Thalassemias

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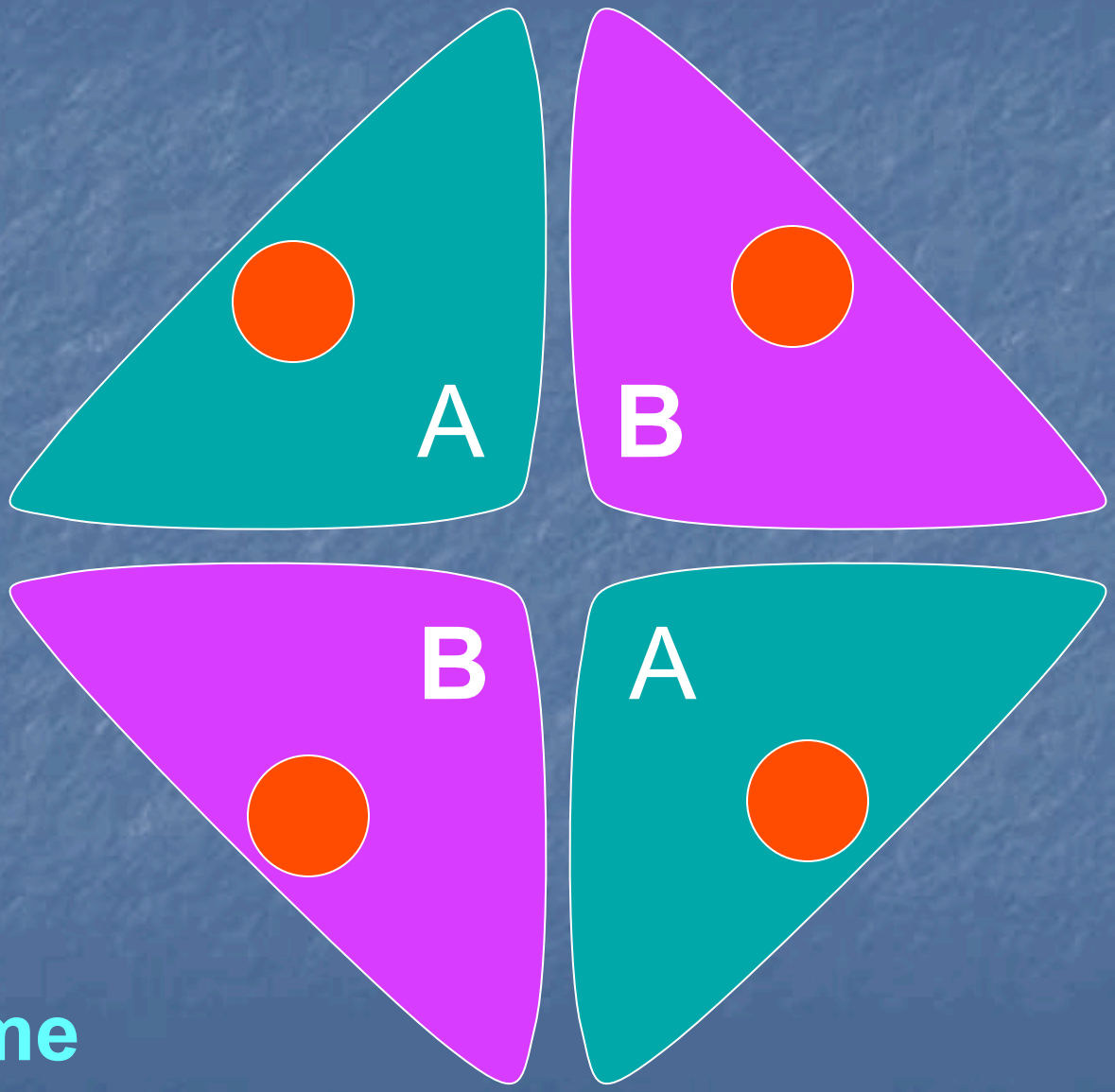
Review of Hb Structure

- Delivers oxygen to the cells
- Tetramer (4 subunits – 2 'A' and 2 'B') plus Heme groups

- A = Alpha like genes and pseudo-genes : 141 amino acid (Chromosome 16); ξ, α, θ

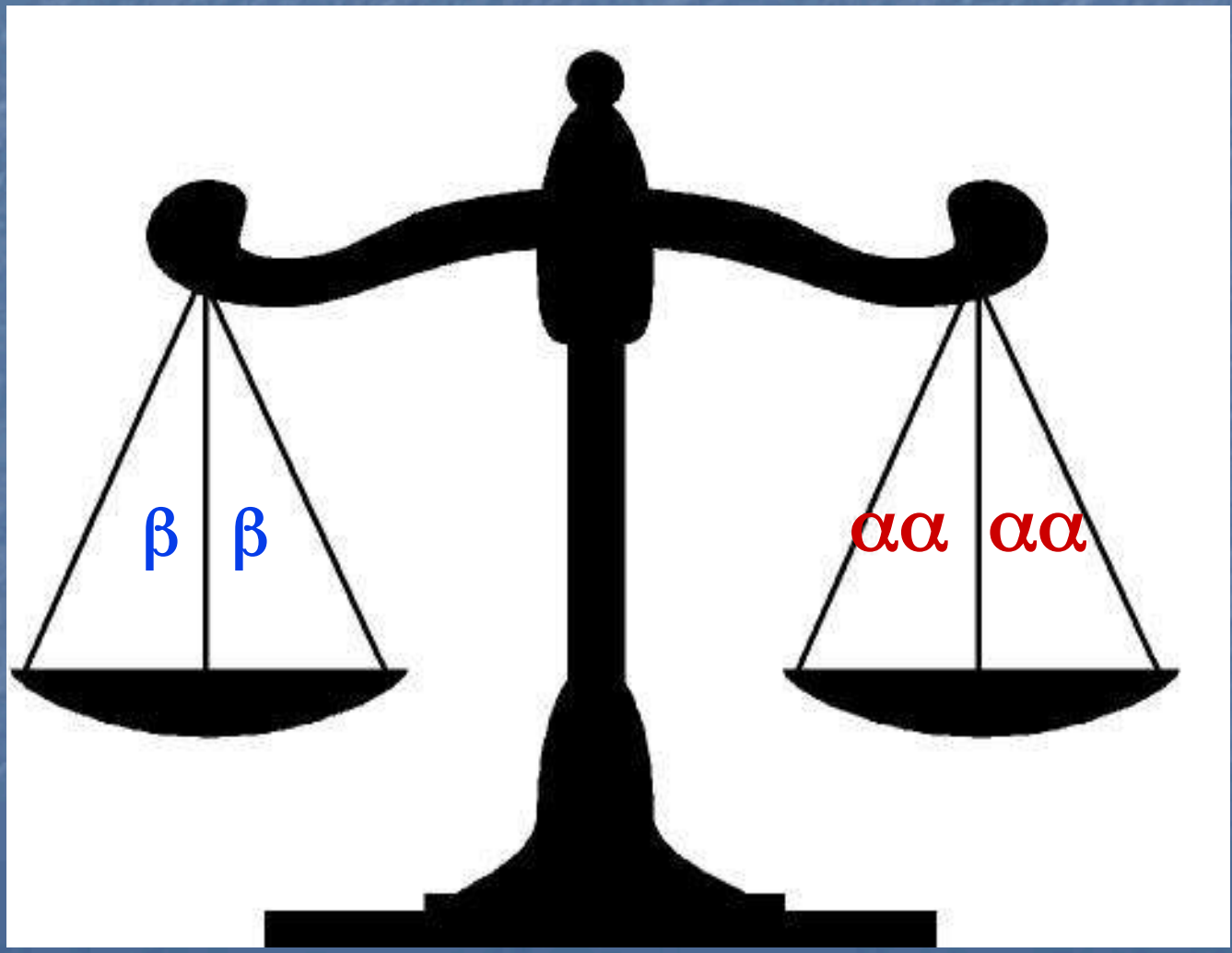
- B = Beta like genes and pseudo genes:146 amino acid (Chromosome 11); ε, γ, β, δ

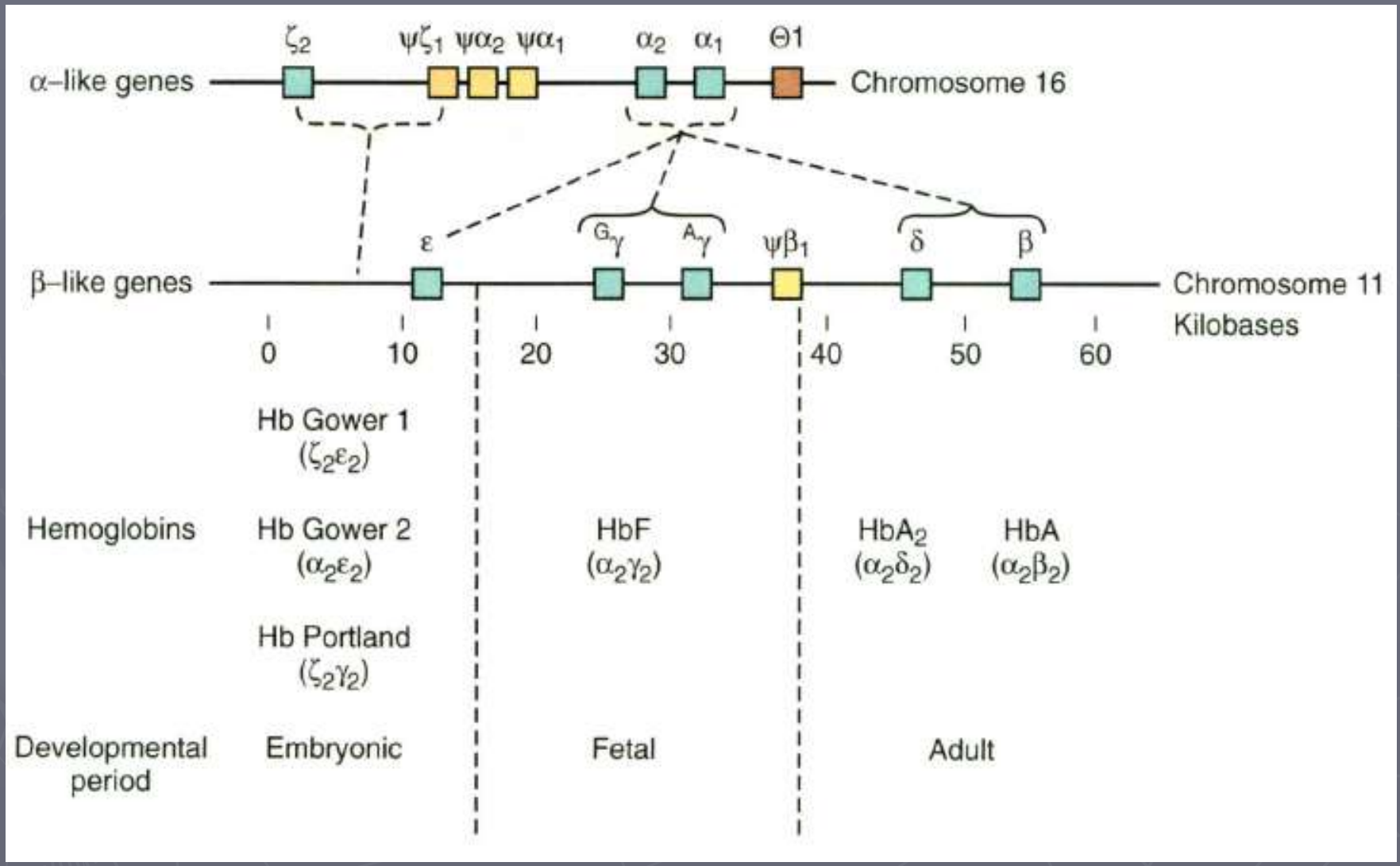
Hemoglobin structure



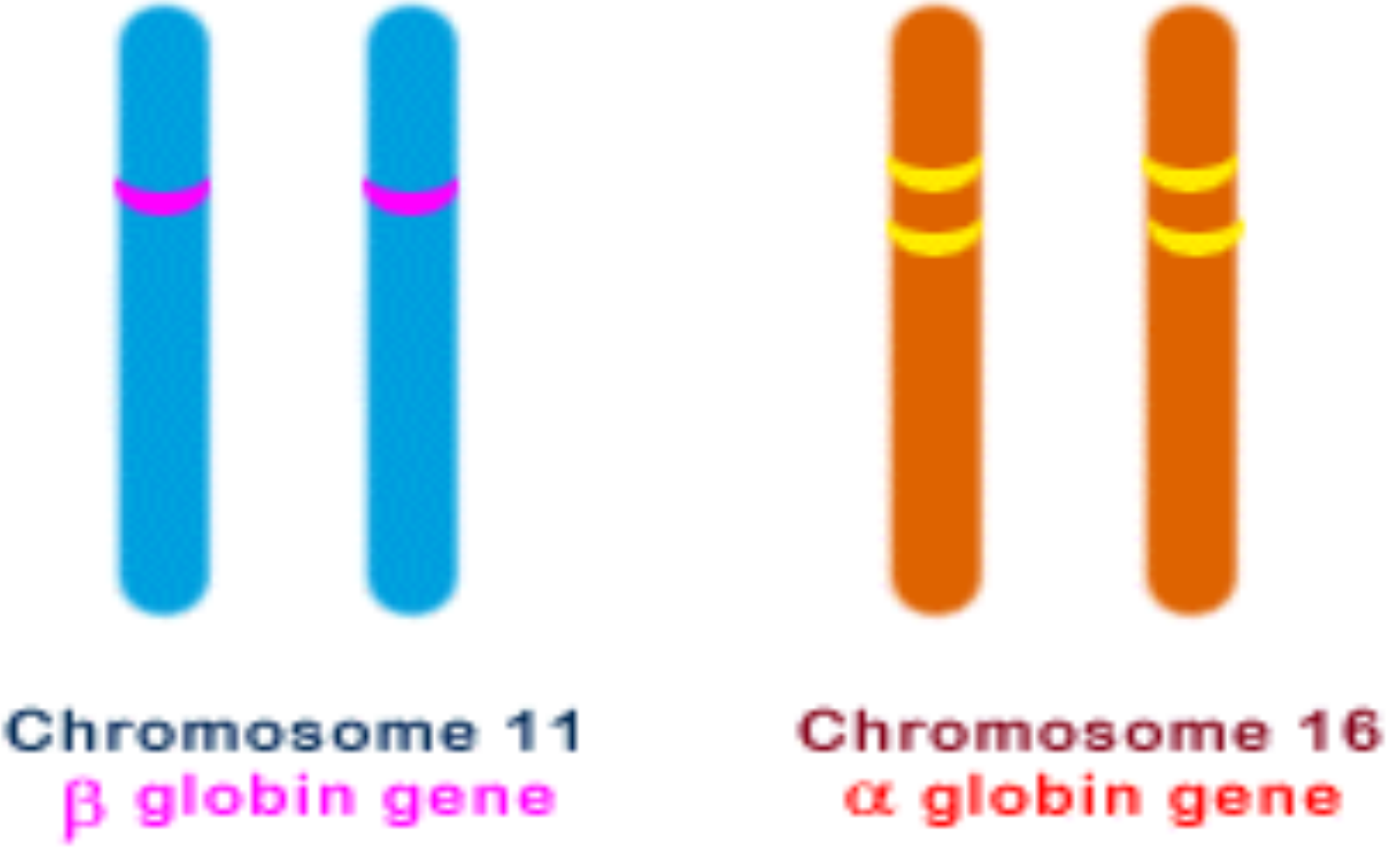
Normal hemoglobin production

chain balance




ζ2
ψζ1 ψα2 ψα1
α2 α1
Θ1
α–like genes
Chromosome 16
ε
Gγ
Aγ
ψβ1
δ
β
β–like genes
Chromosome 11
Kilobases
0
10
20
30
40
50
60
Hb Gower 1
(ζ2ε2)
Hemoglobins
Hb Gower 2
(α2ε2)
HbF
(α2γ2)
HbA2
(α2δ2)
HbA
(α2β2)
Hb Portland
(ζ2γ2)
Developmental period
Embryonic
Fetal
Adult

Chromosomes



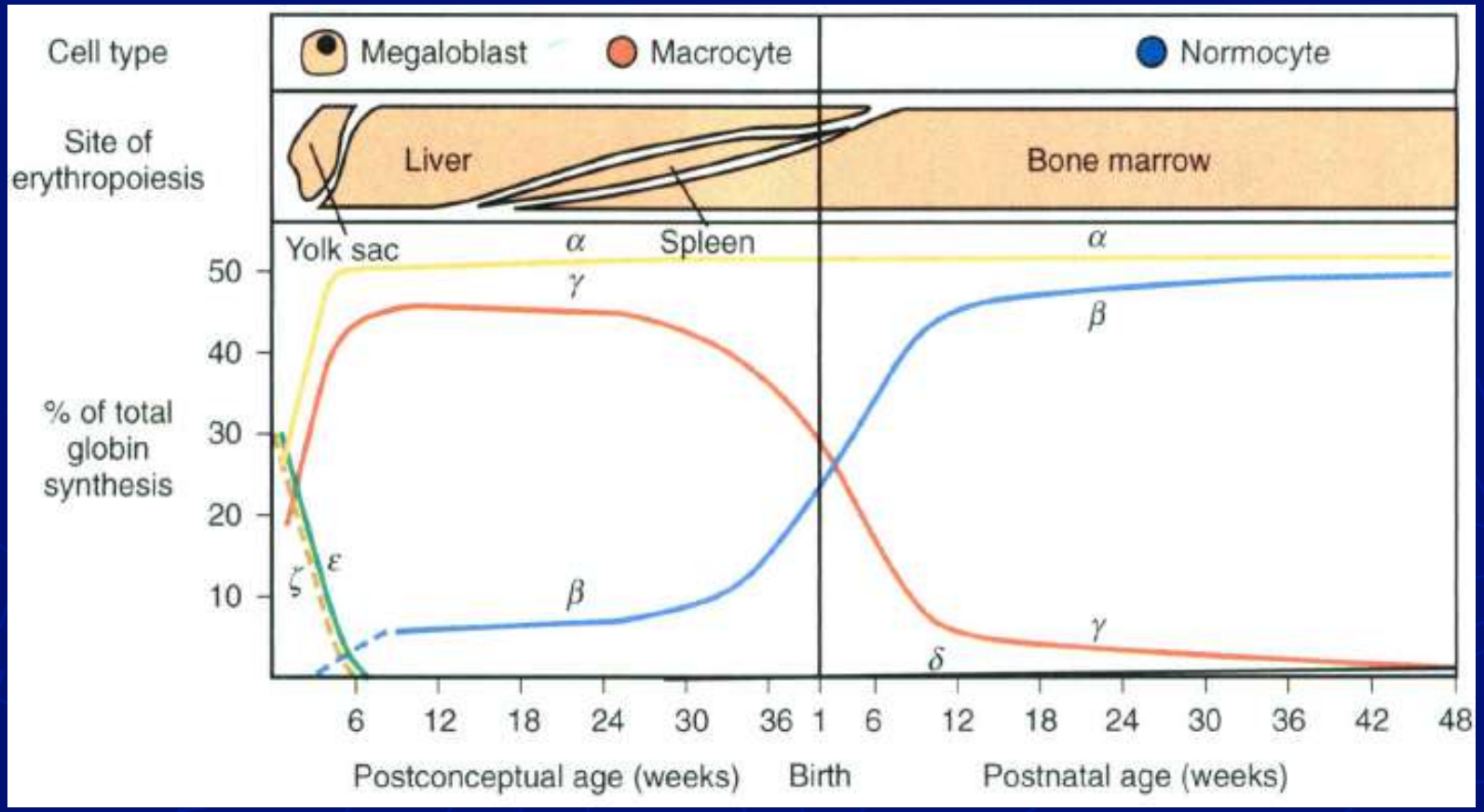


FIGURE 20-3. Sites of erythropoiesis and pattern of globin biosynthesis during development. Nucleated megaloblasts are produced predominantly in the yolk sac. They are replaced by macrocytic fetal red cells produced in the liver and subsequently in the spleen and bone marrow. The height of the *shaded area* approximates the proportion of circulating red cells produced by each organ. Globin biosynthetic measurements were made to obtain the data shown in the lower part of the figure through incubation of intact cells in the presence of radioactive amino acids followed by globin chain separation. *(Redrawn from Weatherall DG, Clegg JB. The Thalassemia Syndromes. Oxford, Blackwell Scientific, 1981, p 54.)*

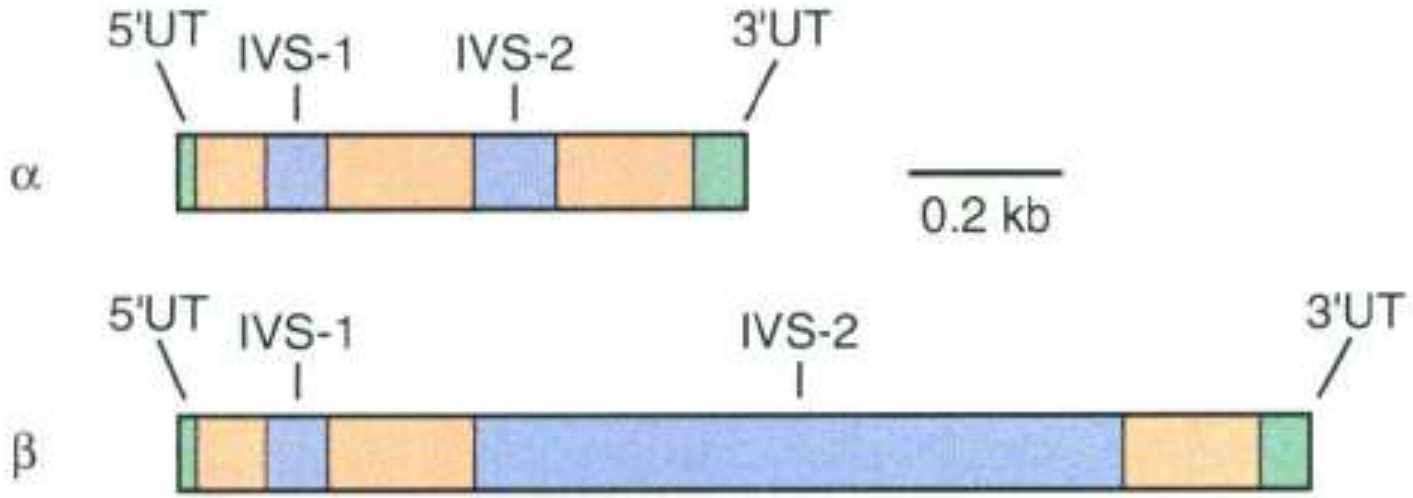
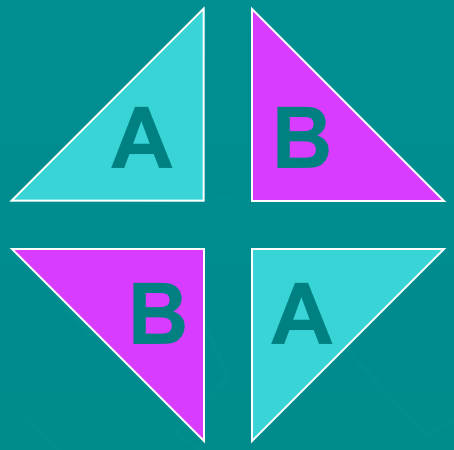
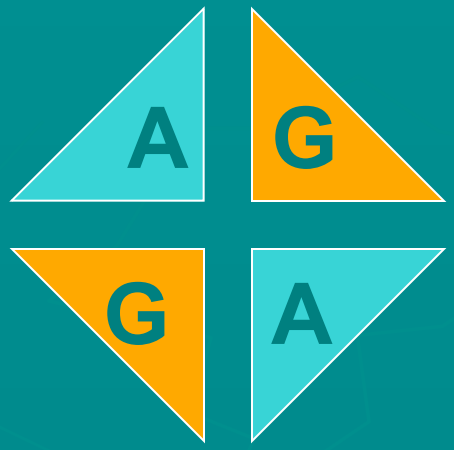


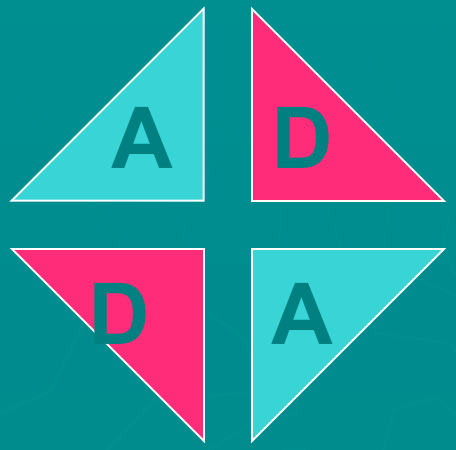
FIGURE 20-4. Structure of the human α- and β-globin genes. Untranslated (UT) regions, exon, and intervening sequences (IVS, introns) are depicted by green, salmon, and blue boxes, respectively.

Hemoglobin Type	Name	Components
Adult	A	$\alpha_2\beta_2$
	A2	$\alpha_2\delta_2$
Fetal	F	$\alpha_2\gamma_2$
Embryonic	Portland	$\zeta_2\gamma_2$
	Gower 1	$\zeta_2\varepsilon_2$
	Gower 2	$\alpha_2\varepsilon_2$
Abnormal	H	$\beta 4$
	Bart's	$\gamma 4$

Hemoglobins in normal adults







HbA	HbF	HbA_2
98%	~1%	<3.5%

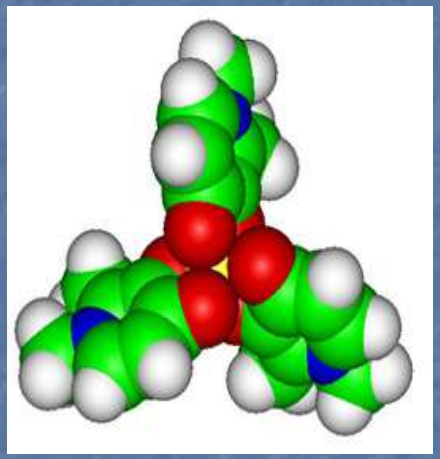
Disorders of Hemoglobin

1. **Thalassemia:** globin chains structurally normal(*quantitative*), but have imbalance in production of two different types of chains
2. **Hemoglobinopathies:** globin chain is abnormal (*qualititative*). Hb S, Hb C, Hb E

- **Hb S** (b6 Glu → Val) mutation, a A → T substitution at codon 6
- **Hb C** (b6 Glu → Lys) mutation, a G → A
- **Hb E** (b26 Glu → Lys) mutation, a G → A
- **Hb O Arab** (b121 Glu → Lys) mutation, a G → A
- **Hb D** (b121 Glu → Gln) mutation

What is Thalassemia ?

Thalassaemia is a group of inherited disorders of hemoglobin synthesis characterized by a reduced or absent one or more of the globin chains of adult hemoglobin .



The name is derived from the Greek words Thalassa = Sea" and "Hemia = Blood" in reference to anemia of the sea.

The first description of Cooley's anaemia. From the *Transactions of the American Pediatric Society, 37, 29–30, 1925.*

SECOND SESSION

A Series of Cases of Splenomegaly in Children, with Anemia and Peculiar Bone Changes. Presented by Dr. Thomas B. Cooley and Dr. Pearl Lee.

Five cases are reported, four from the Children's Hospital of Michigan and one from Dr. Abt's clinic.

All five presented the clinical syndrome ordinarily known as Von Jaksch's disease or pseudoleukemic anemia. There was anemia, splenomegaly, and some enlargement of the liver, discoloration of the skin, and in some of the sclerae, without bile in the urine. The blood showed normal or increased resistance to hypotonic solutions. There was moderate leukocytosis in all, not of the leukemic type, nucleated red cells, chiefly normoblasts, and in two, many reticulated cells. In all of these cases the symptoms were noted by the parents as early as the eighth month, when they were apparently well advanced. Rickets was not probable in any, and in only one was there definite ground for believing that syphilis might be a contributing factor.

In addition to the splenomegaly and the blood picture, in the four cases from the Children's Hospital attention was called to a peculiar mongoloid appearance, caused by enlargement of the cranial and facial bones, combined with the skin discoloration. In Dr. Abt's patient the cranial enlargement was also noted. Roentgen-ray examination of the skulls showed peculiar alterations of their structure, which the roentgenologist considered pathognomonic of this condition. The long bones also showed striking changes. These changes were identical in kind, varying only in degree in all four of the Detroit cases, while gross and microscopic examination in Dr. Abt's case showed a condition which would have given a similar picture.

Three of the patients died. One, who went through a course of antisyphilitic treatment because of a not thoroughly substantiated diagnosis of congenital syphilis, began to improve nearly a year after cessation of all treatment, and seems to be on the road to recovery. The fifth is living, after splenectomy, which is not believed to have improved his condition. He had, in addition to the ordinary symptoms, achlorhydria and some peculiarities in calcium and phosphorus metabolism, which could not be shown to be related to the anemia. He shows frequent hemoglobinuria and hemoglobin is constant in the blood serum. Since splenectomy he has had, for seven months, enormous numbers of nucleated red cells in his blood, reaching as high as 200,000. The only results in treatment have been with a mixture of spleen and red bone marrow, combined with administration of hydrochloric acid. One transfusion caused only slight, transient blood change, and urine examination showed that the transfused blood underwent rapid hemolysis. A more recent transfusion was followed by a better blood picture and less hemolysis.

Microscopic study of the tissues shows fibrous hyperplasia of the spleen, pigment deposit in the liver, and general leukoblastic hyperplasia of all of the bones, with erythroblastic aplasia. This general aplasia of the red cell-forming tissue seems probably to be the cause of the clinical manifestations, and from the early period at which they were noted, and apparently well advanced, it is suggested that the aplasia is congenital, and the disease to be considered a form of myelophthisic anemia. Case 3 may be considered to show that the body may compensate, through secondary hematopoietic areas, for the primary aplasia.

The desirability of roentgen-ray studies of the bones in other forms of anemia with splenomegaly is suggested.

Acknowledgments are made to Drs. P. F. Morse, E. R. Witwer and Lawrence Reynolds for pathologic and roentgenologic studies, and to Drs. A. Abt and O. T. Schlutz for the loan of their material, with Dr. Schlutz's complete analysis.

Thomas B. Cooley (1871–1945). Cooley was born at Ann Arbor, Michigan, graduated MD in 1895 and interned at the Boston City Hospital. After studying in Germany he returned to Boston to work in contagious disease. After further appointments in Ann Arbor and Detroit, and a period of service in France during the First World War, he settled in Detroit, where he spent the rest of his life in paediatric practice.

Thalassemia

- Results in overall decrease in amount of hemoglobin produced and may induce hemolysis.
- Results in microcytic, hypochromic anemias of varying severity.
- May be either homozygous defect or heterozygous defect.

- May contribute protection against malaria.

Demographics: Thalassemia

- Found most frequently in the Mediterranean, Africa, Western and Southeast Asia, India and Burma

Genetic Types of Thalassemia

two basic groups of thalassemia:

- Alpha (α)Thalassaemia
- Beta (β)Thalassaemia

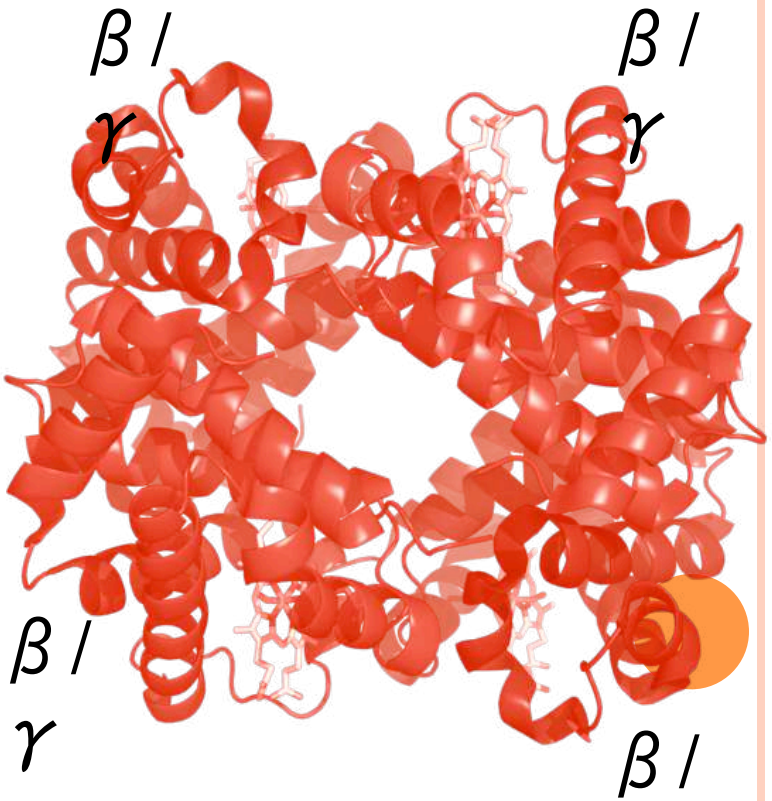
- Genetic: autosomal recessive
- Alpha thalassemia usually caused by gene deletion; Beta thalassemia usually caused by mutation.

Other Thalassemias Caused by Defects in the Beta-Cluster Genes

- Delta Beta Thalassemia
- Hb Lepore
- HPFH
- Beta Thalassemia with Hb S
- Beta Thalassemia with Hb C
- Beta Thalassemia with Hb E

Alpha Thalassemia

- Alpha Thalassemia: deficient/absent alpha subunits
  - Excess beta subunits
  - Excess gamma subunits newborns
- Tetramers formed:
  - Hemoglobin H adults
  - Hemoglobin Bart's newborns
- Five types:
  - Silent Carrier
  - Trait (Minor)
  - Hemoglobin H Disease
  - Major (Hemoglobin Bart's)
  - Hemoglobin Constant Spring



Genetic basis of Alpha Thalassemia

- Encoding genes on chromosome 16 (short arm)
- Each cell has 4 copies of the alpha globin gene
  - Each gene responsible for ¼ production of alpha globin
- 4 possible mutation states:
  - Loss of ONE gene → silent carrier
  - Loss of TWO genes → thalassemia minor (trait)
  - Loss of THREE genes → Hemoglobin H
    - Accumulation of beta chains(b_4)
  - Loss of FOUR genes → Hemoglobin Barts(g_4)
    - NO alpha chains produced ∴ only gamma chains present

- Deletions named according to their size
  - 3.7kb; 4.2kb; 5.2kb; 20.5kb
- Deletions named according to their origin
  - Med, Fil, Thai, SE Asian

Common Alpha Thalassaemia deletion mutations

Disorder	Deletion mutation
α^0 thalassaemia	$--^{SEA}$
	$--^{MED}$
	$-(\alpha)^{20.5}$
	$--^{FIL}$
	$--^{THAI}$
α^+ thalassaemia	$-\alpha^{3.7}$
	$-\alpha^{4.2}$

Non-Deletional Alpha Thal

- Usually represented as $\alpha\ \alpha/\alpha^{T}\alpha$
- May be more severe than deletional form – there is an abnormal product made; can cause more cellular damage
- Most common is Hb Constant Spring

Classification & Terminology

Alpha Thalassemia

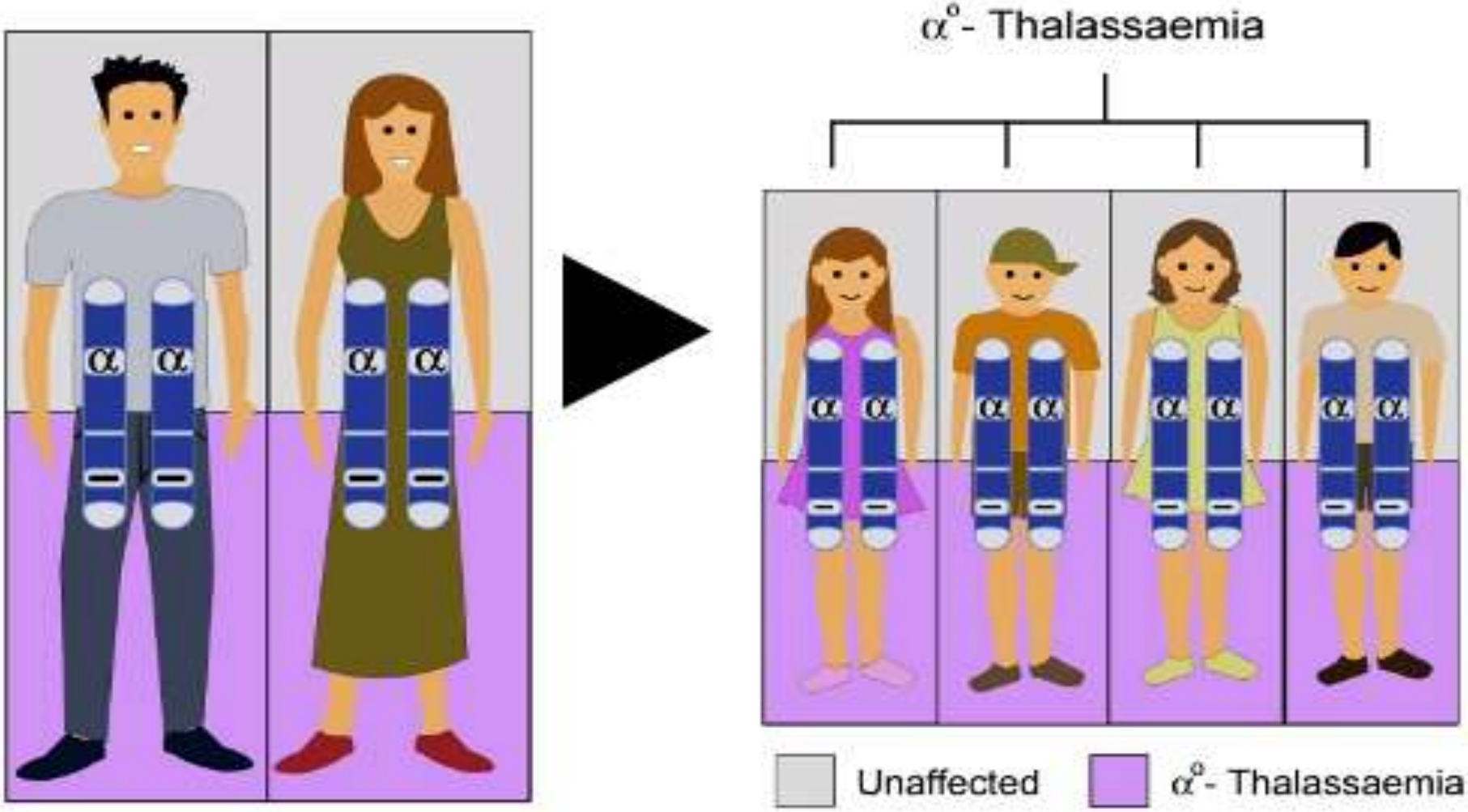
- Normal αα/αα
- Silent carrier - α/αα
- Minor(trait) -α/-α
  --/αα
- Hb H disease --/-α
- Barts hydrops fetalis --/--

TABLE 20-6 α-Thalassemia Syndromes

Syndrome	Clinical Features	Hemoglobin Pattern	α-Globin Genes Affected by the Thalassemia Mutation
Silent carrier (α-thal-2)	No anemia, normal red cells	1-2% Hb Bart's (γ_4) at birth; may have 1-2% Hb Constant Spring; remainder HbA	1
Thalassemia trait (α-thal-1)	Mild anemia, hypochromic and microcytic red cells	5-10% Hb Bart's (γ_4) at birth; may have 1-2% Hb Constant Spring; remainder HbA	2
Hemoglobin H (HbH) disease	Moderate anemia; fragmented, hypochromic, and microcytic red cells; inclusion bodies may be demonstrated	5-30% HbH (β_4); may have 1-2% Hb Constant Spring; remainder HbA	3
Hydrops fetalis	Death in utero caused by severe anemia	Mainly Hb Bart's; small amounts of HbH and Hb Portland also present	4

Both parents have α^{o}- Thalassaemia trait

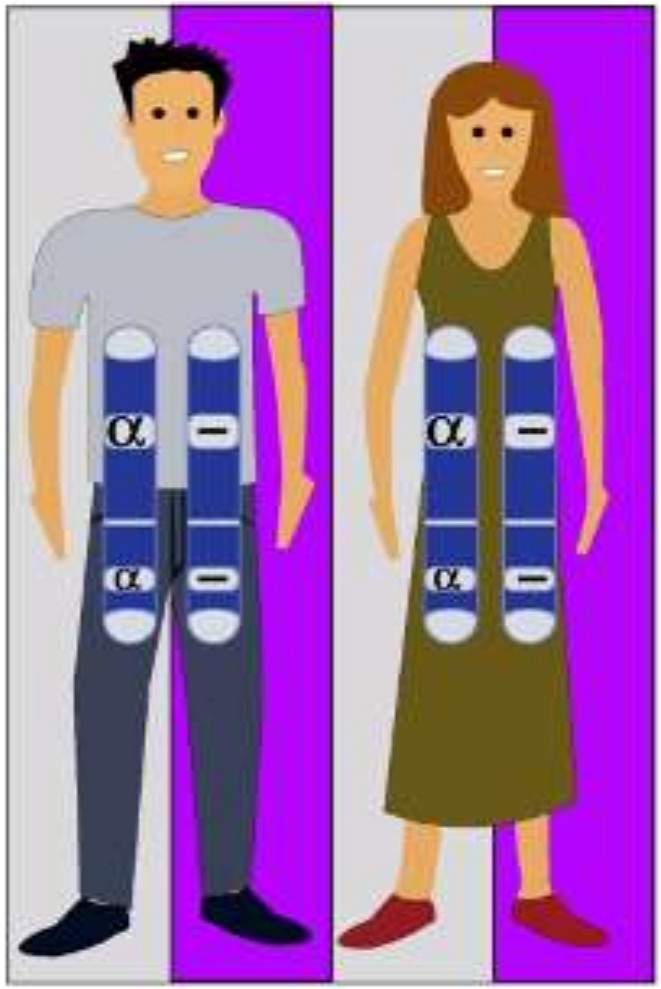
Thalassaemia genes on different chromosomes

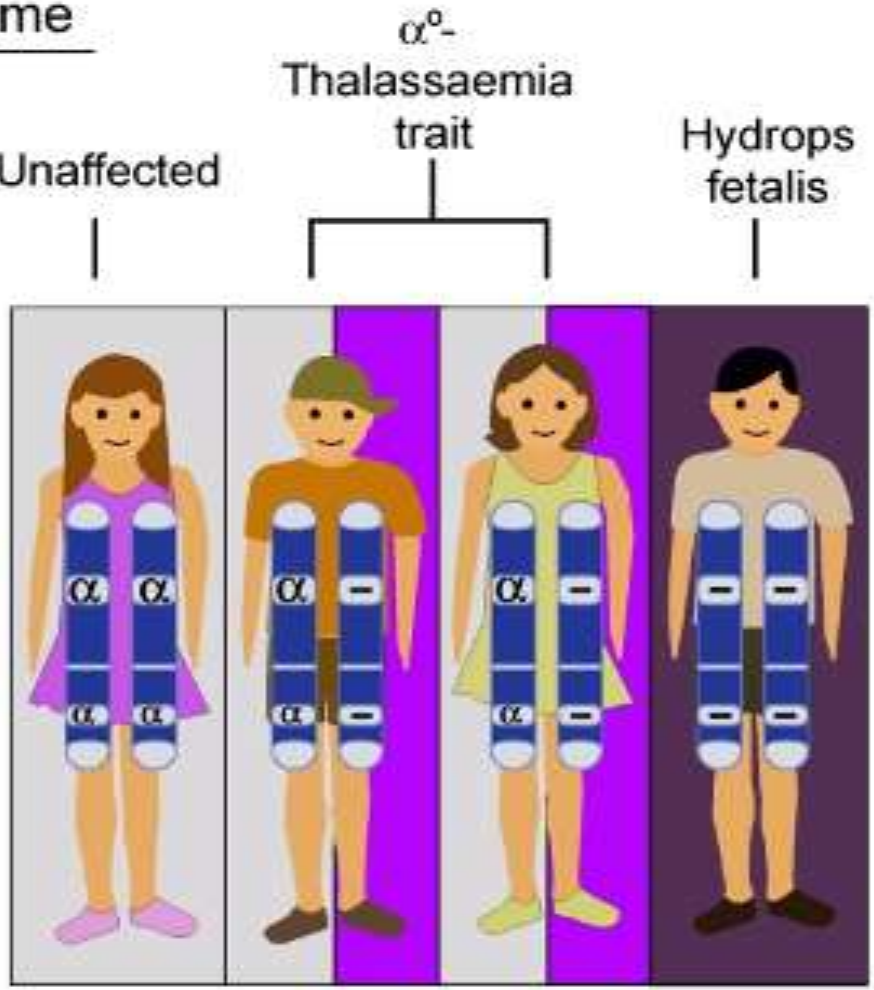


If both parents are α^{o}- Thalassaemia carriers with a functional and a non-functional gene on each chromosome, then all their children will be carriers, exactly as their parents.

Both parents have α^{o}- Thalassaemia trait

Thalassaemia genes on same chromosome

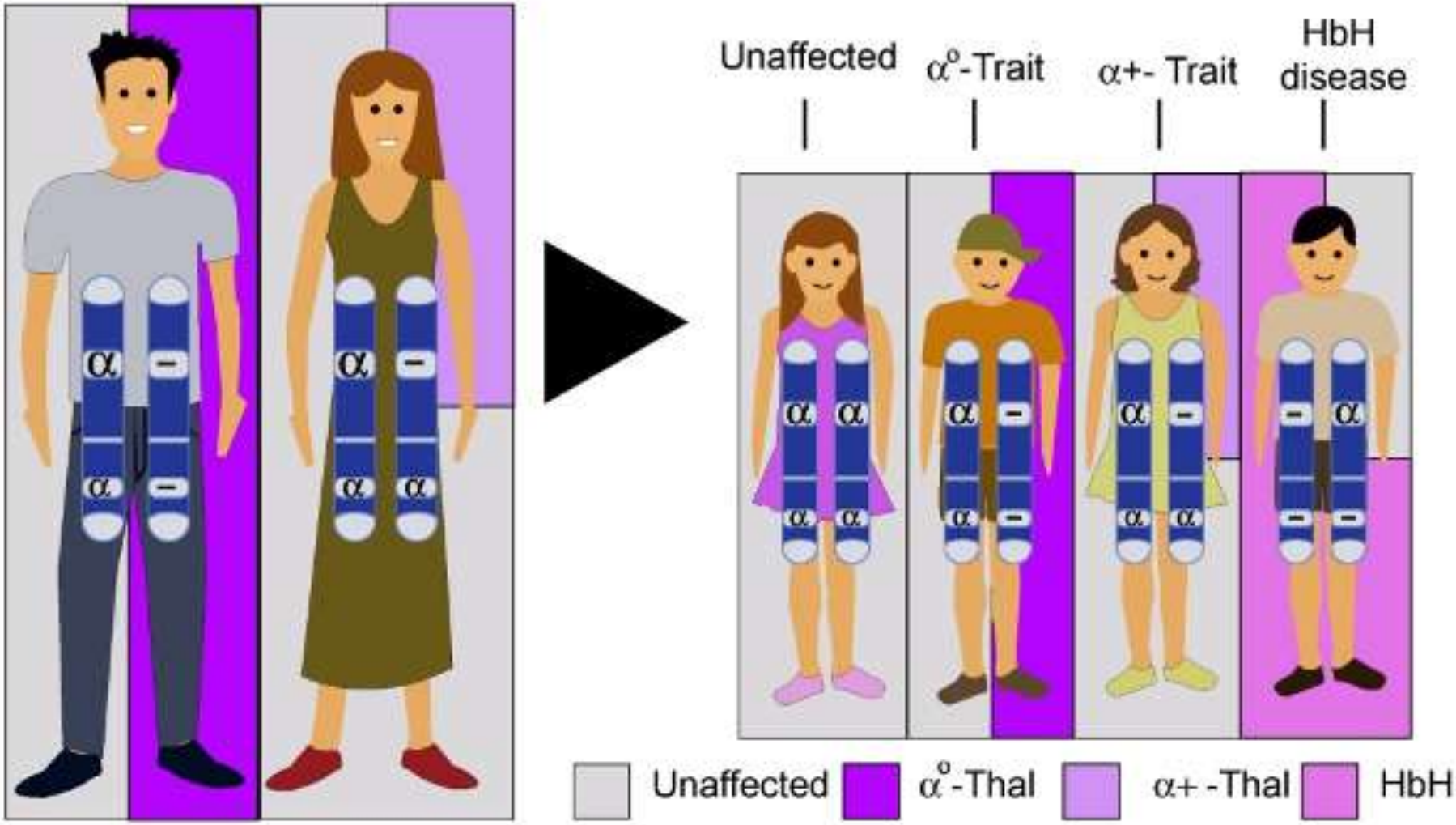




Unaffected α^{o}- Thal Hydrops

If both parents have two non- functioning genes on the same chromosome and normal genes on the other then there is a 1:4 chance of a child inheriting the normal genes, a 1:2 chance of being a carrier like the parents, but also a 1:4 chance of inheriting only the non functioning chromosomes which means that this child will have hydrops fetalis.

Parents are different types of carriers



One parent (the father in this case) has two non functional genes on one chromosome while the other chromosome is "normal" (α^{o}- trait). The other parent (in this case the mother) has one non functional gene (α+ trait). Each Child has a 1:4 chance of being either totally unaffected, or have the α^{o}trait, or the α+ trait or being affected by HbH disease.

Clinical Outcomes of Alpha Thalassemia

- Silent carriers
  - asymptomatic , normal
- Alpha Thalassemia minor (trait)
  - no anemia
  - microcytosis
    -unusually small red blood cells due to fewer Hb in RBC
  - “normal”
- Alpha Thalassemia intermedia (Hb H)
  - microcytosis & hemolysis
  - clinically variable, results in severe anemia
  - Mild bone changes
  - splenomegaly
  - Hb H is susceptible to oxidation, therefore oxidant drugs and foods are avoided
  - Cells: "golf ball" appearance, especially when stained with brilliant cresyl blue

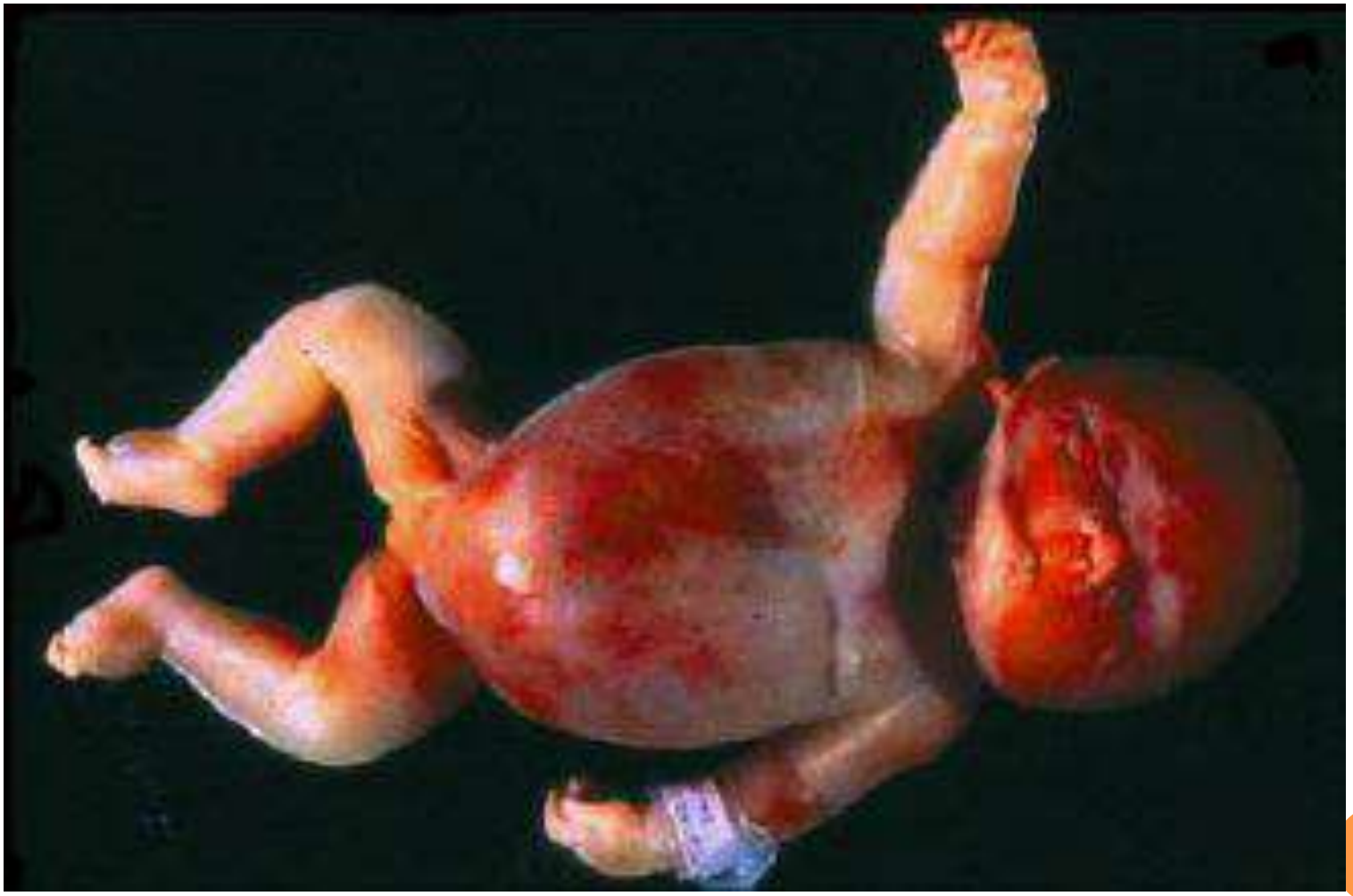
Clinical Outcomes of Alpha Thalassemia

- Alpha Thalassemia major

  - occurs in utero
  - Since alpha chains are synthesized in fetal life, symptoms of Alpha-Thalassemia Major begin in fetal life
  - Hb Bart's has high oxygen affinity so cannot carry oxygen to tissues

  - At birth, see severe hypochromic, microcytic anemia with numerous NRBCs
  - fatal hydrops fetalis
    - Edema , ascites caused by accumulation serous fluid in fetal tissues as result of severe anemia. Hepatosplenomegaly, cardiomegaly., leads to death

Hydrops Fetalis



Beta Thalassemia

- Commonly found in Mediterranean, Middle East, Asia, and Africa

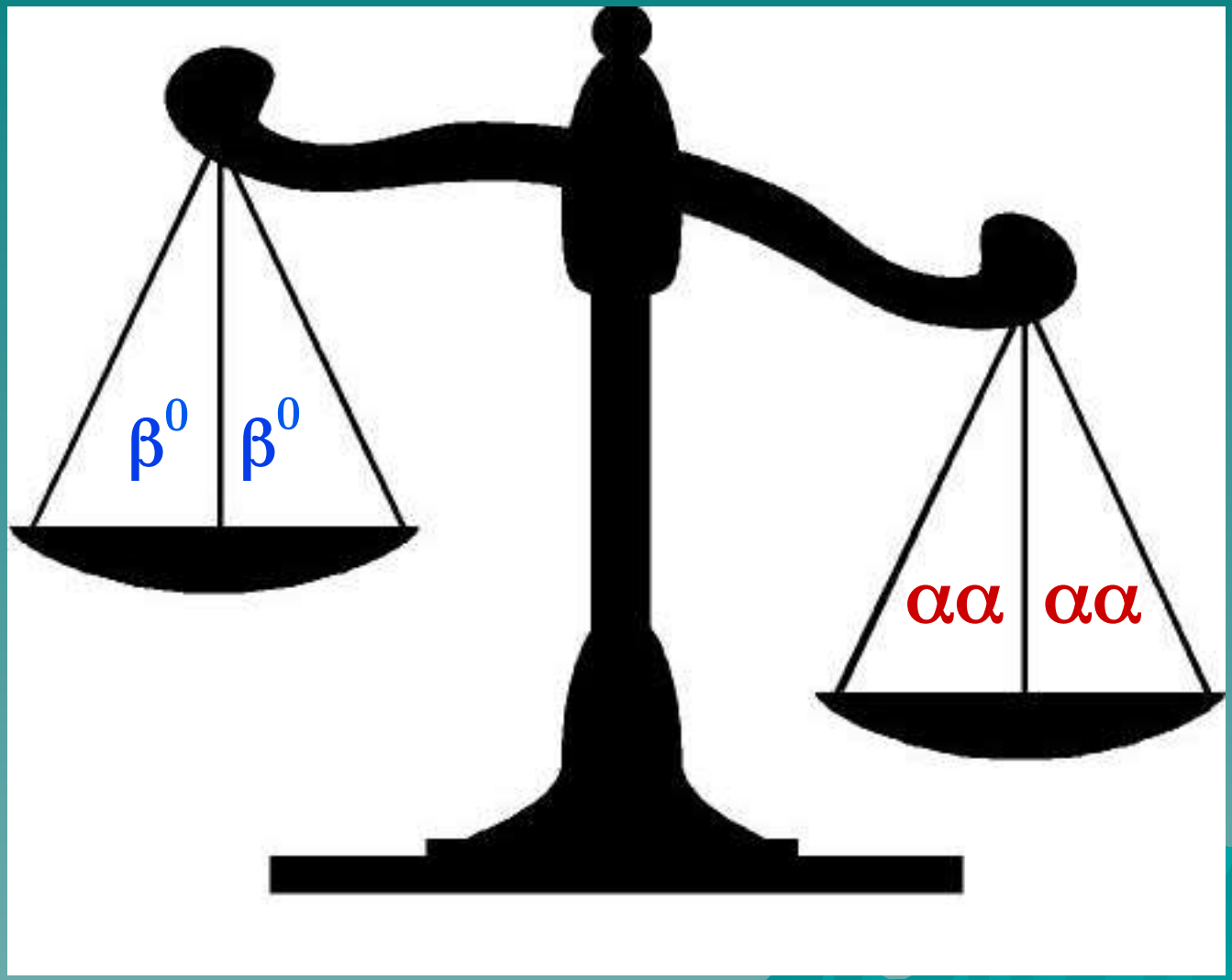
- Three clinical types:
  - Minor
  - Intermedia
  - Major (Cooley anemia)
    - May be asymptomatic at birth as HbF functions

Classification & Terminology Beta Thalassemia

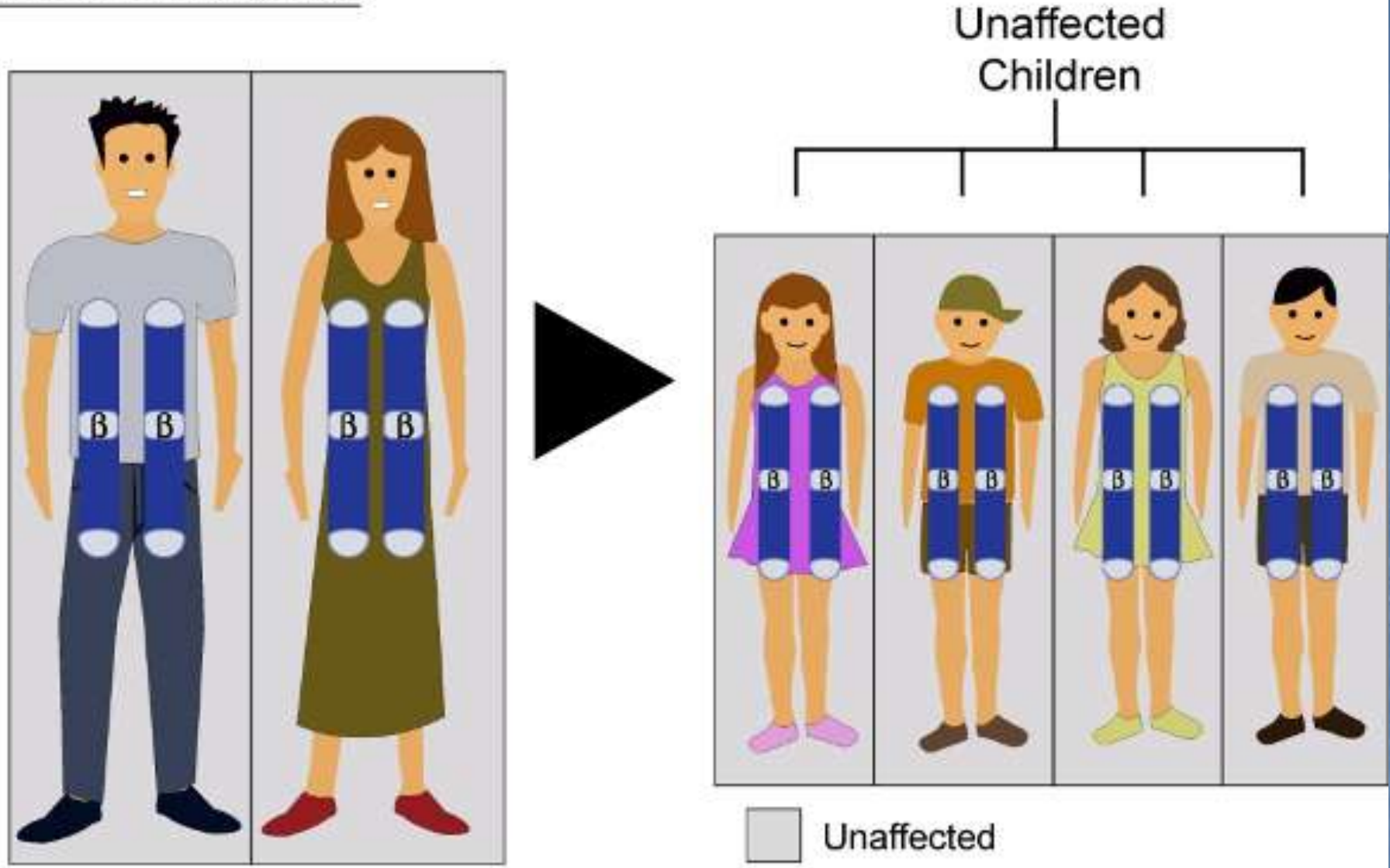
- Normal β/β
- Minor β/β^0
  β/β^+
- Intermedia β^0/β^+
  β^+/β^+
- Major β^0/β^0
  β^+/β^+
  β^0/β^+

Beta Thalassemia

Chain imbalance

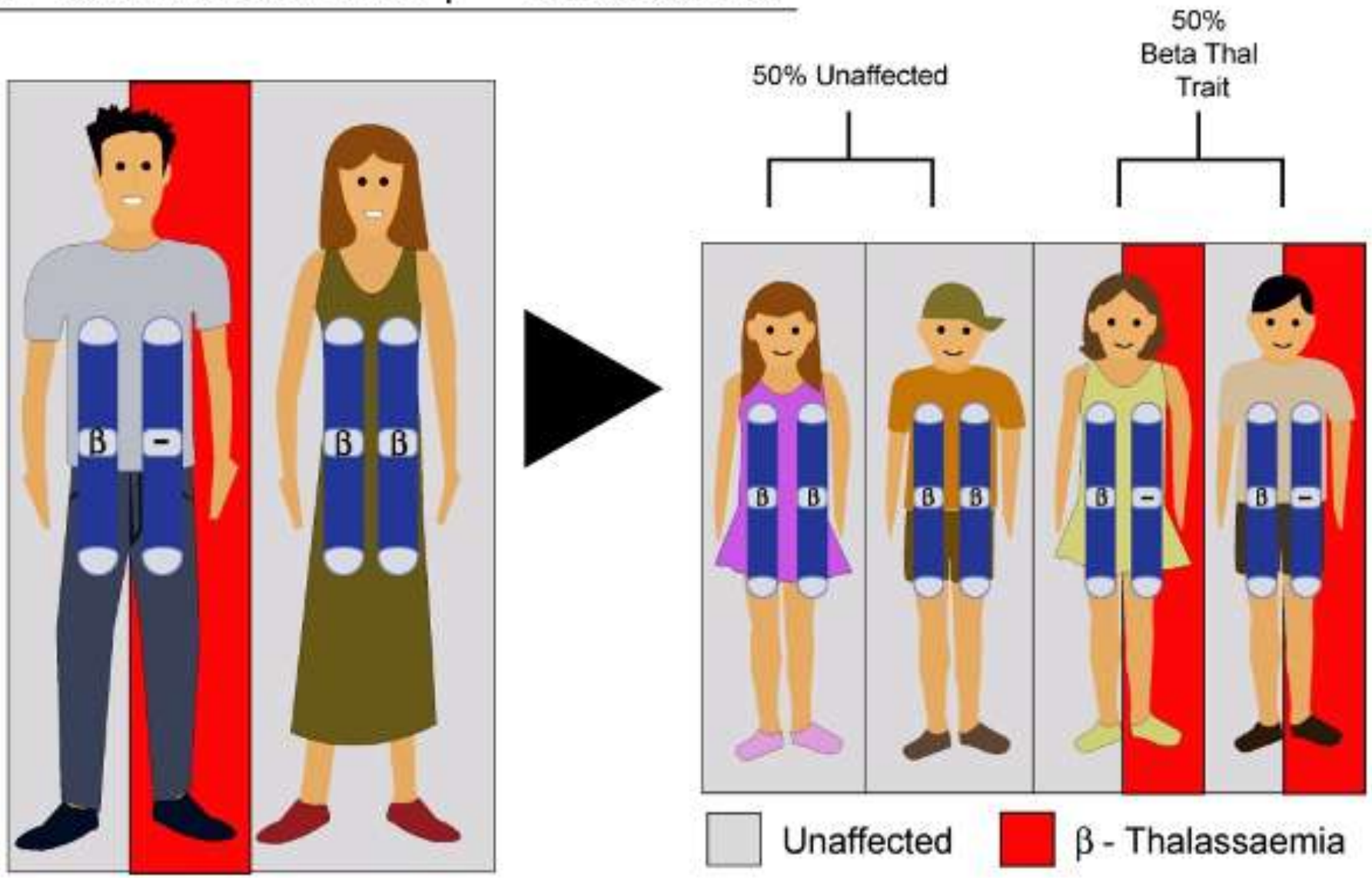


Normal Inheritance



When both globin genes of each parent are functioning normally, then all the children will carry functioning genes and none will have the Thalassaemia trait.

One Parent is a carrier of β – Thalassaemia

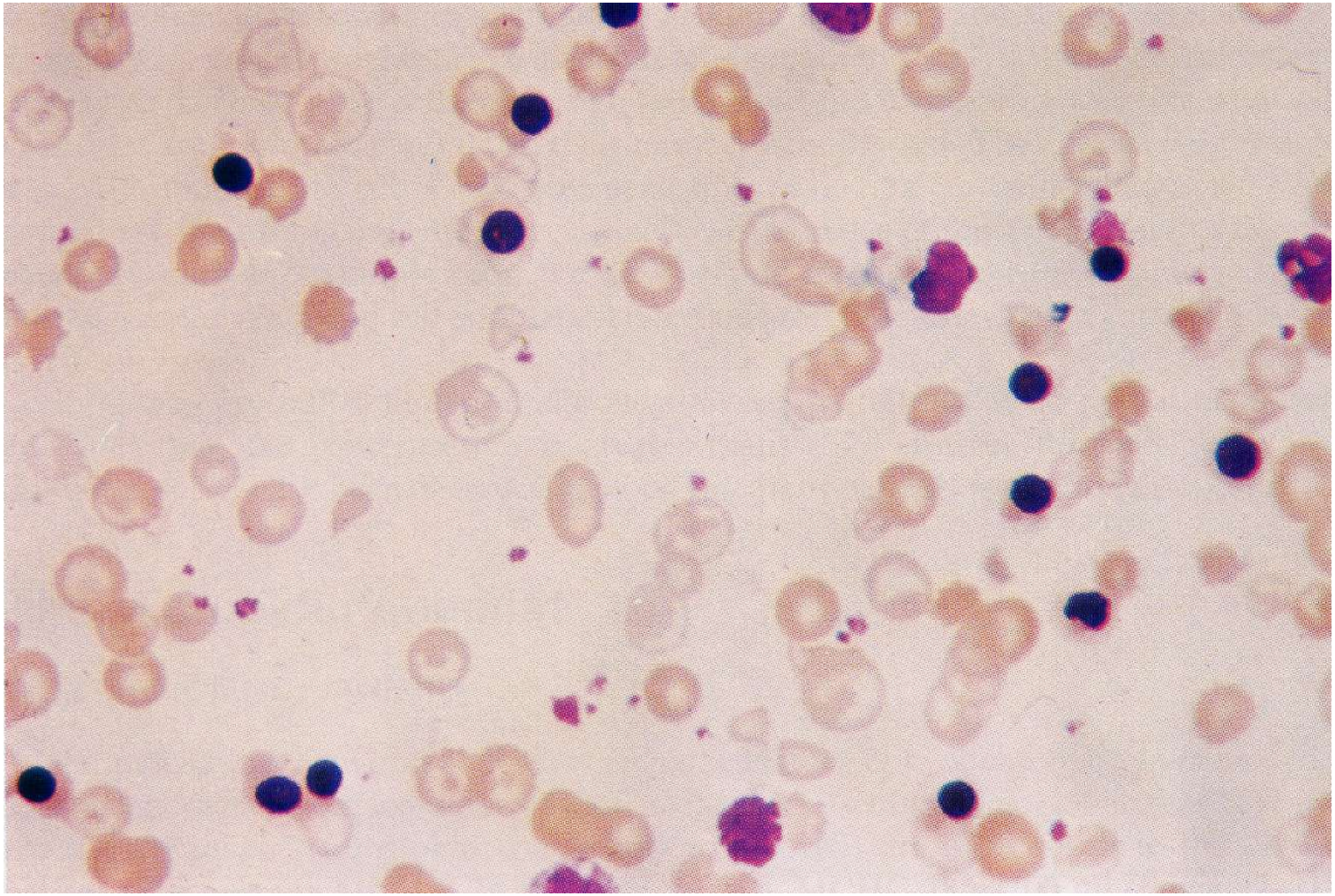


When one parent carries a β - Thalassaemia gene, then each child will have a 50:50 chance (1:2) of also being a carrier (or have the trait, or be heterozygote or have Thalassaemia minor)

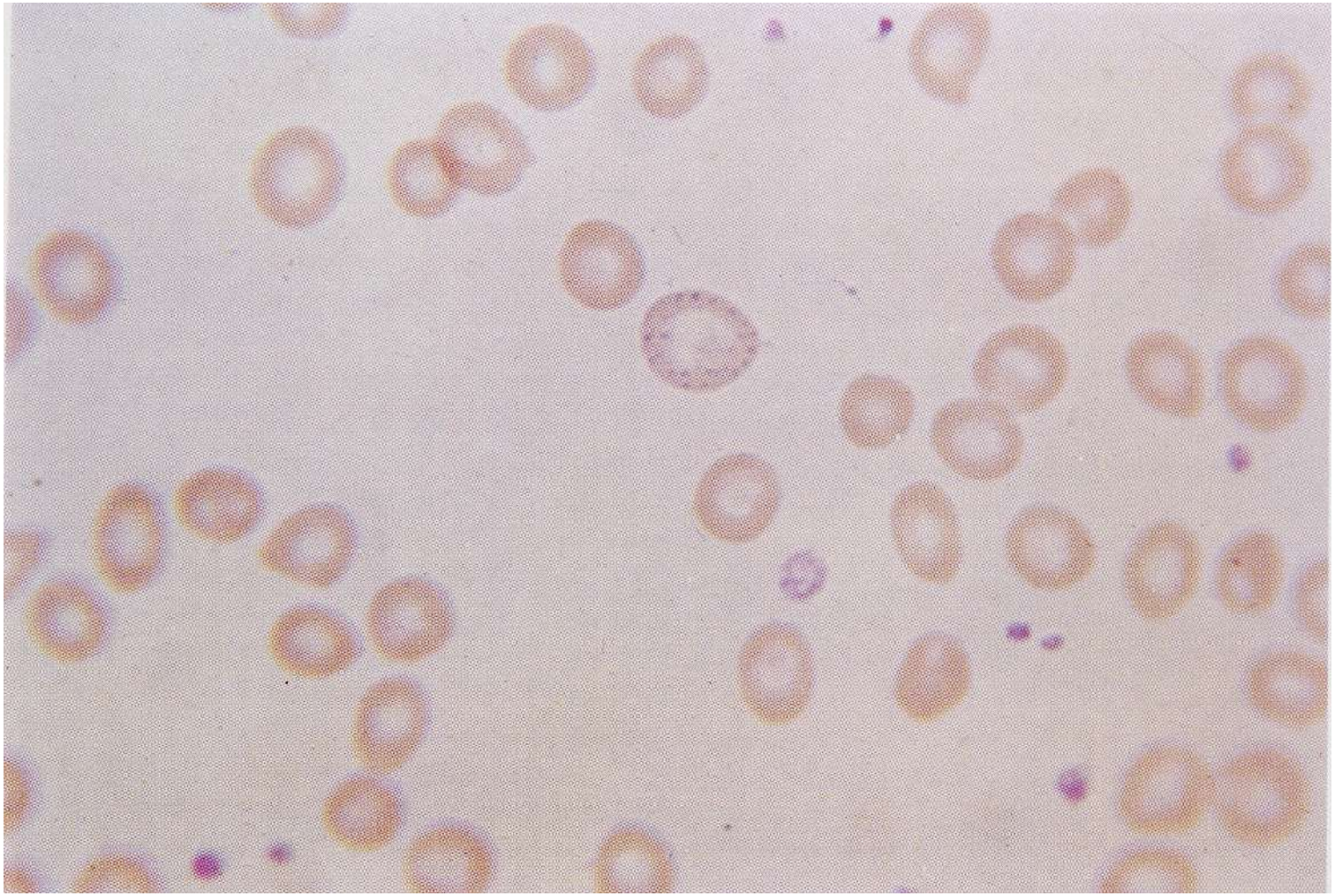
Clinical Outcomes of Beta Thalassemia

- Beta Thalassemia minor (trait)
  - asymptomatic
  - microcytosis
  - mild anemia
- Beta Thalassemia intermedia
  - symptoms similar to Cooley Anemia but less severe
- Beta Thalassemia major (Cooley Anemia)
  - most severe form
  - moderate to severe anemia
  - intramedullary hemolysis (RBC die before full development)
  - peripheral hemolysis & splenomegaly
  - skeletal abnormalities (overcompensation by bone marrow)
  - increased risk of thromboses
  - pulmonary hypertension & congestive heart failure

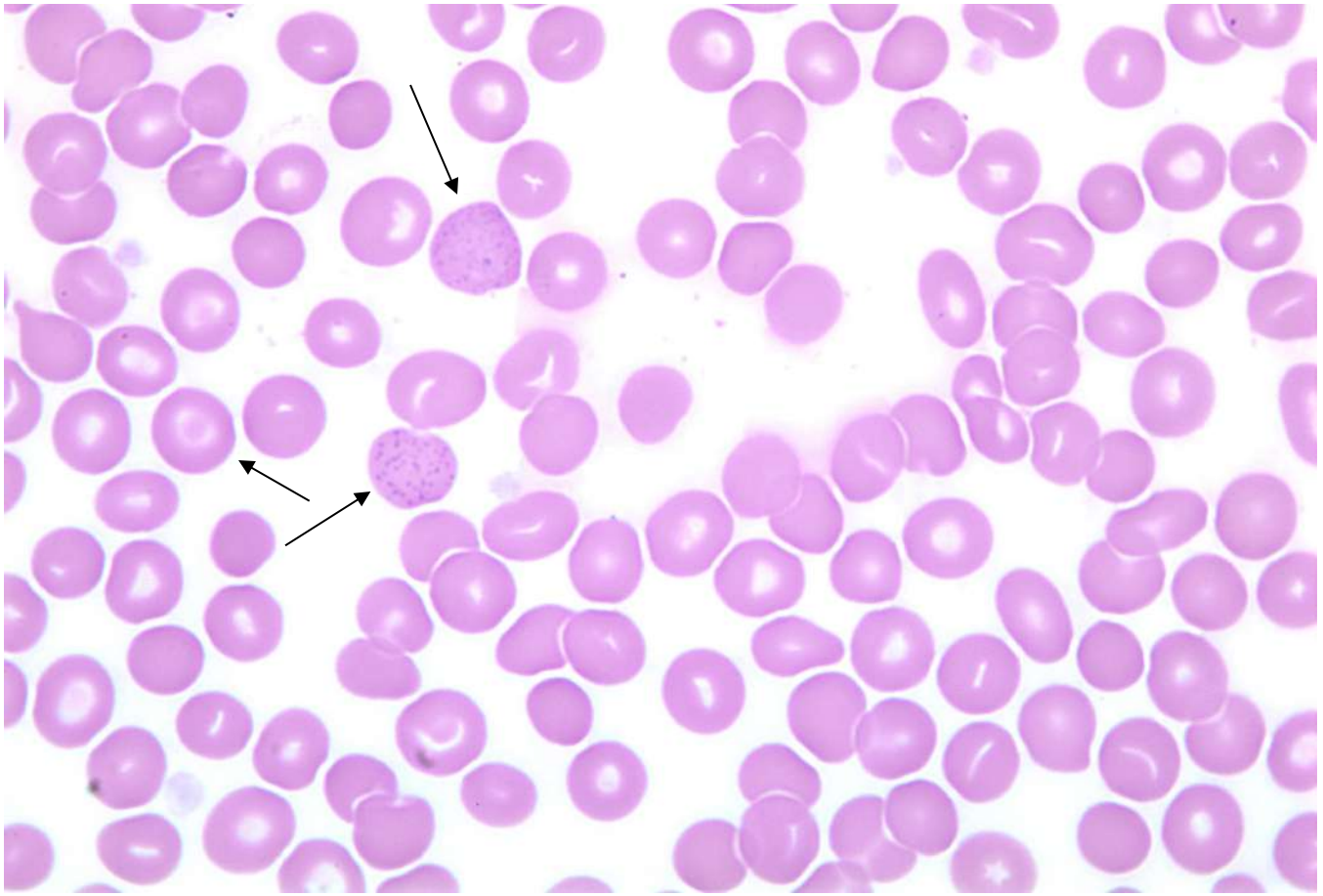
Thalassemia major



Thalassemia minor



Basophilic stippling, Target cell



Pathophysiology

- Disturbance of ratio between Alpha & non alpha globin chain synthesis then absent or decrease production of one or more globin chains
- Formation of abnormal Hb structures
- Ineffective erythropoiesis
- Excessive RBCs Destruction
- Iron Overload
- Extra-medullary hematopoiesis

Pathophysiology

- α-chain excess
  - unstable
  - Precipitates within the cell, causes damage
  - Macrophages destroy the damaged RBCs in the bone marrow, leads to ineffective erythropoiesis
  - Spleen also removes damaged RBCs, leads to chronic extravascular hemolysis

Pathophysiology

- **β-chain excess**
  - Unstable
  - Combines to form hgb molecules with 4 β-chains (hemoglobin H)
    - Infants: excess gamma chains combine with hgb molecules (hemoglobin Bart's)
  - High oxygen affinity, poor transporter of oxygen

Signs & Symptoms

- **Thalassemia Minor :**
  Usually no signs or symptoms except for a mild anemia.

Signs & Symptoms

- **Thalassemia Intermedia:**
- clinical presentation typically occurs at 2-4 years of age
- Hb levels 7 g/dL without Tx support
- When their Tx requirements reach 8 units per year, they are reclassified as –TM
- Anemia, hyperbilirubinemia, hepatosplenomegaly
- The majority of the patients will require Tx at some point in their lives or when hemolytic or aplastic crises associated with acute infections, folate deficiency,hypersplenism, or pregnancy occur.

- Indications for regular Tx in TI
- growth failure or cosmetic facial and bony abnormalities
- Massive splenomegaly , hypersplenism
- progressive anemia, fatigue, cardiopulmonary complications

Signs & Symptoms

- **Thalassemia Major :**

  1. Severe anemia, Jaundice or yellow colored skin.
  2. Growth retardation.
  3. Bony abnormalities specially of the facial bones.
  4. Pathological fractures
  5. Hepatosplenomegaly

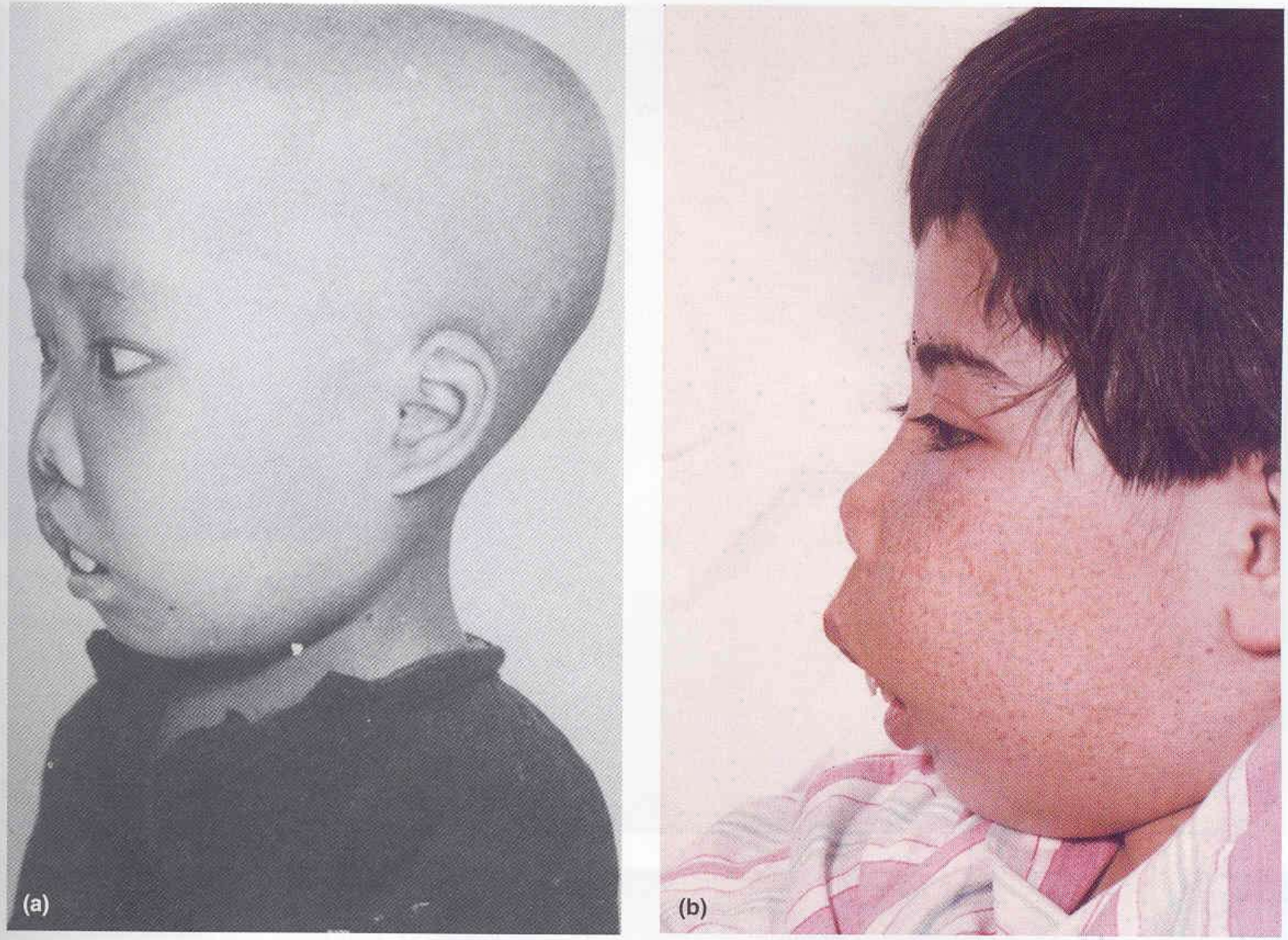


Fig. 7.2 Facial appearances in severe β thalassaemia. (a) Bossing of the skull. (b) Typical dental deformity.

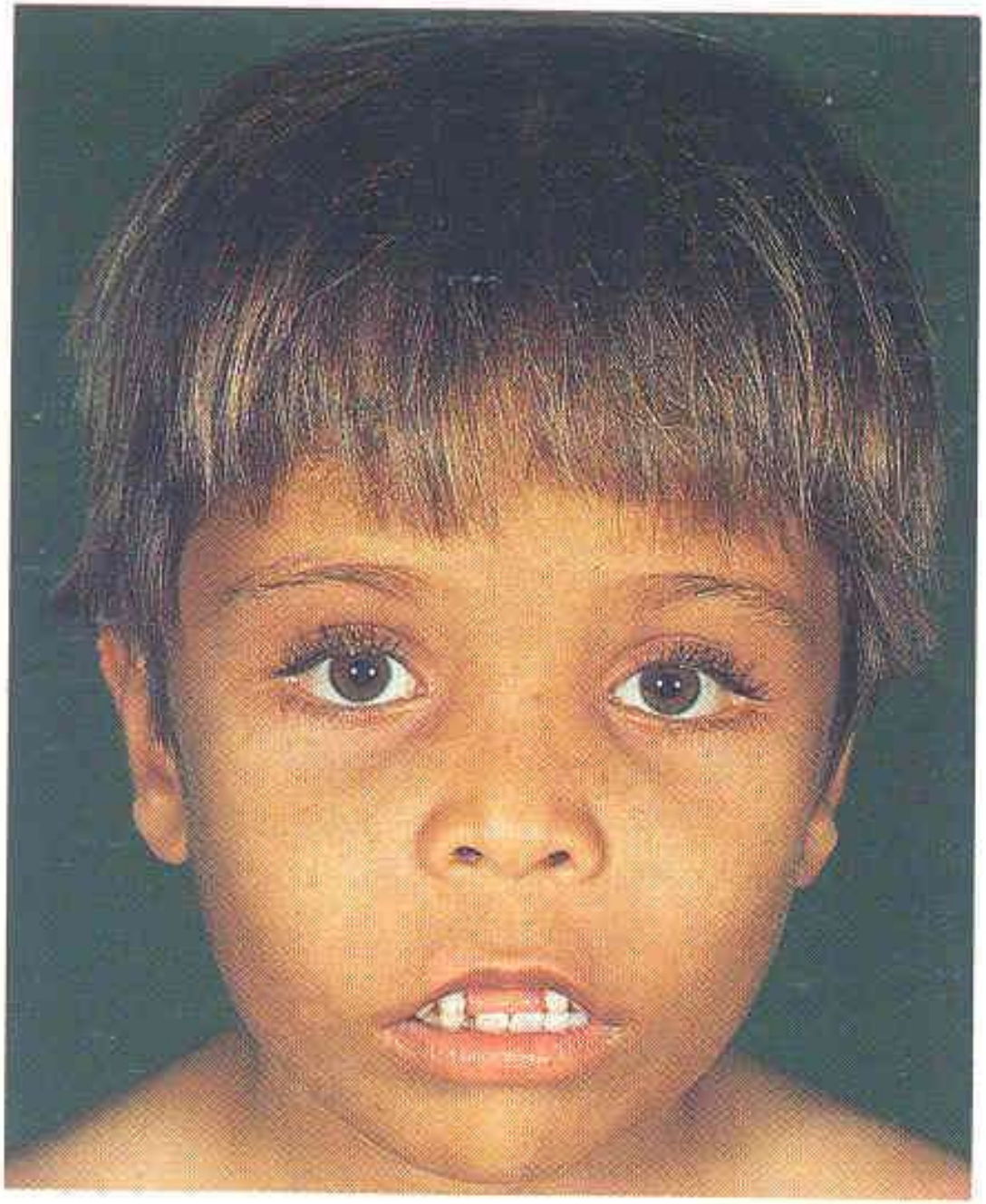
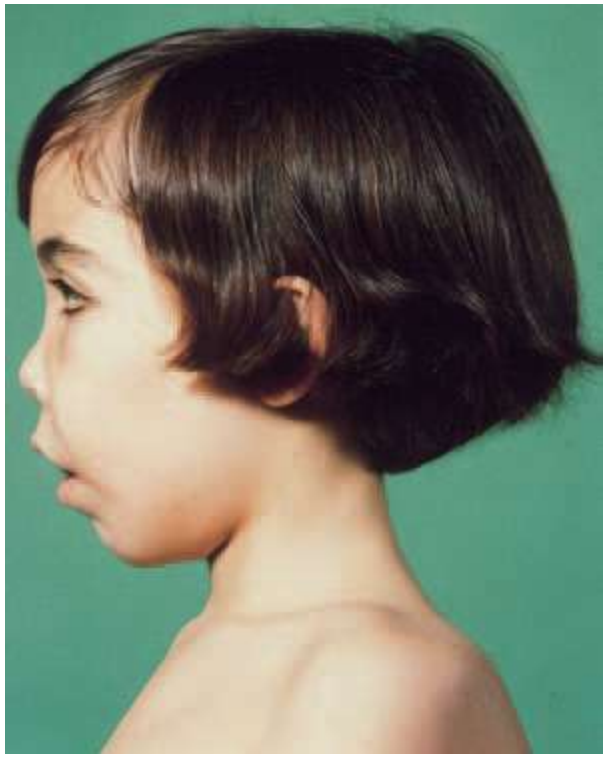
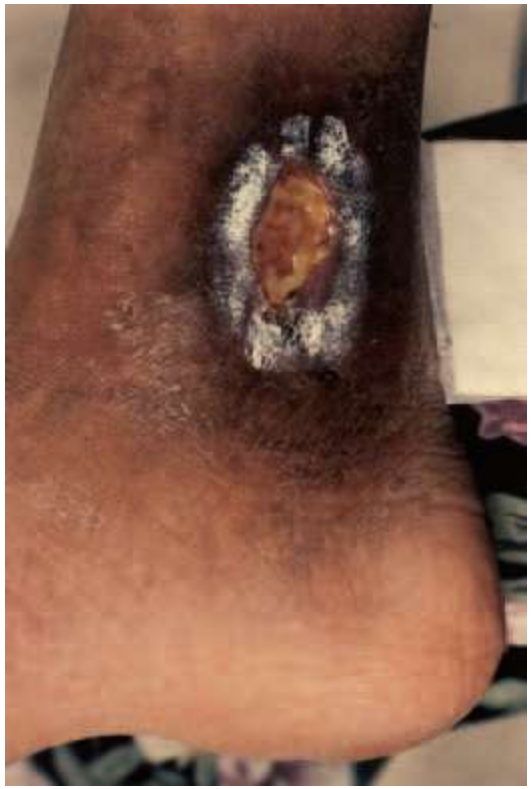


Fig. 5.6
β-Thalassaemia major: characteristic facies of a 7-year-old Middle Eastern boy includes prominent maxilla and widening of the bridge of the nose. There is also marked bossing of the frontal and parietal bones and zygomata giving a mongoloid appearance.

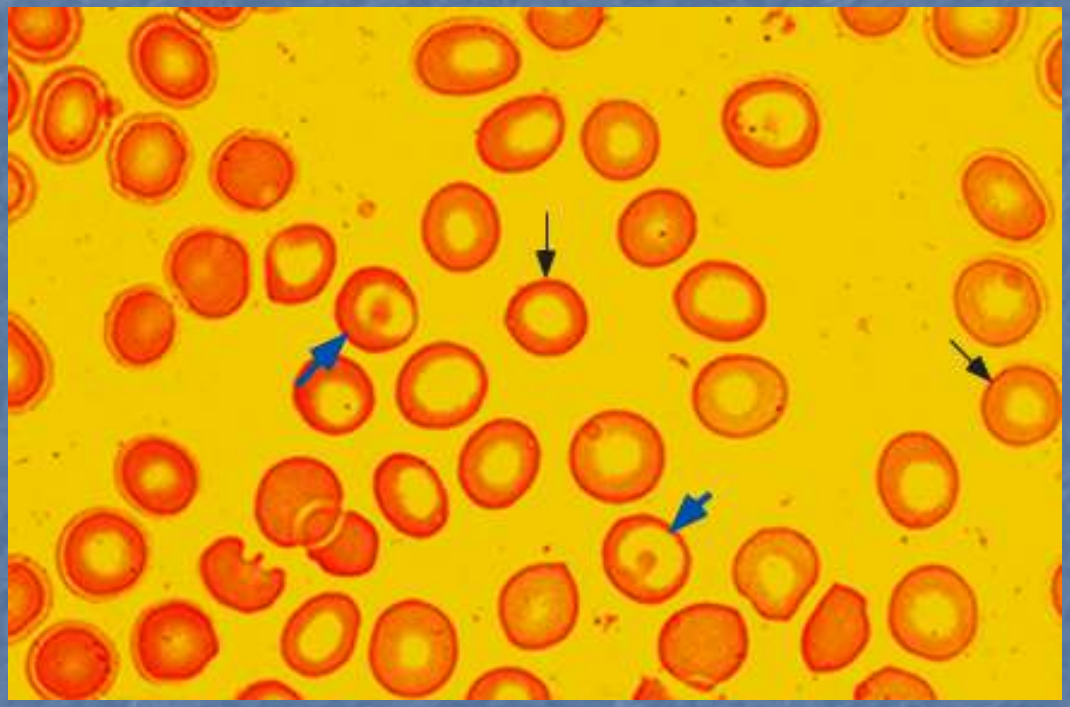
Clinical features of severe b thalassemia intermedia. (a,b) Facial appearances; (c) chronic leg ulcer

Laboratory Diagnosis of Thalassemia

Laboratory Diagnosis

- Thalassemia minor:
- Hemoglobin : Hb level is usually normal or mildly reduced.
- PBS : Hypochromia and Microcytosis, basophilic stippling, target cell.
- Low MCV, Nl RDW, elevated RBC count .
- Reticulocyte Count increases
- Hb electrophoresis

Beta thalassemia trait



Peripheral smear from a patient with beta thalassemia trait.
The field shows numerous hypochromic and microcytic red cells (thin arrows), some of which are also target cells (blue arrows).

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آزمایشگاه بیمارستان حضرت علی اصغر (ع)

زاهدان - خیابان آزادی - تلفن: ۳۲۲۹۶۸۸

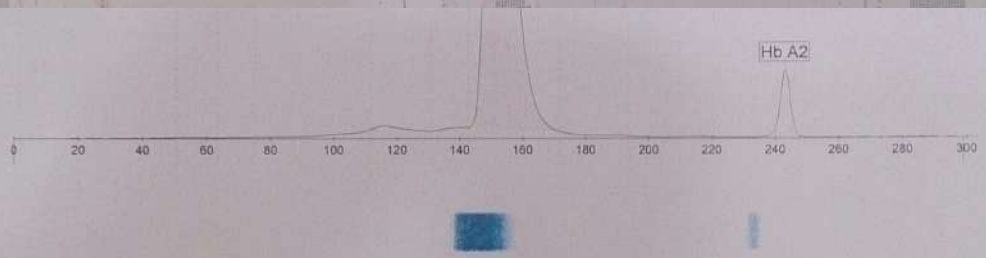
SYSMEX Hematology Analyzer

Patient Name: عبدالغفور کهادزاده ID.NO: 38 Date: 16/

Doctor: Sex/Age: Time: 10:

WBC	4.7	x10³/µl	[4-10]	RBC	6.62	x10⁶/µl	[3.9-5.8]	PLT	162 x10³/µ
Lymph	36.1	%		HGB	13.1	gr/dl	[12-17]	PDW	15.7 fl
Neut	51.0	%		HCT	44.9	%	[36-53]	MPV	10.6 fl
Mixed*	12.9	%		MCV	67.8	fl	[80-100]	P-LCR	31.8 %
*(Mono+Eos+Baso)				MCH	19.8	pg	[27-32]		
				MCHC	29.2	gr/dl	[31-36]		
				RDW-CV	15.9	%	[11.5-15]		
				RDW-SD	39.9	fl	[40-53]		

WBC RBC



Hemoglobin Capillary Zone Electrophoresis

Name	%		Normal Values %
Hb A	94.5	<	96.5 - 98.5
Hb A2	5.5	>	2.0 - 3.5

17 yr/ old male

Hb patterns in haemoglobin disorders

% Haemoglobin	A	F	A_2	S	Other
Normal	**97**	**<1**	**2–3**		
β thalassaemia trait	80–95	1–5	3–7		
β thalassaemia intermedia	30–50	50–70	0–5		
β thalassaemia major	0–20	80–100	0–13		
HPFH (Black heterozygote)	60–85	15–35	1–3		
HPFH (Black homozygote)		100			
α thalassaemia trait	85–95				Bart's 0–10% at birth
HbH disease	60–95				H 5–30% Bart's 20–30% at birth
HbBart's hydrops					Bart's 80–90%

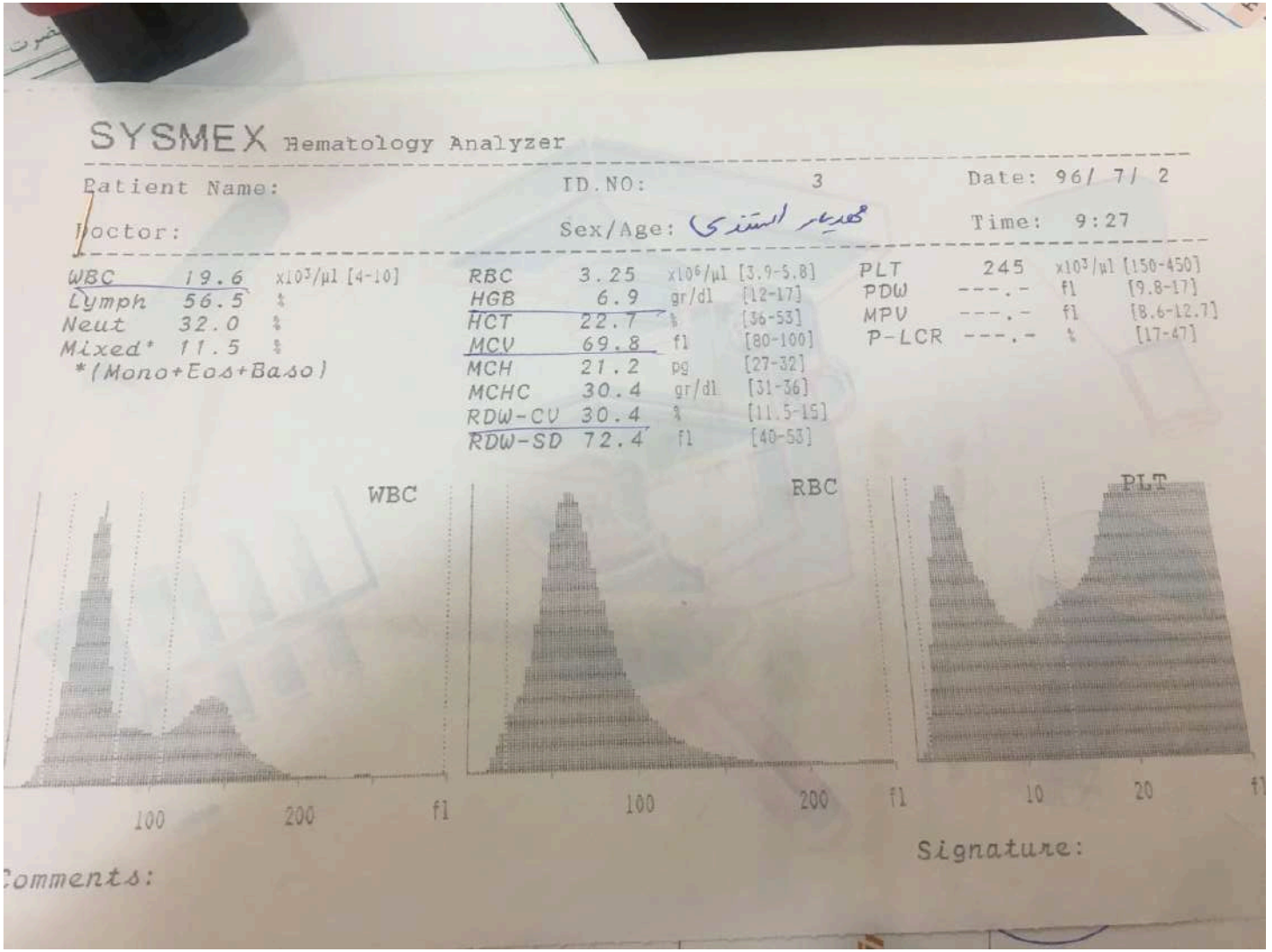
DDx of Microcytic, Hypochromic Anemia

- Iron Deficiency
- Alpha Thal
- Beta Thal
- Hb E Disease
- Anemia of Chronic Disease
- Sideroblastic Anemia
- Lead Poisoning

TABLE 20-8 Formulas for Differentiation of Thalassemia Trait from Iron Deficiency

	Thalassemia Trait	Iron Deficiency
Mentzer index (552)*		
MCV/RBC	<13	>13
Shine and Lal (562)		
(MCV) 2 × MCH	<1530	>1530
England and Fraser (563)		
MCV − RBC −(5 × Hb) − 8.4	Negative values	Positive values

*Numbers in parentheses are reference citations.
MCV, mean corpuscular volume; RBC, red blood cell.



SYSMEX Hematology Analyzer

Patient Name: ID.NO: 3 Date: 96/ 7/ 2

Doctor: Sex/Age: محمد استدي Time: 9:27

WBC	19.6	x10³/µl	[4-10]	RBC	3.25	x10⁶/µl	[3.9-5.8]	PLT 245 x10³/µl [150-450]
Lymph	56.5	%		HGB	6.9	gr/dl	[12-17]	PDW ---.- fl [9.8-17]
Neut	32.0	%		HCT	22.7	%	[36-53]	MPV ---.- fl [8.6-12.7]
Mixed*	11.5	%		MCV	69.8	fl	[80-100]	P-LCR ---.- % [17-47]
*(Mono+Eos+Baso)				MCH	21.2	pg	[27-32]	
				MCHC	30.4	gr/dl	[31-36]	
				RDW-CV	30.4	%	[11.5-15]	
				RDW-SD	72.4	fl	[40-53]	

WBC

100 200 fl

RBC

100 200 fl

PLT

10 20 fl

Comments:

Signature:

7 months/old/ male

Electrophoresis Systems 17. 4. 8

20 September 2017

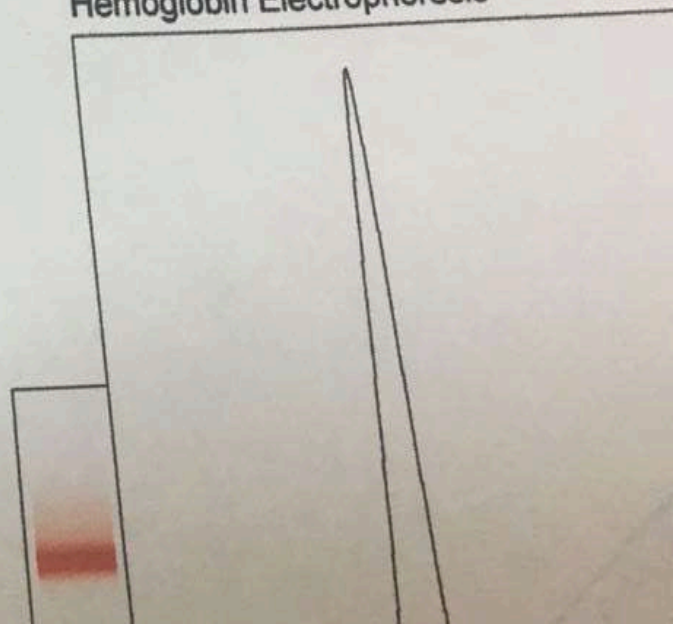
مهدیار استندی ۹۶_۶_۲۸

Name Mahdiar Estandi
Date of Birth **Age** 1 **Sex** M **ID Patient** 96-06-6023
Department

Strip 1 **Trace** 1 **Fractions** 3 **Scan(mm)** 51
Test Date 09/20/2017 **Strip Id:**

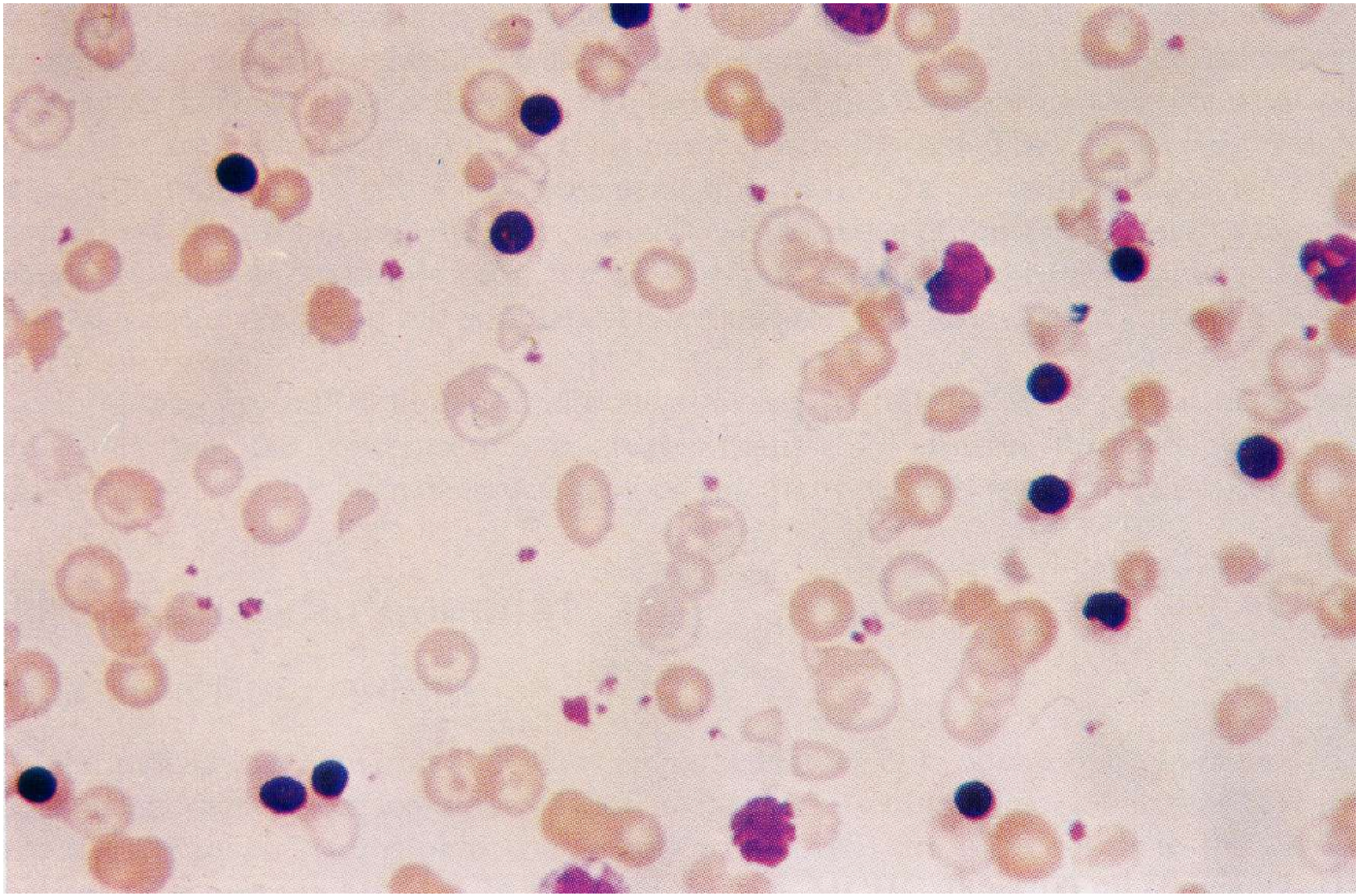
Fractions	%	% Normal	Conc.	Conc. Normal
HbA	96.9	96.0-98.0	7.3	0.0- 0.0
HbF	0.6	0.0- 2.0	0.0	0.0- 0.0
HbA2	2.5	1.5- 3.5	0.2	0.0- 0.0
Total Hb			7.5↑	0.0- 0.0

Hemoglobin Electrophoresis



Reviewed by:

Thalassemia major



sebia

آزمایشگاه بیمارستان حضرت علی اصغر (ع)

زاهدان - خیابان آزادی - تلفن: ۳۲۲۹۶۸۸

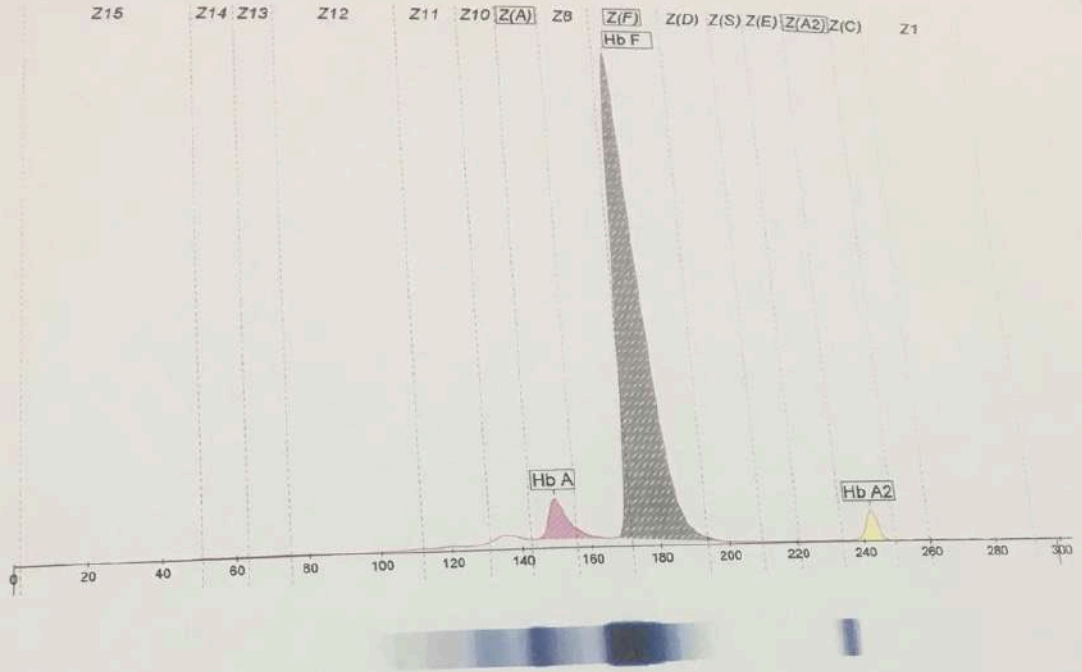
Name:
Mahdiyar Estandi

Date : 24/9/17

Sex:

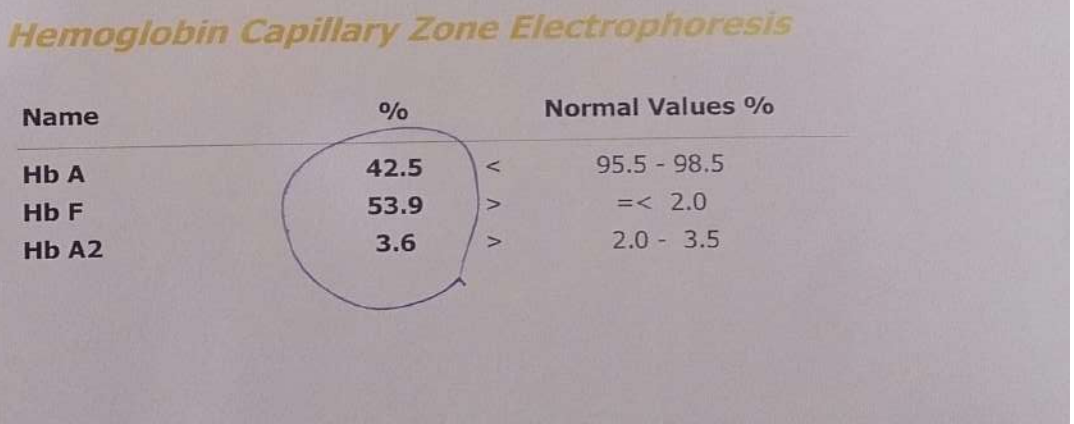
Age :

Sample # : 22



Hemoglobin Capillary Zone Electrophoresis

Name	%	Normal Values %
Hb A	5.5	
Hb F	91.8	
Hb A2	2.7	



4 yr/old female, splenomegaly(+), no history of blood Tx.

زمان چاپ:۱۳۹۹/۰۹/۲۴ - ۱۸:۵۲
آزمایشگاه بیمارستان علی اصغر(ع) زاهدان

کودك محمد ایوب یارمحمدزائي سن : ۱ سال تاریخ پذیرش: ۱۳۹۹/۰۹/۲۴ تاریخ جواب: ۱۳۹۹/۰۹/۲۵
کد : 99/33454 پزشك : جناب آقاي دکتر قاسم میری

Hematology

Hematology

CBC*

Test	Result	Units	Reference Range	Differential	Result
W.B.C	28.0 H	*1000/micL	4-10	Neutrophils	*00.0
R.B.C	3.51	Mil C/micL		Mixed Cell(Eos.Bas.Mono.)	*00.0
Hb	7.1	gr/dl		Lymphocyte	66.1
Hct	22.4	%			
M.C.V	63.8 L	fl	80-96		
M.C.H	20.2 L	pg	27-33		
M.C.H.C	31.7 L	gr/dl	33-36		
R.D.W	40.6 H	%	10-13.5		
Platelet	1156 H	*1000/micL	140 - 450		

Hematology

RDW_SD	*00.0	fl	37-54	
PDW	*00.0	fl	9-17	
MPW	*00.0	fl	9-13	
P-LCR	*00.0	%	13-43	

Comment : زمان تکمیل جواب 1399/09/24 18:52

Comment : L : Low H : High

آزمایشگاه بیمارستان

TOHID LABORATORY
Khayam Square,Ghadir St, Zahedan. Tel: 33446770

Name: **Anas Eim**

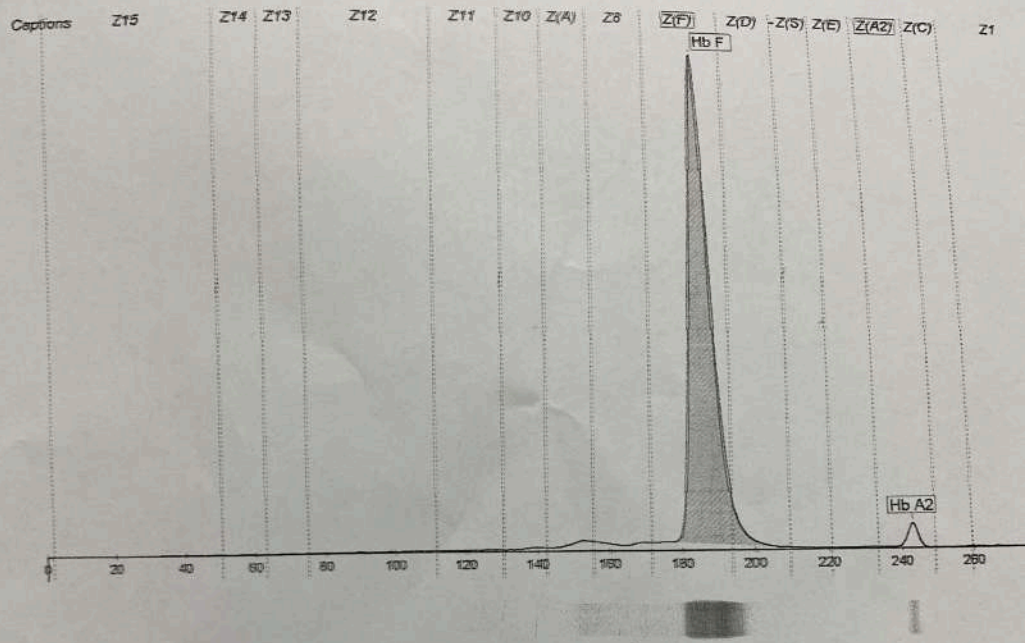
ID : **2033**

Sex: F

Sample Num: **12**

Date : **5/4/2020**

Haemoglobin Capillary Electrophoresis



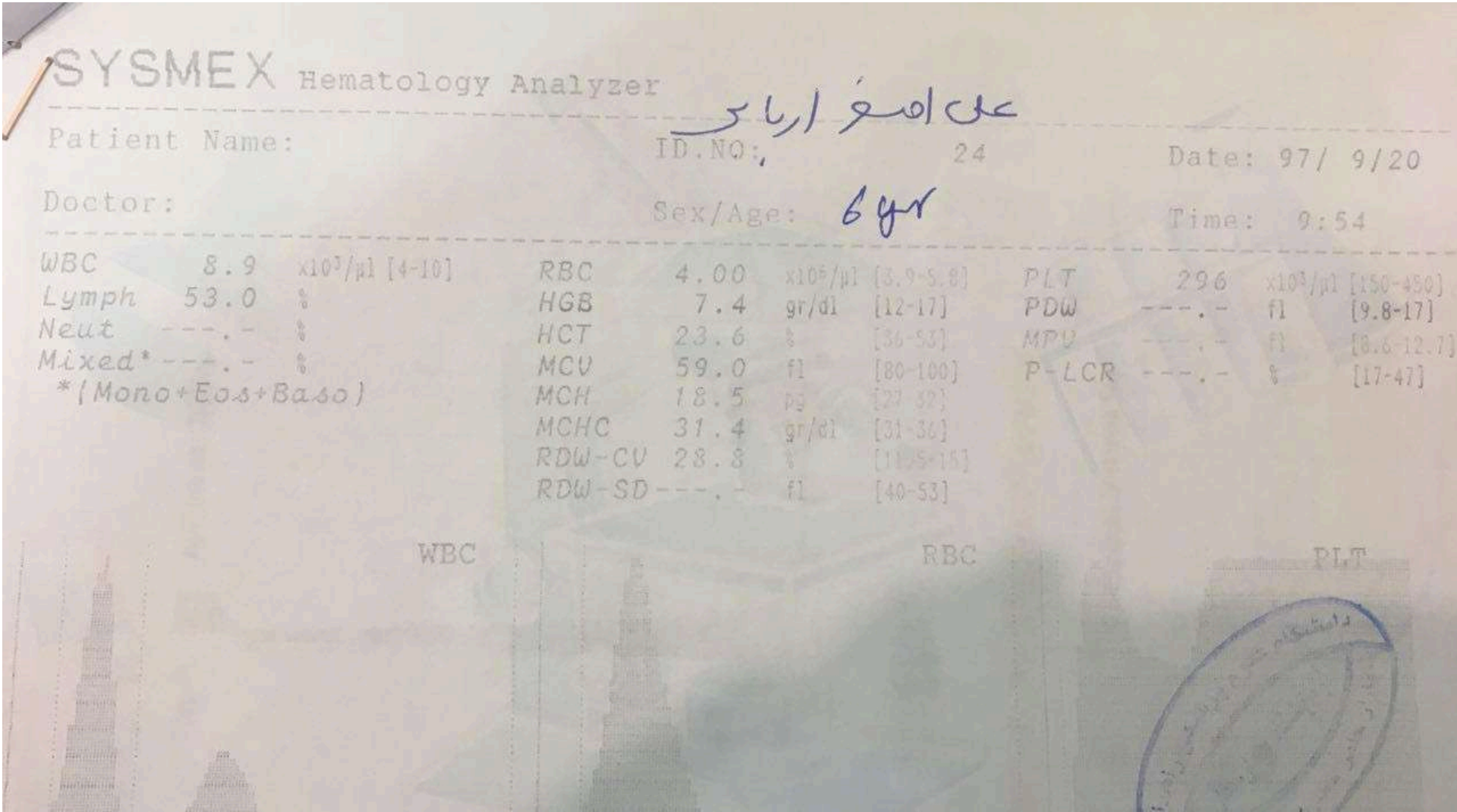
Name	%
Hb F	**97.6**
Hb A2	**2.4**

Normal Range (%)

Hb A	96.5 - 98.5
Hb F	<= 2
Hb A2	1.5 - 3.5

Comments:

6 years old boy, no history of Tx



آزمایشگاه بیمارستان علی اصغر(ع) زاهدان

آقای علی اصغر اربابی سن : ۶ سال تاریخ پذیرش: ۱۳۹۷/۰۹/۲۰ تاریخ جواب: ۱۳۹۷/۰۹/۲۲

کد: 97/33583 پزشک : جناب آقای دکتر

Hormone

Ferritin	325	ng/ml	ECL

Hormones and immunologic tests done by fuly automated electro chemiluminescence (ECL) cobase e 411

Comment : زمان تکمیل جواب 1397/09/20 13:26

Best regards,Dr saravani

sebia

آزمایشگاه بیمارستان حضرت علی اصغر (ع)

زاهدان - خیابان آزادی - تلفن: ۳۲۲۹۶۸۸

Name: Ali asghar Arbabi

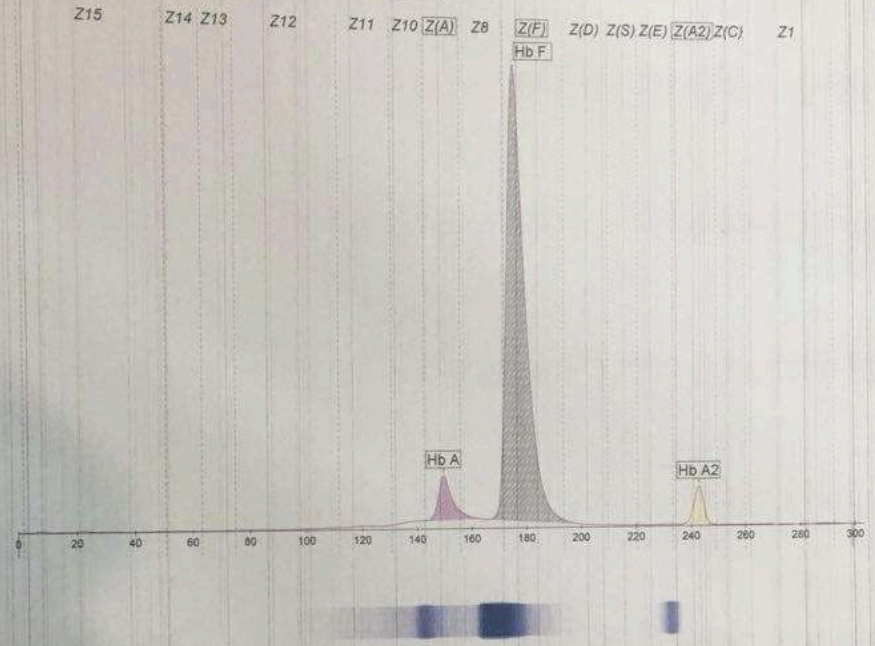
Rack: SEBIA Pos.: 7

Date : 11/12/18

Sex:

Age :

Sample # : 15



Hemoglobin Capillary Zone Electrophoresis

Name	%	Normal Values %
Hb A	6.6	
Hb F	89.4	
Hb A2	4.0	

Comment:

Treatment

- Transfusions
- Iron chelation
- Splenectomy
- Folic acid
- BMT

Course and treatment of thalassemia

Untreated

- β thalassemia Major :

  Death in first or second decade of life

- Intermedia: variable life span
- Minor/Minima: Normal life span

For deciding whom to transfuse

- **Confirmed laboratory diagnosis of thalassaemia major**
- **Laboratory criteria:**

  Hb < 7g/dl on 2 occasions, > 2 weeks apart (excluding all other contributory causes such as infections) or
- **Laboratory and clinical criteria, including:**

  Hb > 7g/dl with: - Facial changes - Poor growth - Fractures, and - Extramedullary haematopoiesis

Compatibility testing

- **Development of one or more specific red cell antibodies (alloimmunisation) is a common complication of chronic transfusion therapy**
- **Anti-E, anti-C and anti-Kell alloantibodies are the most common.**
- ***Before the first transfusion, patients should have extended red cell antigen typing that includes at least C, c, E, e and Kell***
- ***All patients with thalassaemia should be transfused with ABO and Rh(D) compatible blood***

بسمه تعالی

سازمان انتقال خون ایران

اداره کل منطقه ای آموزشی استان سیستان و بلوچستان

S&b Educational Regional Blood Transfusion Center

سازمان انتقال خون ایران

شماره: ۲۱۰/۳۲۹۷

تاریخ: ۹۶/۰۶/۲۷

پیوست:

همکار ارجمند جناب آقای دکتر میری علی آباد

باسلام

احتراماً نتایج آزمایش نمونه آقای حارث اقبالی قنبرزهی به شرح ذیل اعلام می گردد:

نام بیمار / متولد	ABO	Rh (D)	Antibody Screen result	DAT	
حارث اقبالی قنبرزهی	B	POS	-	Anti-IgG + Anti-C3d	-
1395				-	-
Auto Antibody				-	-

Patient phenotype	K	E	e	C	c	M	N	Fya	Fyb	JKa	JKb	S	s
	0	0	+	+	0	+	+	+	0	0	+	0	+

توضیحات مهم :

۱-در صورت نیاز به تزریق خون Crossmatch ABO&Rh compatible , c negative, E negative, K negative , Leukoreduced RBCs through AHG

۲- جهت ارسال نتیجه تائیدیه آزمایش فنوتیپ بیمار پیشنهاد می گردد سه ماه بعد یا قبل از تاریخ بعدی تزریق خون، بیمار به سازمان انتقال خون مراجعه فرماید.

پایگاه انتقال خون زاهدان
آزمایشگاه تشخیص طبی

از طرف

دکتر سهیلا خسروی

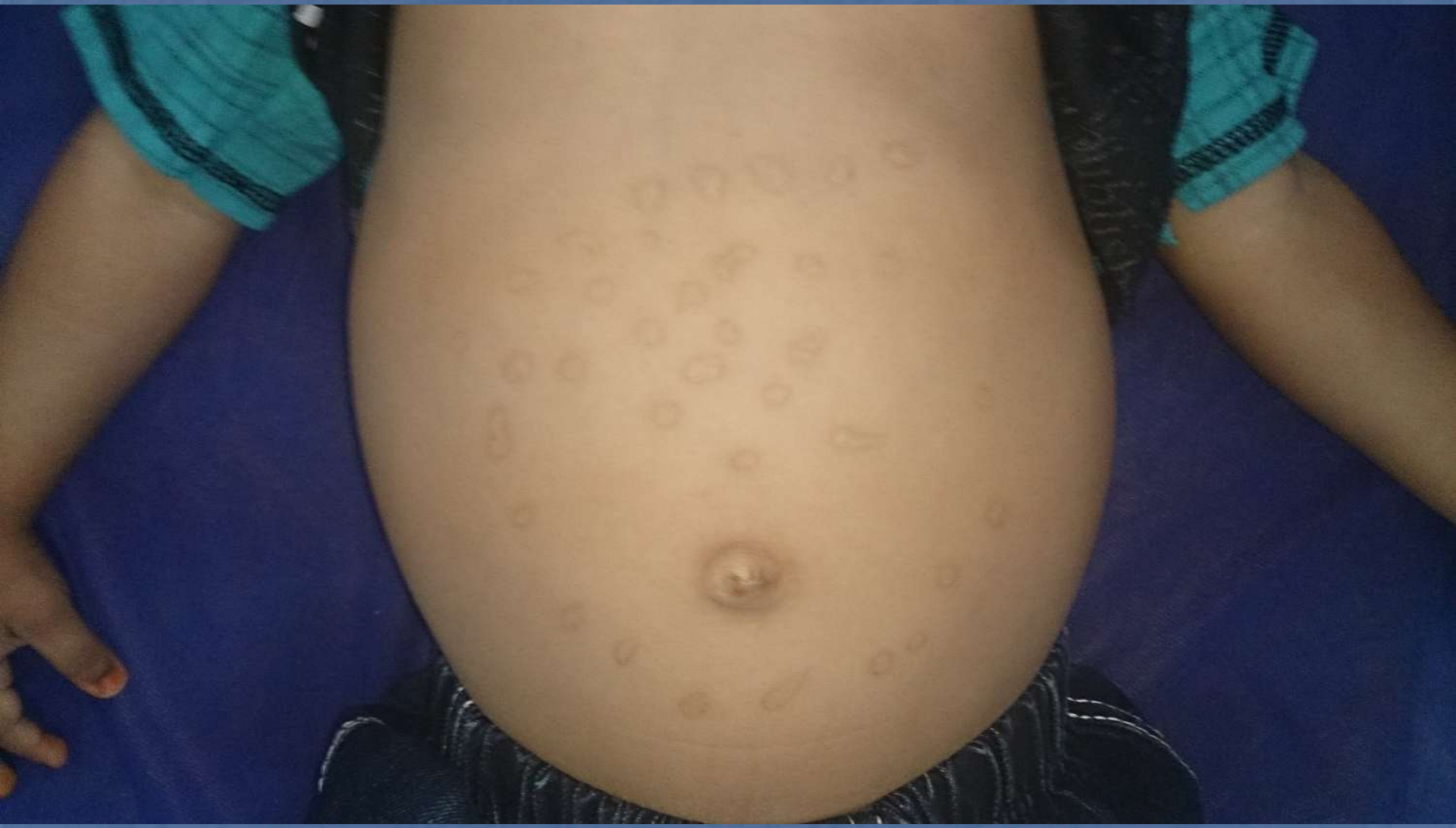
مدیرکل انتقال خون استان سیستان و بلوچستان

اهداء خون سالم اهداء زندگی

- the use of blood that is also **matched for the C, E and Kell antigens is highly recommended** in order to avoid alloimmunisation

- ***Before each transfusion it is necessary to perform a full crossmatch and screen for new antibodies***

- **Transfusion from first degree relatives should be avoided.**



What to transfuse

- Patients should receive transfusions of PRBC, preferably not more than 7 days old.

- **Patients should not be given packed red cells more than two weeks old.**

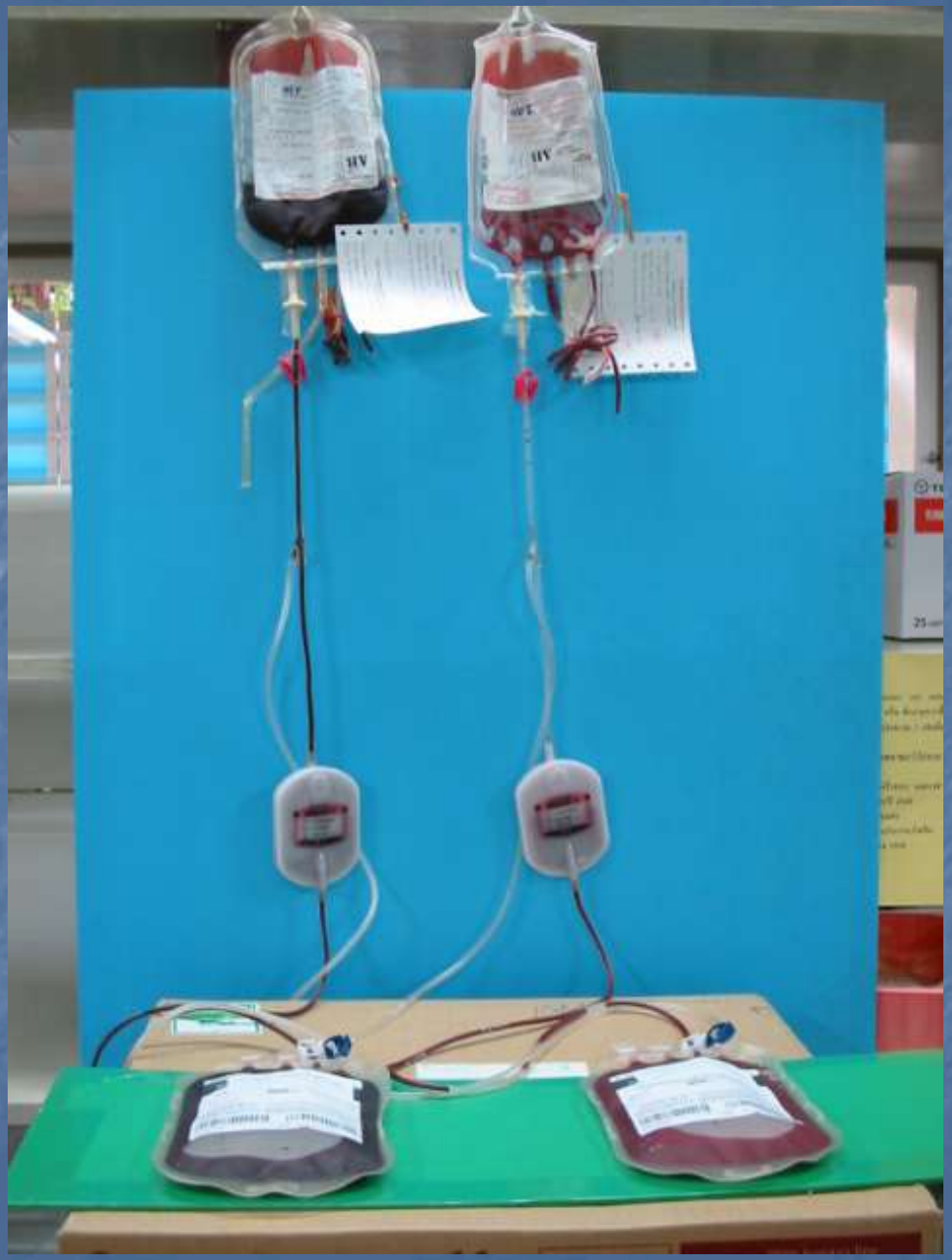
Transfusion programmes

- *The recommended treatment: lifelong regular blood Tx, usually every 2-5 weeks, to maintain the pre-Tx Hb level above 9-10.5 g/dl.*

- *The rate of fall in levels of Hb, which should not exceed 1g/dl/week in splenectomised patients and 1.5g/dl/week in non-splenectomised patients.*

Recommended blood product

- *Patients with TM should receive **leucoreduced** packed RBC*



Increased transfusion requirements

1) *Alloimmunisation(Alloantibody)*
2) *Autoantibody*
3) *Hypersplenism*
4) *Poor quality blood(eg. Low HCT)*
5) *Infection(eg. HPV-B19)*
6) *Bleeding*
7) *Use of medication (e.g. ribavirin)*

- A higher target pre-transfusion Hb level of 11-12 g/dl may be appropriate for patients with heart disease or other medical conditions and for those patients with inadequate suppression of bone marrow activity at the lower Hb level.

- ***The post-transfusion Hb should not be greater than 14-15g/dl***

Blood products for special patient populations

- **Washed red cells**

to remove the maximum amount of plasma and proteins.

they usually have to be used within 24 hours.

- **Frozen RBC**
- **Irradiated RBC**

Indications for regular Tx in TI

- Growth failure
- Cosmetic facial abnormalities
- Bone abnormalities
- Massive splenomegaly
- Hypersplenism
- Progressive anemia, fatigue
- Cardiopulmonary complications

transfusion reactions

- *Acute reactions*
- *Hemolytic(Intravascular)(AHTR)*
- Febrile non hemolytic transfusion reactions
- Anaphylactic transfusion reactions
- Allergic reactions
- Transfusion Related Acute Lung Injury(TRALI)
- *Delayed reactions*
- *Hemolytic(Extravascular), DHTR*
- Post-transfusion purpura(PTP)
- GVHD
- Transfusion associated circulatory overload (TACO)
- Iron Overload
- Infectious Complications

Acute Hemolytic Transfusion Reaction

complications

Usually due to iron overload

- Cardiac complications
- Liver disease
- Endocrine dysfunction (diabetes,hypothyroidism, hypoparathyroidism, growth retardation, hypogonadism
- Failure of compliance with chelation regimen
- Spontaneous bone fractures
- hyprsplenism
- Extra-medullary hematopoesis
- Gallstones
- Leg ulcers
- Blood born infections (HIV, Hepatitis, etc)
- Transfusion reactions (errors)

Iron Loading From Blood Transfusions

- 1 unit of blood contains approximately 200 mg of iron
  - Normally, total body iron is approximately 3 to 4 g
  - Chronic transfusion-dependent patients have an iron excess of 0.3 to 0.7 mg/kg/day, equivalent to 4 to 10 g of iron per year
- Iron accumulates with repeated blood transfusion

Initiation of Therapy for Iron Overload

- Chelation treatment is generally initiated after 10 to 20 transfusions or when serum ferritin > 1000 µg/L

- Alternatively, if iron loading is unclear, LIC may be measured

3 major classes of iron chelators:

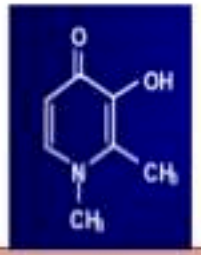
❖Hexadentate (deferoxamine [DFO], Desferal), in which 1 atom of iron is bound to 1 DFO molecule

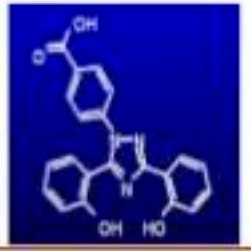
❖bidentate (deferiprone, L1 [DFP]), in which 1 atom of iron is bound to 3 DFP molecules

DFP (L1) is a synthetic compound originally identified in the 1980s in London, hence the designation L1

tridentate (deferasirox [DFX], Exjade), in which 1 atom of iron is bound to 2 DFX molecules,
DFX , approved in 2005 for use in transfusional overload patients

Iron Chelators

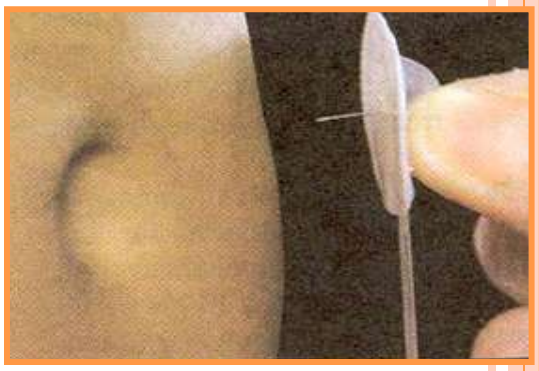


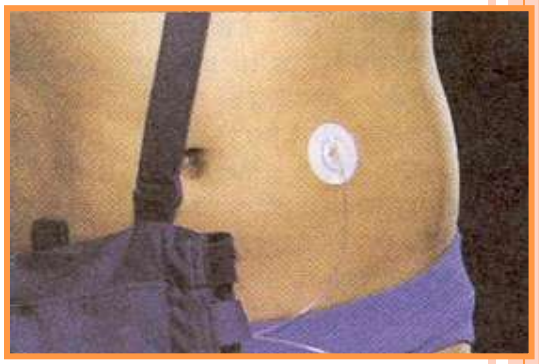


	Deferoxamine	Deferiprone	Deferasirox
Brand Name	**Desferal**	**Ferriprox**	**Exjade**
Half-life	20 minutes	2-3 hours	8-16 hours
Route	SQ, IV infusion	PO	PO
Dose (mg/Kg/d)	20-60	75-100	20-40
Frequency	5-7 days/week	3 times daily	Once daily
Iron Excretion	Urine/Stool	Urine	Stool
Side Effects	Vision, Hearing, Growth, Local Reactions, Allergy	Gastro-intestinal symptoms, Kidney dysfunction, Hepatitis	Gastrointestinal symptoms, agranulocytosis/ neutropenia, Arthralgia

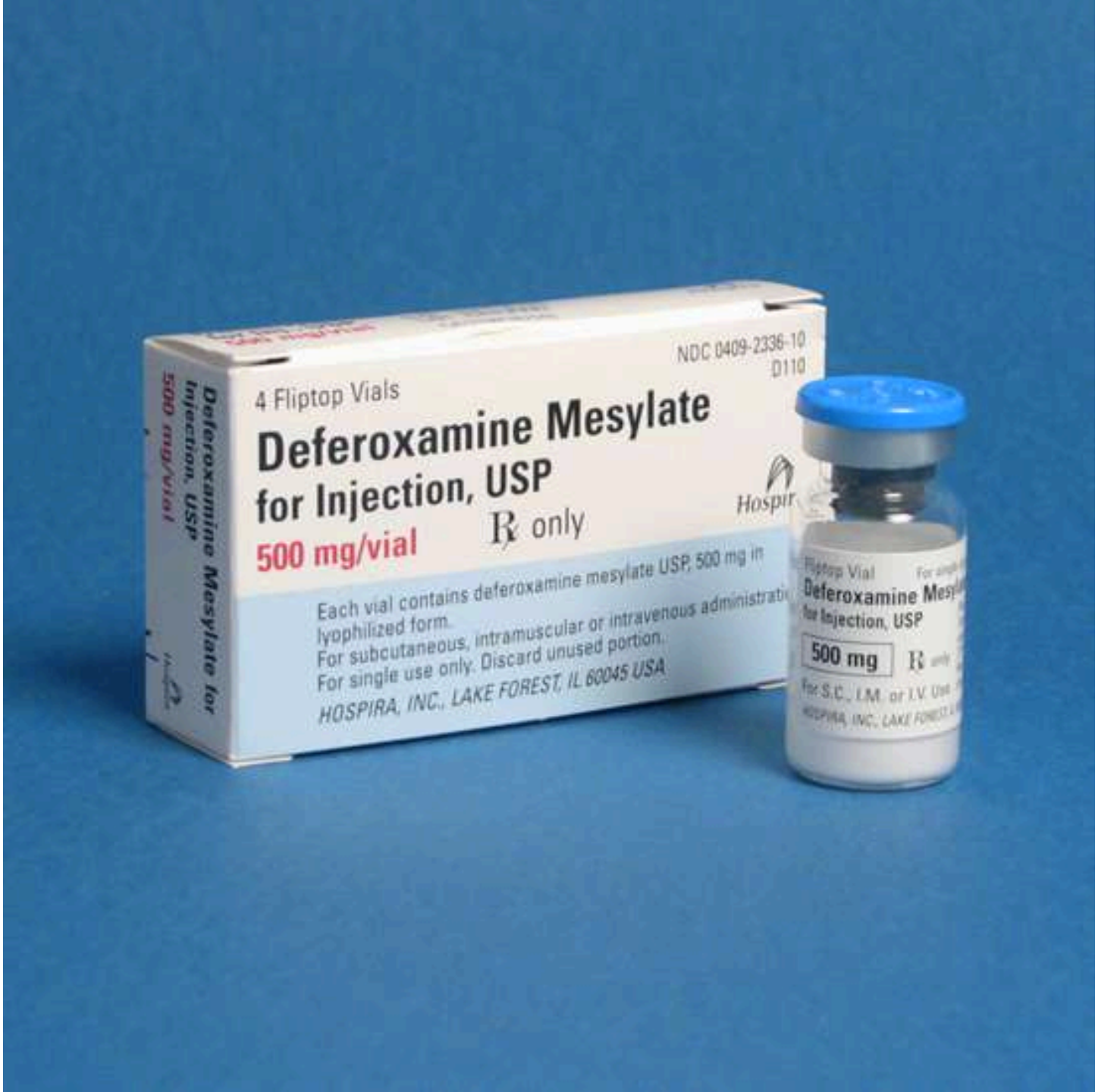
DESFERRIOXAMINE

- Clinical use: Since 1970's
- Available for > 4 decades with improving survival
- not absorbed from gut
- Short half-life (20 min), so must be given by continuous infusion
  - 8 –12 h/d, 5 – 7 d/w (40–50 mg/kg SC)
- Commenced after 10–20 transfusions or when ferritin >1000 µg/L
- Audiometric, retinopathic, and growth effects at high doses and low iron loading
- Compliance often is poor, leading to variable outcome





Courtesy of Dr. J. Porter


4 Fliptop Vials
Deferoxamine Mesylate
for Injection, USP
500 mg/vial
℞ only
NDC 0409-2336-10
D110
Each vial contains deferoxamine mesylate USP, 500 mg in
lyophilized form.
For subcutaneous, intramuscular or intravenous administrati
For single use only. Discard unused portion.
HOSPIRA, INC., LAKE FOREST, IL 60045 USA
Deferoxamine Mesylate for
Injection, USP
500 mg/vial
Fliptop Vial
Deferoxamine Mesyl
for Injection, USP
500 mg
℞
For S.C., I.M. or I.V. Use

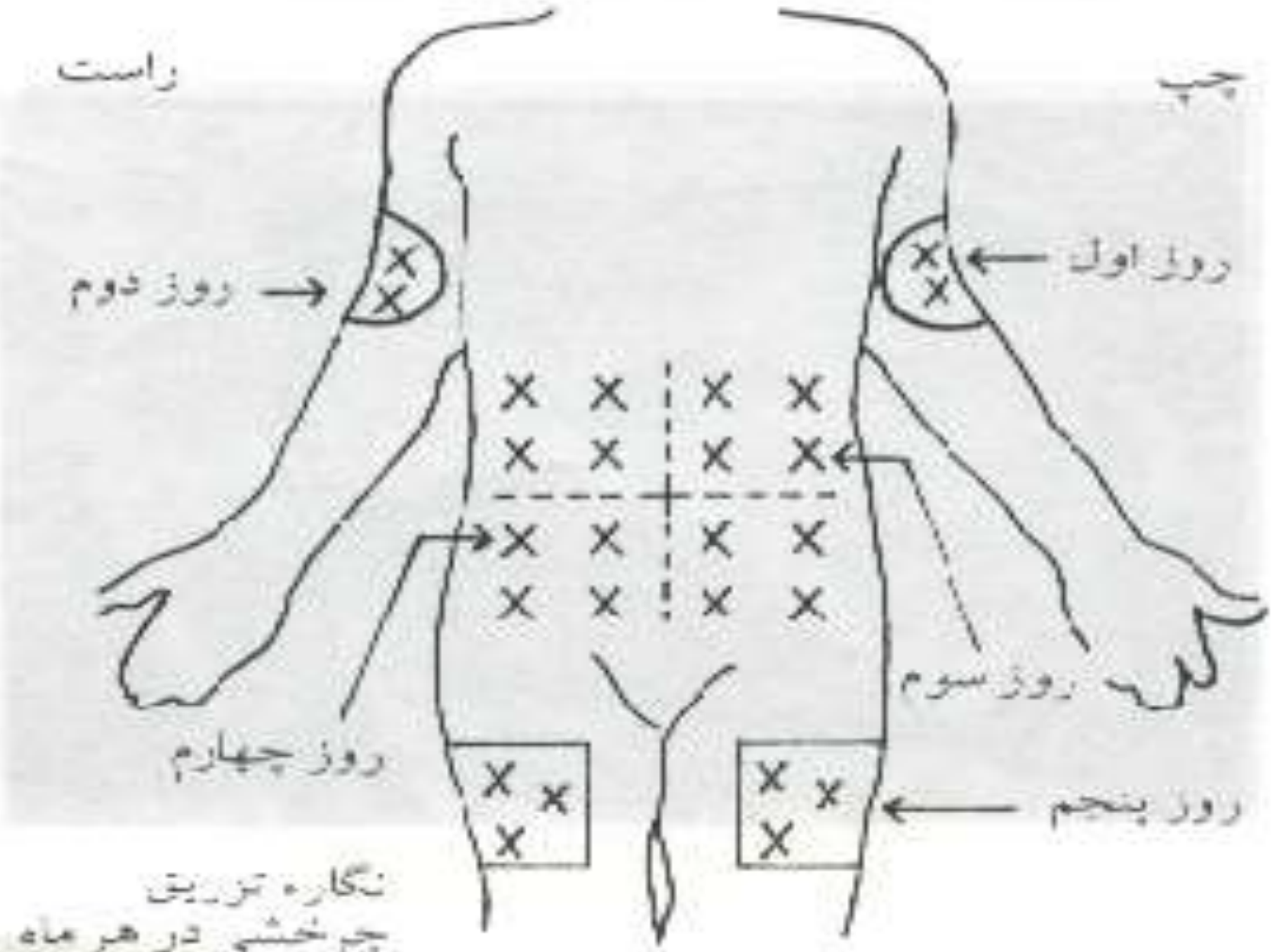
Side Effects of Desferrioxamine

- Retinopathy , night blindness, colour vision, visual field, Visual Acuity
- Ototoxicity : high frequency SNL, tinnitus, deafness
- CNS, coma
- Growth retardation

- Bony changes
- Yersinia infection
- Sensitivity

Toxicity of deferoxamine

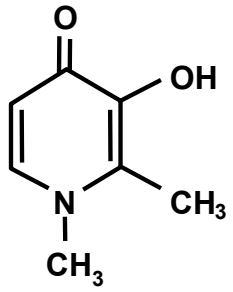
- Local erythema ,painful subcutaneous nodule at infusion site
- Allergic reaction
- Neurosensory toxicity
  - high frequency hearing loss
  - night & color blindness
- Cartilagenous dysplasia: interfere linear growth



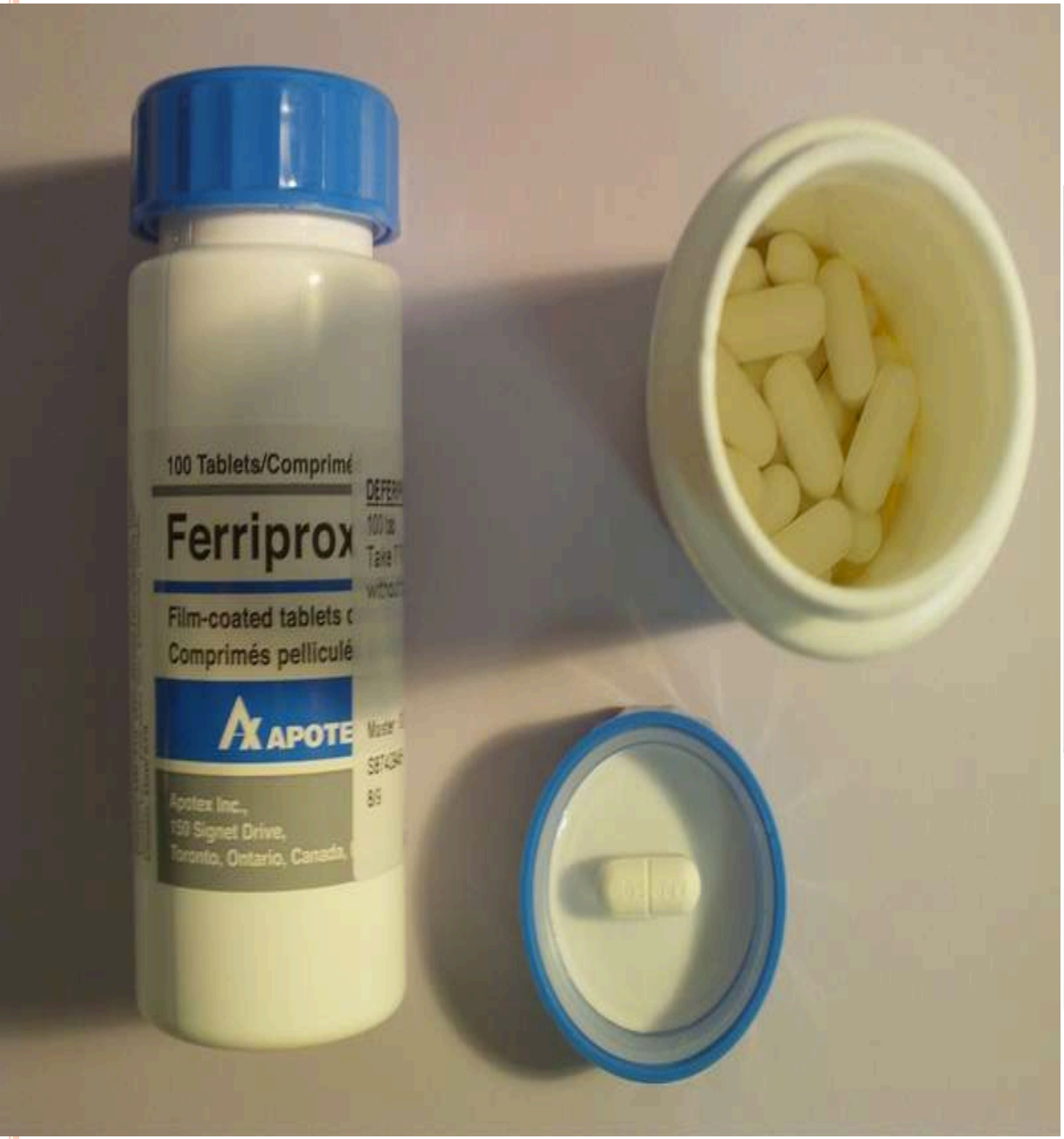
نگاره تزریق
چرخشی در هر ماه

Deferiprone

- History
  - Patented 1982; licensed in EU 1999
- Pharmacology
  - Bidentate, short plasma half-life — given TID
  - Urine excretion
- Efficacy
  - Indicated for *treatment of iron overload in patients with thalassaemia major when desferrioxamine therapy is contraindicated or inadequate*
  - May be less effective than desferrioxamine in reducing LIC
  - Possible cardioprotective effect
- Side effects
  - Neutropaenia/agranulocytosis (weekly neutrophil count recommended)
  - Nausea, vomiting, abdominal pain
  - Arthralgia and arthritis



EU = European Union; LIC = liver iron concentration.


100 Tablets/Comprimé
Ferriprox
Film-coated tablets
Comprimés pelliculé
APOTEX
Apotex Inc.,
150 Signet Drive,
Toronto, Ontario, Canada


Rx only
Ferriprox®
(Deferiprone) Tablets
500 mg
Attention Pharmacist: Dispense the accompanying Medication Guide to each patient.
100
Tablets

DEFERIPRONE: *SUMMARY*

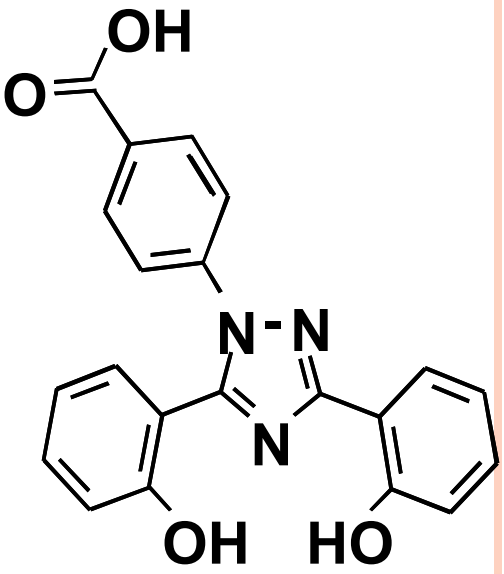
- **Advantages**
  - Orally active
  - Enhanced removal of cardiac iron
  - Increased effectiveness when combined with desferrioxamine
- **Disadvantages**
  - Short plasma half-life and rapid inactivation by metabolism
  - Administered 3 times daily—may negatively impact patient compliance and outcome
  - May not achieve negative iron balance at 75 mg/kg/day
  - Risk of agranulocytosis and need for weekly blood counts

Effects of Monotherapy and Combined Therapy

- DFO 40 mg/kg/d given at night
  - No protection during the day
- DFP 75 mg/kg/d given during the day
- DFO 40mg/kg/d given at night + DFP 75 mg/kg/d given during the day
  - Provides 24 hour protection

Deferasirox (Exjade, Osveral, Deferazex, Jadenu, Nanojade, Avesirox)

- Half-life of 8 to 16 hours supports once-daily dosing
- Primarily excreted in faeces
- Given as once-daily drink




OSVERAL® 500
Deferasirox
84 Dispersible Tablets
OSVERAL® 250
Deferasirox
84 Dispersible Tablets
Each tablet contains:
Deferasirox 250 mg
The tablet must not be chewed or swallowed whole.
OSVERAL® 125
Deferasirox
84 Dispersible Tablets
Each tablet contains:
Deferasirox 125 mg
Keep in the box, below 30°C and protect from moisture and light.
Keep out of the reach of children.
Disperse each tablet in a glass of water, orange or apple juice and shake it with a plastic spoon until you have a suspension, drink at least 30 minutes before meal.
The tablet must not be chewed or swallowed whole.
See enclosed leaflet for more information.
OSVAH Pharmaceutical Co. Tehran-Iran
www.osveral.com


نانوجید۱۰
نانوجید۱۸۰
نانوجید۲۱۰

Initial Dosing

- Initiate therapy after the transfusion of approximately 20 U (equivalent to 100 mL/kg) of PRBC or when there is evidence from clinical monitoring that iron overload is present (e.g., the serum ferritin level is > 1000 µg/L)

- The recommended initial daily dose is 20 mg/kg

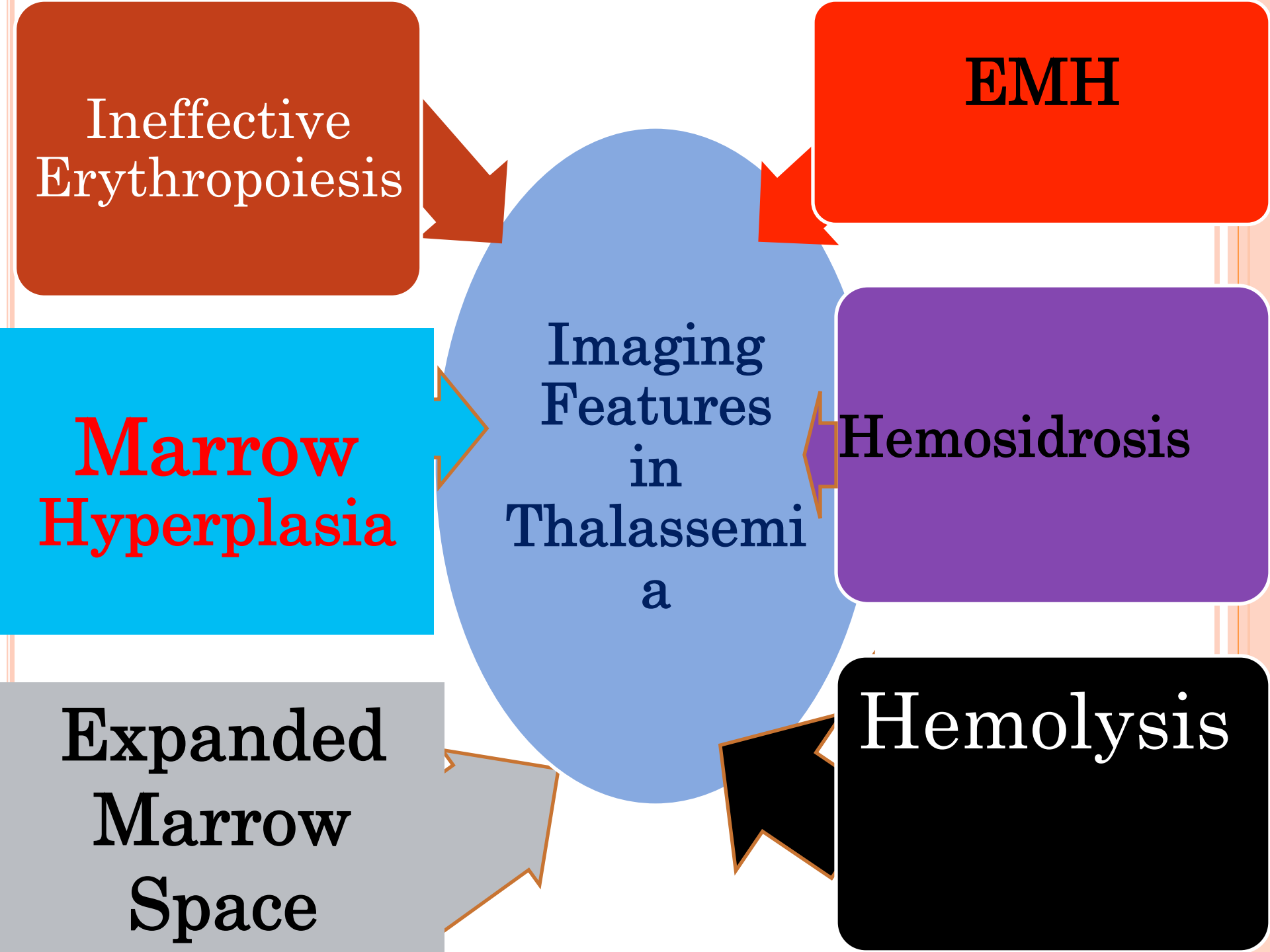
- An initial daily dose of 30 mg/kg may be considered for patients with severe iron overload (e.g., serum ferritin > 2500 µg/L)

Side effects

- GI side effects
- Skin rash
- increases in serum Cr
- increases in transaminases
- Proteinuria

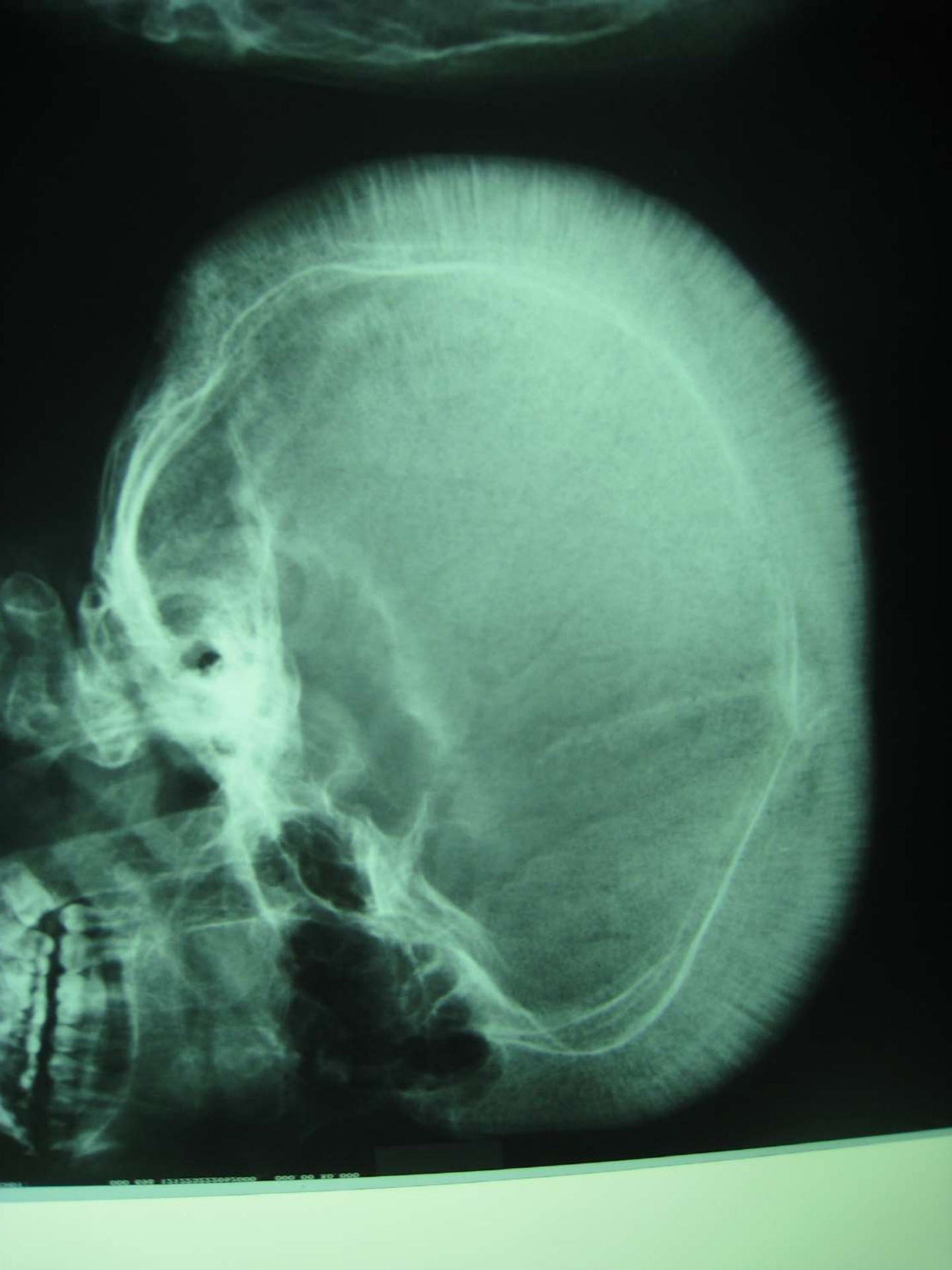
Monitoring of Therapy

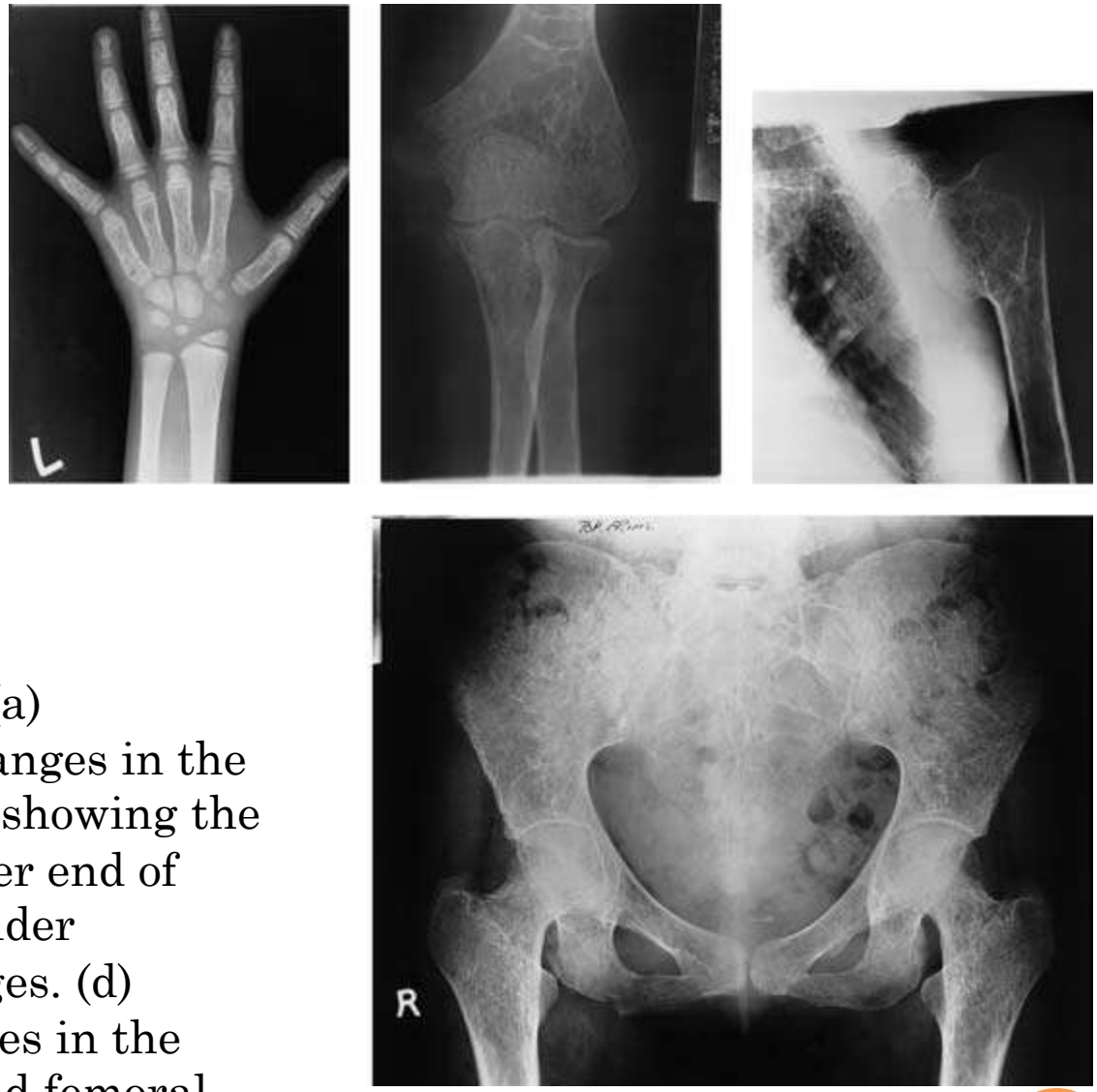
- Ferritin: monthly
- Bun, Cr: monthly
- AST, ALT: monthly
- Urine Random Pro/Cr: monthly


Ineffective Erythropoiesis
EMH
Marrow Hyperplasia
Imaging Features in Thalassemia
Hemosidrosis
Expanded Marrow Space
Hemolysis

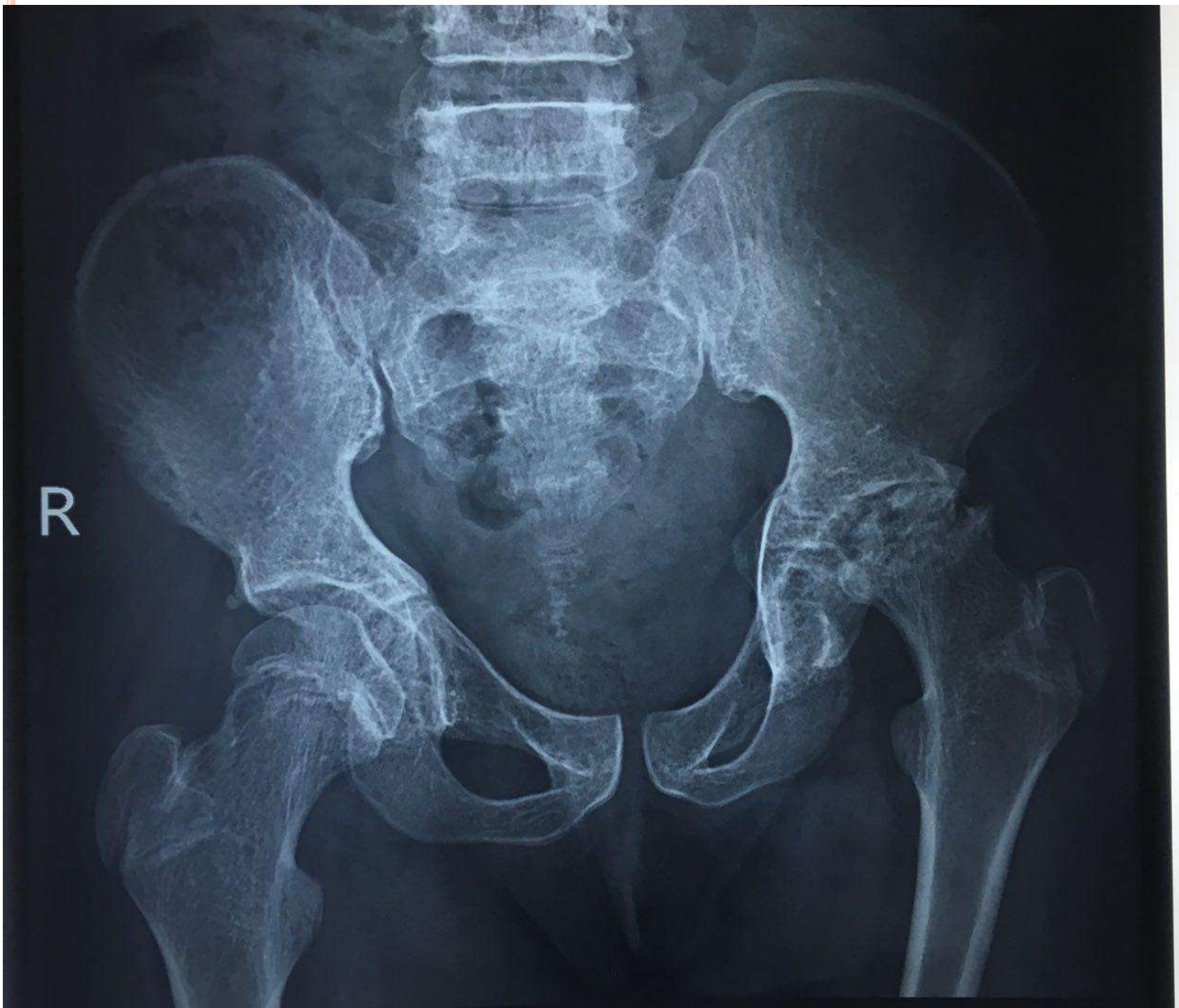
Skeletal Imaging Features in Thalassemia

- Osteoporosis
- Expansion of marrow space
- EMH
- Fracture





Radiological changes in b thalassaemia intermedia. (a) Moderate thalassaemic changes in the hands. (b) The right elbow showing the lacy appearance of the lower end of the humerus. (c) Left shoulder showing severe bone changes. (d) Pelvis showing bone changes in the upper end of the femora and femoral necks and the lacy appearance of the pelvic bones.



18 YR/ OLD GIRL

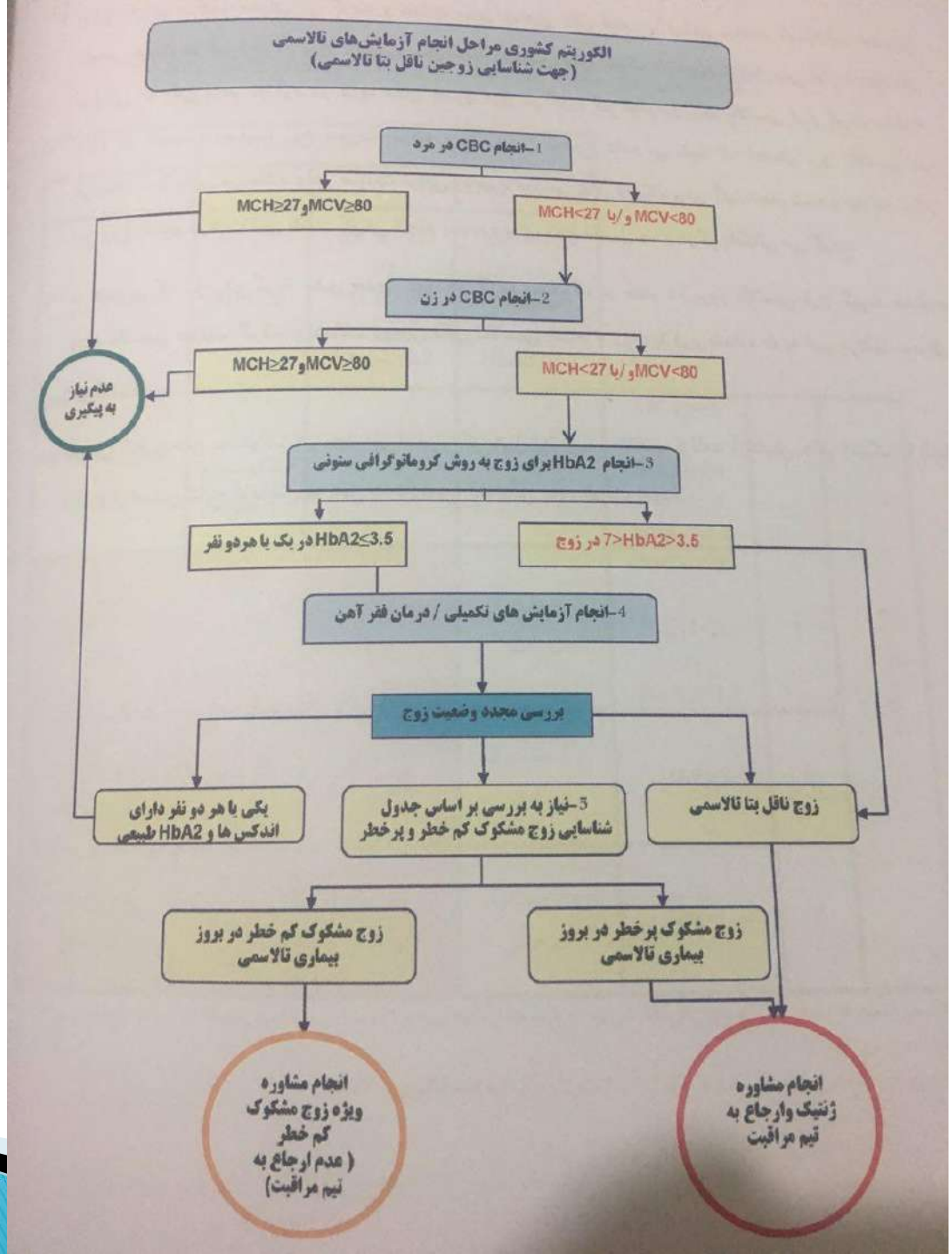
Screening

- CBC to look for MCV and MCH
  - Will be reduced in both thalassemias (microcytic anemia)

- Hb Electrophresis to look for A_2: Will be elevated in B-thal, normal on A-thal. May also be elevated in HbS

Screening

- Hb Electrophresis may also identify abnormal hemoglobins
  - Structural Hb Variants
  - Some Hb Bart's or Hb H
  - Won't find unstable variants except in exceedingly small quantities – may be missed
- Iron studies to rule out iron deficiency


الگوریتم کشوری مراحل انجام آزمایش‌های تالاسمی
(جهت شناسایی زوجین ناقل بتا تالاسمی)
1-انجام CBC در مرد
MCH≥27و MCV≥80
MCH<27 و/یا MCV<80
2-انجام CBC در زن
عدم نیاز به پیگیری
MCH≥27و MCV≥80
MCH<27 و/یا MCV<80
3-انجام HbA2 برای زوج به روش کروماتوگرافی ستونی
HbA2≤3.5 در یک یا هردو نفر
7>HbA2>3.5 در زوج
4-انجام آزمایش های تکمیلی / درمان فقر آهن
بررسی مجدد وضعیت زوج
یکی یا هر دو نفر دارای اندکس ها و HbA2 طبیعی
3-نیاز به بررسی بر اساس جدول شناسایی زوج مشکوک کم خطر و پرخطر
زوج ناقل بتا تالاسمی
زوج مشکوک کم خطر در بروز بیماری تالاسمی
زوج مشکوک پرخطر در بروز بیماری تالاسمی
انجام مشاوره ویژه زوج مشکوک کم خطر (عدم ارجاع به تیم مراقبت)
انجام مشاوره ژنتیک وارجاع به تیم مراقبت

جدول شناسایی زوج مشکوک کم خطر و پرخطر در بروز بیماری بتا تالاسمی ماژور

خصوصیات زن		جدول الف	خصوصیات مرد ۱	۲	۳	۴
			MCV≥75 و MCH≥26 و HbA2≤3.2	MCV<75 و/یا MCH<26 و/یا HbA2>3.2	HbF≥3	ناقل بتا تالاسمی
۱	MCV≥75 و MCH≥26 و HbA2≤3.2		زوج مشکوک کم خطر	زوج مشکوک کم خطر	زوج مشکوک کم خطر	*زوج مشکوک کم خطر
۲	MCV<75 و/یا MCH<26 و/یا HbA2>3.2		زوج مشکوک کم خطر	زوج مشکوک پر خطر	زوج مشکوک پر خطر	زوج مشکوک پر خطر
۳	HbF≥3		زوج مشکوک کم خطر	زوج مشکوک پر خطر	زوج مشکوک پر خطر	زوج مشکوک پر خطر
۴	ناقل بتا تالاسمی		*زوج مشکوک کم خطر	زوج مشکوک پر خطر	زوج مشکوک پر خطر	**زوج ناقل تالاسمی

*در این قسمت در صورتی که مرد یا زن ناقل تالاسمی بوده و طرف مقابل سابقه بیماری تالاسمی در خویشاوندان نزدیک داشته باشد زوج بعنوان پرخطر طبقه بندی می گردد.

** زوج ناقل تالاسمی هستند که قبلا در مراحل ۳ و ۴ الگوریتم برای آنها تصمیم گیری شده است.

CBC و الکتروفورز یک زوج قبل از ازدواج را مشاهده کنید

آقا: RBC: 6.9, Hb:15, MCV: 72, MCH: 22

Hb A: 65%, A2: 3%, F:1%, S: 31%

خانم: RBC: 5.09, Hb:11.5, MCV:79, MCH:23

Hb A: 95.8%, A2: 3.7%, F: 0.5

الف تشخیص هر کدام از زوجین چیست؟

ب چه توصیه برای ازدواج این دو فرد دارید

ج فرزندان این زوج به چه اختلالاتی ممکن است مبتلا شوند(با درصد ذکر شود)

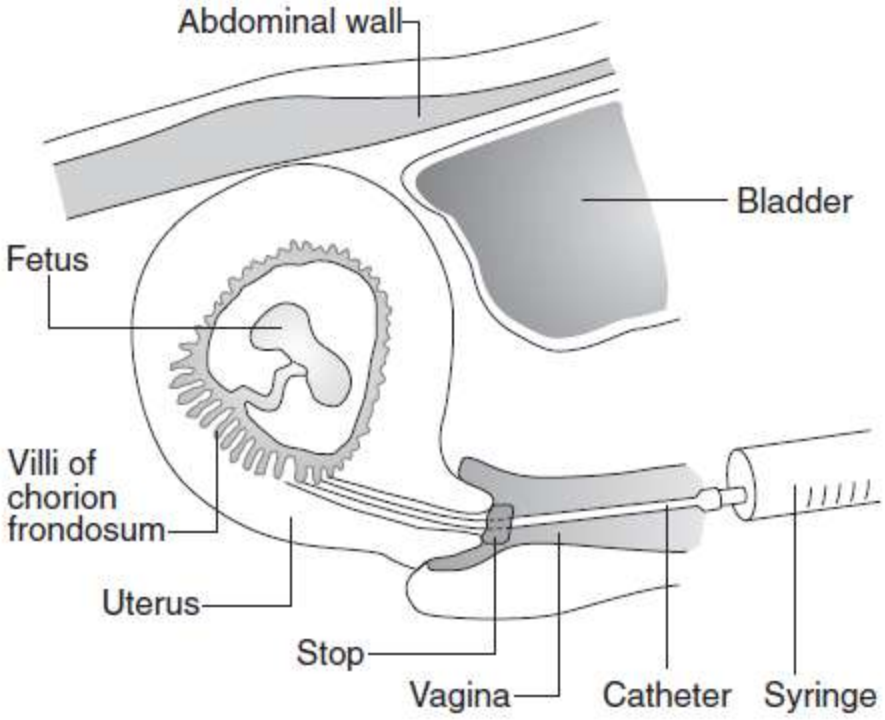
Mutation Identification

- Not usually a diagnostic tool. You can narrow down the diagnosis well with non-molecular blood testing, smears, etc.
- Necessary for prenatal diagnosis
- Helpful in estimating severity

Options for couples at risk for having a child with a severe form of thalassaemia

- Avoid pregnancy
- Adoption
- Risk having an affected child
- Prenatal diagnosis: termination if fetus is affected
- Pre-implantation diagnosis
- Use of egg or sperm donor with normal globin genotype

Chorionic villus sampling



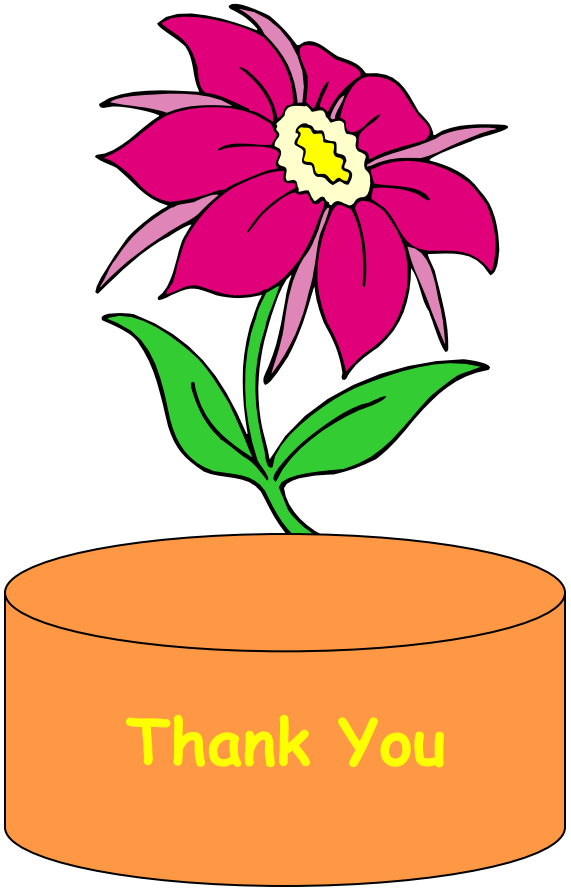
Some characteristic findings in the genetic interactions between b thalassaemia, db thalassaemia or hereditary persistence of fetal haemoglobin (A) and the common b-chain variants (B)

(A)

Thalassaemia type	Homozygote	Heterozygote
β^0 thalassaemia	Thalassaemia major: HbF 98%; HbA_2 2%; no HbA	Thalassaemia minor: HbA_2 3.7–7.0%; HbF 1–3%; α/β 2.0
β^+ thalassaemia (severe)	Thalassaemia major: HbF 70–95%; HbA_2 2%; trace of HbA	Thalassaemia minor: HbA_2 3.7–7.0%; HbF 1–3%; α/β 2.0
Mild β^+ thalassaemia	Thalassaemia intermedia to thalassaemia major: HbF 20–80%; HbA_2 2–5%	Thalassaemia minor: HbA_2 3.5–7.0%; α/β 1.5–2.0
'Silent' β thalassaemia	Asymptomatic to mild thalassaemia intermedia: HbF 10–30%; HbA_2 2–5%	Usually 'silent': HbA_2 3.3–3.5%; α/β 1.2–1.5
Normal HbA_2 β^+ or β^0 thalassaemia	Thalassaemia major: HbA_2 absent to trace; HbF 95–100%; HbA absent to trace	Thalassaemia minor: HbA_2 normal; HbF 1–3%; α/β 2.0
Deletion HPFH	Asymptomatic; normal to increased Hb levels with mildly hypochromic microcytic red blood cells; HbF 100%; α/γ ~ 1.5	Mild anaemia; normal RBC indices; HbA_2 normal; F-cell distribution–pancellular
Non-deletion HPFH	Asymptomatic; normal Hb levels with normal red blood cell indices; HbF 20–40%; HbA_2 1–1.5%; α/non-α ~ 1.2	Normal to mild anaemia; borderline red blood cell indices; HbA_2 normal; F-cell distribution–pancellular
δβ thalassaemia	Mild anaemia to thalassaemia major: hypochromic microcytic red blood cells; HbF 100%; α/γ 2.5–5.0	Mild anaemia; hypochromic microcytic red blood cells: HbA_2 normal; HbF 5–20%; F-cell distribution–heterocellular
Hb Lepore	Severe thalassaemia intermedia to thalassaemia major: HbF 80%; Hb Lepore 20%	Thalassaemia minor: Hb Lepore 8–20%; HbF 2–4%

Some characteristic findings in the genetic interactions between b thalassaemia, db thalassaemia or hereditary persistence of fetal haemoglobin (A) and the common b-chain variants (B)

(B)		
HbS/β^0 thalassaemia	Sickle-cell anaemia	HbS 75–100%; HbF 0–20%; HbA_2 4–6%; no HbA
HbS/β^+ thalassaemia (severe type)	Sickle-cell anaemia	HbS 50–80%; HbF 0–20%; HbA 10–30%; HbA_2 4–6%
HbS/β^+ thalassaemia (mild type)	Sickle-cell trait	HbS 50–65%; HbA ~ 25%; HbA_2 4–6%; HbF ~ 5%
HbE/β^0 thalassaemia	Thalassaemia intermedia to thalassaemia major	HbE 30–40%; no HbA, rest HbF
HbE/β^+ thalassaemia	Thalassaemia intermedia to thalassaemia major	HbE 50–70%; HbF 15–30%; HbA trace to 10%


Thank You