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Hemoglobinopathies

David Ginsburg, MD

Reading:

Principles of Medical Genetics 2E

Chapter 6

Fall 2012

University of Michigan
Medical School

Relationships with Industry

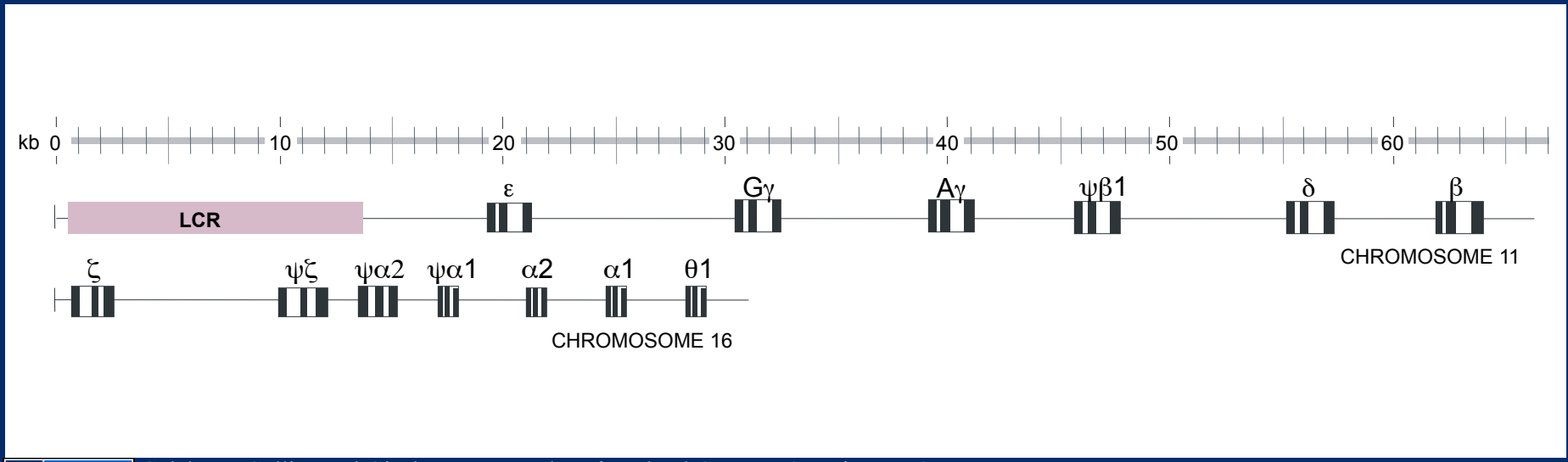
UMMS faculty often interact with pharmaceutical, device, and biotechnology companies to improve patient care, and develop new therapies. UMMS faculty disclose these relationships in order to promote an ethical & transparent culture in research, clinical care, and teaching.

- I am a member of the Board of Directors for Shire plc.
- I am a member of the Scientific Advisory Boards for Portola Pharmaceuticals and Catalyst Biosciences.
- I benefit from license/patent royalty payments to Boston Children's Hospital (VWF) and the University of Michigan (ADAMTS13).

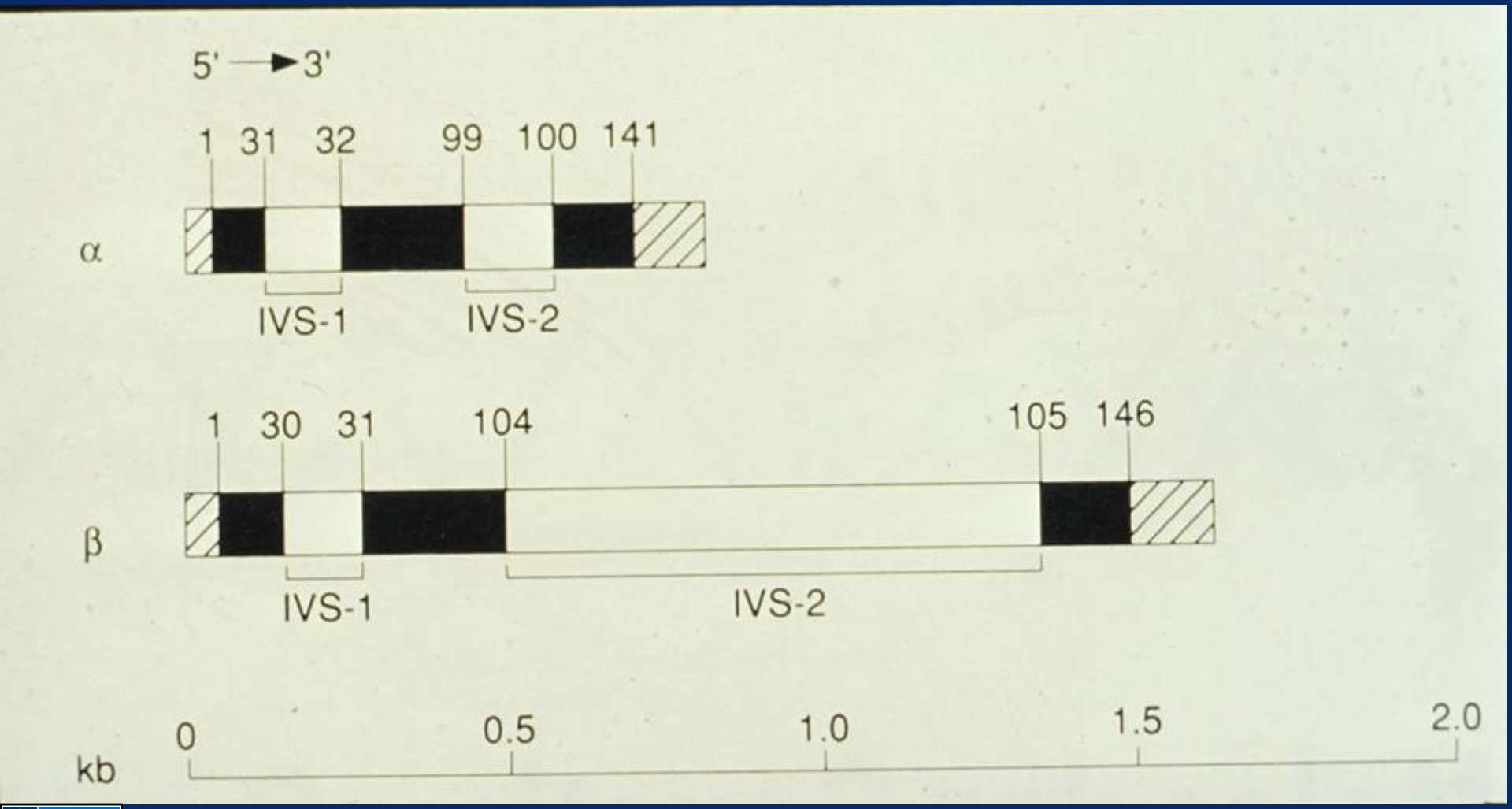
Disclosure required by the UMMS Policy on Faculty Disclosure of Industry Relationships to Students and Trainees.

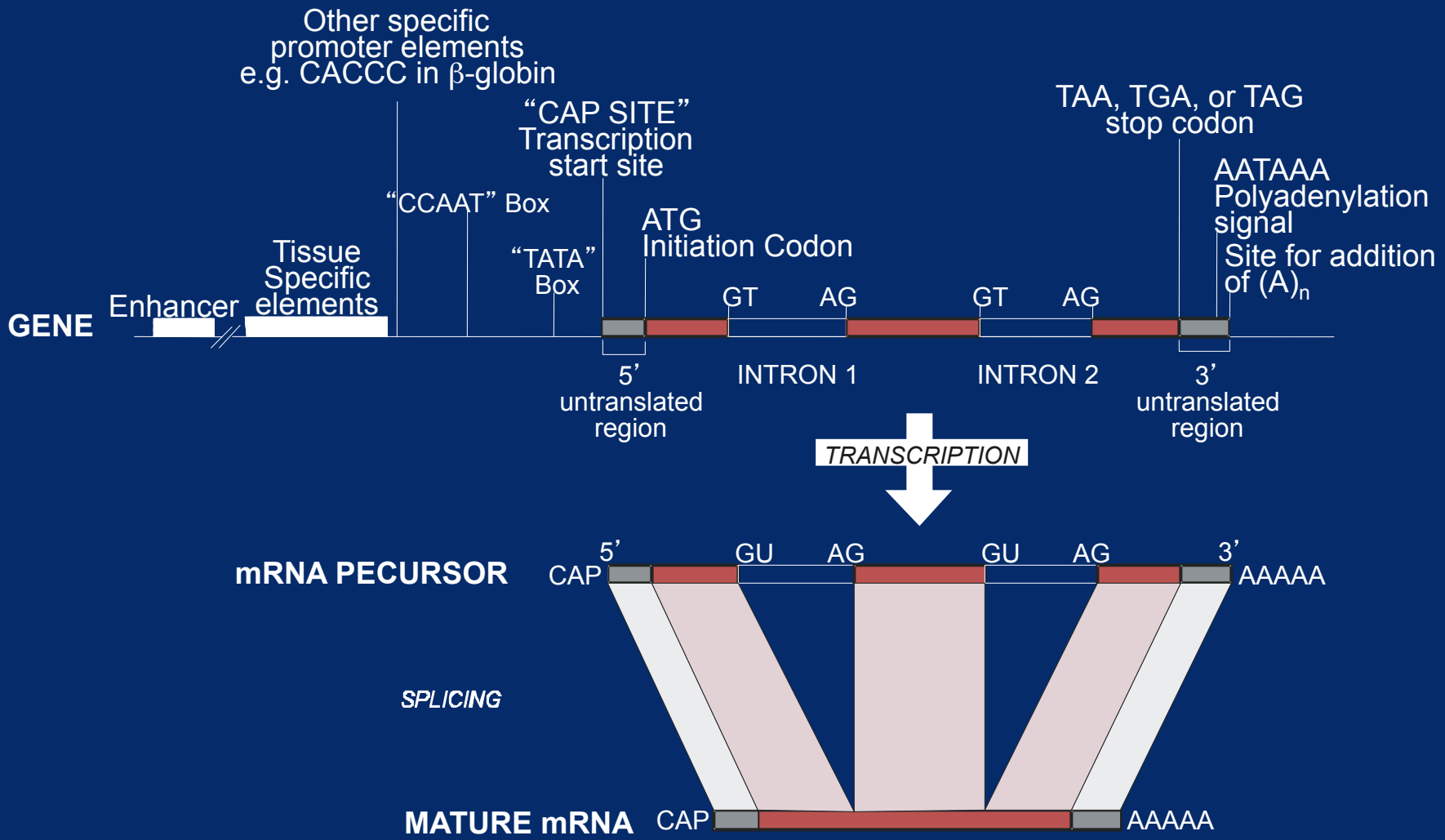
Learning Objectives

- Understand how the basic *anatomy of a gene* has a direct bearing on the occurrence of genetic disease.
- Know the normal and abnormal *expression patterns* of the hemoglobin genes.
- Understand the mutations that cause *quantitative* abnormalities in globin.
  - Unequal crossing over, and every other possible type of mutation
- Recognize mutations that cause *qualitative* abnormalities in globin.
- Understand the *molecular basis of sickle cell anemia.*

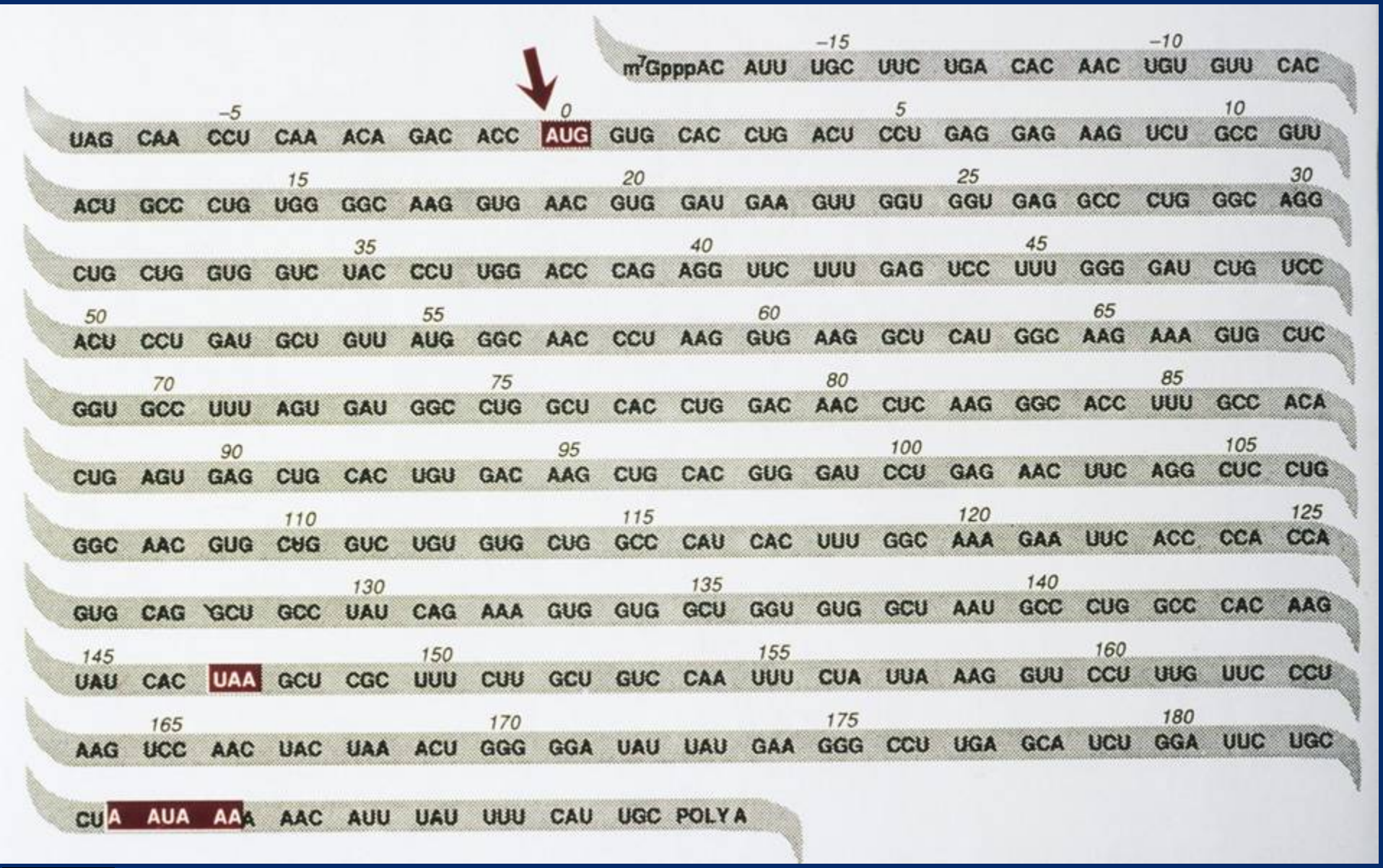


 Gelehrter, Collins and Ginsburg: *Principles of Medical Genetics 2E;* Figure 5.2

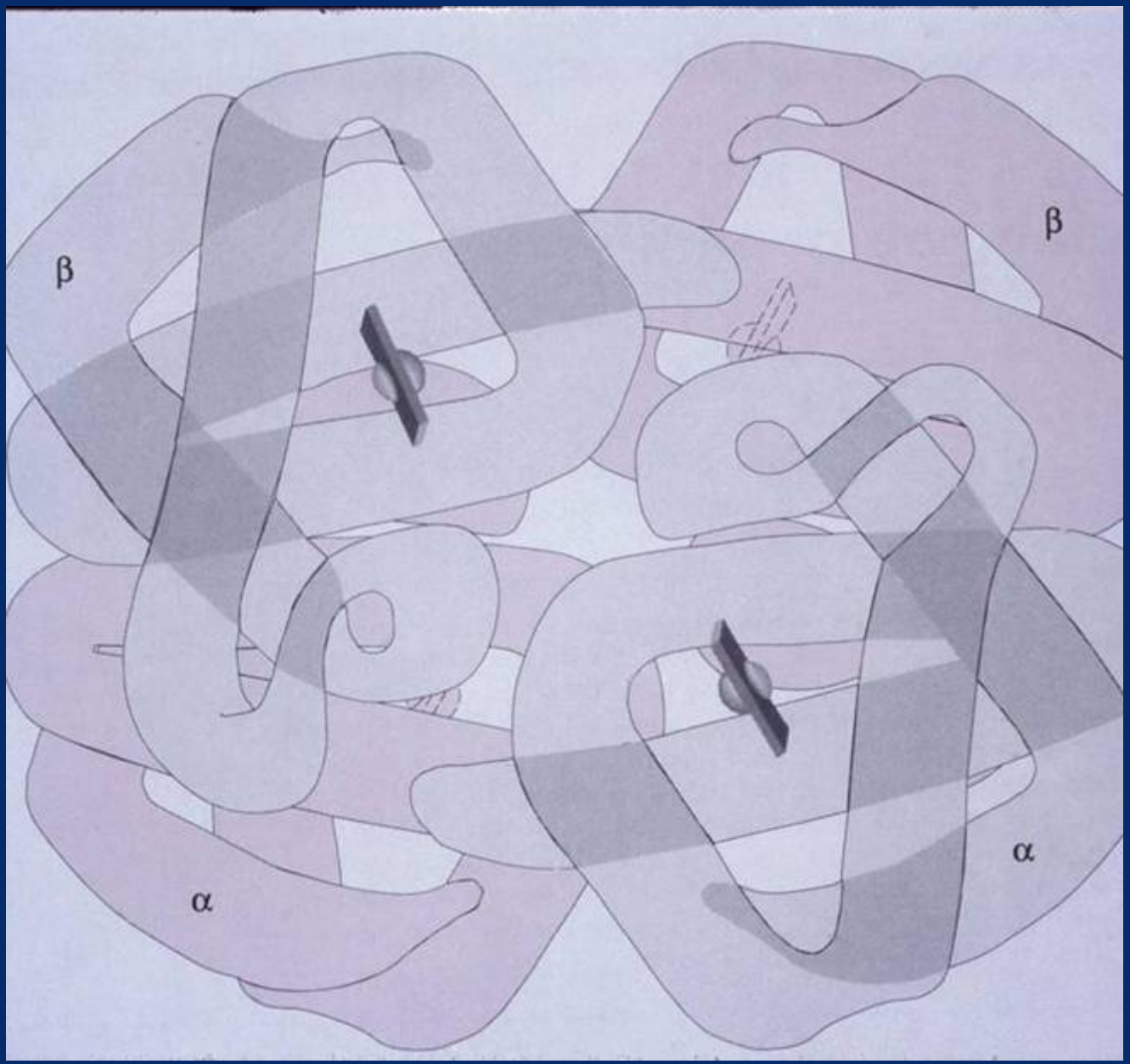

5' → 3'
1 31 32 99 100 141
α
IVS-1
IVS-2
1 30 31 104 105 146
β
IVS-1
IVS-2
0 0.5 1.0 1.5 2.0
kb



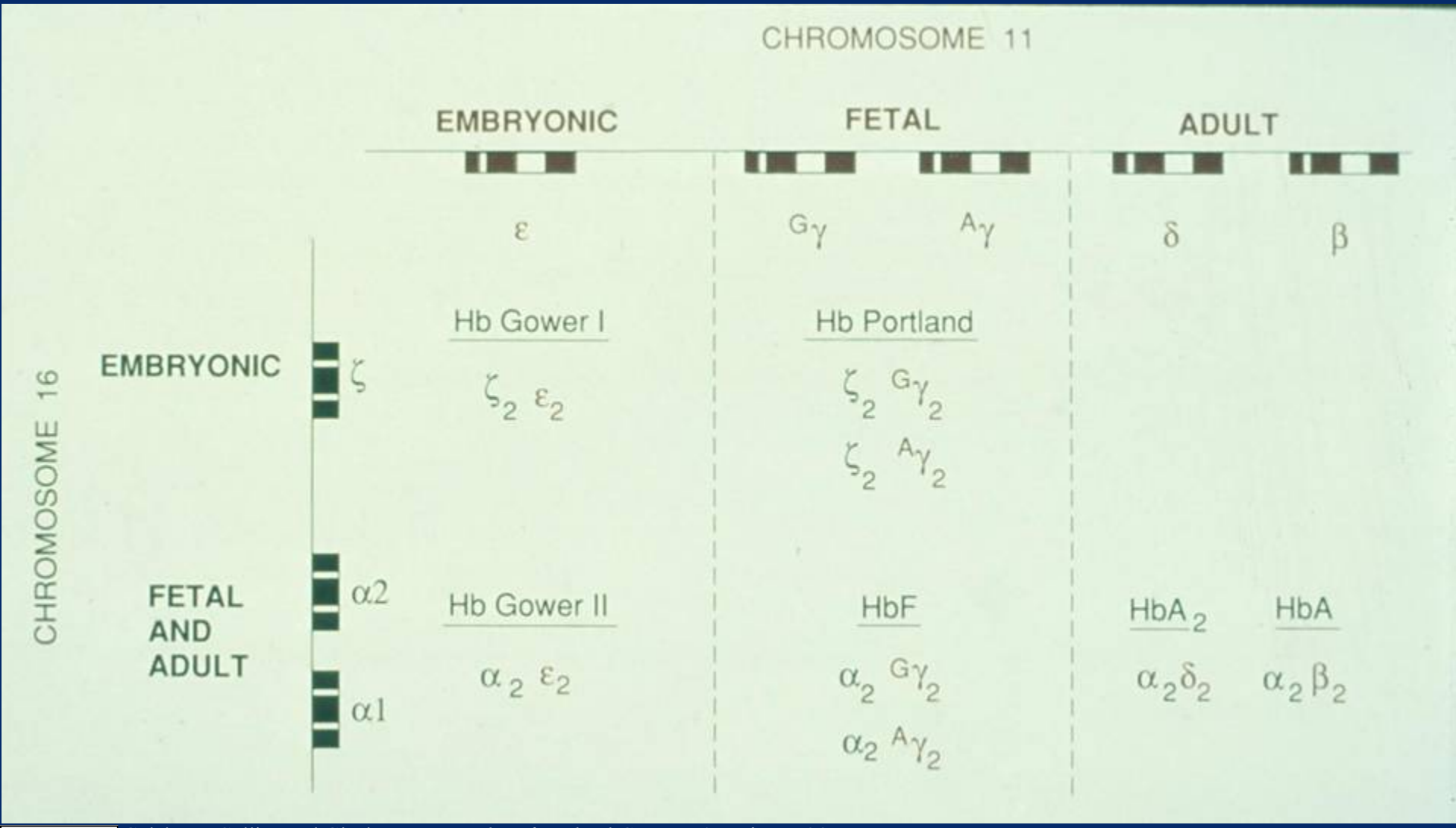
 Gelehrter, Collins and Ginsburg: *Principles of Medical Genetics 2E;* Figure 5.1



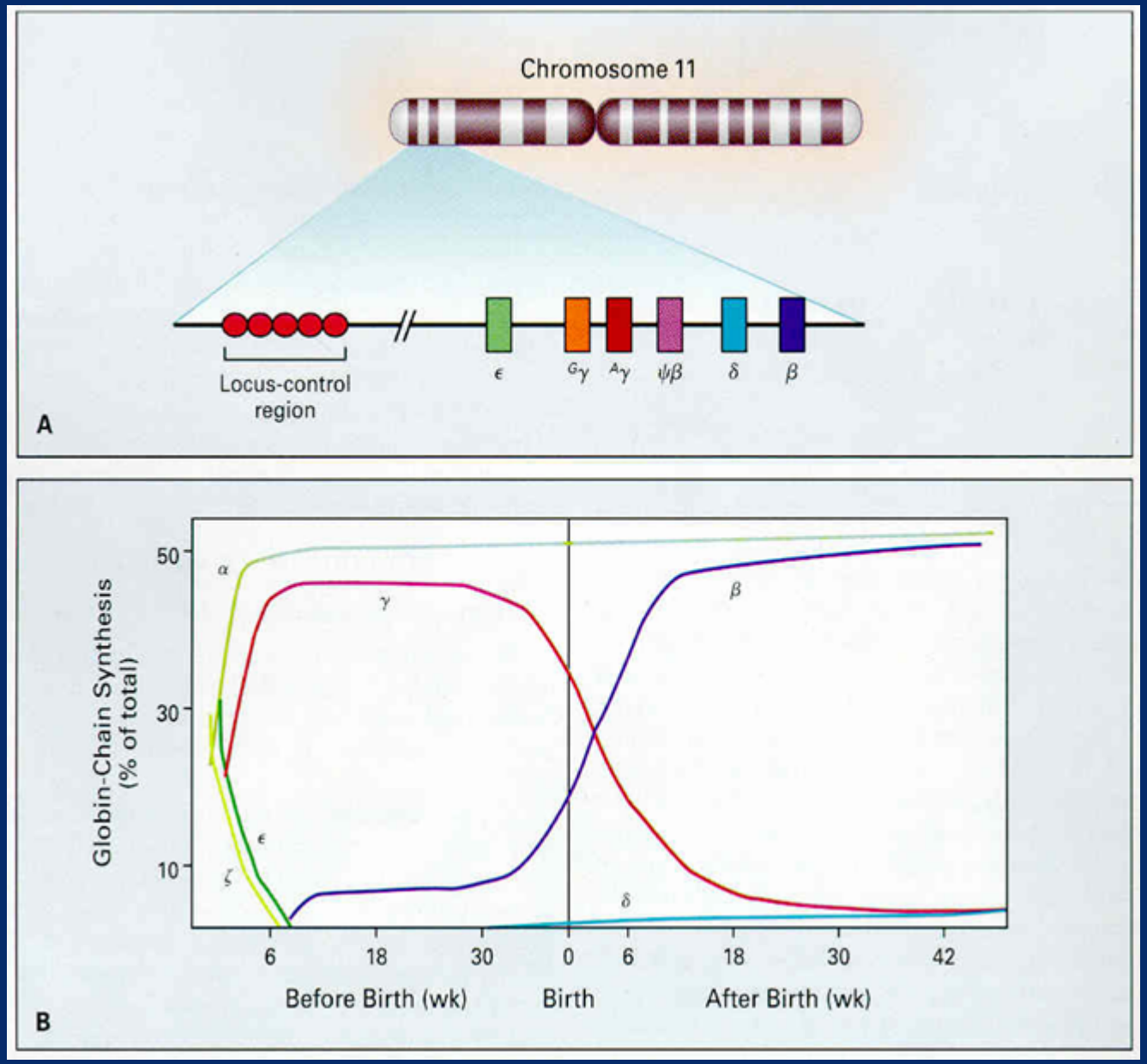
 Gelehrter, Collins and Ginsburg: *Principles of Medical Genetics 2E;* Figure 6.5



 Gelehrter, Collins and Ginsburg: *Principles of Medical Genetics 2E;* Figure 6.1



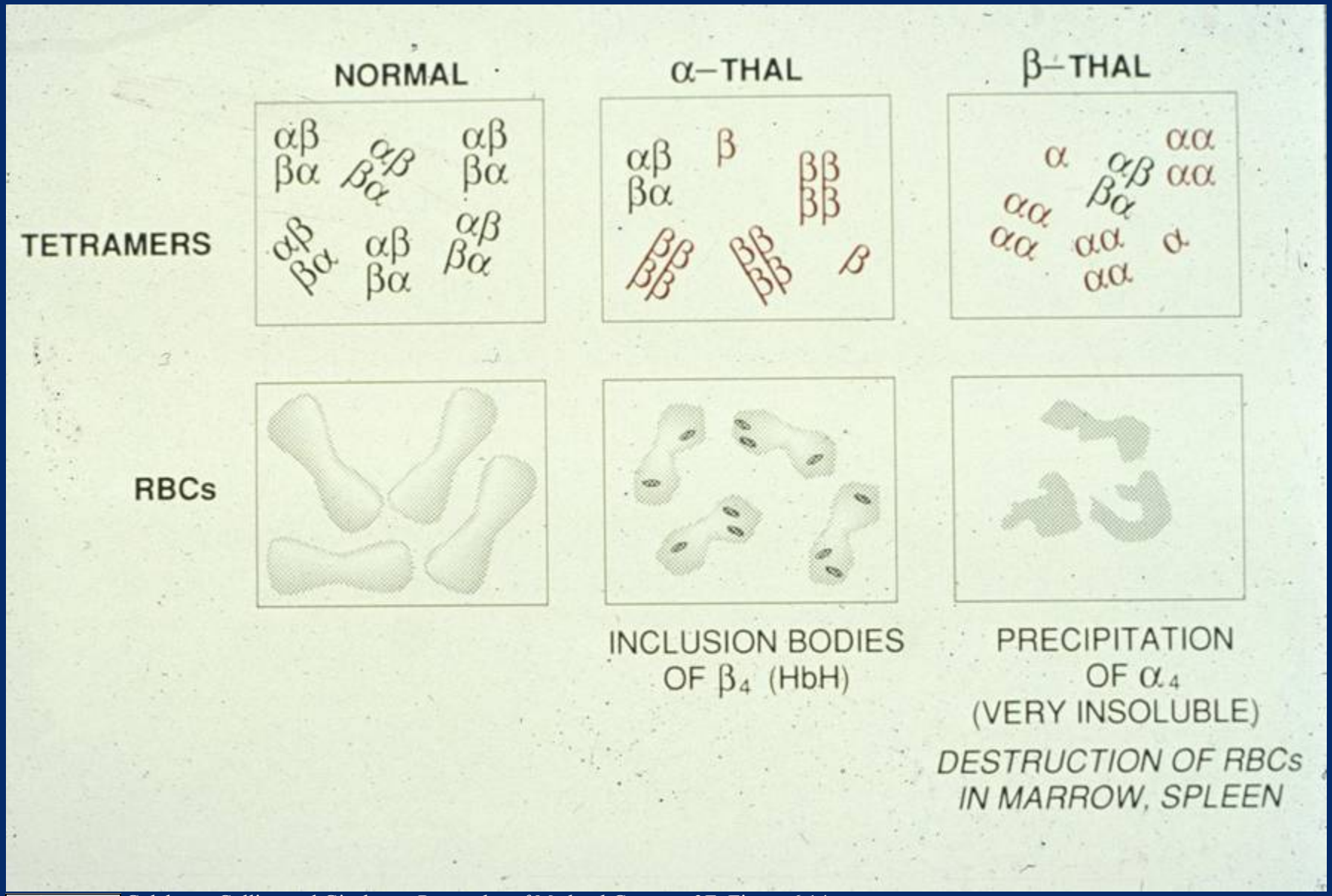
 Gelehrter, Collins and Ginsburg: *Principles of Medical Genetics 2E;* Figure 6.3



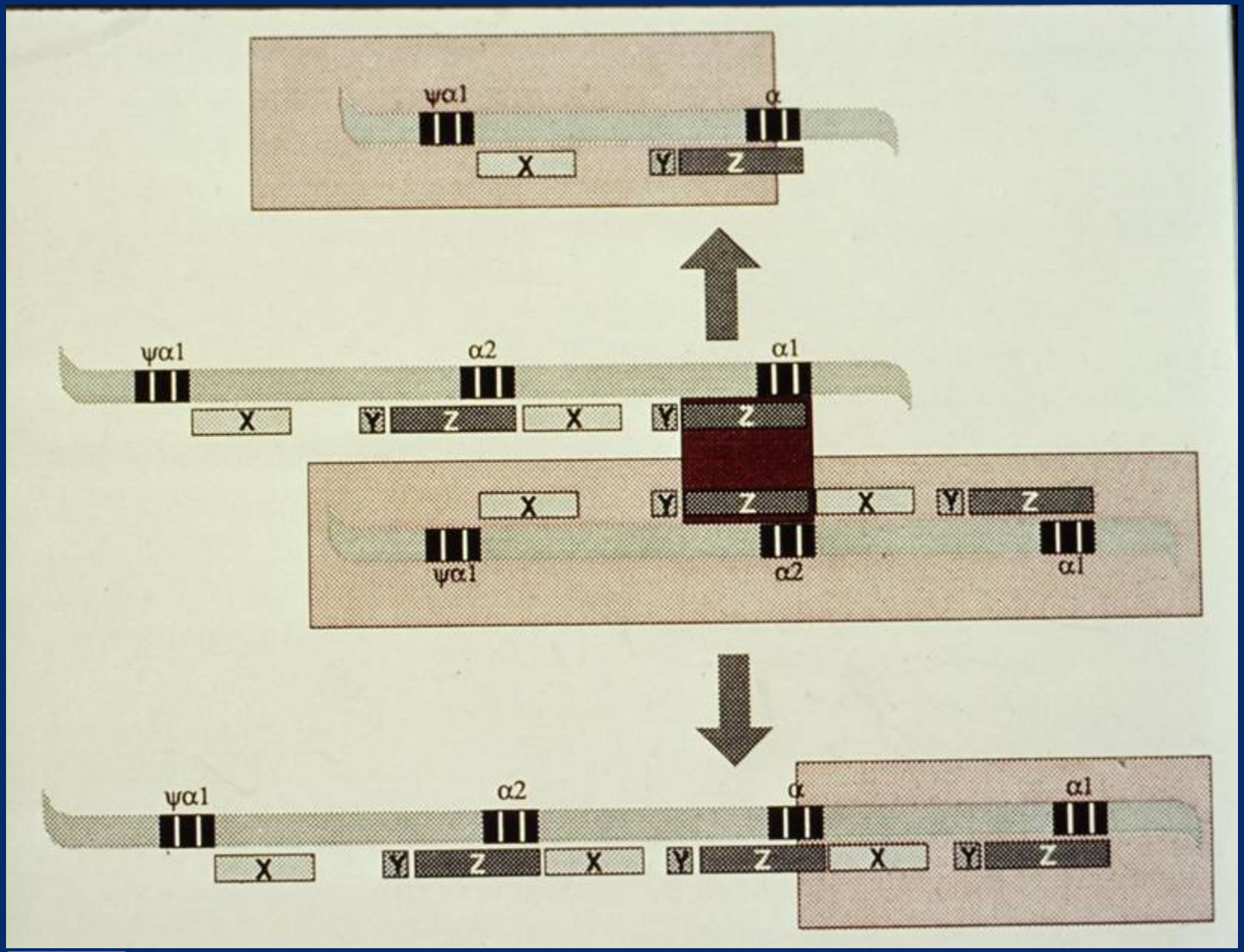
 NF Olivieri, ***NEJM* 341**:99, 1999. (or *Principles of Medical Genetics*: Figure 6.2)

Quantitative Abnormalities of Hemoglobin

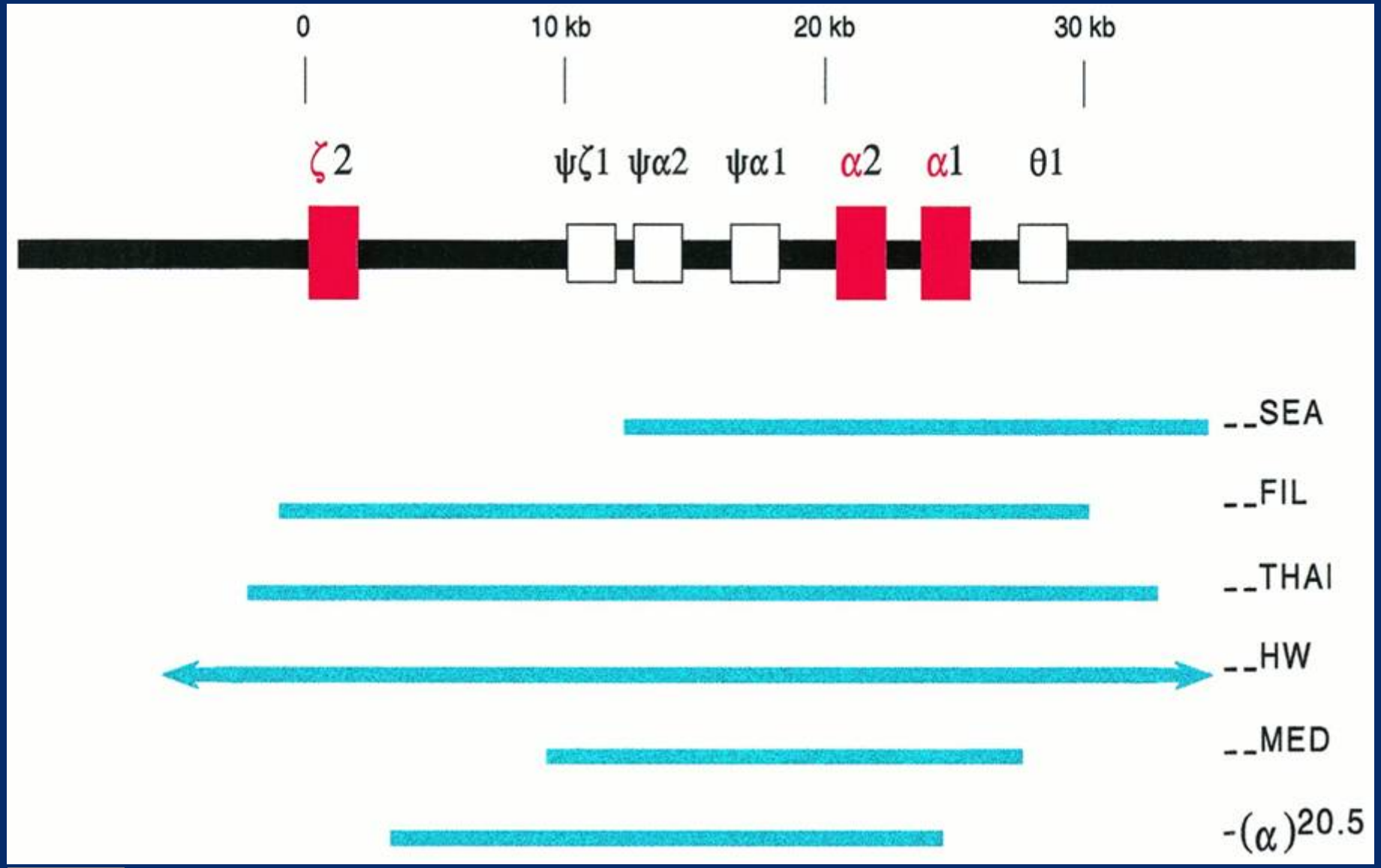
- **α Thalassemia**
  - deficiency of α globin chains
- **β Thalassemia**
  - deficiency of β globin chains
- **HPFH**
  - Hereditary persistence of fetal hemoglobin



 Gelehrter, Collins and Ginsburg: *Principles of Medical Genetics 2E;* Figure 6.14



 Gelehrter, Collins and Ginsburg: *Principles of Medical Genetics 2E;* Figure 6.16

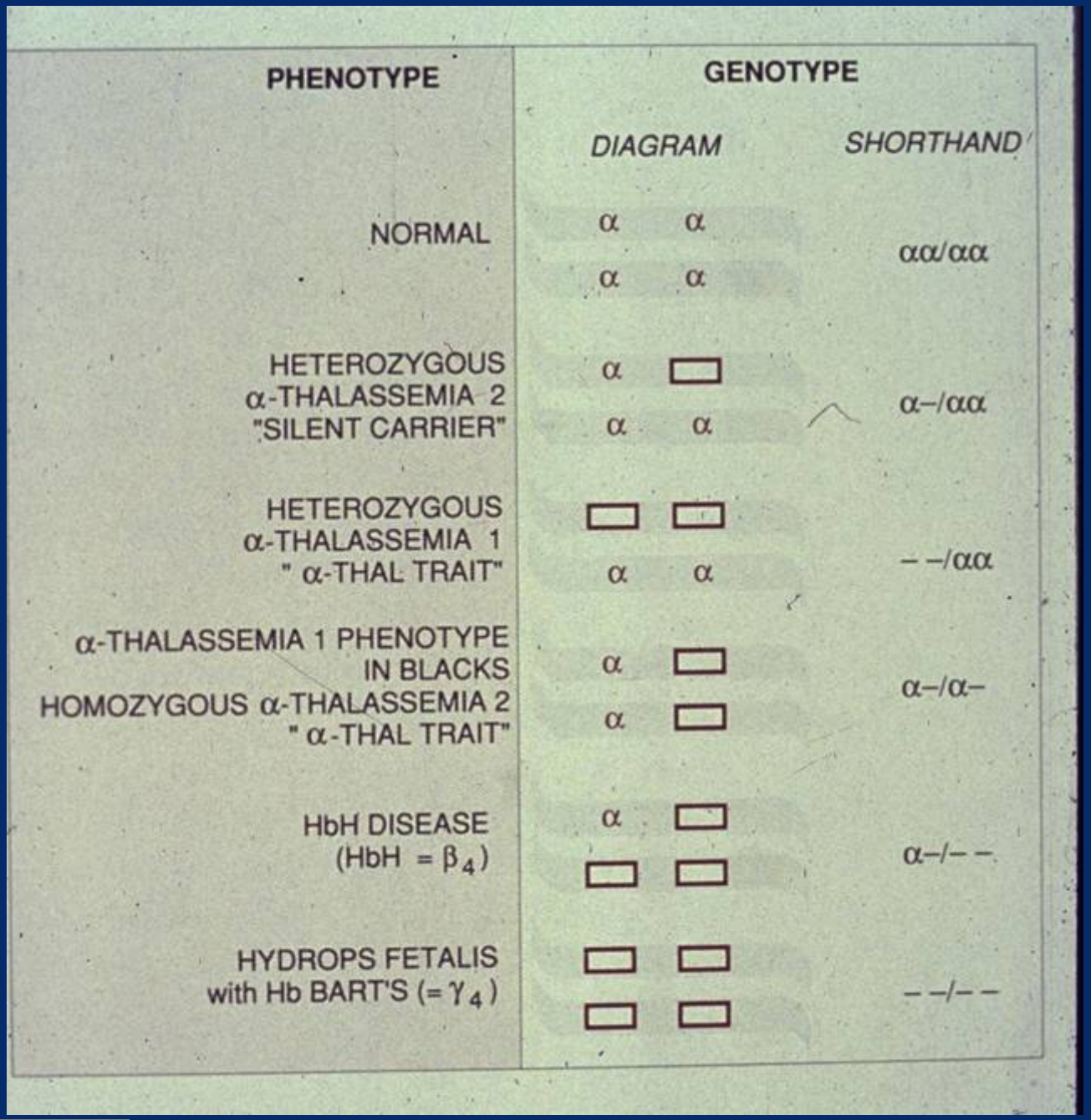


 DHK Chui & JS Waye, ***Blood*** **91**:2213, 1998.

Table 1. Point Mutations in α-Thalassemia

Mutant Class	Origin	Reference
I. Nonfunctional mRNA		
a. Nonsense mutants:		
1) codon 116 (G-T)	Black	86
b. Frameshift mutants:		
1) codon 30/31 (−4nts)	Black	65
c. Initiator codon mutants:		
2) ATG-ACG	Mediterranean	110
3) CCCACCATG-CCCCATG	Mediterranean	90a
4) ATG-GTG	Mediterranan, Black	90, 96
d.Terminator codon mutants		
5) α^{CS} of HB Constant Spring (TAA-CAA)	Black	30
6) α^{KD} of Koya Dora (TAA-TCA)	Indian	34
7) α^{IC} of Hb Icaria (TAA-AAA)	Mediterranean	29
8) α^{SR} of Hb Seal Rock (TAA-GAA)	Black	15
II. RNA Processing mutants		
a. Splice junction changes:		
1) IVS-1 donor site (GGTGAGGCT-GGCT)	Mediterranean	100a
b. RNA cleavage and polyandenylation site		
1) AATAAA-AATAAG	Arab	64
III. Unstable globins		
1) $\alpha^{Quong\ Sze}$ (codon 125 Leu-Pro)	SE Asian	59
2) $\alpha^{Suan\ Dok}$ (codon 209, Leu-Arg)	SE Asian	129
3) $\alpha^{Petah\ Tikvah}$ (codon 110, Ala-Asp)	Middle East	65
4) $\alpha^{Evanston}$ (codon 14, Trp-Arg)	Black	68

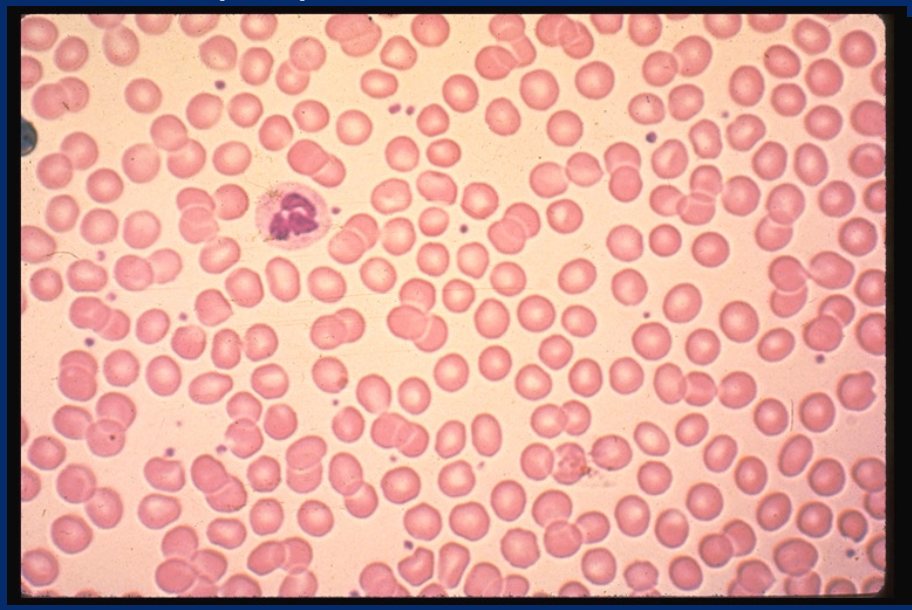
Note. Total number = 15; November, 1989.

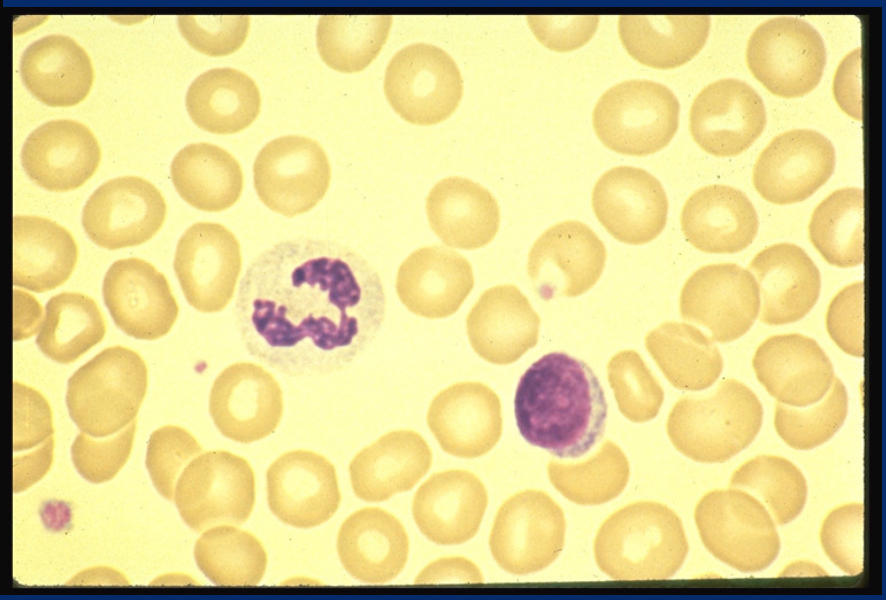


Principles of Medical Genetics: : Fig. 6.15

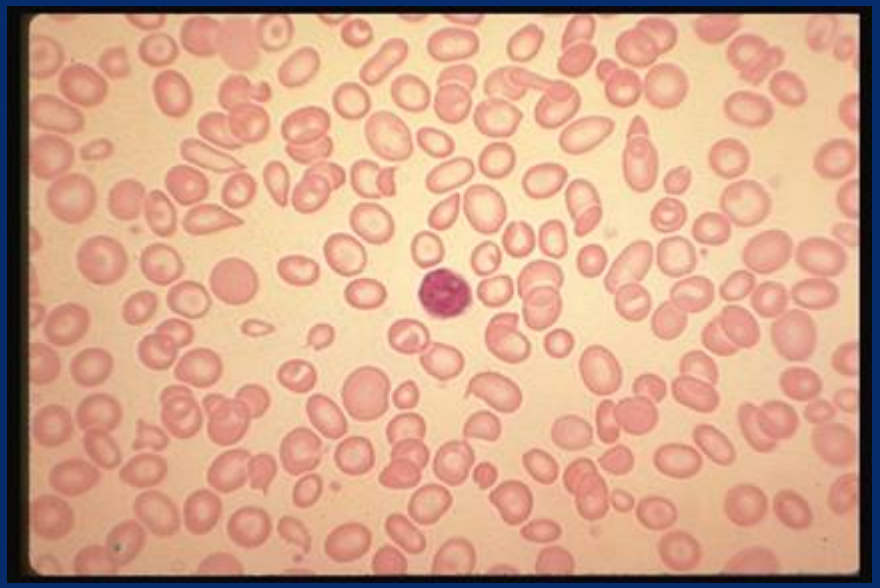
 Gelehrter, Collins and Ginsburg: *Principles of Medical Genetics 2E;* Figure 6.15

Normal peripheral blood smear





Hgb H disease



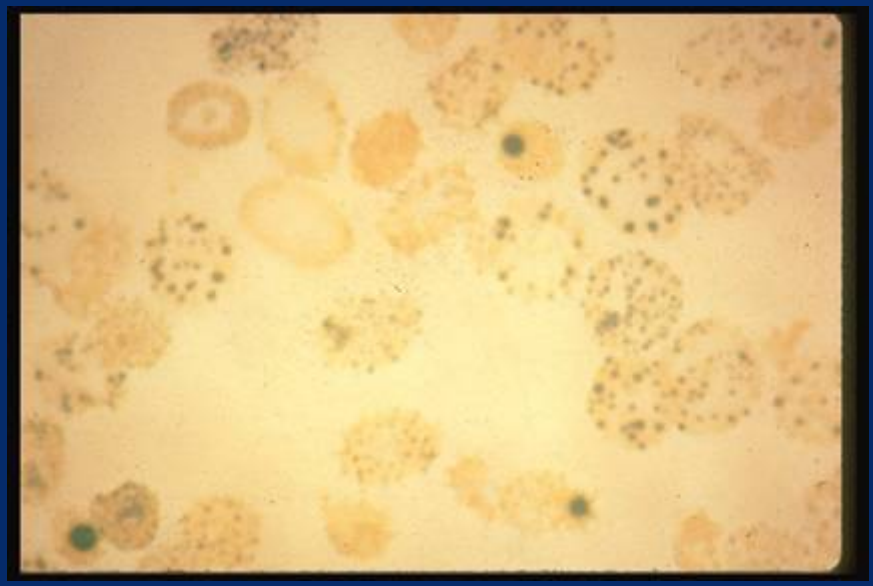
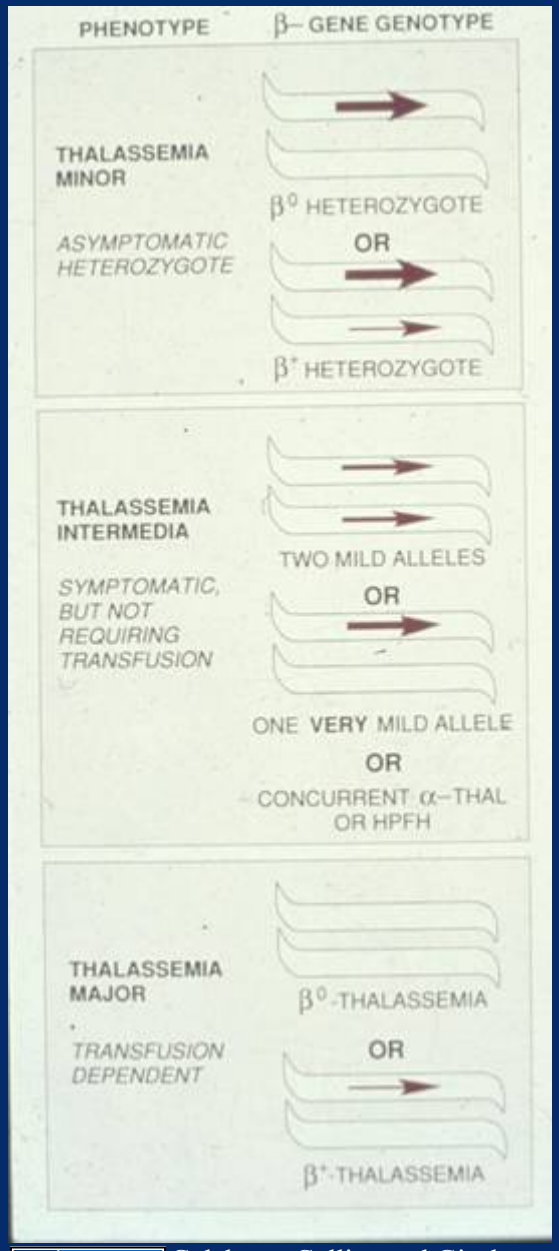
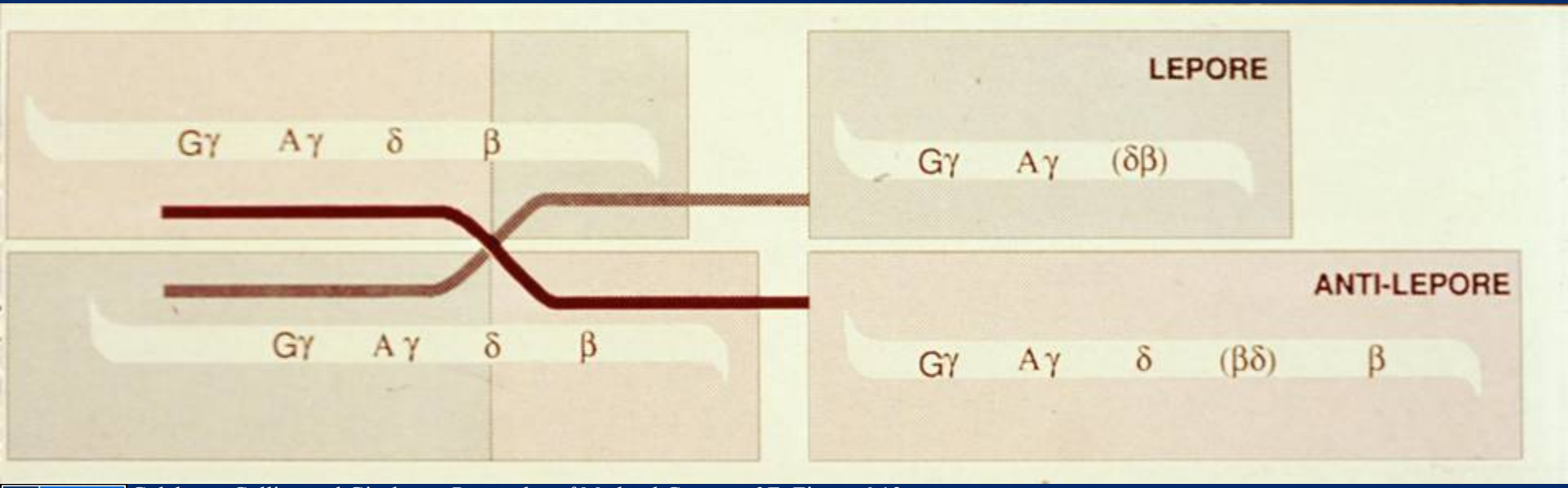


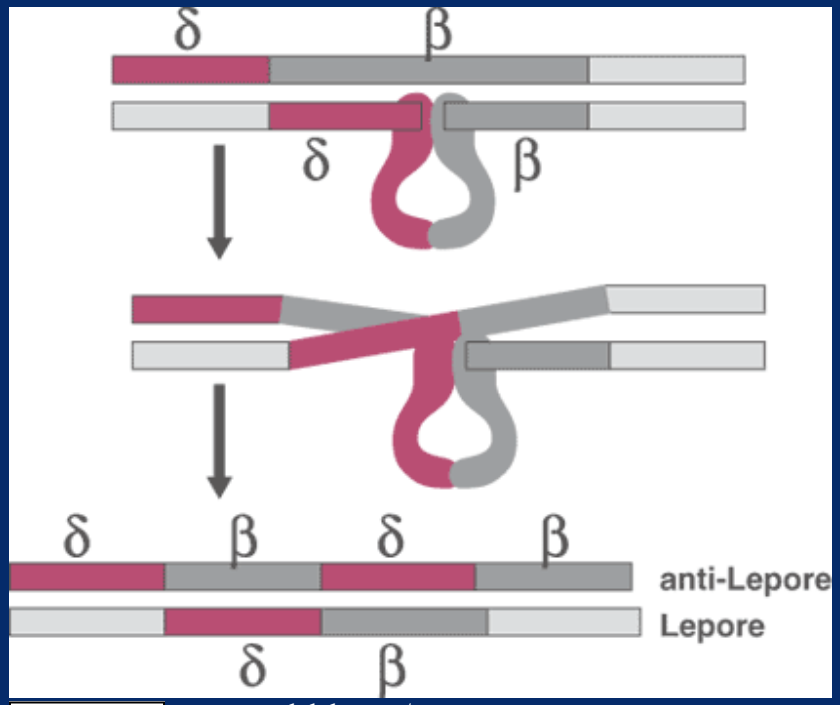
Image removed. See Miller LH. *Nature,* **383**:480, 1996.



Gelehrter, Collins and Ginsburg: *Principles of Medical Genetics 2E;* Figure 6.16



 Gelehrter, Collins and Ginsburg: *Principles of Medical Genetics 2E;* Figure 6.13



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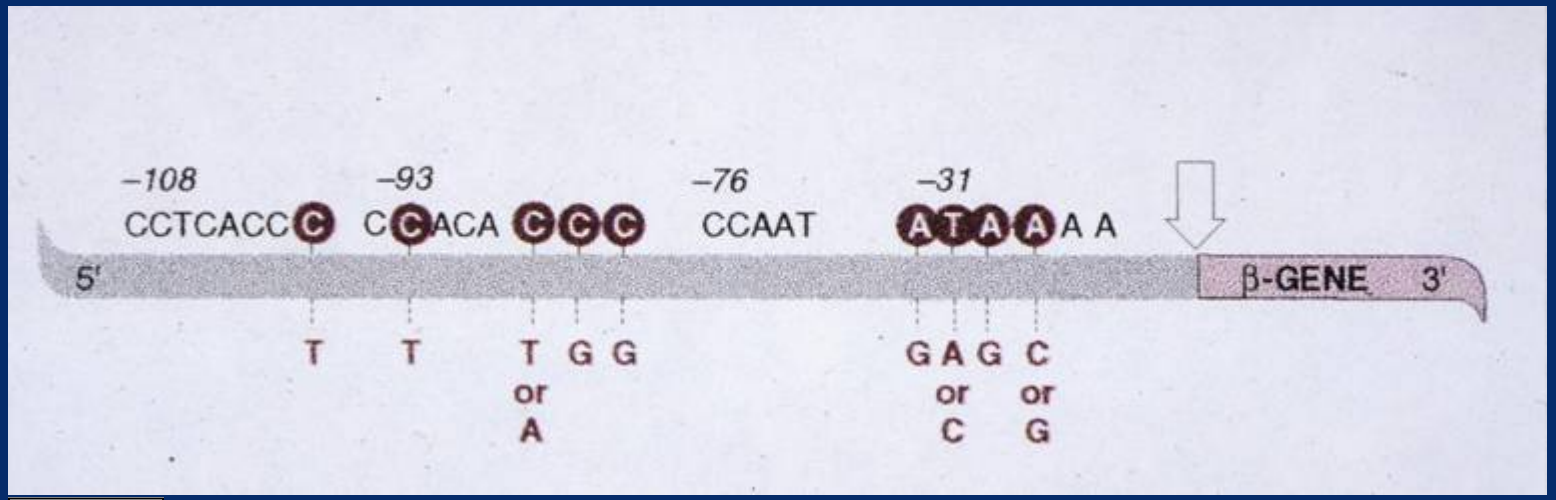
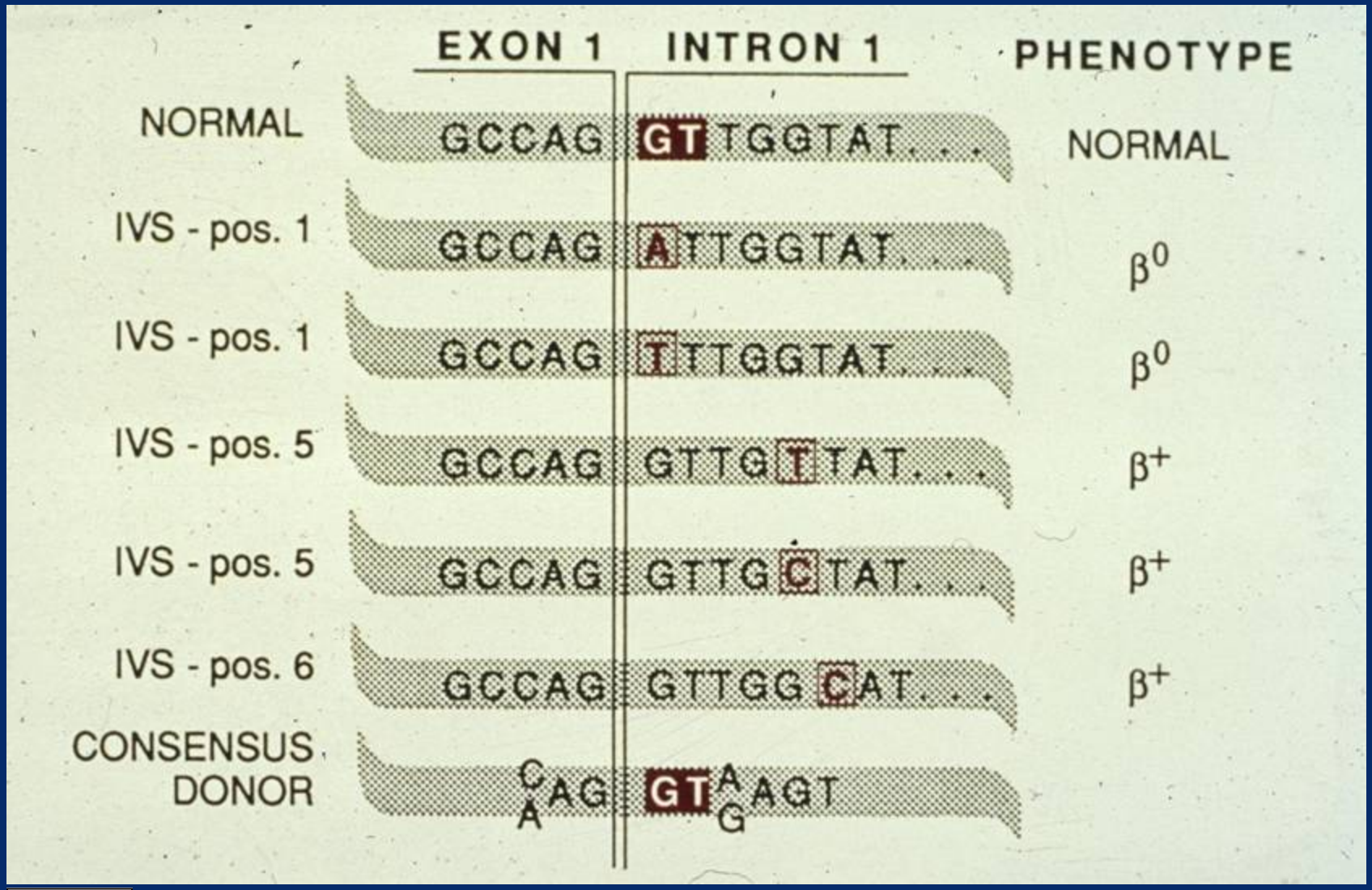
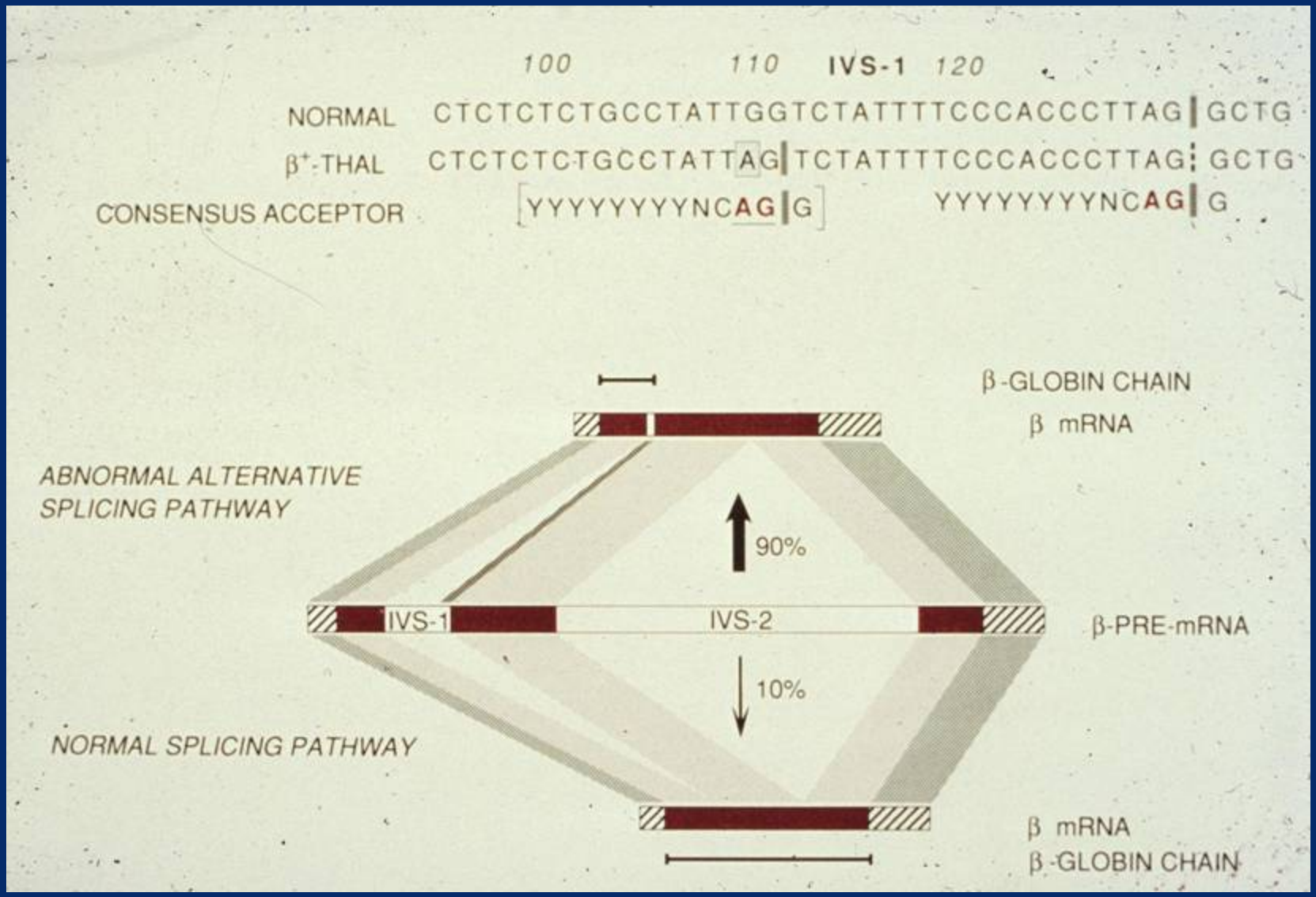


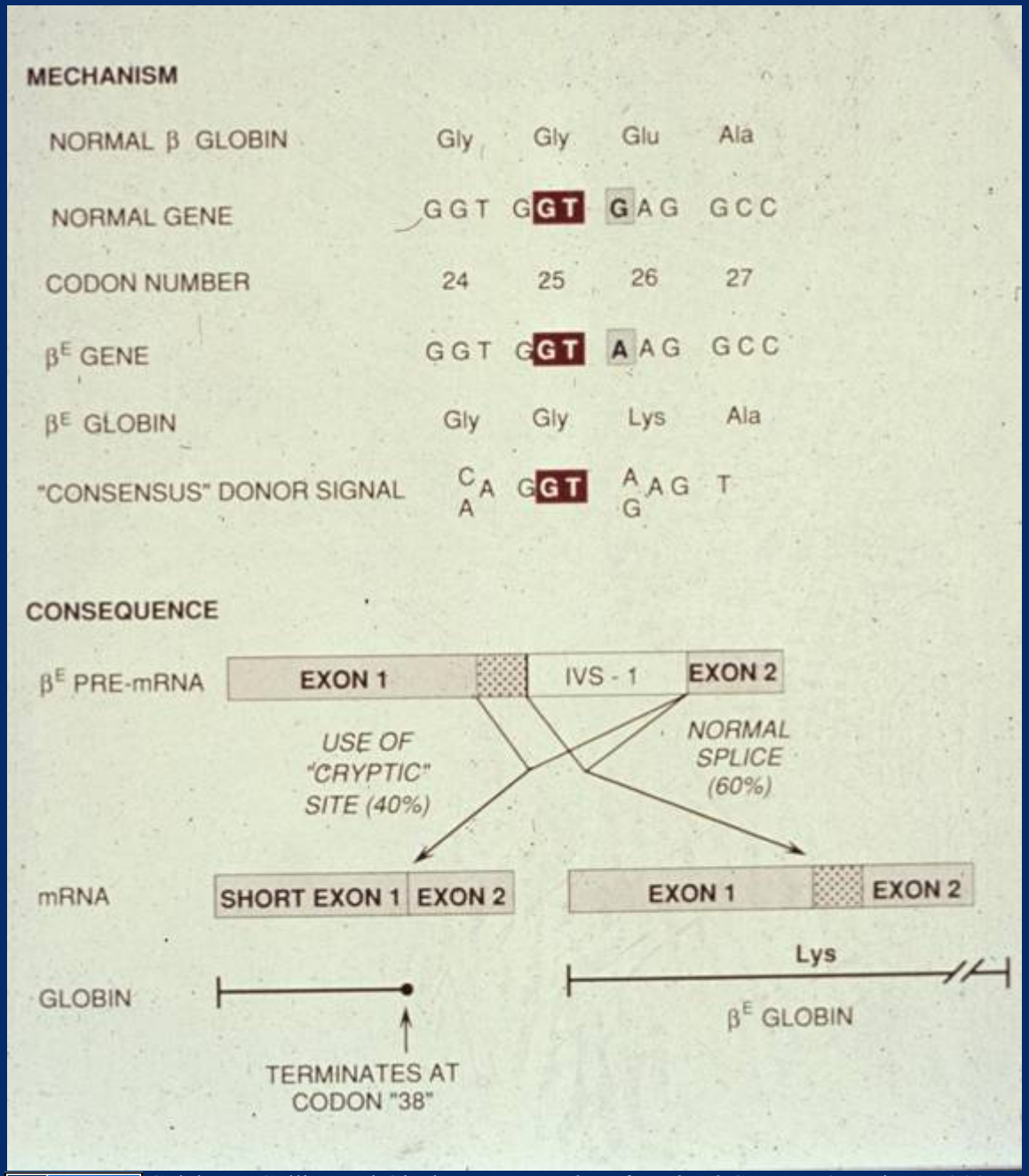
 Gelehrter, Collins and Ginsburg: *Principles of Medical Genetics 2E;* Figure 6.19



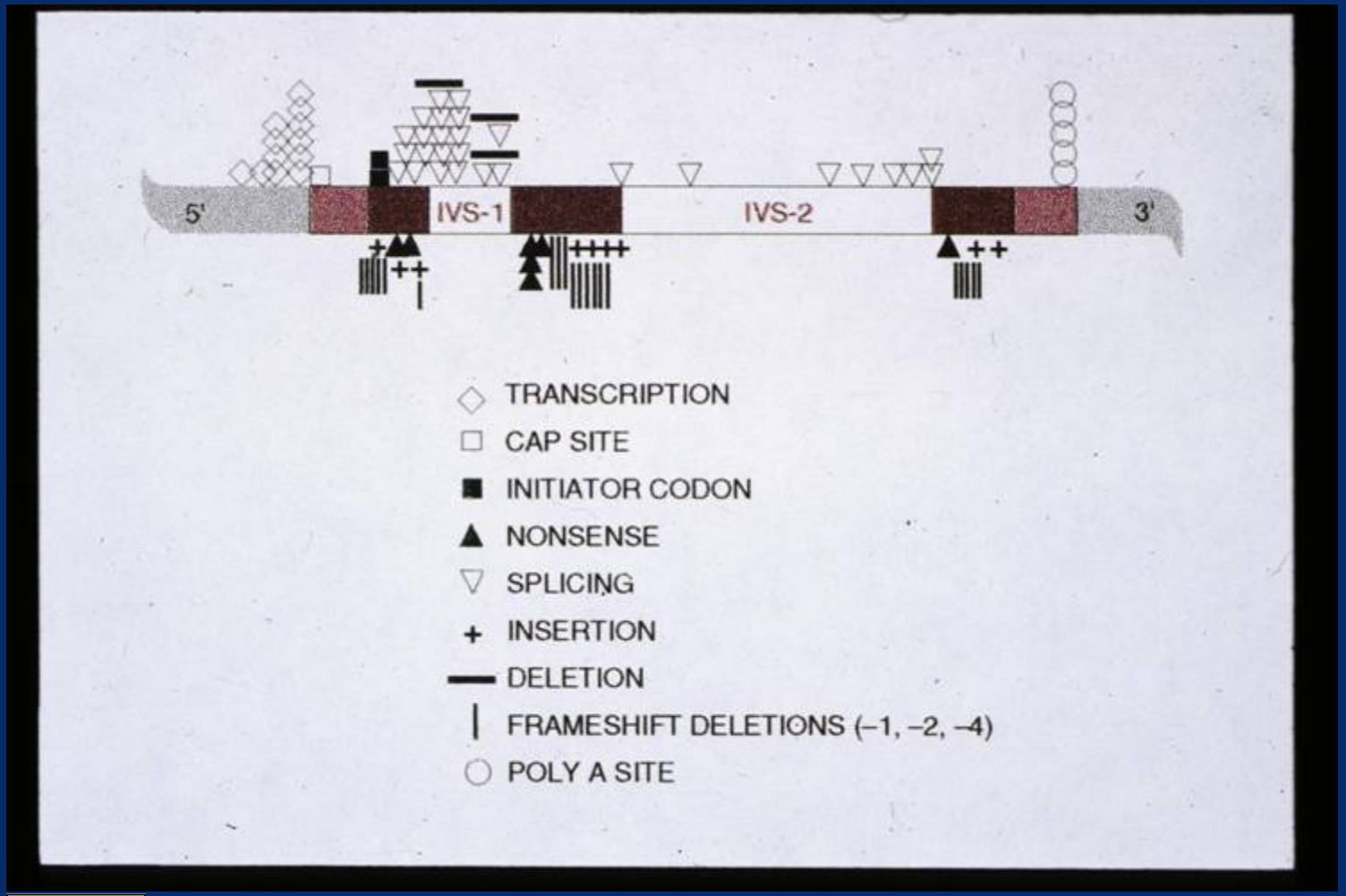
 Gelehrter, Collins and Ginsburg: *Principles of Medical Genetics 2E;* Figure 6.20



Principles of Medical Genetics: Figure 6.21

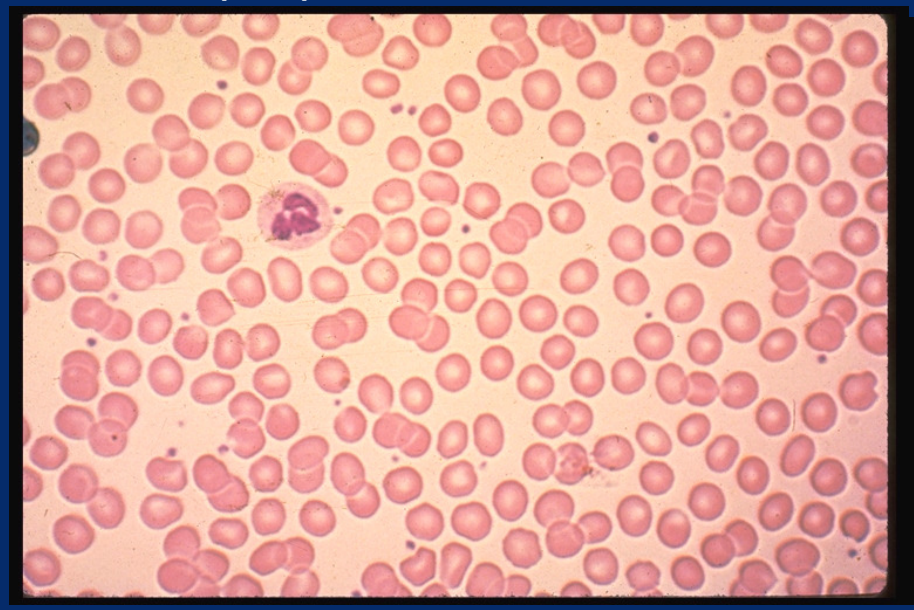


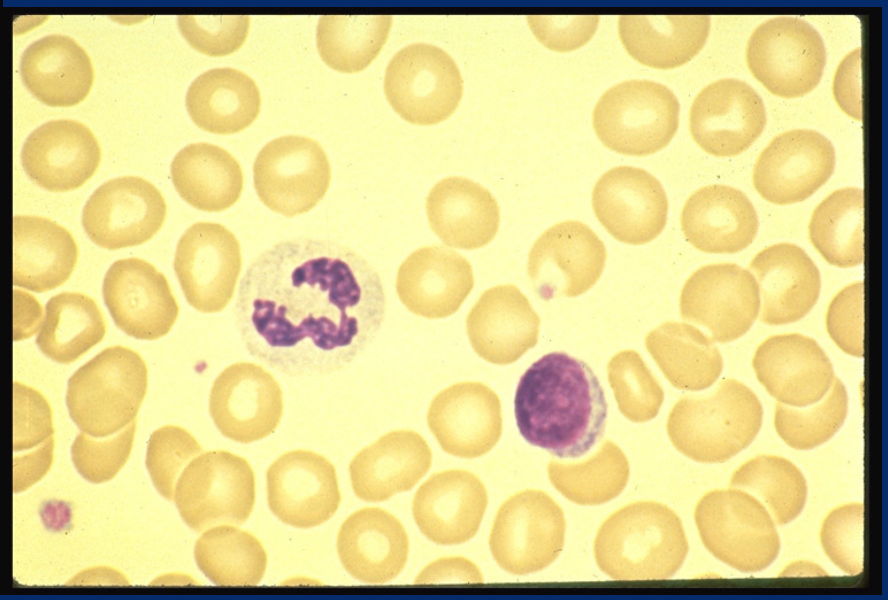
 Gelehrter, Collins and Ginsburg: *Principles of Medical Genetics 2E;* Figure 6.22



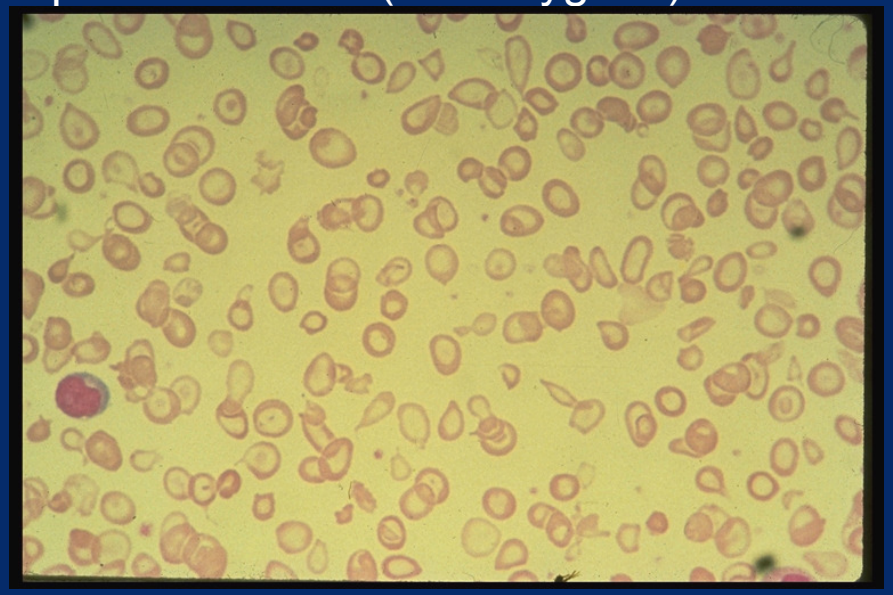
 Gelehrter, Collins and Ginsburg: *Principles of Medical Genetics 2E;* Figure 6.18

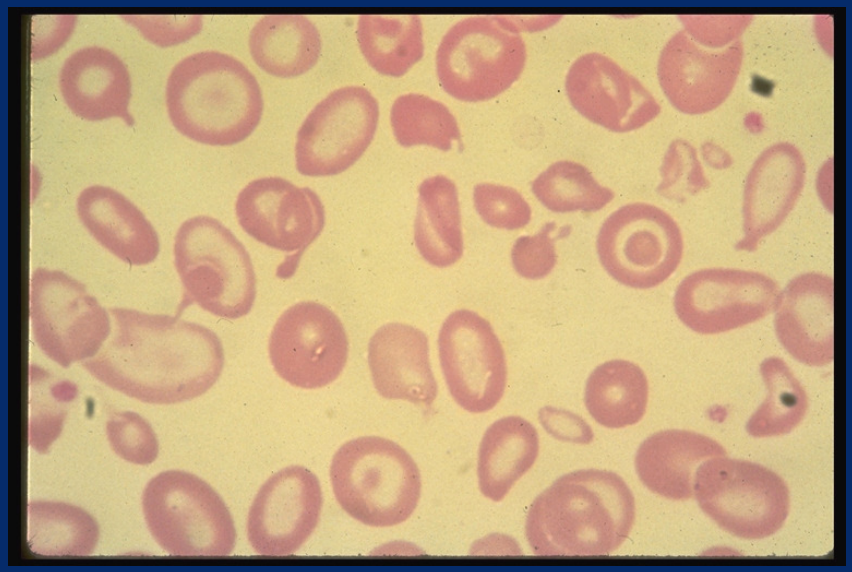
Normal peripheral blood smear

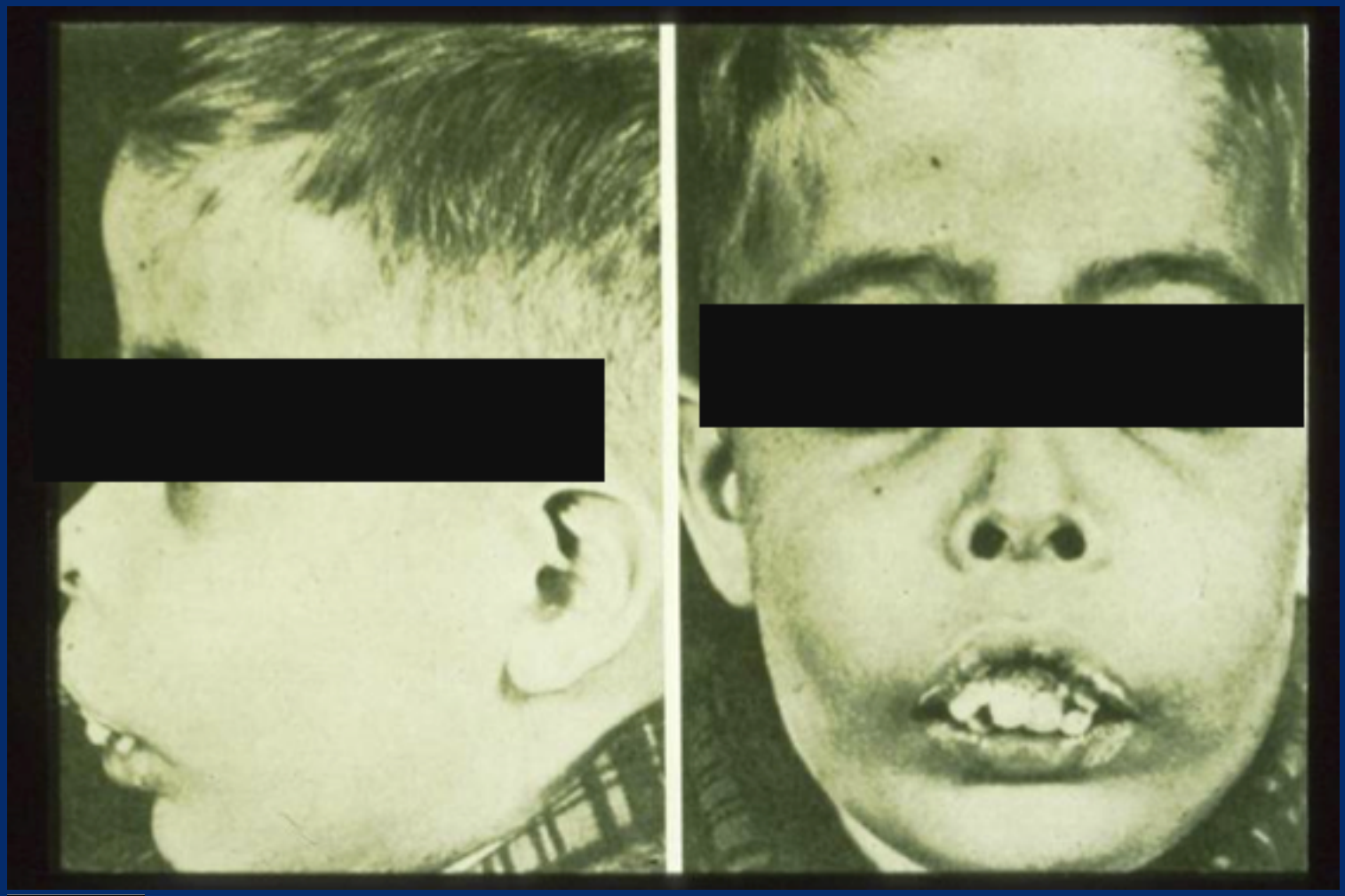


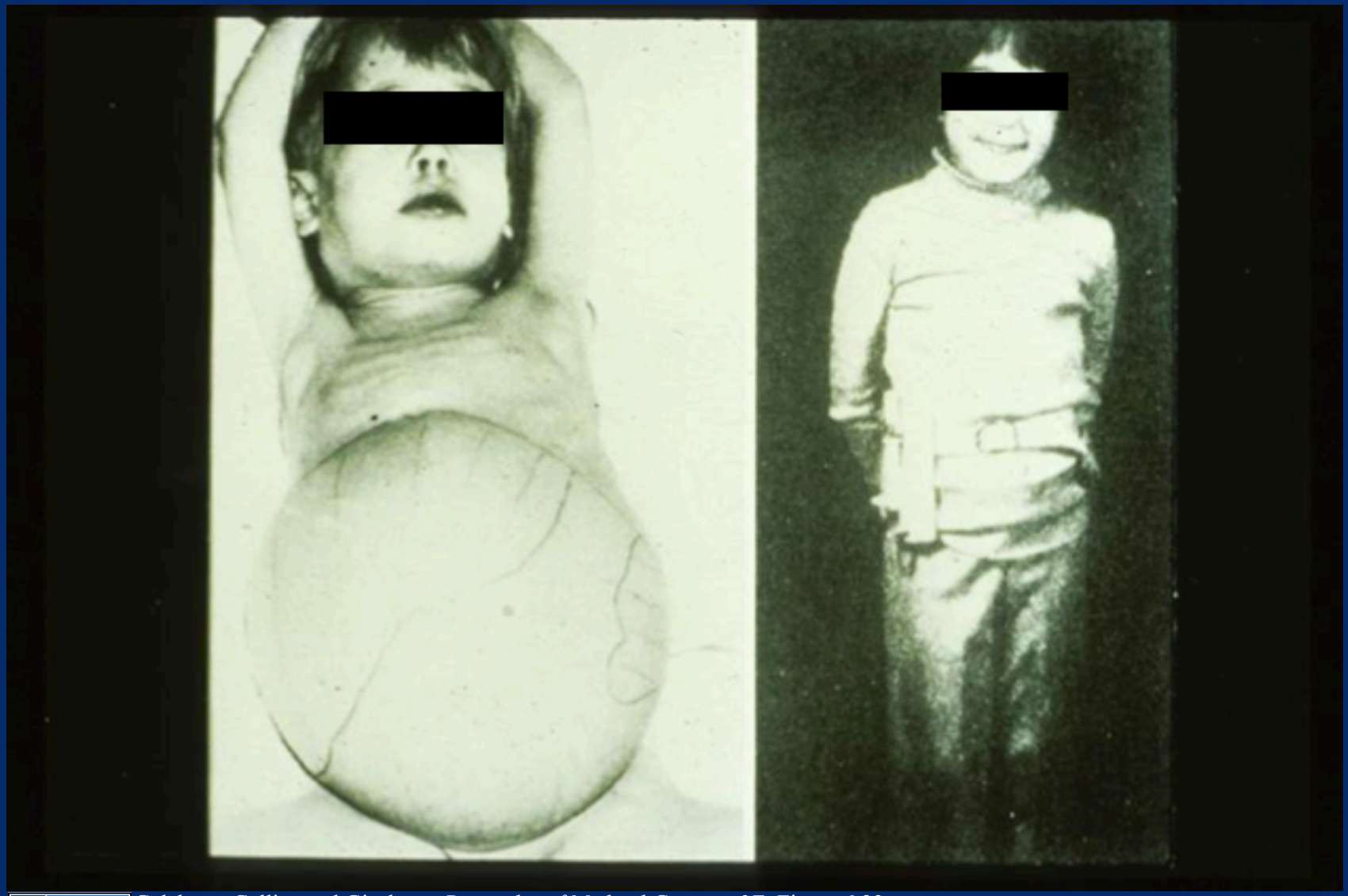


β-Thalassemia (homozygous)

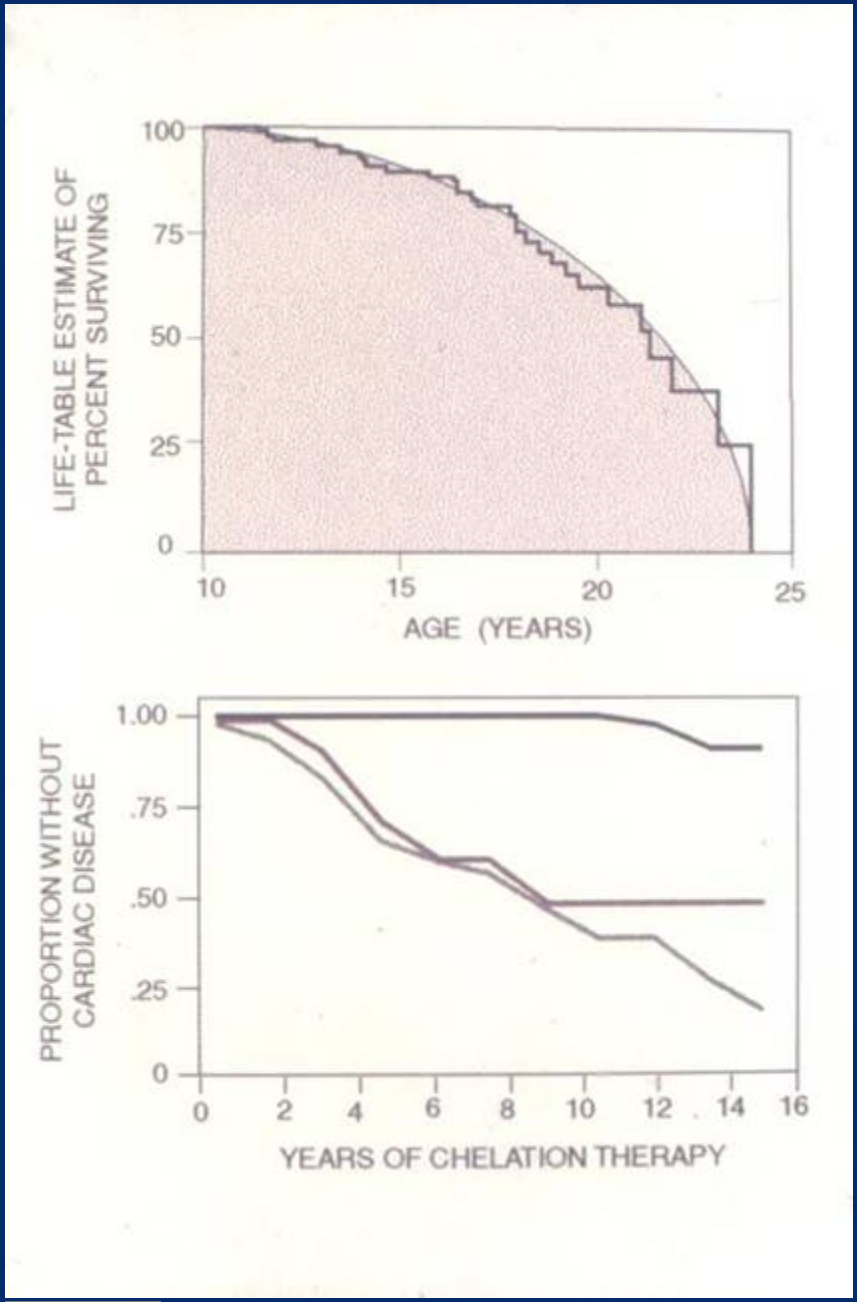








 Gelehrter, Collins and Ginsburg: *Principles of Medical Genetics 2E;* Figure 6.23



 Gelehrter, Collins and Ginsburg: *Principles of Medical Genetics 2E;* Figure 6.24

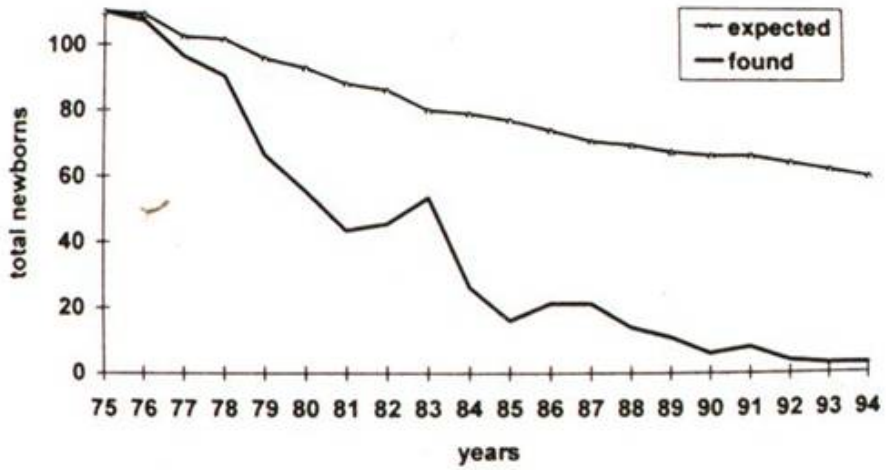


Fig 3. Fall in the birth rate of β-thalassemia homozygotes in Sardinia.

 Gelehrter, Collins and Ginsburg: *Principles of Medical Genetics 2E;* Figure 6.25

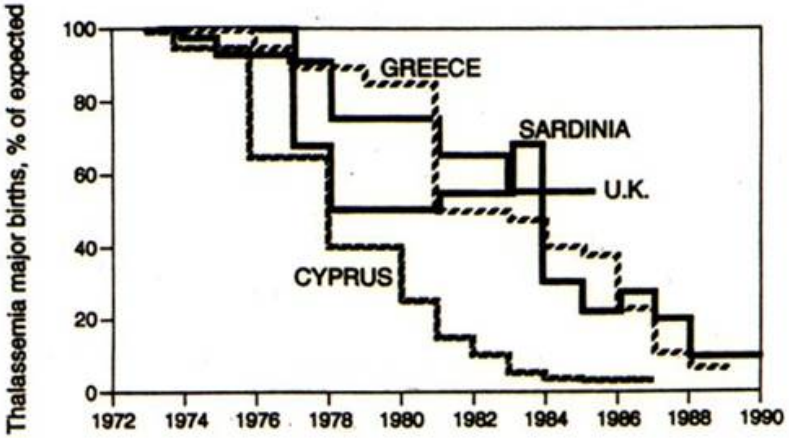
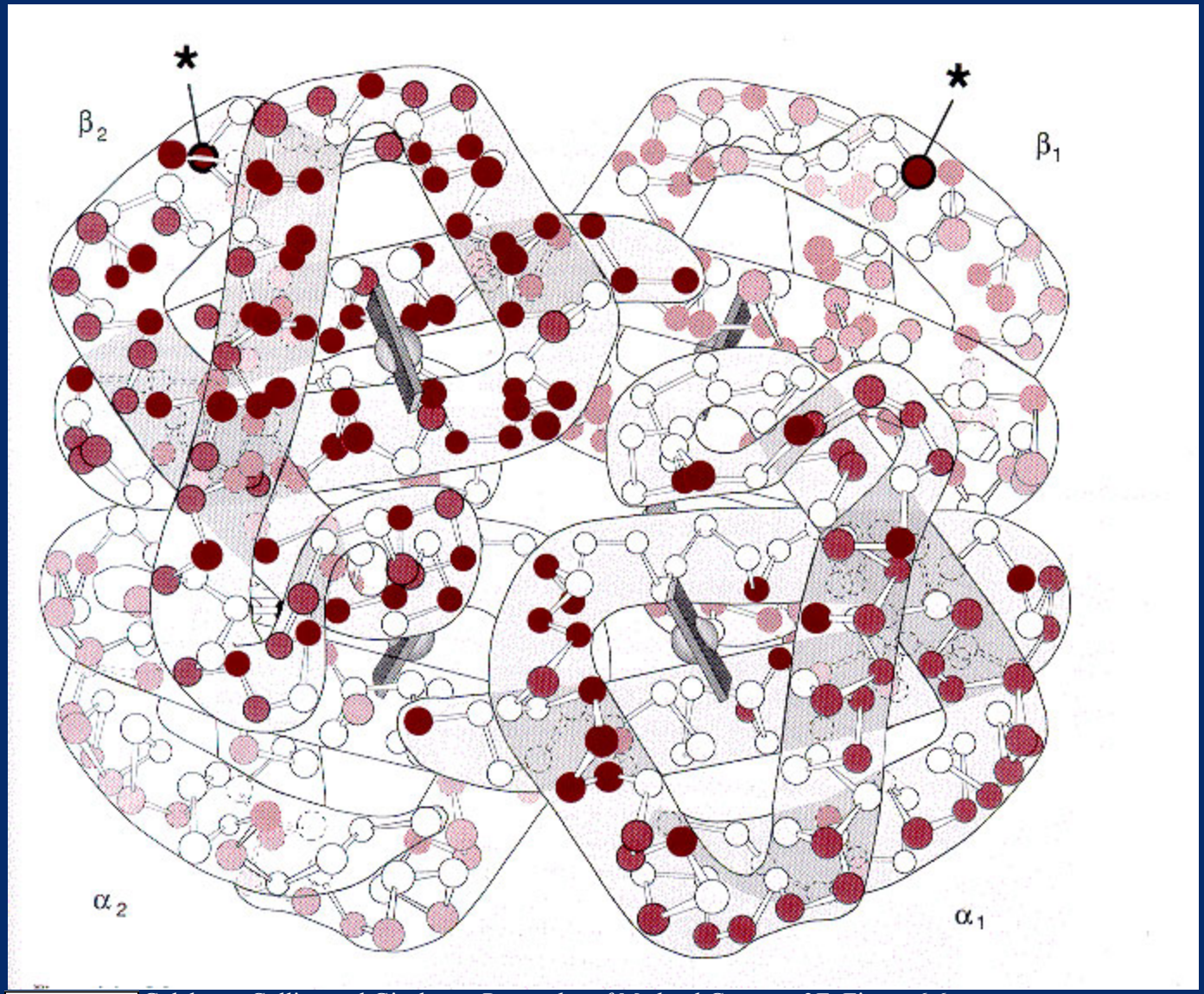


Fig 8. Change in birth rate of thalassemic children in four countries after the introduction of preventive programs. Adapted with permission.[55,88]



 Gelehrter, Collins and Ginsburg: *Principles of Medical Genetics 2E;* Figure 6.6

Qualitative Abnormalities of Hemoglobin

- **Silent Variants**
- **Unstable hemoglobins**
  - Heinz body hemolytic anemia
- **Methemoglobinemia**
- **High affinity hemoglobins**
  - polycythemia (↑hematocrit and hemoglobin)
- **Low affinity hemoglobins**
  - mild anemia (↓hematocrit and hemoglobin)
- **Hemoglobin S**
- **Hemoglobin C**

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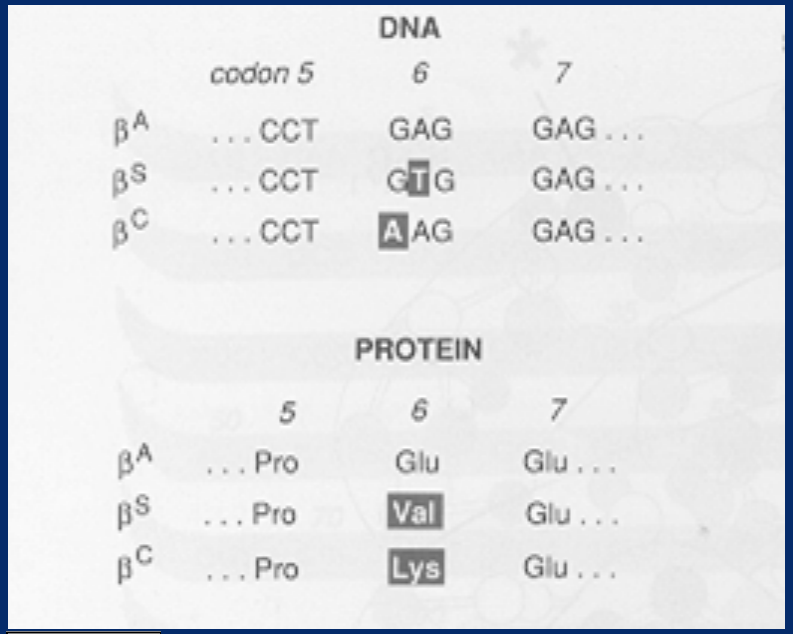


DNA

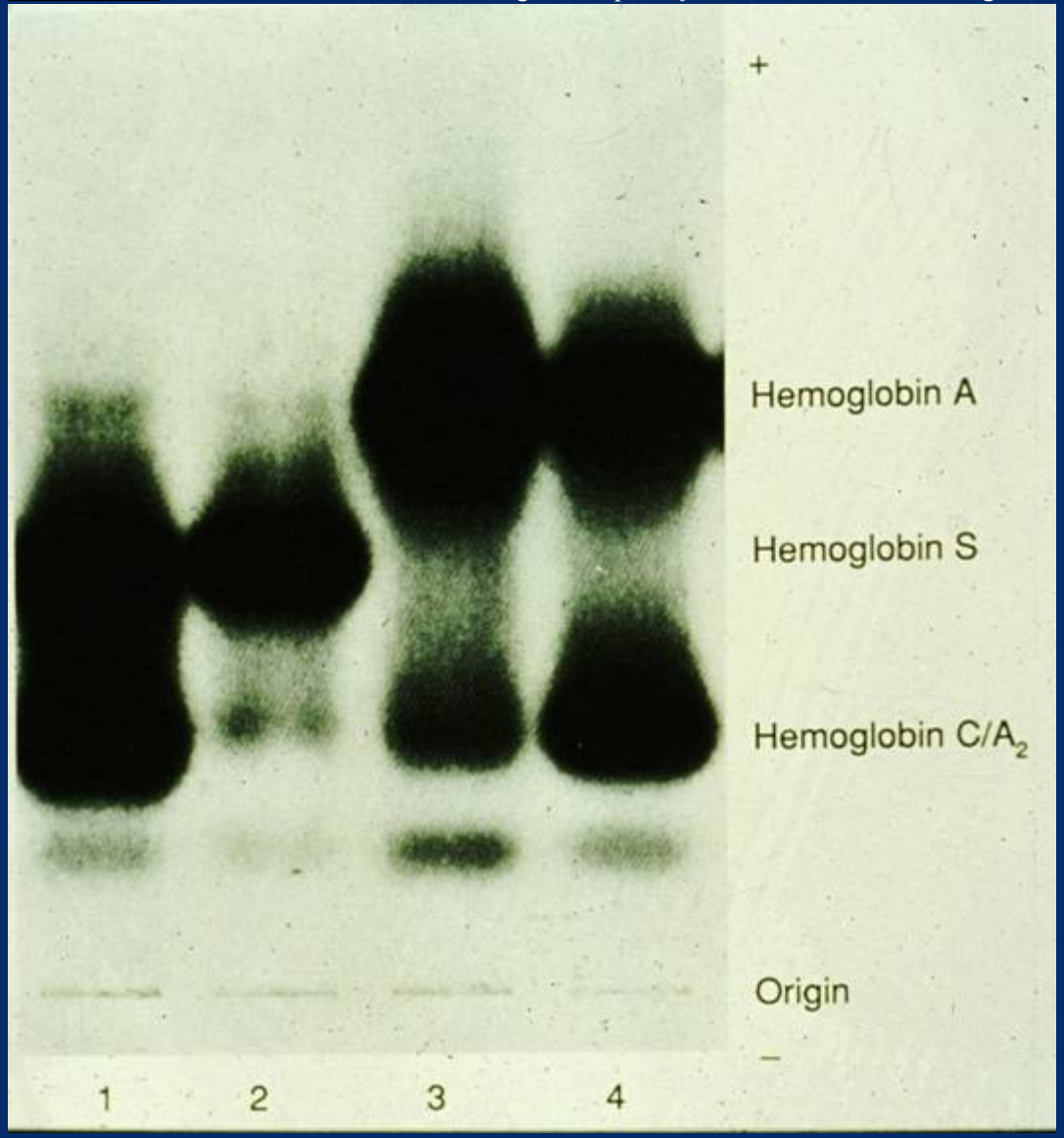
	codon 5	*6*	*7*
β^A	. . . CCT	GAG	GAG . . .
β^S	. . . CCT	GTG	GAG . . .
β^C	. . . CCT	AAG	GAG . . .

PROTEIN

	5	*6*	*7*
β^A	. . . Pro	Glu	Glu . . .
β^S	. . . Pro	Val	Glu . . .
β^C	. . . Pro	Lys	Glu . . .

 Gelehrter, Collins and Ginsburg: *Principles of Medical Genetics 2E;* Figure 6.7

 Gelehrter, Collins and Ginsburg: *Principles of Medical Genetics 2E;* Figure 6.9

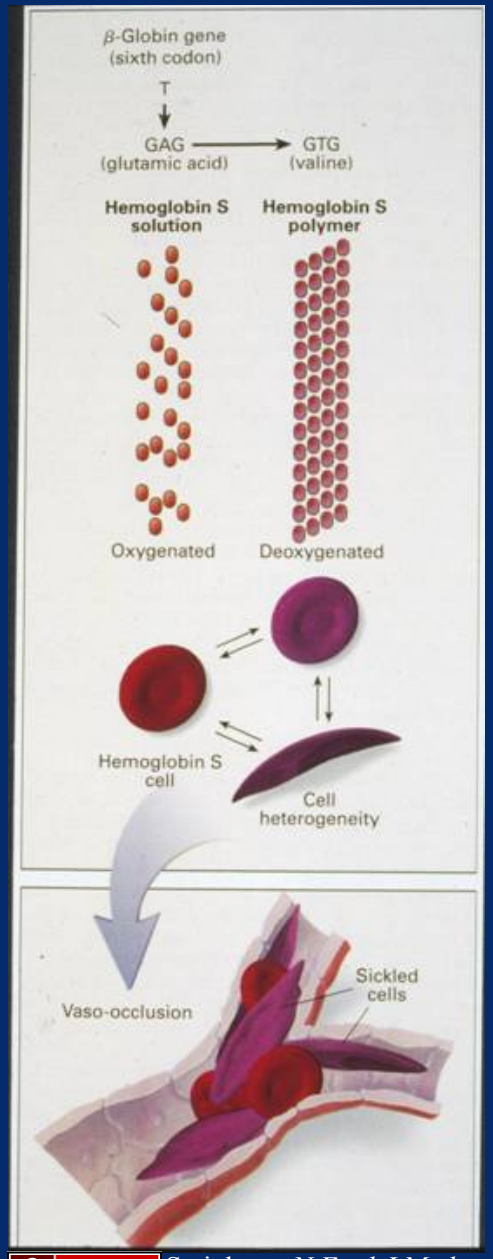


SC

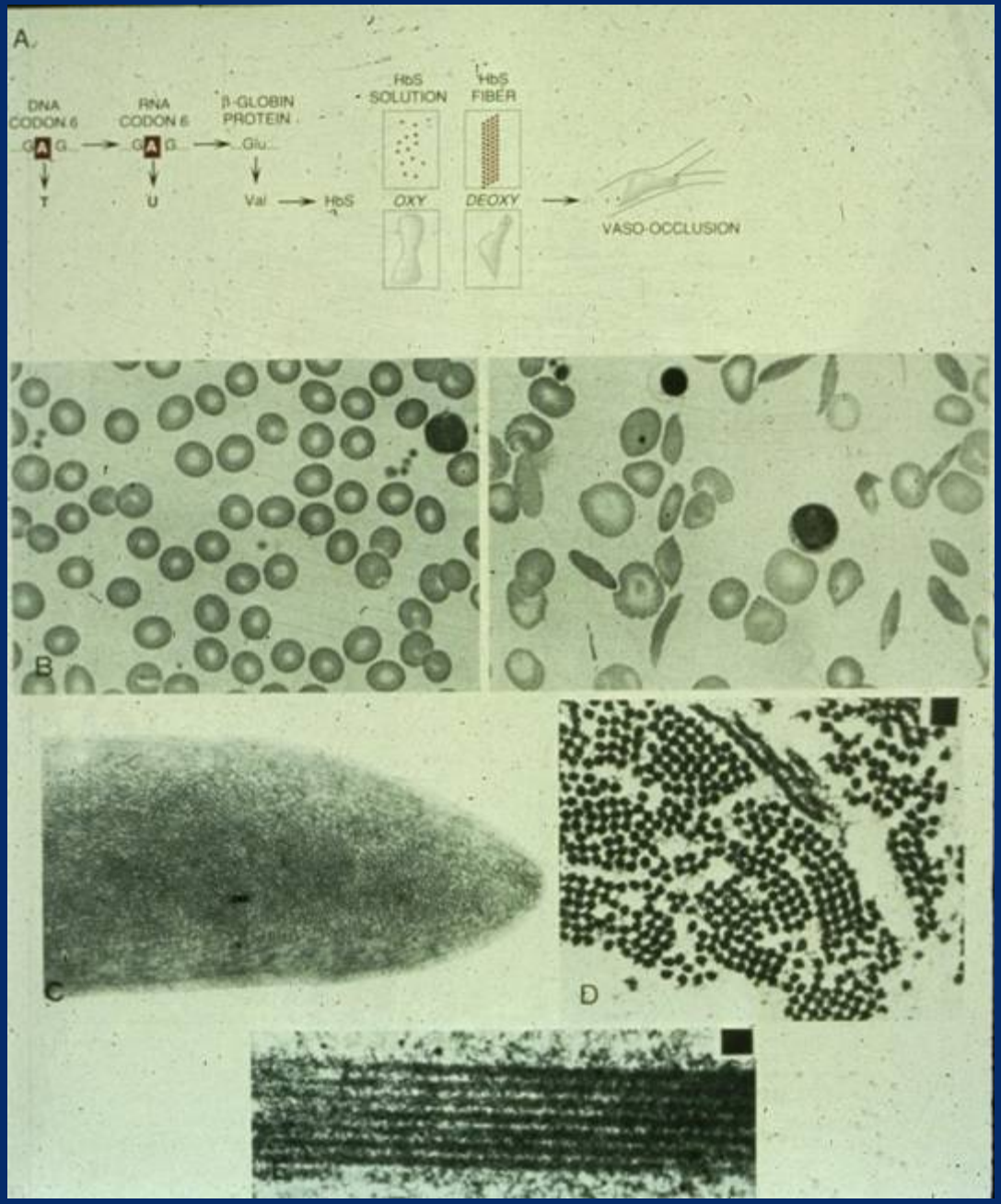
SS
sickle

AA
Nl

AC
trait

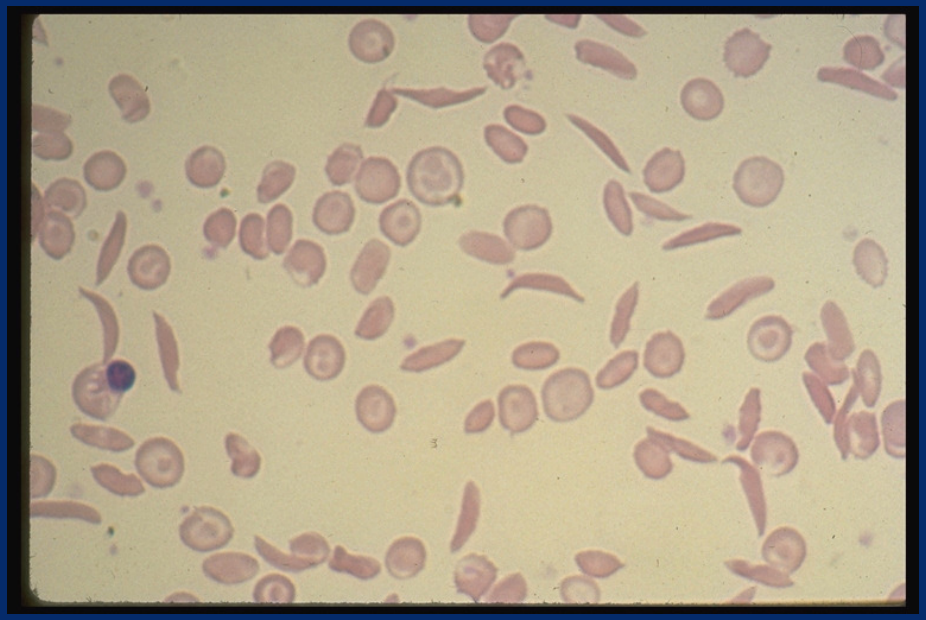


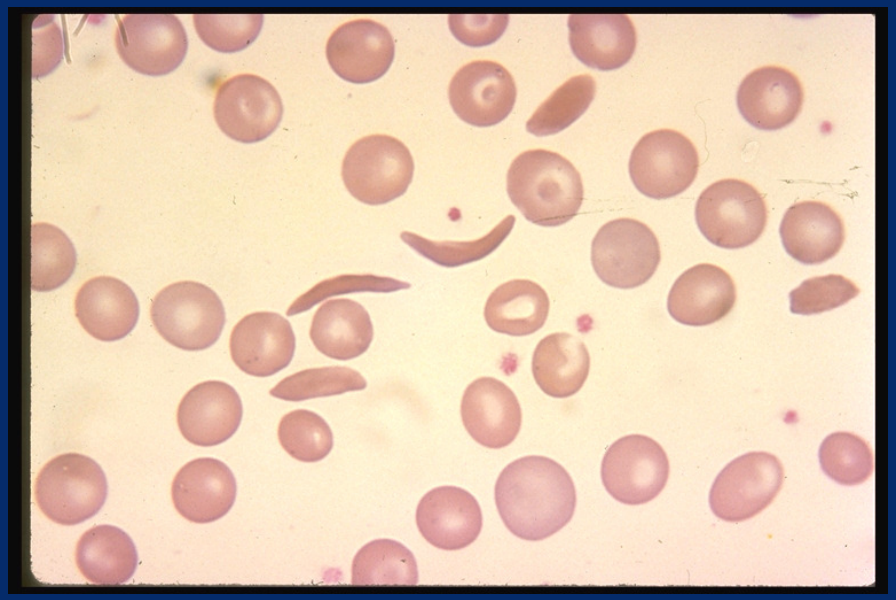
 Steinberg. *N.Engl.J.Med.* 340:1021, 1999.



 Gelehrter, Collins and Ginsburg: *Principles of Medical Genetics 2E;* Figure 6.8

Hemoglobin SS Disease





Complications of Sickle Cell Anemia

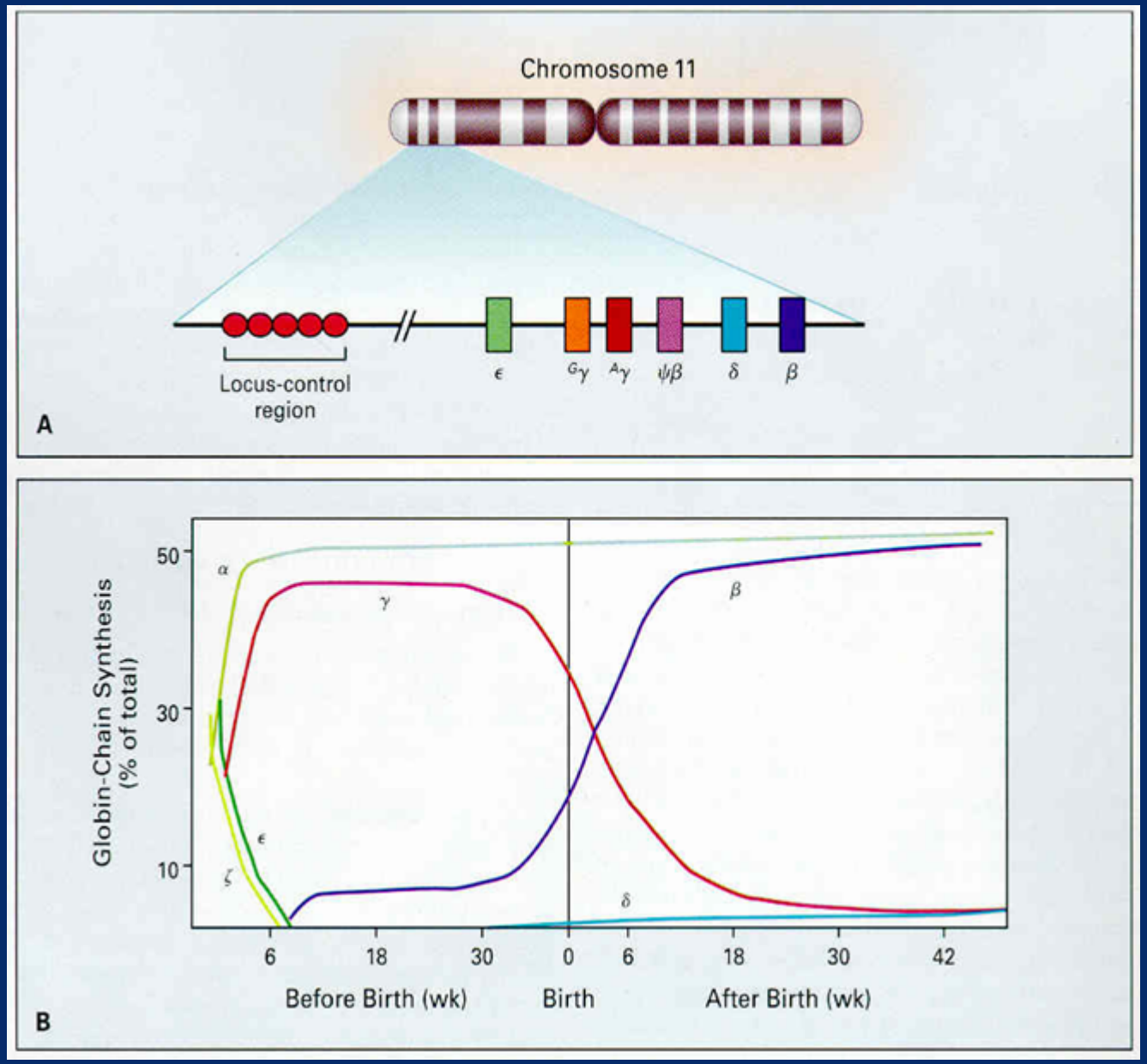
- autosplenectomy
- hyposthenuria
- Infections
  - encapsulated organisms-- pneumococcus
  - salmonella, staph
- Painful crises
- Bone infarcts, aseptic necrosis
- Stroke
- Acute chest syndrome
- Hand-foot syndrome
- Chronic organ damage

Table 10–11. FREQUENCY OF HEMOGLOBIN GENOTYPES AMONG BLACK AMERICANS

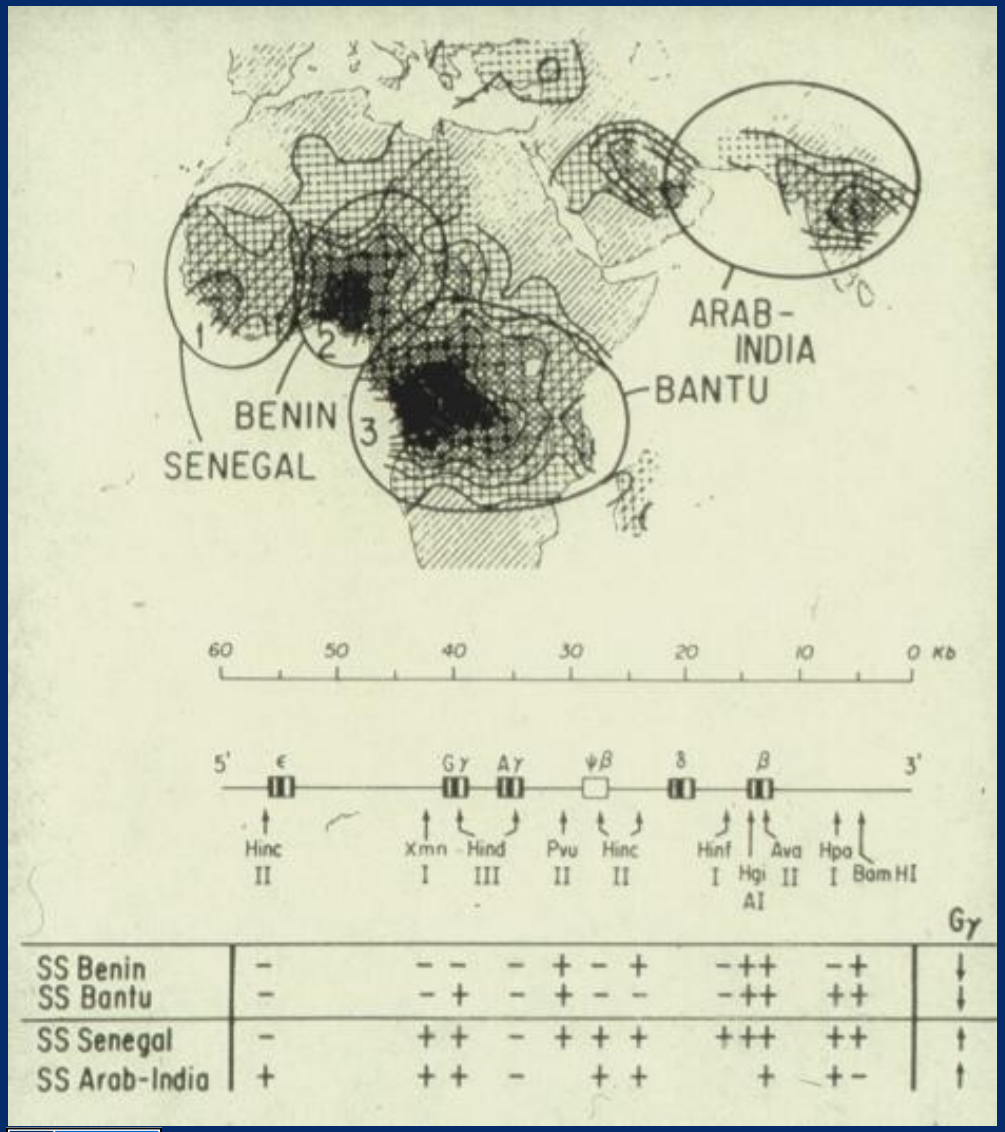
Genotype	Percentage of Population *	Percentage of Population **
AS	8.6	8.0
SS	0.14	0.16
AC	2.4	3.0
CC	0.02	0.02
SC	0.13	0.12

*Survey of 250,000 black Americans[556]

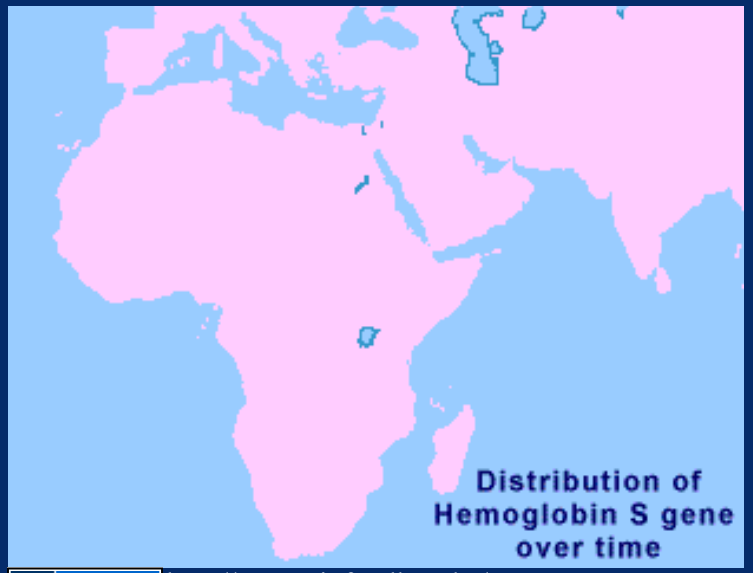
**Review of literature[557]



 NF Olivieri, ***NEJM* 341**:99, 1999. (or *Principles of Medical Genetics*: Figure 6.2)

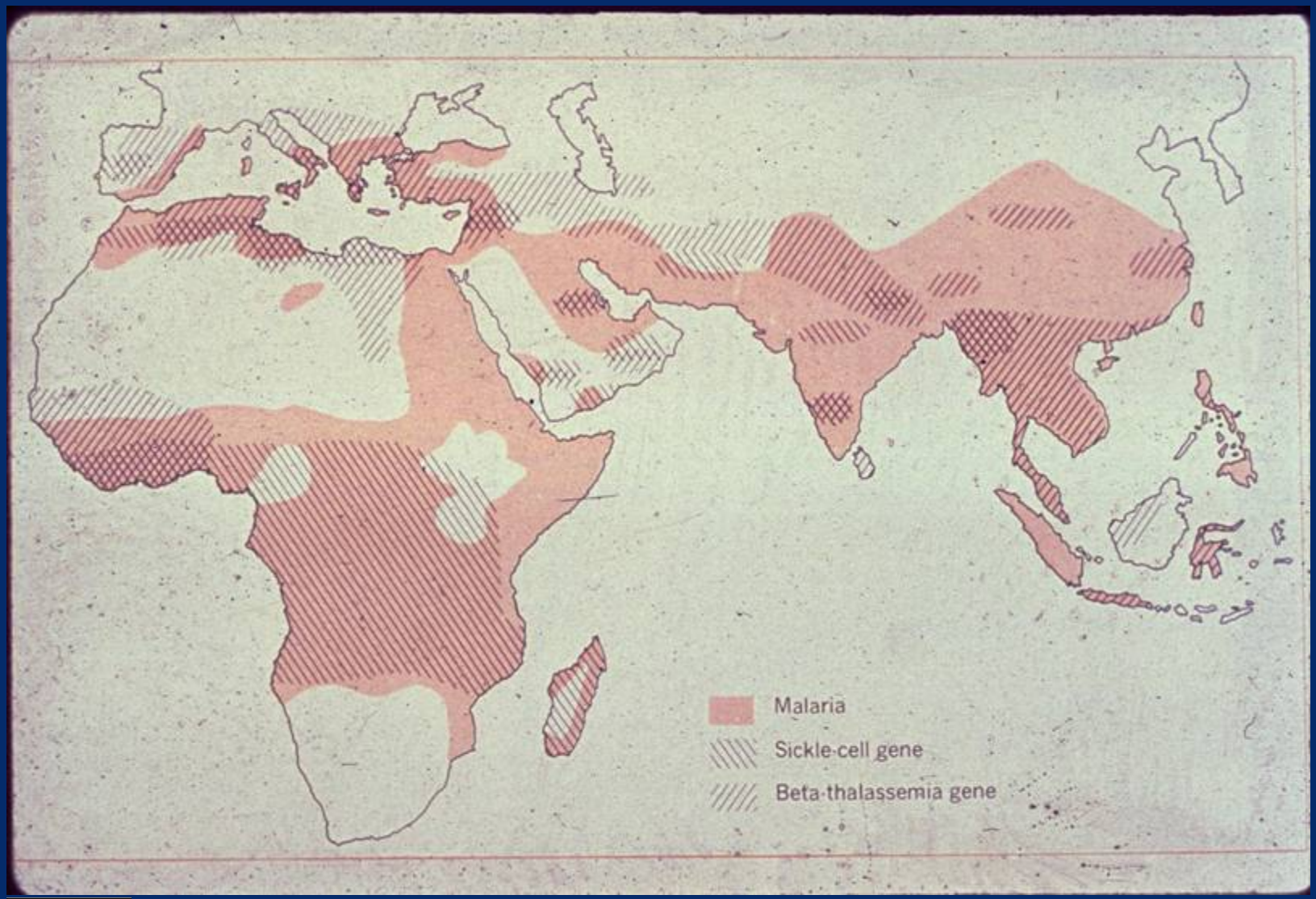


PD-INEL



PD-INEL http://erasmeinfo.ulb.ac.be/

Hb S only occurs on 4 haplotypes…only occurred 4 times in history



 Gelehrter, Collins and Ginsburg: *Principles of Medical Genetics 2E;* Figure 4.2

Hb S is a balanced polymorphism

* homozygotes (1 in 500) are selected against
* heterozygotes (1 in 12) are selected for

Sickle Cell Anemia: Treatment

- IV fluids
- Analgesia
- Infection
  - penicillin prophylaxis
  - vaccines
- Oxygen
- Transfusion
- Erythropoietin
- Hydroxyurea
- Bone Marrow Transplantation

Learning Objectives

- Understand how the basic *anatomy of a gene* has a direct bearing on the occurrence of genetic disease.
- Know the normal and abnormal *expression patterns* of the hemoglobin genes.
- Understand the mutations that cause *quantitative* abnormalities in globin.
  - Unequal crossing over, and every other possible type of mutation
- Recognize mutations that cause *qualitative* abnormalities in globin.
- Understand the *molecular basis of sickle cell anemia.*