The SCIENCE of SICKLE CELL DISEASE

JULIE KANTER MD

DIRECTOR, SICKLE CELL RESEARCH

DIRECTOR, LIFESPAN COMPREHENSIVE SICKLE CELL CENTER

MEDICAL UNIVERSITY OF SOUTH CAROLINA

Conflict of Interest Disclosure

- Research advisory boards/steering commitees: Pfizer, Astrazeneca, Novartis, Bluebird Bio, Global Blood Therapeutics, Eli Lilly
- Patent pending: paper based hemoglobin disease diagnostics
- Pharmaceutical Sponsorship: Medical University of South Carolina have received funding for sponsored studies with which I participated including: Mast pharmaceuticals, Apopharma, Lilly, Novartis pharmaceuticals, Purdue Pharmaceuticals, Astrazeneca, Bluebird Bio

Presented y:

Objectives:

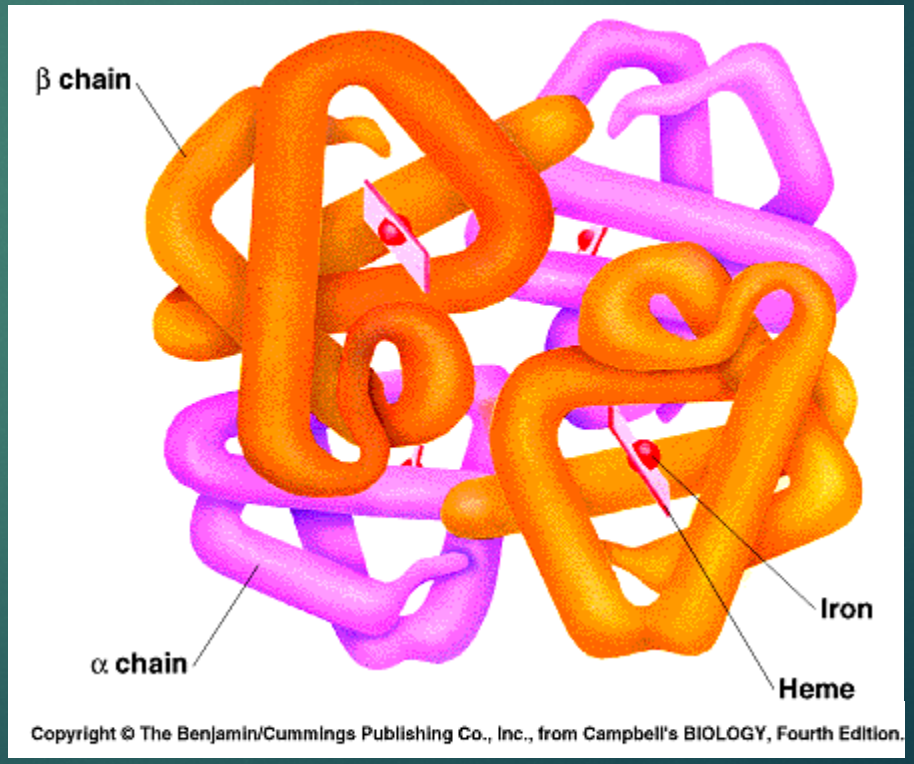
- Empower stakeholders to understand sickle cell disease
- What is sickle cell disease?
- How did I (or someone I love) get sickle cell disease
- What type of complications occur in sickle cell disease?
- Why do individuals with sickle cell disease have pain?
- What is sickle cell trait and how does it affect us?

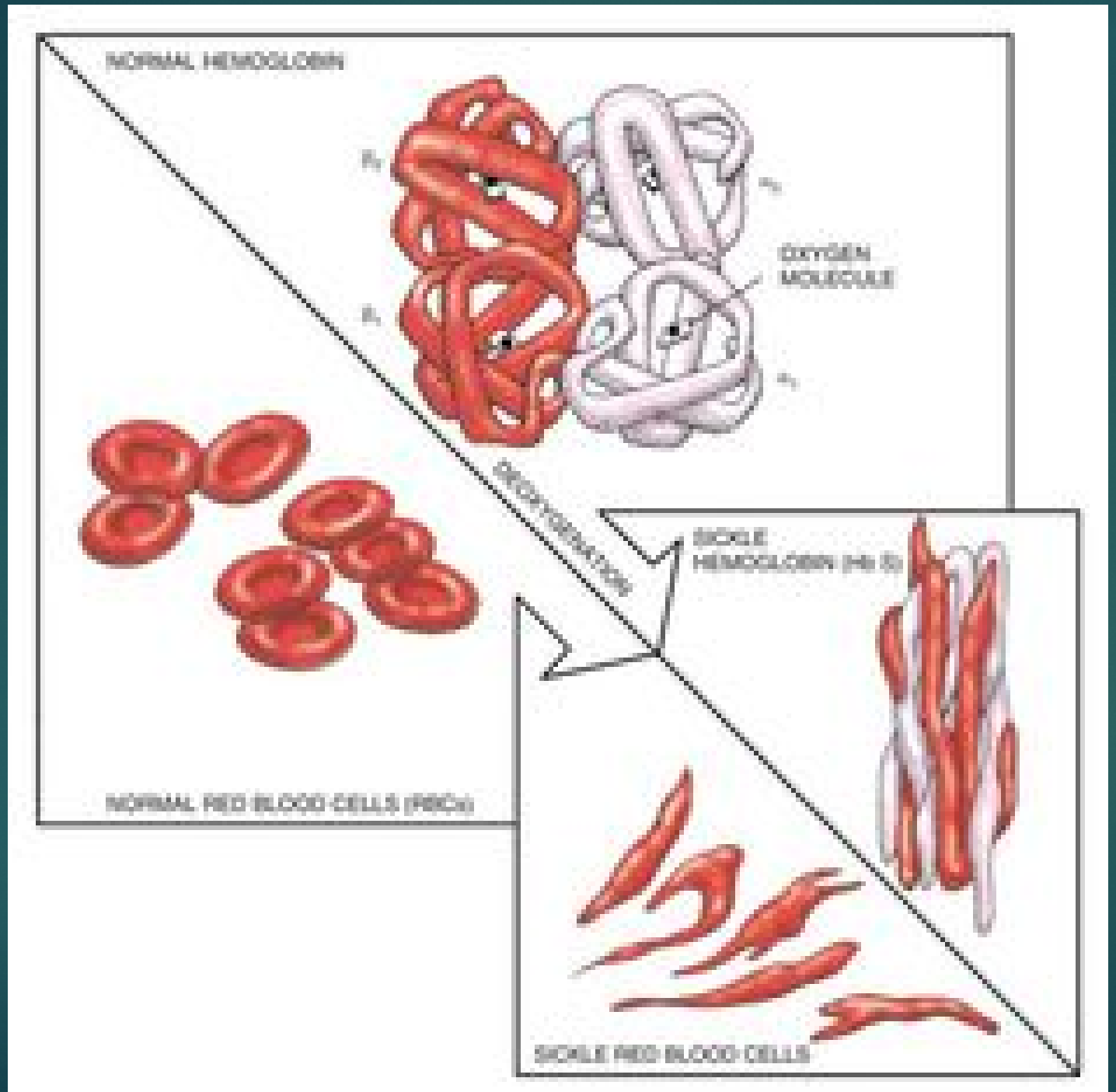
What is Sickle Cell Disease?

- Sickle Cell Disease is caused by broken/dysfunctional hemoglobin
- What is Hemoglobin?
- Protein is the building block of our body
- Hemoglobin is the protein inside the red blood cell that carries Oxygen

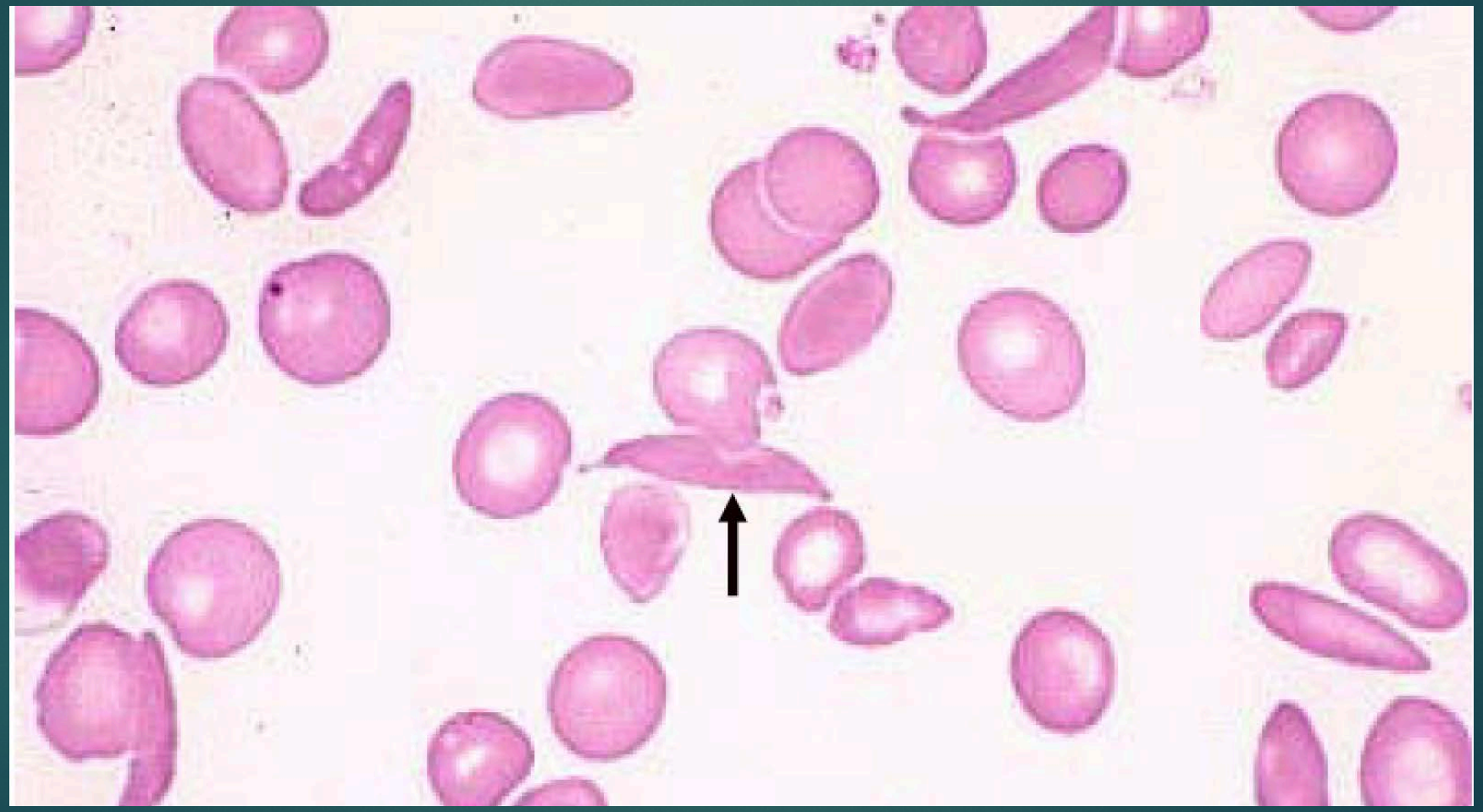
Hemoglobin

- Multi-subunit protein (tetramer-4 pieces)
  - 2 alpha (α) and 2 beta (β) subunits
- Heme
  - One per subunit
  - Has an iron component
- Pathology
  - Broken: qualitative
  - Not enough Quantitative
- Function: red blood cells
  - To carry and release O2

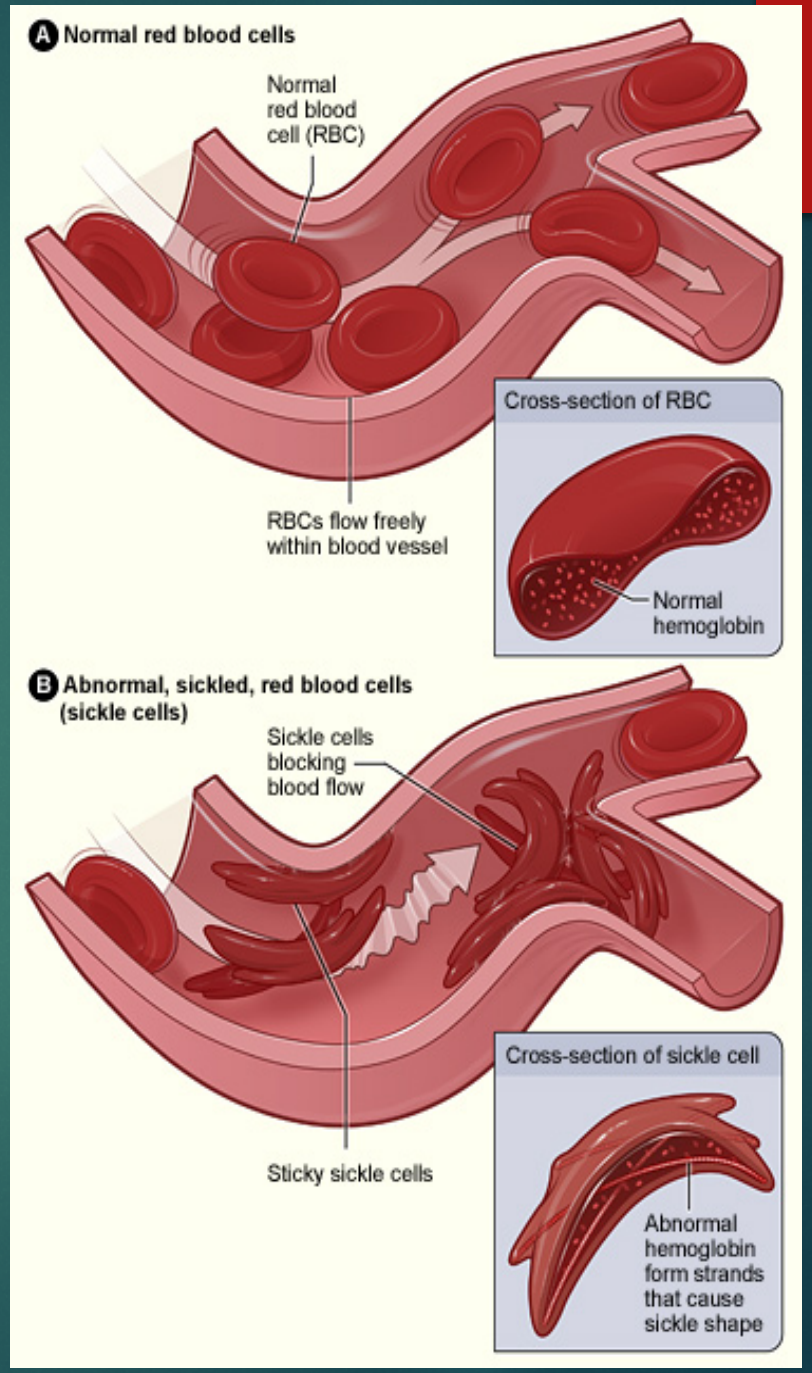



NORMAL HEMOGLOBIN
OXYGEN MOLECULE
DEOXYGENATION
SICKLE HEMOGLOBIN (Hb S)
NORMAL RED BLOOD CELLS (RBCs)
SICKLE RED BLOOD CELLS

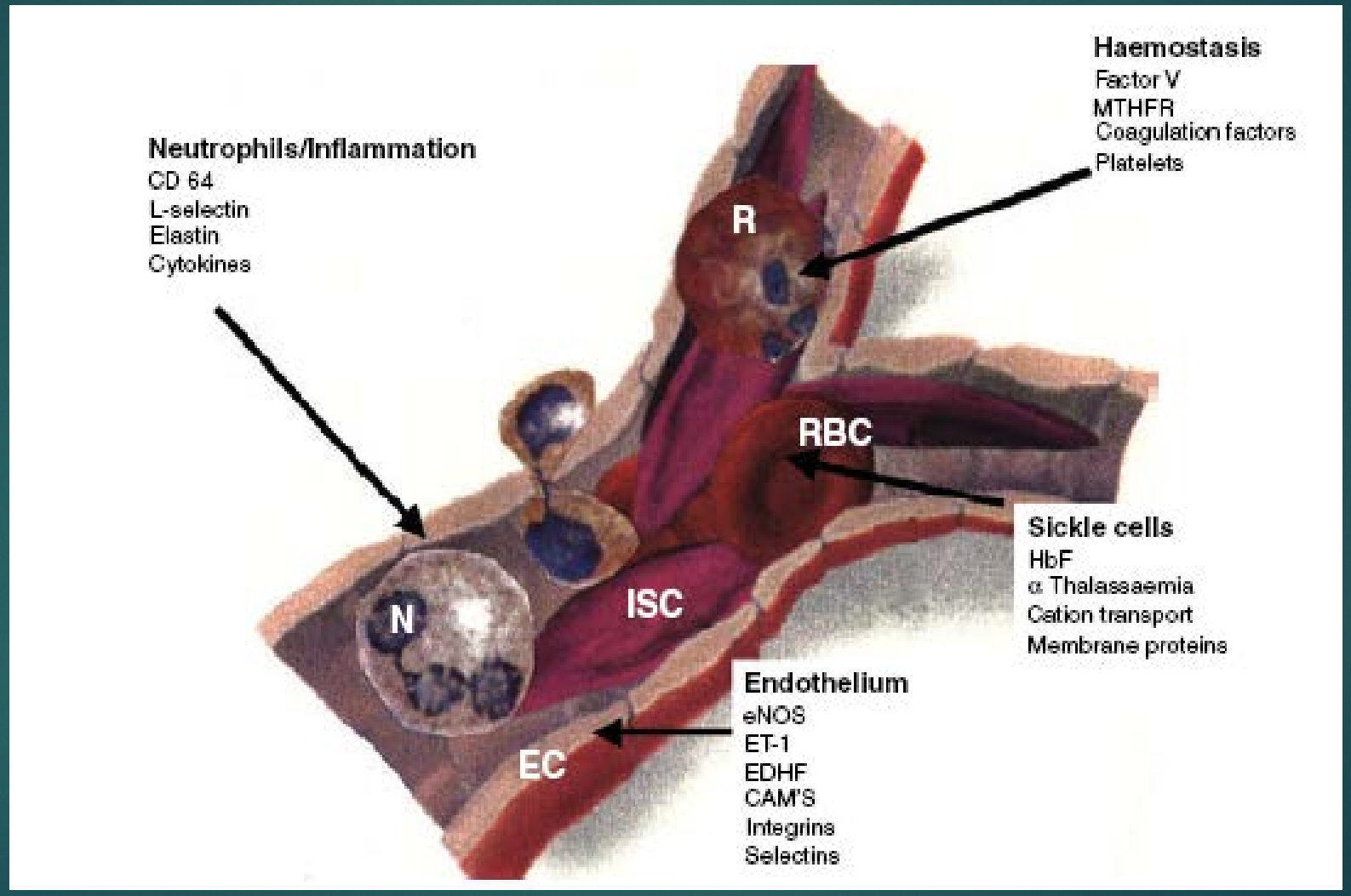
Sickle Cell Disease



- What happens to red blood cells in sickle cell?

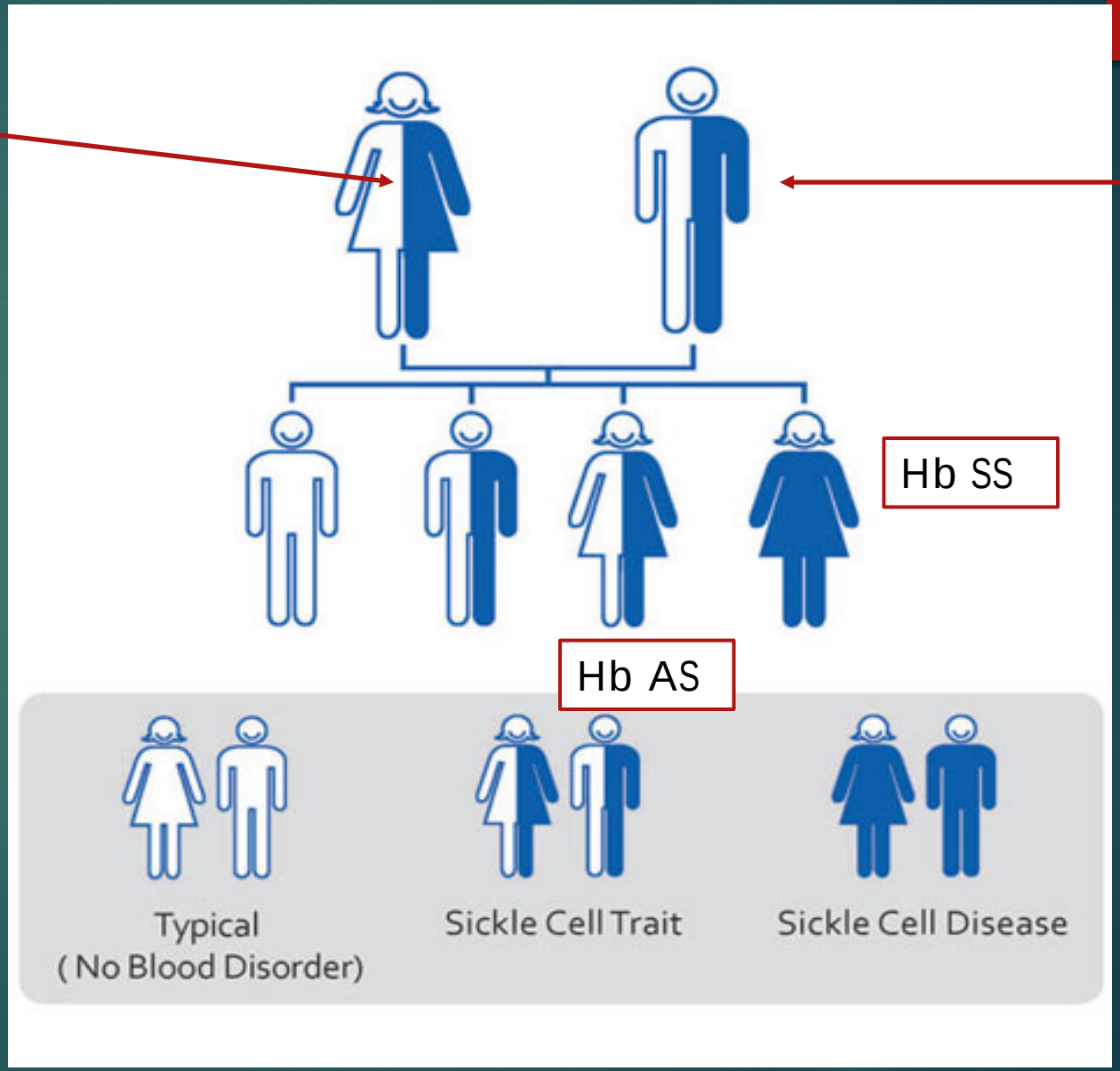


Vaso-occlusion

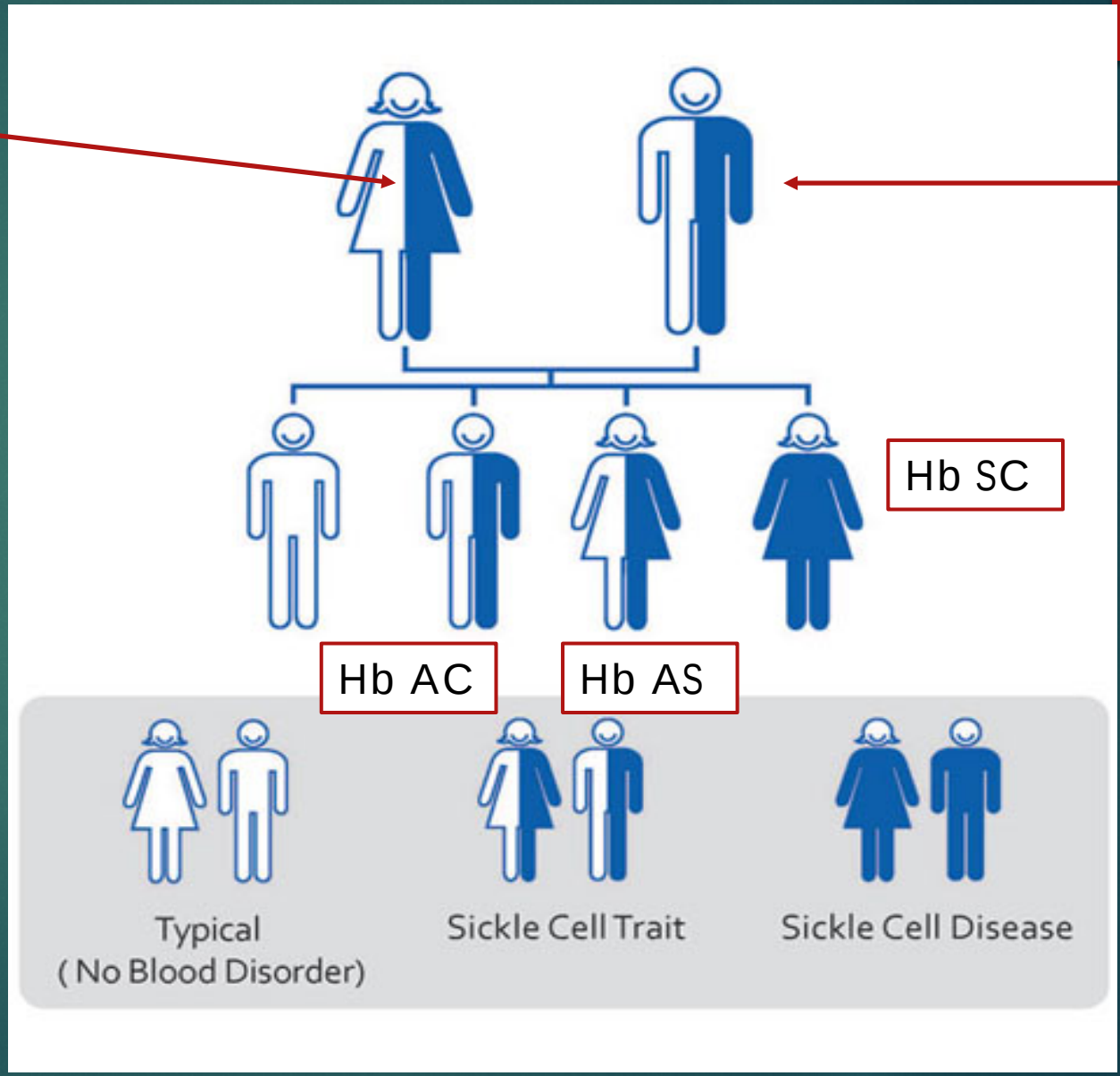


Steinberg MH Br J Haematol 2005; 129:465-81

How did I get sickle cell disease?



How did I get sickle cell disease?

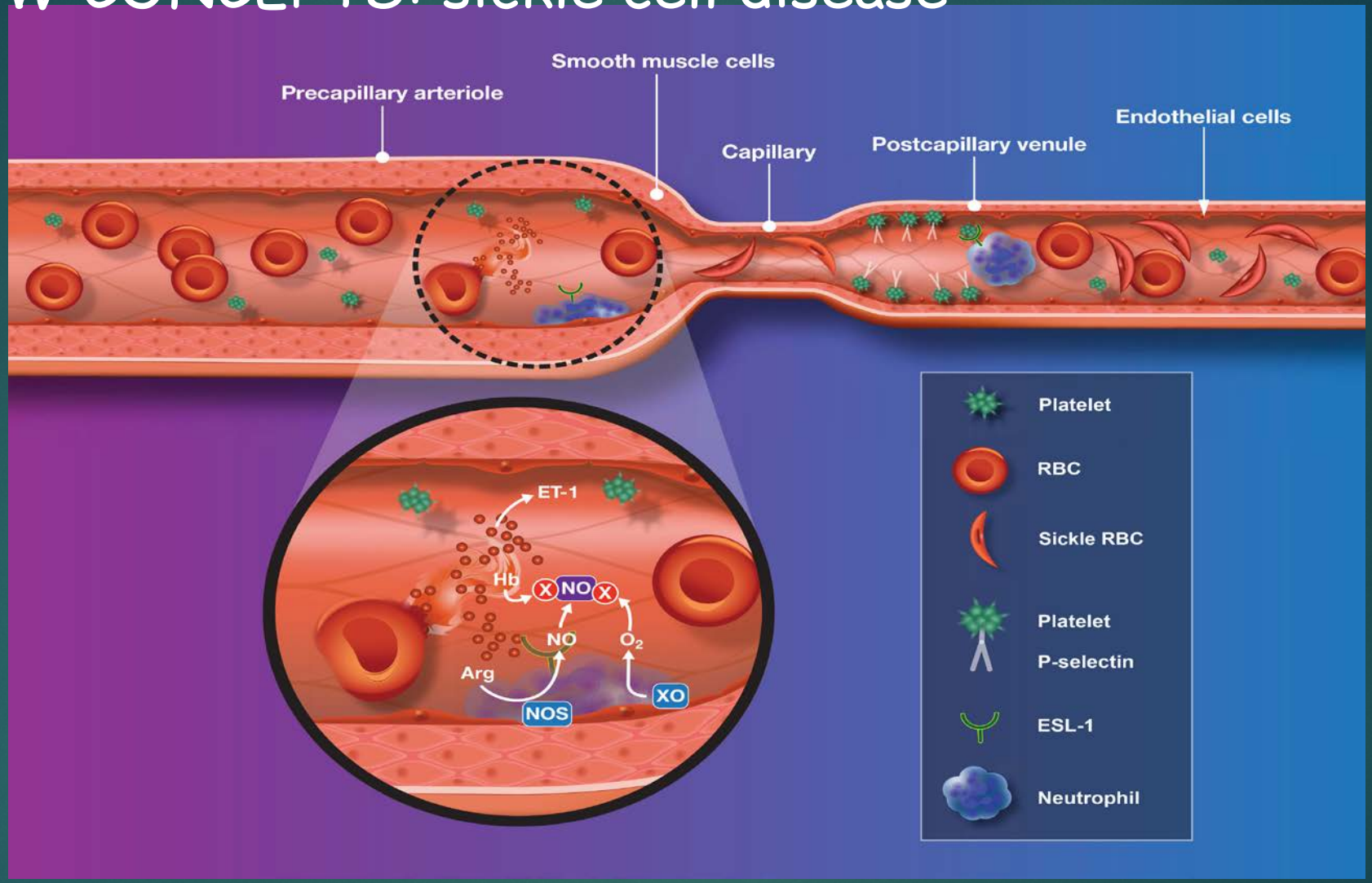


Sickle Cell Disease is a Multigenic Disorder

- This means EVERYONE IS DIFFERENT
- A single gene mutation is responsible for Hemoglobin S
- There are other genes (that we don't understand) and environments that affect how each person reacts to their sickle cell disease
- The diversity not accounted for by hemoglobin genotypes
- Although patterns exit, every patient is different

Chui DH and Dover GJ Curr Opin Ped 2001; 13:22

NEW CONCEPTS: sickle cell disease



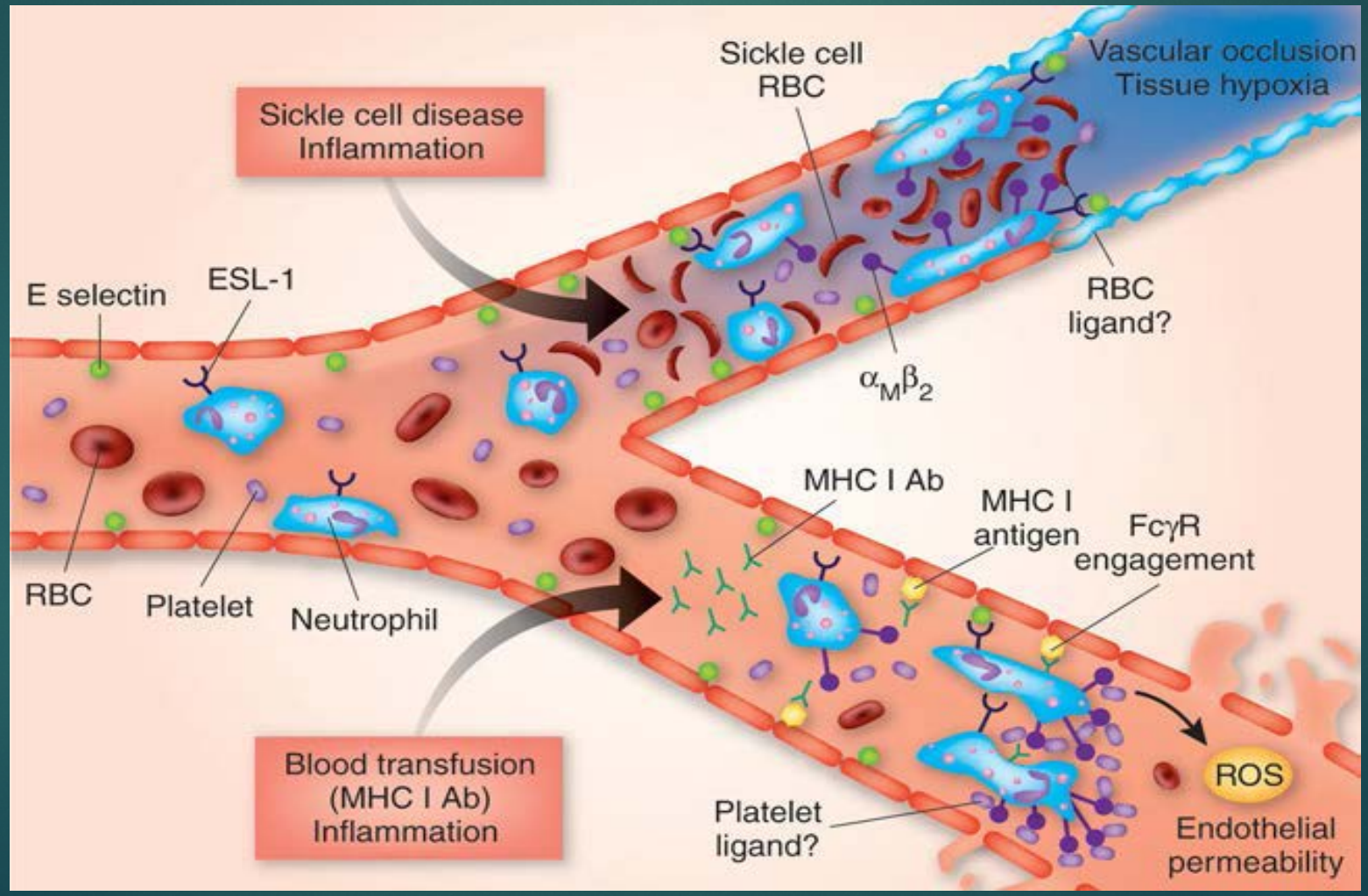
Kanter J, Kruse-Jarres. "Update on the management of Sickle Cell Disease from childhood through adulthood. Blood reviews. 2013

Sickle Cell: new concepts

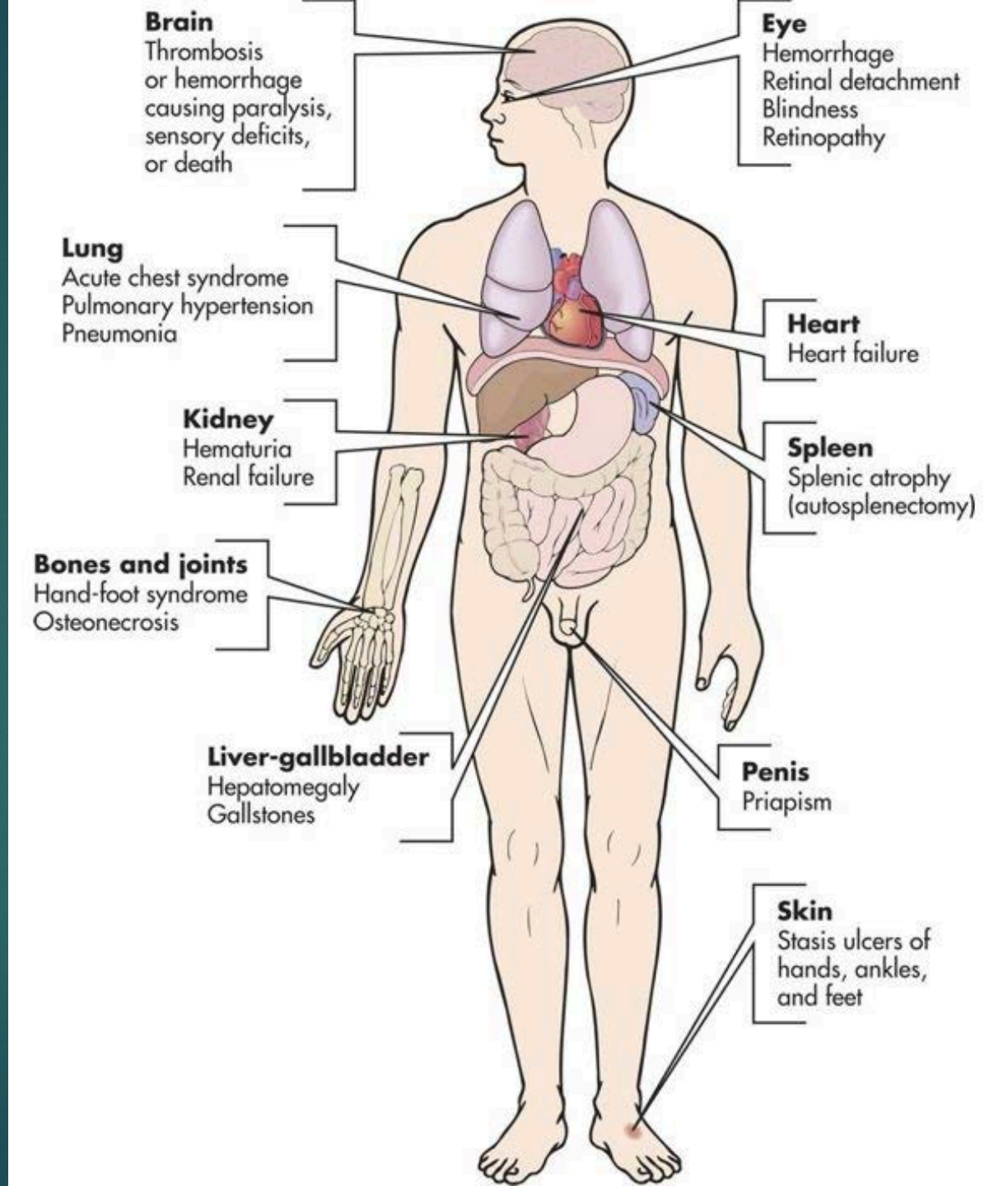
- It is NOT just a crescent or sickle shape that slow or block blood flow
- There are multiple complications caused by this one messed up protein:
  - CELLS SICKLE
  - CELLS BREAK APART FREQUENTLY
  - The result of the cells sickling and breaking is inflammation and blood vessel damage

Inflamed microvasculature.

Mark R Looney & Michael A Matthay. Neutrophil sandwiches injure the microcirculation. *Nature Medicine 15, 364 - 366 (2009)* doi:10.1038/nm0409-364



SCD patients can get "Normal" health problems as well.



↑Pregnancy complications
↑Dental complications
↑Psychological and social complications
Early mortality

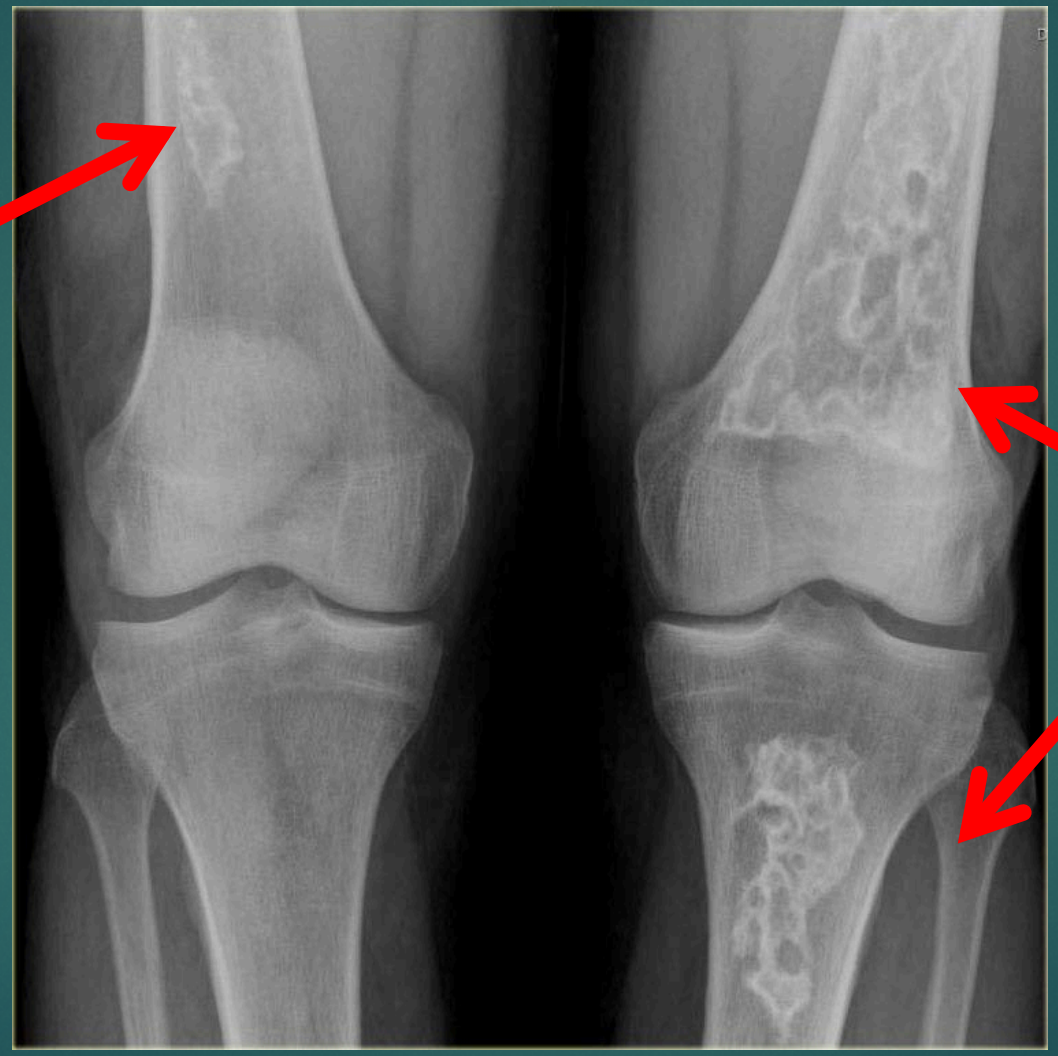
Complications of Sickle Cell Disease

- Infection
- Swelling of hands/feet
- Sickle cell crisis pain: bones, abdomen, back pain
- Gall bladder stones
- Yellow eyes
- Spleen problems
- Stroke
- Enlarged Tonsils
- Bone infarcts

Complications of Sickle Cell Disease

- As Individuals age-more issues can develop
  - Pregnancy
  - Hormones
  - Chronic (daily) pain
  - Heart problems
  - Ulcers
  - More acute pain with new triggers of pain
  - Dental problems
  - Retinopathy (eye issues)
  - Medication tolerance and side effects

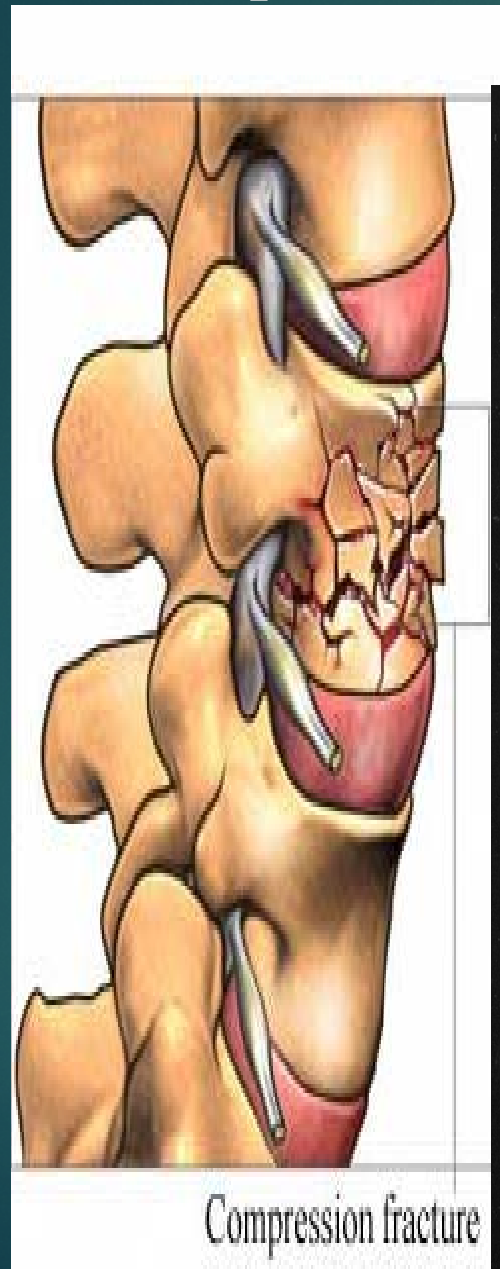
Why does Sickle Cell Disease Cause pain

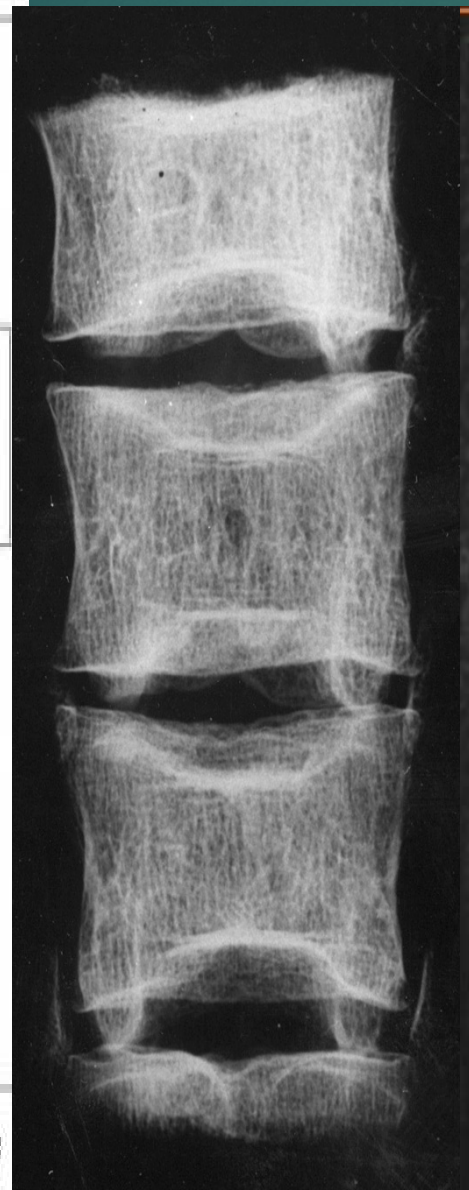


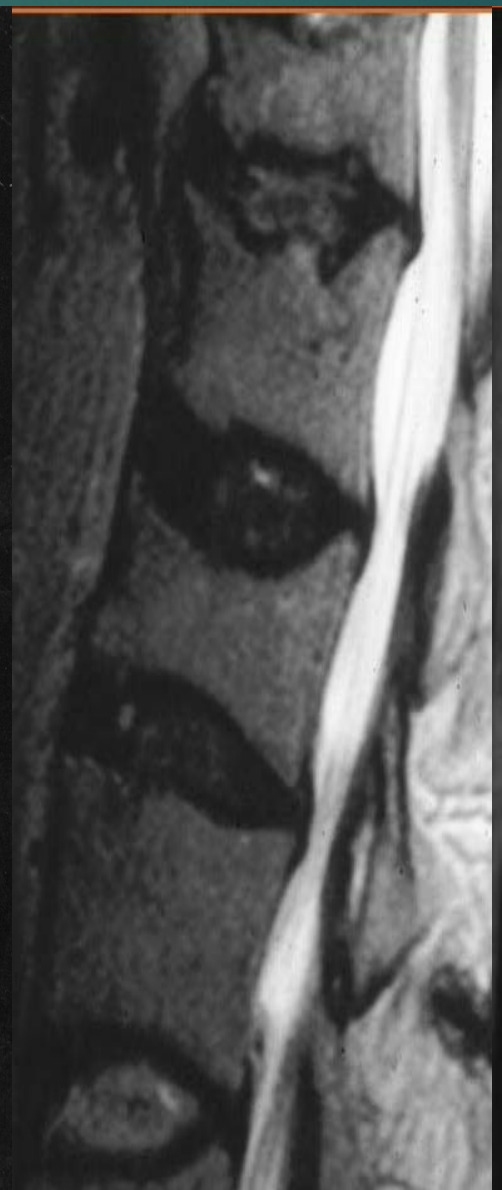
From lack of blood to bone for a prolonged period

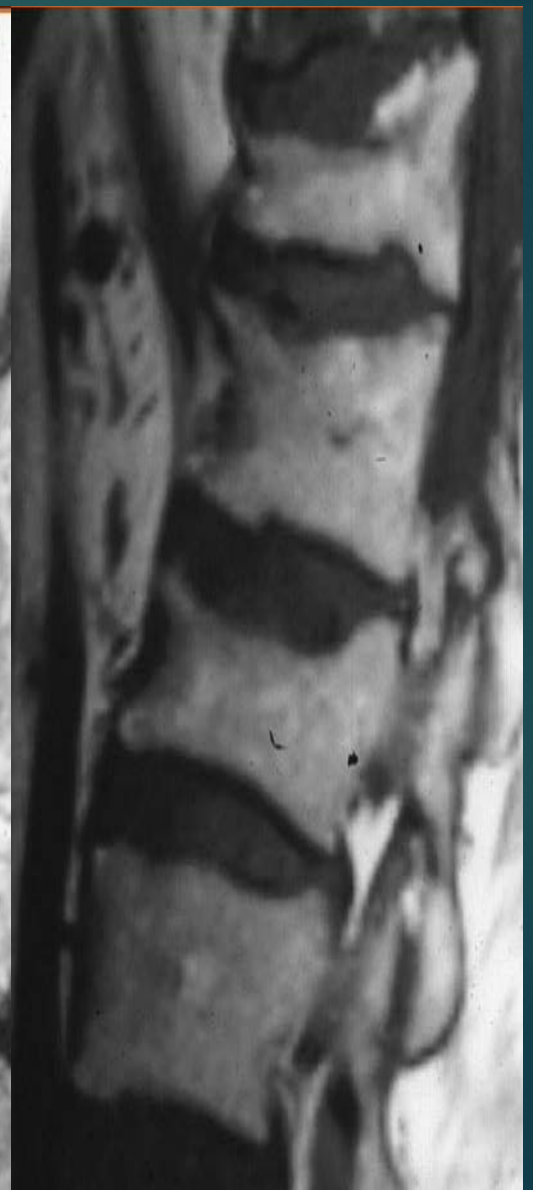
Bone infarcts
Hurt for a Long Time
(up to 3-6 mo

Compression spine deformities

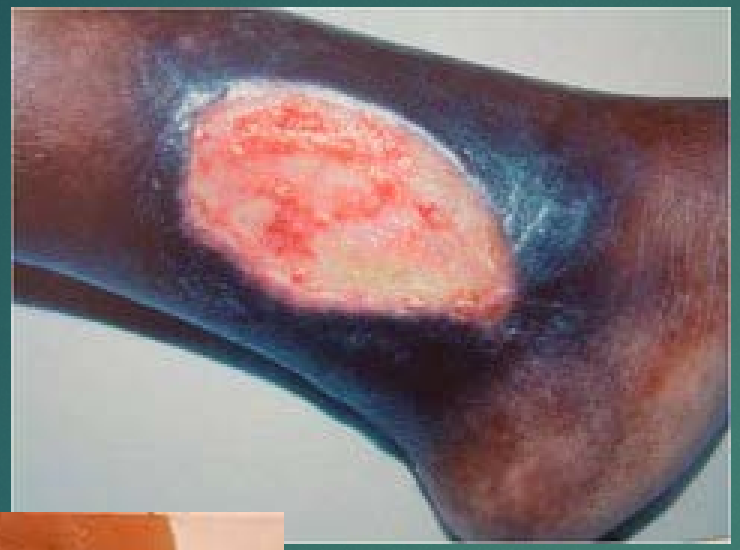


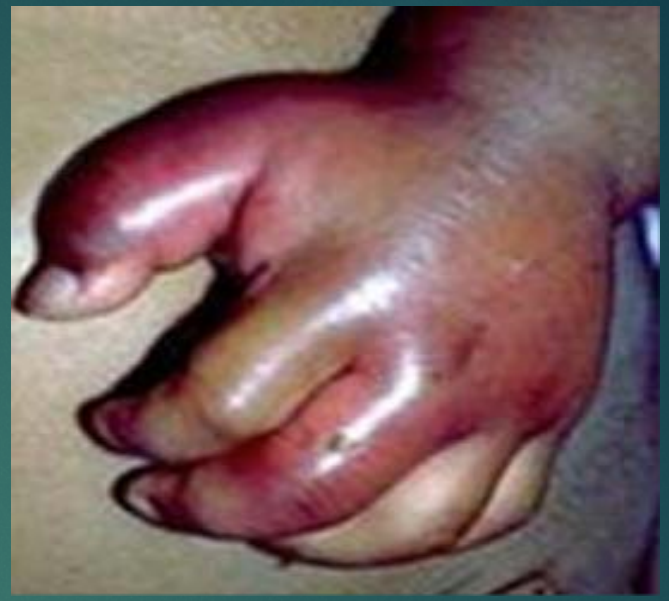


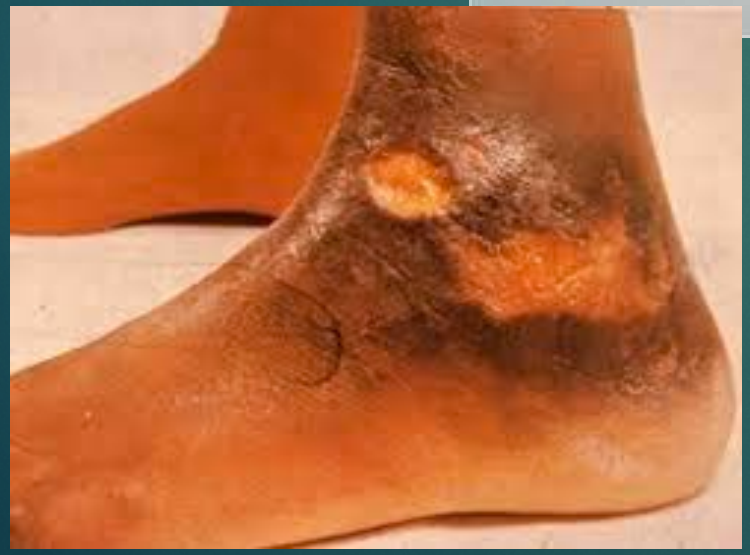


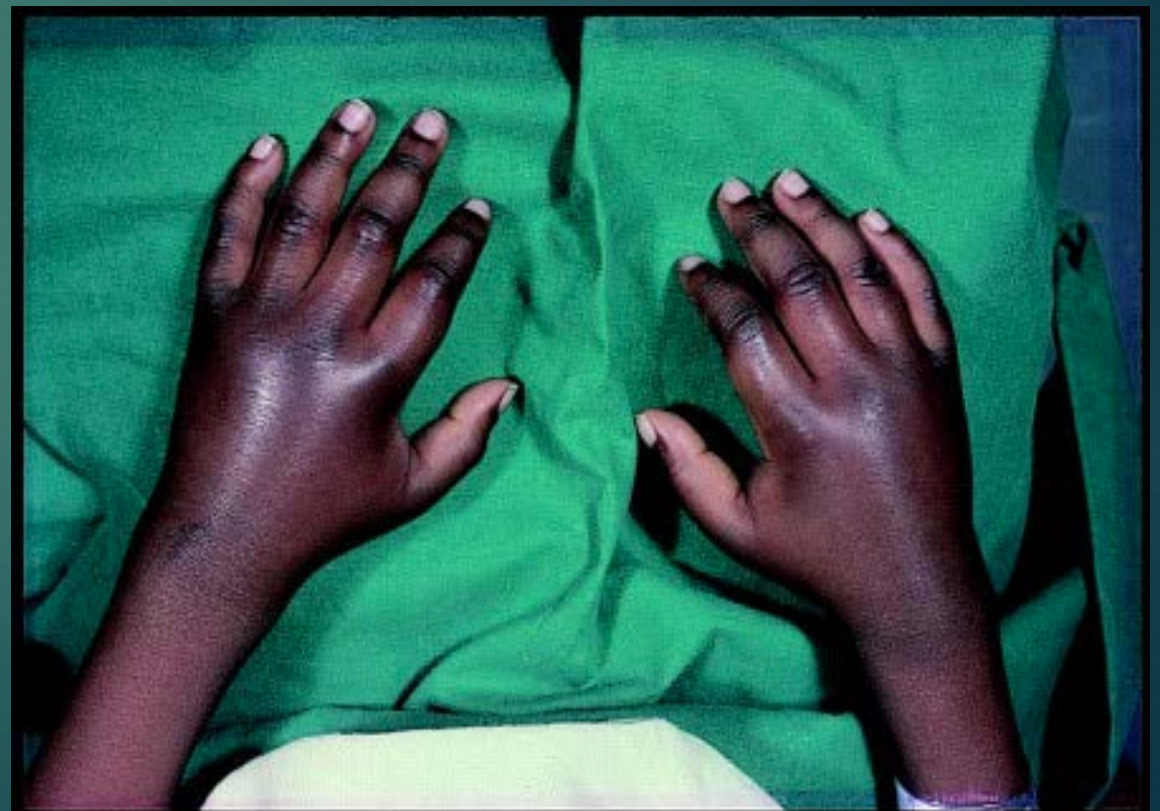


Leg Ulcers, Dactylitis





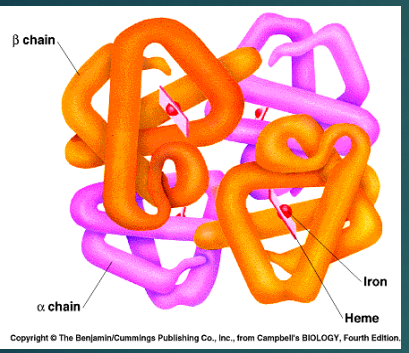


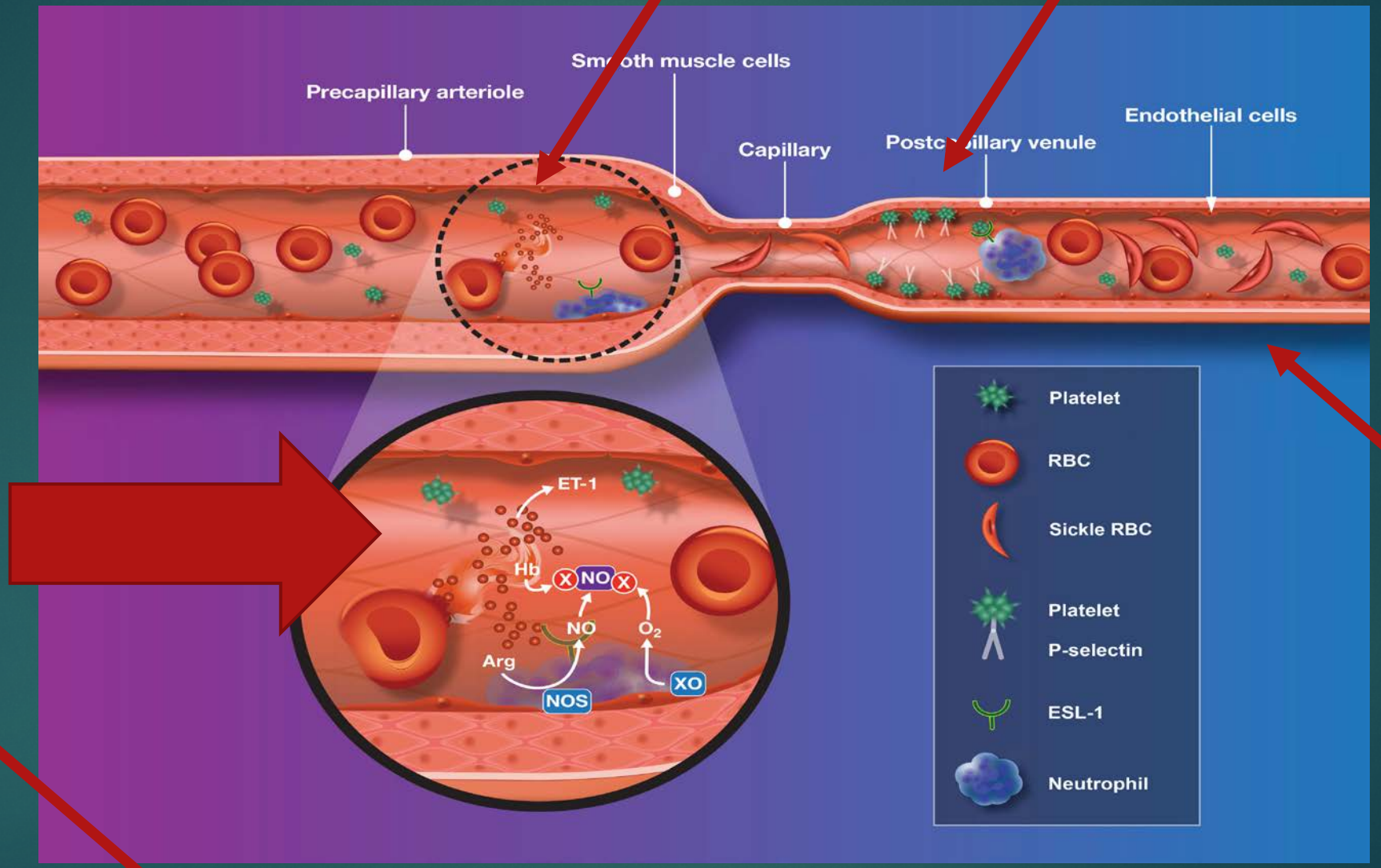


Sickle Cell Disease: New concepts

1. Sickled RBC are fragile and easily breakdown and release proteins that increase inflammation, clotting, endothelial damage and cause vasoconstriction
2. SCD is a complex, multi-system illness rather than a simple disorder involving oddly shaped red blood cells and pain
3. Vascular Occlusion is more than just a sickle cell pile up

NEW TARGETS: sickle cell disease

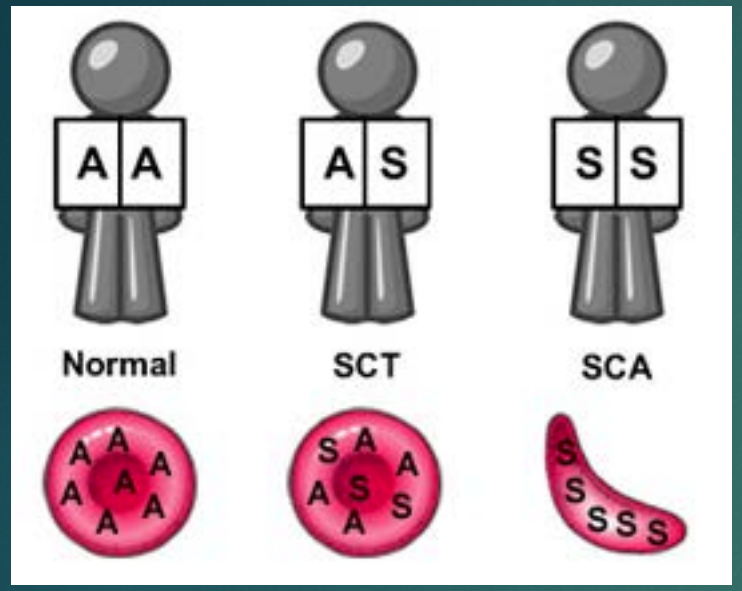




Possible Clinical Complications of Sickle Cell Trait

- Age-related loss of maximal urinary concentration, episodic hematuria, mild increase in UTI of pregnancy
- Altitude & exercise related splenic infarction
- Altitude can induce other complications (eg. ACS)
- Traumatic hyphema
- Renal medullary carcinoma
- Increased risk of thromboembolism
- Complications from Increased pressure (scuba diving)
- Unexpected INTENSE exercise-related death in military recruits and young athletes

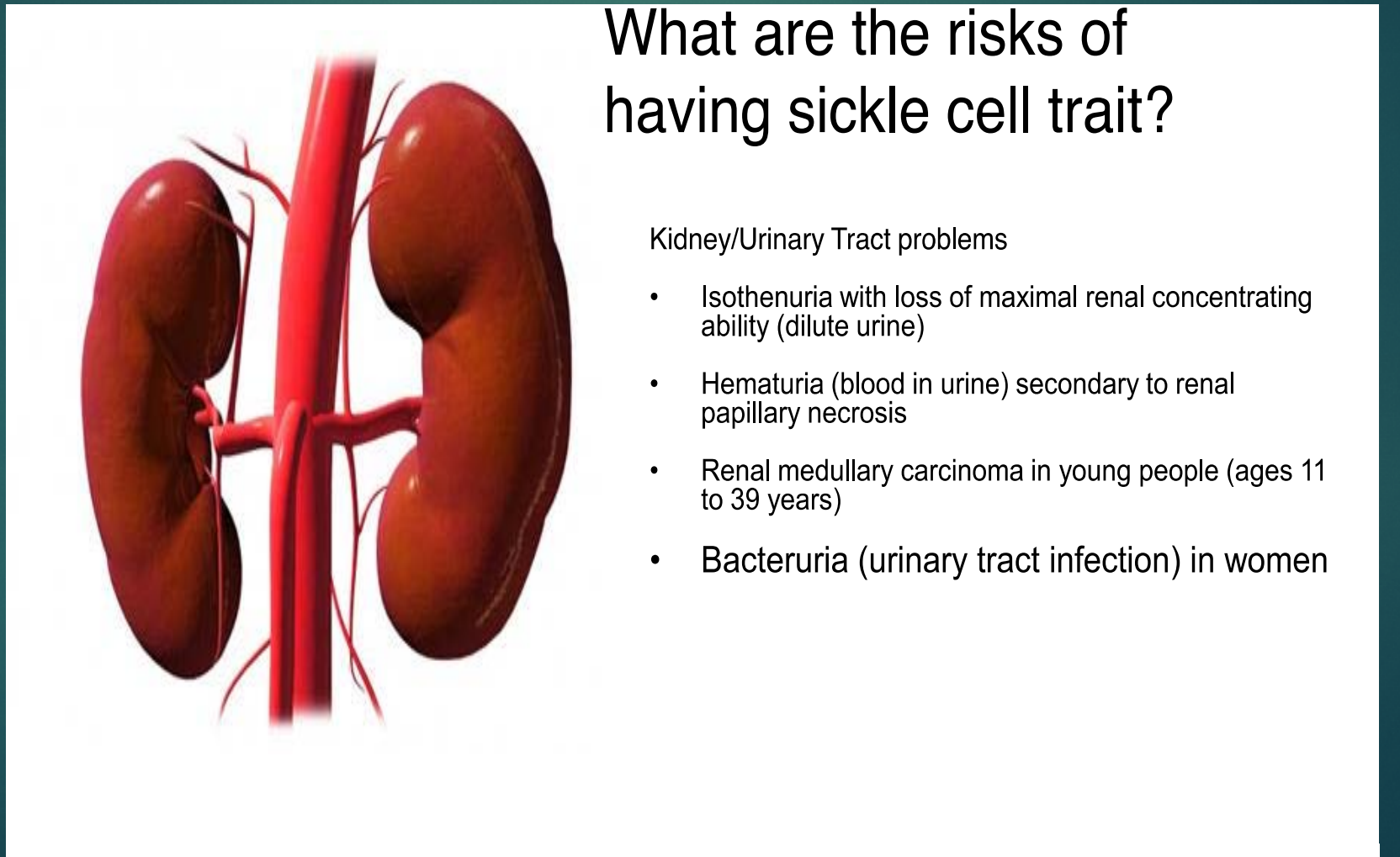
What about Sickle Cell Trait?



Athletes with SCT:

- RARE RISK compared to those without SCT to experience heat stroke and muscle breakdown when doing intense exercise, such as competitive sports or military training have that
- The chance of this problem can be reduced by avoiding dehydration and getting too hot during training.

More important concern about sickle cell trait?



What are the risks of having sickle cell trait?

Kidney/Urinary Tract problems

- Isothenuria with loss of maximal renal concentrating ability (dilute urine)
- Hematuria (blood in urine) secondary to renal papillary necrosis
- Renal medullary carcinoma in young people (ages 11 to 39 years)
- Bacteruria (urinary tract infection) in women

Most important thing about Sickle cell trait?

- All expectant couples and those planning to have children should be offered the option to test for gene mutations that cause sickle cell disease
- People with a family history of sickle cell disease
- People with a family history of thalassemia

Conclusions:

- WE LEARN MORE ABOUT SICKLE CELL DISEASE and SICKLE CELL TRAIT ALL THE TIME
- WE have new medications and new curative options in development
- There are many, many, many things individuals with sickle cell disease and those who care for people with sickle cell disease can do to help
- Say “yes” to research
- Ask questions and DEMAND answers

Questions?