron: 23 ug/dl (60-180)
TIBC : 650 ug/dl (250-400)
Serum Ferritin 6 ng/ml (15-150)

DIAGNOSIS:

IRON DEFICIENCY ANAEMIA.
HAEMOPOIETIC SYSTEM

IRON METABOLISM:
Diet / source
Absorption
Transport
Utilization & excretion
Storage
deficiency
The best source of iron is lean red meat. Iron can also be found in chicken, turkey, eggs, and cereals.
Figure 4. Hepcidin regulation by erythroid-iron- and hypoxia-related signals in iron-loading anemias. (GDF = growth differentiation factor; TWSG = twisted gastrulation; TF = tissue transferrin; HIF = hypoxia inducible factor)
HAEMOPOIETIC SYSTEM

Iron conc in males = 50 mg/kg
females = 40 mg/kg
Total body iron = 3-5 gm
7-8 yrs for depletion
6 months-2 yrs physiological iron def
# HAEMOPOIETIC SYSTEM

<table>
<thead>
<tr>
<th>Absorption increased</th>
<th>absorption decreased</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heme iron, animal food</td>
<td>Opposite</td>
</tr>
<tr>
<td>Ferrous salts</td>
<td>Ferric salts</td>
</tr>
<tr>
<td>Acid gastric pH</td>
<td>Alkalis</td>
</tr>
<tr>
<td>Vit C, amino acids, sugars</td>
<td>Phytates, tannates, tea</td>
</tr>
<tr>
<td>Iron deficiency</td>
<td>Iron overload</td>
</tr>
<tr>
<td>↑ erythroopoiesis</td>
<td>↓ erythroopoiesis</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Inflammatory disorders</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>------</td>
</tr>
</tbody>
</table>
HAEMOPOIETIC SYSTEM

Causes of iron deficiency:
Dietary lack
  poverty
  old age
  vegetarians
Increased demand
  pregnancy & lactation
  infants & children
  puberty
HAEMOPOIETIC SYSTEM

Impaired absorption
  malabortion syndromes
  achlorhydria
  gastrectomy
  atrophic gastritis
Chronic blood loss
  GIT, genitourinary, respiratory
hook worm infestation
Demographic factors:
- Elderly
- Teenager
- Female
- Immigrant
- Aborigine
- Widower

Dietary factors:
- Low iron, haem iron
- Low Vitamin C
- Excess phytate
- Excess tea/coffee
- Fad diets

Social/physical factors:
- Poverty
- Poor detention
- Candle burning
- Alcohol abuse
- GIT disease
- Depression
HAEMOPOIETIC SYSTEM

Clinical presentation:
- symptoms of anaemia
- symptoms related to cause

Examination:
- pallor
- angular cheilosis
- koilonychia

Absence of certain features
HAEMOPOIETIC SYSTEM

Diagnosis:
History
Examination
Routine investigations
Serum ferritin
Serum iron TIBC
Bone marrow examination.
HAEMOPOIETIC SYSTEM

Treatment:
Treatment of cause
Iron supplements
   oral
   injectable
There are only two ways to live your life. One is as though nothing is a miracle. The other is as though everything is a miracle.
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

↑ Hb breakdown $\rightarrow$ ↑ bilirubin $\rightarrow$ jaundice $\rightarrow$ gall stones
### HAEMOPOIETIC SYSTEM

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

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

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

$\rightarrow$ Leukoerythroblastic blood picture

$\rightarrow$ Gall stones

$\rightarrow$ haemosiderosis
Never look down on anybody unless you're helping him up
HAEMOPOIETIC SYSTEM

HEREDITARY SPHEROCYTOSIS:
HAEMOPOIETIC SYSTEM

Autosomal dominant
Intrinsic membrane defect
Deformability of RBC due to cytoskeletal Proteins
Spectrin
Actin
Ankyrin
Band 4.2 & 3
Reduced membrane stability
Reduced deformability $\rightarrow$ spheroidal
Trapped in spleen $\rightarrow$ lactic acid $\leftrightarrow$
$\rightarrow$ 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
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

Intravascular hemolysis
Extravascular hemolysis
Heinz Bodies (G6PD Deficiency)
HAEMOPOIETIC SYSTEM

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

6th position β globin chain
Valine → Glutamic acid → HbS
Deoxy Hb
↓
Crystallization/polymerization HbS
↓
Tactoid formation (reversible)
↓
Repeated sickling de-sickling
↓
Irreversibly sickled
↓
Vascular occlusion
Normal hemoglobin forms long, inflexible chains.

Normal Red Blood Cells

Sickled Red Blood Cells

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.
HAEMOPOIETIC SYSTEM

Membrane damage $\rightarrow$ ↑ Ca $\rightarrow$ ↓ K+

↓

Intracellular dehydration

↓

Sticky RBCs

↓

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
→ 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

HAEMOGLOBIN:
Heme + 4 Globin chains

HbA → 2a/2β
HbA2 → 2a/2δ
HbF → 2a/2γ

ξ and ζ embryonic chains
Synthesis of globin chains:
  Haemopoietic GF
  ↓
  Gene activation
  ↓
  Transcription
  ↓
  Translation
  ↓
  Post translation stability
Transcription & Translation

DNA

RNA synthesis (transcription)

Introns are removed (RNA splicing)

mRNA

Protein synthesis (translation)

Protein
HAEMOPOIETIC SYSTEM

1.5 year girl
Failure to thrive
pallor and abdominal distension
Cousin died at 3 years with similar problems
One transfusion 2 months back

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

TLC :  24.6
Hb :  6.2
Plt :  130
MCV :  72
MCH :  21
NRBC : 43/100 WBC
Left shift in neutrophils
HbF : 97%

DIAGNOSIS:
Clinical, blood and electrophoresis findings are consistent with
β - THALASSAEMIA MAJOR (β°)
HAEMOPOIETIC SYSTEM

THALASSAEMIAS:
Reduced or no synthesis of one or more globin chains of Hb.

Autosomal recessive
α chain deficiency → α thalassaemia
β chain deficiency → β thalassaemia
HAEMOPOIETIC SYSTEM

CLASSIFICATION:
Clinical
Genetic

Thalassaemia major
  homozygous $\beta^+$ (\(\beta^+ / \beta^+\))
  homozygous $\beta_{o}$ (\(\beta_{o} / \beta_{o}\))
  $\beta / \text{Hb Lepore}$
  $\beta / \text{HbE}$
HAEMOPOIETIC SYSTEM

Thalassaemia Intermedia:

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

Thalassaemia minor:
Silent carriers
  α + thalassaemia trait
  rare β thalassaemia trait
Mild anaemia
  α o thalassaemia trait
  α+/α+ thalassaemia
  β o trait
  β + trait
  δβ trait
BETA THALASSAEMIA:
Mutations in \( \beta \) globin gene

- Transcription
  - promoter region mutations
  - chain terminator mutations

- Processing of mRNA
  - splicing mutations
  - splice site in exon

- IVS
- CAP site
HAEMOPOIETIC SYSTEM

Translation
nonsense
frameshift
initiation site
Post translational stability
Exon 3
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
HAEMOPOIETIC 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”
HAEMOPOIETIC SYSTEM

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
## HAEMOPOIETIC SYSTEM

<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>Extravascular</td>
<td>Extravascular &lt;</td>
</tr>
<tr>
<td>Fc receptor mediated macrophage</td>
<td>Complement activation, C3b macro</td>
</tr>
</tbody>
</table>

- Fc receptor mediated macrophage参与溶血。
## HAEMOPOIETIC SYSTEM

<table>
<thead>
<tr>
<th>Spherocytosis</th>
<th>RBC agglutinates</th>
</tr>
</thead>
<tbody>
<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.

**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.
ABILITY IS OF LITTLE ACCOUNT WITHOUT OPPORTUNITY
MEGALOBLASTIC ANAEMIA:
A group of disorders characterized by presence of MEGALOBLASTS in the bone marrow.
Impaired DNA synthesis
HAEMOPOIETIC SYSTEM

Causes:
Cobalamine deficiency or defect in metabolism
Folate deficiency or defect in metabolism
MDS, AML
Antifolate drugs, drugs interfering with DNA synthesis
Orotic aciduria
Lesh-Nyhan syndrome
HAEMOPOIETIC SYSTEM

DNA synthesis
Rapidly proliferating cells
  haemopoietic cells ....
  GIT ....
    diarrhoea can be cause or effect
  GUT ....
respiratory ..... 
prematurity
neural tube defects
HAEMOPOIETIC SYSTEM

Methylation of biogenic amines (dopamine)
psychiatric symptoms
Of myelin proteins, phospholipids
Neurologic symptoms
  bilateral peripheral neuropathy
degeneration of dorsal columns & pyramidal tracts
  optic atrophy
  mental abnormalities (poor brain dev)
HAEMOPOIETIC SYSTEM

Haematological findings:
- oval macrocytosis
- MCV > 100 fl
- pancytopenia
- hypersegmented neutrophils
Oval macrocyte

Small lymphocyte
Bone marrow findings:
Hypercellular
Dyserythropoiesis
Ineffective erythropoiesis
Megaloblasts
Giant myeloid precursors
Hyperlobated megakaryocytes
Abnormal mitotic figures
MEGALOBLAST:

Large abnormal erythroid precursors
nuclear cytoplasmic asynchrony
COBALAMINE (VITAMIN B12)
Only source animal food
Body stores = 2-3 mg
Sufficient for 3-4 years
Absorption (ileum, IF)
Transport (transcobalamines)
VITAMIN B12

Normal digestion and absorption

- Stomach secretions
- Intrinsic factor

Gastric mucosa

Duodenum

Parietal cells

Ileal absorption

Vit. B12
R-binding protein
Gastric secretion
Intrinsic factor (FI)
HAEMOPOIETIC SYSTEM

Causes of Cobalamin deficiency:

1. Vegans
2. Malabsorption
   Pernicious anaemia
   gastric causes
   IF def
   gastrectomy
HAEMOPOIETIC SYSTEM

intestinal causes
stagnant loop syndromes
ileal resection
crohn’s disease
tropical sprue
fish tape worms
TC deficiency
PERNICIOUS ANAEMIA
Specific type of MBA
Severe lack of Intrinsic factor due to gastric atrophy
Autoimmune disorder
Anti IF antibodies
Anti Parietal cell antibodies
HAEMOPOIETIC SYSTEM

Diagnosis:
History
Examination
Blood CP
Bone marrow examination
Serum B12 levels
Schillings test
IF & PC antibodies
Elevated homocystine & CH3-malonic acid
Therapeutic response
HAEMOPOIETIC SYSTEM

FOLIC ACID (Pteroylglutamic acid)
Liver, yeast, spinach, greens, nuts
Total store = 10 mg
For 4-6 months
Absorbed from upper small intestine
Polyglutamates $\rightarrow$ monoglutamates
Transported by albumin
HAEMOPOIETIC SYSTEM

Causes of deficiency:
1. Dietary:
   old age, poverty, infancy, alcoholism, psychiatrics
2. Malabsorption
   tropical sprue
   celiac disease
   intestinal resection
   crohns disease
HAEMOPOIETIC SYSTEM

3. Excess demand:
   physiological
   pregnancy, prematurity, lactation
   pathological
   hemolytic anaemias, malignancies
   inflammatory conditions
   homocystinuria
   hemodialysis patients
HAEMOPOIETIC SYSTEM

4. Anti-folate drugs:
   anticonvulsants
   antiTB
tetracyclins

5. Liver disease, alcoholism
HAEMOPOIETIC SYSTEM

Treatment:
1. Of cause
2. Cobalamine injections
3. Folic acid tablets
HAEMOPOIETIC SYSTEM

APLASTIC ANAEMIA:
“Presence of pancytopenia in the peripheral blood & a hypocellular marrow in which normal haemopoietic marrow is replaced by fat cells.”
HAEMOPOIETIC SYSTEM

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
"You make the world a better place by making yourself a better person."
HAEMOPOIETIC SYSTEM

WHITE BLOOD CELLS (LEUKOCYTES)

TLC = 4 – 11 x 10^3/ul
Platelets = 150 – 400 x 10^3/ul
Myelopoiesis
Thrombopoiesis
HAEMOPOIETIC SYSTEM

GRANULOPOIESIS
Myeloblast $\rightarrow$ Promyelocyte $\rightarrow$
Myelocyte $\rightarrow$ Metamyelocyte $\rightarrow$ Band
$\rightarrow$ Granulocyte
Myeloblast  Promyelocyte  Myelocyte
Metamyelocyte  Band  Segment
WBC - GRANULOCYTOPOIESIS

MATURATION (5 - 6 DAYS)

MULTIPLICATION BY MITOTIC DIVISION

STEM CELLS

Myeloblast

PROMYELOCYTES

MYELOCYTES

METAMYELOCYTES

BAND NEUTROPHILS

NEUTROPHILS

CIRCULATION

BLOOD TISSUE

BONE MARROW
Lymphocyte development

- Pluripotent stem cell
  - Lymphoid stem cell
    - Pre B cell
      - Small B lymphocyte
      - Follicle center B cell
      - Plasma cytoid B cell
      - Plasma cell
  - Myeloid stem cell
    - Pre T cell
      - Inducer/helper T cell
      - Cytotoxic/suppressor T cell
      - Granulocyte
  - Lymphocyte development
Diseases of leukocytes:
Benign disorders
  Reactive leukocytosis
  leukopenia
  Lymphadenitis
    regional
    generalized
HAEMOPOIETIC SYSTEM

Malignant disorders
  Leukaemias
    acute
      myeloid (AML)
      lymphoblastic (ALL)
    chronic
      myeloid (CML)
      lymphocytic (CLL)
  Lymphomas
    Hodgkin & NHL
HAEMOPOIETIC SYSTEM

Lymphoid neoplasms:
  Leukaemias
  Lymphomas
  Multiple Myeloma

Myeloid neoplasms:
  Leukaemias
  Myeloproliferative disorders
  Myelodysplastic syndromes

Histiocytic neoplasms
HAEMOPOIETIC SYSTEM

40 yrs male
Unexplained fever for 1 month
Bleeding gums, epistaxis & bruising
Weakness & anorexia
O/E sick looking, febrile
Petechial haemorrhages on limbs and trunk
Blood CP:
TLC = 35,000-/cumm
Hb = 7.5 gm/dl
Platelets 25,000/cumm
P = 6%
L = 4%
Blasts 90%
HAEMOPOIETIC SYSTEM

8 yrs girl
Fever, pallor  2 months
Poor feeding & weakness
O/E pallor ++
Generalized lymphadenopathy
Liver 3 cm
Spleen 4 cm
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLC</td>
<td>110,000/cumm</td>
</tr>
<tr>
<td>Hb</td>
<td>9.0 gm/dl</td>
</tr>
<tr>
<td>Plt</td>
<td>100,000/cmm</td>
</tr>
<tr>
<td>P</td>
<td>12%</td>
</tr>
<tr>
<td>L</td>
<td>23%</td>
</tr>
<tr>
<td>Blasts</td>
<td>65%</td>
</tr>
</tbody>
</table>
HAEMOPOIETIC SYSTEM

Bone Marrow examination:
Blasts > 20% of ANC
→ ACUTE LEUKAEMIA

Typing:
  - Morphology
  - Cytochemistry
  - Immunophenotyping
  - Cytogenetics
HAEMOPOIETIC SYSTEM

ACUTE LEUKAEMIAS:
Accumulation of immature myeloid/lymphoid precursors in bone marrow & suppression of normal Haemopoiesis.
Stem cell disorders
HAEMOPOIETIC SYSTEM

Aetiology:
Ionizing radiation
Chemicals
   Benzene & petroleum derivatives
   alkylating agents
Chromosomal abnormalities
Viruses
   HTLV 1
   EBV
Conditions predisposing to acute Leukaemia:

1. Genetic/constitutional
   - Down’s syndrome (ALL, AML)
   - Bloom’s syndrome
   - Fanconi’s anaemia (AML)
   - Ataxia telangiectasia (AML)
2. Acquired

MDS (AML)

Chemo, radio $\rightarrow$ MDS $\rightarrow$ AML

Aplastic anaemia (ALL)

PNH (AML)

MPD (AML)
Acquired genetic alterations → inhibit myeloid differentiation
Progressive marrow replacement

FAB Classification
WHO Classification
HAEMOPOIETIC SYSTEM

FAB CLASSIFICATION:
Degree of maturation
Differentiation / Lineage of leukaemic blasts
Cytotoxic biochemical stains
  MPO /SBB (myeloid)
  PAS (Lymphoid)
esterases (Monocytic)
## HAEMOPOIETIC SYSTEM

<table>
<thead>
<tr>
<th>M 0</th>
<th>Minimal differentiation</th>
<th>MPO -</th>
</tr>
</thead>
<tbody>
<tr>
<td>M 1</td>
<td>Without maturation</td>
<td>&gt; 3% MPO, SBB +</td>
</tr>
<tr>
<td>M 2</td>
<td>With maturation</td>
<td>Auer rods+, t (8:21)</td>
</tr>
<tr>
<td>M 3</td>
<td>Promyelocytic leukaemia</td>
<td>Hypergranular, Hypogranular variant, faggot cells, DIC, t(15:17)</td>
</tr>
</tbody>
</table>
# HAEMOPOIETIC SYSTEM

<table>
<thead>
<tr>
<th>M 4</th>
<th>Myelomonocytic</th>
<th>Granulocytic &amp; monocytic</th>
</tr>
</thead>
<tbody>
<tr>
<td>M 5</td>
<td>Monocytic</td>
<td>5a monoblasts &gt; 80%, 5b promonocytes &gt; 80%</td>
</tr>
<tr>
<td>M 6</td>
<td>Erythroleukaemia</td>
<td>EB &gt; 50% ANC, MB &gt; 30% NEC, PAS +</td>
</tr>
<tr>
<td>M 7</td>
<td>Megakaryocytic</td>
<td>Marrow fibrosis, cell markers</td>
</tr>
</tbody>
</table>
HAEMOPOIETIC SYSTEM

WHO Classification:
AML with recurrent chromosomal abn
   AML t(8:21)         good
   AML inv(16)         good
   AML t(15:17)        intermediate
   AML t(11q23:v)      poor
AML with multilineage Dysplasia
   with or without prior MDS   poor
AML, therapy related

Alkylating agents poor
Epipodophyllotoxin related poor

AML not specified
M 0 – M 7 interim
<table>
<thead>
<tr>
<th>ALL</th>
<th>Small, monomorphonic, high N:C ratio, Inconspicuous nucleoli (score, 0, 1, 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L 1</td>
<td></td>
</tr>
<tr>
<td>ALL</td>
<td>Large, heterogenous, nucleolated, low N:C ratio (score -1, -2, -3)</td>
</tr>
<tr>
<td>L 2</td>
<td></td>
</tr>
<tr>
<td>ALL</td>
<td>Burkitt – cell type, vacuolated, basophilic, heterogenous</td>
</tr>
<tr>
<td>L 3</td>
<td></td>
</tr>
</tbody>
</table>
## HAEMOPOIETIC SYSTEM

<table>
<thead>
<tr>
<th>AML</th>
<th>ALL</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;Adults</td>
<td>&gt;Children</td>
</tr>
<tr>
<td>Bleeding ++</td>
<td>Bleeding +-</td>
</tr>
<tr>
<td>No Lymphadenopathy</td>
<td>Lymphadenopathy</td>
</tr>
<tr>
<td>Visceromegaly only in M4,5</td>
<td>Usually present</td>
</tr>
<tr>
<td>Poorer prognosis</td>
<td>Better. B &gt; T lineage</td>
</tr>
<tr>
<td>CNS only M4, 5</td>
<td>CNS +, gonads +</td>
</tr>
<tr>
<td>Chemotherapy different</td>
<td>-----</td>
</tr>
<tr>
<td>CD 13, 33, 14, 41, 42, glycophorin,</td>
<td>19, 10, 22, 79a, SmIg, 2, 3, 5, 7</td>
</tr>
</tbody>
</table>
The purpose of life is to live a life of purpose.
CHRONIC MYELOID LEUKAEMIA (CML) (CGL)
Clonal disorder
Acquired genetic defect in pleuripotent Haemopoietic stem cell → Differentiated cells grow → BM Replacement → expanded total myeloid mass
HAEMOPOIETIC SYSTEM

PHILADELPHIA CHROMOSOME (Ph)
Reciprocal t (9:22)
BCR : ABL
210 kDa protein
↑ Tyrosine Kinase activity
95% +
Ph –ive CML 5%, poor prognosis
25 – 60 yrs (40-50)
Insidious onset
Anemia & hypermetabolic state
Splenomegaly
Satges:
  chronic phase
  accelerated
  blast crisis
HAEMOPOIETIC SYSTEM

70% crisis → AML
20% → ALL
10% → Mixed

Diagnosis:
Clinical assessment
Blood CP:
TLC > 50,000/cmm
Hb → normal/decreased
Plts → high/low
HAEMOPOIETIC SYSTEM

All stages of granulocyte maturation
Bimodal peaks
Basophilia
Bone marrow:
  very hypercellular
  3 cell lines hyperplastic
  sea-blue histiocytosis
  fibrosis
HAEMOPOIETIC SYSTEM

LAP score:
  reduced (30 – 100)

Cytogenetics:
  Ph chromosome +

PCR:
  BCR:ABL fusion gene
HAEMOPOIETIC SYSTEM

CHRONIC LYMPHOCYCTIC LEUKAEMIA: (CLL)

SMALL LYMPHOCYCTIC LYMPHOMA (SLL): Morphologically, phenotypically & genotypically similar.
# HAEMOPOIETIC SYSTEM

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 yrs male</td>
<td></td>
</tr>
<tr>
<td>Fever off and on</td>
<td>6 months</td>
</tr>
<tr>
<td>Weakness</td>
<td>6 months</td>
</tr>
<tr>
<td>Dragging in LHC</td>
<td>4 months</td>
</tr>
<tr>
<td>Epigastric discomfort</td>
<td>4 months</td>
</tr>
<tr>
<td>O/E pallor</td>
<td>+-</td>
</tr>
<tr>
<td>Spleen</td>
<td>12 cm</td>
</tr>
<tr>
<td>Liver</td>
<td>edge</td>
</tr>
<tr>
<td>HAEMOPOIETIC SYSTEM</td>
<td></td>
</tr>
<tr>
<td>---------------------</td>
<td></td>
</tr>
<tr>
<td>TLC</td>
<td>250,000/cmm</td>
</tr>
<tr>
<td>Hb</td>
<td>10 g/dl</td>
</tr>
<tr>
<td>Plts</td>
<td>450,000/cmm</td>
</tr>
<tr>
<td>P</td>
<td>48 %</td>
</tr>
<tr>
<td>L</td>
<td>05 %</td>
</tr>
<tr>
<td>M</td>
<td>01 %</td>
</tr>
<tr>
<td>E</td>
<td>06 %</td>
</tr>
<tr>
<td>Basophils</td>
<td>05 %</td>
</tr>
</tbody>
</table>
Ann Arbor staging for Hodgkin's disease

- **Stage I** - disease in single lymph node or lymph node region.
- **Stage II** - disease in two or more lymph node regions on same side of diaphragm.

Note: Stage II *contiguous* means two or more lymph nodes in close proximity (side by side).

- **Stage III** - disease in lymph node regions on both sides of the diaphragm are affected.
- **Stage IV** - disease is wide spread, including multiple involvement at one or more extranodal (beyond the lymph node) sites, such as the bone marrow.
HAEMOPOIETIC SYSTEM
Ann Arbor staging further classifies patients with lymphoma into A or B categories

- **A** = without symptoms
- **B** = with symptoms including unexplained weight loss (10% in 6 months prior to diagnosis, unexplained fever, and drenching night sweats.)
HAEMOPOIETIC SYSTEM
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