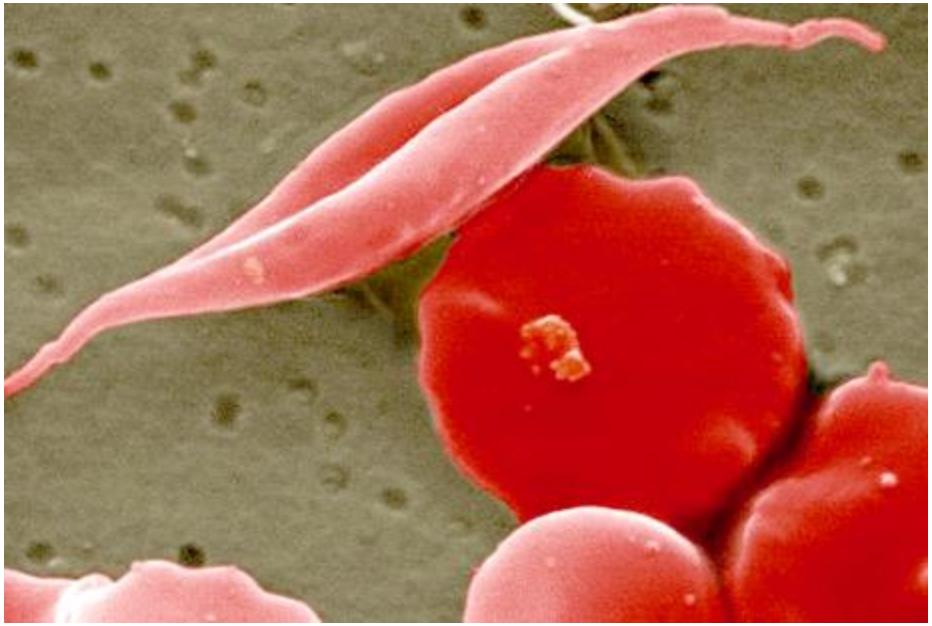
Sickle Cell Disease (SCD)



Howard J. Sachs, MD

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Sickle Cell Disease: Renaming

AR disorder characterized by a point mutation…

…resulting in an abnormal hemoGLOBIN

…which polymerizes when deoxygenated

Polymerization is the essential step in the molecular pathogenesis of this disorder. Hgb polymerizes creating the characteristic cresentic or sickle cell

Sickle Cell Disease: Renaming

AR disorder characterized by a point mutation…

…resulting in an abnormal hemoGLOBIN

…which polymerizes when deoxygenated

…resulting in fragile cells with abnormal deformability

The fragility results in hemolysis…
The abnormal deformability results in vaso-occlusion

Vaso-occlusion = Ischemia

Why does the NBME love SCD?

Why does the NBME love SCD?

Heme

OSD

Why does the NBME love SCD?

Heme

Genetics

Hemoglobinopathy

Hemolysis

Peripheral smear

Why does the NBME love SCD?

Heme

- Genetics
- Hemoglobinopathy
- Hemolysis

OSD

Vaso-occlusion:

- Spleen
- Bone
- Kidney
- Lung
- CNS

Why does the NBME love SCD?

Heme

OSD

Genetics

Hemoglobinopathy

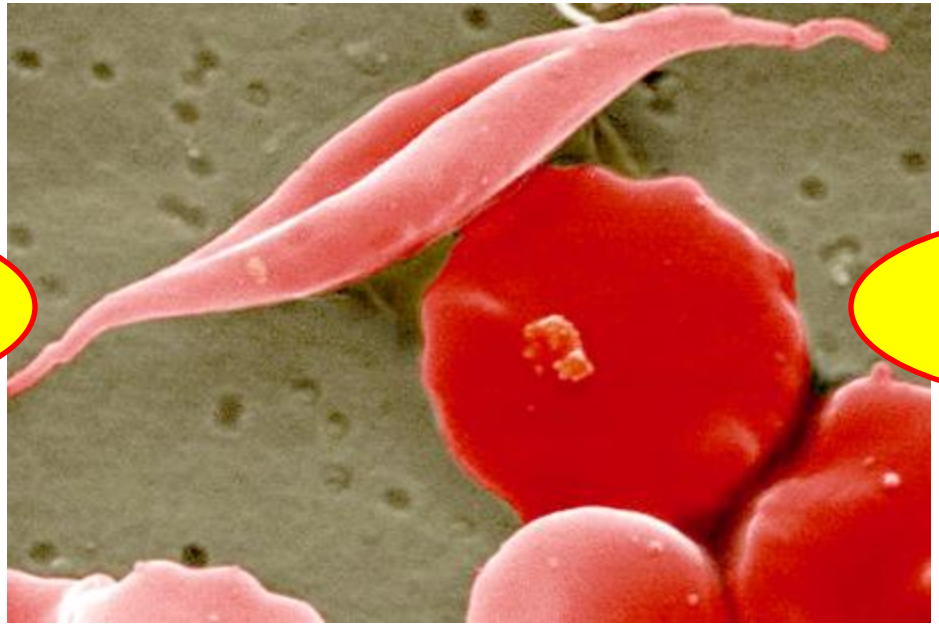
Hemolysis

<u>Vaso-occlusion</u>:
Spleen
Bone
Kidney
Lung
CNS

You can count on at least 3-5 direct questions and 5-7 questions with SCD listed in the distractors

Sickle Cell Disease

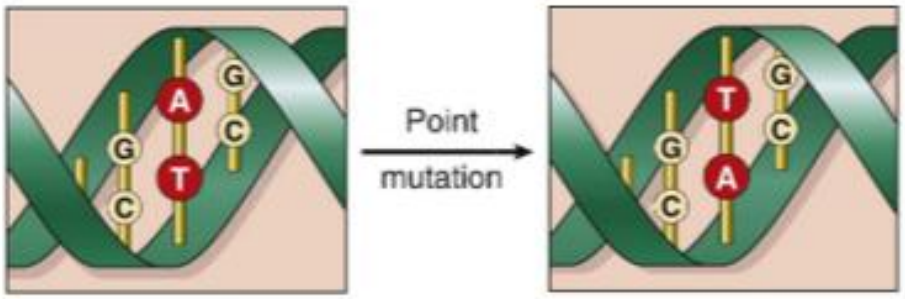
Heme



Organ Systems

Key Derivatives

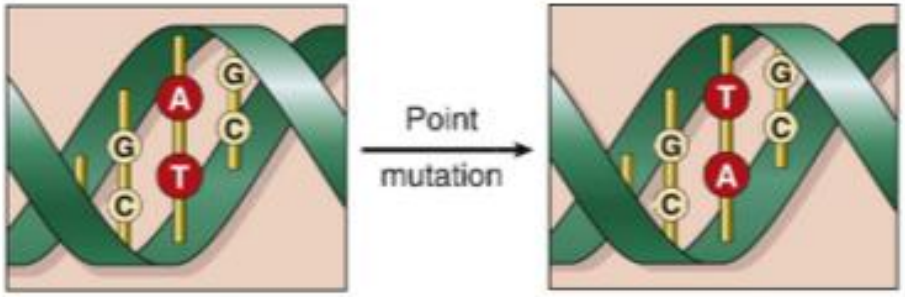
Position 6 β-globin chain



Glutamic Acid ⟶ Valine

Hemoglobin S

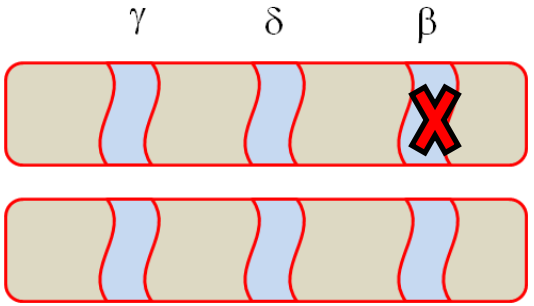
Position 6 β-globin chain



Glutamic Acid ⟶ Valine

Hemoglobin S

SS Trait



Chr 11

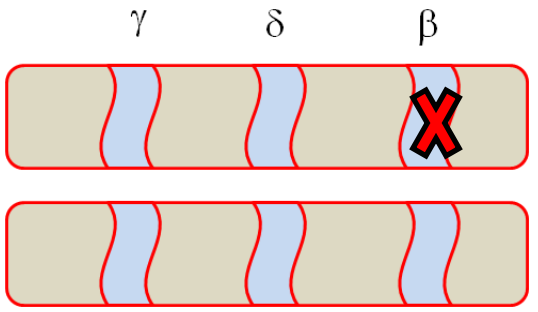
HbA ($\alpha_2\beta_2$) PLUS HbS ($\alpha_2\beta^s$)

Single mutation → Trait

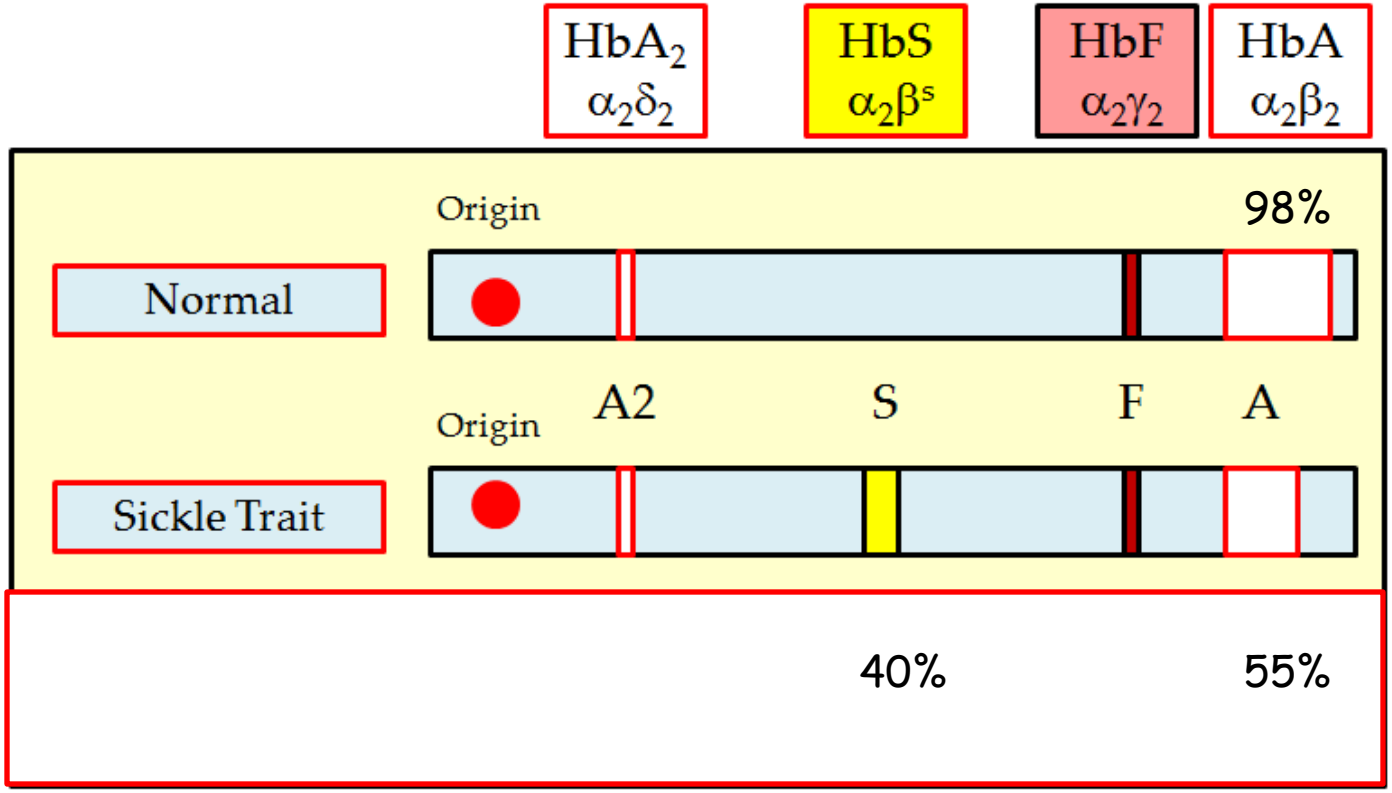
Sickling (polymerization) is dependent on PROPORTION of Hgb S and degree of oxygen saturation

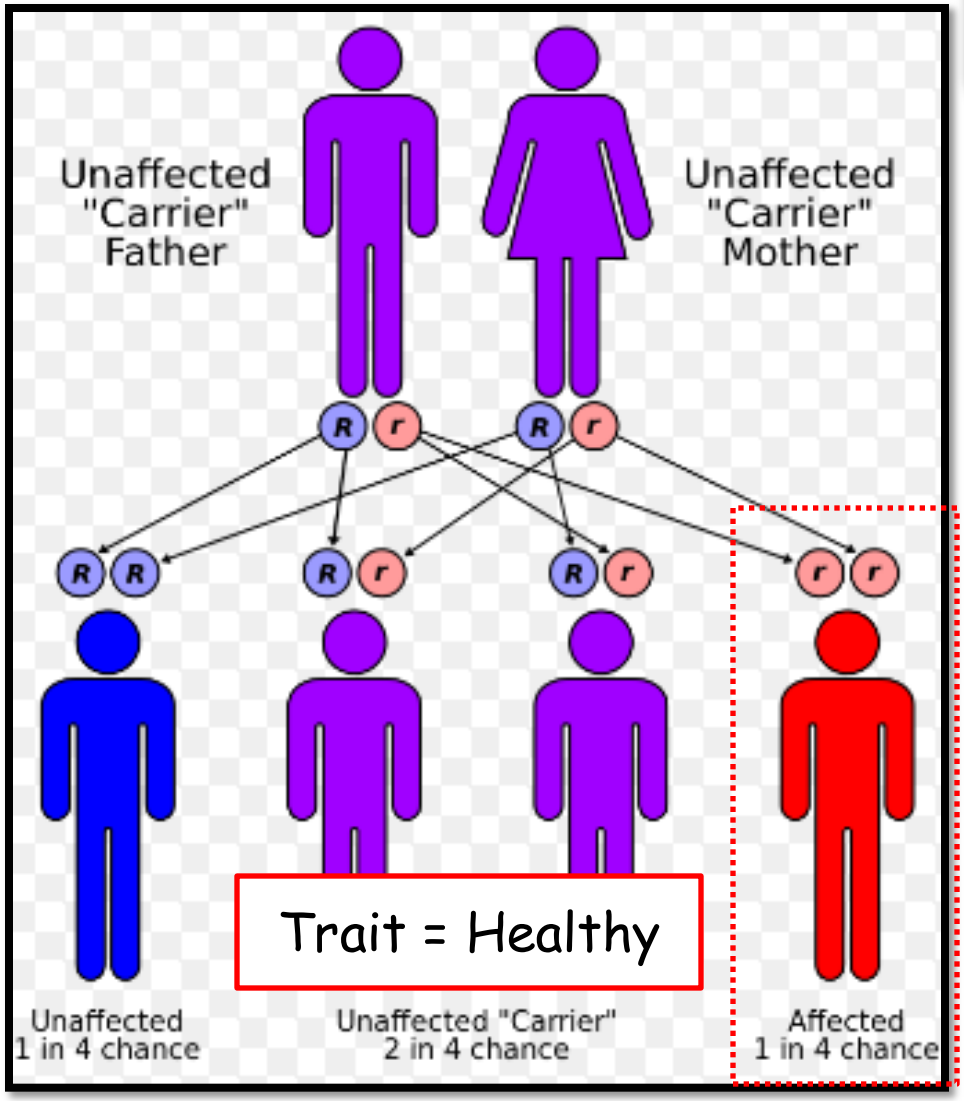
Position 6 β-globulin chain

Glutamic Acid ⟶ Valine

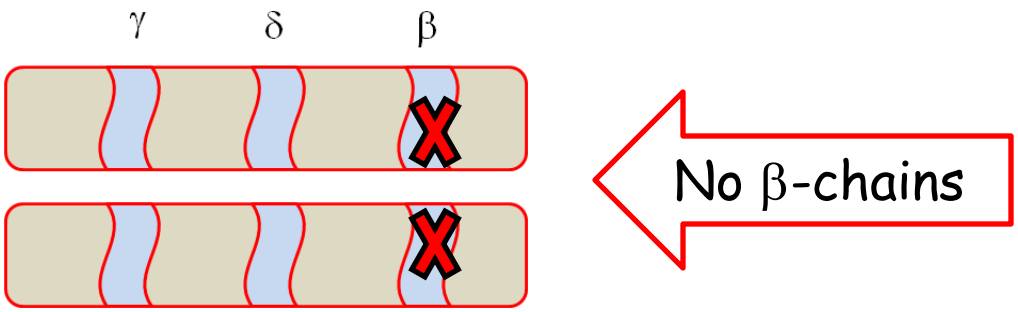


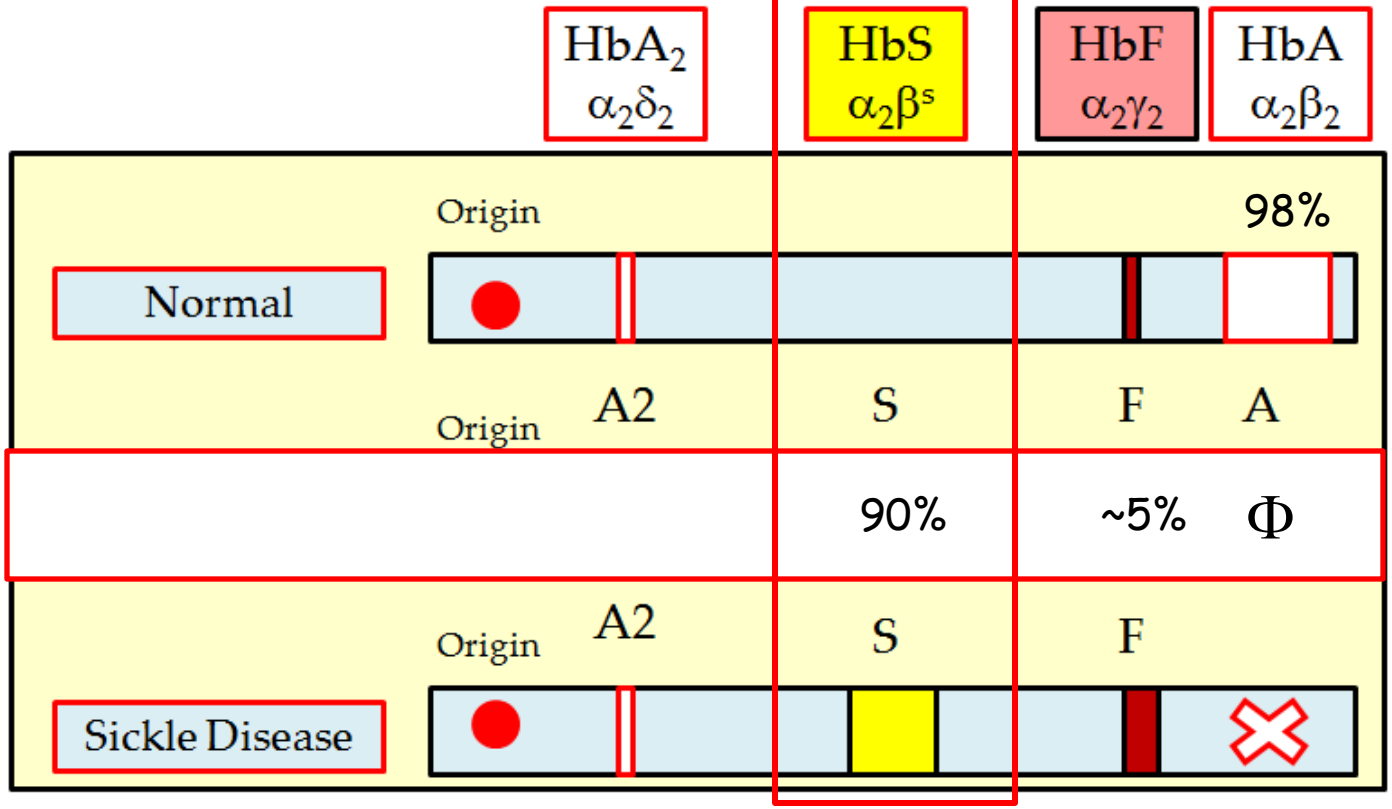
HbA ($\alpha_2\beta_2$) PLUS HbS ($\alpha_2\beta^s$)



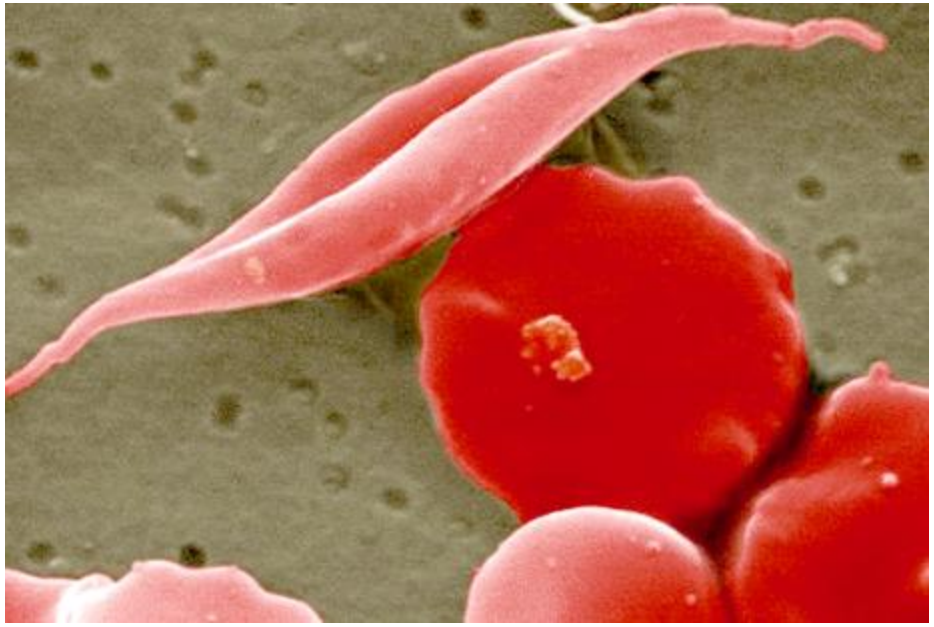

Unaffected "Carrier" Father
Unaffected "Carrier" Mother
R r
R r
R R
R r
R r
r r
Trait = Healthy
Unaffected 1 in 4 chance
Unaffected "Carrier" 2 in 4 chance
Affected 1 in 4 chance

Sickle Cell Disease (Hemoglobinopathy)





Sickle Cell Disease: Hematologic Manifestations

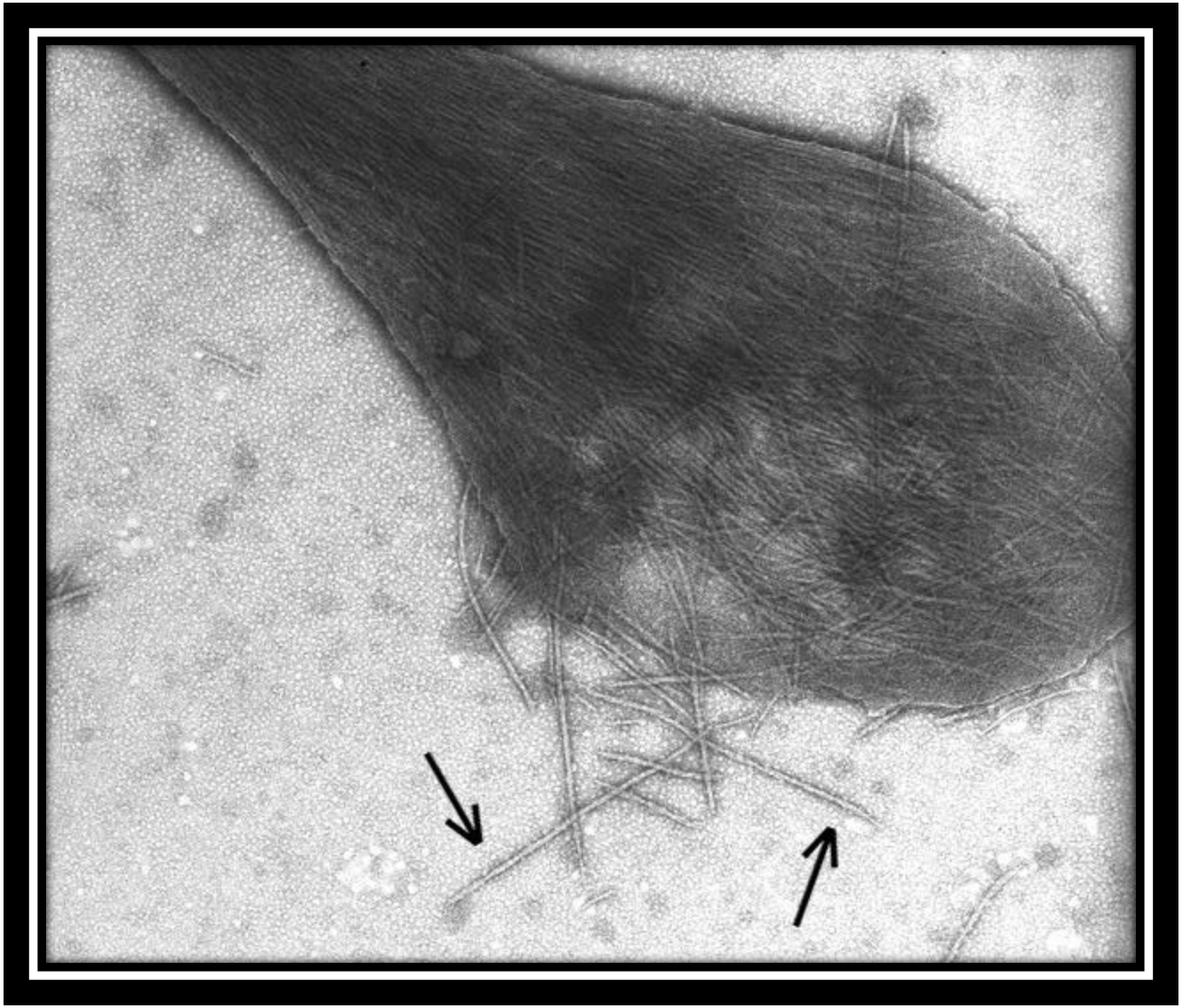


Polymerization

Polymerization
(When Hgb S is deoxygenated)

1. What are they?
   - Long fibers each consisting of 7 intertwined double strands with stacking and cross linking.

<u>Molecular Pathogenesis</u>:
Deoxygenation of Hgb S results in polymerization ('sickling')



Polymerization:
Fragile Cell with Poor Deformability
Result: hemolysis and microvascular occlusion

What you need to know about the deformed cell:

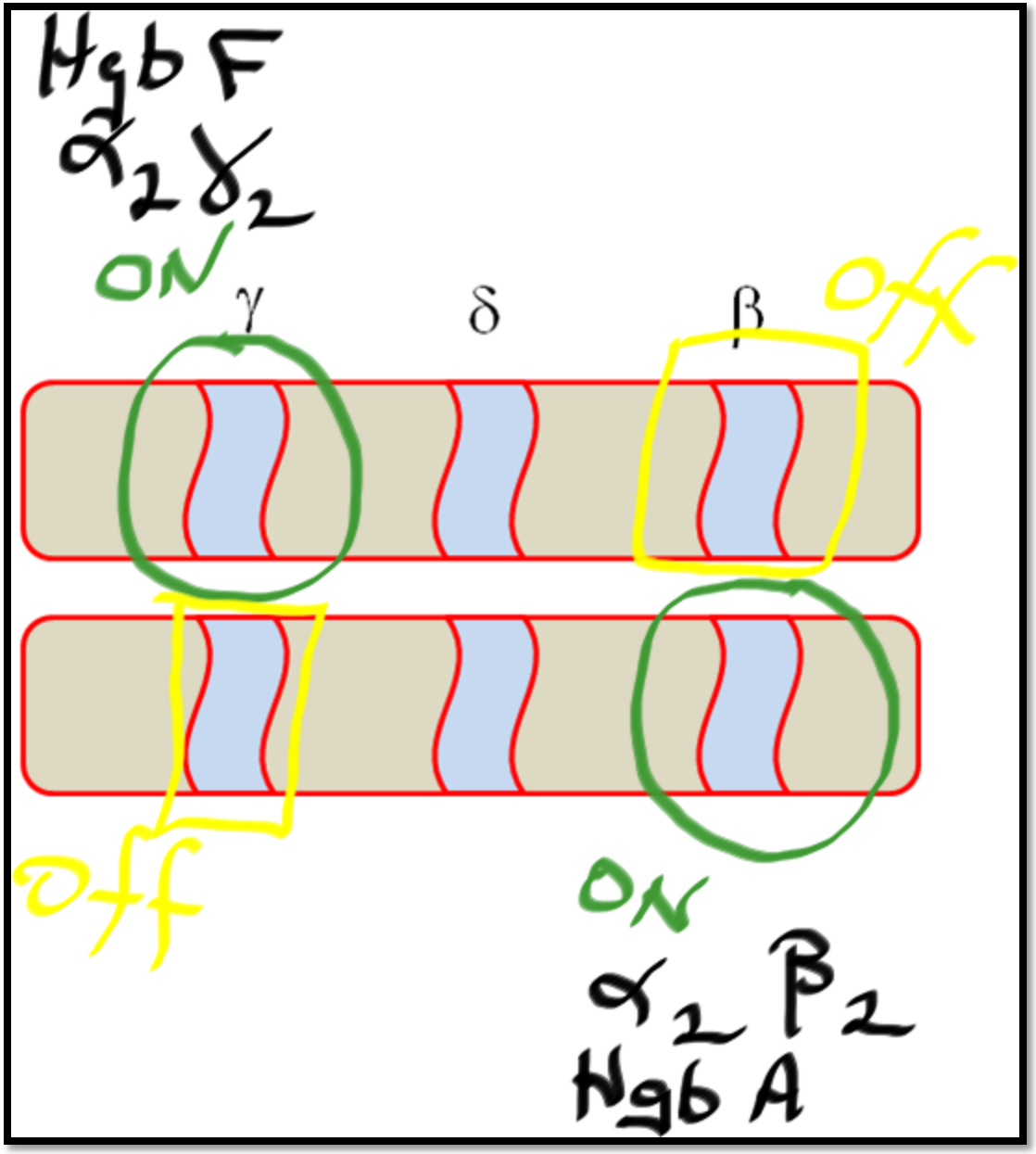
1. Triggers?
   - Φ, infection, dehydration, acidosis (shifts to right)

2. Is this reversible?
   - Partially with oxygenation, but does become irreversible

3. Does this start at birth?
   - When does Hgb F turns off and Hgb A turn on?:
     - 3-6 months

Fetal Liver, BM

Adult Bone Marrow



What you need to know about the deformed cell:

4. Does polymerization impact red cell function?
   - Reduces deformability (liquid → viscous gel)
   - Alters membrane permeability (Ca in/K, H2O efflux out)

5. Does this impact red cell survival?
   - Yes → hemolysis (~17d)
   - Extravascular: RES clears irreversibly damaged cells
   - Intravascular: cells are fragile due to damaged membranes

What you need to know about the deformed cell:

4. Does [illegible] impact red cell function?
   - [illegible]l)
   - [illegible]2O

Hemolysis Labs:
High indirect bilirubin
High LDH
Low Haptoglobin (hemoglobin binding protein)

5. Does this impact red cell survival?
   - Yes → hemolysis (~17d)
   - Extravascular: RES clears irreversibly damaged cells
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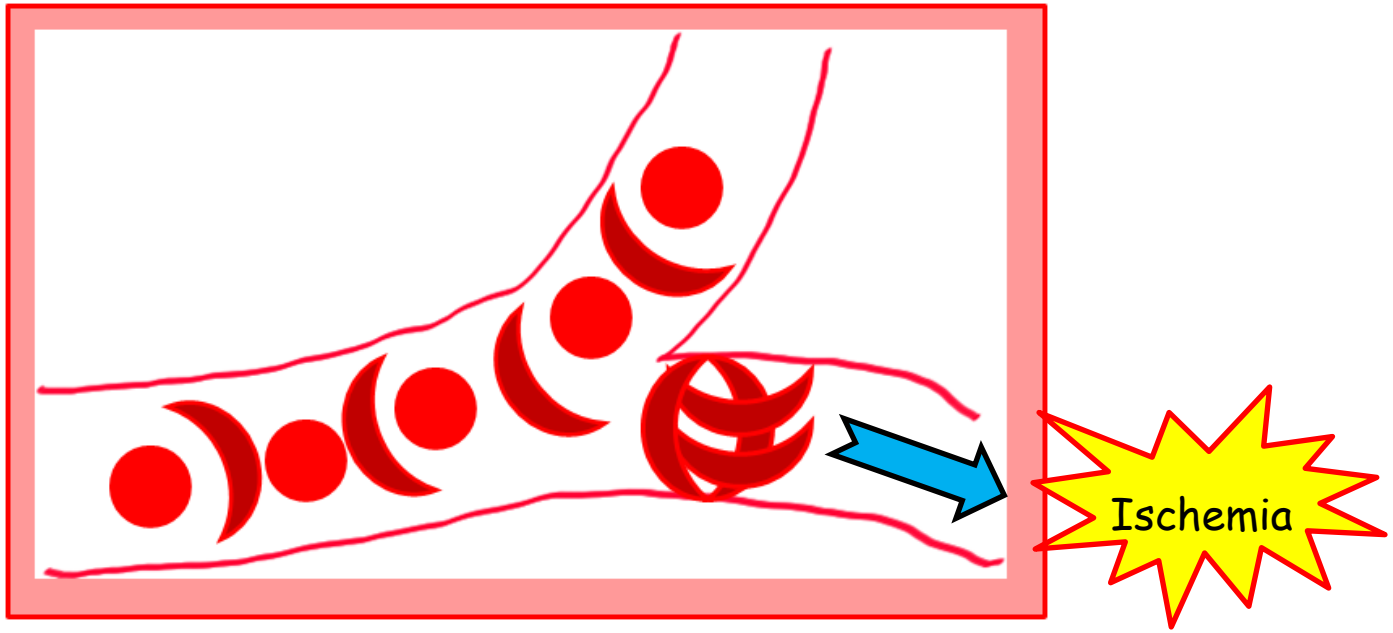
Vaso-occlusive Manifestations

- Abnormal erythrocytes aggregate in the microvasculature especially where the oxygen tension is low → ischemic tissue injury.



Abnormal structure (sickled), function (gel/viscosity) and adherence all contribute

Spleen (3)

Sequestration (kids)
Pain, shock → death

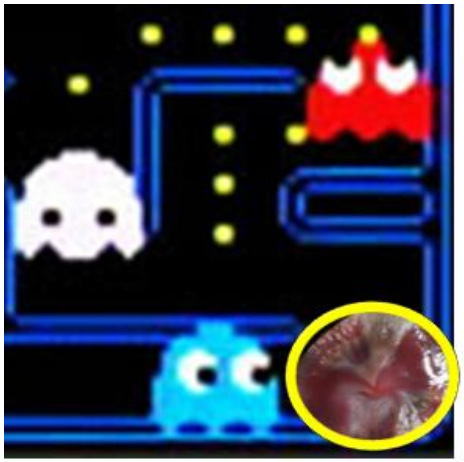
Spleen (3)

Autoinfarction

1. Encapsulated organisms
   - Filter bacteria (MΦ)
   - Opsonizing antibodies
2. Immunizations:
   - PVX, Hib, Meningococcus
3. RES: Howell Jolly Bodies
   - DNA remnants

Key derivatives

Spleen (3)



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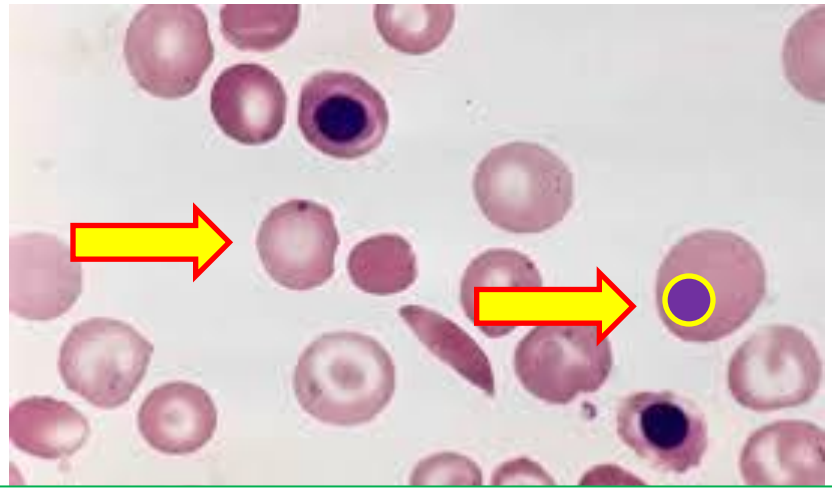

Howell-Jolly Bodies (DNA remnants)

Key derivatives

MSK (4)

Dactylitis (inflamed digit):
May be initial manifestation

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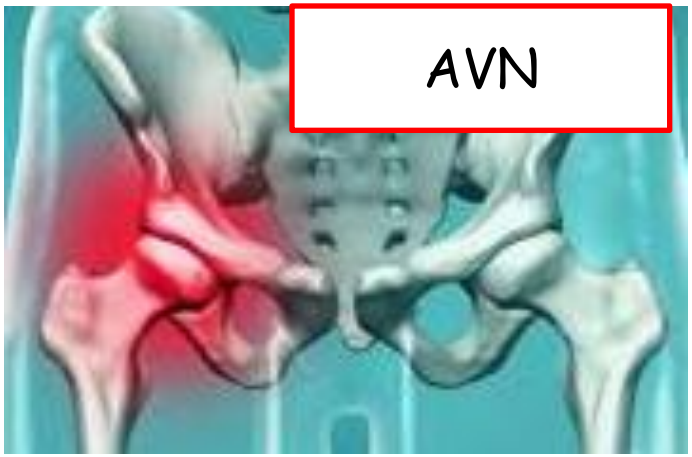
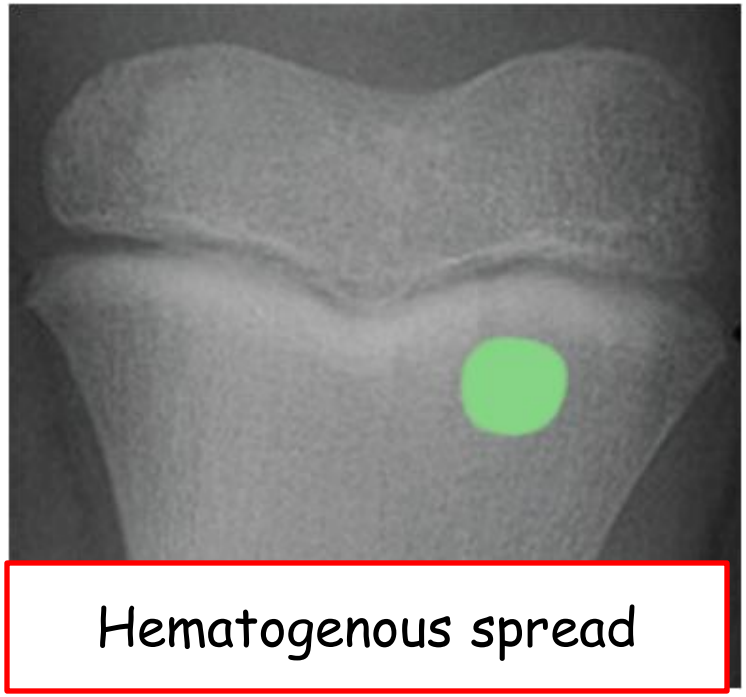
Dactylitis (inflamed digit):
May be initial manifestation



AVN

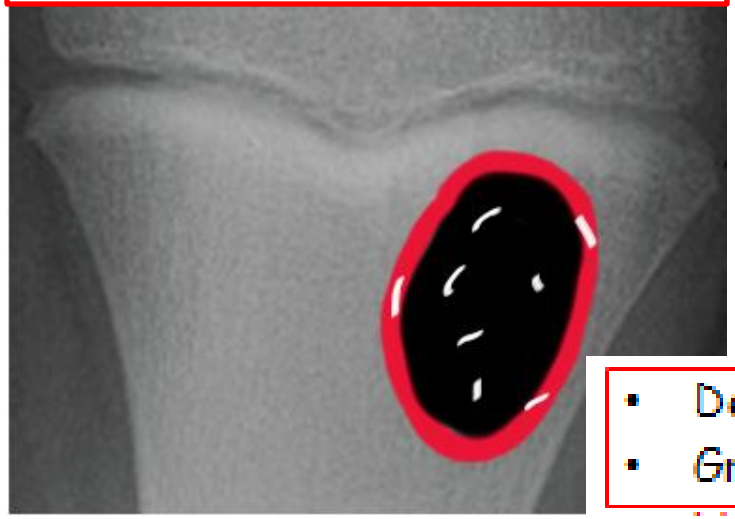
Collapse of femoral head

MSK (4)



Hematogenous spread

Sequestrum and Involucrum



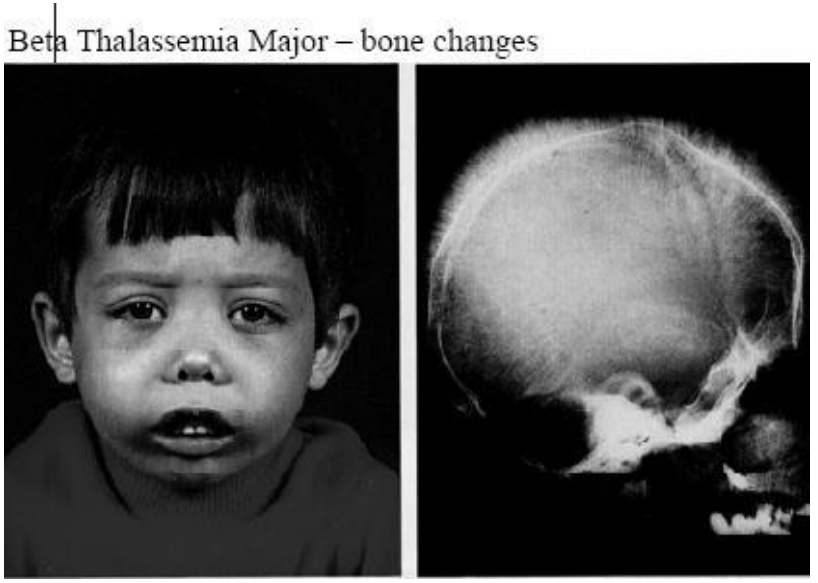
Salmonella - motile
Non Lactose Fermenter
Oxidase (-); H_2S (+)
Rx: debridement, quinolone

- Dead bone = '**Sequestrum**';
- Granulation tissue encases sequestrum = '**Involucrum**'

MSK (4)

Bone Marrow: hypercellular with erythroid hyperplasia, expansion of bone marrow (skull, cheekbones); extramedullary poiesis

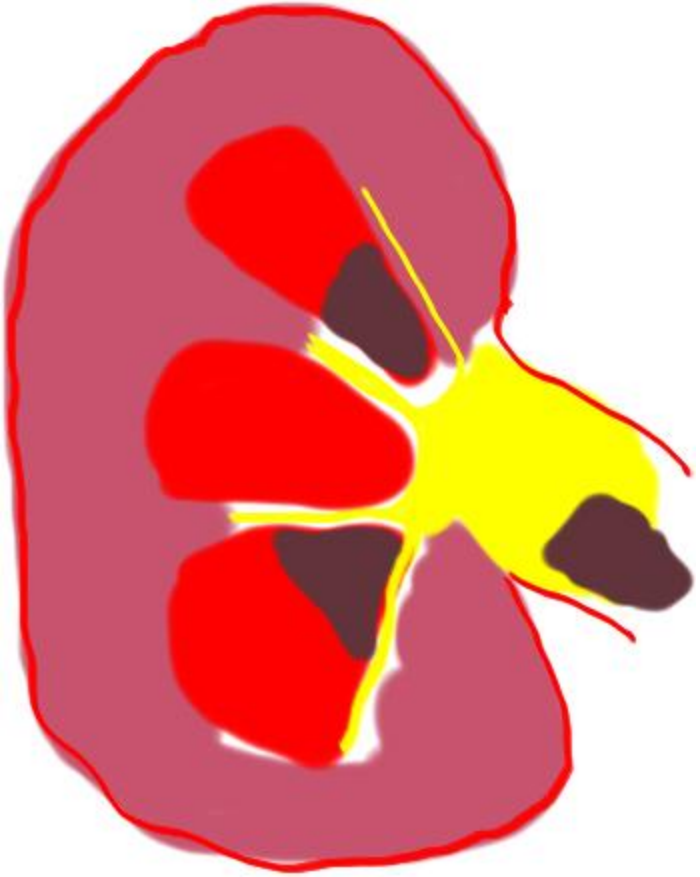
Crew cut appearance
'Hair on end'



Chipmunk facies

Language of extramedullary poiesis

Kidney (3)

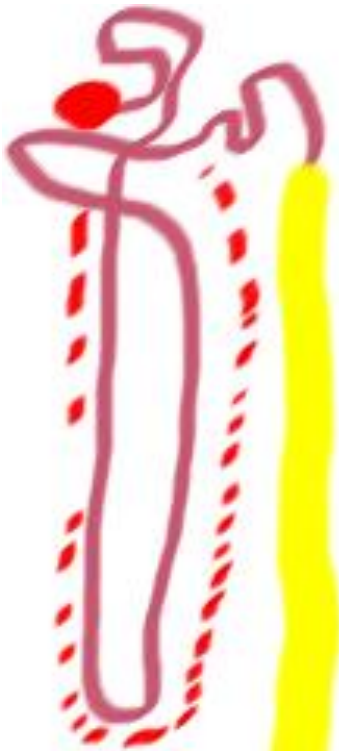


This picture is as good as the image they'll show.

Papillary Necrosis

- Manifestation of renal ischemia
- Coagulative necrosis of the distal portion of renal pyramids
- Presentation: Hematuria and Colic from sloughed tissue
- Other causes: Pyelo, DM, Analgesics

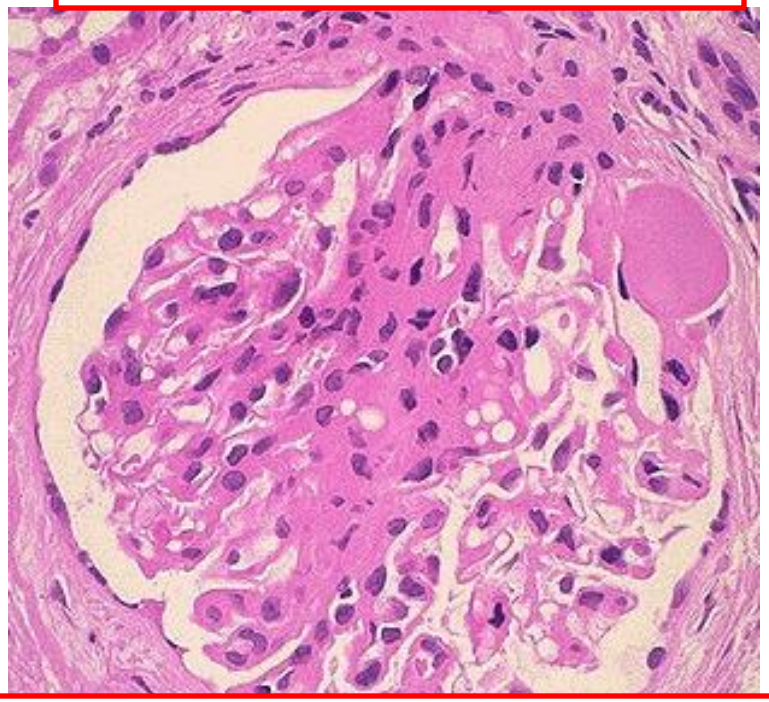
Kidney (3)



Vasa recta

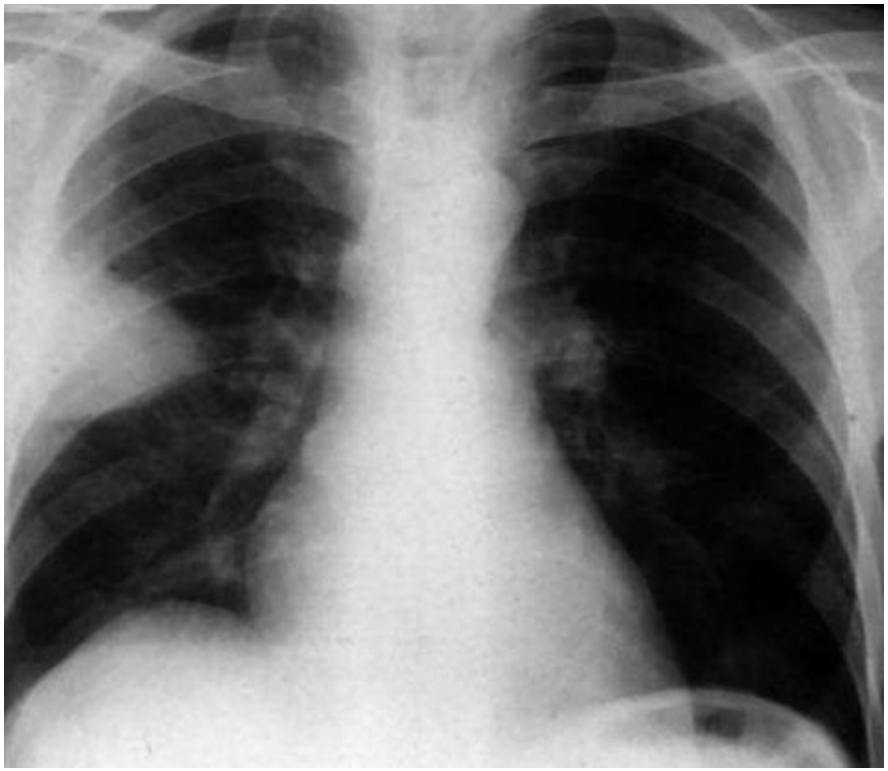
Inability to concentrate urine

FoKal SeGmental Glomerusclerosis

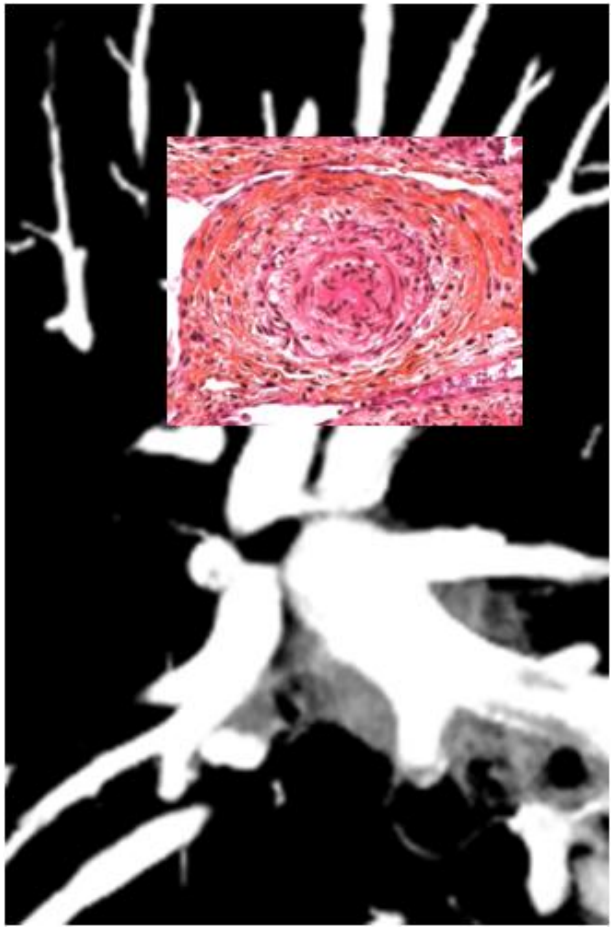


<u>Nephrotic</u>
Sclerotic version of Minimal Change
Foot process effacement
No immune deposits

Demographics: SCD, Heroin, HIV



Acute Chest (Pain) Syndrome
Vaso-occlusive
Infarction/Infiltrate
Fever/SOB
Significant cause of mortality



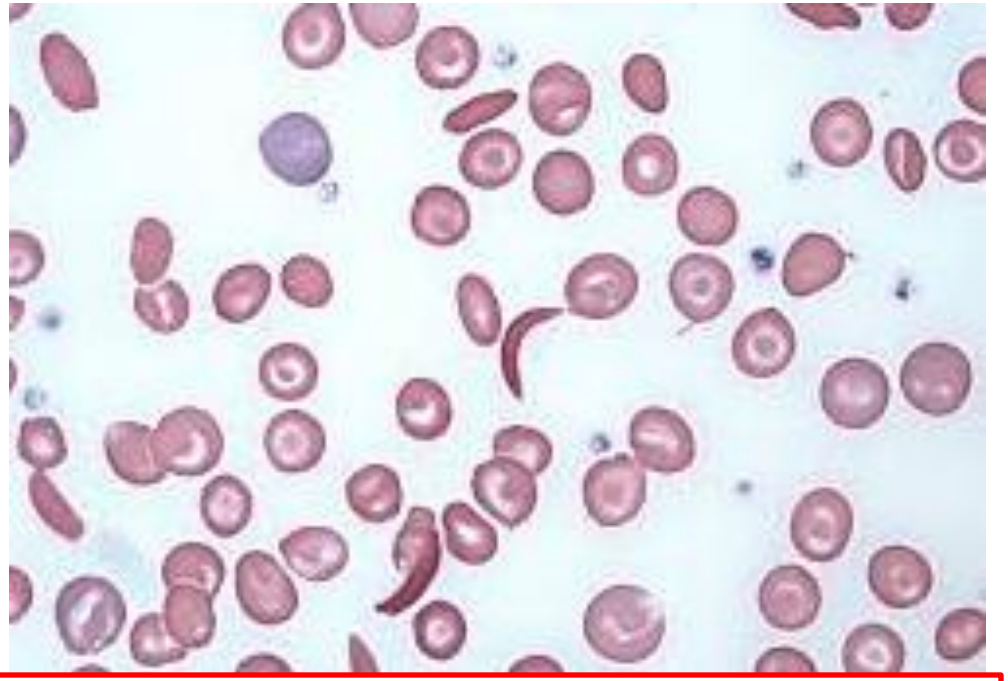
Late Complication
↑ Risk of thrombus in situ with development of Pulmonary HTN

Stroke ~ 25% by 45 y.o.

Vaso-occlusive Manifestations

- Spleen
  - Sequestration → shock, death
  - Autoinfarction → infection encapsulated organisms
  - Smear manifestions
- Bone
  - Dactylitis
  - AVN
  - Osteomyelitis
  - Extramedullary hematopoiesis
- Kidney
  - Papillary necrosis
  - FSGN
- Pulmonary
  - Infarct/Acute CP syndrome
  - Pulmonary HTN
- CNS
  - Stroke

Diagnostics



Smear: sickle cells, target cells, reticulocytosis, HJ bodies (asplenia); nucleated RBCs (normoblast)

Labs:

Anemia

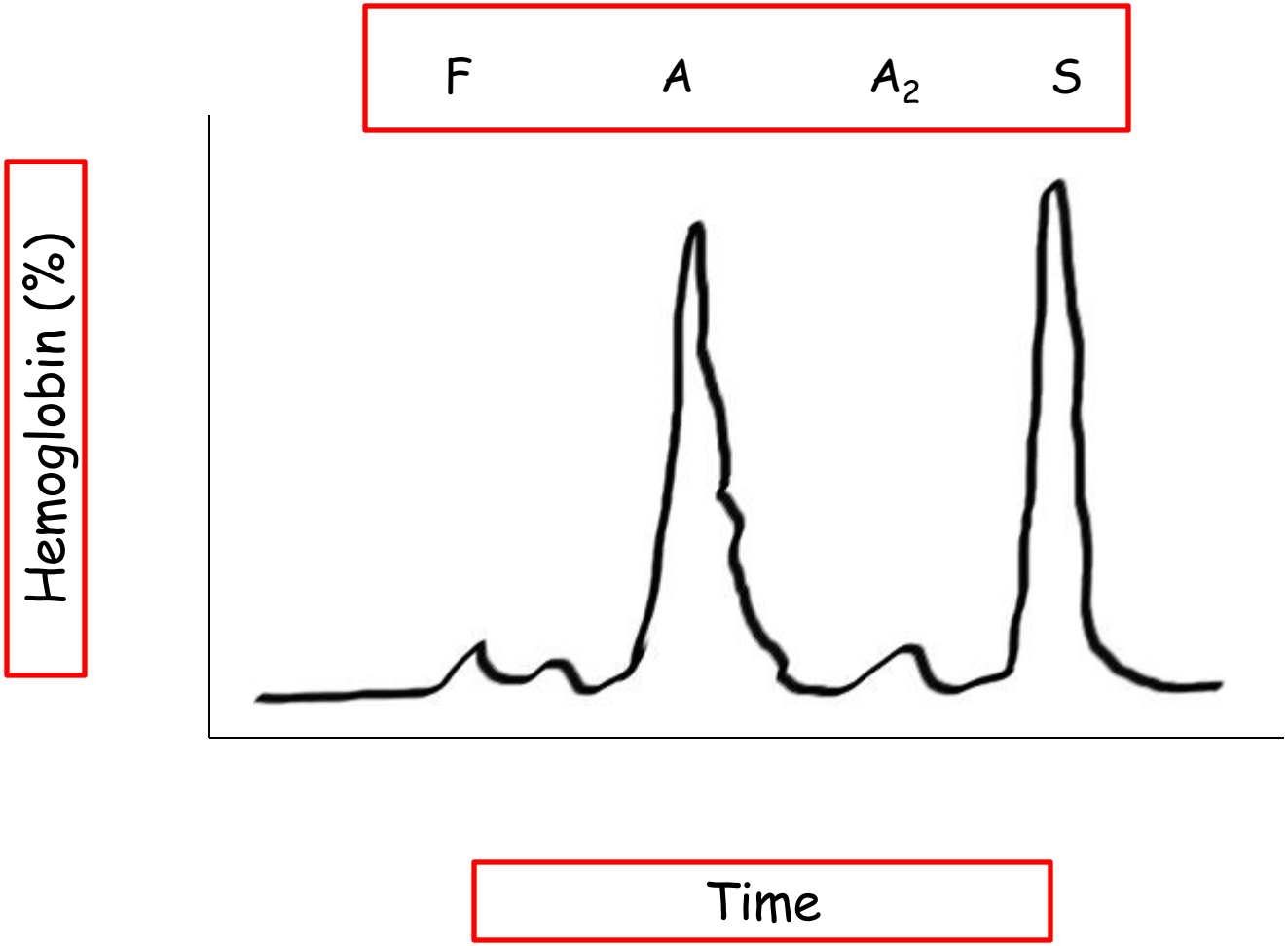
Indices of hemolysis
↑ indirect bili/LDH
↓ haptoglobin

Hemoglobin electrophoresis
(↑ Hgb F, S)

Sickle Cell Disease

- Treatment
  - Underlying trigger, oxygen, volume repletion
  - Transfusion, exchange transfusion
  - Stem Cell transplant (evolving)
  - Hydroxyurea: ↑ Hgb F (unknown mechanism; ↓ polymerization)

- Special Notes:
  - Parvovirus: transient aplastic crisis
  - Pigment stones: secondary to hemolysis



Trait or Disease?

Why does the NBME love SCD?

Heme

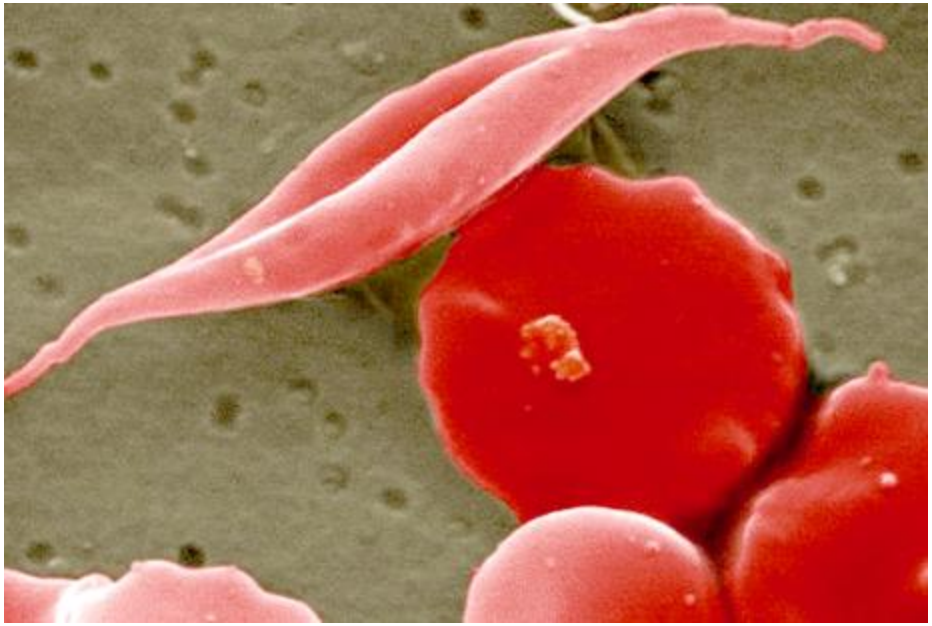
- Genetics
- Hemoglobinopathy
- Hemolysis

OSD

- Spleen
- Bone
- Kidney
- Lung
- CNS

You can count on at least 3-5 direct questions and 5-7 questions including SCD distractors

Sickle Cell Disease (SCD)



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