

## *Lecture 14*

# Sickle Cell Anemia

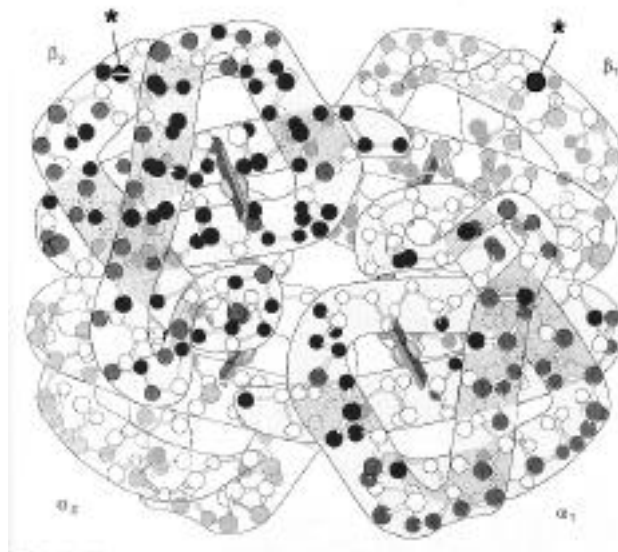
November 8, 2002

### *Learning Objectives*

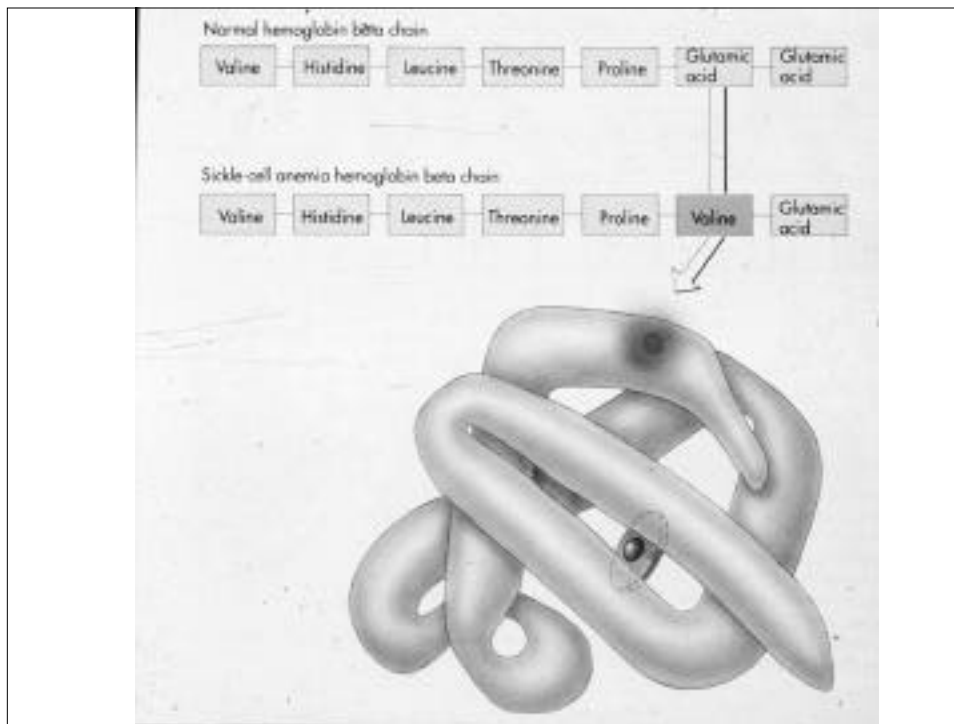
- Understand the molecular basis of sickle cell anemia and how to make a diagnosis
- Begin to recognize the clinical features sickle cell anemia
- Know that Hgb S is a balanced polymorphism, and understand the meaning of a haplotype.
- Know the conditions that facilitate sickling
- Understand why patients with sickle cell who co-inherit thalassemia trait will have a milder course

## Qualitative Abnormalities of Hemoglobin

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



Textbook Figure 6.6



		DNA		
		codon 5	6	7
$\beta^A$	...	CCT	GAG	GAG ...
$\beta^S$	...	CCT	<b>G</b> TG	GAG ...
$\beta^C$	...	CCT	<b>A</b> AG	GAG ...

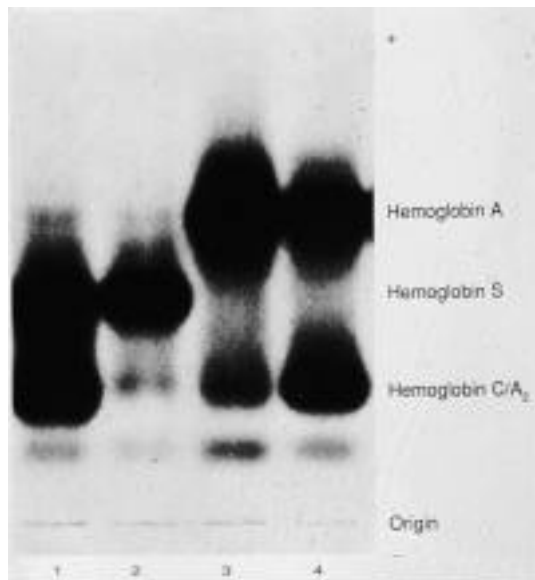
		PROTEIN		
		5	6	7
$\beta^A$	...	Pro	Glu	Glu ...
$\beta^S$	...	Pro	<b>Val</b>	Glu ...
$\beta^C$	...	Pro	<b>Lys</b>	Glu ...

**Figure 6.7.** The DNA and protein abnormalities in codon 6, which lead to sickle hemoglobin ( $\beta^S$ ) and hemoglobin C ( $\beta^C$ ).

DISEASE	ORIGIN	A <sub>2</sub>	C	S	F	A
Normal						
Sickle cell trait						
Sickle cell disease						
Sickle - c						
C - trait						
Thalassemia major						
Thalassemia minor						
Sickle - thalassemia						

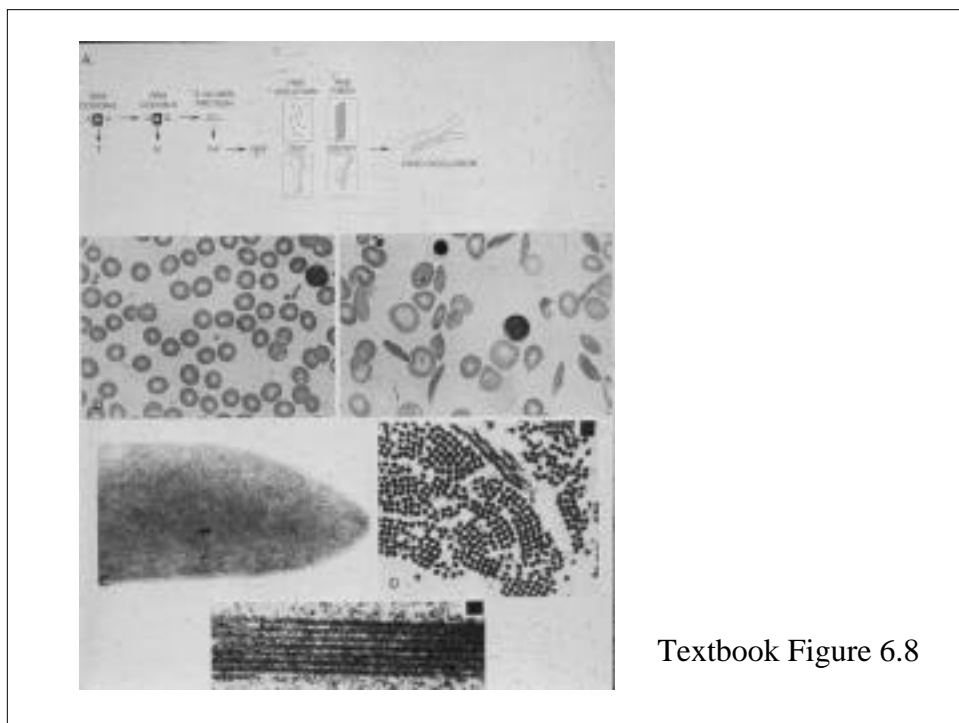
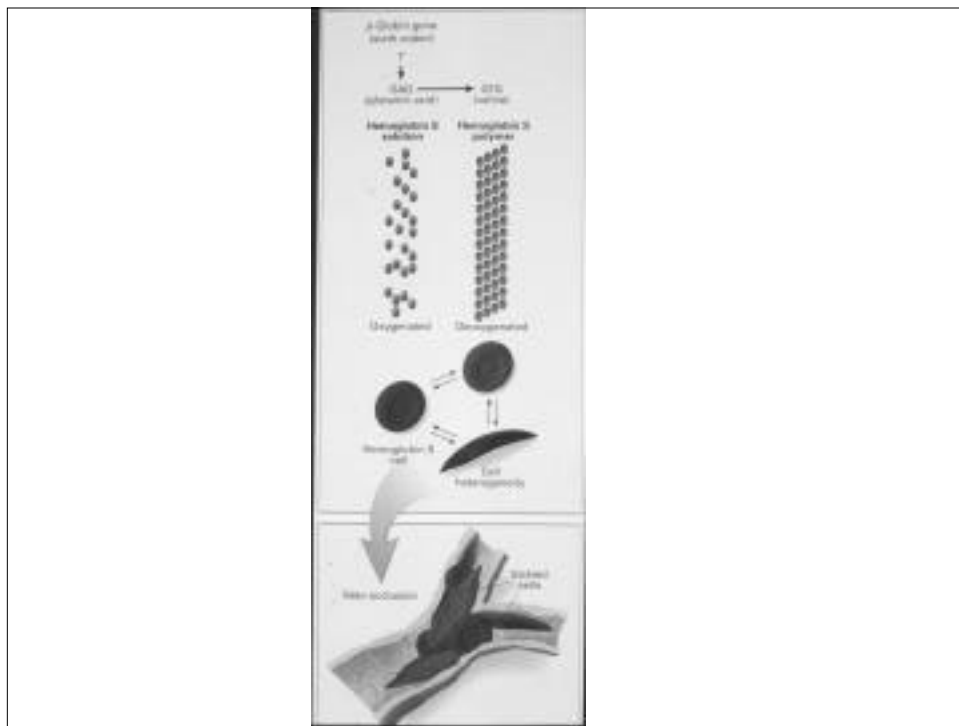
Cellulose acetate electrophoretic patterns for common hemoglobinopathies

*from the Red Cell Manual*



SC    SS    AA    AC  
*interm*   *sickle*   *Nl*   *C trait*

Textbook Figure 6.9



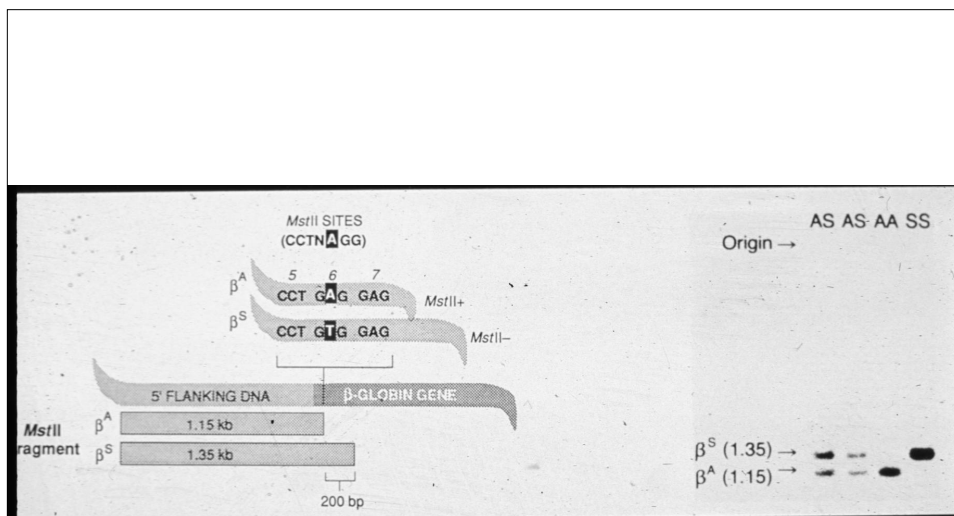
Textbook Figure 6.8

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

Genotype	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

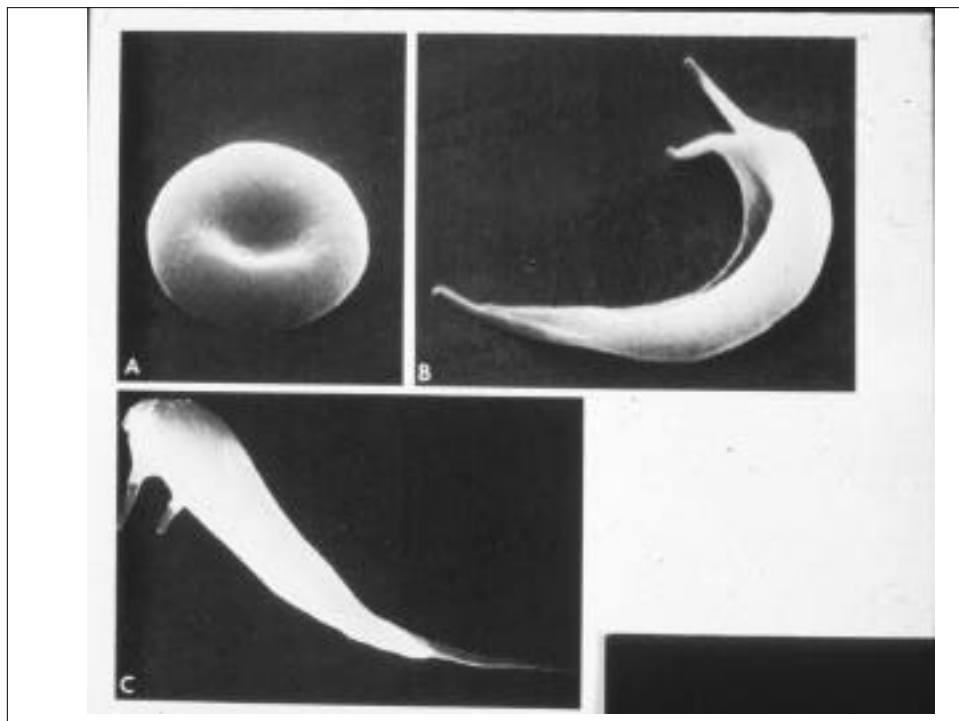
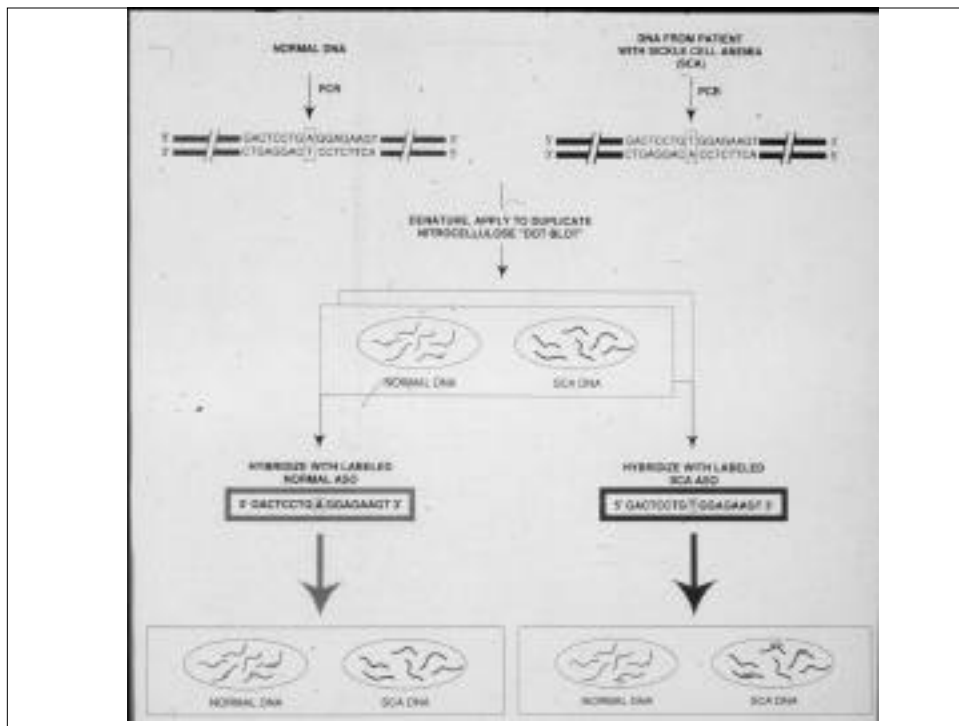
\*Survey of 250,000 black Americans<sup>556</sup>

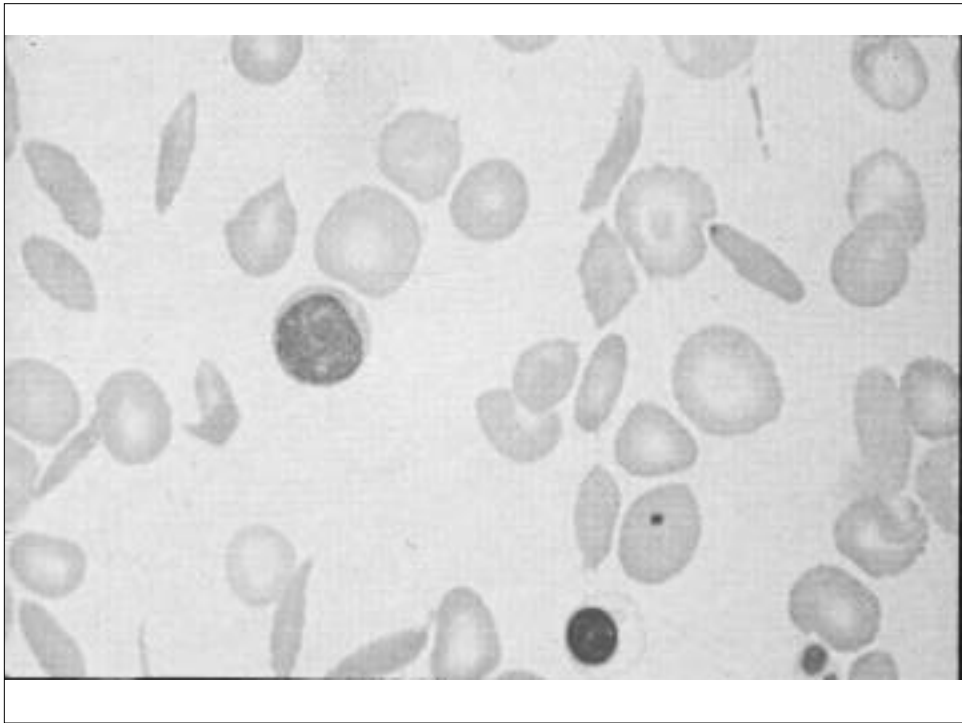
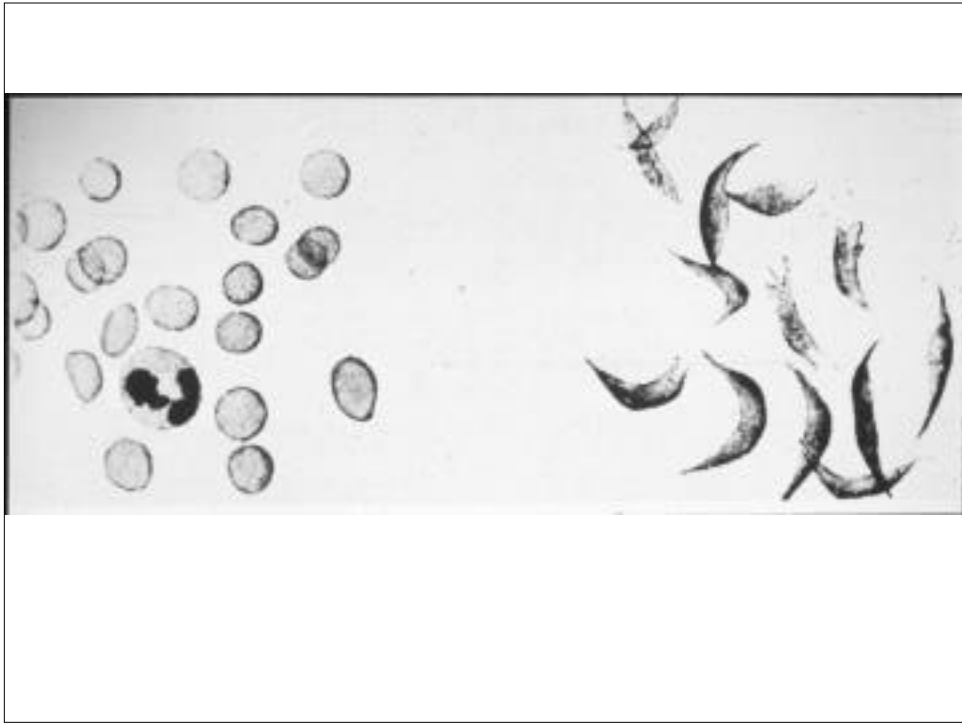
\*\*Review of literature<sup>557</sup>



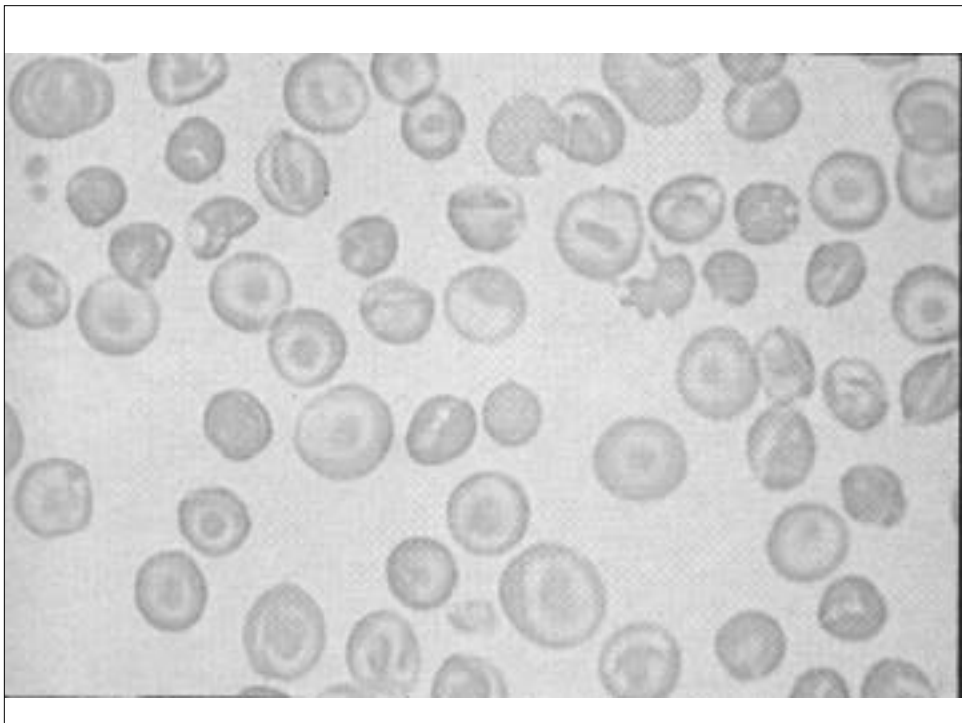
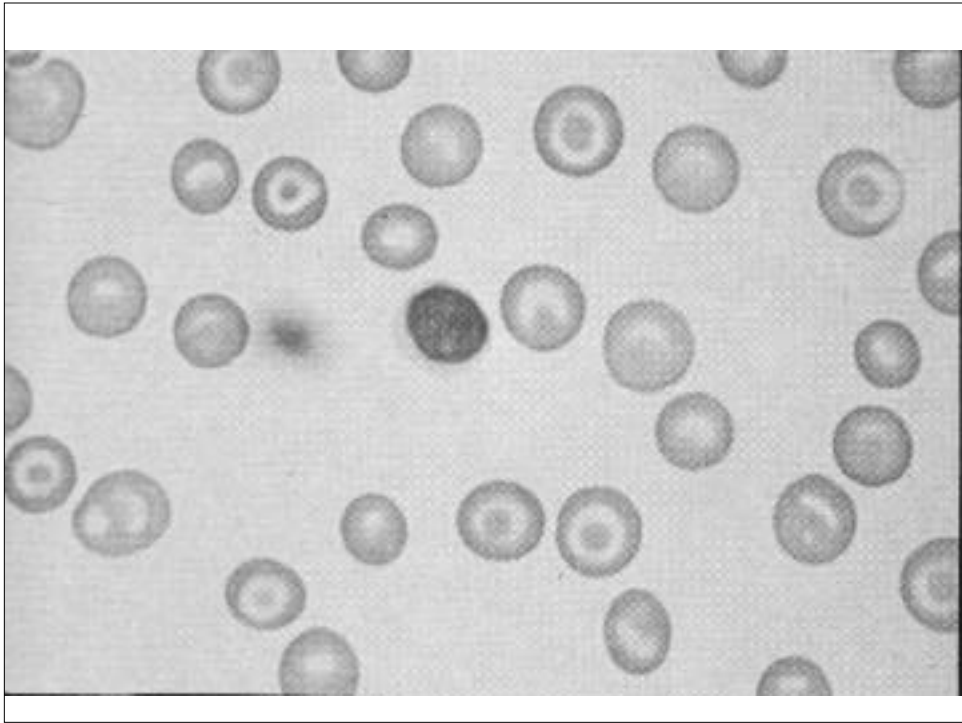
Diagnosis of the sickle mutation using Southern blot analysis

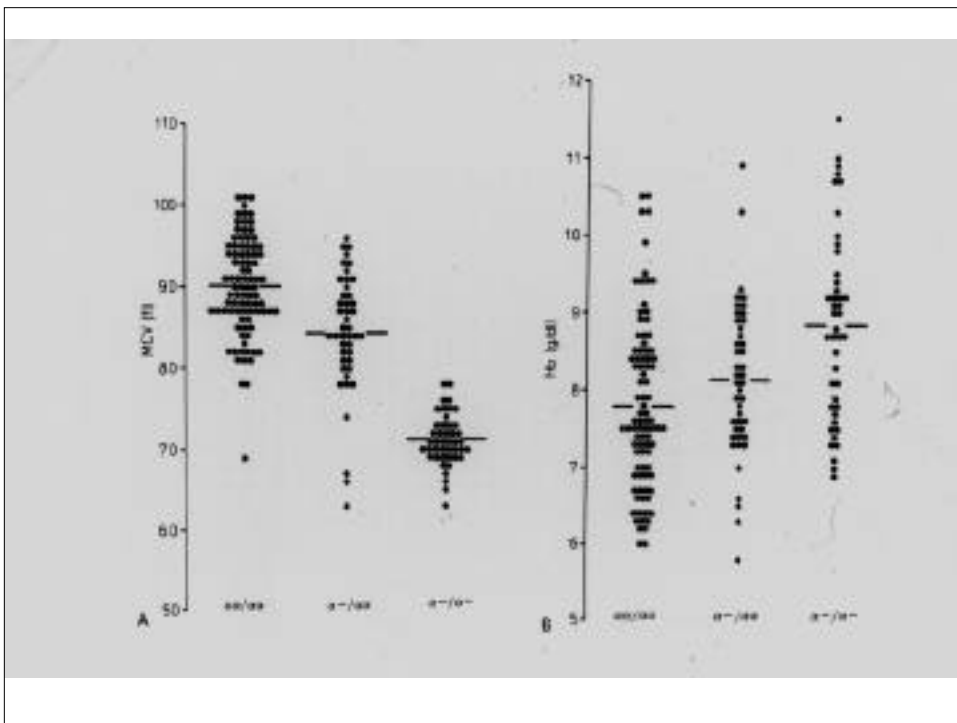
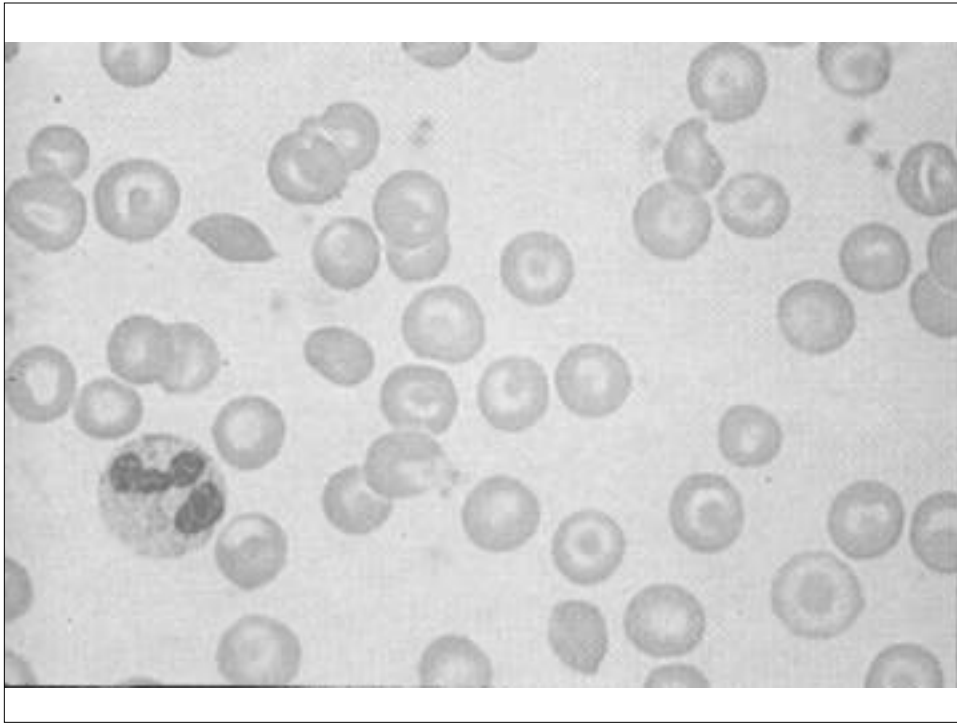
Textbook Figure 6.10











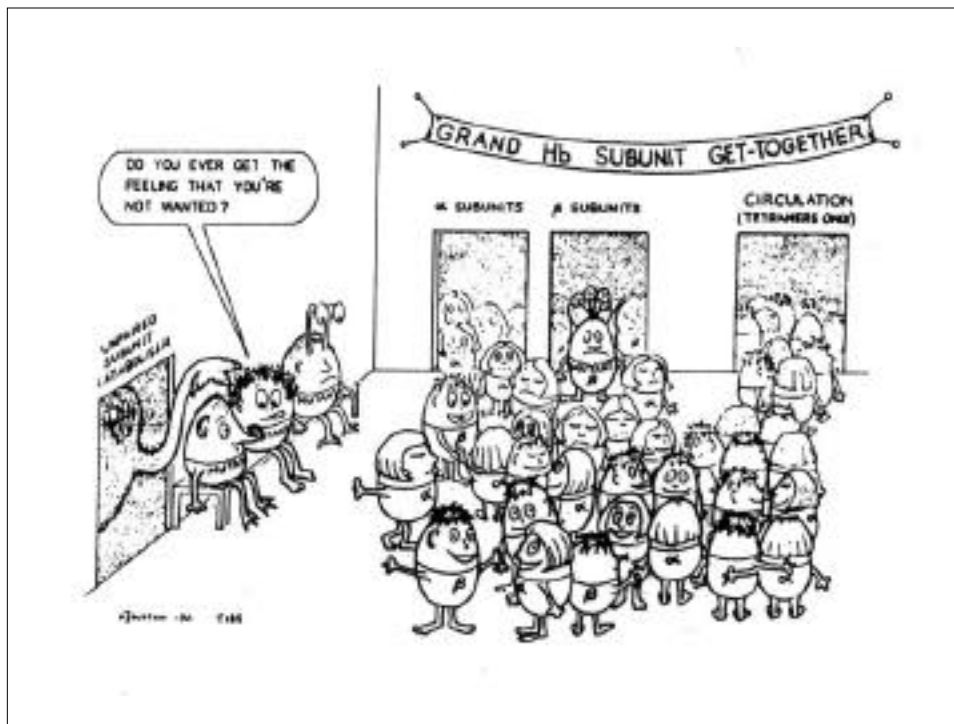
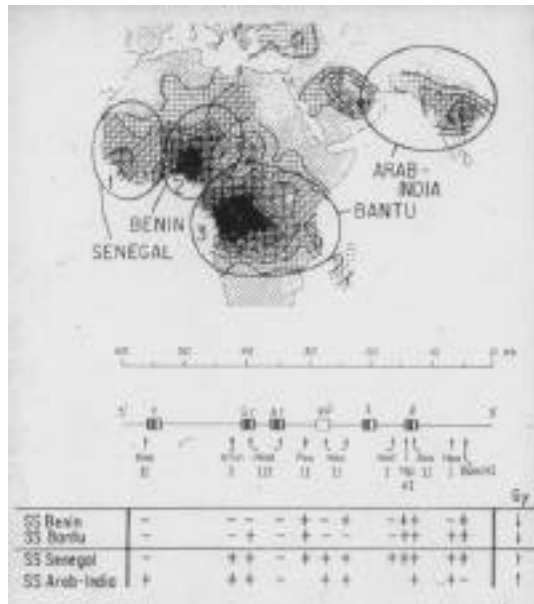


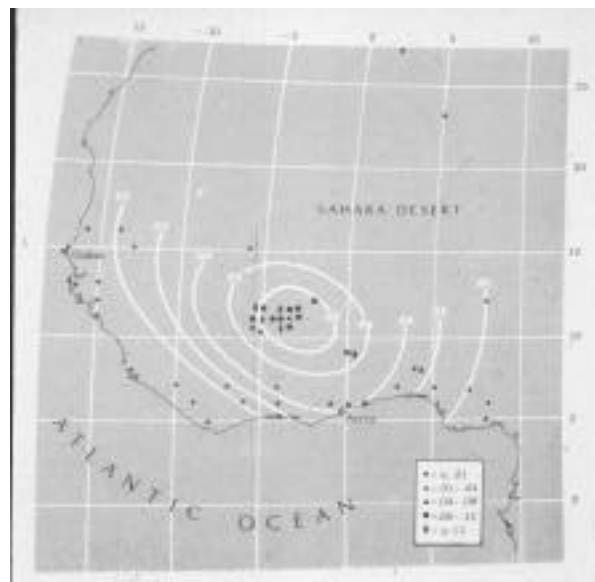
Table 10-10. EFFECT OF  $\alpha$  THALASSEMIA ON THE PERCENTAGE OF  $\beta$ -CHAIN VARIANT HEMOGLOBIN IN HETEROZYGOTES

	Percentage of Variant in Hemolysate					
	AS	(Ref)	AC	(Ref)	AE	(Ref)
Normal ( $\alpha\alpha/\alpha\alpha$ )	41 $\pm$ 1.8	(631)	43.8 $\pm$ 1.5	(631)	30 $\pm$ 1.5	(662)
$\alpha\alpha/\alpha-$	35.4 $\pm$ 1.0	(631)	37.5 $\pm$ 1.4	(631)	27 $\pm$ 2	(662)
$\alpha-\alpha$ or $\alpha\alpha--$	28.1 $\pm$ 1.4	(631)	32.2 $\pm$ 0.8	(631)	22 $\pm$ 2	(662)
$\alpha^{0/0}$ (Hb H)	17	(632)			15	(666)
Iron deficiency*	30-42	(633)			18-27	(668)

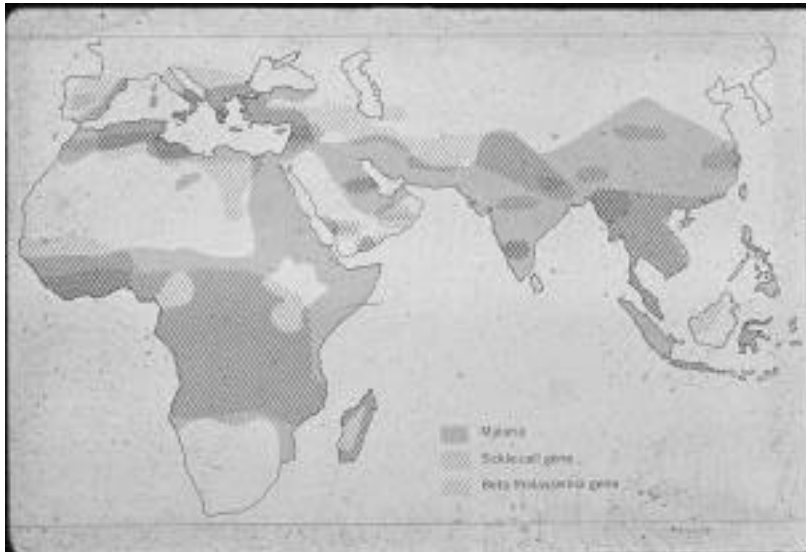
\*Before and after correction.



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



One single mutation in history accounts for Hb C

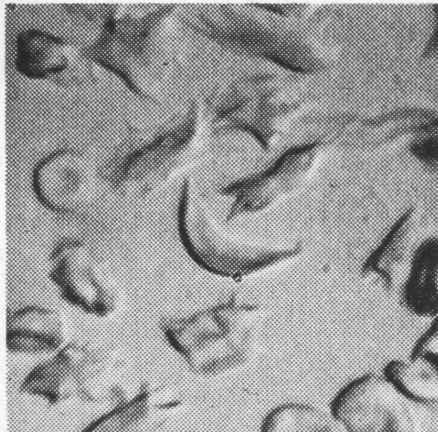


Hb S is a balanced polymorphism

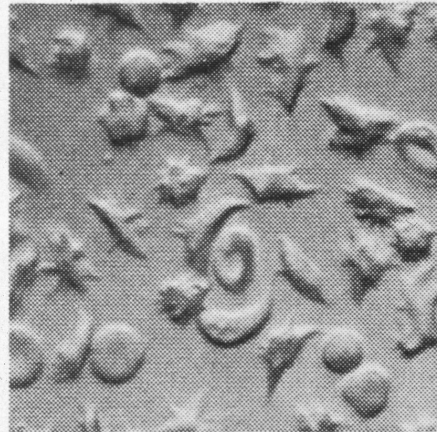
\* homozygotes (1 in 500) are selected against

\* heterozygotes (1 in 12) are selected for

**Human Hb S**

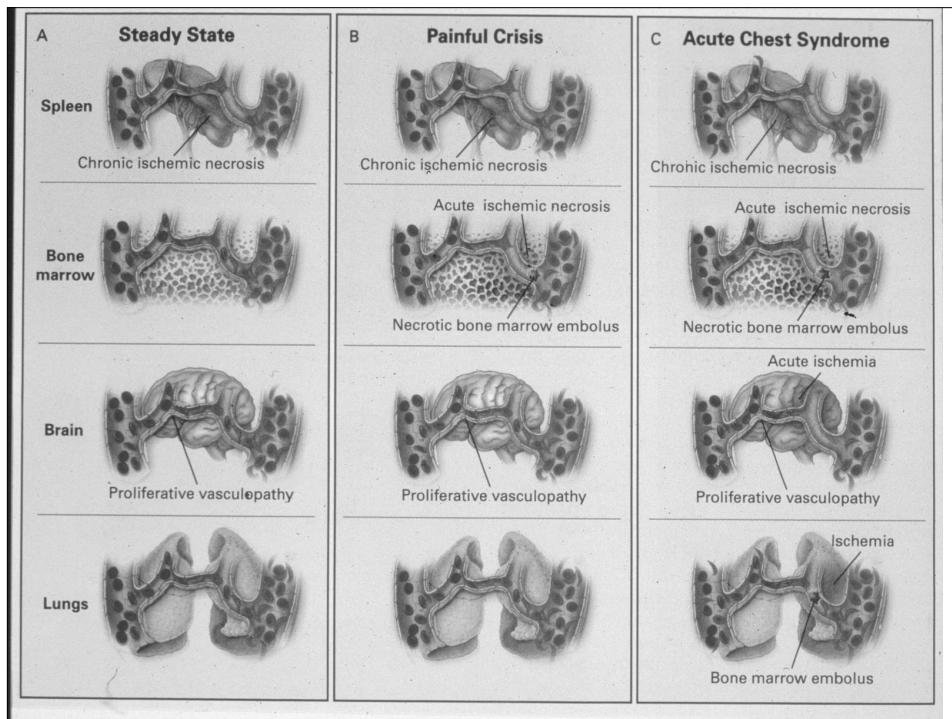


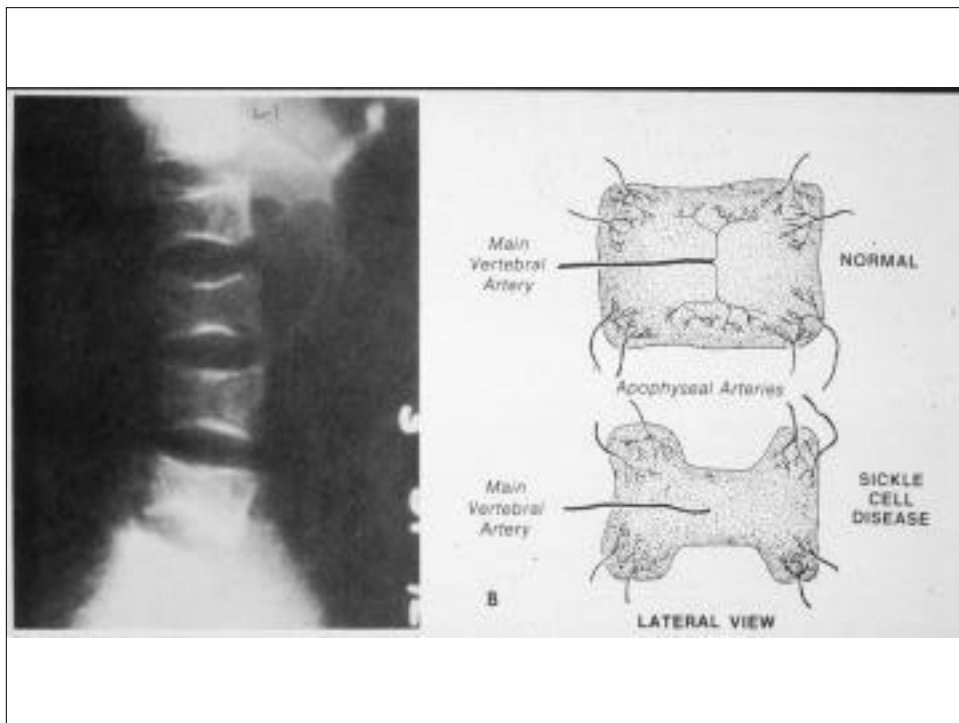
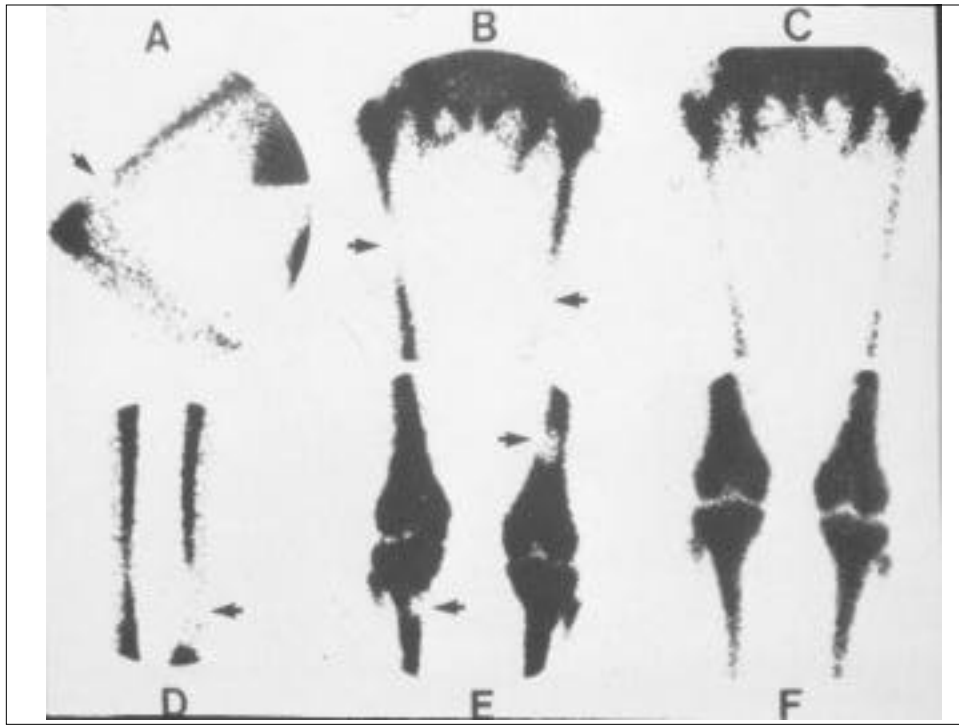
**Mouse Hb S/  $\beta$ -thal**

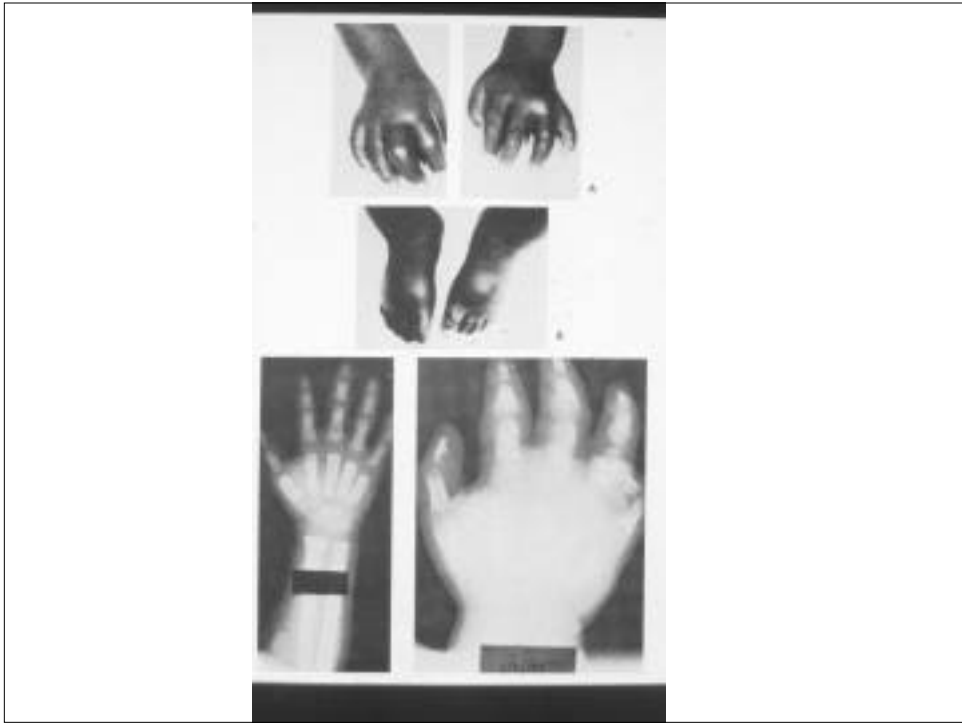


## Complications of Sickle Cell Anemia

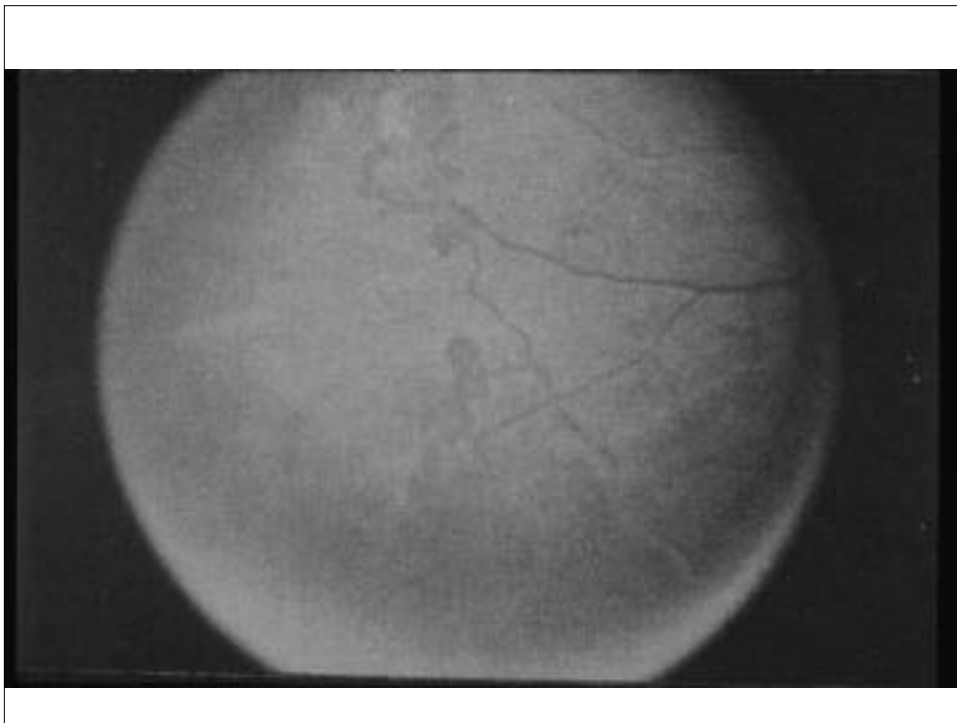
- autosplenectomy
- hyposthenuria
- Infections
  - encapsulated organisms-- pneumococcus
  - salmonella, staph
- Painful crises
- Bone infarcts, aseptic necrosis
- Stroke
- Acute chest syndrome
- Hand-foot syndrome
- Chronic organ damage











% of SS and SC patients developing retinopathy

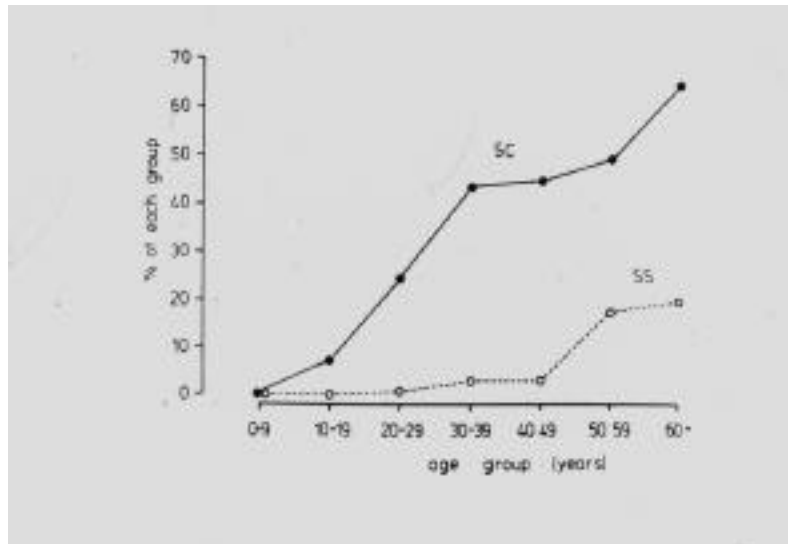


Table 35-4. Infections in Sicca Cell Disease

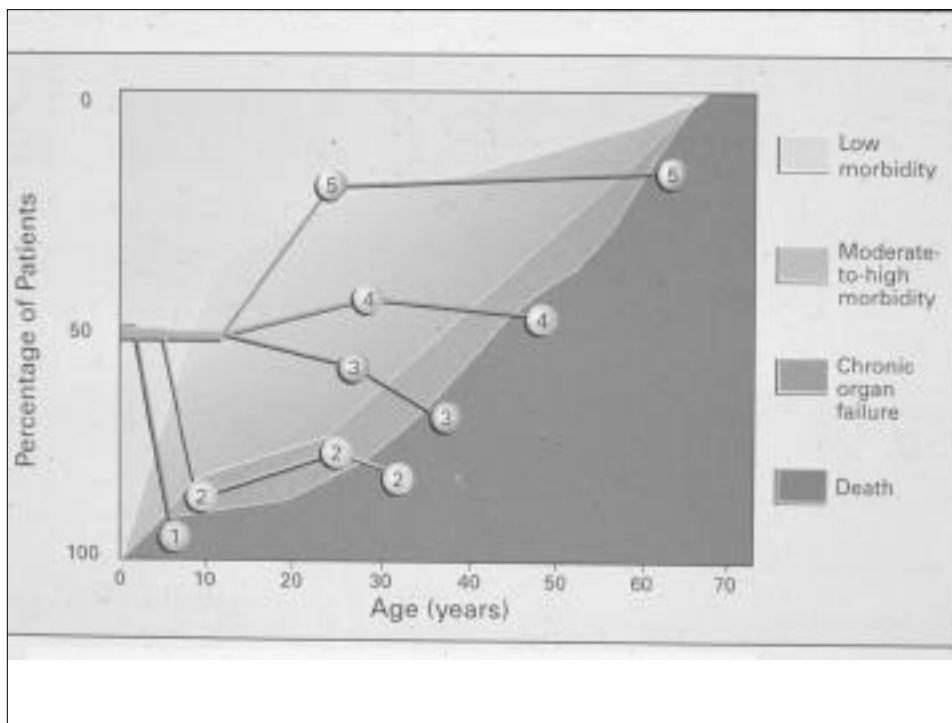
Infection	Usualty	No. Episodes	%
Pneumonia*	No bacterial confirmation	344	83
	Pneumococci	29	7
	Enteric gram-negative rods	17	4
	<i>S. aureus</i>	9	1
	Mycoplasma	5	1
	<i>Salmoneilla</i>	4	1
	<i>H. influenzae</i>	3	1
	Others ( <i>M. tuberculosis</i> , <i>Chlamydia</i> , <i>Streptococcus</i> , partially treated)	12	3
	420 total		
Meningitis*	Pneumococci	26	57
	Partially treated	13	29
	<i>H. influenzae</i>	5	11
	<i>Ascoli</i>	4	9
	Others ( <i>E. coli</i> , <i>S. aureus</i> , <i>Streptococcus meningitidis</i> )	4	9
		61 total	
Otitis media**	<i>Salmoneilla</i>	14	33
	<i>S. aureus</i>	3	7
	Pneumococci	3	7
		20 total	
Sepsis†	Pneumococci	12	40
	<i>H. influenzae</i>	3	11
	Gram-negative enterics	3	11
	<i>Salmoneilla</i>	3	11
	<i>S. aureus</i>	2	7
	<i>Ascaris lumbricoides</i>	2	7
	<i>Streptococcus pyogenes</i>	1	4
		25 total	
Urinary tract**	<i>E. coli</i>	25	83
	<i>Klebsiella</i>	13	43
	<i>Ascoli</i>	2	7
	Others ( <i>S. aureus</i> , <i>Merkel's</i> <i>Streptococcus</i> <i>parvulus</i> )	4	13
		35 total	

\*Data from two retrospective studies covers 859 patients (328 SS, 74 SC, 315 unclassified) for 4,123 patient-years.  
 †Data covers 420 patients (323 SS, 83 SC, 16 others) for 2,442 patient-years.  
 \*\*Bacteriologically confirmed cases only.  
 ††Single organism culture cases only.  
 Modified from Platt and Nathan,<sup>137</sup> with permission.

**Table 12-6. CAUSES OF DEATH AMONG CHILDREN WITH SICKLE CELL DISEASE\***

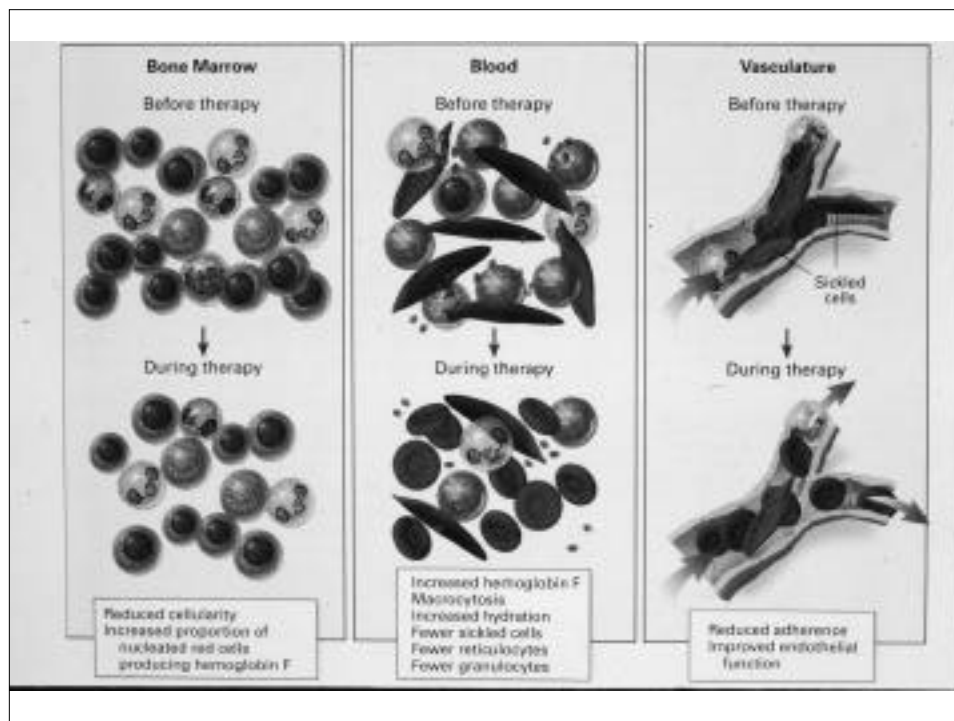
Cause	Percentage of Total Deaths
Infection	44
Splenic sequestration	16
Sudden, unexpected death	14
Cerebrovascular accident	12
Congestive heart failure	7
Miscellaneous	7
	100

\*From Mentzer, W. C., and Wang, W. C.: *Pediatr. Ann.* 9:297, 1980. Compiled from data on 43 children followed by Powars<sup>83</sup> and Seeler.<sup>158</sup>



## Sickle Cell Anemia: Treatment

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



### *Summary*

- Understand the molecular basis of sickle cell anemia and how to make a diagnosis
- Begin to recognize the clinical features sickle cell anemia
- Know that Hgb S is a balanced polymorphism, and understand the meaning of a haplotype.
- Know the conditions that facilitate sickling
- Understand why patients with sickle cell who co-inherit thalassemia trait will have a milder course