Thalassemias

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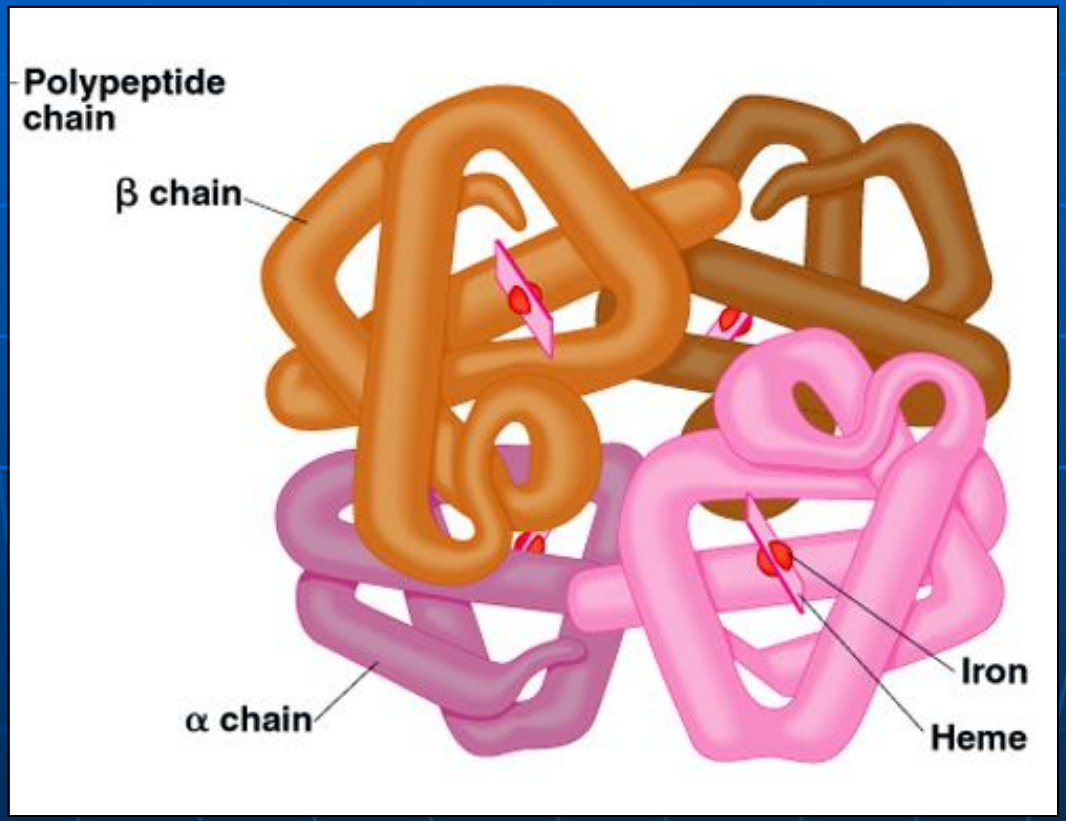
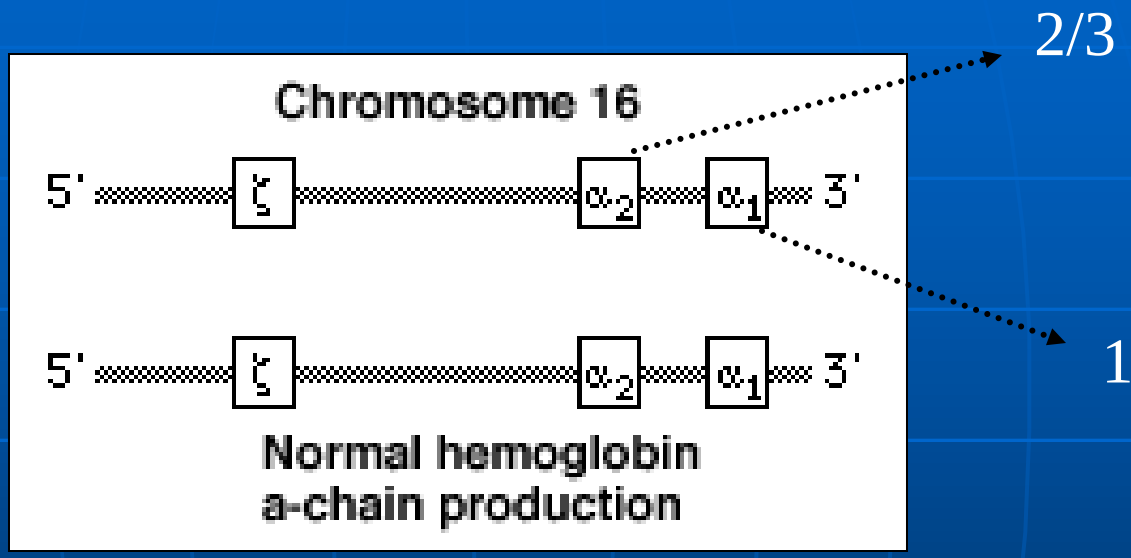
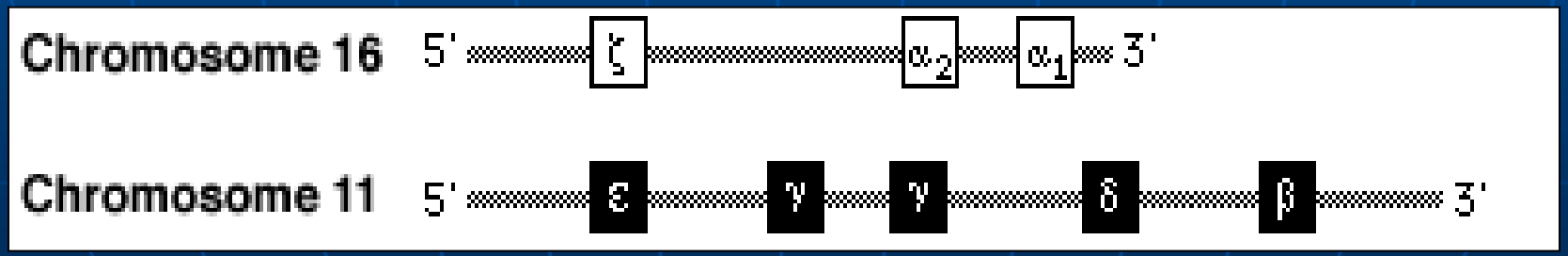
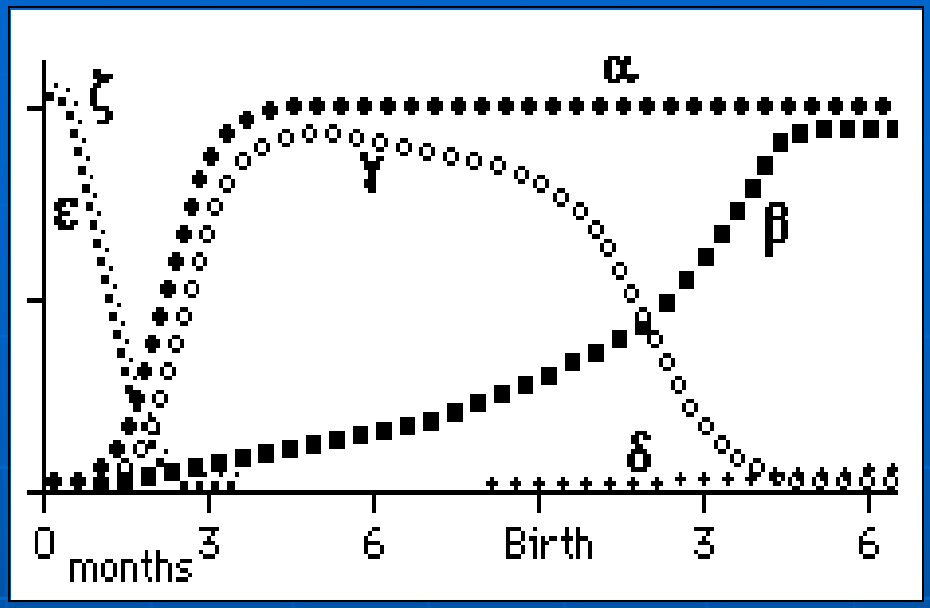
Structure and Function of normal Hemoglobin molecules:




2/3
Chromosome 16
5'
ζ
α2
α1
3'
5'
ζ
α2
α1
3'
1/3
Normal hemoglobin
a-chain production


Chromosome 16
5'
ζ
α2
α1
3'
Chromosome 11
5'
ε
γ
γ
δ
β
3'

β: increases from 6th week of fetal life to 12 months of age



At birth:

- HbF: 75-90%
- HbA: 10-25%
- HbA_2: 0.5%

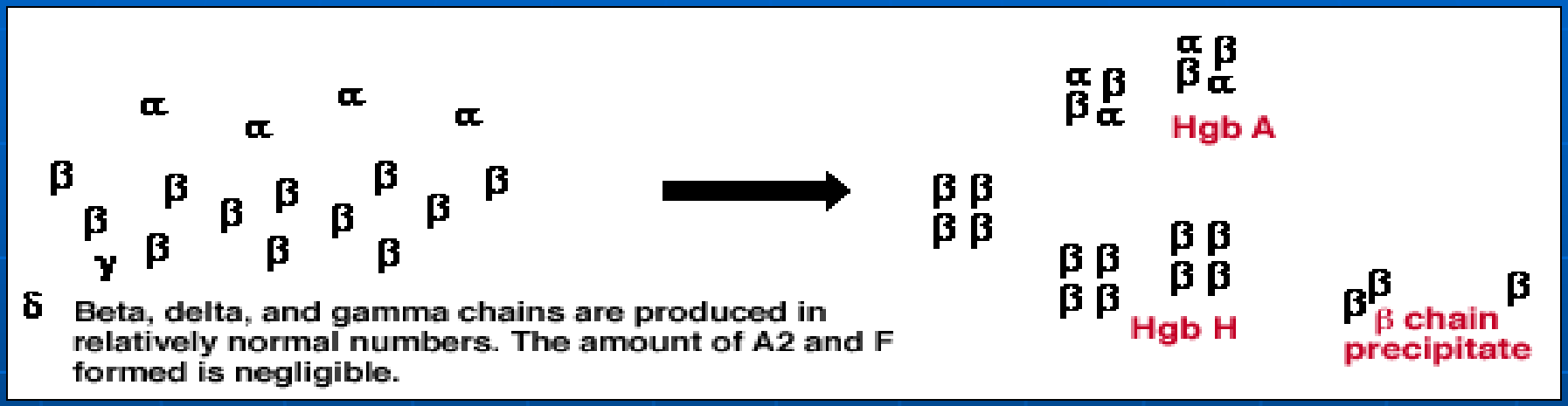
Beyond 1 yr:

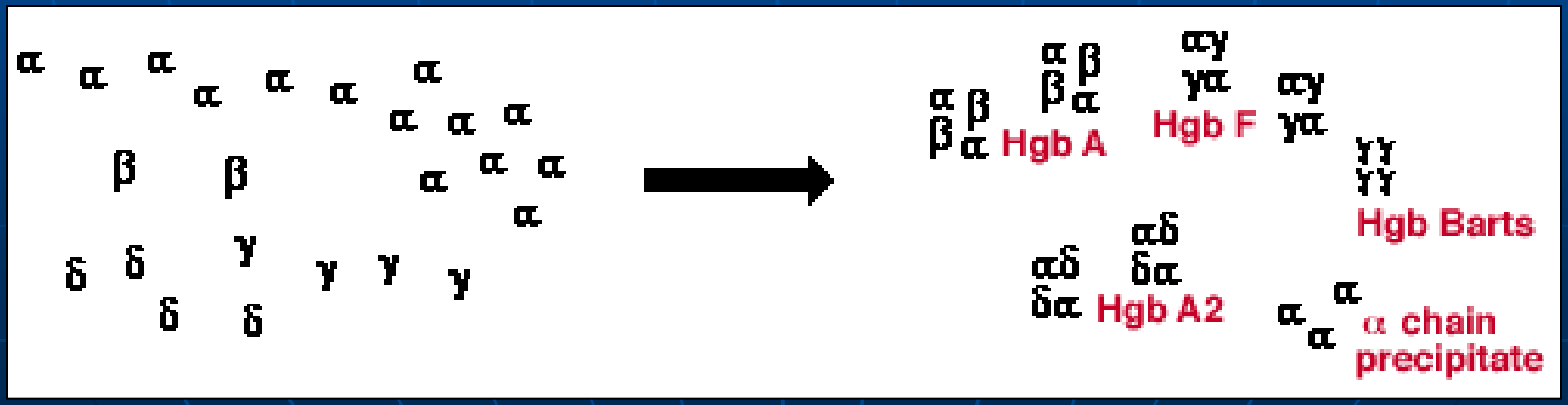
- HbF: < 1%
- HbA: 96%
- HbA_2: 2.5%

HbA: α2β2
HbF: α2γ2
HbA2: α2δ2
Gower 1: ζ2ε2
Gower 2:
α2ε2

Thalassemias

- Quantitative abnormalities
- Decreased/absent rate of production of certain globin chains
- Imbalance of globin chains available for hemoglobin dimer construction
- Formation of abnormal amounts of structurally normal hemoglobins

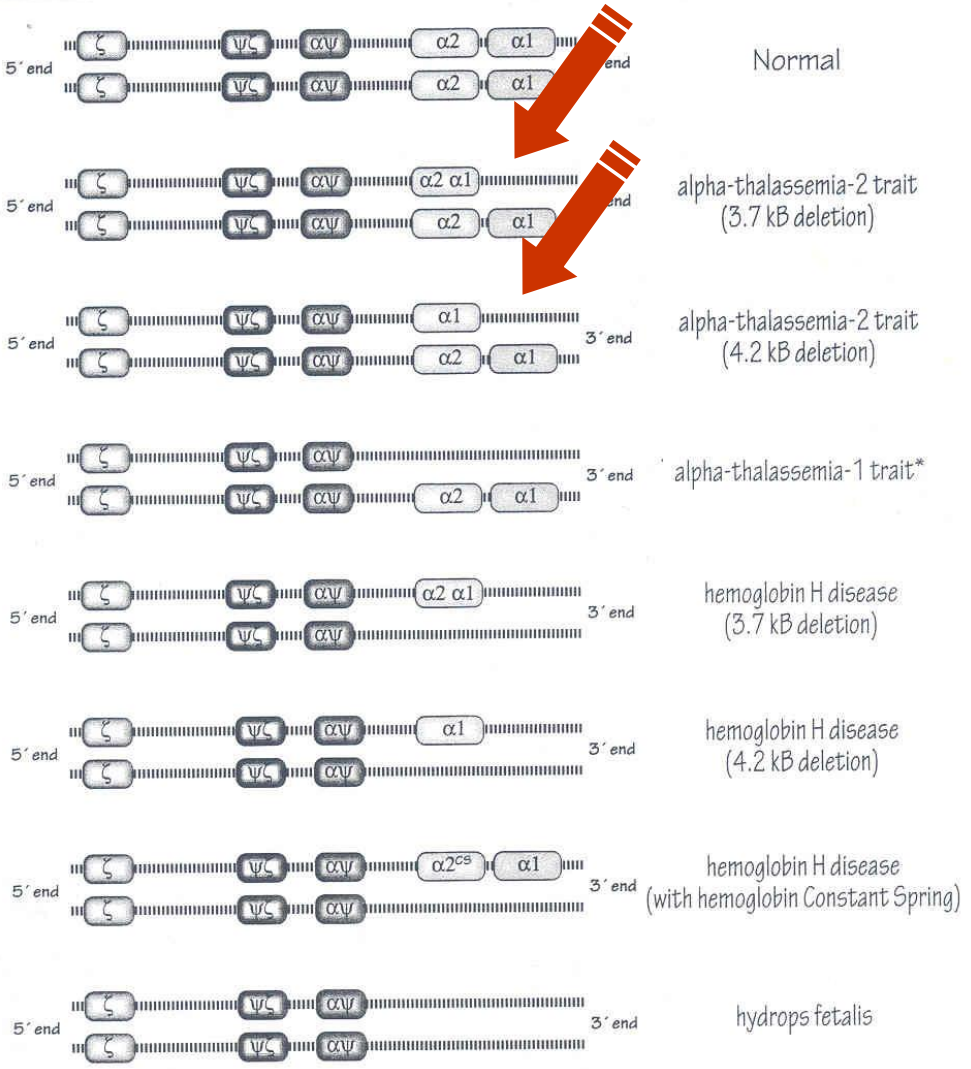

α α α α
β β β β β β β β γ
Hgb A
Hgb H
β chain precipitate
Beta, delta, and gamma chains are produced in relatively normal numbers. The amount of A2 and F formed is negligible.


α α α α α α α α α α α α α
β β
γ γ γ γ
δ δ δ δ
Hgb A
Hgb F
Hgb Barts
Hgb A2
α chain precipitate

α-Thalassemia

- Inherited disorder
- Deletion of all or part of one or both α-globin genes on chromossome 16
- 8 known deletions→ 2 very common:
- -3.7kb (rightward)→ common worldwide
- -4.2kb (leftward)→ Southeast Asia and Saudi Arabia
- Dx: Southern blot analysis

Figure 2.2 Alpha-Thalassemia Mutations



α-Thalassemias syndromes

- α-Thalassemia-1: --/αα (heterozygous)

  Southeast Asians
  Mediterranean basin
  Middle Eastern

  α-Thalassemia trait

  --/-- (homozygous)

  Hydrops fetalis γ_4

  tetramers

- α-Thalassemia-2: -α/αα (heterozygous)

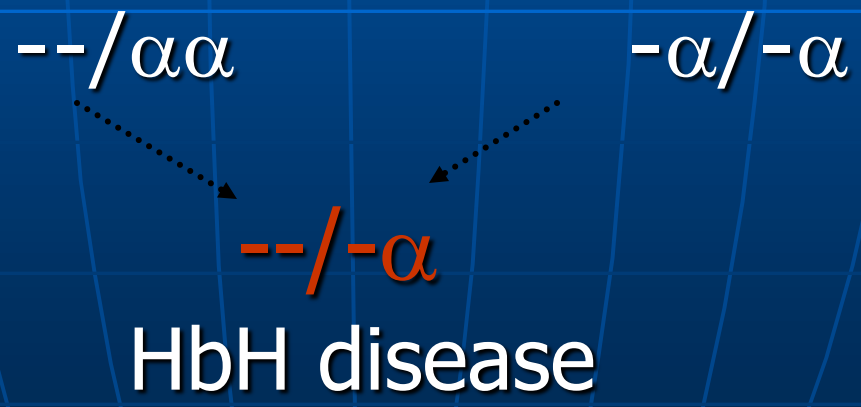
  African Americans

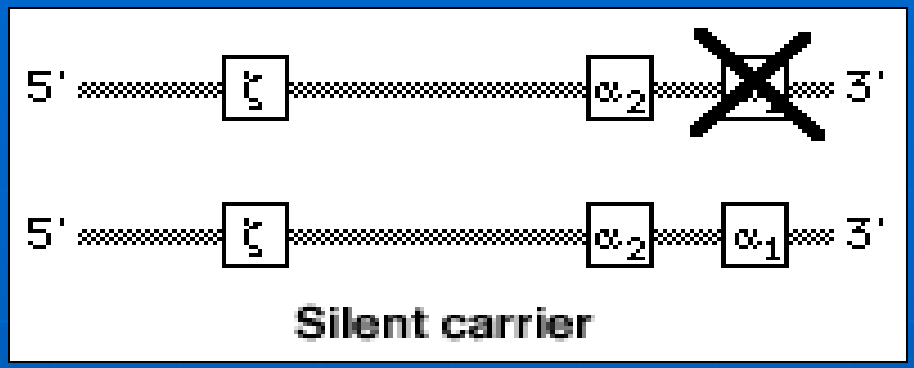
  Silent carrier

  -α/-α (homozygous)

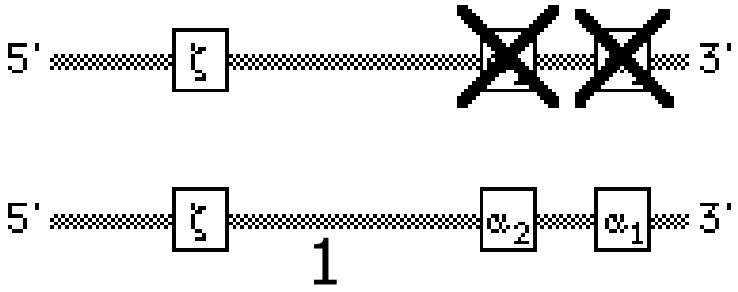
  α-Thalassemia trait

- α-Thalassemia-1 heterozygous / α-Thalassemia-2 homozygous:



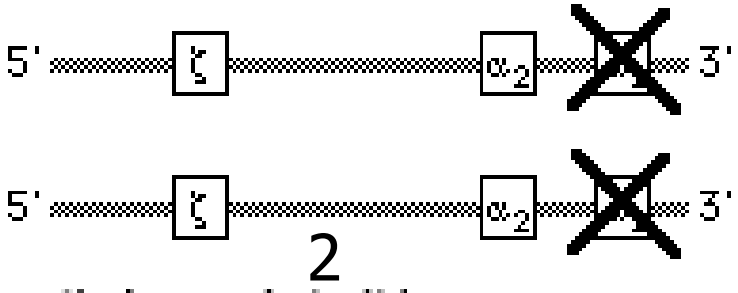


Silent carrier



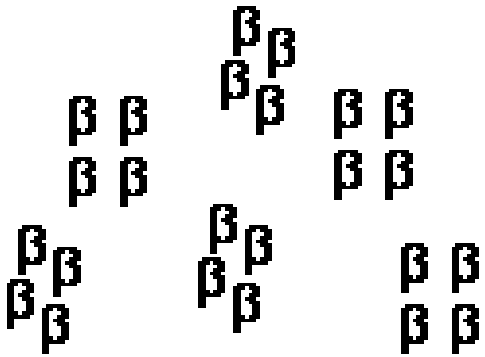
1

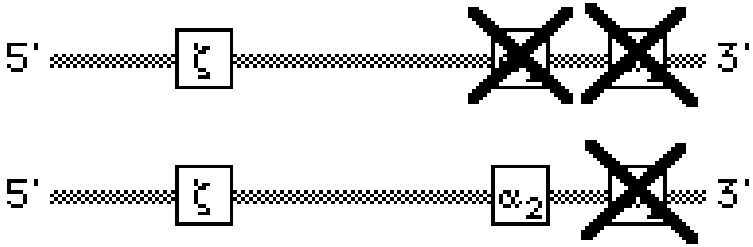
α -thalassemia trait heterozygous



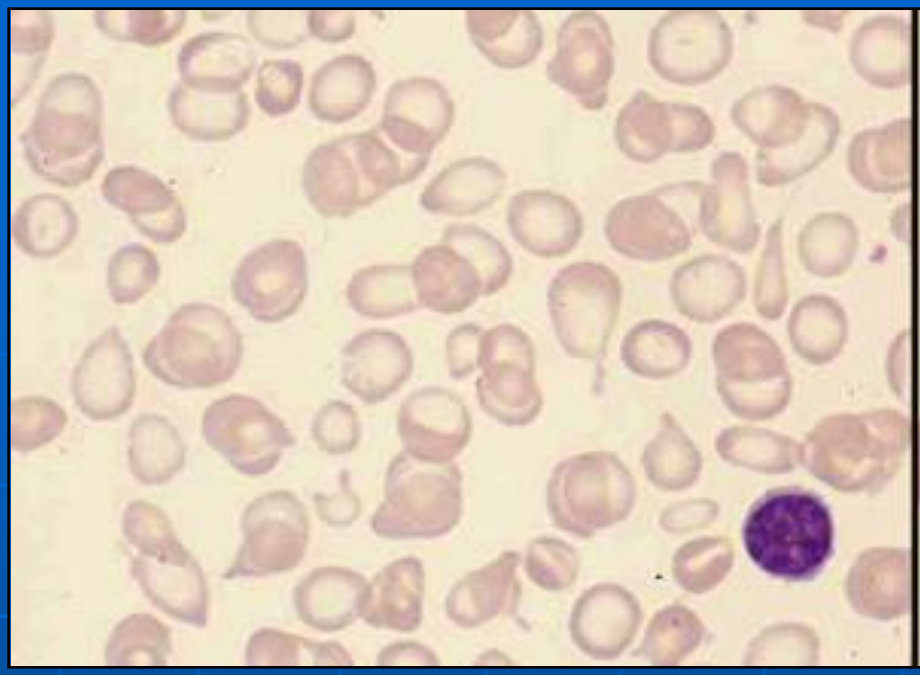
2

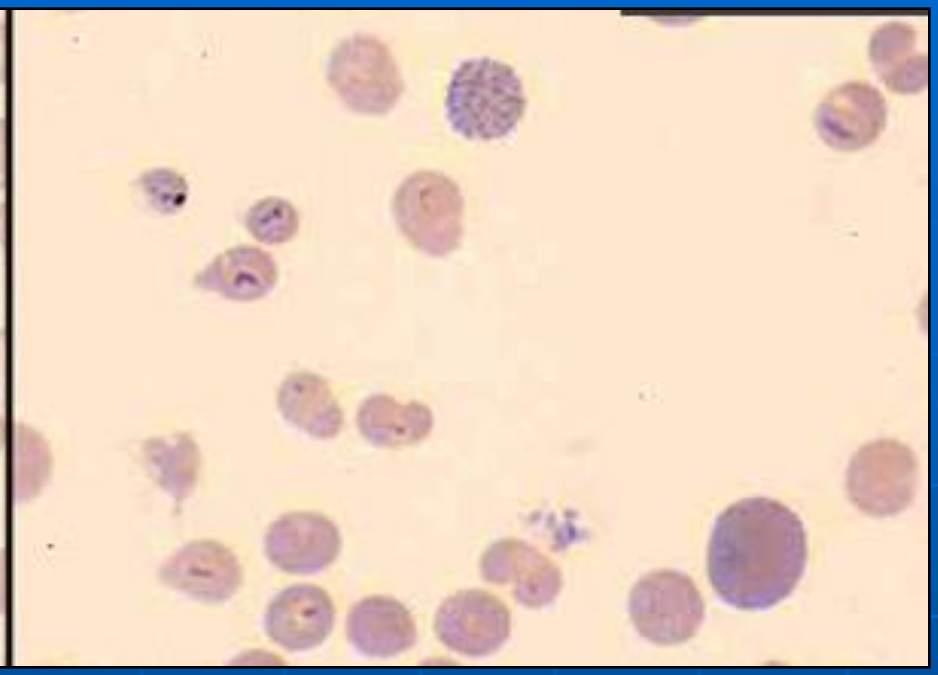
α -thalassemia trait homozygous



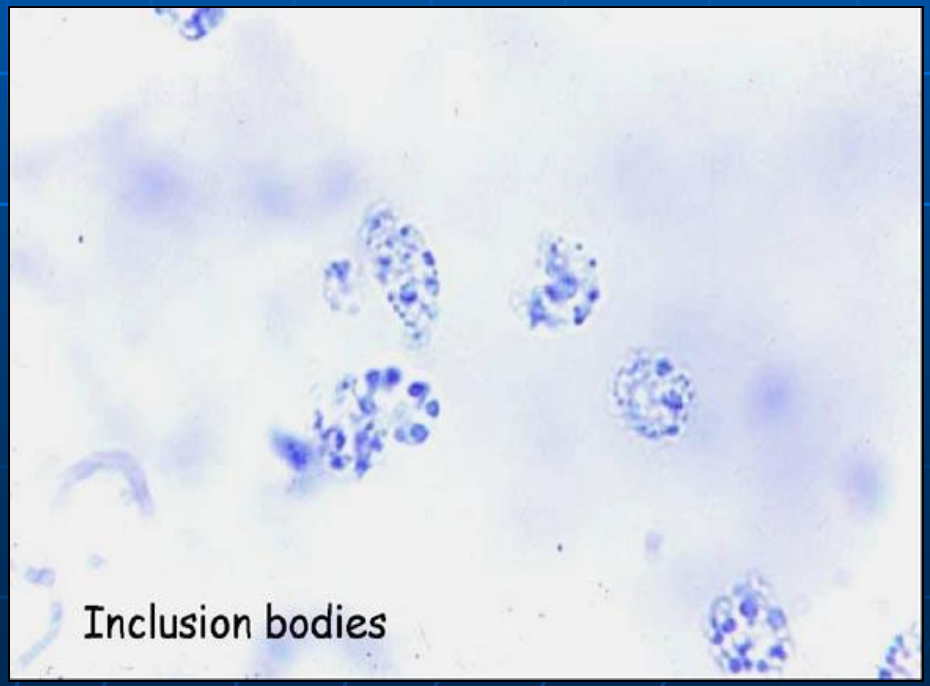


Hemoglobin H disease

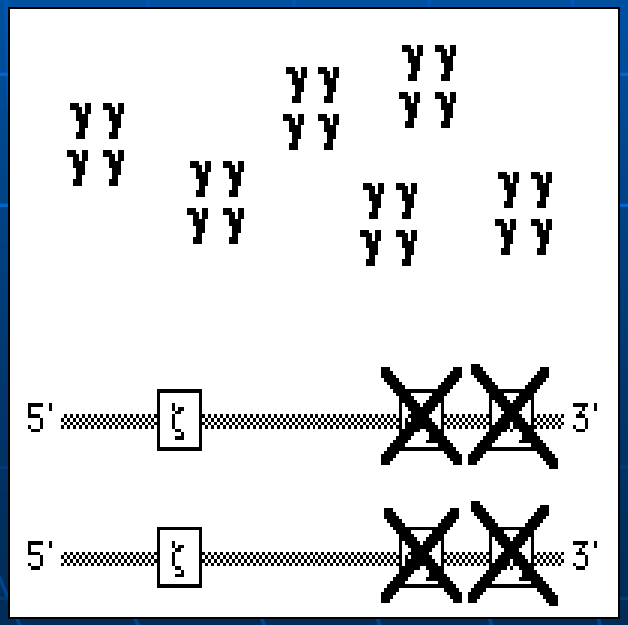




- Is there any other clinical situation in which you could find a HbH in electrophoresis?
- Ans: AML M6 (FAB6)



- --/--:75% of Bart's Hb; 10-30% of Hb Portland ($\zeta_2\gamma_2$) and trace of HbH



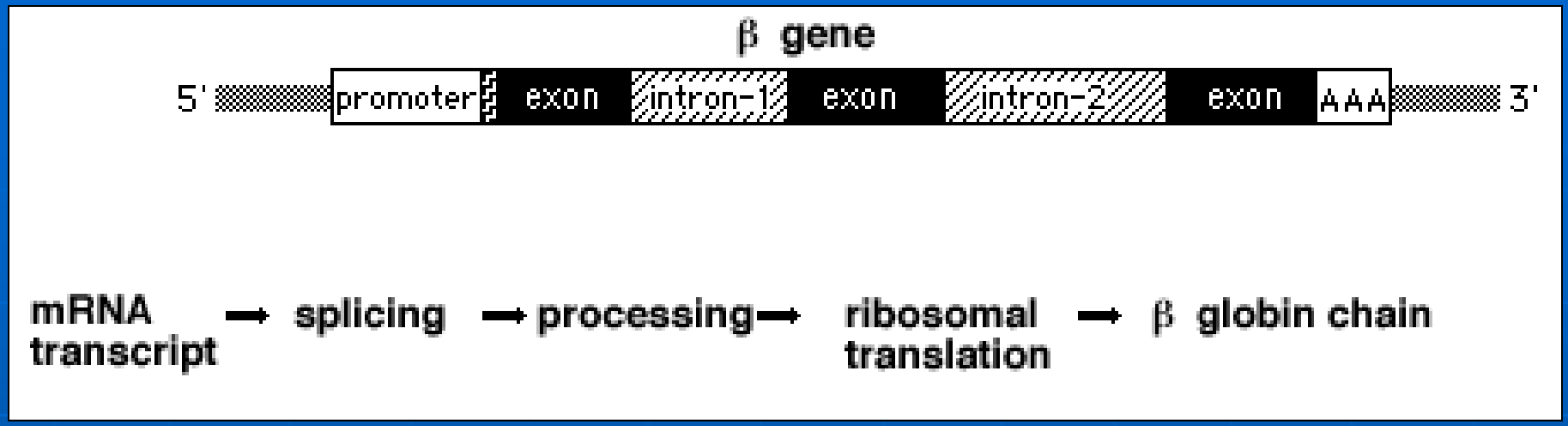

Hydrops fetalis

Summary of findings

Subtype	alpha genes deleted	genotype	associated disorder	clinical effect	Hb H	Hb Bart	Electrophoresis	CBC
Normal	0	αα/αα	none	none	0	0	normal	normal
Heterozygous alpha-thal-2	1	-α/αα	silent carrier	assymptomatic	1-2%	1-3% (neonate)	normal	normal
Homozygous alpha-thal-2	2	-α/-α	Thalassemia minor/trait	microcytosis +/- mild anemia	5-10%	4-10% (neonate)	normal	normal
Heterozygous alpha-thal-1	2	--/αα	Thalassemia minor/trait	microcytosis +/- mild anemia	5-10%	4-10% (neonate)	normal	thalassemic indices
Heterozygous alpha-thal-1/homozygous alpha-thal-2	3	--/-α	HbH disease	chronic hemolytic anemia	5-40%	20-40%(neonate)	fast-migrating HbH	thalassemic Heinz bodies **CS
Homozygous alpha-thal-1	4	--/--	Bart's hydrops fetalis	lethal	trace	predominant Hb	fast-migrating Hb Bart's	hypochromia nRBCs

β-Thalassemia

- Imbalance in globin chains due to reduction/absence of β-globin chains
- Mutations are almost exclusively point mutations
- Most common in Mediterranean populations
- Two main groups:
- β^0 : absence of production
- β^+ : reduction in production (β^{++} ; American and β^+ Mediterranean



- Mutations involving exons or frameshift mutations: absence of β-globin chains→ β^0-Thalassemia
- Mutations involving the introns (close to splice junctions) or promoter region: abnormal processing of mRNA→ β^+-Thalassemia

β-Thalassemias syndromes

- β-Thalassemia syndromes:
- Manifestations become evident at 6-9 months of age (wheras α-Thalassemias→ anemia at birth)

- β-Thalassemia minor:
- Inheritance of one abnormal gene: β^0 or β^+

- β-Thalassemia major:
- Inheritance of two abnormal genes: β^0 or β^+

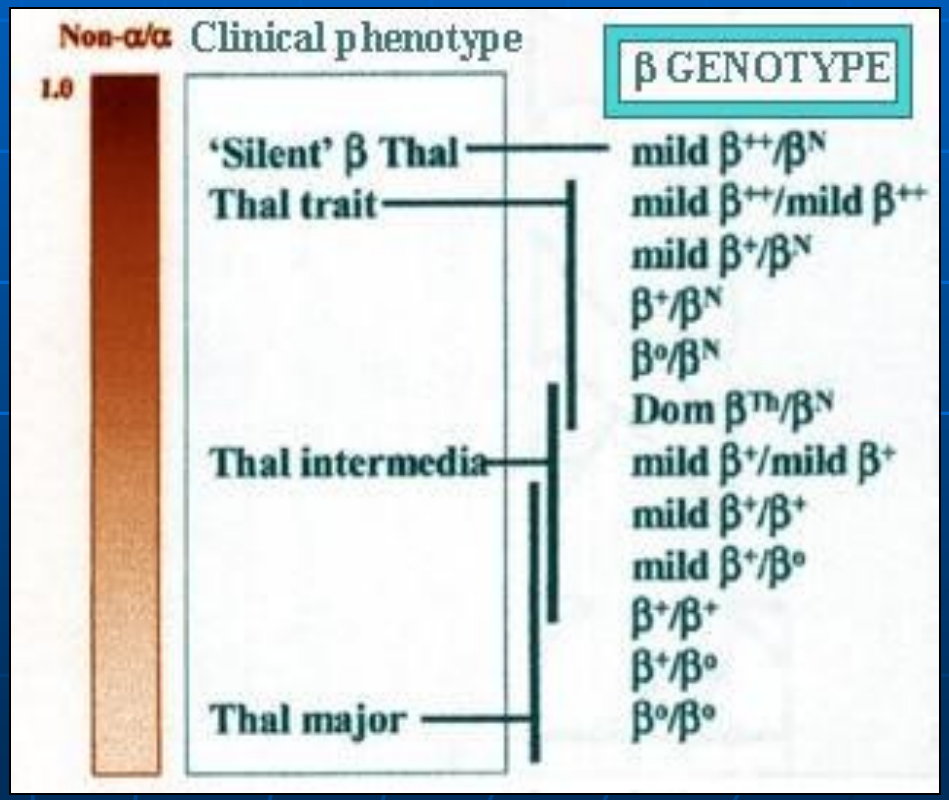
- Hallmark of disease: HbA_2: 3-8%
- What is the exception to that?
  Answer: Pt has comcomitant iron deficiency anemia

β-Thalassemia minor

- β^0/β or β^+/β (heterozygous):
- Minimal clinical effects
- Borderline anemia (Hct ~ 35 %)
- Disproportionate microcytosis (MCV ~ 60 fL)
- High RBC count (~ 6 x 10^6/μL)
- Hb A2 is increased (almost never more than 10% of total Hb)

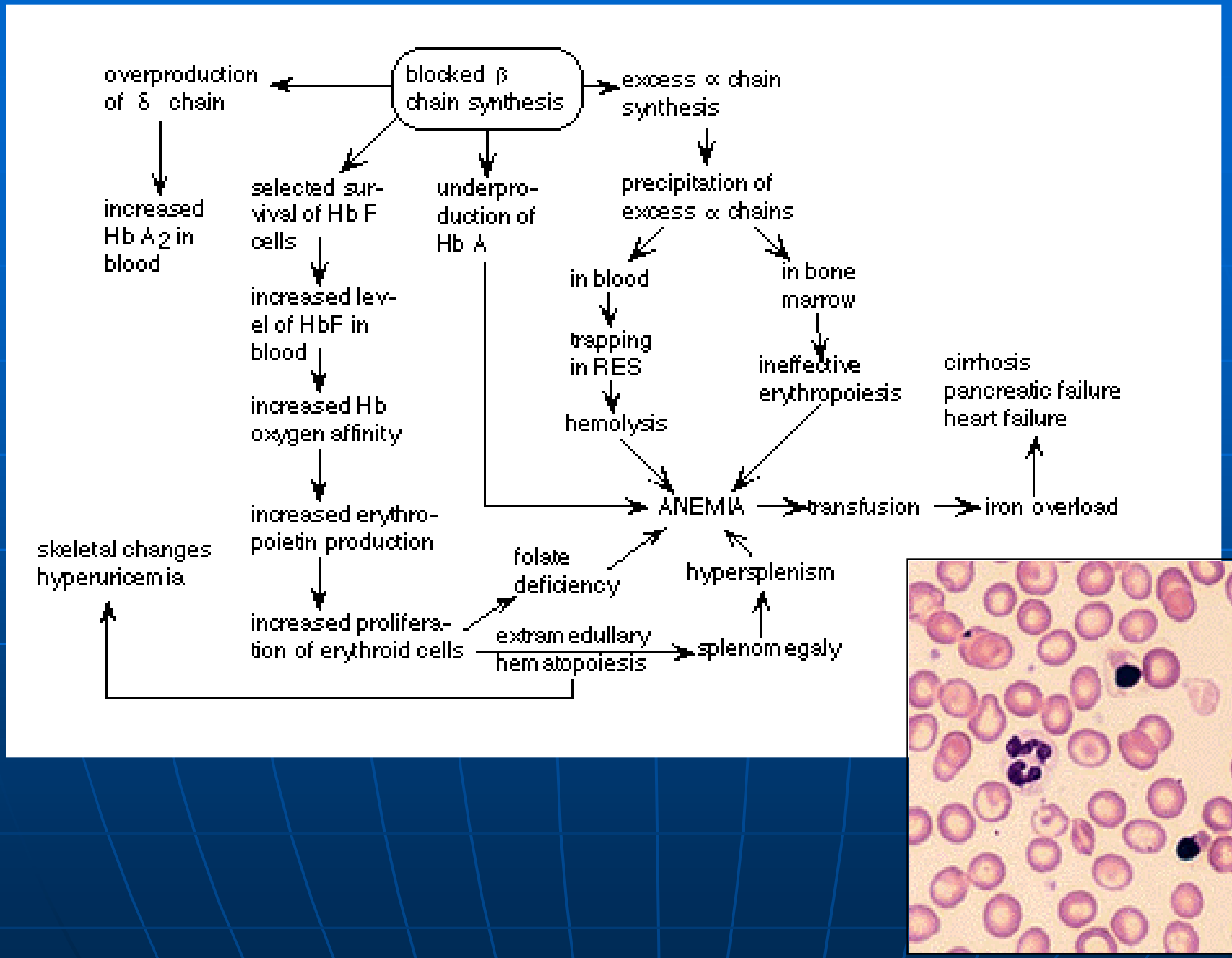
β-Thalassemia intermedia

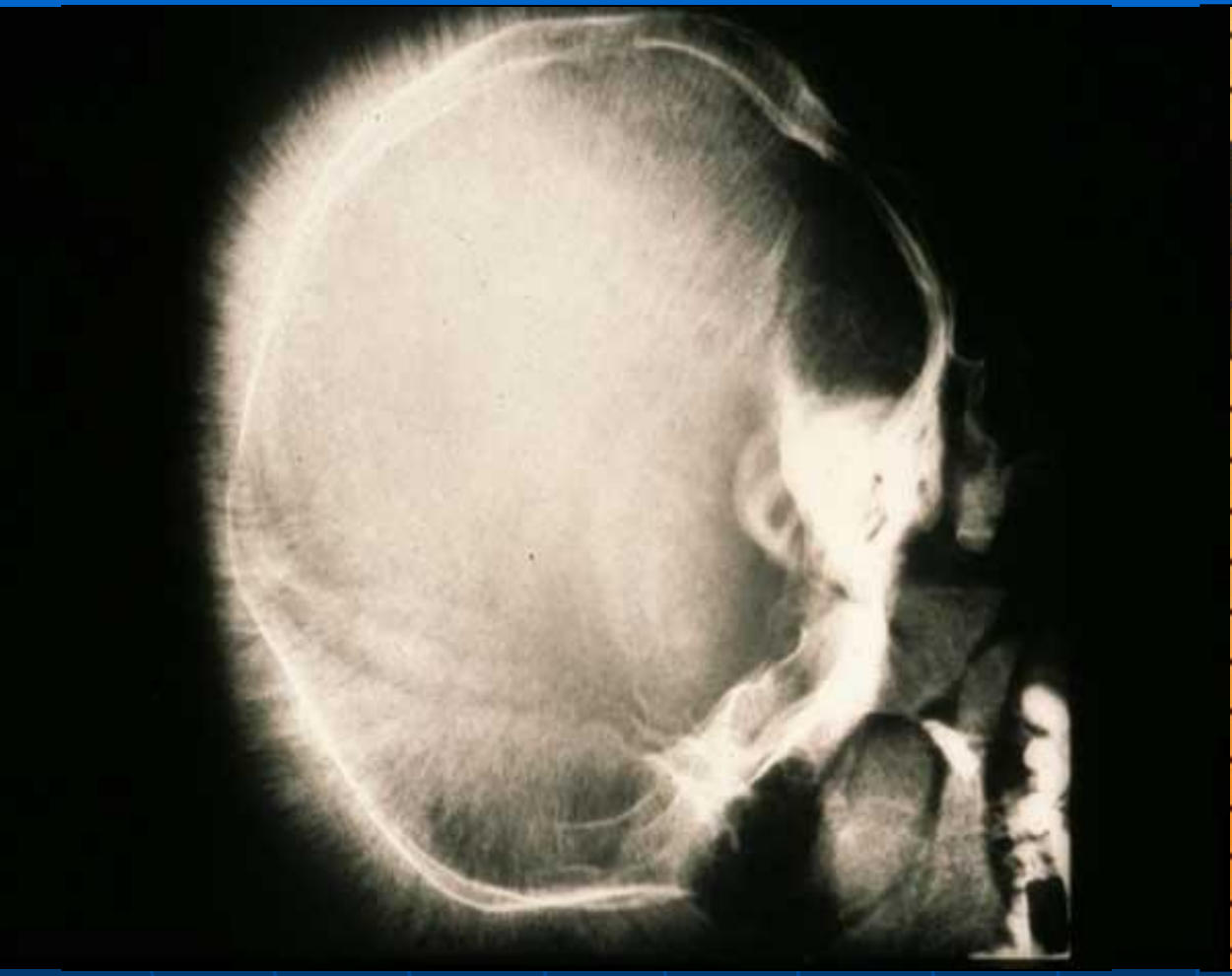
- β^+/β^+
- HbF: 50-95% in heterocellular distribution
- HbA_2: 3-8%

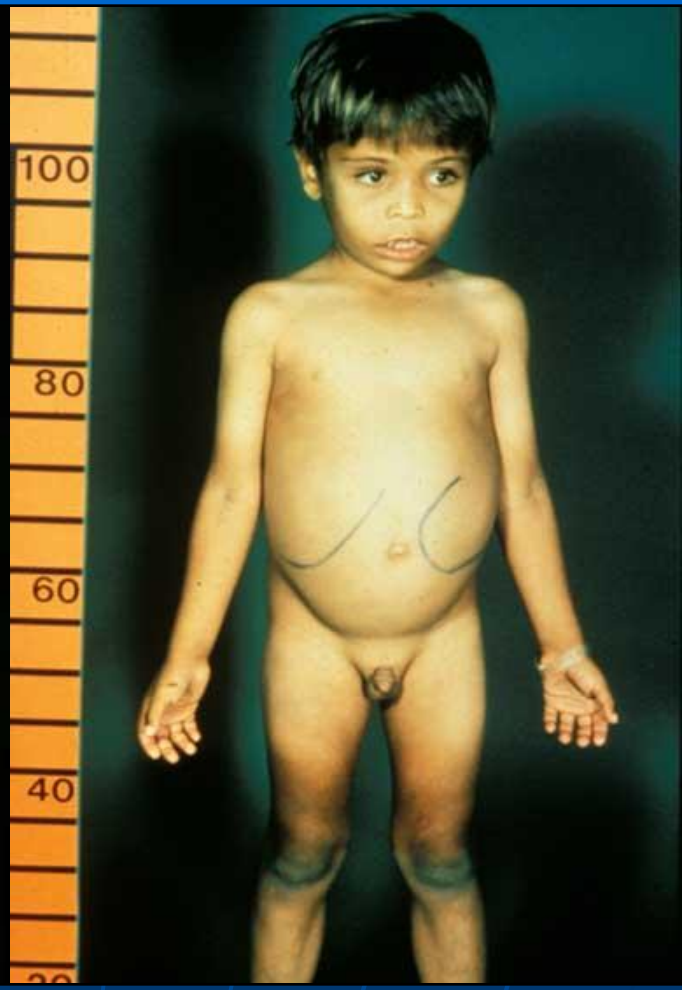


Cooley's anemia or β-Thalassemia major

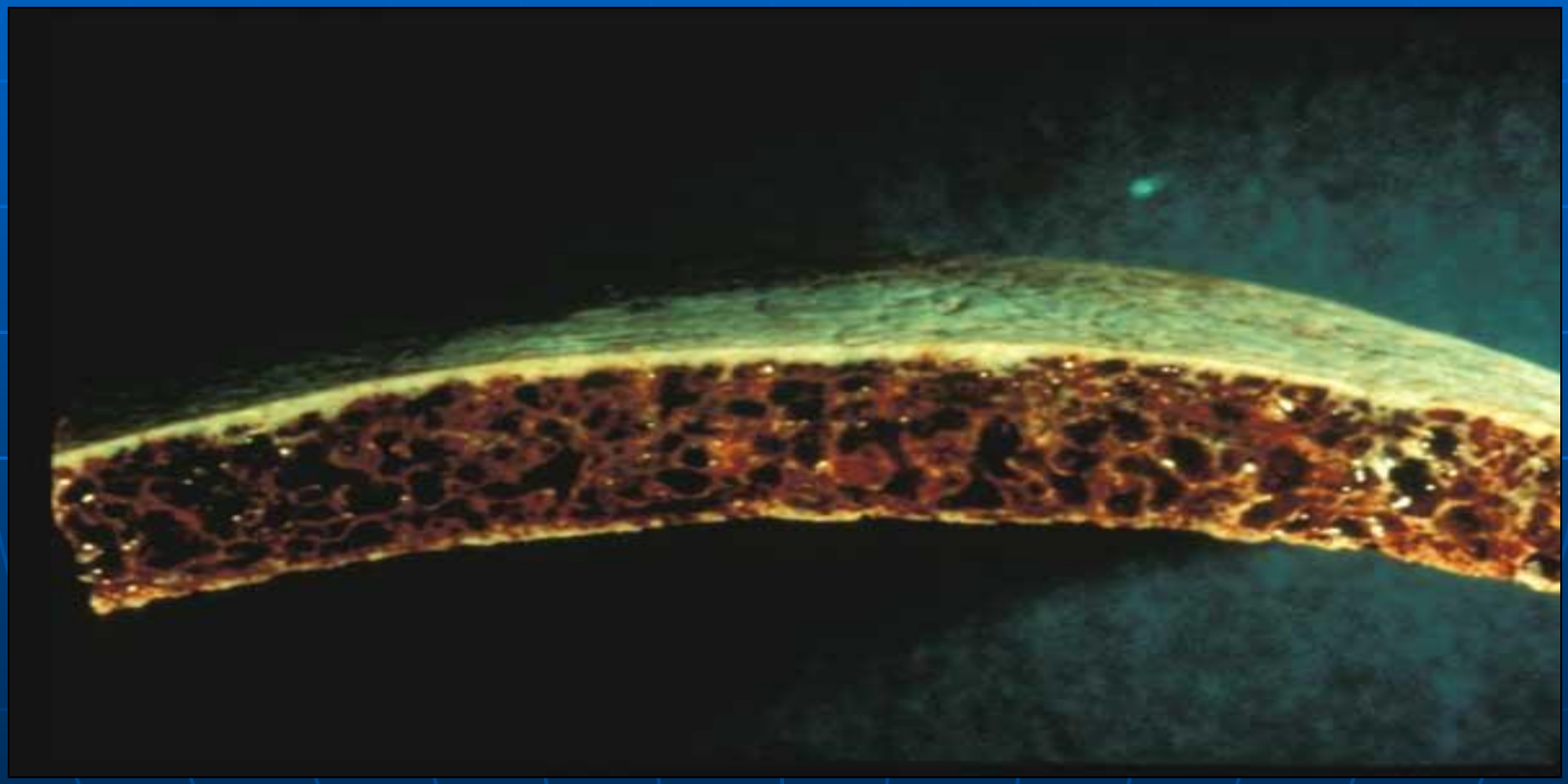
- β^0/β^0: produce only HbA_2, Hb F (and very little of that after six months of age), and unstable (insoluble) α_4 tetramers
- Severe anemia + pathophysiological consequences


blocked β chain synthesis
overproduction of δ chain
increased Hb A2 in blood
selected survival of Hb F cells
increased level of HbF in blood
increased Hb oxygen affinity
increased erythropoietin production
increased proliferation of erythroid cells
underproduction of Hb A
excess α chain synthesis
precipitation of excess α chains
in blood
trapping in RES
hemolysis
in bone marrow
ineffective erythropoiesis
ANEMIA
transfusion
iron overload
cirrhosis
pancreatic failure
heart failure
folate deficiency
hypersplenism
extramedullary hematopoiesis
splenomegaly
skeletal changes
hyperuricemia





- "hair-on-end appearance" or the "guy-who-accidentally-sat-on-a-Van-de-Graaff-generator appearance"

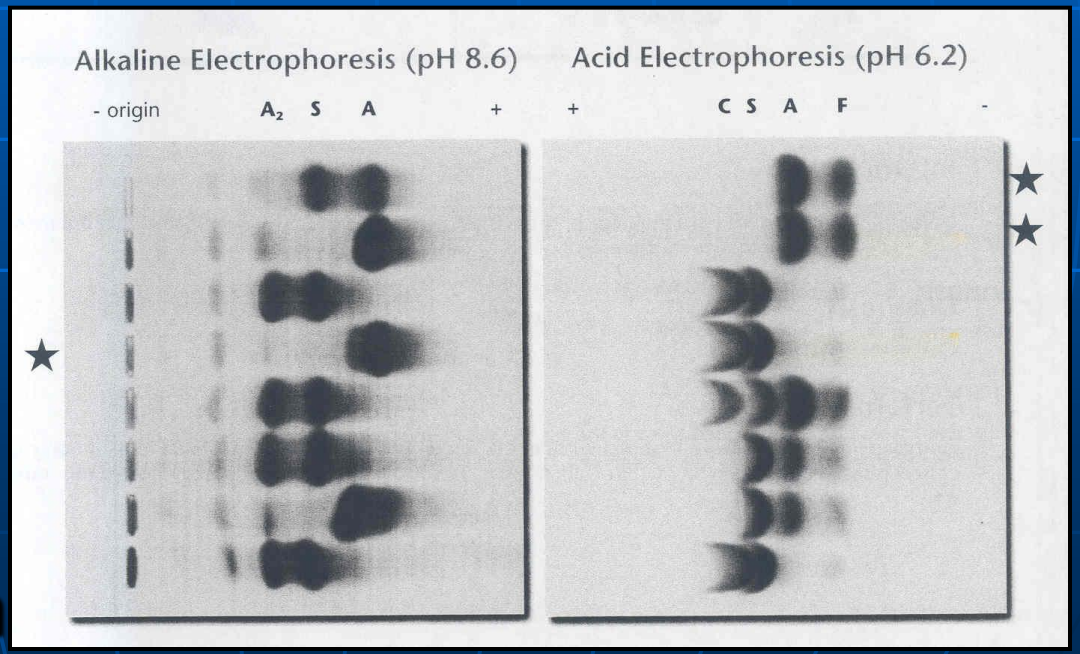


Constant Spring hemoglobin

- Mutation in the alpha globin gene stop codon produces an alpha globin chain that is abnormally long
- mRNA for hemoglobin Constant Spring is unstable→ degraded prior to protein synthesis
- Constant Spring alpha chain protein is itself unstable→ thalassemic phenotype
- Constant Spring district of Jamaica→ isolation of the hemoglobin variant in a family of ethnic Chinese background
- --/$\alpha^{CS}\alpha$ trait→ HbH disease

Quiz Case

- HbF: 15% (heterocellular); HbA2: 1%
- Microcytosis without anemia



- Dx?
- δβ-Thalassemia

δβ-Thalassemia

- Deletions in large segments of DNA on chromosome 11, including both δ and β genes
- Most common: Sicilian type
- Persistent elevation of Hb F into adulthood
- α chain excess→ β-Thalassemia phenotype