Anemias

Dr. Isam Haddadin
Pediatric Hematologist/Oncologist
Amman-Jordan
July,2023

Anemia **is defined as a reduction of the red cell volume or hemoglobin conc. Below the range of the values for age occurring in healthy person.**

Classification of Anemias

1. Inadeguate intake
2. Production(Bone Marrow)
3. Hemolytic Anemias
4. Blood Loss

Inadequate intake

1. Deficiency of specific factors

   a. Iron def.

   b. Vit. B12

   c. Folic acid

Production

1. Congenital pure red cell Anemia
2. Anemia of infection
    a. Renal failure
    b.Cancer
3. Ineffective Erythropiosis
    Cong.D.A

Hemolytic Anemias

RBC defects : Spherocytosis

Elliptocytosis

Enzyme defects : G6PD

pyruvate kinase

Defect in synthesis of Hb : HbS , C , D , …

Thalassemia

Immunologic : Rh incompatibility

ABO incompatibility

Physiology of Anemia in infancy

- Newborn : higher Hb
- Physiologic anemia : 2-3 months
- Premature baby : exaggerated anemia

Megaloblastic Anemia

Presence of Megaloblasts in BM and Macrocytes in the blood.

Folic acid def : Inadequate intake,poverty,Goats milk

Absorption-congenital or acquired

Increase Requirement;Hemolysis

Disorder of Metabolism;MTHFR def.

Onset : 4-7 months (infant)

Megaloblastic Anemia

Vit. B12 def. :

-Inadeguate intake;Diet or mother

-Defective absorption,Intrinsc factor

-G.I.T;malabsorpion,surg,crohn disease

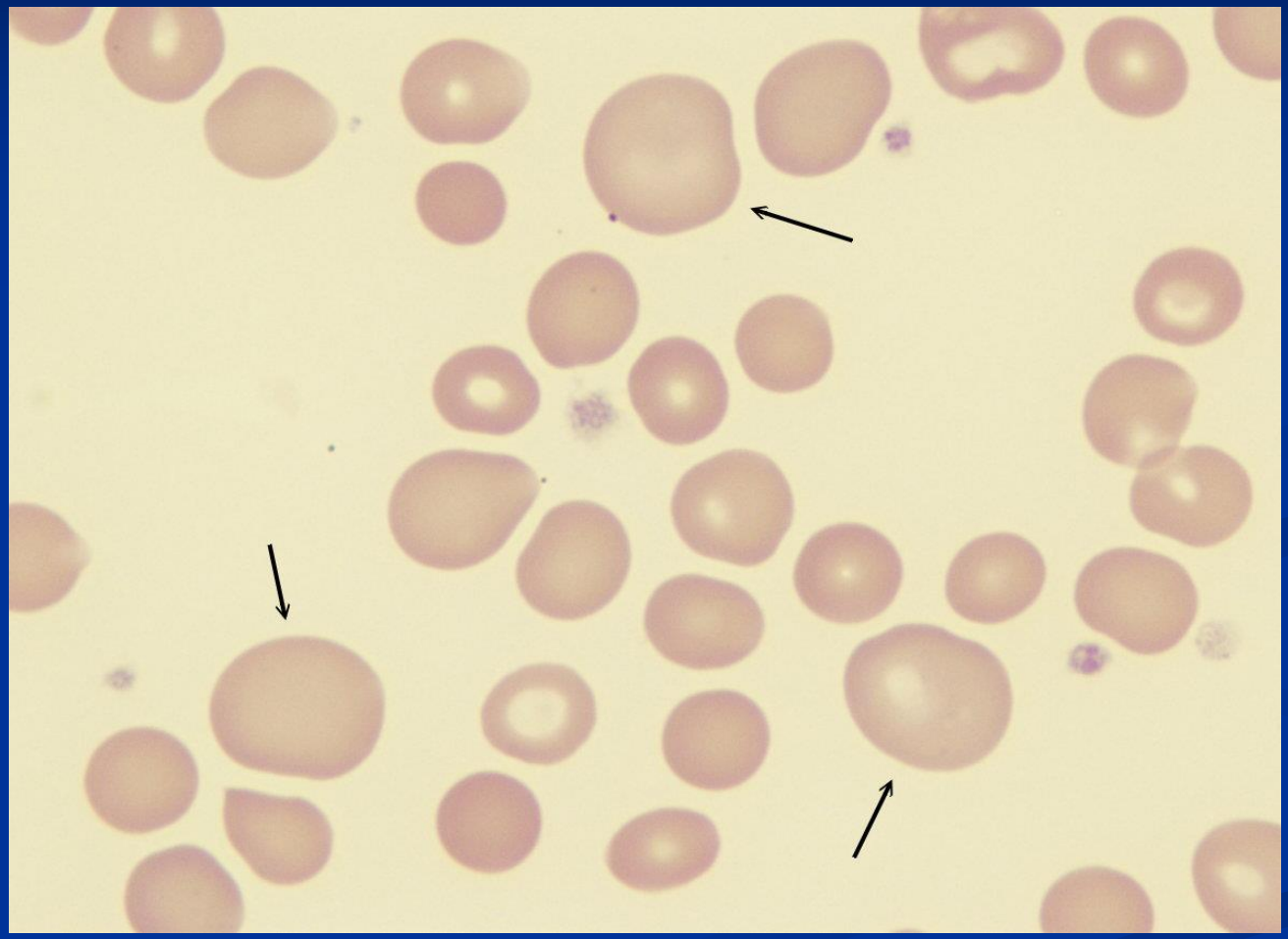
-Defective B12 transport;Cong TCII def

-Acquired; drugs

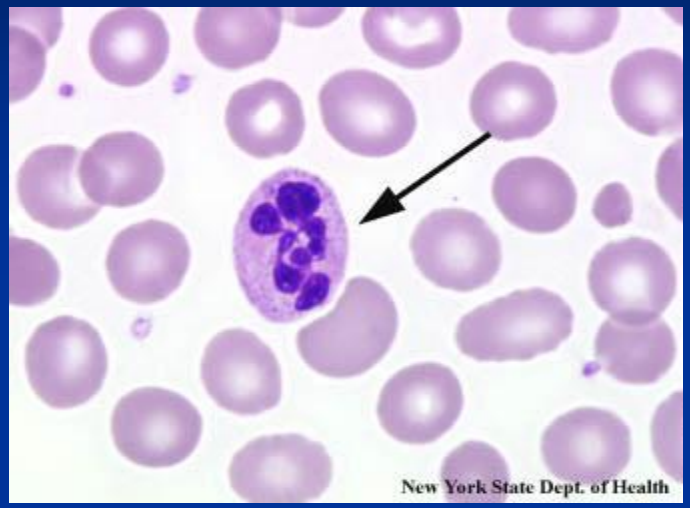
Age : 9 month – 10 years

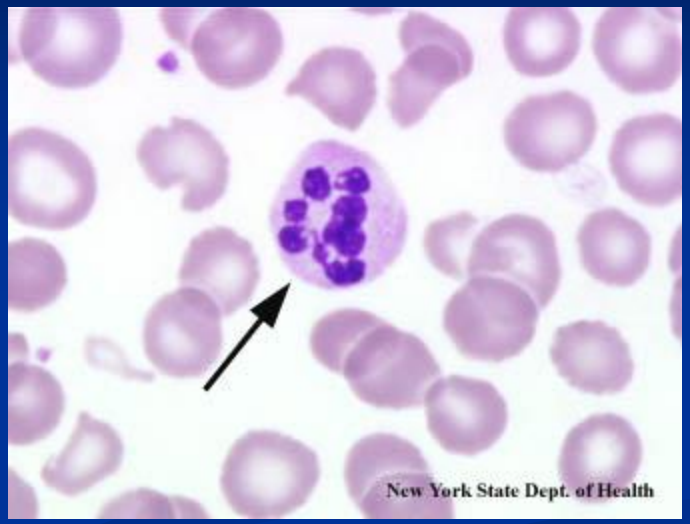
Lab : Macrocytic , pancytopenia,hypersegmented neutrophil,Megaloblastic BM

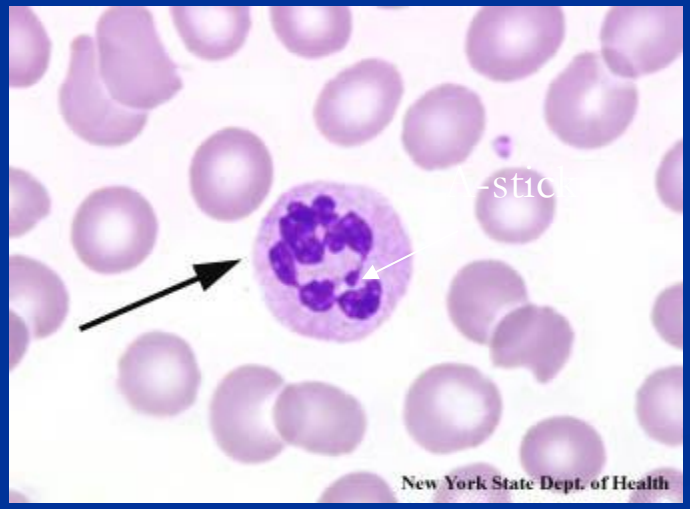
Macrocytes *100x*

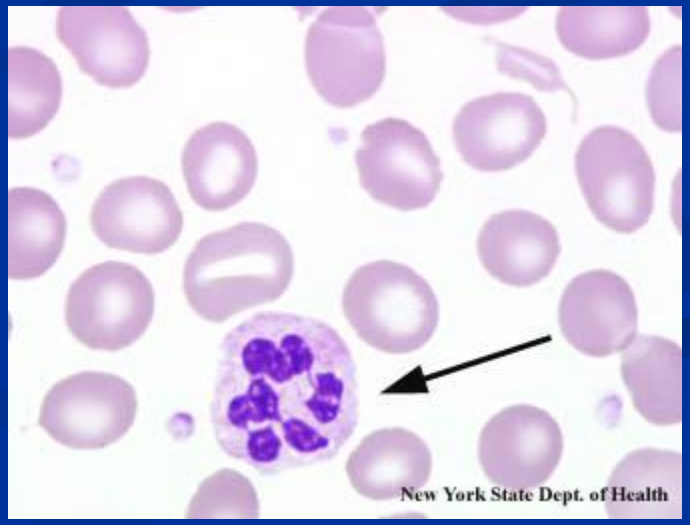


Hypersegmentation
Neutrophil and Nuclear Sticks









Clinical Manifestation

- Failure to thrive
- Generalized Weakness
- Glossitis
- Anorexia
- Pallor
- Jaundice
- Neurolgic Manif;Ataxia,paresthesia,hyporeflexia

Treatment of Megaloblastic Anemia

1. Folic acid : 5 mg Tab/day

Higher dose in cong. def.

2. Vit. B12 : I mg I.M daily for 2 weeks (if neurologic defect,subacute dorsolateral degeneration of cord),then monthly.

3.Vit.B12: 200-1000 microgm/week x 4 Then monthly

4.Transcobalamin II def;Large doses Vit.12

Case

-A 20 month old girl is brought by her mother to clinic because her physician noticed that the child is pale during her routine check up – she is born at full term and has had no history of bleeding from any site .

Q.1 What are the important elements of history you want to ask ? Mention 3

Answer

1. Detailed nutritional history
2. G.I symptoms , chronic diarrhea
3. Family history of anemia or blood loss

- Q.2 what basic investigations would you like to order ?

- Answer: Hb , PCV , WBC , Plat. , MCV , RDW ,Retic
- If lab. results are : Hb 5 gm
- WBC 6.0
- Plat. 850
- MCV 50
- RDW 20
- Retic 3%

- Q.3 what's your diagnosis?

Answer

Iron def Anemia

- Q.4 . what is the first response after therapy why ?

Answer

Increase appetite

Increase activity

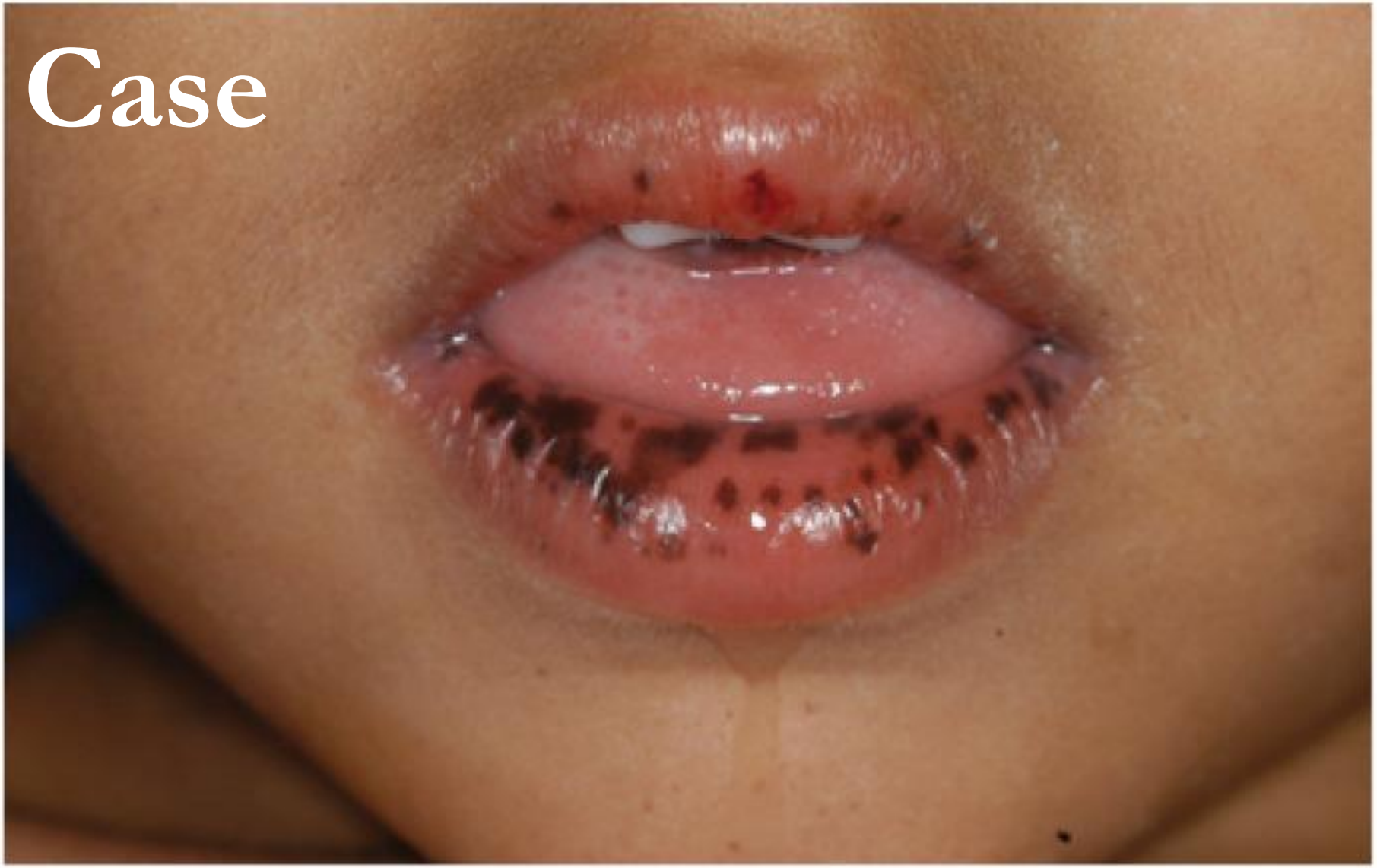
Because some enzymes need Iron

- Q.5 What is the first change in blood test ?

Answer

Increase Retic after 3-5 days

Case



1. Describe the finding
2. What is the associated anemia in this condition ?

Answer

Brown pigmentation on lips and gum

IDA

Peutz Jeghers Syndrome

Case

A 15 year-old child is evaluated in follow-up for anemia diagnosed during a recent evaluation for symptoms of fatigue. She reports no shortness of breath, dizziness. Medical history is notable only for heavy menses. Family history is remarkable for anemia in her mother. Her only medication is an iron supplement. .

On physical examination, the patient appears well. Temp is 36.9C, BP is 100/60mmHg, HR 80/min . No Lymphoadenopathy Spleen is 3cm BCM, and remainder of physical exam is unremarkable.

Laboratory Studies

- Hemoglobin 8.5g/dl
- MCV 68fl
- Platelets count 400,000/microL
- Retic count 6%
- Bilirubin total 2.0mg/dl
- LDH 300U/L
- Ferritin 450ng/ml
- Iron 60MicroG/dl
- TIBC 300 MicroG/dl

- What do you need more?

Hemoglobin electrophoresis

- HbA 92% (slightly low)
- HbA2 4% (increased)
- HbF 4% (increased)
- Hb S 0% (NL)

Question

Which of the following is the most likely diagnosis?

A. Anemia of chronic disease
B. Iron malabsorption
C. Alpha-Thalassemia
D. Beta-Thalassemia
E. Iron def. Anemia

Cont.Case

- Answer ; B-Thalassemia Intermedia

Iron def. Anemia

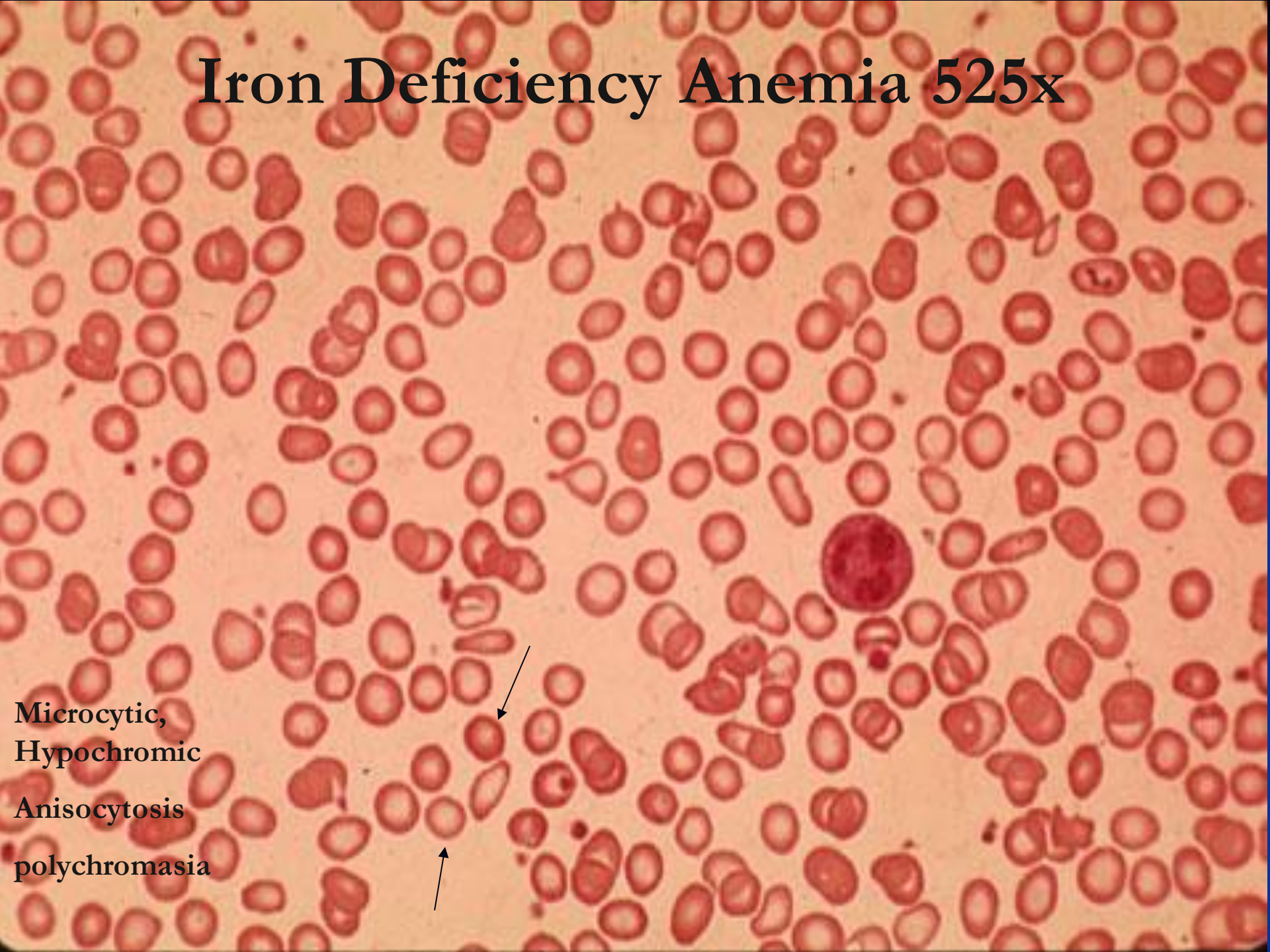
Most common 5.5% among chlid

Requirement;2 mg/kg/day

.Peak at 9-24 months

- **Inadeguate intake;Diet,Breast milk**
- **Impaired absorption;Celiac**
- **Blood loss ; G.I;Mickel,cow milk allergy,Liver,Lung**

Iron Deficiency Anemia 525x



Microcytic,
Hypochromic

Anisocytosis

polychromasia

Tissue Effect Of Iron Def. Anemia

- 1.G.I: Anorexia,pica,atrophic glossitis,dysphagia,Guaiac positive
- 2.CNS: Irritability,fatique decrease activity,breath holding spells.
- 3.Cardiovascular: Tachycardia,cardiac hypertrophy and H.F
- 4.Immne system: Increase infection,impaired granulocytes killing.

Diagnosis OF Iron Def.

1. History and physical examination;Diet,Family hist,Pallor, No hepatosplenomegaly
2. CBC; Hb,PCV,MCV,MCH,MCHC are low and RDW is >15.
3. Platelets are increased.
4. Blood Film:Hypoch,Microcytic,Anisocytosis,poikiloct
5. Serum Ferritin<12 ng/ml. Iron level is low
6. Diff Diag: Thalassemia,Lead poisoning,Sideroblstic anemia,Chronic infection,Malignancy

Treatment Of Iron Def

- 1.Diet;fortified with iron milk,Cereals,Vit,C,
- 2.Rx:Oral Ferrous; Dose 6.omg/kg/day.3 doses and betwee meals.Duration for 2-3 month.
- 3.Response: Increase appetite,then Retic count,Hb and the stores.
- 4.Failure to Response: poor compliance
  Blood loss
  Inadequate dose
  Coexistent disease,malabsorption,
  thyroid,malignancy,VitB12 def.

5.Parenteral Rx: Iron Dextran I.M in Bowel disease , no compliance

Hemolytic Anemia :

Evidence of Hemolysis

1. PCV ↓
2. Bilirubin indirect ↑
3. Retic count ↑
4. haptoglobin ↓

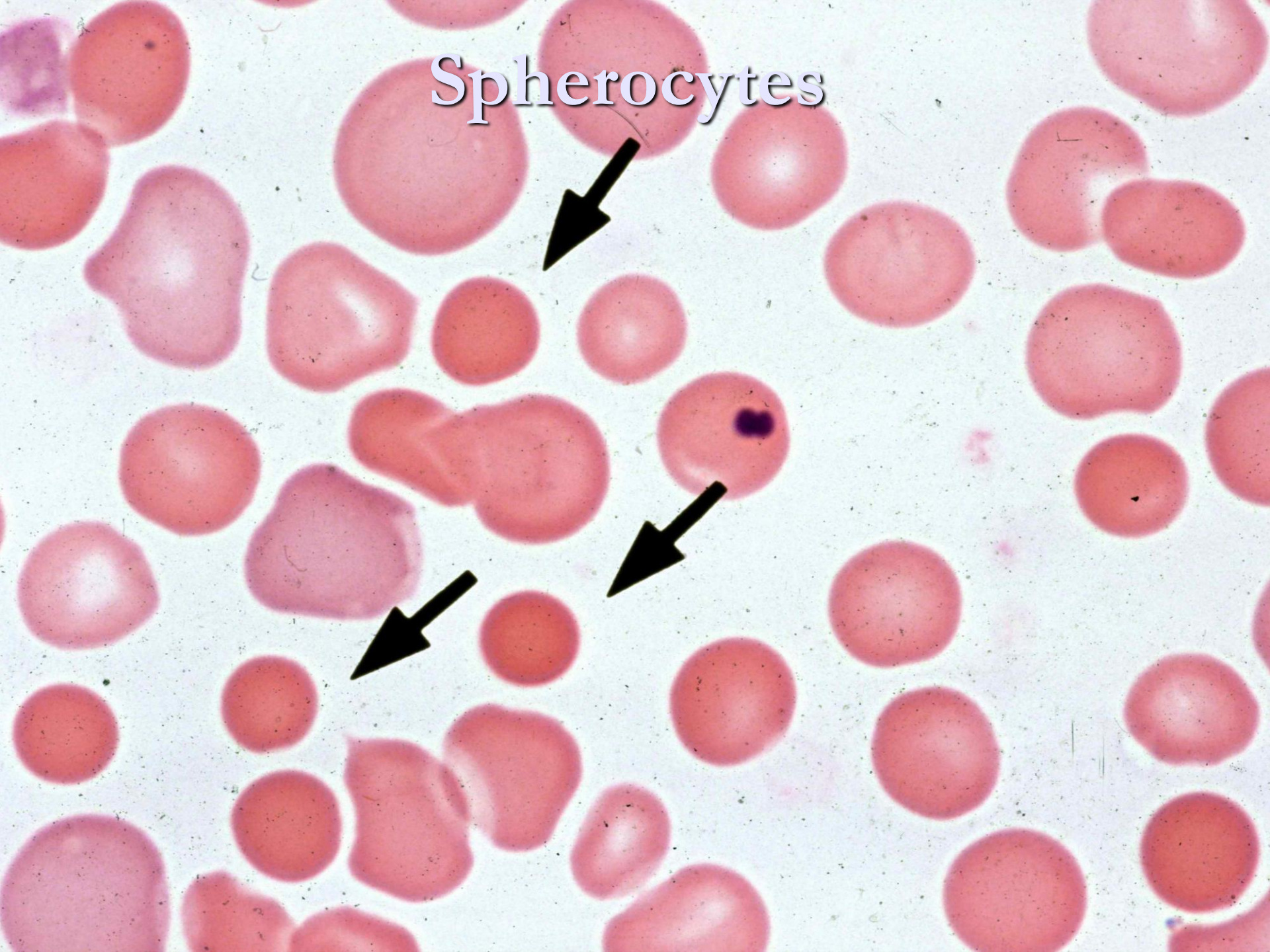
Hereditary Spherocytosis

- **Aut- Dominant:** 75% , Mutation : 25%
- **Defect in cell membrane** : spectrin ,Ankyrin
- **Clinical:** Mild HS,Moderate Anemia ,Severe HS 10%

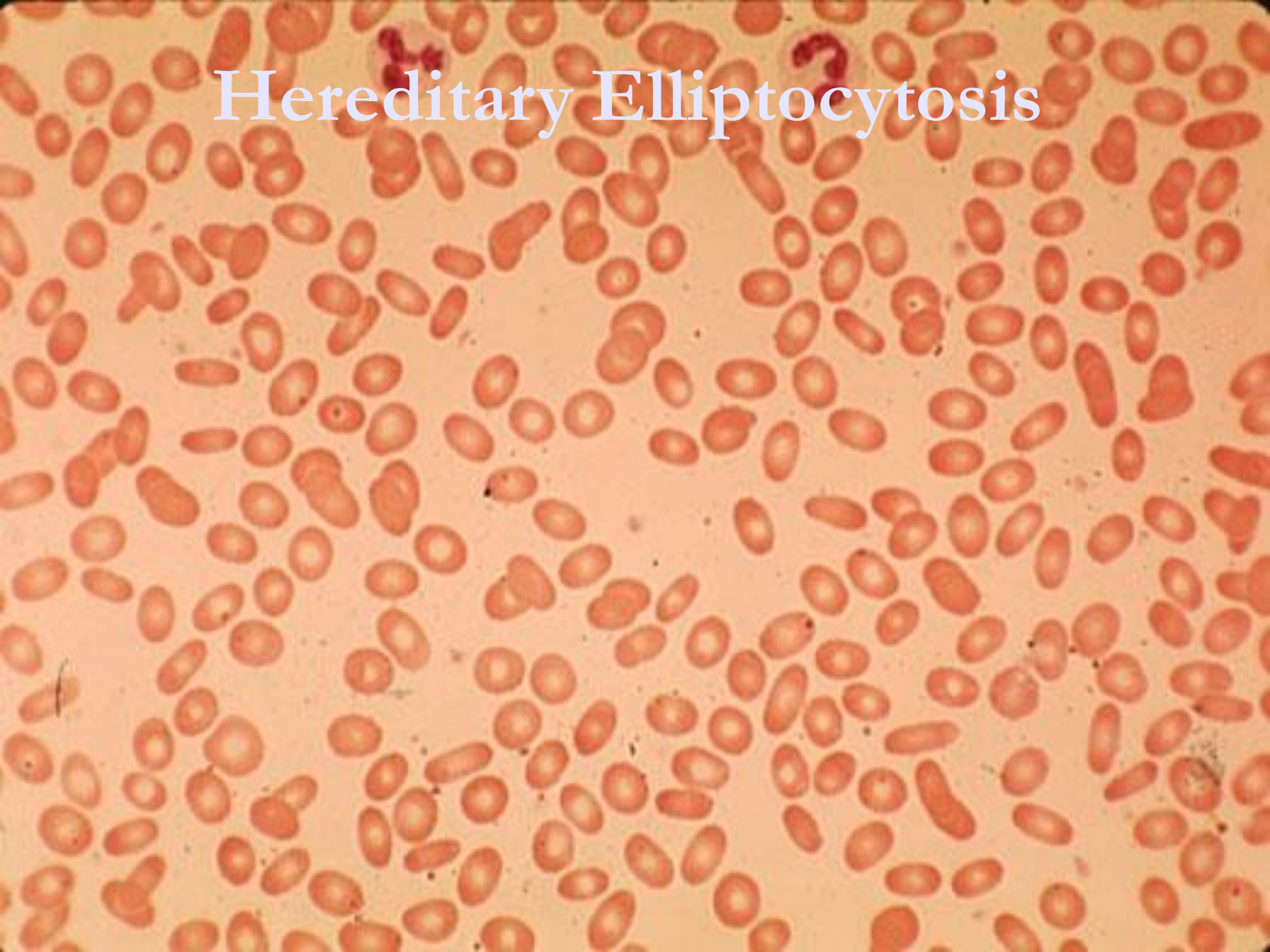
  Splenomegally,Gall stones .
- **Lab:** Low PCV,MCV High MCHC,RDW,Retic.Spherocytosis

  Osmotic Fragility test positive .Flowcytometry high sensitive and specific for diagnosis
- Present at newborn as Hemolytic Anemia, Jaundice
- **Management** ; Blood transfusion, splenectomy

Spherocytes



Hereditary Elliptocytosis



G6PD Glucose-6-phosphate Dehydroginase Deficiency

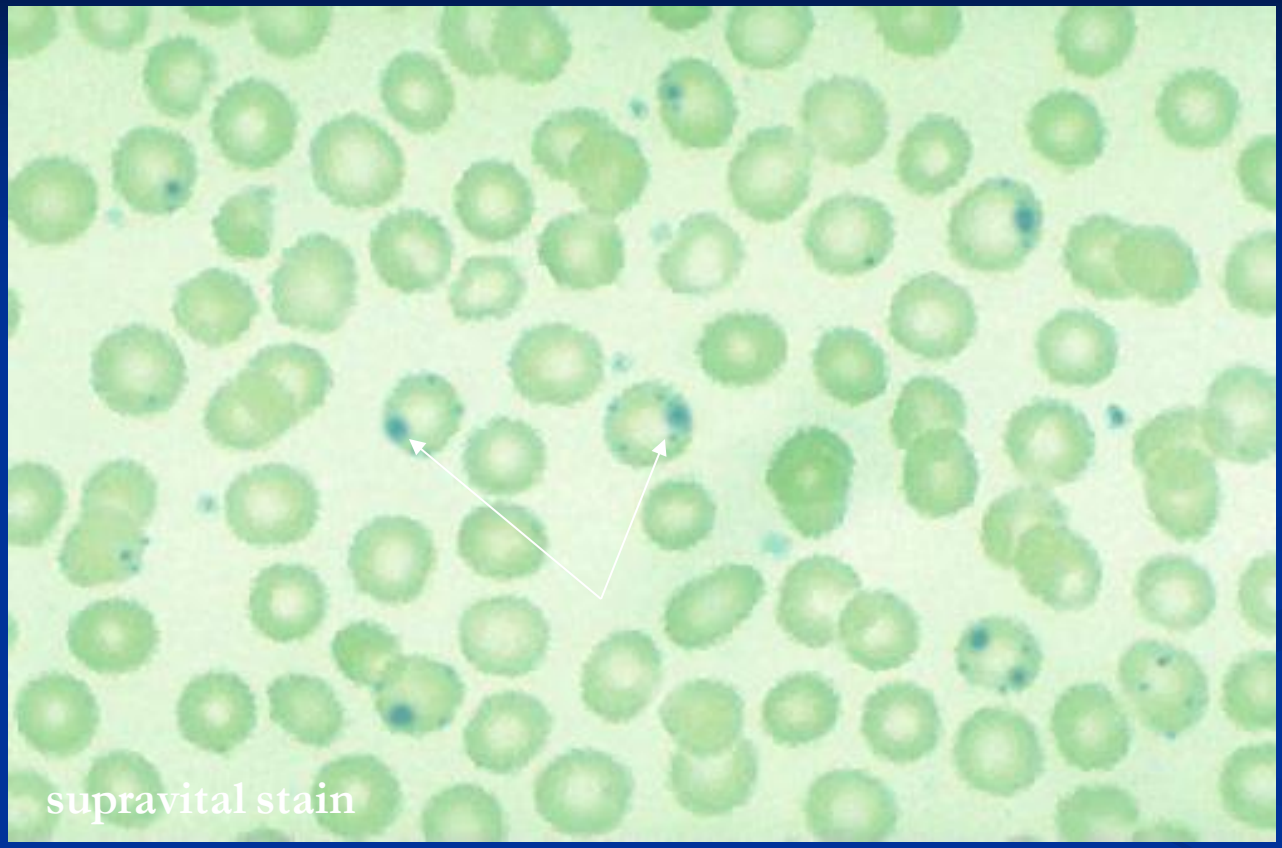
- **X-linked , more in male**
- **Most common RBC enzyme defect**
- **Hemolysis with oxidant stress(infection,drugs,fava beans)**
- **Drugs ; Asprin , Sulfa , Nitrofurantion,**
- **Hb precipitation,RBC membrane damage leading to premature red cell destruction.**

.Mediterranean type Severe. Others like US usually moderate.

.Lab: Evidence of hemolysis

.Management:Obtain sample,Remove Oxidant,Transfusion

Heinz Bodies



- Heinz bodies are denatured globin, and represent the end-product of oxidative degradation of haemoglobin.
- Presence of stained inclusions close to the red cell membrane (Heinz bodies).

Immune Hemolytic Anemia

Extracorpuscular H.A

- Isoimmune; Rh-Incomp. And ABO- Incomp.
- .Autoimmune: Idiopathic-----IgG warm Ab
  IgM cold Ab.
  Secondary-----Infection;EBV,CM
  Drugs---Cephalosp,Penicillin
  Malignancy---Lymphoma
- Lab:CBC, Retic , Coombs test,Spherocytes.
- Treatment: Steroid
  Transfusion
  IVIG
  Splenectomy
  Immunotherapy

Hematological Manifestation Of Systemic Diseases

- Results from:
- 1.BM dysfunction—Anemia,Polycythemia
- Thrombocytopenia,Leukopenia,Leukocytosis
- 2.Hemolysis
- 3.Immune Reaction
- 4.Altered in Hemostasis, Inhibitors to factors

Hematologic Manif. Cont…

1 .*Heart*: Prosthetic valves—Thrombocytopenia
Anemia due to hemolysis, Iron def.

2.*G.I.T*: Reflux, Stomach(Vit.B12),Celiec,
Bowel disease, Bleeding(Mickles)

3*Liver* : Hypersplenism,Wilson disease
Shortened RBC survival,Bleeding.

4.*Renal*: Erythropoeitin,Uremia,Blood loss
Dialysis,RBC survival decreased.

5.Chronic Illness: Decrease Fe flow from RES.

6.*Skin*: Dyskeratosis Congenita,Eczema

Case

A one month old baby was referred because of anemia and jaundice since birth, he received 3 times blood transfusion since that time. On examination he is pale, mild jaundiced, no dysmorphic features, spleen 2cm below costal margin.

Q1. what are the differential diagnosis of his anemia?

Answer

1. ABO incompatibility
2. Rh incompatibility
3. G6PD def.
4. Infection
5. Spherocytosis
6. Alpha thalassemia

The mother blood group is AB+

The baby blood group is B+

Hb of baby : 10 gm

Bilirubin : 22mg, direct : 2mg at age of 5 days

Blood film: spherocytes

Test to do ?????

Family history: 3 siblings normal and no similar condition.

Q1: what is your most likely diagnosis?

Answer

Do minor group Rh C and E

Result: baby Rh E+

mother Rh E-

What is the treatment?

Answer

To give :Rh E negative blood

phototherapy for jaundice

IV Ig

Question

Persistent Reticulocytosis in a newborn baby suggest the presence of all the following except;

A. Hypoxia
B. Blood loss
C. Hypoglycemia
D. Fetoplacental blood transfusion
E. ABO blood group incompatibility

Answer

C. Hypoglycemia

Question

Each of the following Rh antigens have been implicated as causes of significant hemolytic disease of the fetuses and newborn except one;

A. D antigen

B. d antigen

C. E antigen

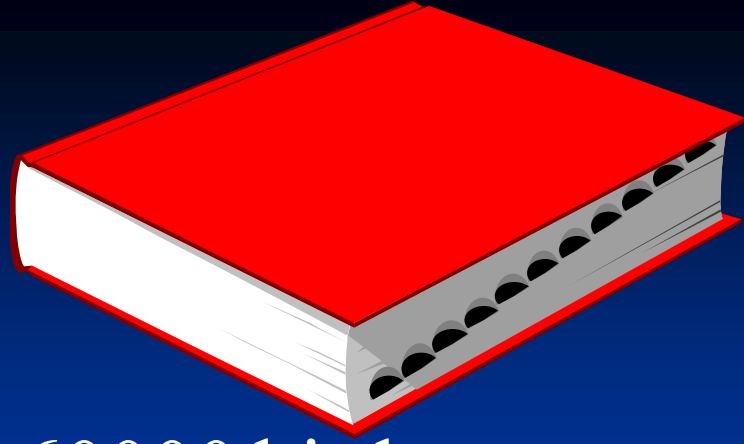
D. e antigen

E. c antigen

Answer

B. d antigen

Thalassemia



Introduction:

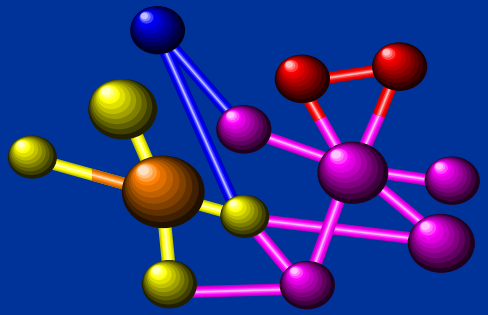
Beta thalassemia major affects 60000 births per year worldwide. A mutation in the B-globin gene causes defective erythopoiesis ,which in its homozygous form results in a severe anemia ,rendering the individual dependent on lifelong blood transfusions .

Long term survival remains poor ,with data from UK showing 50% of patients dead by the age of 35 years

Major Classification of Thalassemia

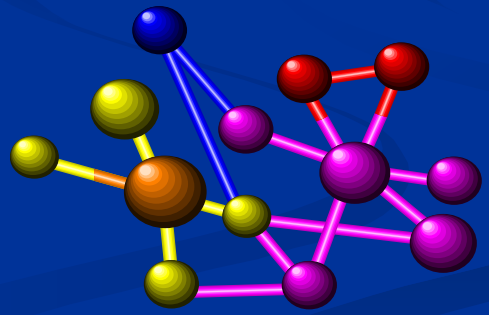
- Alpha Thalassemia
- 4-genes

(~ 600 mutations)



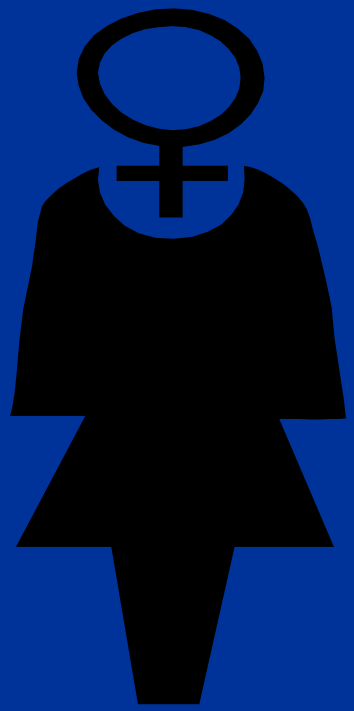
- Beta Thalassemia
- 2-genes (25 mutations)

(~80% of mutations)



Chances to have Thalassemia

- If both parents are Thalassemia Carriers
  - 25% chance of contracting thalassemia major
  - 50% chance of contracting thalassemia minor
  - 25% chance of being Normal



Types of Hb

1.Hb Gower 1; 2 zeta,2 epsilon

2.Hb Gower 2 ;2 alpha, 2 epsilon

3.Hbf ;2 alpha,2 gama

4.Hb A1 ; 2 alpha, 2 beta

5.Hb A2 ; 2 alpha, 2 delta

Globin

4;Alpha globin genes on chromosome 16

2;Beta,Gama,Dalta globin genes on chr. 11

Ratio of HbA1/HbA2=30/1

Thalassemia Major

Clinical

- -Chronic hemolytic anemia
- -Skeletal deformaties
- -Splenomegaly
- -Heart failure
- -Iron overload
- -Gall stones
- -Growth impaired

B-Thalassemia

- .Lab:1. Microcytosis,Hypochromia.Anemia , Target cell.
- 2.Hb-electrophoresis ; HbF increased
  Hb A1 decrease
  Hb A2 normal
- Normal values: Hb A1 95%
  HbA2 2-3.5%
  Hb F 1%

B-Thalassemia

- Treatment:
- 1.Chronic Blood Transfusion.
- 2.Folic Acid.
- 3.Chelation Therapy.
- 4.Splenectomy.
- 5.BMT.

Alpha Thalassemia

1. Silent carrier ; 1 gene deletion
2. Alpha-Thalassemia Trait ; 2 genes deletion
3. HbH disease (B4) ; 3 genes deletion
4. Hydrops Fetalis ; 4 genes deletion

Prevention of Thalassemia

1. Identification of carriers **(long Term prevention)**

2. Genetic counselling of families with known Thalassemia "Clinical" for couples at risk before marriage (**practical term of prevention**)

3. CBC for Couples;

If MCV less than 78 ,do Hb-electroph. to role out Thal. Trait.

Prevention of Thalassemia

Prenatal Screening Of Couples at Risk after Conception (not practical)

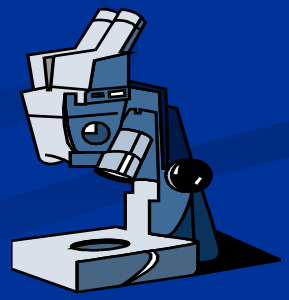
Carrier Identification Standard scheme

1. Peripheral blood count and indices:

(R.B.C, Hb , MCV, MCH, MCHC, RDW)

done by automated counter

2. Hb-electrophoresis



Procedure
Prenatal diagnosis

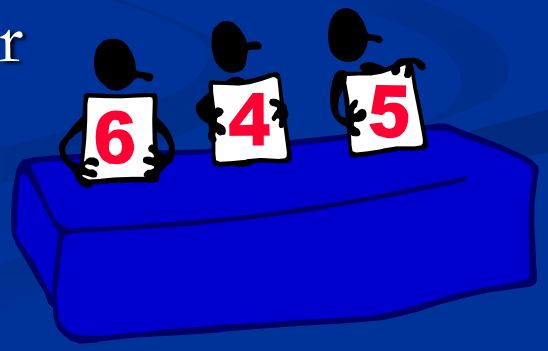
1. CVS* < 8-12 weeks of gestation.
2. AFT** > 15 weeks of gestation.
   - Study fetal cells for parent's same mutation of thalassemia minor they have

* : Chorionic villus sampling

** : Amniotic fluid testing

Incidence of Thalassemia world wide (Carrier's)

- -Pakistan: 5.5% **(4-7 million estimated carriers)**
- -Jordan: 4.5%
- Gaza strip: 3.5%
- -Iran: 3.64% **(8000 pregnancies at risk/year)**
- -Iraq: 3 million carriers, ? 25000 cases.
- -Sri-lanka : 2.0%, 1000 cases thalassemia major
- -Italy : 8000 cases of thalassemia major



Sickle Cell Anemia

.Aut.recessive,Valine substituted for Glutamic acid in the No.6 position of B chain.

.Sickle cell Trait has benign clinical course

.8 % American blacks have the trait.

.HbS about 40%.Severe hypoxia may produce Vaso-occlusive phenomena.

.Carriers should avoid hypoxia.

Sickle Cell Anemia

Sickle Cell Disease: Homozygous for the gene

.Presentation until one year of age.

Clinical Manifestation:

1.Painful Vaso-occlusive crises; Hands,Feets

2.Strokes due to cerebral occlusion.

3.Acute Chest Syndrome.

4.Sequestration crises, pooling of blood in spleen and liver—State of shock.

5.Aplastic crises ,Parvovirus.

6.Sepsis; capsulated organism

Sickle CELL

- Lab: Hb 5-9gm/dl.

  Spontaneous sickling, Target cells

  Retic 5-15%,Bil increased,

  Howell Jolly bodies

  Sickling test .

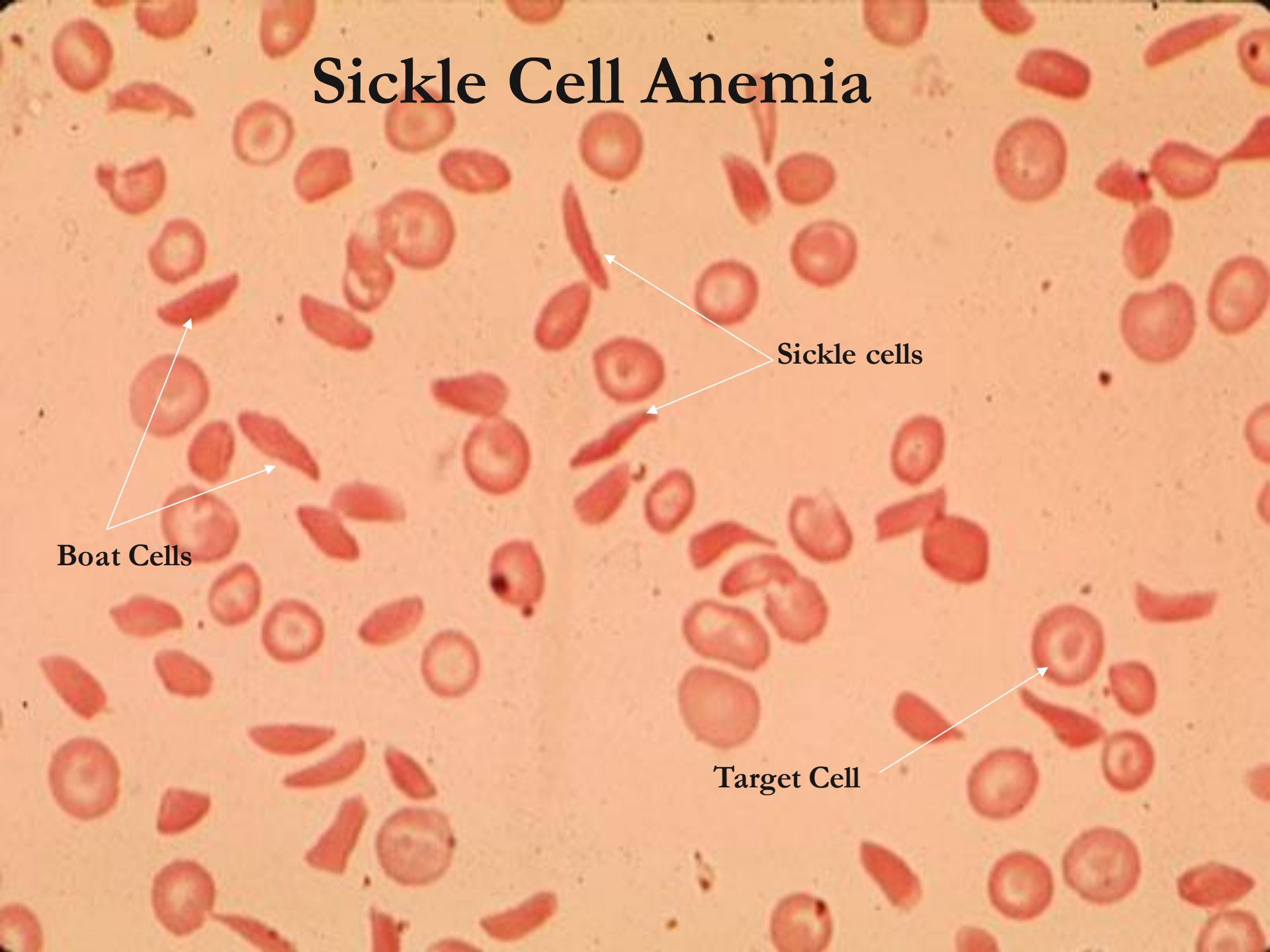
  Hb-electroph; HbS 90 %

  Hb F 2-10%

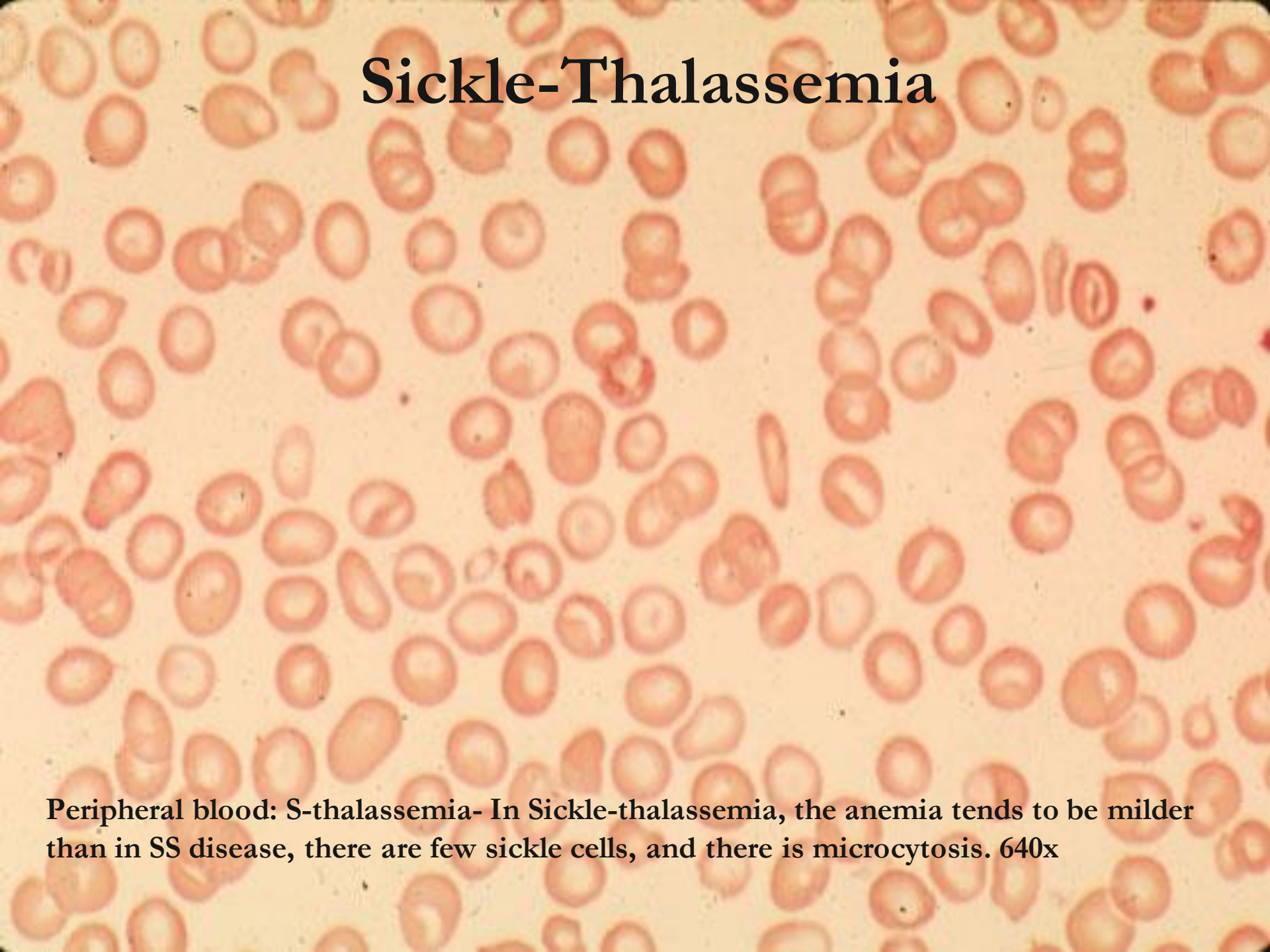
  Hb A 0%

  Hb A2 2.5%

Sickle Cell Anemia



Sickle-Thalassemia



Peripheral blood: S-thalassemia- In Sickle-thalassemia, the anemia tends to be milder than in SS disease, there are few sickle cells, and there is microcytosis. 640x

Sickle cell Treatment

1.Therapy during episodes
2.Tonics: Folic acid.e
3.Analgesics: Paracetamole, Codeine,Morphine
4.Antibiotics; Penicillin, Vaccin
5.Hydration during crises
6.Blood Transfusion not always,Exchange Transfusin in Acute chest syndrome
7.Splenectomy in hypersplenism or sequestration.
8.Hydroxyurea.
9.BMT; in certain cases

Hypertransfusion Protocol :

Hb level 10.5 gm (pretransfusion level)

1.Maximizing growth and development

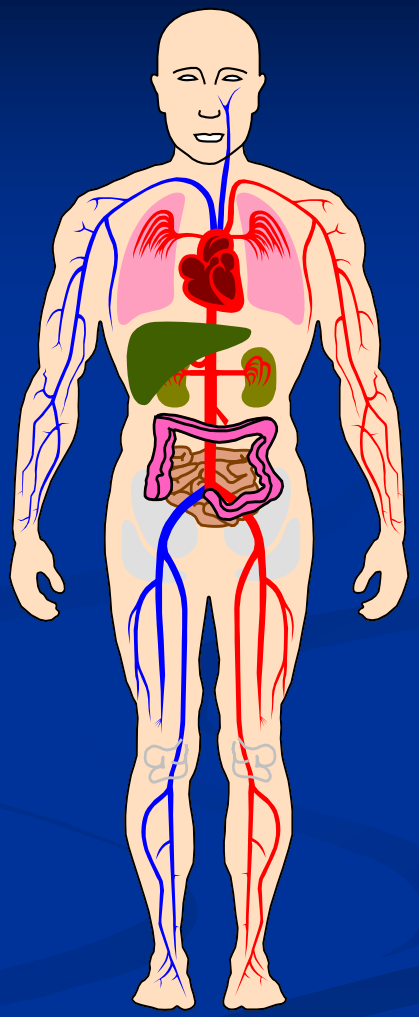
2.Minimizing extramedullary hematopoisis and decreasing skeletal abnormalities

3.Reduce iron absorption from gut

4.Reduce splenomegaly and hypersplenism

Iron overload

1. Ongoing transfusion therapy
2. Increase gut absorption of iron
3. Chronic hemolysis



Chelation Therapy

The objectives are :

1.To bind free extracellular iron

2.To remove excess intracellular iron

3.To attain a negative iron balance (i.e, iron excretion > iron input)

Iron Chelating Agents

Desferal

1.Iron binding efficiency 1:1

2.Iron slectivity is high

3.Regimen Sc or iv infusion

4.Dose 40mg/kg

5.Safety: good, poor compliance

Iron Chelating Agents

Ferriprox

1.Binding 3:1

2.Iron selectivity some report of zinc def.

3.Regimen : oral, three times daily

4.Safety neutropenia, joint problems

5.Dose 75mg/kg

Iron Chelating Agents

Deferasirox (Ex jade)

1. **Iron binding 2:1**
2. **Iron selectivity highly selective**
3. **Regimen oral, once daily**
4. **Safety skin rashes, kidney toxicity**
5. **Dose 20mg/kg**

Case . 5 Year old male child with the following lab data?

- **PCV 24%**
- **WBC 10.0**
- **PLat 200**
- **MCV 80**
- **Hb – electrophoresis: - Hbs 80**
  - Hbf 15
  - HbA2 3.0

What is the Diagnosis ?

ANSWER

- *Hbss*

Case . Pt with pallor, found to have:

PCV 24%

WBC 10.0

PLT 200

MCV 65

Hb – electrophoresis: - Hbs 75

- Hbf 18

- HbA2 4.5

What is the Diagnosis ?

ANSWER

- *Hb SB° thalassemia*

Case . Pt with pallor, found to have :

PCV 24%

WBC 10

PLT. 200

MCV 65

Hb – electrophoresis: - Hbs 70

- Hbf 10

- HbA1 15

- HbA2 4.2

What is the Diagnosis ?

ANSWER

- *Hb SB+ thalassemia*

Case . Pt with pallor, found to have :

PCV 28%

WBC 9.0

Plat. 200

MCV 80

Hb – electrophoresis: - Hbs 36

- HbA1 60

- HbA2 2.5

- **Asymptomatic**

What is the Diagnosis ?

ANSWER

- *Hb SA*

Case . Pt with pallor, found to have PCV 25%.WBC 5.O Plat.200

MCV 69

Hb – electrophoresis: - Hbs 80

- Hbf 15

- HbA2 3.0

What is the Diagnosis ?

ANSWER

- *Hb SS WITH Alfa. thalassemia*

Question

- If one parents is carrier of HbS and the other is a patient with Sickle cell disease HbSS.What are the chances in each pregnancy?

Answer

1. HbSS Disease 50%
2. HbS Carrier 50%

Bone Marrow Failure

- Bone marrow failure syndromes include a group of disorders that can be either inherited or acquired. These are disorders of the hematopoietic stem cell that can involve either one cell line or all lines, with hypoplastic or aplastic B.M.

Bone Marrow Failure

- BM failure manifest as isolated one cell line or pancytopenia;quantitative or qualitative failure.
- Single Line RBC:
- 1.Diamod-Blackfan
- 2.Cong. Dyserthropoietic anemia
- 3.Pearson Syndrome
- 4.Acquired; TEC,Drugs,Infection
- Single Line WBC:
- 1.Shwachman Diamond Syndrome
- 2.Kostman Syndrome

BM Failure

- Single Line Platelets:
- 1.Cong. Amegakaryocytic Thrombocytopenia
- 2.TAR Syndrome.
- Failure Of 3 Lines:
- 1.Fanconi Anemia.
- 2.Familial Aplastic Anemia.
- 3.Dyskeratosis Congenita.
- 4.Acquired Aplastic Anemia.

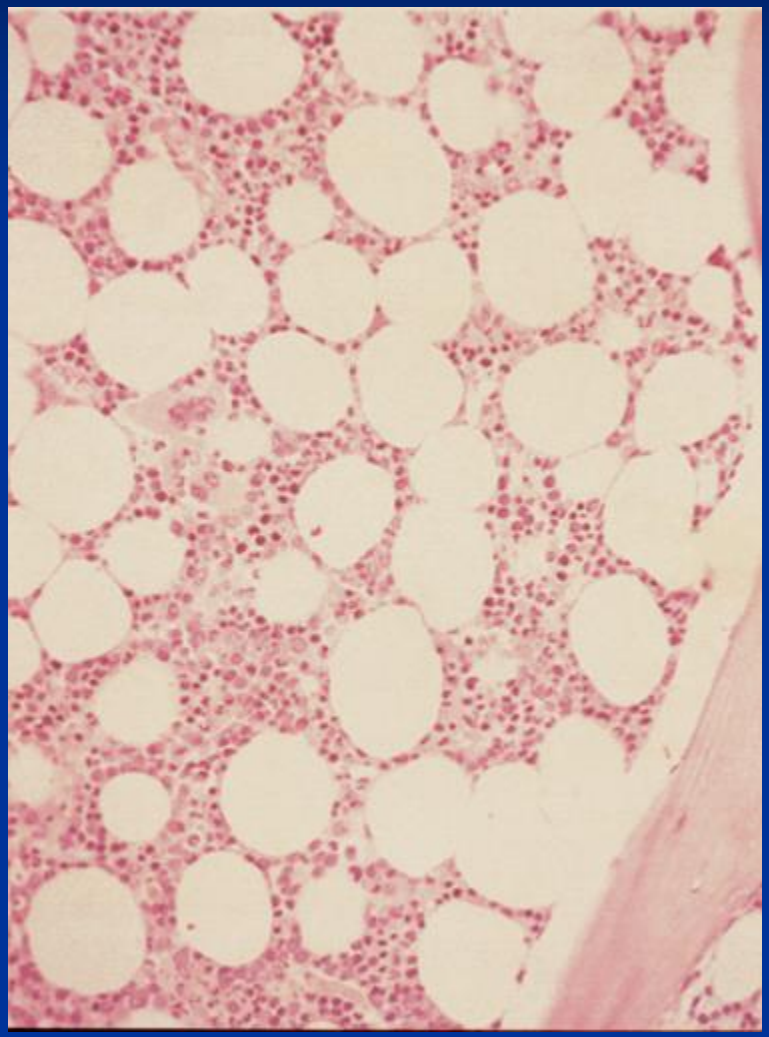
Aplastic anaemia

- Pancytopenia: at least two of anaemia (Hb <10) + neutropenia (<1.5 x10^9/L) and thrombocytopenia (<50 x10^9/L)

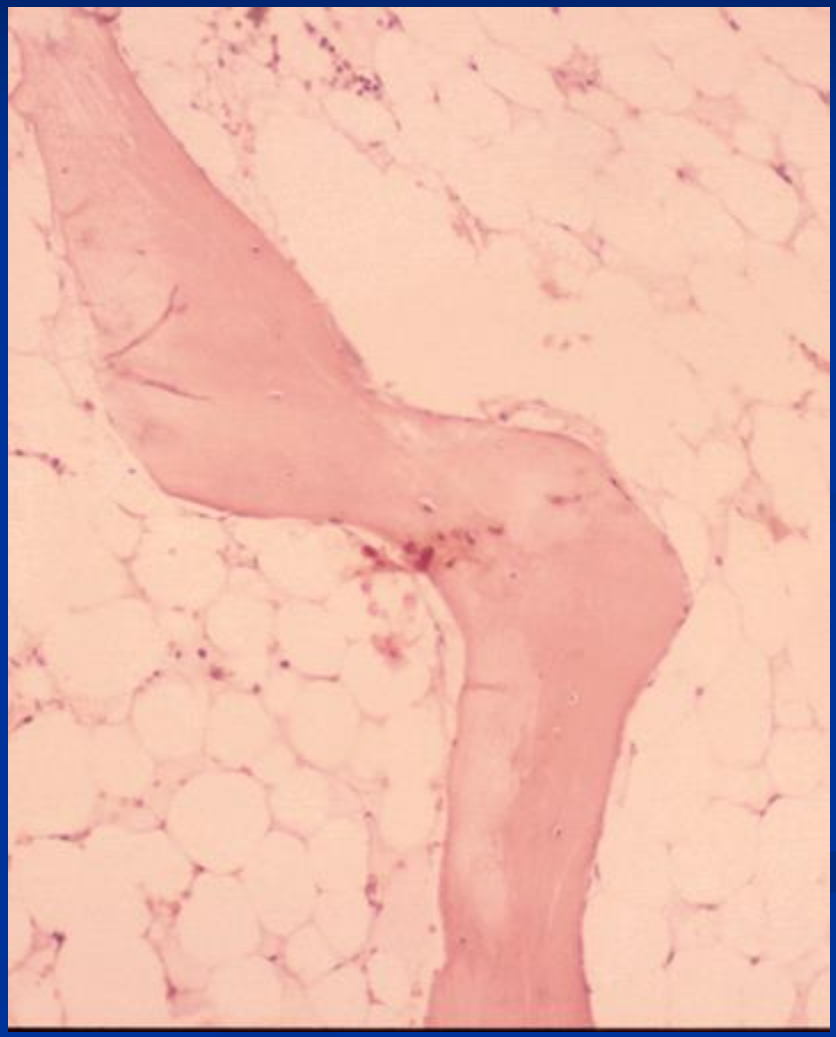
and

- Hypocellular bone marrow

Normal



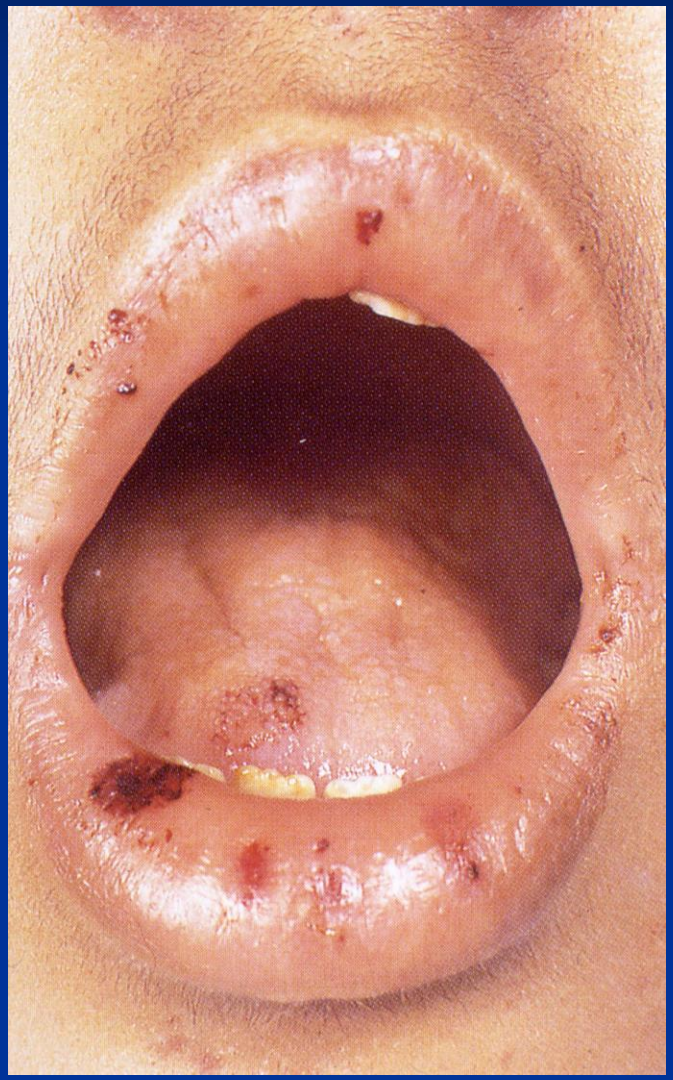
Aplastic anaemia

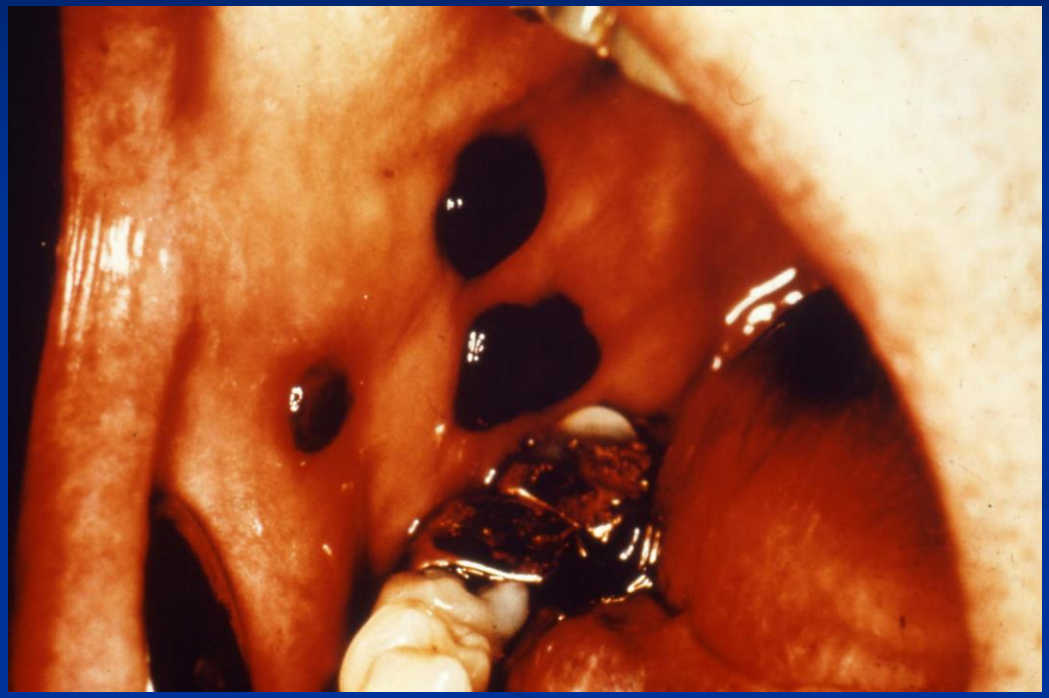


Causes of aplastic anaemia

- Congenital, e.g Fanconi anaemia
- Acquired:
  - idiopathic (80%)
  - viruses: post- hepatitis, EBV, CMV and HIV
  - drugs & chemicals
  - paroxysmal nocturnal haemoglobinuria (PNH)

Mucosal haemorrhage

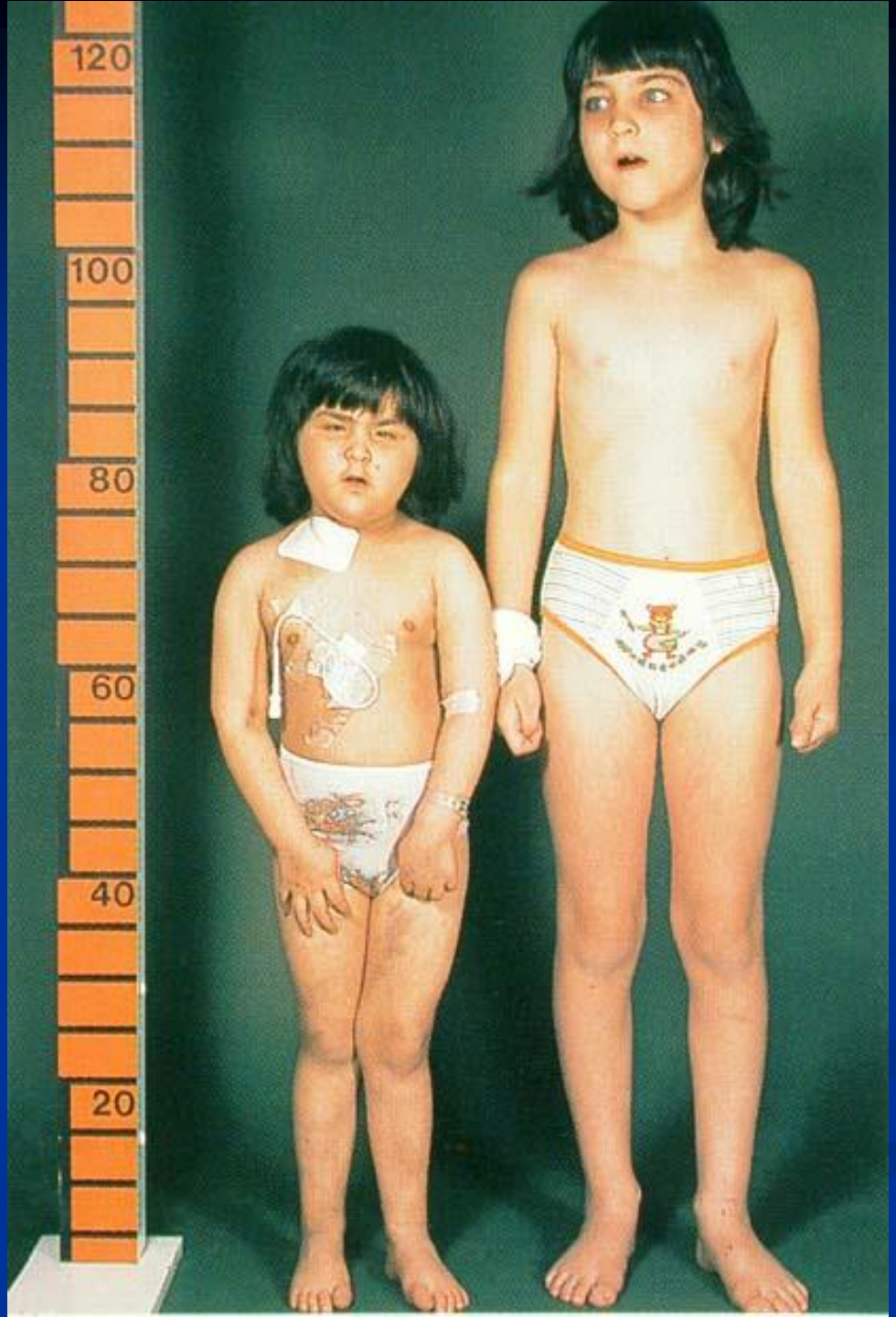


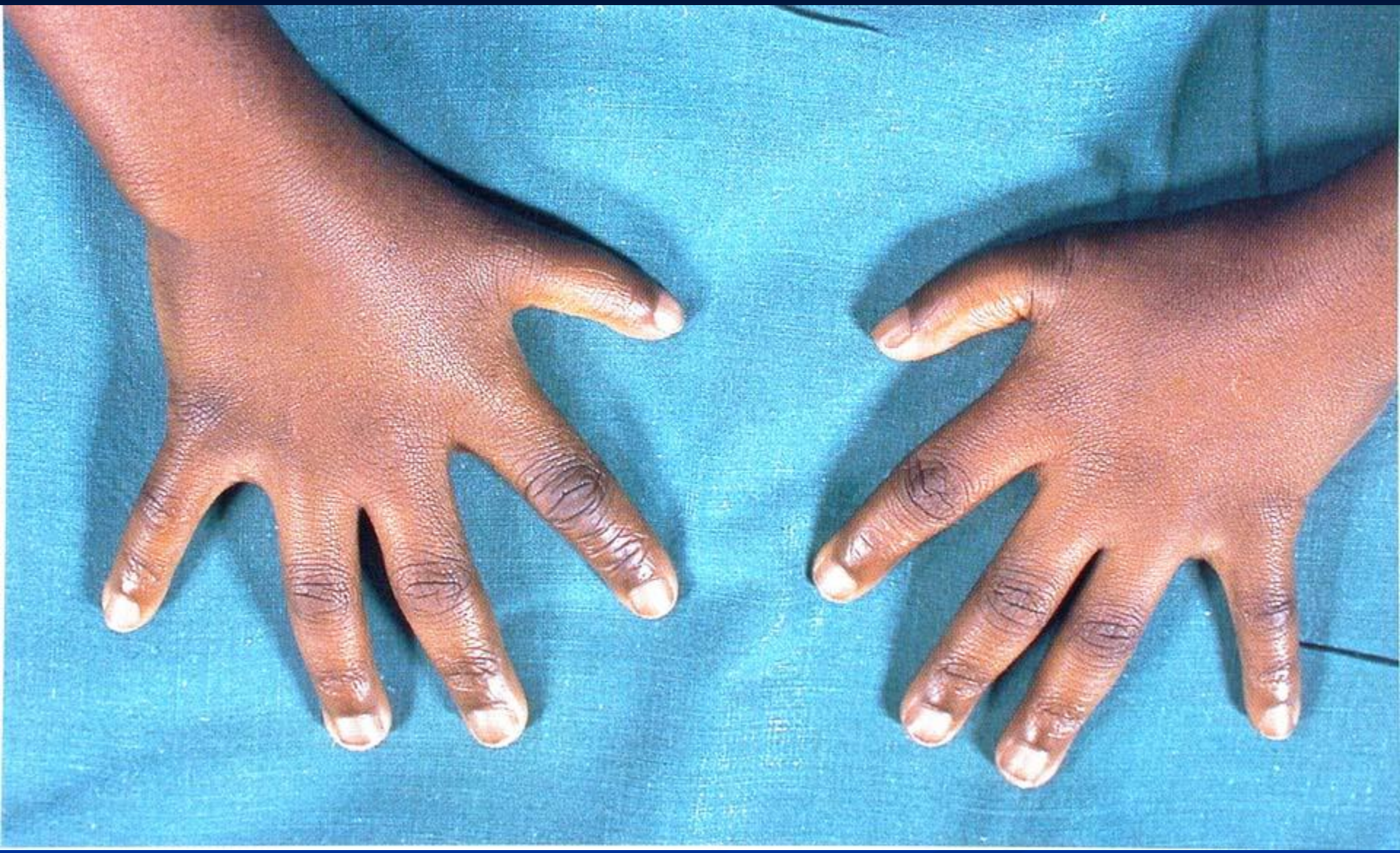


Buccal haemorrhage

FANCONI'S ANAEMIA : PHYSICAL ABNORMALITIES

ABNORMALITY	%
Skin café-au-lait	76
Microsomy	65
Thumb anomalies	40
Microcephaly	39
Hypogenitalia	33
Renal anomalies	32
Skeletal anomalies	28
Strabismus	23
Hyper-reflexia	20
Microphthalmia	19
Mental retardation	18
Cong. heart disease	7


120
100
80
60
40
20



Management of Aplastic Anemia

- Steroid
- Androgen
- ATG + cyclosporine
- BMT

Transfusion in Aplastic Anemia

.Blood:Packed RBC 10-15 ml/kg.

Side Effect:

1.Allergy

2.Fever;Non-hemolytic febrile reaction.

3.Transmission of Viruses

4.Hemolytic Reaction.

5.Transfusion GVHD.

Platelets Transfusion

BMT in Thalassemia

leukemia. History :first BMT was done 1969 in

first BMT in Thalassemia was reported
in USA by Thomas 1981.

First report of BMT in Thalassemia

Problems: 1.Rejection

2.Regimen toxicity

Risk factors in Thalassemia

(pesaro classification)

1. Hepatomegaly
2. liver fibrosis
3. Quality of chelation

BMT in Thalassemia

The finding of a suitable related donor:

25% in Thalassemia
20% in sickle cell

Indication of BMT

1- Severe Aplastic anemia.
2- CML
3-AML in CR1 or CR2
4-ALL in CR2
5-SCID
6-B-Thalassemia
7- Lymphoma with relapse

Types Of BMT

1. Allogenic BMT
2. Peripheral Stem Cell Transplantation
3. Matched Unrelated Donor
4. Human Umbilical Cord Blood Transplant
5. Autologous BMT

THANK YOU