HAEMOGLOBINOPATHIES

DR. SHIHAB AL-MASHHADANI
Consultant Haematologist
Head of Haematology Division
Department of Pathology

HAEMOGLOBINOPATHIES

A - THALASSAEMIAS

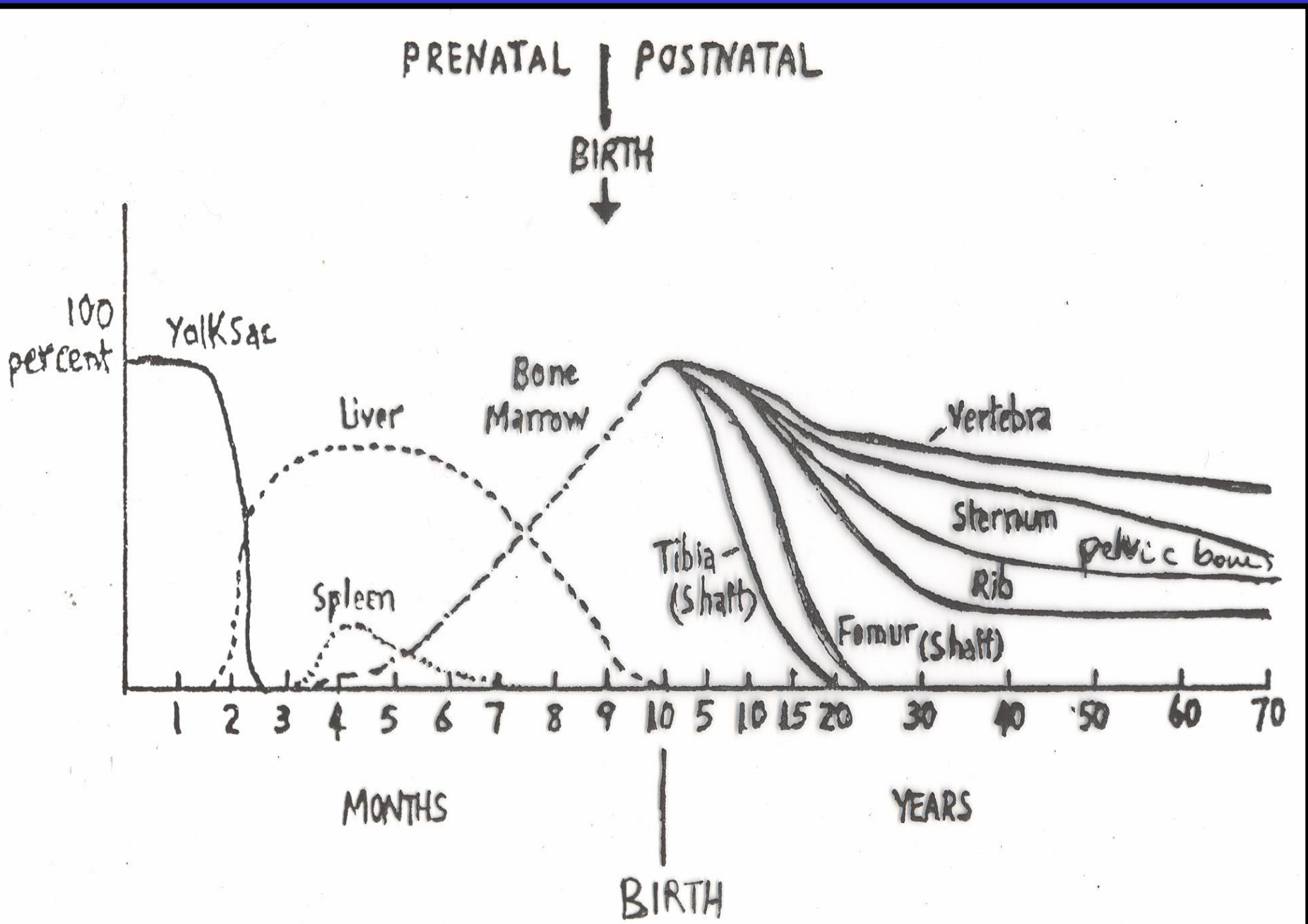
B - ABNORMAL HAEMOGLOBINS

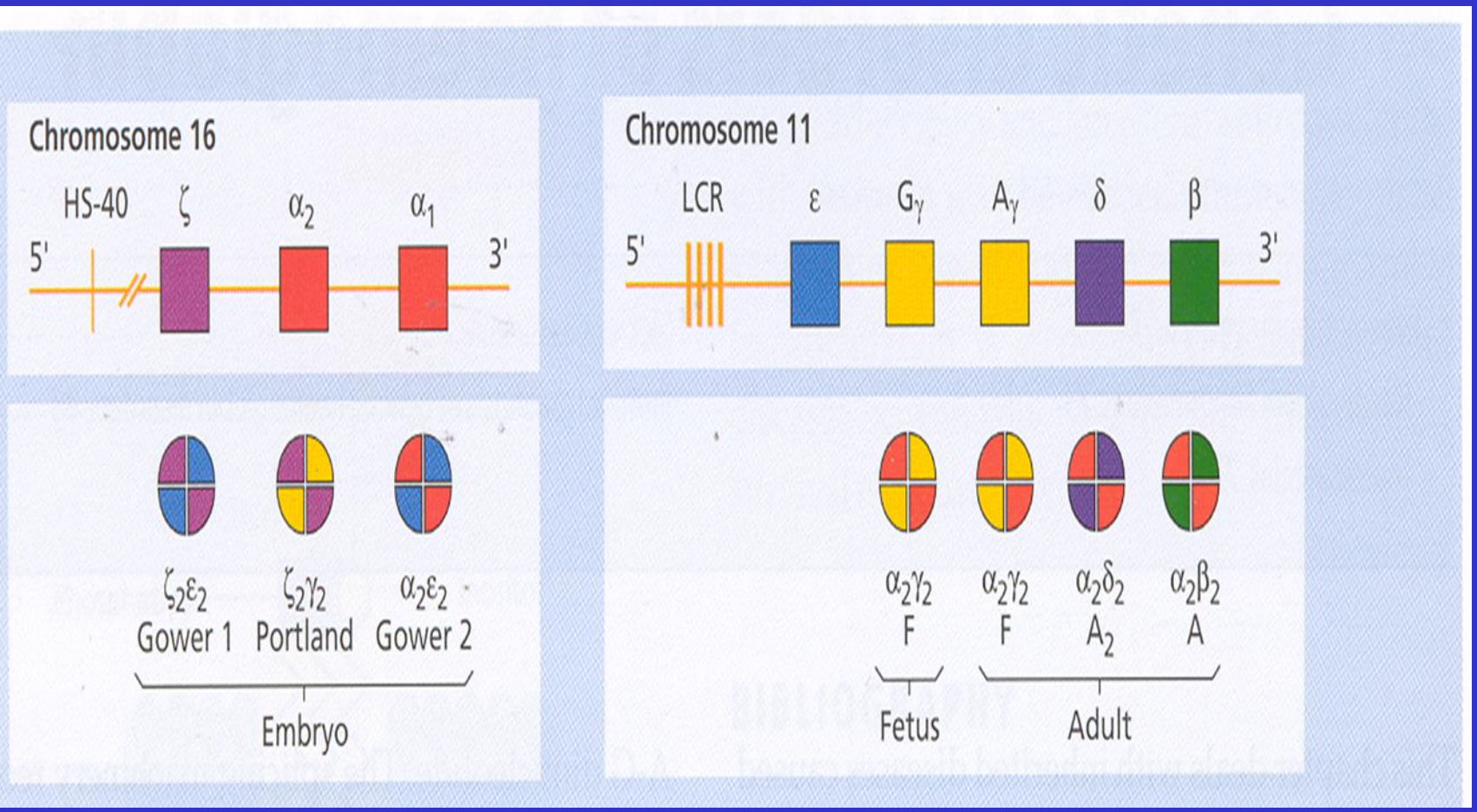
LEARNING OBJECTIVES

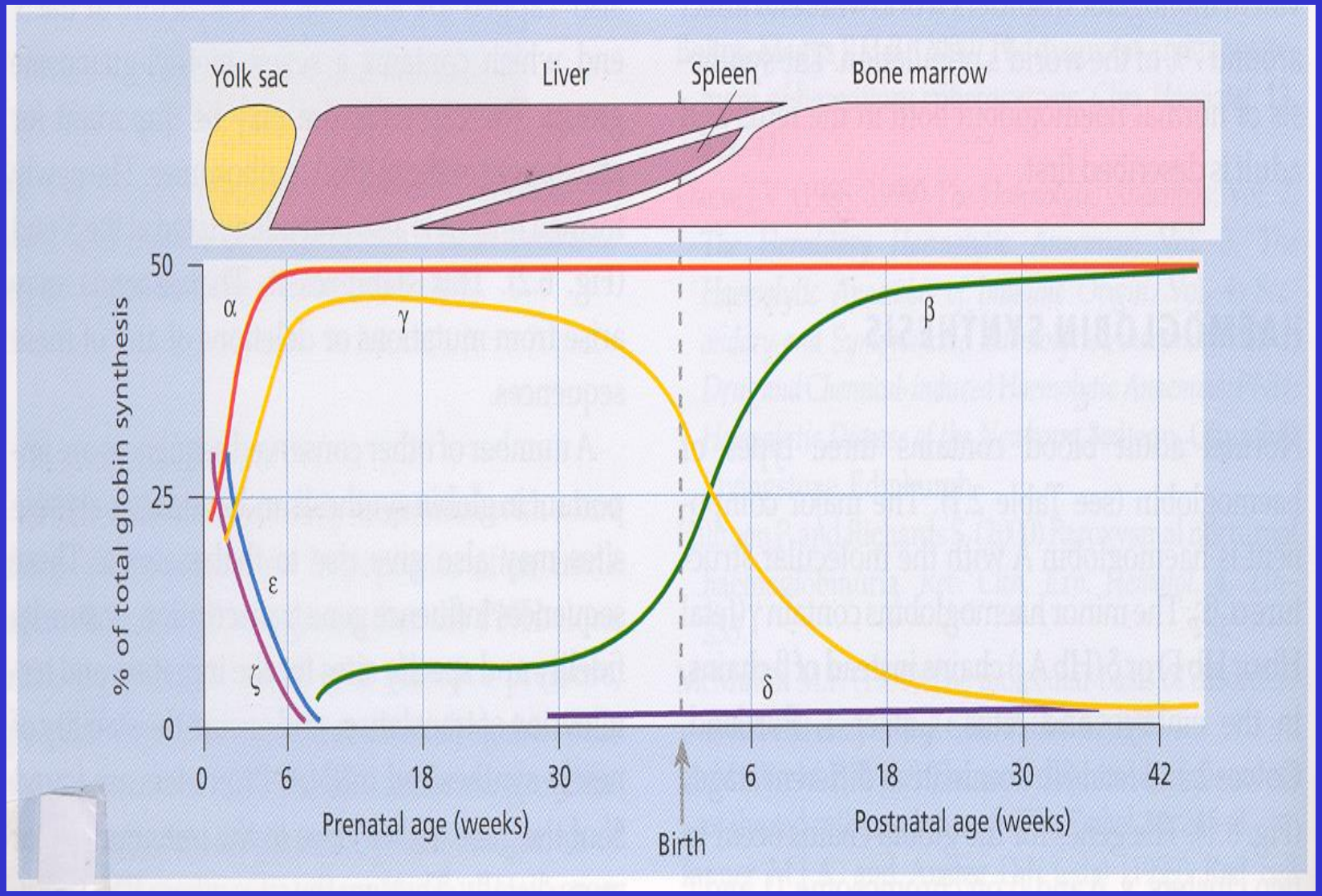
- To understand the normal structure and function of haemoglobin
- To understand how the globin components of haemoglobin change during development, and postnatally
- To understand the mechanisms by which the thalassaemias arise
- To appreciate the clinical presentations and complications of thalassaemia
- To appreciate the contribution of haemolysis and ineffective erythropoiesis to the pathophysiology of thalassaemia

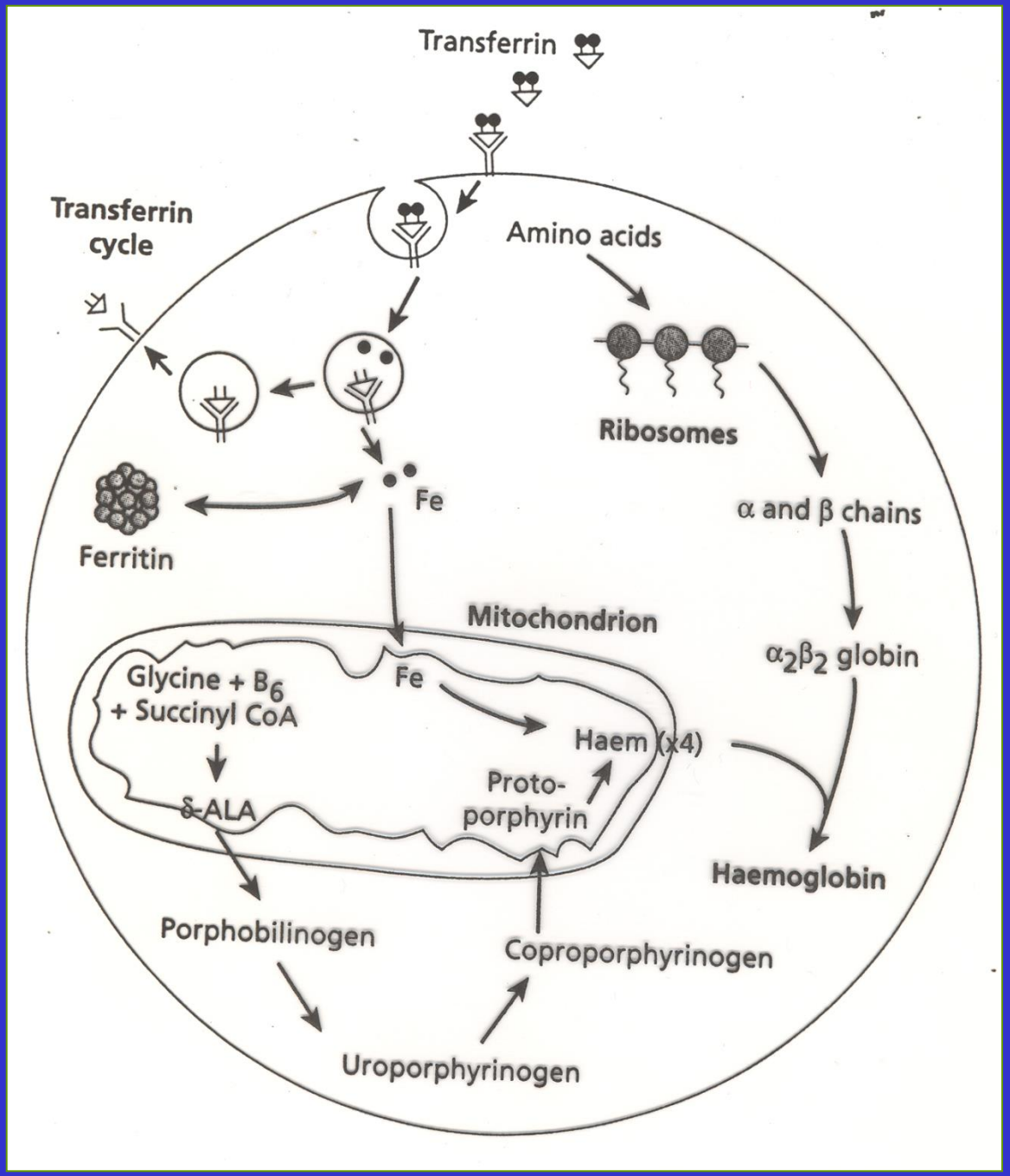
cont'd…

- To understand the pathophysiology of sickle cell anaemia
- To be able to describe the clinical presentation and complications of sickle cell anaemia
- To understand the role of haemoglobin electrophoresis and high performance liquid chromatography in the investigation of globin disorders
- To appreciate the many other haemoglobin variants associated with disease


PRENATAL
POSTNATAL
BIRTH
100 percent
Yolk Sac
Liver
Bone Marrow
Spleen
Vertebra
Sternum
pelvic bones
Rib
Tibia (Shaft)
Femur (Shaft)
1 2 3 4 5 6 7 8 9 10 5 10 15 20 30 40 50 60 70
MONTHS
YEARS
BIRTH

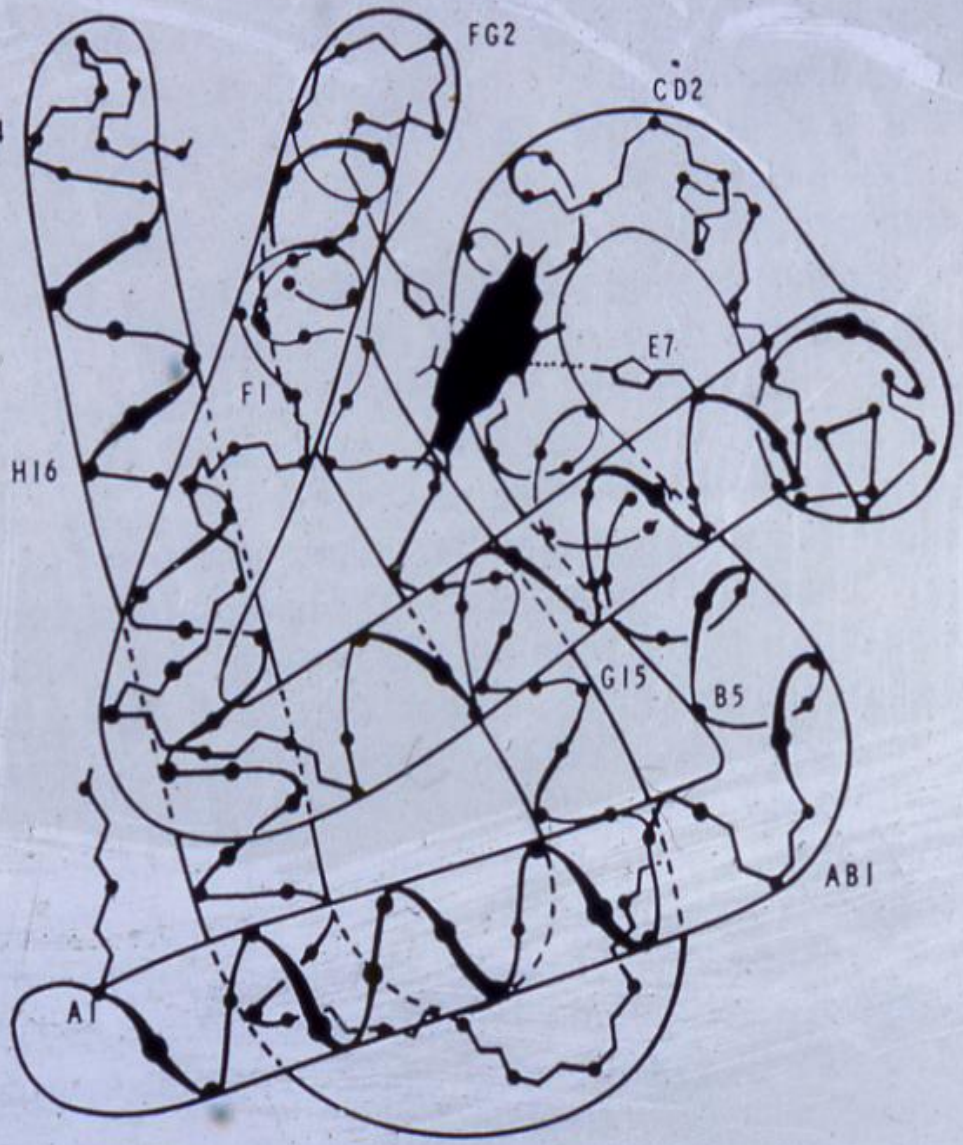

Chromosome 16
HS-40
ζ
α2
α1
5'
3'
ζ2ε2
Gower 1
ζ2γ2
Portland
α2ε2
Gower 2
Embryo
Chromosome 11
LCR
ε
Gγ
Aγ
δ
β
5'
3'
α2γ2
F
α2γ2
F
α2δ2
A2
α2β2
A
Fetus
Adult


Yolk sac
Liver
Spleen
Bone marrow
% of total globin synthesis
50
25
0
α
γ
β
ε
ζ
δ
0
6
18
30
6
18
30
42
Prenatal age (weeks)
Birth
Postnatal age (weeks)


Transferrin
Transferrin cycle
Amino acids
Ribosomes
Fe
Ferritin
α and β chains
Mitochondrion
$\alpha_2\beta_2$ globin
Glycine + B_6 + Succinyl CoA
Fe
Haem (x4)
Proto-porphyrin
δ-ALA
Haemoglobin
Porphobilinogen
Coproporphyrinogen
Uroporphyrinogen

```
 1   2   3   4   5   6   7   8   9   10  11  12  13  14  15
VAL-LEU-SER-PRO-ALA-ASP-LYS-THR-ASN-VAL-LYS-ALA-ALA-TRY-GLY

 16  17  18  19  20  21  22  23  24  25  26  27  28  29  30
LYS-VAL-GLY-ALA-HIS-ALA-GLY-GLU-TYR-GLY-ALA-GLU-ALA-LEU-GLU

 31  32  33  34  35  36  37  38  39  40  41  42  43  44  45
ARG-MET-PHE-LEU-SER-PHE-PRO-THR-THR-LYS-THR-TYR-PHE-PRO-HIS

 46  47  48  49  50  51  52  53  54  55  56  57  58  59  60
PHE-ASP-LEU-SER-HIS-GLY-SER-ALA-GLN-VAL-LYS-GLY-HIS-GLY-LYS

 61  62  63  64  65  66  67  68  69  70  71  72  73  74  75
LYS-VAL-ALA-ASP-ALA-LEU-THR-ASN-ALA-VAL-ALA-HIS-VAL-ASP-ASP

 76  77  78  79  80  81  82  83  84  85  86  87  88  89  90
MET-PRO-ASN-ALA-LEU-SER-ALA-LEU-SER-ASP-LEU-HIS-ALA-HIS-LYS

 91  92  93  94  95  96  97  98  99 100 101 102 103 104 105
LEU-ARG-VAL-ASP-PRO-VAL-ASN-PHE-LYS-LEU-LEU-SER-HIS-CYS-LEU

106 107 108 109 110 111 112 113 114 115 116 117 118 119 120
LEU-VAL-THR-LEU-ALA-ALA-HIS-LEU-PRO-ALA-GLU-PHE-THR-PRO-ALA

121 122 123 124 125 126 127 128 129 130 131 132 133 134 135
VAL-HIS-ALA-SER-LEU-ASP-LYS-PHE-LEU-ALA-SER-VAL-SER-THR-VAL

136 137 138 139 140 141
LEU-THR-SER-LYS-TYR-ARG
```

```
 1   2   3   4   5   6   7   8   9   10  11  12  13  14  15
VAL-HIS-LEU-THR-PRO-GLU-GLU-LYS-SER-ALA-VAL-THR-ALA-LEU-TRY

 16  17  18  19  20  21  22  23  24  25  26  27  28  29  30
GLY-LYS-VAL-ASN-VAL-ASP-GLU-VAL-GLY-GLY-GLU-ALA-LEU-GLY-ARG

 31  32  33  34  35  36  37  38  39  40  41  42  43  44  45
LEU-LEU-VAL-VAL-TYR-PRO-TRY-THR-GLN-ARG-PHE-PHE-GLU-SER-PHE

 46  47  48  49  50  51  52  53  54  55  56  57  58  59  60
GLY-ASP-LEU-SER-THR-PRO-ASP-ALA-VAL-MET-GLY-ASN-PRO-LYS-VAL

 61  62  63  64  65  66  67  68  69  70  71  72  73  74  75
LYS-ALA-HIS-GLY-LYS-LYS-VAL-LEU-GLY-ALA-PHE-SER-ASP-GLY-LEU

 76  77  78  79  80  81  82  83  84  85  86  87  88  89  90
ALA-HIS-LEU-ASP-ASN-LEU-LYS-GLY-THR-PHE-ALA-THR-LEU-SER-GLU

 91  92  93  94  95  96  97  98  99 100 101 102 103 104 105
LEU-HIS-CYS-ASP-LYS-LEU-HIS-VAL-ASP-PRO-GLU-ASN-PHE-ARG-LEU

106 107 108 109 110 111 112 113 114 115 116 117 118 119 120
LEU-GLY-ASN-VAL-LEU-VAL-CYS-VAL-LEU-ALA-HIS-HIS-PHE-GLY-LYS

121 122 123 124 125 126 127 128 129 130 131 132 133 134 135
GLU-PHE-THR-PRO-PRO-VAL-GLN-ALA-ALA-TYR-GLN-LYS-VAL-VAL-ALA

136 137 138 139 140 141 142 143 144 145 146
GLY-VAL-ALA-ASN-ALA-LEU-ALA-HIS-LYS-TYR-HIS
```


FG2
CD2
H24
E7
F1
H16
G15
B5
AB1
A1

NAME	Chains	
Haemoglobin A	α2	β2
Haemoglobin A2	α2	δ2
Haemoglobin F	α2	γ2
Haemoglobin H	-	β4
Haemoglobin Bart's	-	γ4
Haemoglobin Gower I	ζ2	Є2
Haemoglobin Gower II	α2	Є2
Haemoglobin portland	ζ2	γ2
Haemoglobin Lepore	α2	(δβ)2

THE HAEMOGLOBINS PRESENT AT BIRTH IN NORMAL NEWBORN

NAME	%
HbA	15 – 40
HbA_2	< 0.3
HbF	60 – 85
Hb Bart's	< 0.5

THE NORMAL HUMAN HAEMOGLOBINS

EMBRYONIC

(Upto 8 Weeks gestation)

$\zeta_2 \epsilon_2$ Hb Gower I

$\zeta_2 \gamma_2$ Hb Portland

$\alpha_2 \epsilon_2$ Hb Gower II

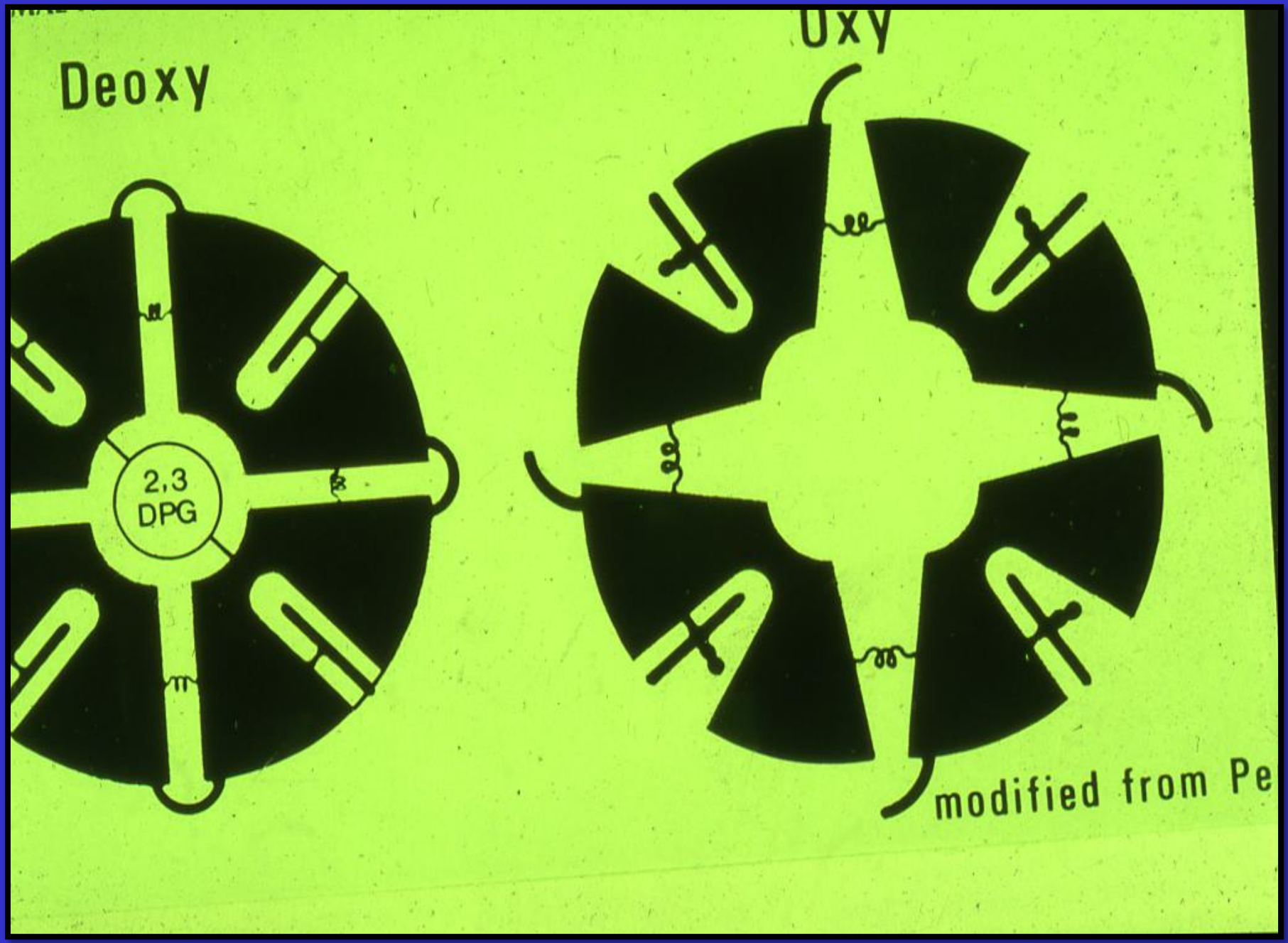
FETAL

$\alpha_2 \gamma_2$ HbF 60 - 85%

$\alpha_2\beta_2$ HbA 15 – 40 %

ADULT

	Caucasian	Saudi
$\alpha_2 \beta_2$ HbA	97.0%	95.0%
$\alpha_2\delta_2$ HbA_2	2.5%	3.5%
$\alpha_2 \gamma_2$ HbF	0.5%	1.5%


Deoxy
Oxy
2,3
DPG
modified from Pe

α and β THALASSAEMIA

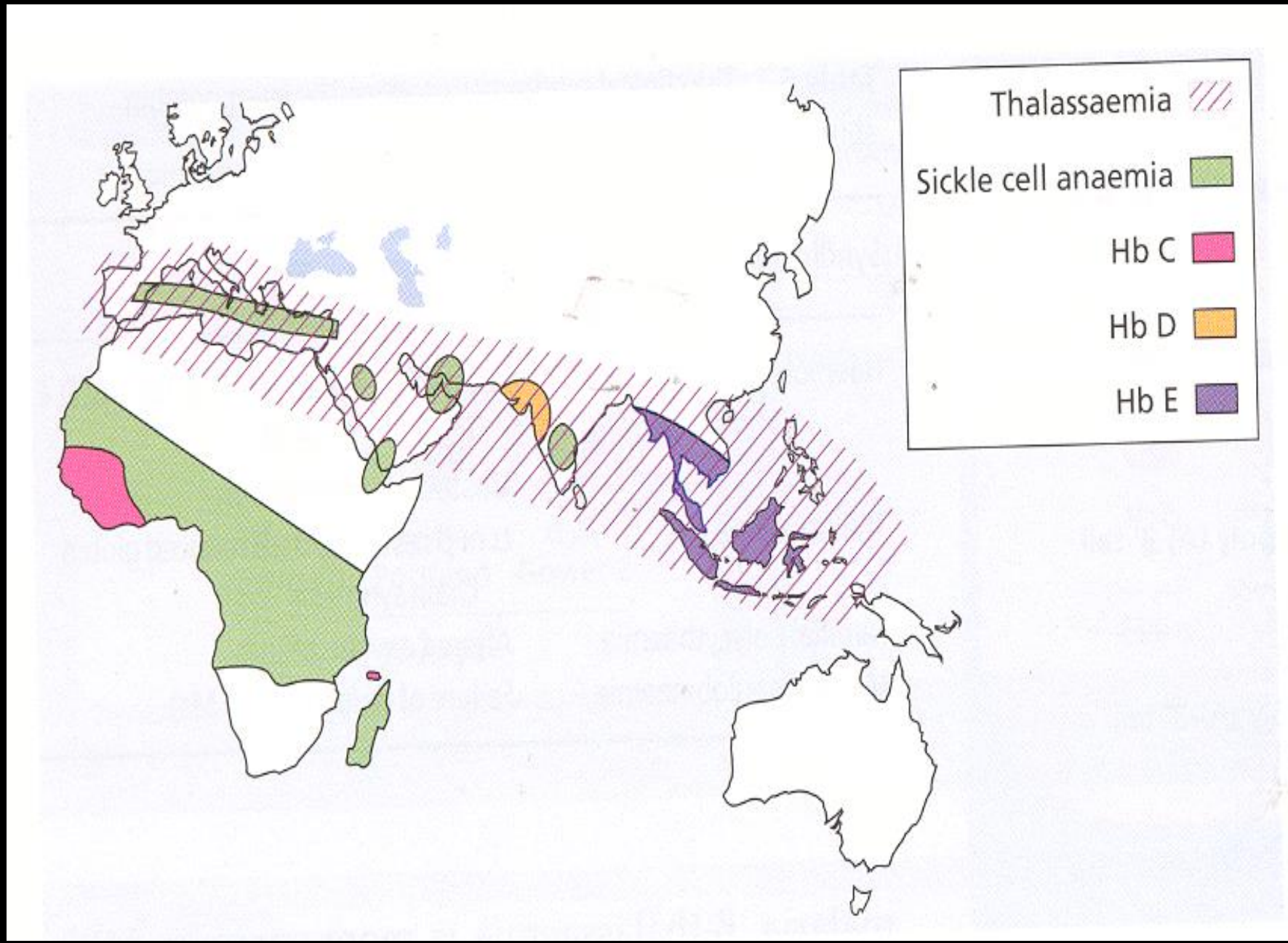
- The thalassaemias are divided into two main groups, the α-thalassaemias and the β-thalassaemias, depending on whether the defect lies in the synthesis of α- or β-globin chains respectively.
- The pathophysiology reflects the impact of an imbalance in the expression of α and β globin chains.

cont'd…

- The chains which are present in excess will precipitate in the precursor red cells, leading to their premature death prior to release from the bone marrow (ineffective erythropoiesis).
- The resulting anaemia leads to an increased erythroid drive.

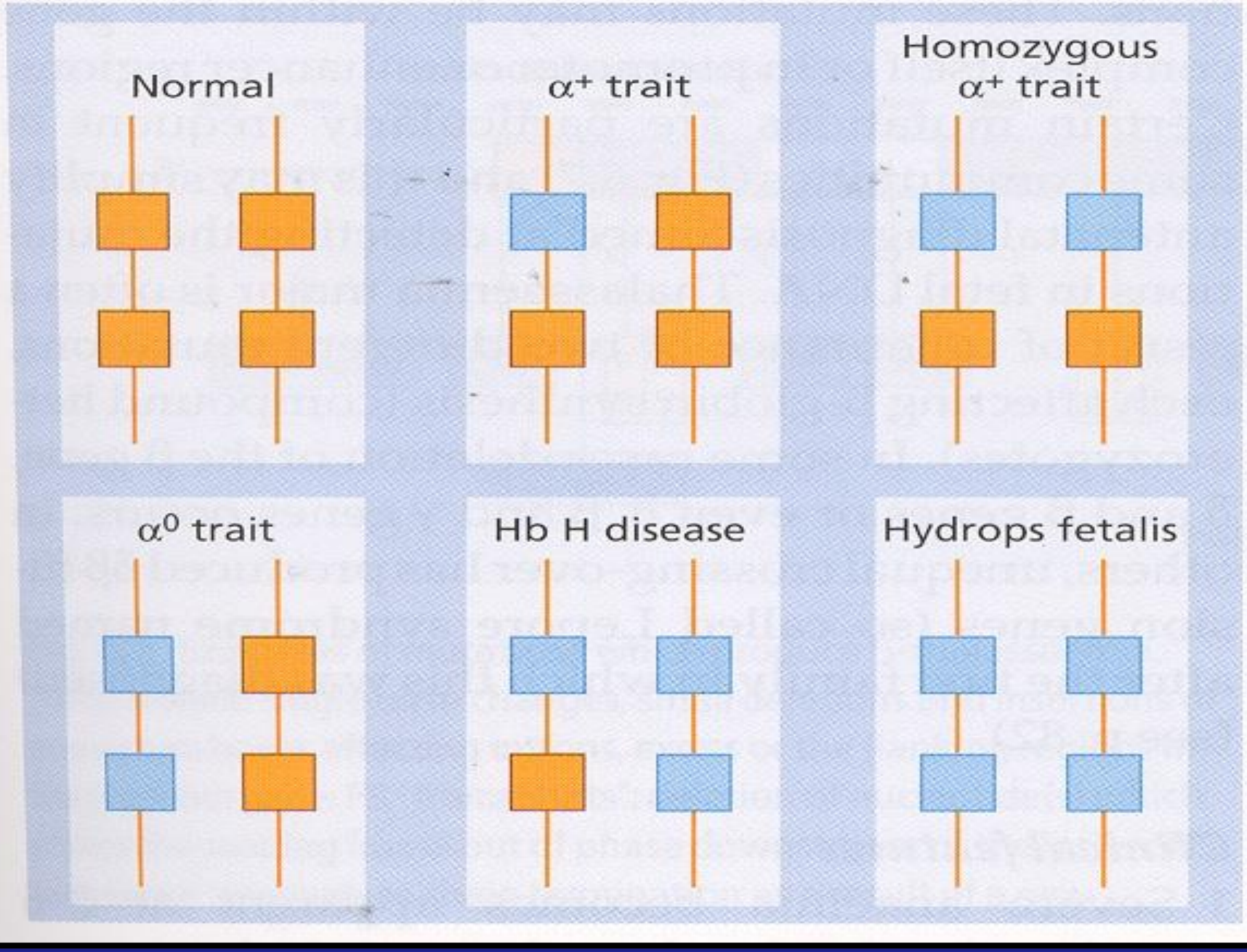
cont'd…

- There is further expansion of the marrow into bones not typically used for haemopoiesis, and into the spleen.
- The long-term consequences of thalassaemia therefore include splenomegaly, bony deformities and iron excess as well as chronic anaemia.


Thalassaemia
Sickle cell anaemia
Hb C
Hb D
Hb E

α - THALASSAEMIA

- **HETEROZYGOUS**
- **HOMOZYGOUS**


Normal
α+ trait
Homozygous α+ trait
α0 trait
Hb H disease
Hydrops fetalis

α^+-Thalassaemia trait (deletion of one or two α globin genes)

This is seen when an individual inherits the α^+-thalassaemia allele from one parent or two parents and a normal chromosome 16 from one or two parents (i.e. heterozygotes for the α^+ determinant or homozygous α^+ trait). Affected individuals are asymptomatic, although they have minor haematological changes such as slight reductions in mean cell volume (MCV) and mean cell haemoglobin (MCH).

α^0-Thalassaemia trait (deletion of both α-globin genes on one chromosome 16)

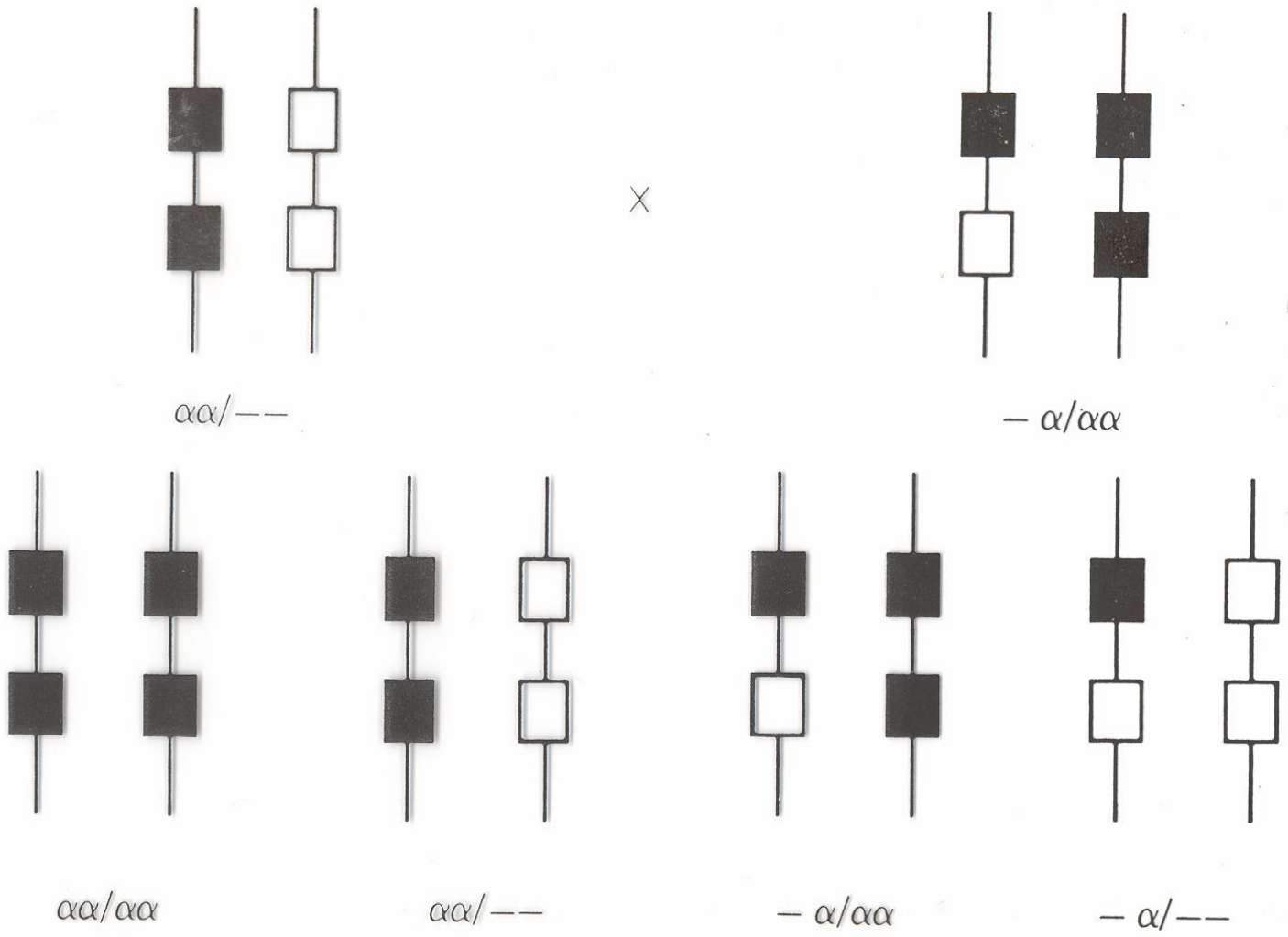
The Hb is either normal or slightly reduced and the MCV and MCH are low.

Haemoglobin H disease (deletion of three α-globin genes)

- This chronic haemolytic anaemia results from the inheritance of both the α^{+}- and α^{0}-thalassaemia alleles, leaving one functioning α-globin gene per cell. α-globin chains are produced at very low rates, leaving a considerable excess of β-chains, which combine to form tetramers (β_4). This tetramer is known as HbH.
- HbH is unstable and precipitates as the erythrocytes age, forming rigid membrane-bound inclusions that are removed during the passage of affected red cells through the spleen. The damage to the membrane brought about by this removal results in a shortened red cell lifespan.

cont'd…

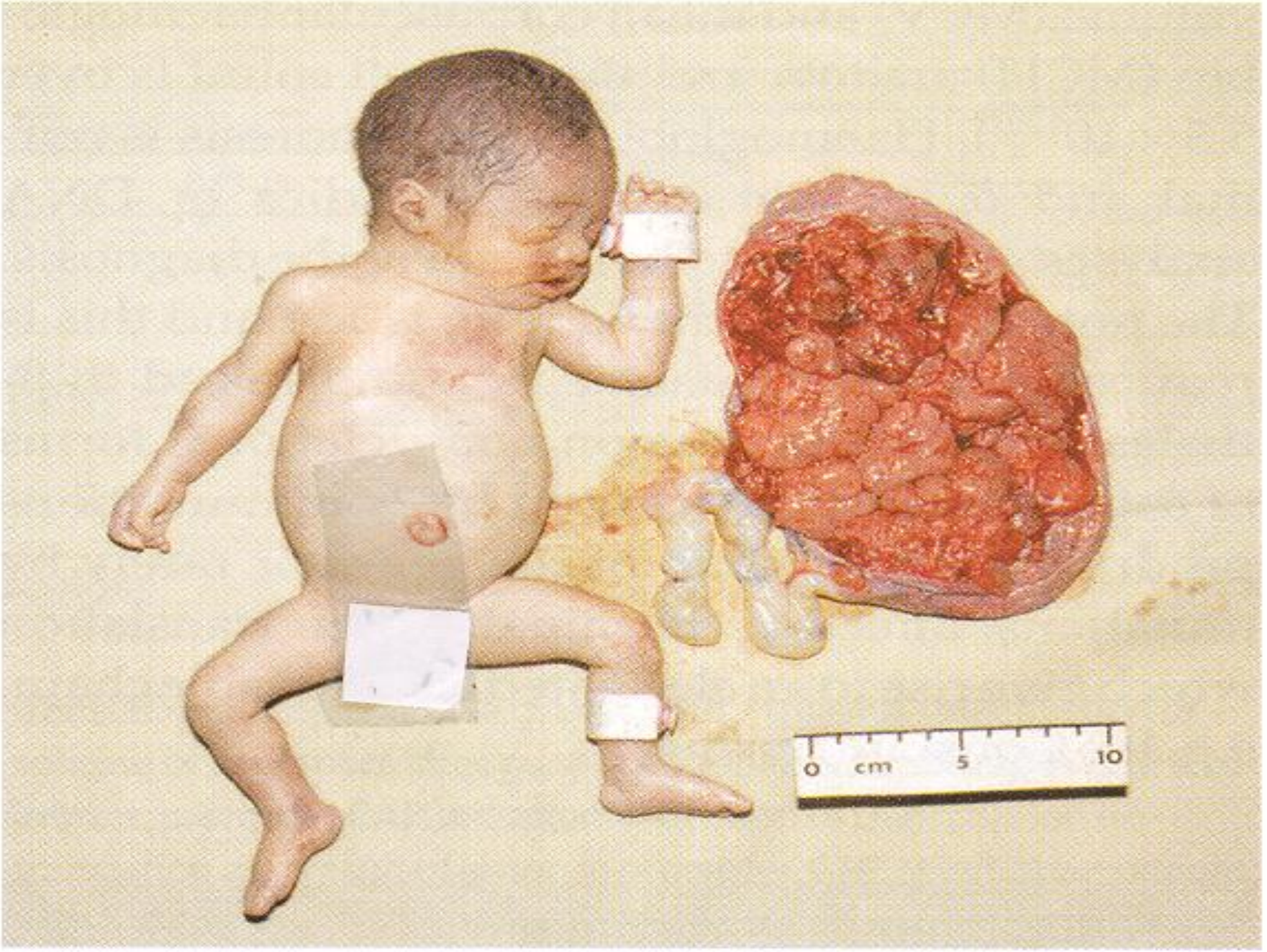
- Most patients are moderately affected, with anaemia of 7-11g/dl and markedly hypochromic, microcytic indices.
- Supravital staining of the blood film demonstrates cells with many HbH inclusions, giving a characteristic 'golf-ball' appearance.
- Most patients will be transfusion independent.
- Splenomegaly is seen in most patients.

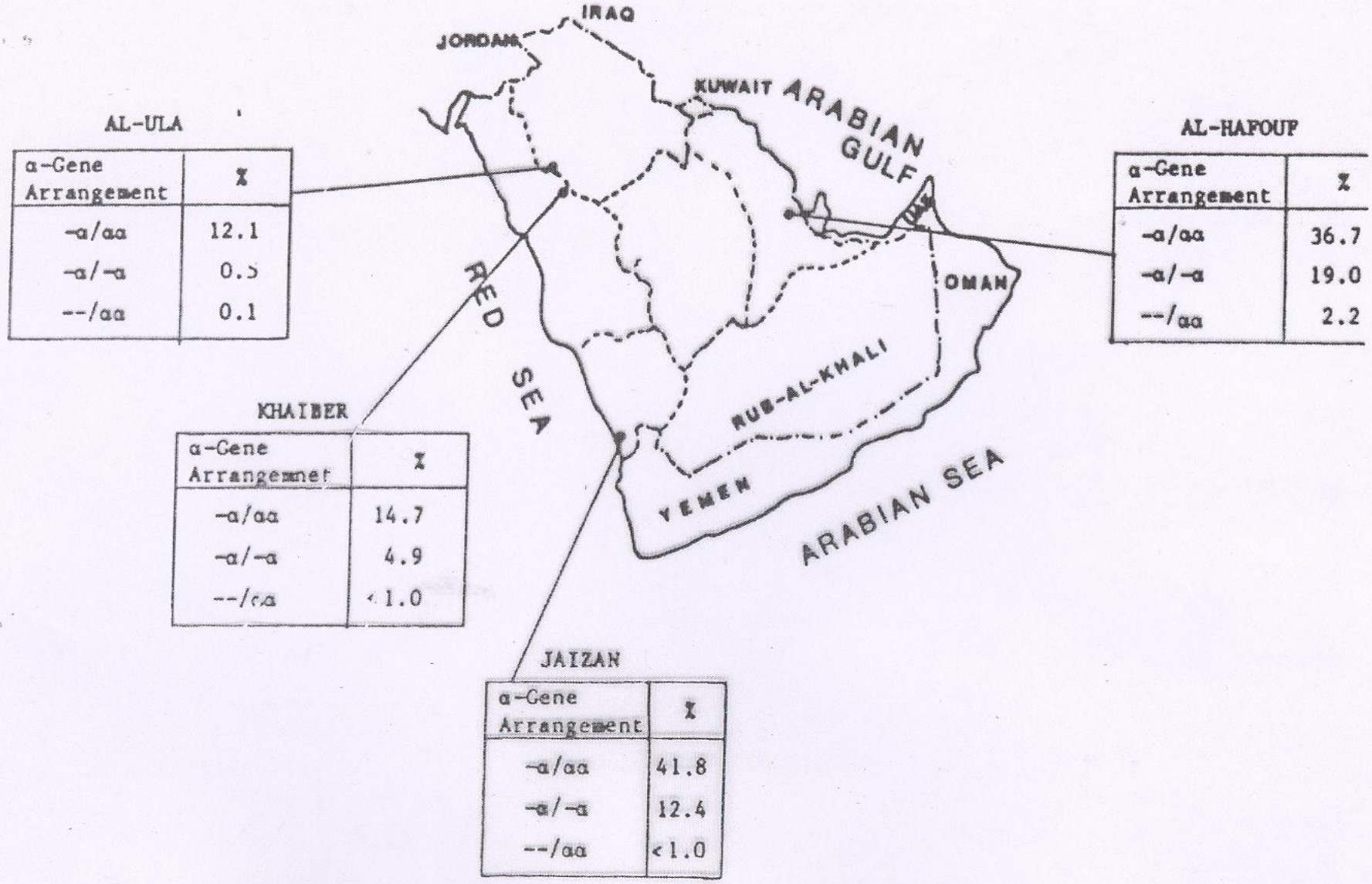


Inheritance of HbH (−α/− −) disease. Normal α-globin genes are shown by closed boxes, and deleted or otherwise inactivated α-globin genes by open boxes.

Hb Bart's hydrops fetalis syndrome (deletion of all four α-globin genes)

No α-chains can be formed, and the fetal β-like chain γ-globin forms tetramers known as Hb Bart's. This haemoglobin is not useful for oxygen transport and, despite the persistence of the embryonic haemoglobin Hb Portland ($\zeta_2\gamma_2$), there is intrauterine or neonatal death due to hydrops.

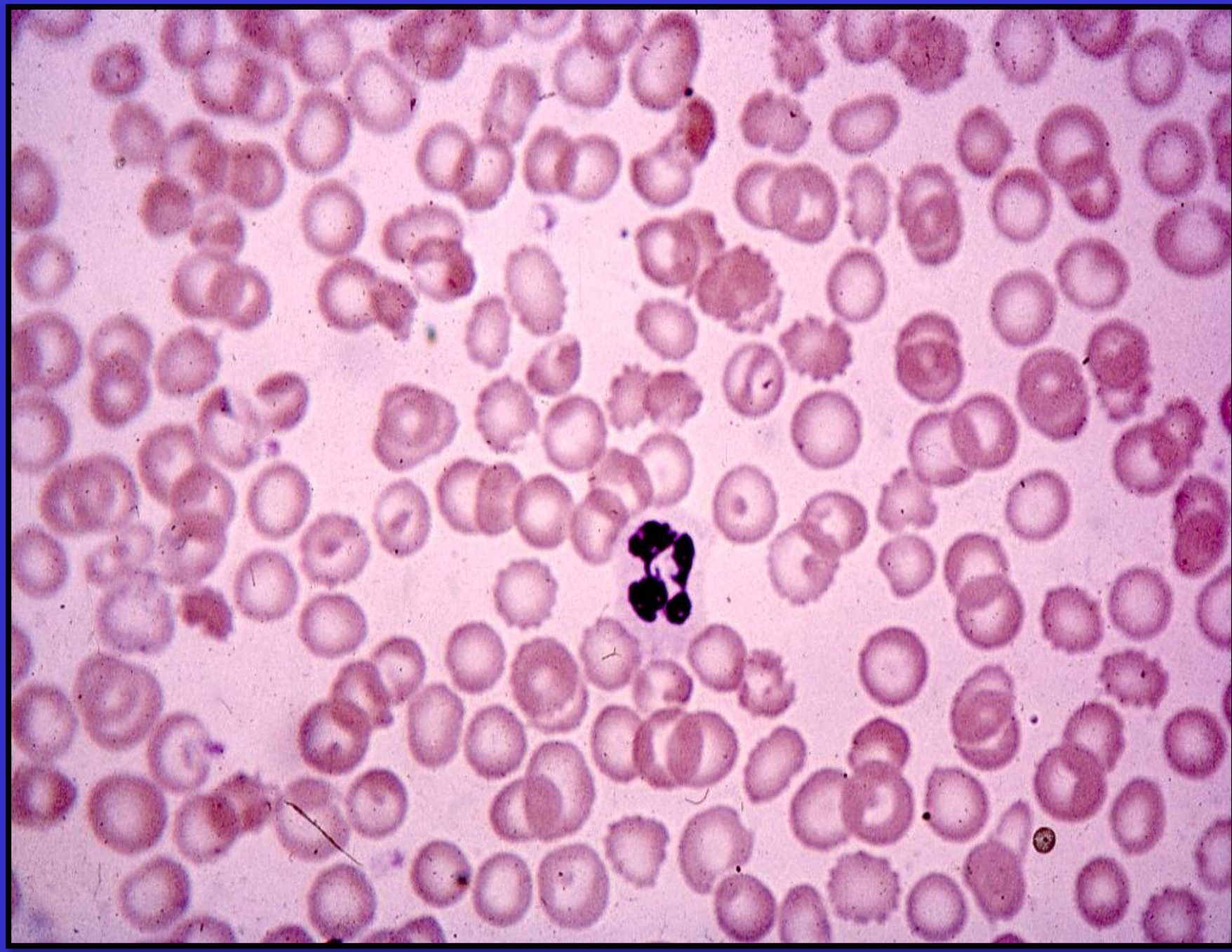

0 cm 5 10

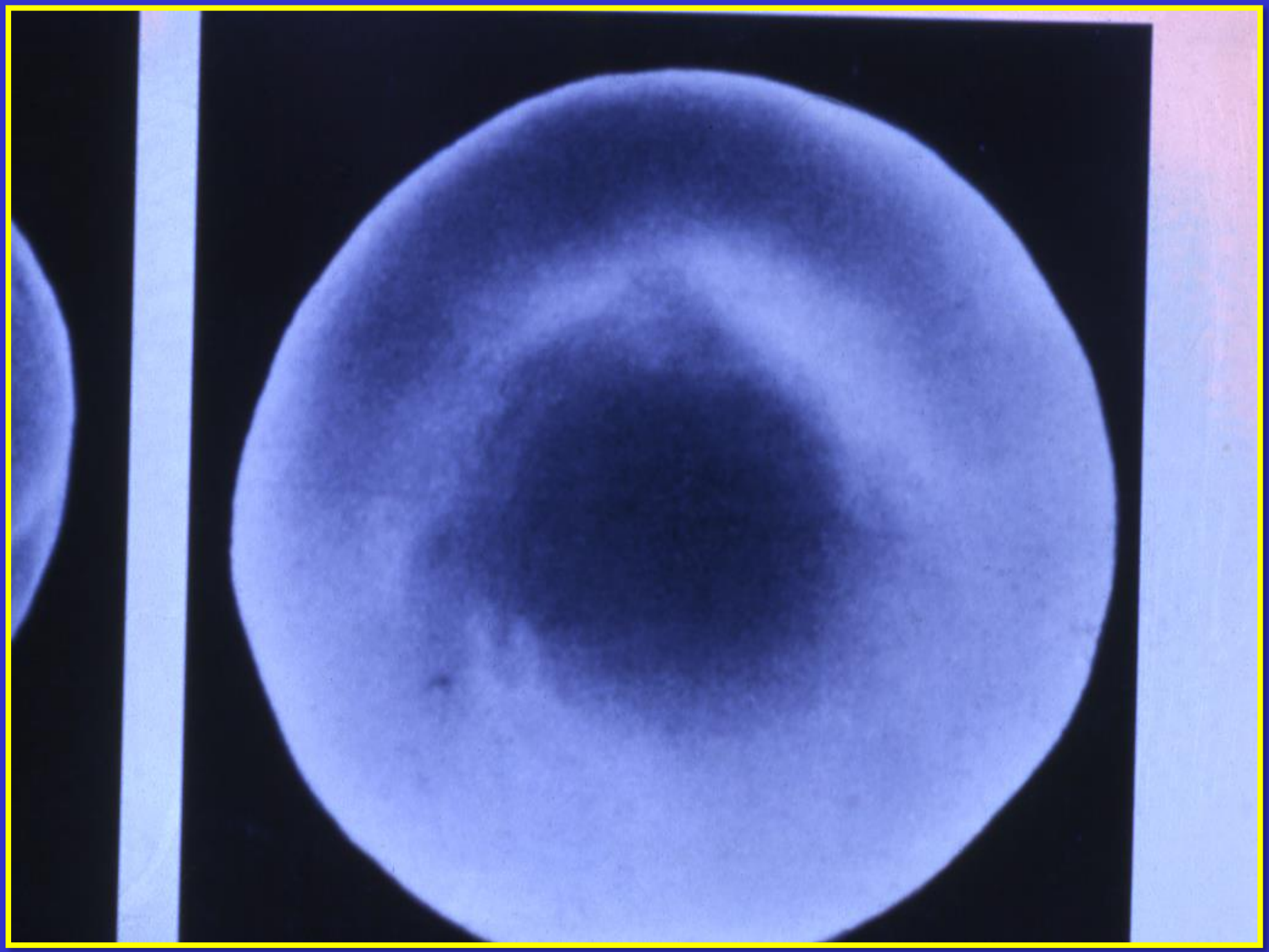


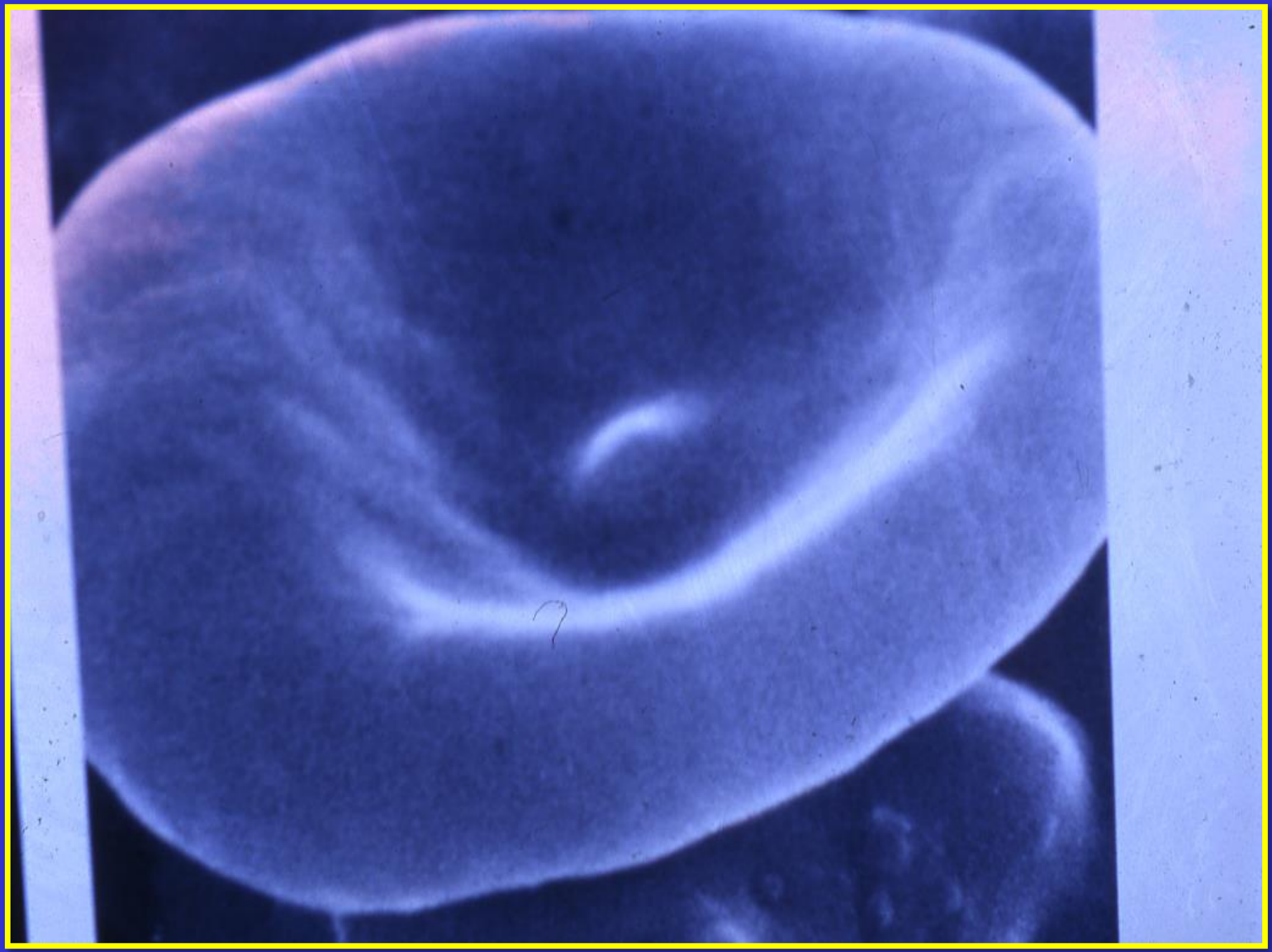
Frequency of α-thalassaemia due to α-gene deletion in different regions of Saudi Arabia (diagnosed using rest iction endonuclease Bam HI).

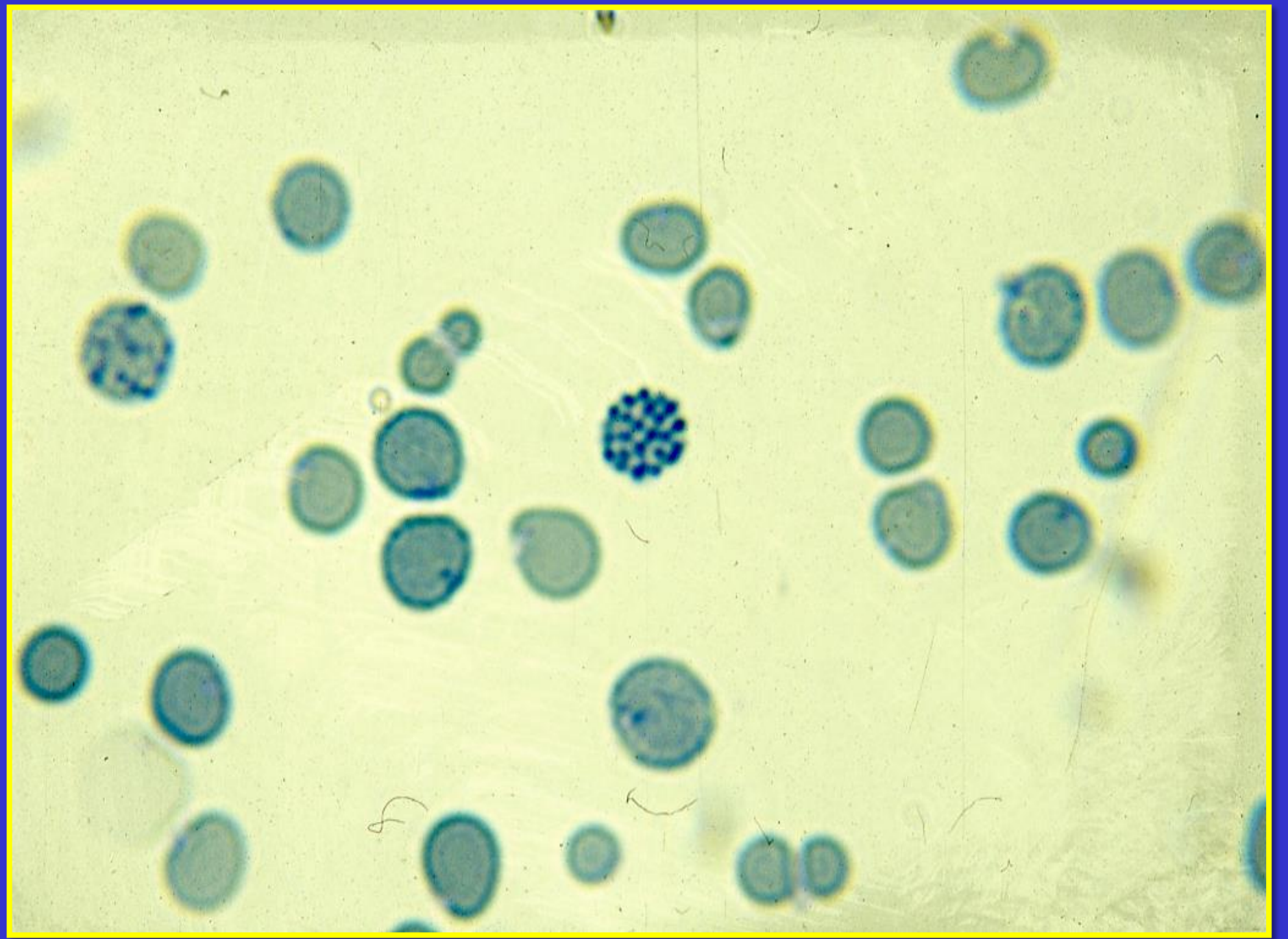
LABORATORY DIAGNOSIS OF ALPHA THALASSEMIA SYNDROME

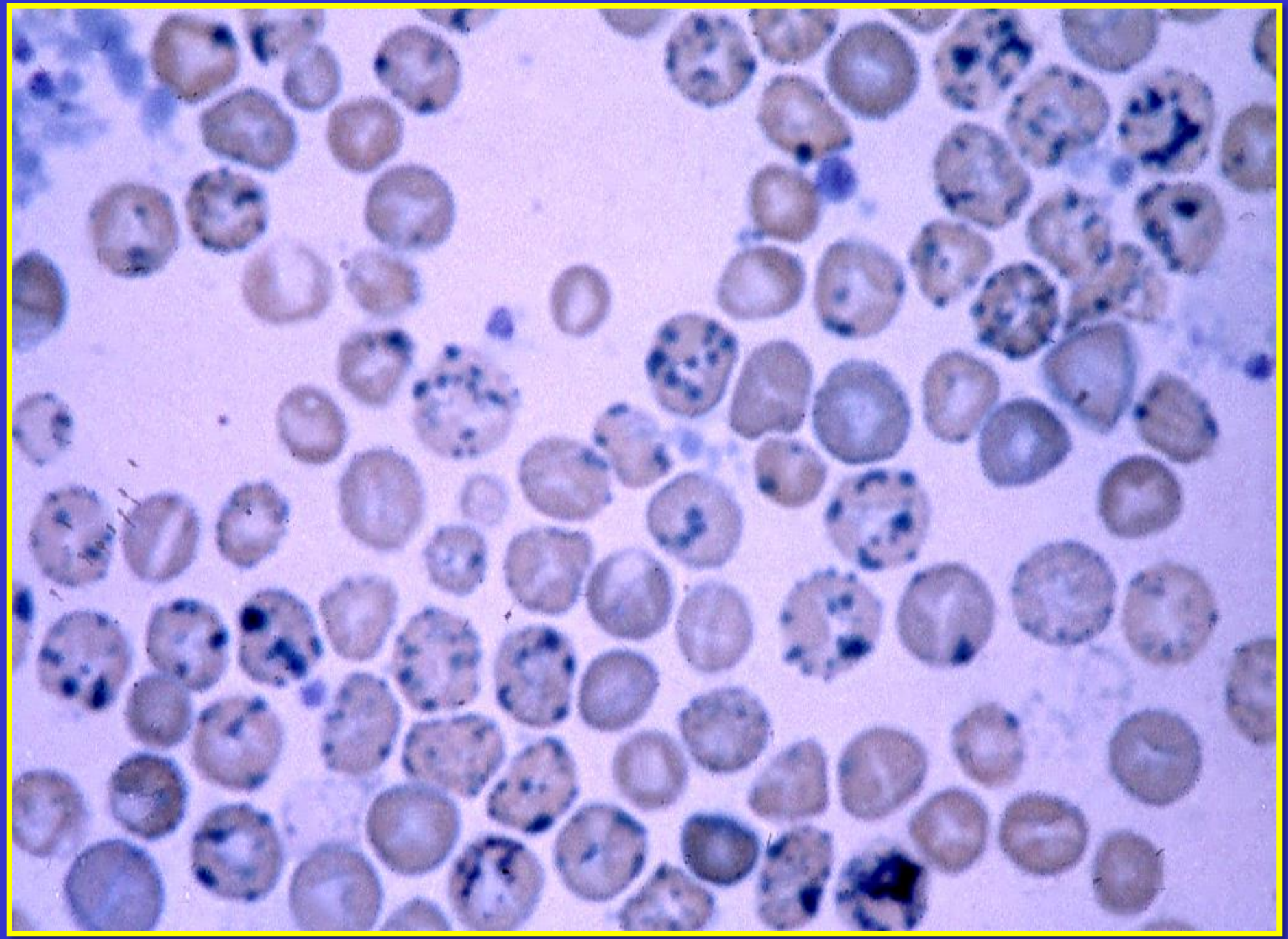
- High red cell count in the trait
- Hypochromic microcytic red cells & target cells
- Normal serum iron or low in children
- Normal total iron binding capacity or high in children
- Positive Hb H inclusion bodies in the blood film preparation & positive Heinz bodies with vital stains
- Hemoglobin electrophoresis show presence of hemoglobin H (Hb H disease)
- Hemoglobin electrophoresis show low Hb A2 level
- Genetic study to confirm the diagnosis

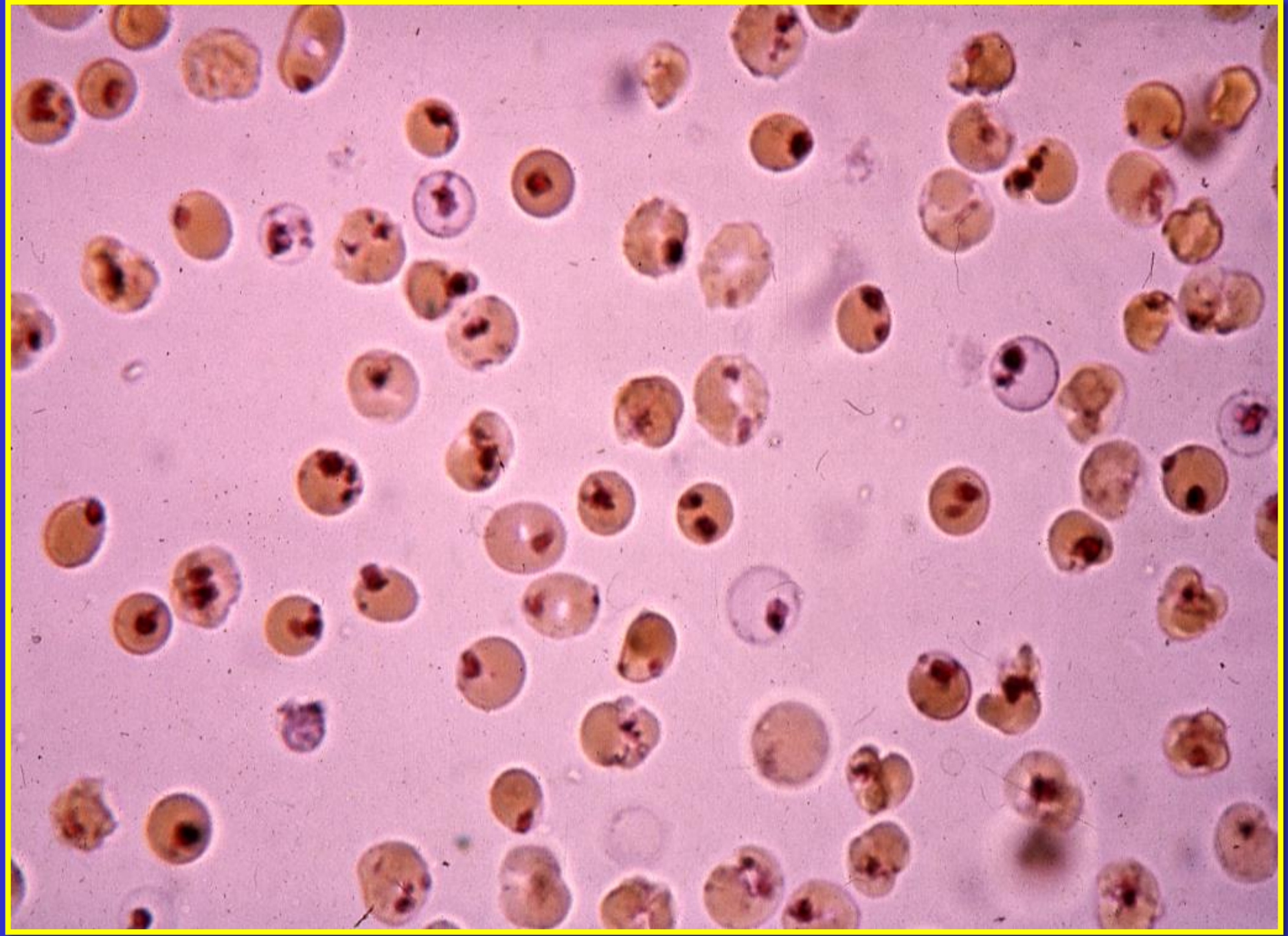


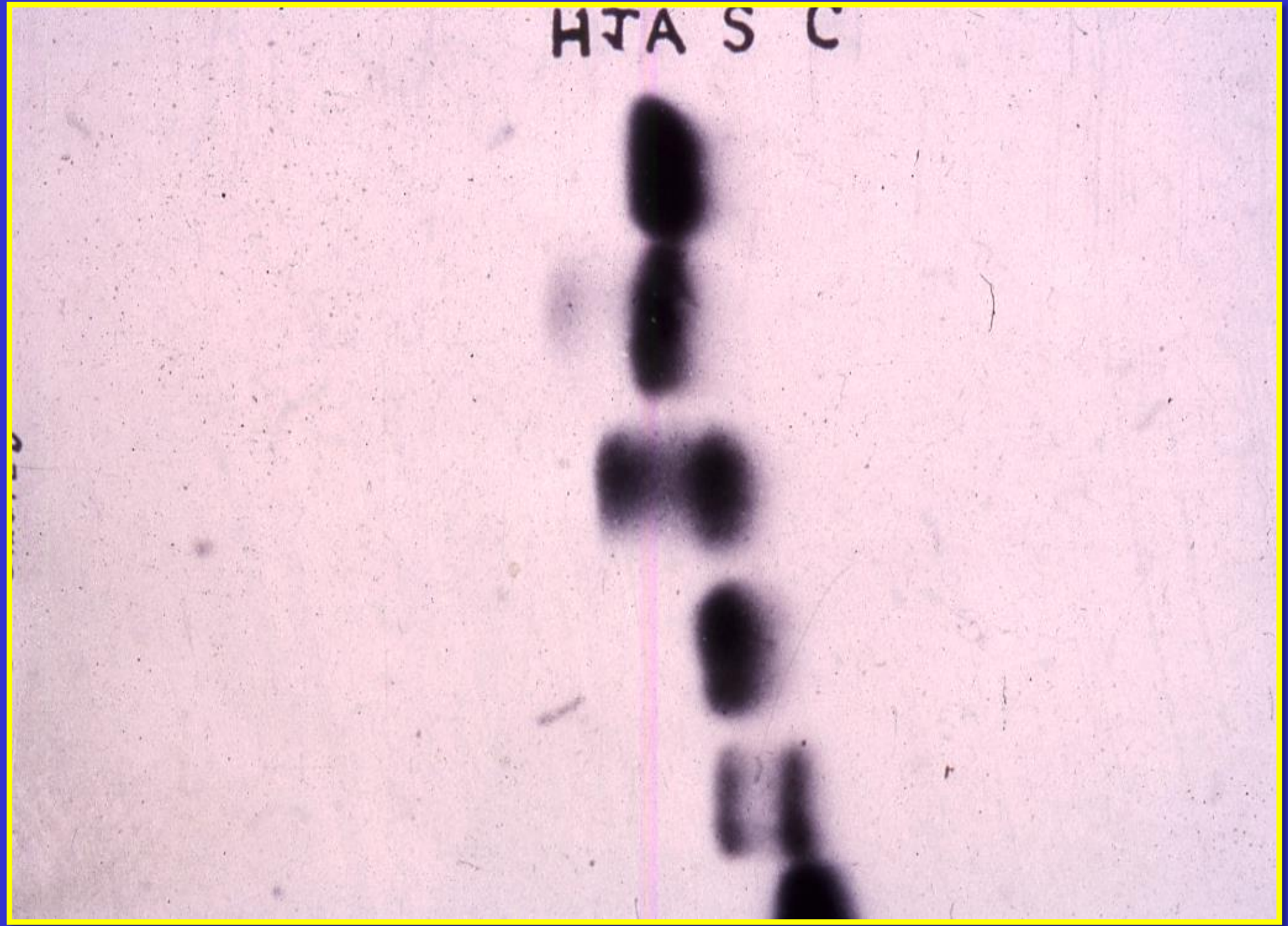






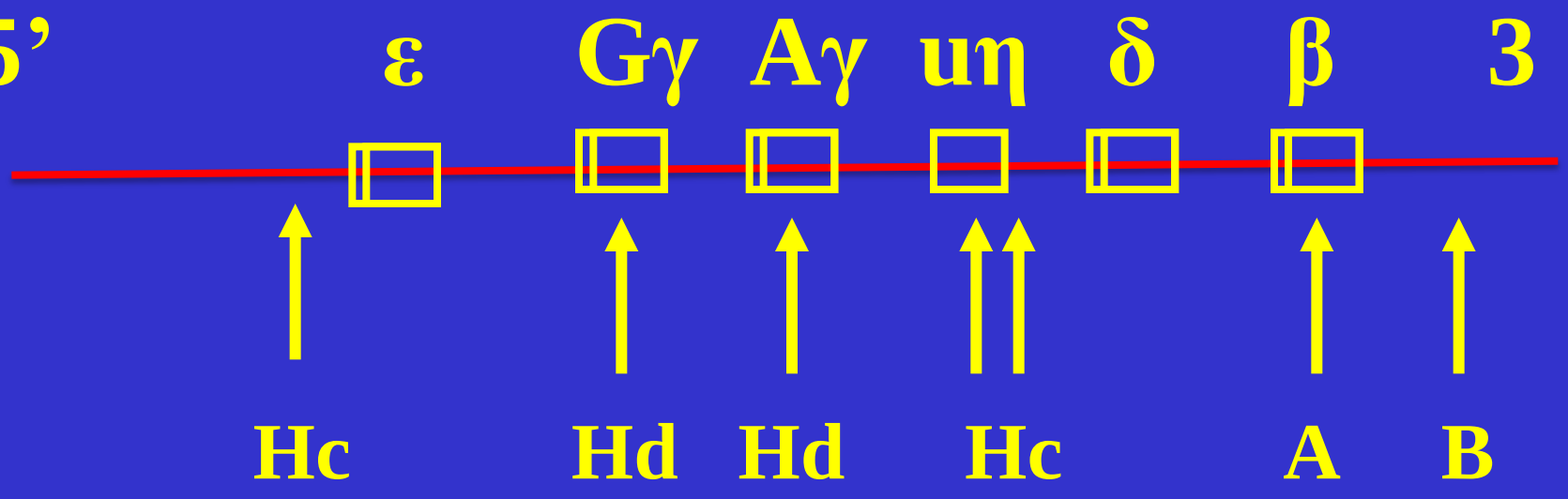





HTA S C

β-THALASSAEMIA

DR. SHIHAB AL-MASHHADANI



The –globin gene cluster showing the position of various common restriction endonuclease polymorphic sites. (Hc, Hinc II; Hd, Hind III; A, Ava II; B, Bam H1).

β-Thalassaemia

- The World Health Organization estimates that 1.5% of the world's population are carriers of β-thalassaemia. The prevalence of the β-thalassaemia trait is particularly high in southern Europe (10-30%) and south-east Asia (5%), common in Africa, the Middle East, India, Pakistan and southern China.
- α-thalassaemia typically arises from gene deletions.
- β-thalassaemia usually results from a multiplicity of different single nucleotide substitutions, insertions or small deletions affecting the β-gene itself.

Heterozygous β-thalassaemia (Beta-thalassaemia trait)

- Most affected subjects with beta thalassaemia trait are asymptomatic.
- The Hb concentration is either normal or slightly reduced, hypochromic and microcytic red cell indices are seen.
- Examination of peripheral blood film may show red cell abnormalities such as target cells and poikilocytes.
- HbA2 levels will be raised above the normal range to 3.5-7.0%.
- Slightly increased HbF levels, in the range of 1-5%.

Homozygous β-Thalassaemia

- Defects of β-globin on both copies of chromosome 11
- Marked anaemia
- Transfusion dependent

Clinical classification of the thalassaemias

1) *Thalassaemia minima* describes the presence of a thalassaemia mutation that is without clinical consequences.
2) *Thalassaemia minor* describes patients with microcytosis and hypochromic red cells secondary to thalassaemia mutations, but with only mild anaemia or a normal haemoglobin. Patients who inherit a single affected allele are usually in this category.

cont'd…

3) *Thalassaemia intermedia* patients will also have a microcytic hypochromic anaemia, increased erythroid drive to maintain their haemoglobin, packed bone marrow with a decreased myeloid:erythroid ratio, and extramedullary haematopoiesis, giving splenomegaly. Transfusion may be required to maintain the haemoglobin at times of additional physiological stress.

cont'd…

4) *Thalassaemia major* have severe anaemia and are transfusion dependent. Their increased erythroid drive leads to a packed erythroid marrow and splenomegaly, development of bony abnormalities secondary to unchecked marrow expansion. Patients in this category are those with complete loss of β-globin expression from both copies of chromosome 11.

Molecular Defects in the β-Thalassaemia Syndrome

	β-Globin synthesis	β^-mRNA	β-Globin Gene	δ-Globin Synthesis	γ-Globin Synthesis
1. β^+-Thalassemia 2. β^0-Thalassemia	Decreased Absent	Decreased Absent	Present Present	Present Present	Present Present
Ferrara Variant Indian Variant	Absent Absent	Inactive Absent	Present Partially Deleted	Present Present	Present Present
3. δβ-Thalassaemia 4. HPFH	Absent Absent	Absent Absent	Deleted Deleted	Absent Absent	Increased increased

Hemoglobin Fractions in the Genotypic Variants of the β-Thalassaemia Syndromes

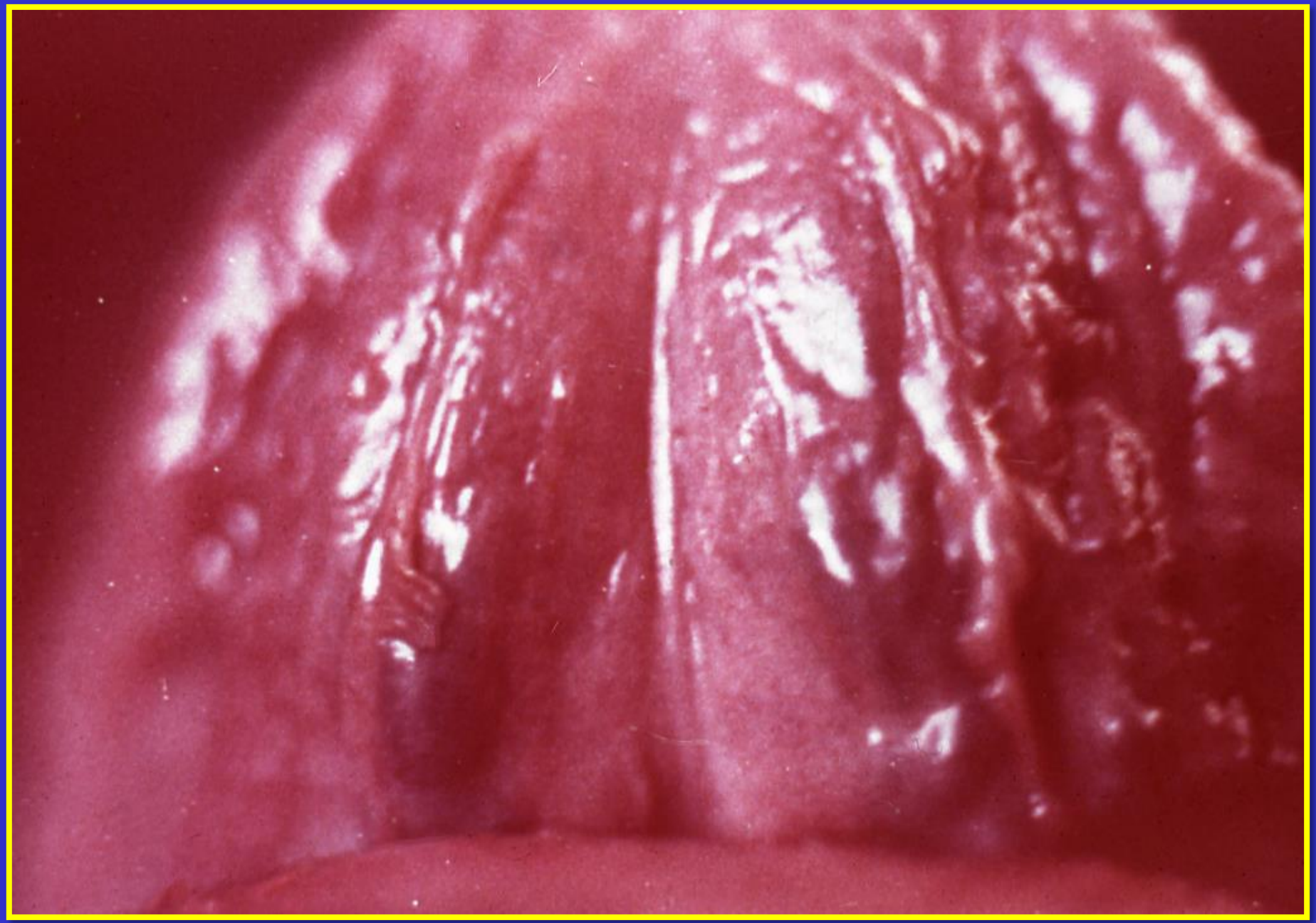
Genotype	HbA	HbA_2	HbF (%)	Other Hemoglobins
Normal				
β/β	97	2.5 – 3.2	<1	None
Thalassaemia major				
β^0/β^0	0	1.0 – 5.9	>94	Free α-chains
$\beta+/\beta^+$ Mediterranean	Present	2.4 – 8.7	20 – 90	Free α-chains
β^0/β^+	Present	0.6 – 3.4	>75	None
$(\delta\beta)$ Lepore/ $(\delta\beta)$ Lepore	0	0	70 – 92	Hb Lepore (8-30%)
Thalassaemia intermedia				
$\beta+/\beta^+$, black	Present	5.4 – 10.0	30 – 73	None
$\beta^0/ (\delta\beta)^0$	0	0.3 – 2.4	60 – 99	None
$\beta^+/ (\delta\beta)^0$	20 – 30	Decreased	Increased	None
$\beta^0/ (\delta\beta)^0$ Lapore	0	Decreased	Increased	Hb Lepore (10%)
$\beta^+/ (\delta\beta)^0$ Lepore	Present	Decreased	Increased	Hb Lepore (10%)
β^0/β	Present	>3.2	1.5 – 12	None
$(\delta\beta)^0 / (\delta\beta)^0$	0	0	100	None
$(\delta\beta)^0/ (\delta\beta)$Lepore	0	0	92	Hb Lepore (8%)
α/β	Present	Increased	Normal or increased	± Hb H

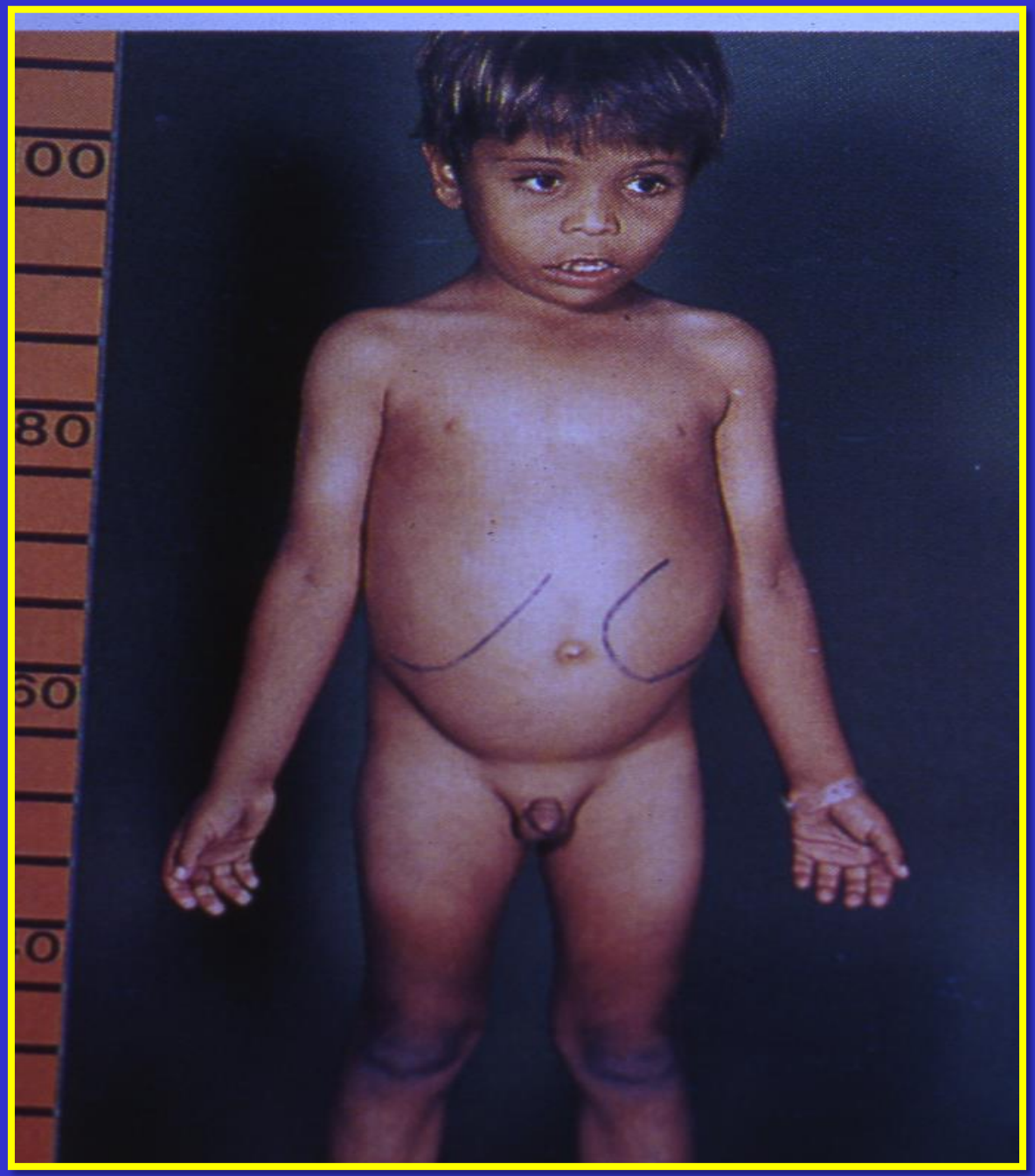
Hemoglobin Fractions in the Genotypic Variants of the β-Thalassaemia Syndromes (Continued)

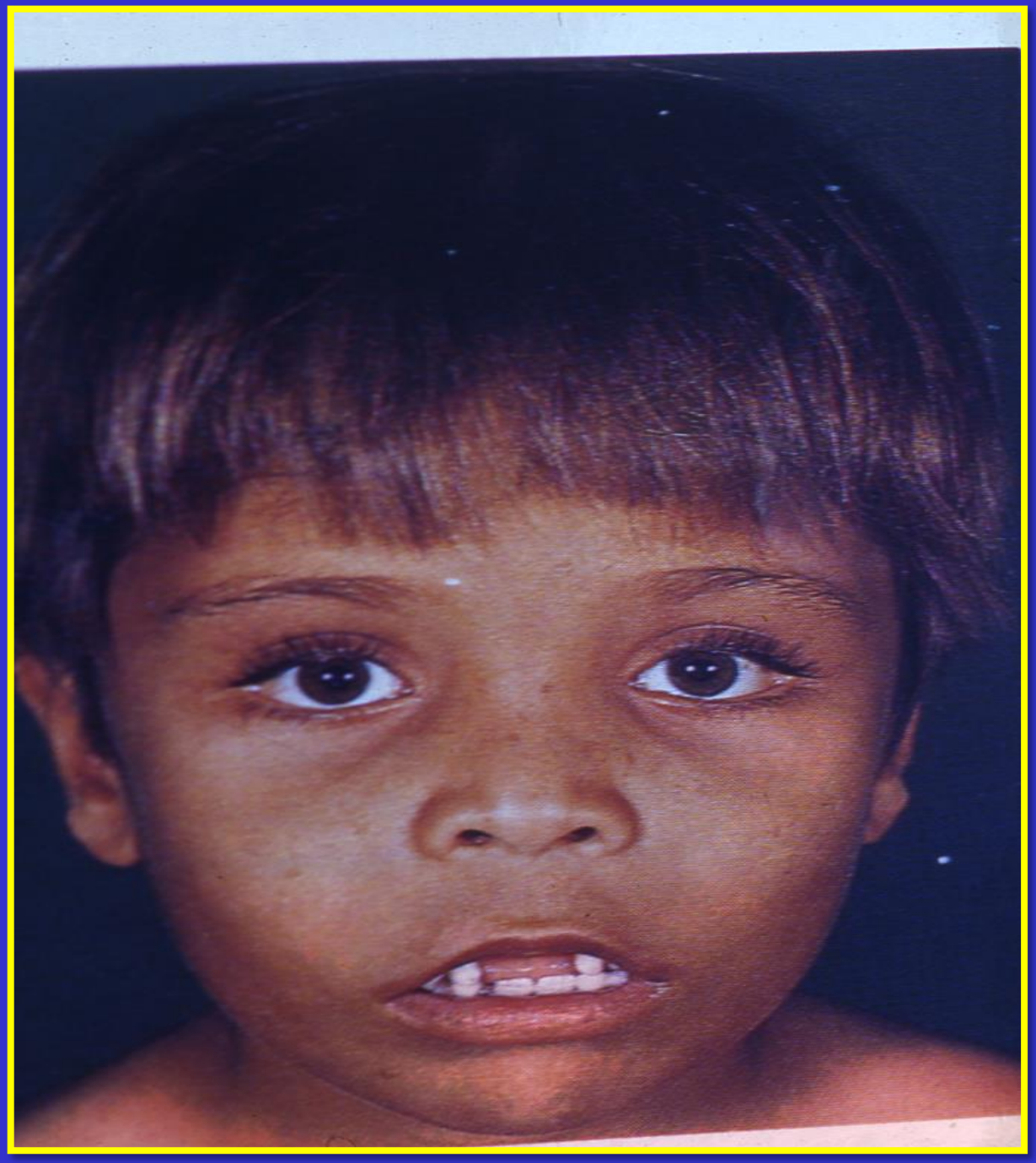
Genotype	HbA	HbA_2	HbF (%)	Other Hemoglobins
Thalassaemia minor				
β^{+}/β	>90	3.5 – 8.0	1 – 2	None
β^{0}/β	>90	3.5 – 8.0	1 – 2	None
$(\delta\beta)^{0}/\beta$	>90	2.5 – 8.0	5 – 20	None
$(\delta\beta)_{Lepore}/\beta$	Present	1.2 – 2.6	1 – 3	Hb Lepore (5 – 15%)
$(\gamma\delta\beta)^{0}/\beta$	Present	2.5 – 3.2	< 1 – 2	None
Thalassaemia minima				
β^{silent}/β	97	<3.2	<1	None

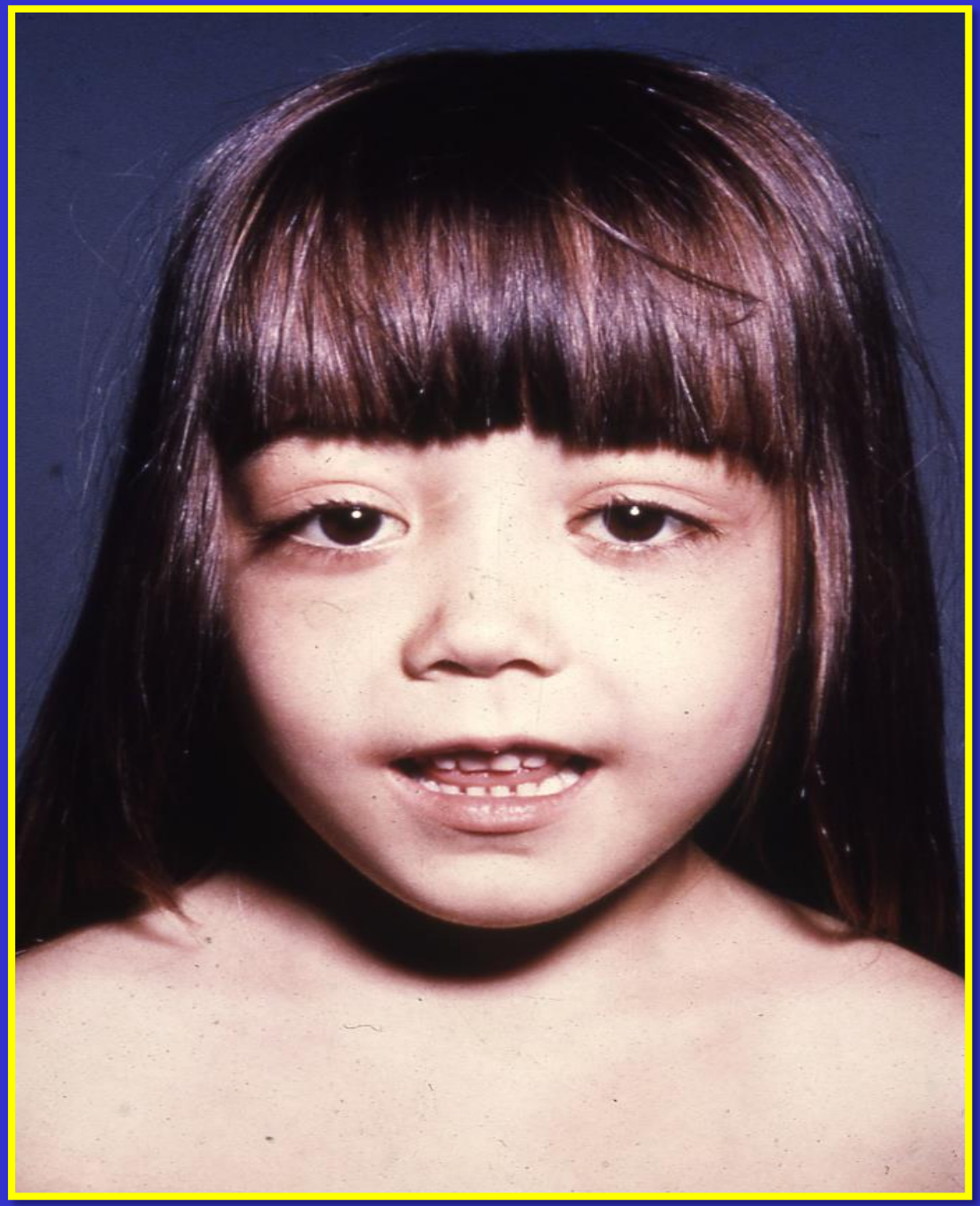
Clinical Manifestations in Thalassaemias

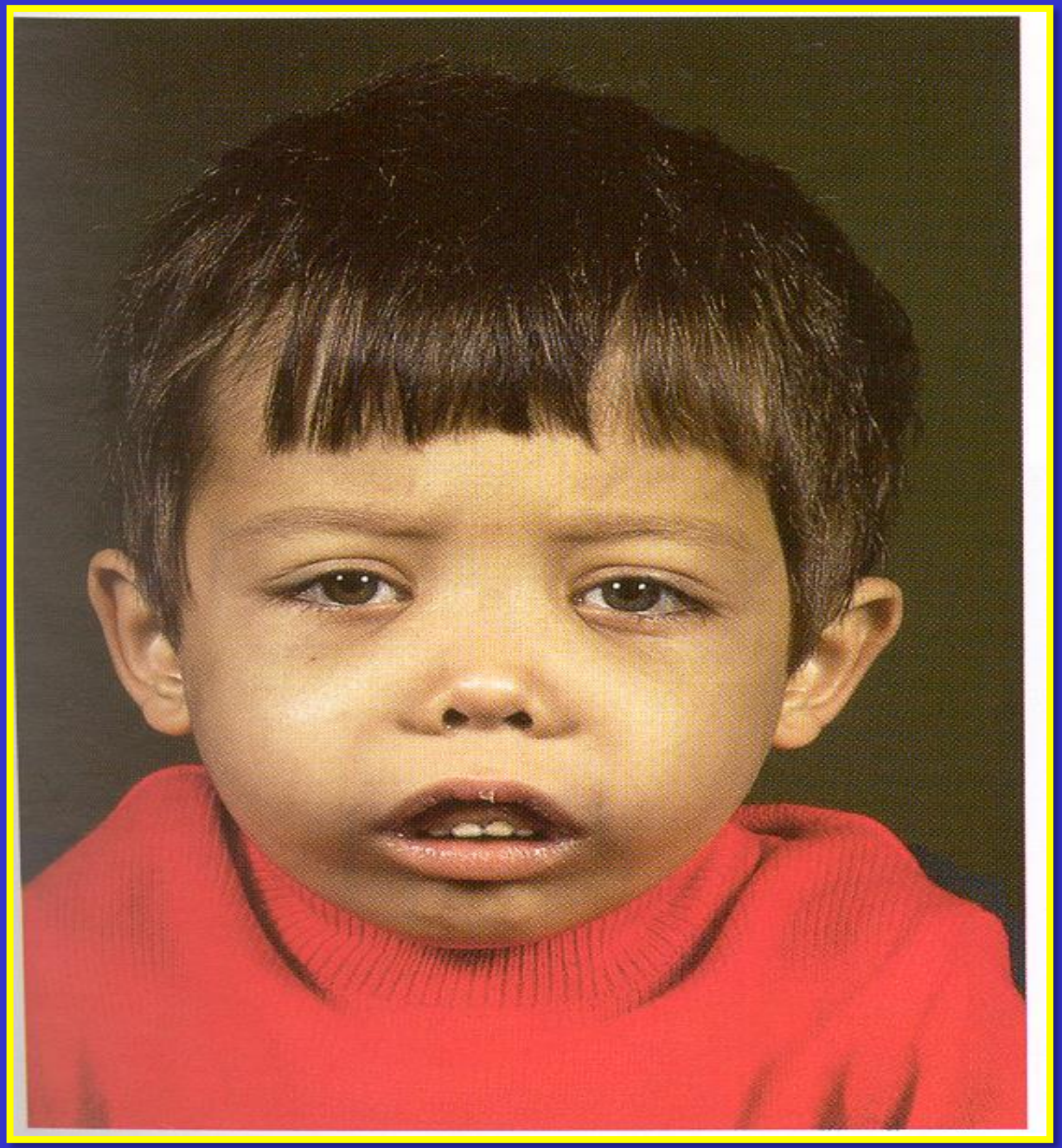
- Pallor
- Jaundice
- Apathy and Anorexia
- Failure to Thrive
- Hepato-splenomegaly
- Skeletal Deformity
- Iron Overload mainfestations

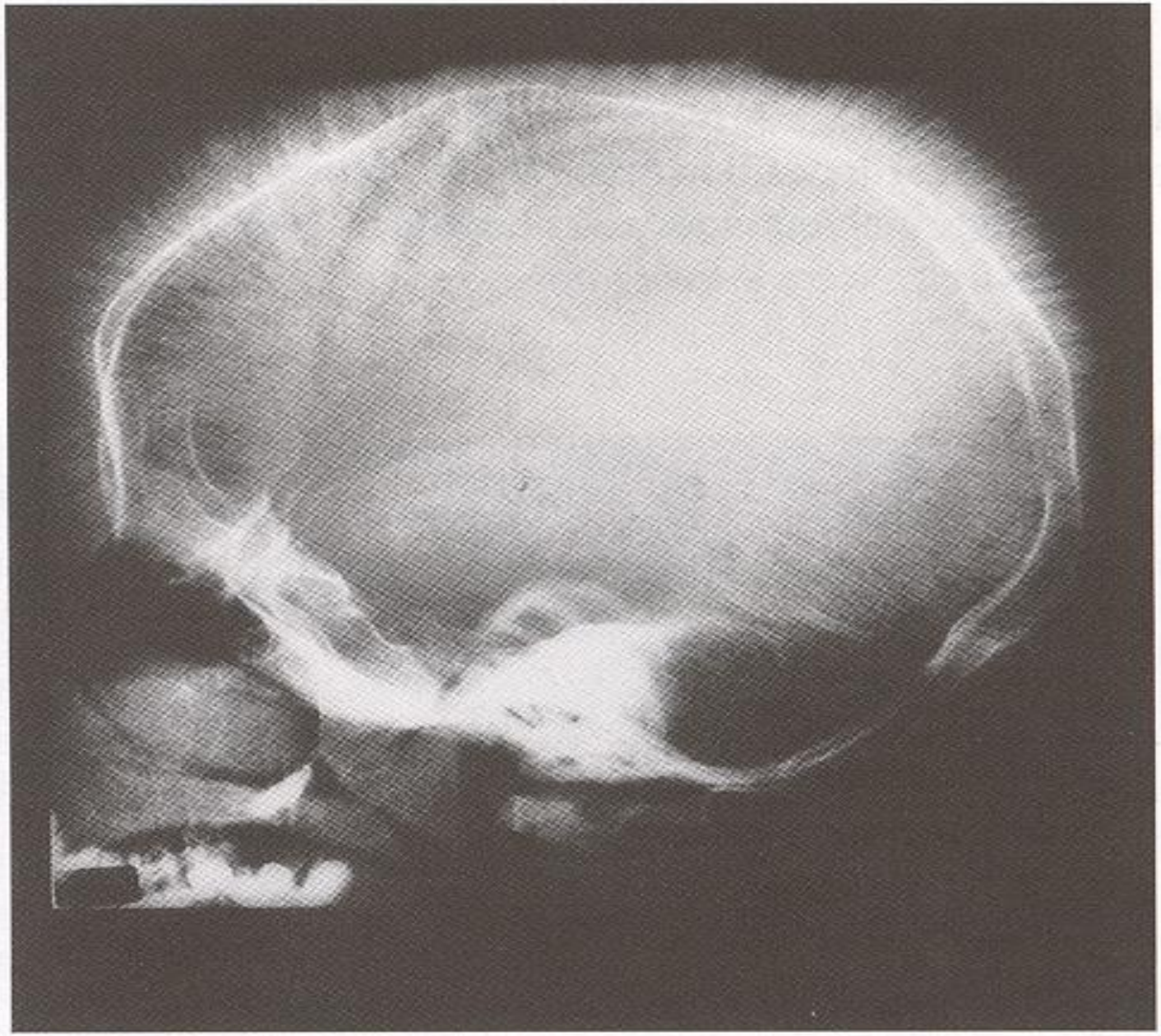


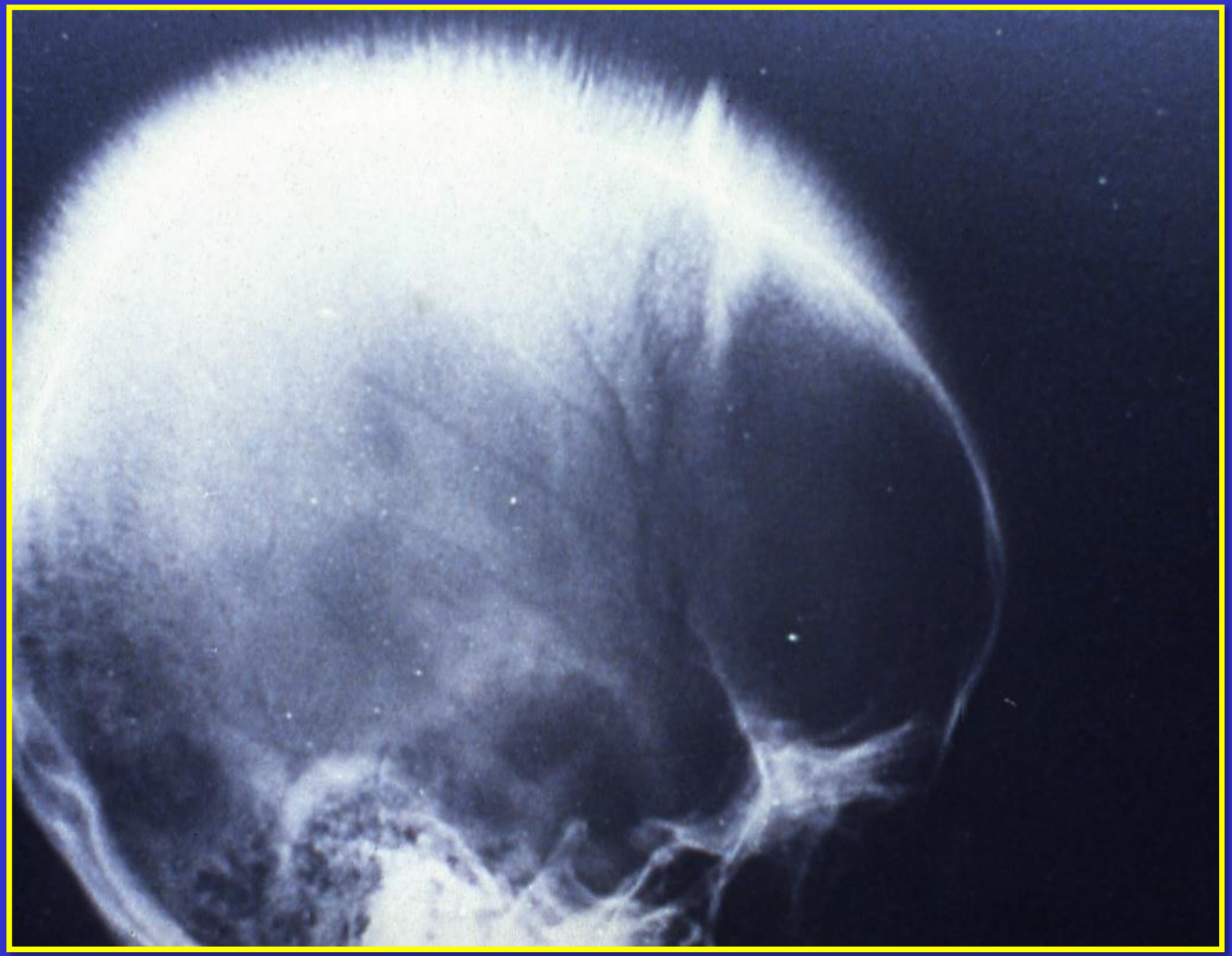


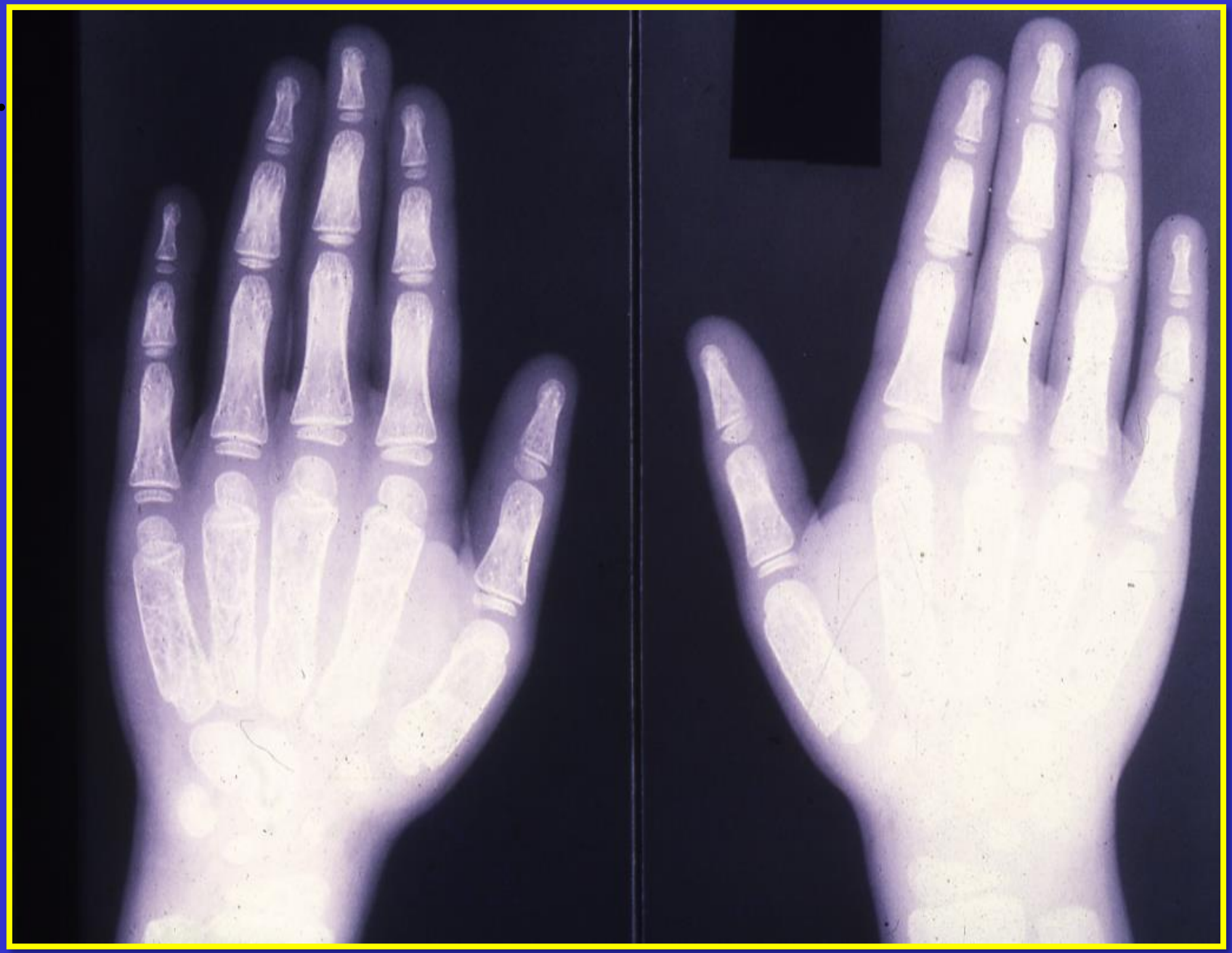


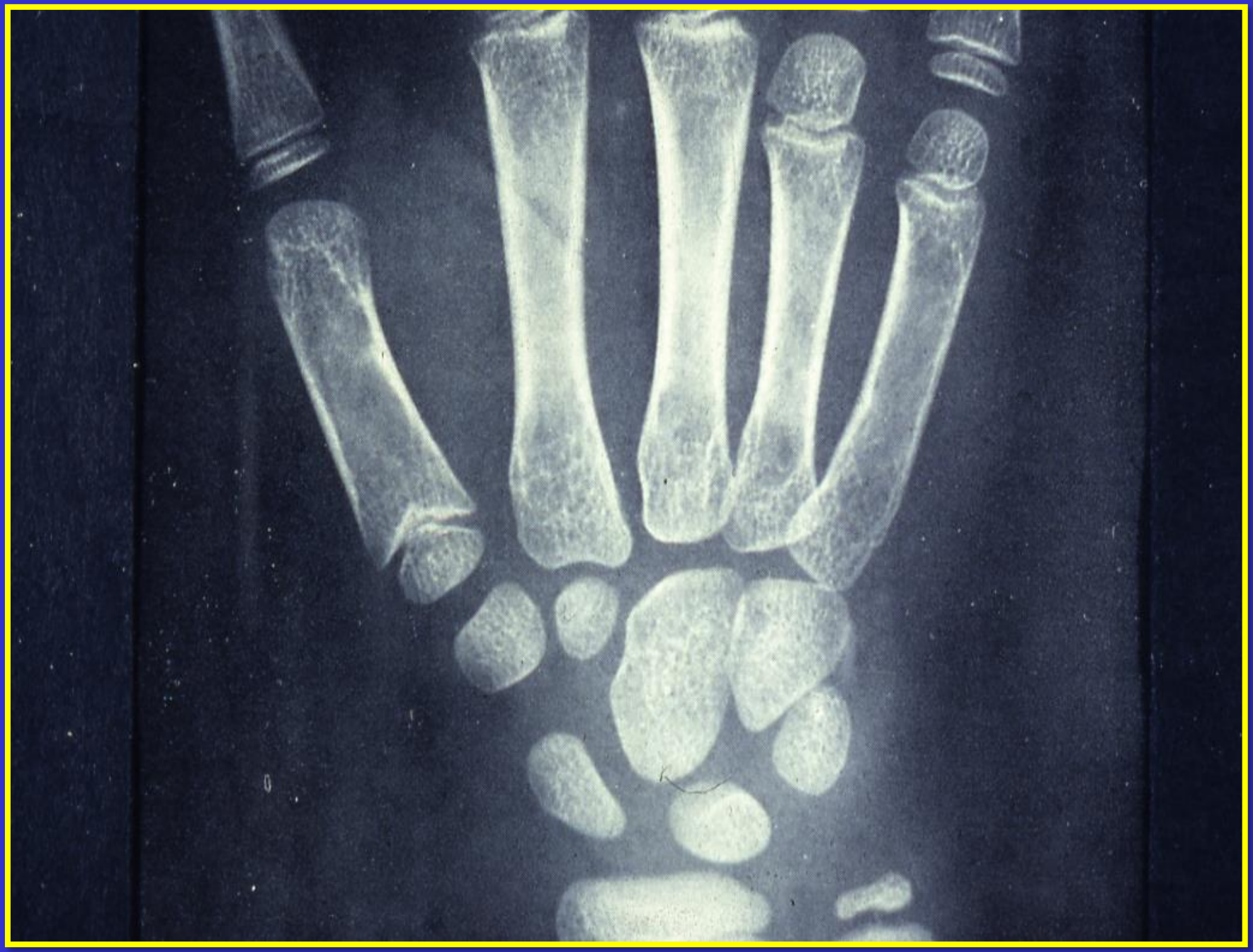










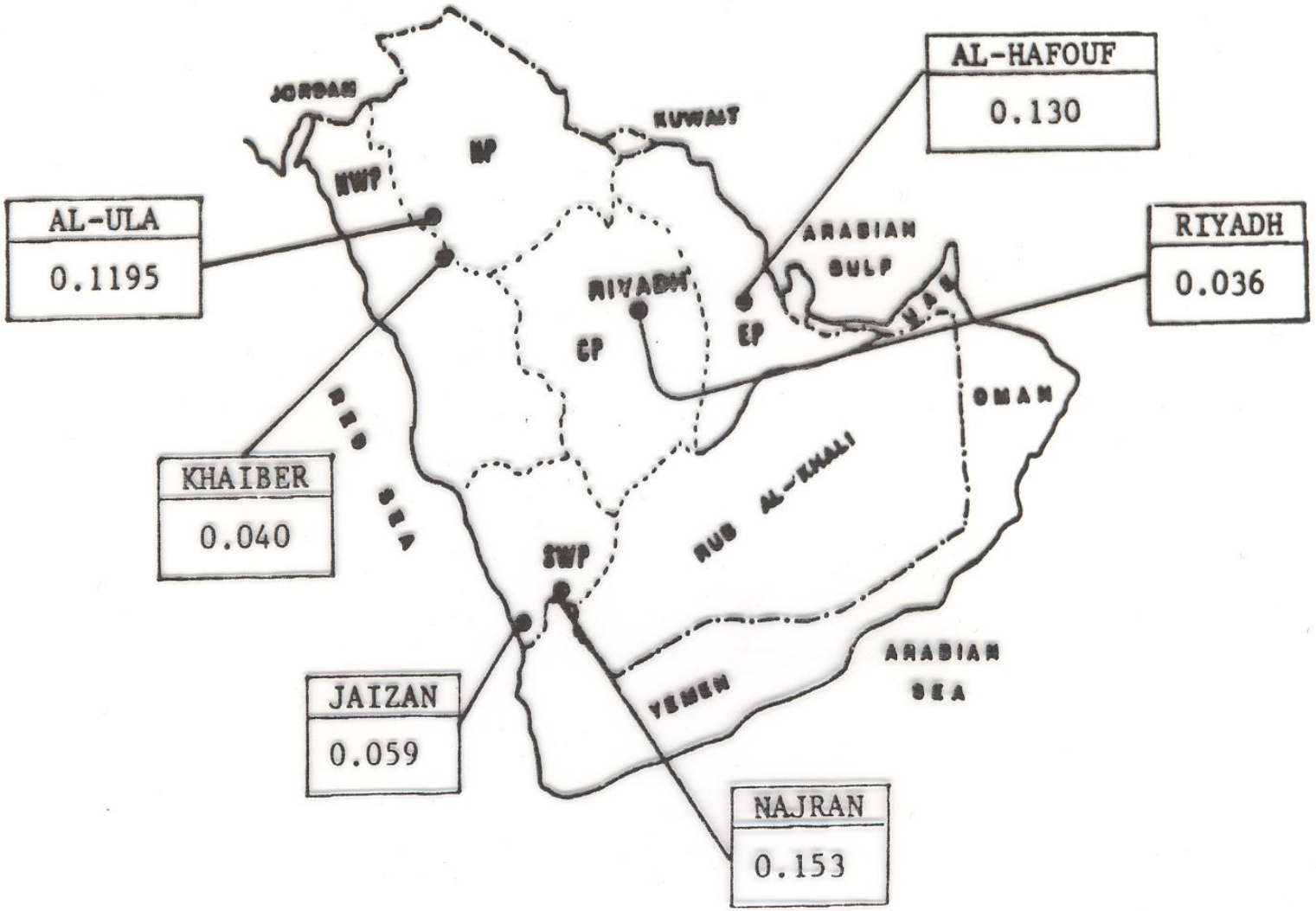


Clinical and Hematological Features of the β-Thalassemia Syndrome

	Major	Intermedia	Minor	Minima
Severity of mainfestations	++++	++	+, ±	±, 0
Genetics	Homozygotes, double heterozygotes	Homozygotes, double heterozygotes, rarely heterozygotes	Heterozygotes	Heterozygotes
Splenomegaly	++++	++,+++	+,0	0
Jaundice	+++	++,+	0	0
Skeletal changes	++++,++	+,0	+,0	0
Anemia (Hb, g/dl)	<7	7 – 10	>10	Normal

Clinical and Hematologic Features of the β-Thalassemia Syndrome (Continued)

	Major	Intermedia	Minor	Minima
Hypochromia	++++	+++	++	+
Microcytosis	+++	++	+	0
Target cells	10 – 35%	++	+	±
Basophilic stippling	++	+	+	0, +
Reticulocytes (%)	5 – 15	3 – 10	2 – 5	1 – 2
Nucleated red cells	+++	+, 0	0	0
±, little or no abnormality; +, mild abnormality; ++++, prominent abnormality				



Frequency of β-thalassaemia in different regions of Saudi Arabia. (From Ref. No. 20.) (No. investigated: Al-Hafouf 300; Riyadh 250; Al-Ula 427; Khaiber 500; Jizan 1271; Najran 301.) $f = 8.8353$; $df = 10$; $p < 0.01$

Diagnosis of Haemoglobinopathies including Thalassaemias

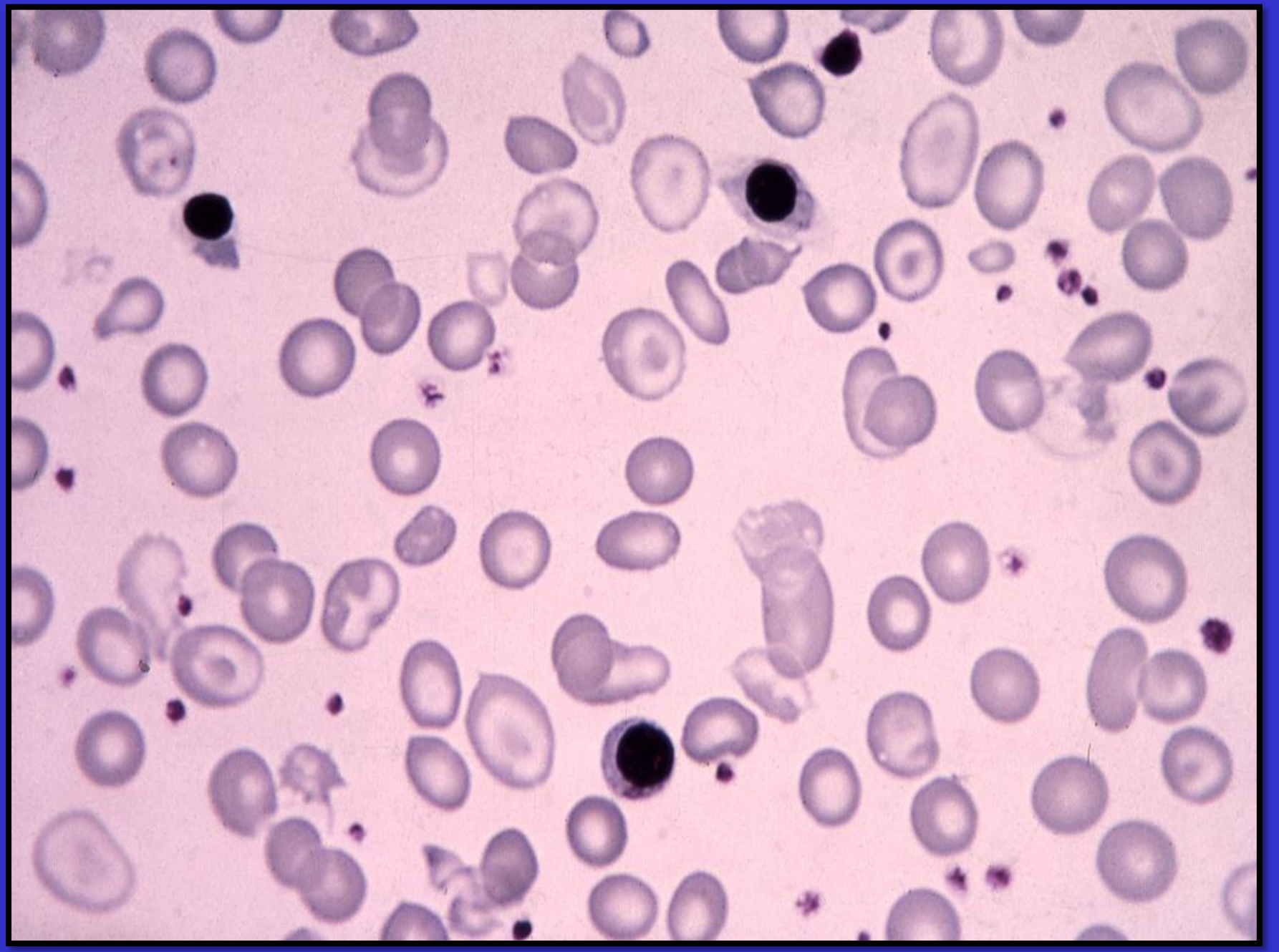
A. Personal & Family History

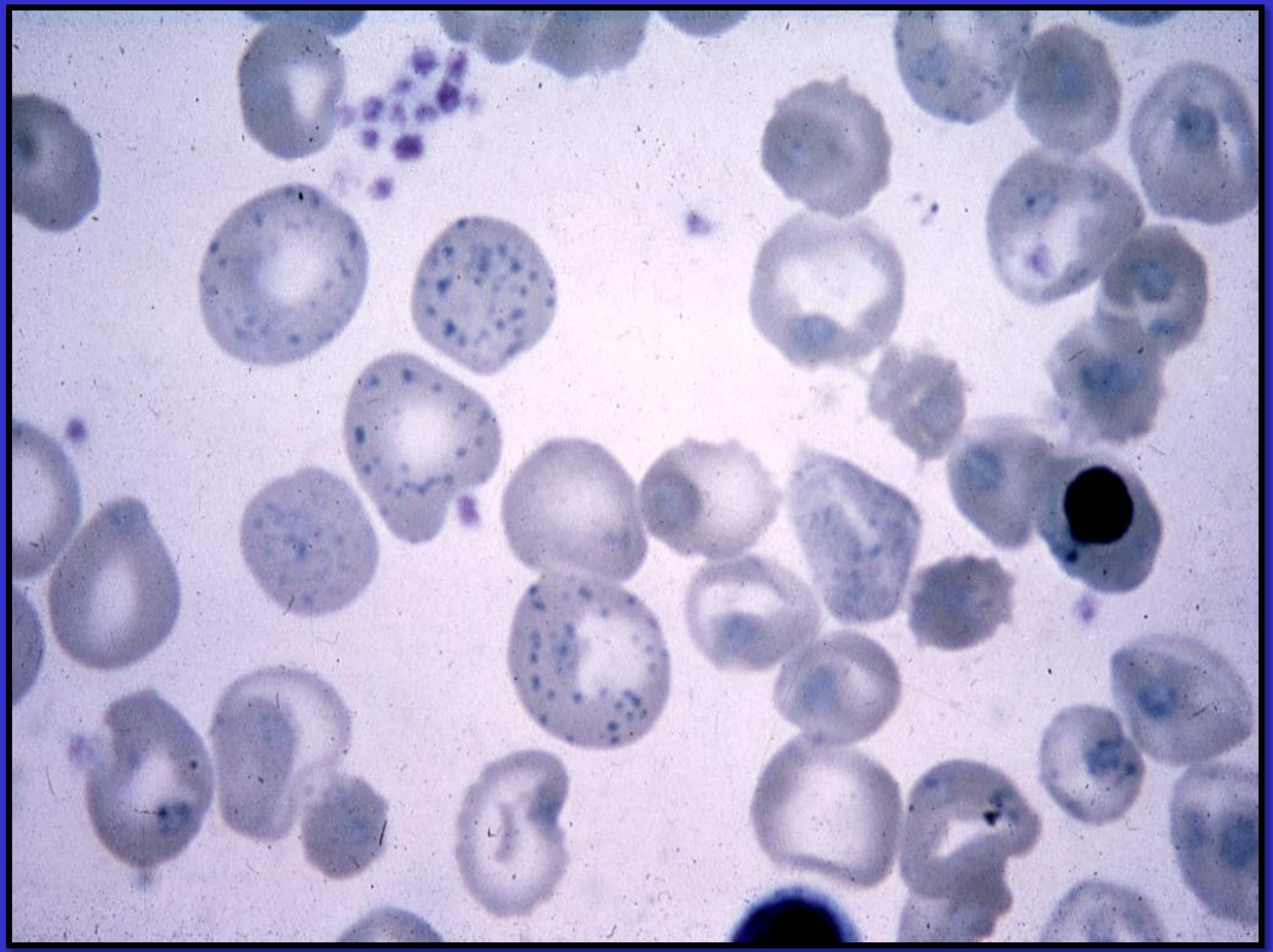
B. Physical Examination

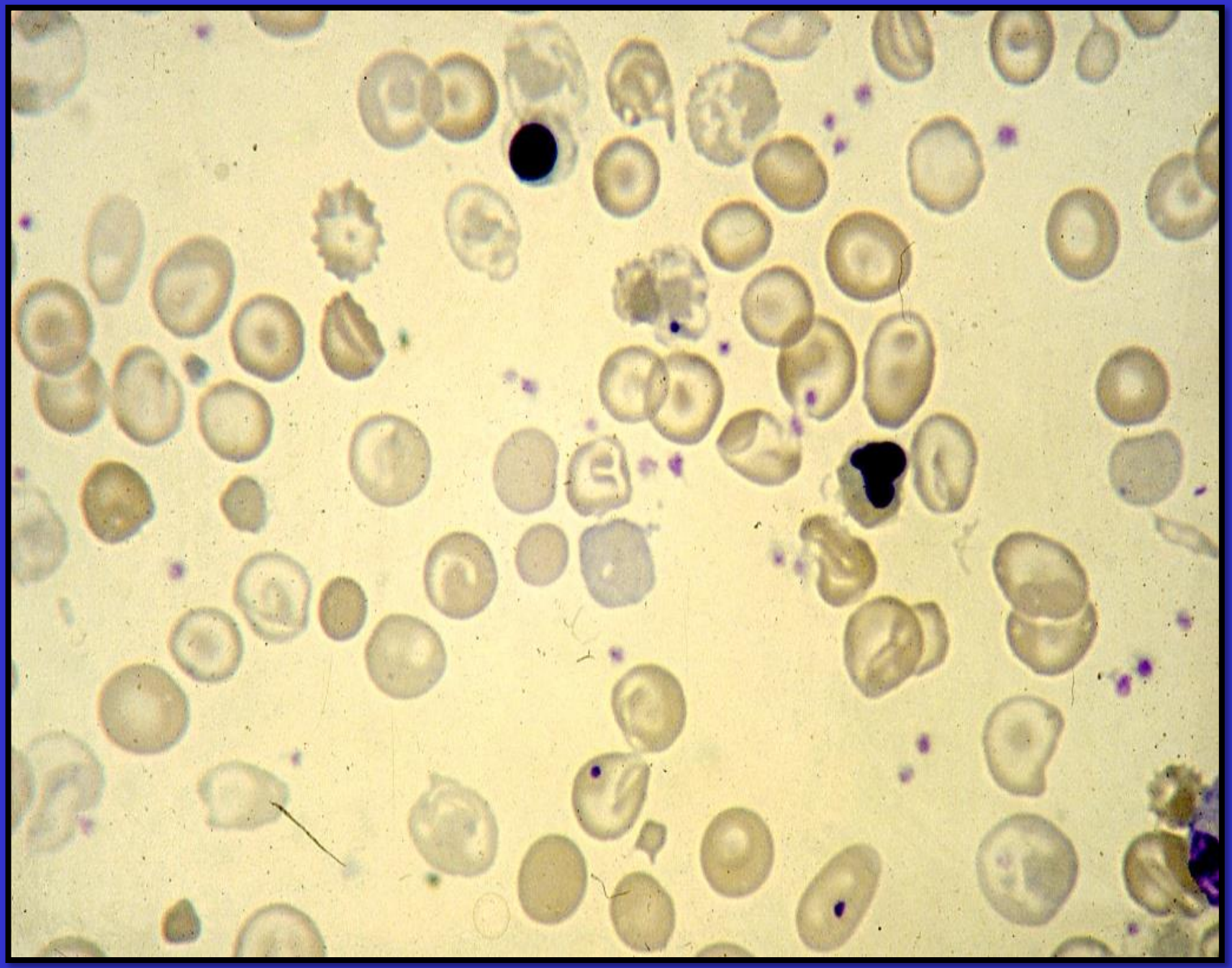
C. Laboratory Investigation

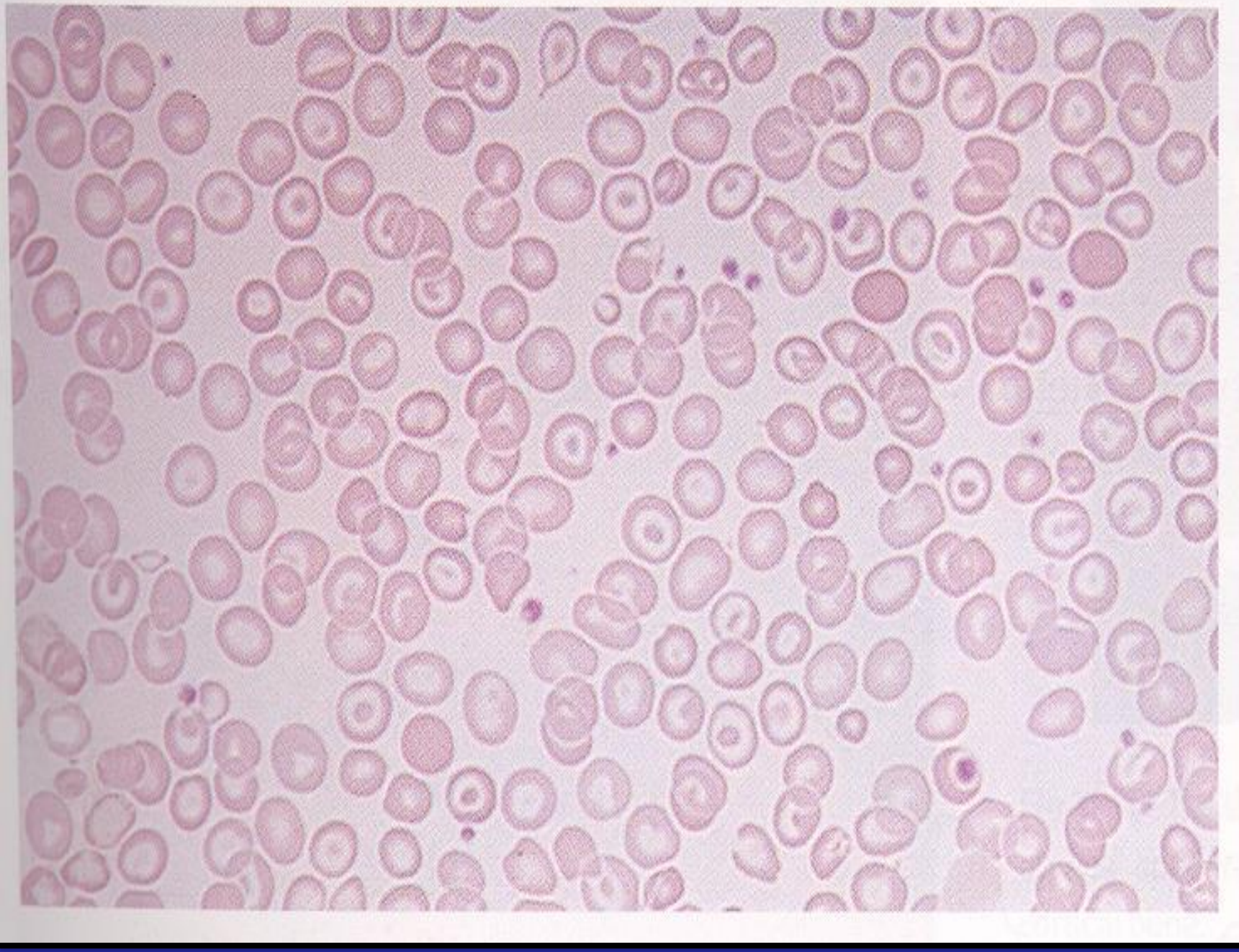
1. Haematological Tests – CBC, Red cell indices, blood film Morphology, reticulocyte count.
2. Sickling Tests – Sickle cell test, Sickle cell solubility test.
3. Hb Electrophoresis at alkaline/acidic pH and quantitation.
4. Quantitation of HbA2 and HbF
5. Serum iron total iron binding capacity and ferritin level
6. Biochemical tests:

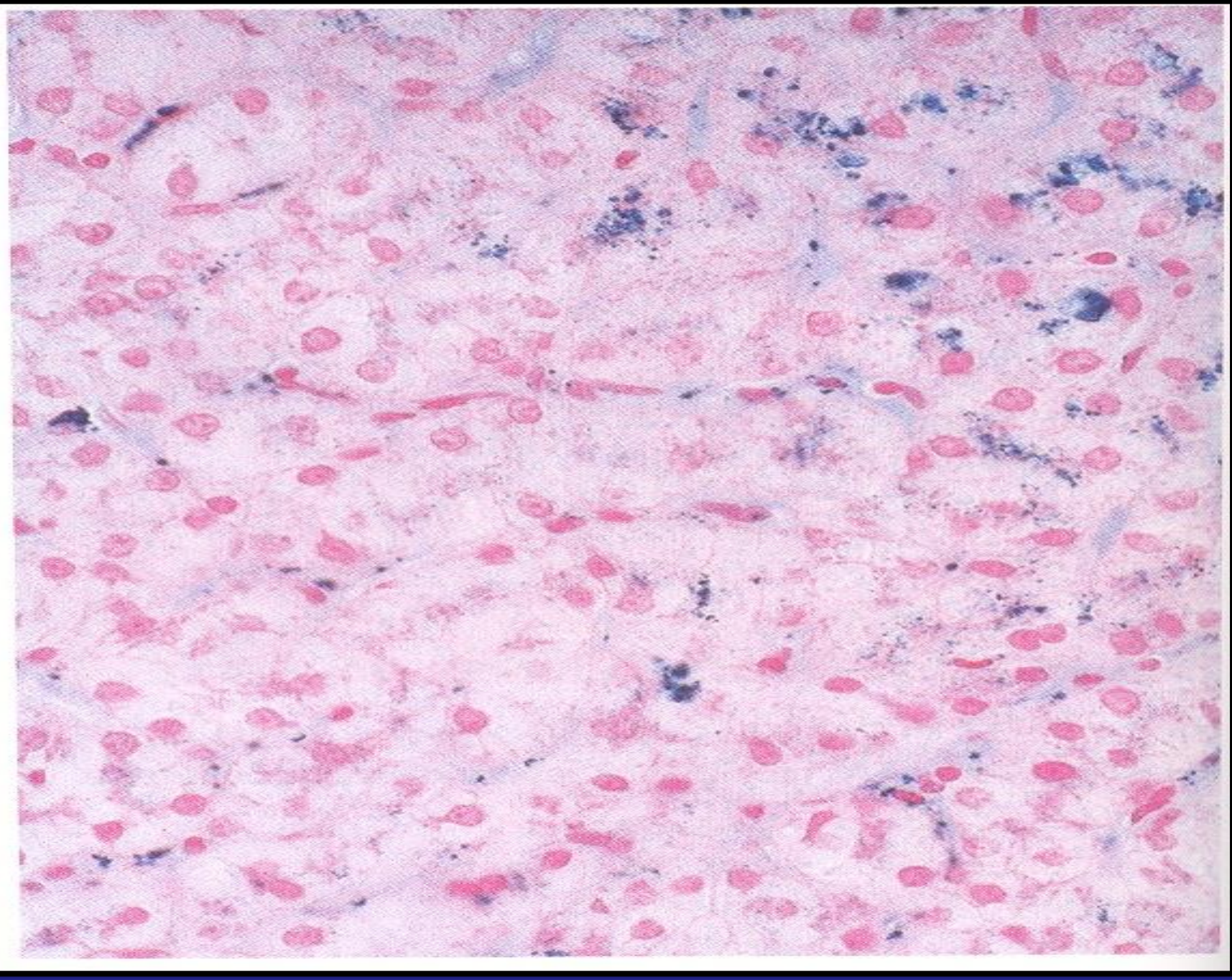
   Liver functions tests, renal function tests, blood gases and acid-base status, bone profile and urine analysis.
7. Special Tests
   A. Family studies (Laboratory Investigations)
   B. Measurement of Alpha/Non-Alpha chain ratio
   C. Gene Studies

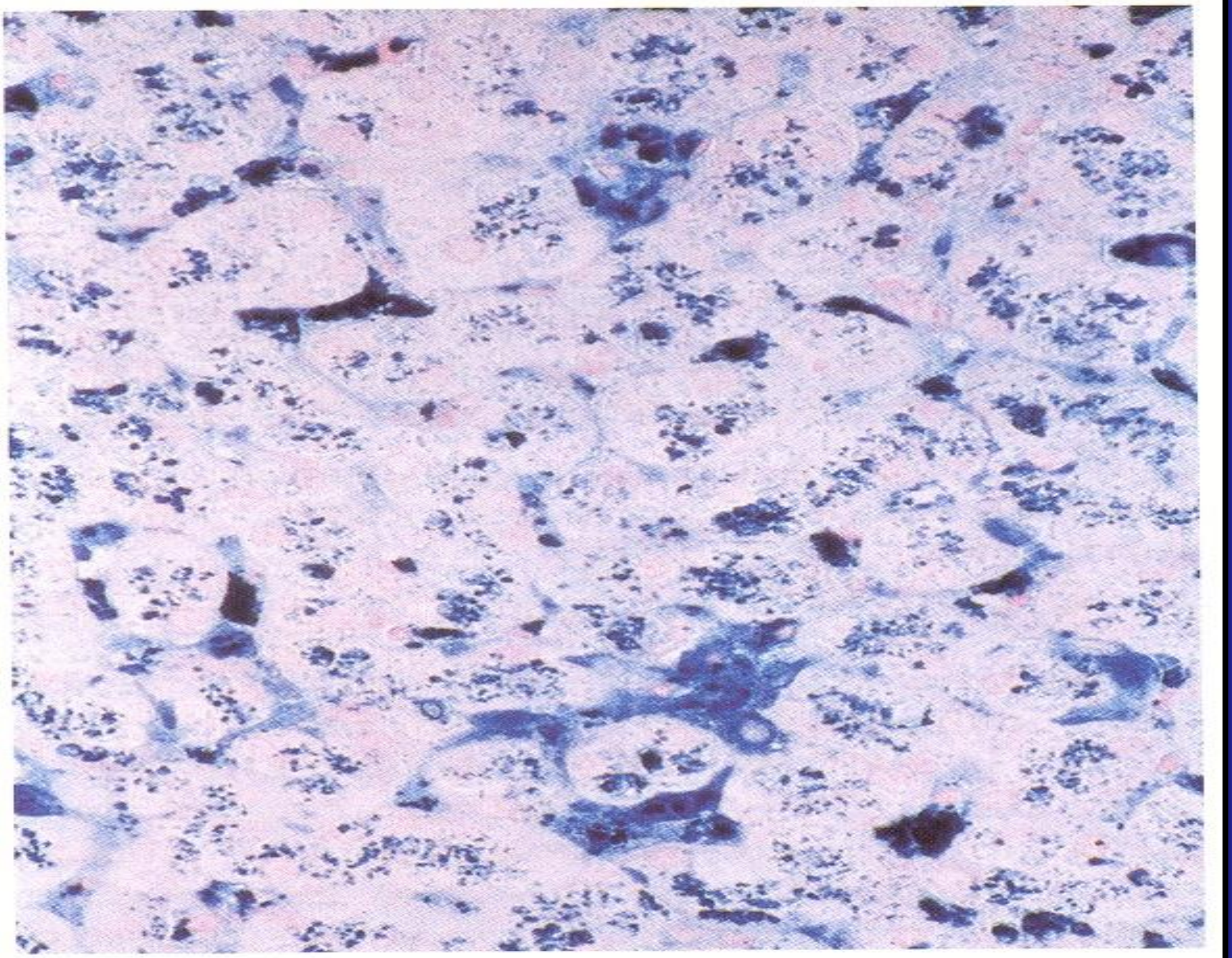












ING KHALID HOSP.
O BOX 7805 RIYADH

HEMATOLOGY UNIT

Page No.:1

Pat.No
Name:
Hospital:KING KHALID UNIVERSITY HOSPITA DOB:
Location: (PCF01) PCC (Female)
Doctor:UNKNOWN *

ref:
eq No.:H02022419 Date Coll.:04/01/23(18/03/02) Date Recd.:04/01/23(18/03/02)
rinted:09/01/1423(23/03/02)08:32 Time Recd.:10:30

DTA Whole Blood

	Full Blood Count				
[*]	WBC	5.60		4 - 11	x10.e9/L
[ ]>	RBC	5.67	H	4.2 - 5.5	x10.e12/L
<[ ]	HGB	98	L	120 - 160	g/L
<[ ]	HCT	31.0	L	37 - 47	%
<[ ]	MCV	54.6	L	80 - 94	fl
<[ ]	MCH	17.3	L	27 - 32	pg
<[ ]	MCHC	315	L	320 - 360	g/L
[ ]>	RDW	15.6	H	11.5 - 14.5	%
[*]	PLT	426		140 - 450	x10.e9/L
[*]	MPV	7.9		7.2 - 11.1	fl
<[ ]	PDW	15.6	L	20 - 70	%
[ ]>	PCT	0.339	H	0.150 - 0.32	%
	Differential				
[*]	%NEUT	74		40 - 75	%
<[ ]	%LYMP	19	L	20 - 45	%
<[ ]	%MONO	2	L	3 - 9	%
[*]	%EOS	5		0 - 6	%
[*]	#NEUT	4.14		2 - 7.5	x10.e9/L
[*]	#LYMP	1.06		1 - 5	x10.e9/L
<[ ]	#MONO	0.11	L	0.2 - 0.8	x10.e9/L
[*]	#EOS	0.28		0.0 - 0.8	x10.e9/L
	Morophology				
	Flag Comments	3+ ,3+			
	Flag Comment 1				
	ANISO				
	MICRO	MK			
	MACRO				
	POIKILO				
	HYPO	MK			
	Polychromasia				
	LSHIFT				
	TARGET CELLS	SL			
	Ovalocytes	SL			
[*]	Retic Count	1.4		0.2 - 2.0	%
[ ]>	ESR	35	H	3 - 9	mm/hr

NG KHALID HOSPITAL | DEPARTMENT OF SPECIAL BIOCHEMISTRY
BOX 7805 RIYADH |==========

|Hosp No. Page No.:1
|Patient: AA
|Hosp Srce:KING KHALID UNIVERSITY HOSPIT DOB: 1
|Location: (EHC) Employee Health Clinic
ef: |Doctor:UNKNOWN *
No.:S0202265 Date Coll.:04/01/23(18/03/02) Date Recd.:04/01/23(18/03/02)
inted:09/01/1423(23/03/02)08:34 Time Recd.:10:51

ious Blood

Hemoglobin Electrophoresis

95 - 99	%	<[ ]	Hemoglobin A	93.5	L
0 - 2.0	%	[*]	Hemoglobin F	2.0	
2.0 - 3.5	%	[ ]>	Hemoglobin A2	4.5	H
			Hemoglobin S	0.0	
			Hemoglobin E	0.0	
			Hemoglobin C	0.0	
	%		Hemoglobin O	0.0	

Kingdom of Saudi Arabia
Ministry of Higher Education
King Saud University
College of Medicine
& king Khalid University Hospital

المملكة العربية السعودية
وزارة التعليم العالي
جامعة الملك سعود
كلية الطب
ومستشفى الملك خالد الجامعي

نموذج فحص ما قبل الزواج

تاريخ سحب العينة : / / ١٤هـ رقم الملف الطبي: ..... رقم المختبر .....

اسم الطبيب المعالج: ..... رقم التحويلة/النداء ..... العيادة .....

البيانات الشخصية:

الاسم ..... الجنسية: ..... العمر: ( ) الجنس : ☐ ذكر ☐ أنثى.

رقم السجل المدني/الإقامة: ..... العنوان: ..... الهاتف: .....

الفحوصات المطلوبة:

١- تعداد الدم الكامل (CBC). ٢- اختبار الخلايا المنجلية (Sickling).

٣- الرحلان الكهربي لخضاب الدم (Hb Electrophoresis). ٤- اختبارات أخرى (Other Tests).

LABORATORY RESULT

TEST	NORMAL RANGE	RESULT	REMARKS
RBCX10^{12}/L	M:4.7 – 6.1 ….F:4.2-5.5		
HBg/dL	M:13 –18 ….F:12-16		
Het%	M:42 – 52 ….F:37- 47%		
MCV fL	80 – 94		
MCH pg	27 – 32		
MCHCg/dL	32 – 36		
RDW	11.5 – 14.5%		
Retic	0.5 – 2%		
Sicking Test	Positive or Negative		
Hb A	95 – 97%		
Hb A2	2.0 – 3.5%		
Hb F	<1.5%		
Abnormal Hemoglobin			
TEST	PATIENT RESULT	HEMOGLOBIN	PATIENT RESULT
Hb S		Hb J	
Hb C		Hb O – Arab	
Hb D		Hb H	
Hb E		Hb Barts	
Hb G		Other Test	
Other Hb			

المشرف الفني بالوحدة: .....

ملاحظات: ..... COMMENTS:.....

.....

.....

استشاري أمراض الدم بالمختبر: ..... التوقيع: .....

✱ **ملاحظة هامة:** هذه الشهادة تبين نتيجة الفحص المخبري لمرضي الأنيميا المنجلية والثلاسيميا فقط، ولا تشمل أي أمراض وراثية أخرى للطرفين المعنيين.

Kingdom of Saudi Arabia
Ministry of Higher Education
King Saud University
College of Medicine
& king Khalid University Hospital

المملكة العربية السعودية
وزارة التعليم العالي
جامعة الملك سعود
كلية الطب
ومستشفى الملك خالد الجامعي

نموذج فحص ما قبل الزواج

تاريخ سحب العينة : / / ١٤ هـ رقم الملف الطبي: رقم المختبر .....

اسم الطبيب المعالج: .. رقم التحويلة/النداء ..... العيادة .....

البيانات الشخصية:

الاسم .. الجنس .. العمر: ( ) الجنس : ☐ ذكر ☐ أنثى

رقم السجل المدني/الإقامة: ..... العنوان: ..... الهاتف: .....

الفحوصات المطلوبة:

١ – تعداد الدم الكامل (CBC). ٢ – اختبار الخلايا المنجلية (Sickling).

٣ – الرحلان الكهربي لخضاب الدم (Hb Electrophoresis). ٤ – اختبارات أخرى (Other Tests).

LABORATORY RESULT

TEST	NORMAL RANGE	RESULT	REMARKS
RBCX10^{12}/L	M:4.7 – 6.1 ....F:4.2-5.5	4.5	
HBg/dL	M:13 –18 ....F:12-16	12.9	
Het%	M:42 – 52 ....F:37- 47%	37.8	
MCV fL	80 – 94	83.9	
MCH pg	27 – 32	28.6	
MCHCg/dL	32 – 36	34.1	
RDW	11.5 – 14.5%	13.6	
Retic	0.5 – 2%	–	
Sicking Test	Positive or Negative	Negative	
Hb A	95 – 97%	96.9	
Hb A2	2.0 – 3.5%	2.6	
Hb F	<1.5%	<0.5	
Abnormal Hemoglobin			
TEST	PATIENT RESULT	HEMOGLOBIN	PATIENT RESULT
Hb S		Hb J	
Hb C		Hb O – Arab	
Hb D		Hb H	
Hb E		Hb Barts	
Hb G		Other Test	
Other Hb			

المشرف الفني بالوحدة: .....

ملاحظات: سالمة من أمراض الدم الوراثية

COMMENTS: .....

استشاري أمراض الدم بالمختبر: ..... التوقيع: 6-2-26

✱ **ملاحظة هامة:** هذه الشهادة تبين نتيجة الفحص المخبري لمرضي الأنيميا المنجلية والثلاسيميا فقط، ولا تشمل أي أمراض وراثية أخرى للطرفين المعنيين.

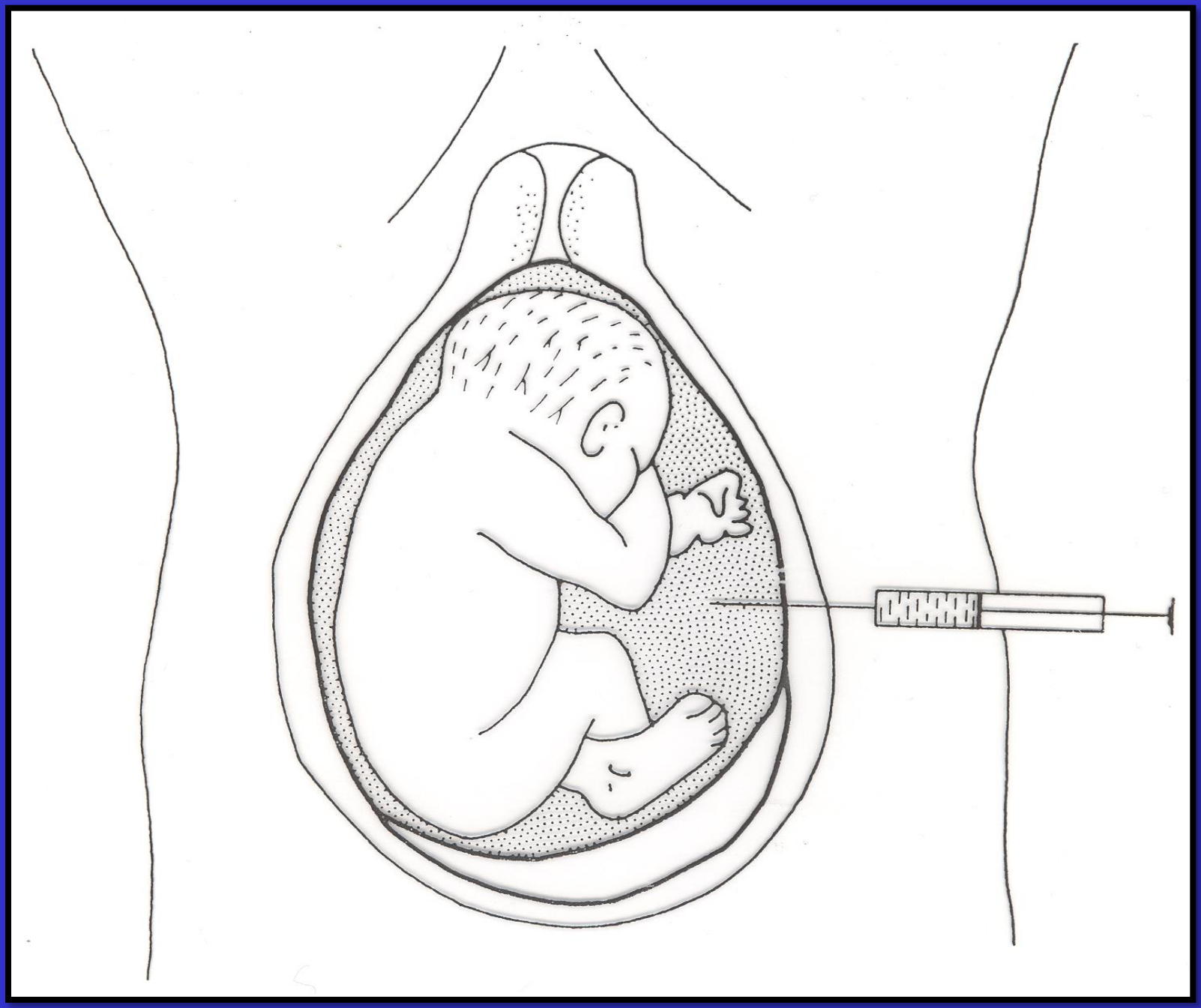
Prenatal diagnosis of the haemoglobinopathies (Including thalassaemia)

DNA Analysis

A. Chorionic villus sampling
   - Transcervical approach (9 – 11 weeks of pregnancy)
   - Transabdominal approach (up to 15 weeks of pregnancy)

B. Amniotic fluid cell analysis (16 – 20 weeks gestation)

C. Fetal blood sampling (> 20 weeks gestation)
   - DNA analysis
   - Haematological parameters
   - Biochemical analysis
   - Globin chain synthesis
     - α/β Ratio
     - α/γ Ratio
     - α/δ Ratio



DNA ANALYSIS

1. **Gene mapping**

2. **RFLPs linkage analysis**
   (Restriction fragment length polymorphisms)

3. **Oligonucleotide probes**
   (Using short gene probes 17 – 19 Nucleotide)

4. **Gene amplification**
   (Enzymatic amplification of DNA sequences)

   DNA polymerase chain reaction technique.

MANAGEMENT OF THE THALASSEMIAS

- **Blood Transfusion**
- **Iron chelation therapy**
- **Splenectomy**
- **Hormone replacement**
- **Bone marrow transplantation**
- **Gene therapy**

SUMMARY OF RECOMMENDATIONS FOR THE TREATMENT OF THALASSEMIA MAJOR

TRANSFUSION

Transfusion, in the absence of cardiopathy:

- **Blood-type the patient completely;**
- **Vaccinate hepatitis B negative patients against hepatitis;**
- **Transfuse when the Hb remains consistently below 8 g/dL, or earlier if there are other indications;**
- **Keep the pretransfusion Hb between 10.5 and 11 g/dL;**
- **Give 10-15 mL/kg of blood preparation in 2 h;**
- **Do not raise the posttransfusion Hb above 16 g/dL;**
- **Choose a 3-4 week transfusion interval.**

SUMMARY OF RECOMMENDATIONS FOR THE TREATMENT OF THALASSEMIA MAJOR (Continued)

TRANSFUSION

Transfusion in the presence of cardiopathy, or when the Hb is less than 5 g/dL:

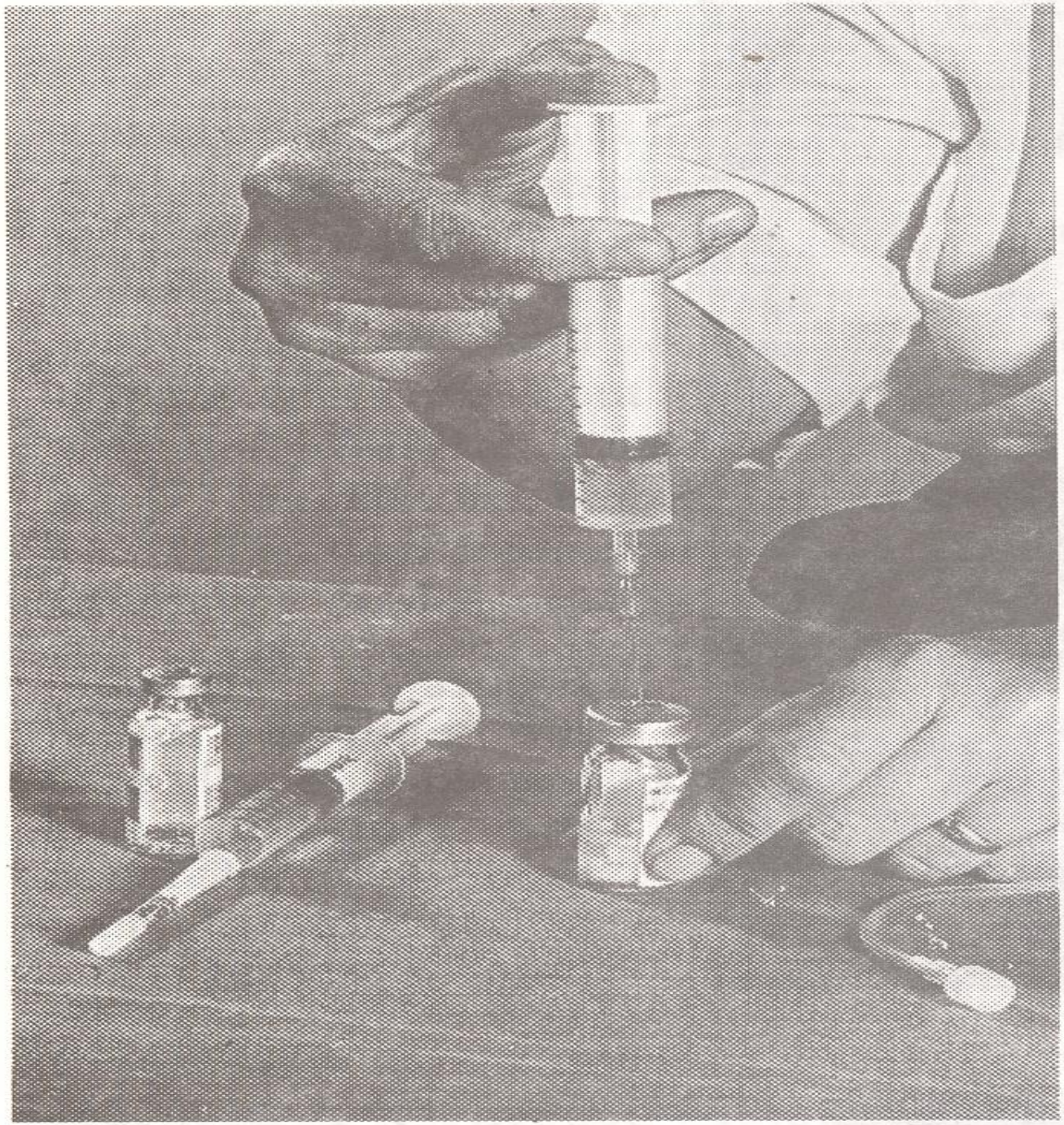
- **Inject furosemide 1-2 mg/kg;**
- **Preferably use fresh blood;**
- **Do not transfuse more than 5 mL/kg of blood;**
- **Do not transfuse faster than 2 mL/kg, or for more than 4 h;**
- **If necessary, divide the blood among 2 or more bags;**
- **Use very short intertransfusion intervals.**

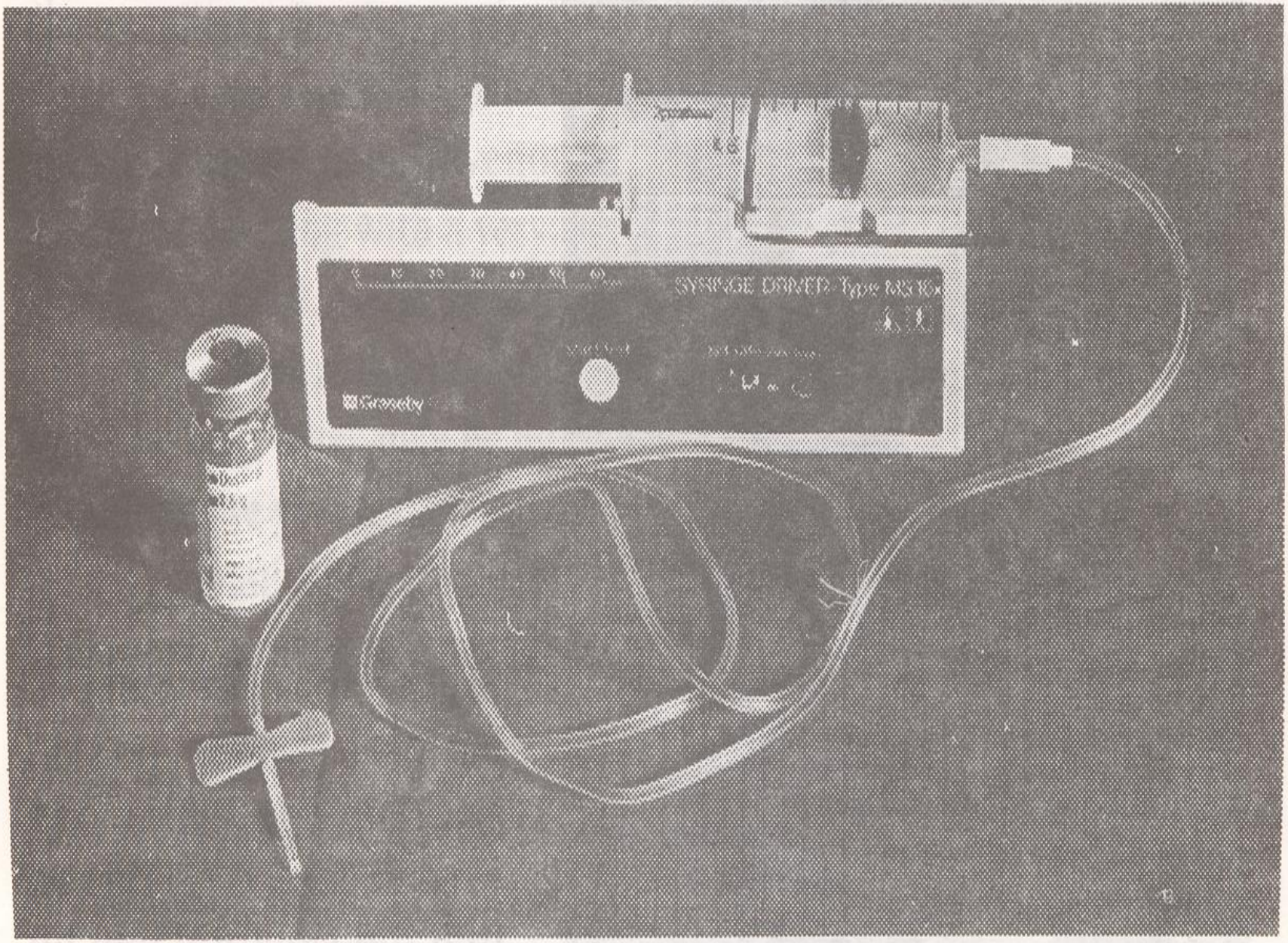
IRON CHELATION THERAPY

1) Desferrioxamine S.C. 20-60 mg/kg/day in 8 h (average 40 mg/kg/day, or 280 mg/kg/ week).
2) In selected subjects, give desferrioxamine i.v. in high dose, maximum 100 mg/kg over 8 h, only on the days of transfusion.

SPLENECTOMY

1) Is indicated when the blood consumption is more than 1.5 times normal.
2) Give anti-pneumococcal vaccine to children more than 2 years old prior to splenectomy.
3) Inform the patients and their family doctors of increased risk of serious infections.
4) Give prophylactic penicillin, and a platelet anti-aggregant when there is thrombocytosis.





ORAL IRON CHELATION THERAPY

- **Deferiprone [Ferriprox]**
- **Oral Tablet or Syrup 5 to 10 mg /kg /day divided in 3 doses.**
- **More effective than desferoxamine in chelating cardiac iron.**
- **Total iron excretion with deferiprone is less than with desferoxamine.**
- **Major adverse effect especially in children include - Gastrointestinal symptoms, joint pain, liver disfunction, neuropenia in 27% of patients.**

ORAL IRON CHELATION THERAPY (CONTINUE)

- ✓ **Deferasirox (EXJADE, NOVARTIS)**
- ✓ **The dose is 20-30 mg/kg/day once daily.**
- ✓ **Approved by FDA.**
- ✓ **Reduction of liver iron to 50%, reduction of serum ferritin to 70% after 1 year treatment.**

Side effects:

- **Nausea, vomiting, diarrhea, abdominal pain, skin rash.**
- **Mid increase in serum cratinine in 30% of patients as with Desferoxamine ocular and auditory disturbance have been reported.**
- **Increase in serum transaminases in 10% of patients.**
- **Reduction of the dose in steps 5-10mg/kg/day every 3-6 months depending on serum ferritin level.**

Assessment of Iron Stores

- Serum ferritin
- Serum iron and percentage saturation of transferrin (iron-binding capacity)
- Bone marrow biopsy (Perl's stain) for reticuloendothelial stores
- DNA test for mutation resulting in Cys282 Tyr in the HFE gene
- Liver biopsy (parenchymal and reticuloendothelial stores)
- Liver CT scan or MRI
- Cardiac MRI
- Desferrioxamine iron excretion test (chelatable iron)
- Repeated phelobotomy until iron deficiency occurs

Assessment of tissue damage caused by iron overload

Cardiac	**Clinical; chest X-ray; ECG; 24-h monitor; echocardiography; radionuclide (MUGA scan to check left ventricular ejection fraction at rest and with stress**
Liver	**Liver function tests; liver biopsy; CT scan**
Endocrine	**Clinical examination (growth and sexual development) glucose tolerance test; pituitary gonadotrophin release tests; thyroid, parathyroid, gonadal, adrenal function, growth hormone assays; radiology for bone age; isotopic bone density study**

CT, computed tomography; ECG, electrocardiography; MRI, magnetic resonance imaging; MUGA, multiple gated acquisition.

INVESTIGATIONS AND FOLLOW-UP

Prior to treatment:	**Study the case, and do complete red cell typing.**
Before each transfusion:	**Hb, cross-match and red cell antibody detection, serum transminases (in areas with a high incidence of hepatitis). Record the date of transfusion, net weight and mean hematocrit of the blood preparation, and the Hb of the patient**
After each transfusion:	**Measure the posttansfusion Hb.**
Every 3 months:	**Measure height and weight**
Every 6 months:	**Ferritin estimation.**
Every year:	**Evaluate growth and development.**
	Calculate the transfusion indices.
	Evaluate iron balance.
	Complete evaluation of the case.
Variable intervals:	**Cardiac and endocrinological investigations according to the clinical state of the patient.**


Thank you !!!