Lecture Presentation

Learning Objectives

UNC SCHOOL OF MEDICINE

- Describe the composition of blood.
- Describe the structure and function of hemoglobin.
- Define anemia and describe common signs and symptoms.
- Define iron-deficiency anemia, including its prevalence
- Explain the pathophysiology of iron-deficiency anemia and list common causes.
- Describe how patients with iron-deficiency anemia typically present.
- Define sickle cell disease (SCD), including its prevalence.
- Describe the clinical presentation of SCD.
- Explain the pathophysiology of SCD.

What is Anemia?

UNC SCHOOL OF MEDICINE

- To understand this question, we have to briefly review the composition of blood!

Four Main Components of Blood

UNC SCHOOL OF MEDICINE

- Three cellular components
  - **Red Blood Cells (erythrocytes)**
  - **White Blood Cells (leukocytes)**
  - **Platelets**
- One liquid component
  - **Plasma**

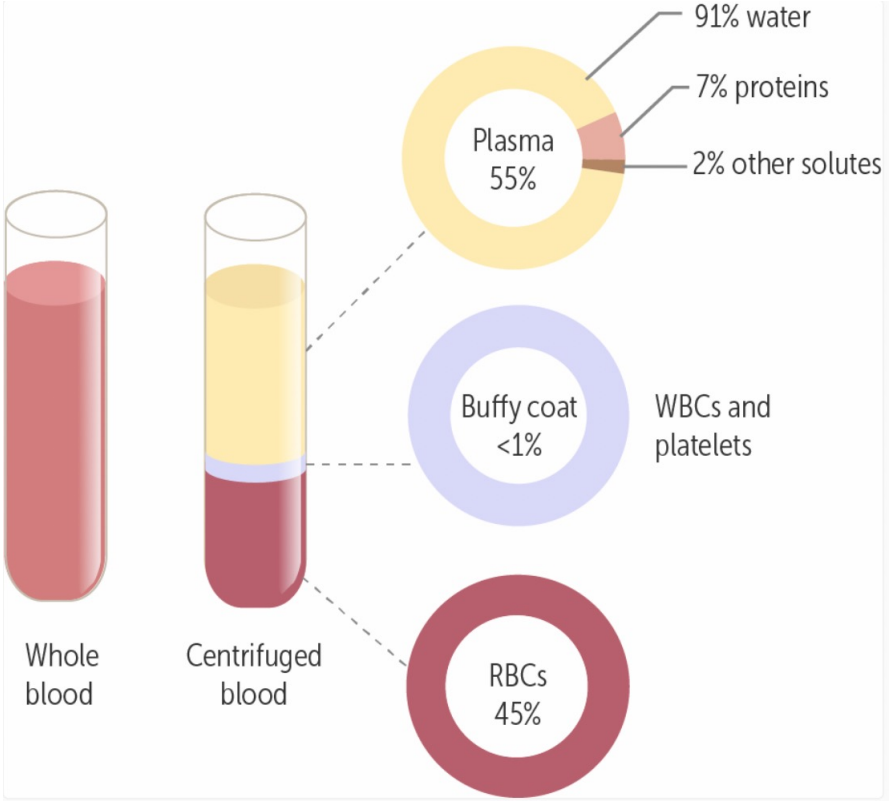


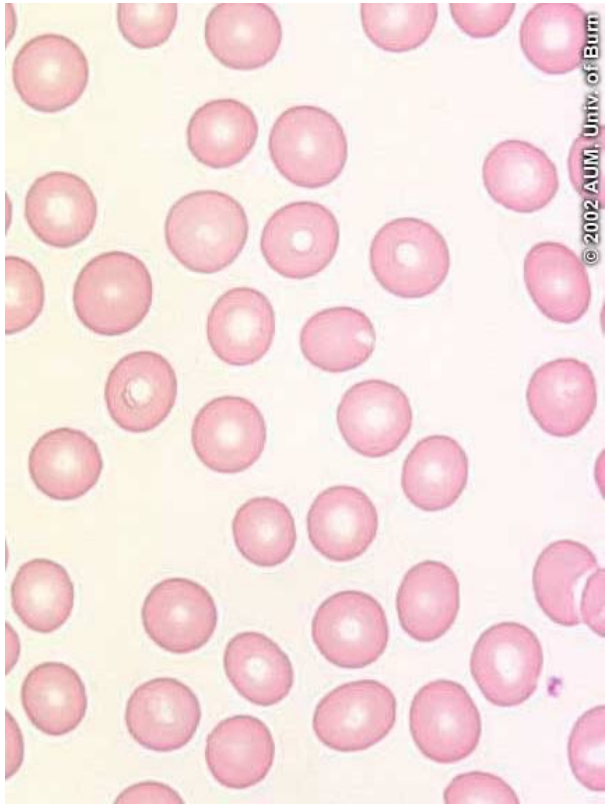
Figure 1

Credit: ScholarRx

Erythrocytes (Red Blood Cells)

UNC SCHOOL OF MEDICINE

- RBCs deliver oxygen from lungs to tissues and returns carbon dioxide from tissues to lungs
- Filled with a protein called **hemoglobin** that carries oxygen
- Iron within the hemoglobin creates a red pigment when bound to oxygen



RBCs Have a Biconcave Shape

UNC SCHOOL OF MEDICINE

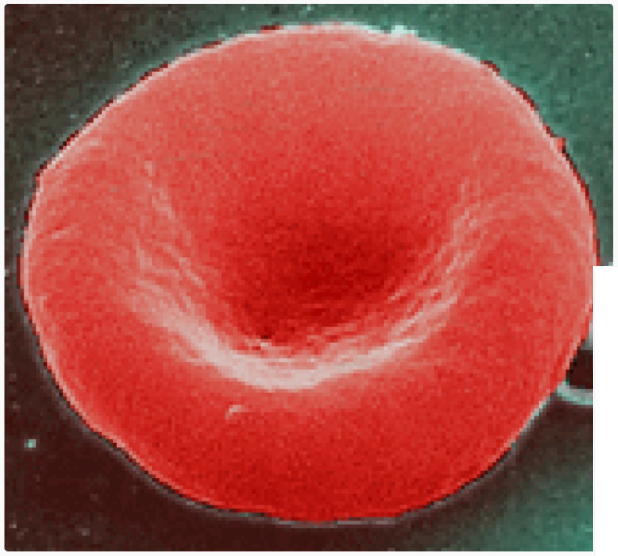


Figure 1

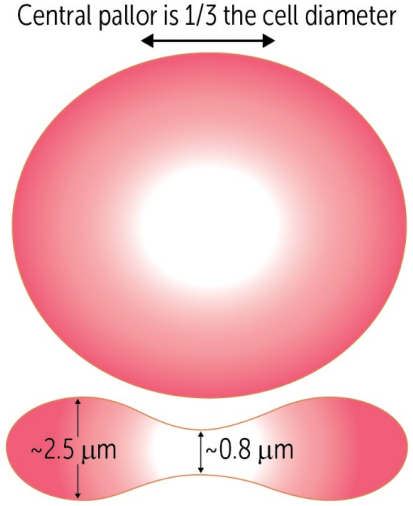


Figure 2

- Allows RBCs to be flexible and squeeze through very small vessels without getting stuck
  - Important for understanding sickle cell disease!

Leukocytes (White Blood Cells)

UNC SCHOOL OF MEDICINE

- Two important functions:
  - Fighting pathogens as a component of the immune system
  - Ridding the body of dying or malignant cells
- Three main types of WBCs:
  - **Granulocytes**
  - **Monocytes/macrophages**
  - **Lymphocytes**

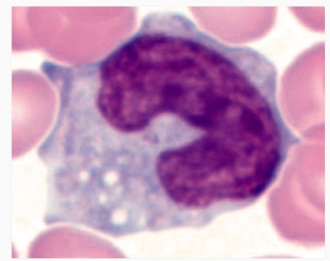


Figure 4

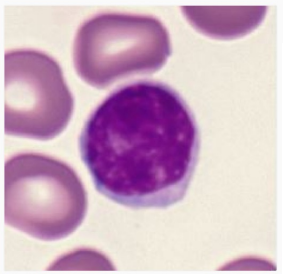
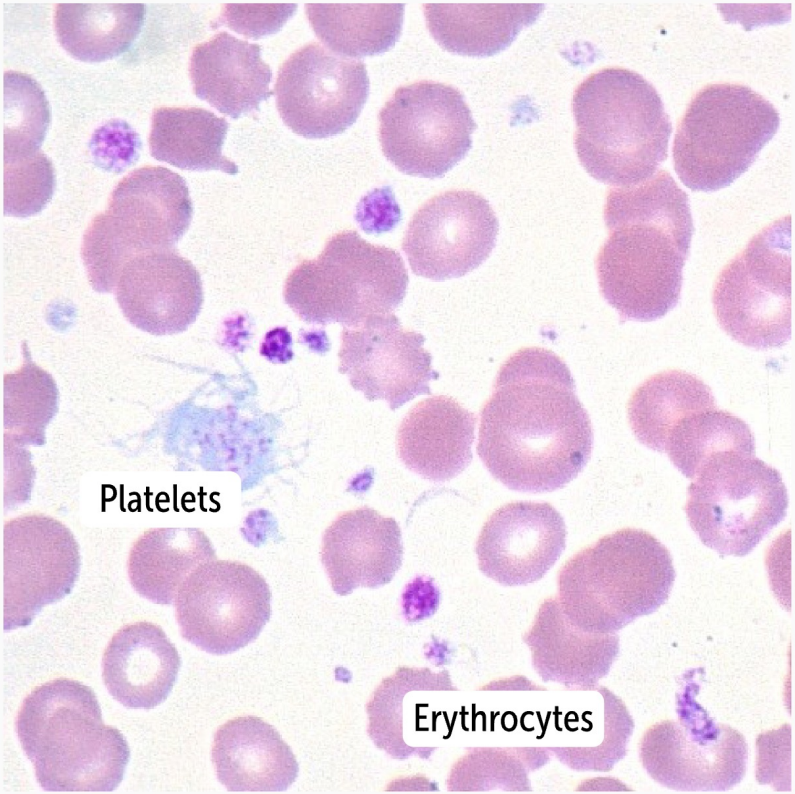


Figure 5

Platelets

UNC SCHOOL OF MEDICINE

- Cytoplasmic fragments of large bone marrow cells called **megakaryocytes**
- Important for clotting of blood
- Contain numerous granules required for clot formation



A Complete Blood Count tells us about each of these cells

UNC SCHOOL OF MEDICINE

CBC Component	Patient Results	Normal
White Blood Cells	18,000	3.6 - 11.2 10*9/L
Hemoglobin	6 g/dL	12.9 - 16.5 g/dL
Hematocrit	18%	39.0 - 48.0 %
Platelets	520	150 - 450 10*9/L

Plasma

UNC SCHOOL OF MEDICINE

- Liquid component of the blood
- Mostly composed of water (92%) – helps blood move through your vessels

UNC SCHOOL OF MEDICINE

- We will focus on Red Blood Cells for the reminder of the lecture.

Red Blood Cells Are Sacks of Hemoglobin!

UNC SCHOOL OF MEDICINE

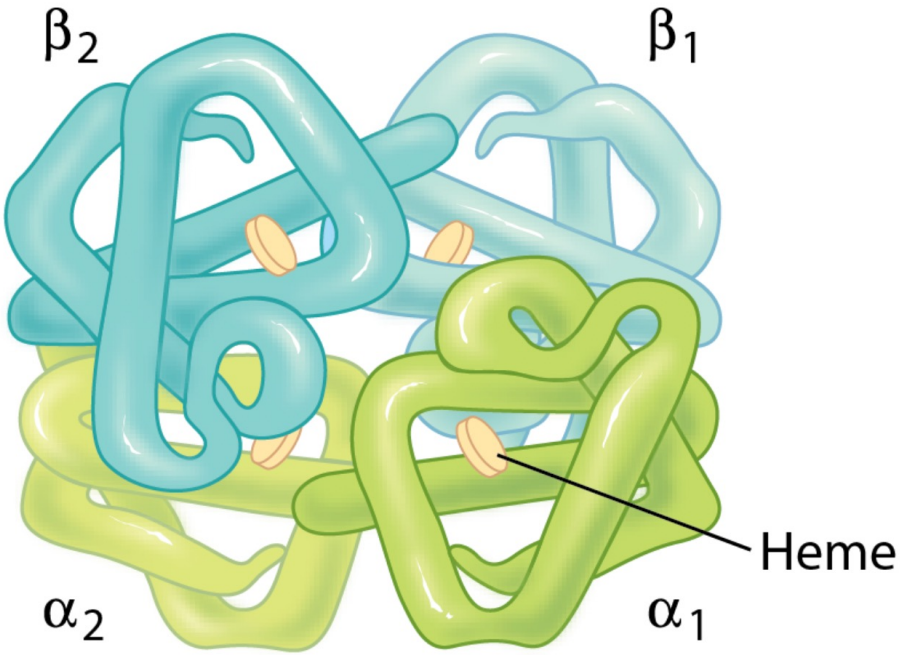


Figure 5

- Mature RBCs do not have a nucleus
- RBCs contain many copies of the protein called: **hemoglobin**
- Hemoglobin carries oxygen throughout the body
- Deposits oxygen in tissues
- Retrieves carbon dioxide from the tissues to return to the lungs for excretion

Structure of Hemoglobin

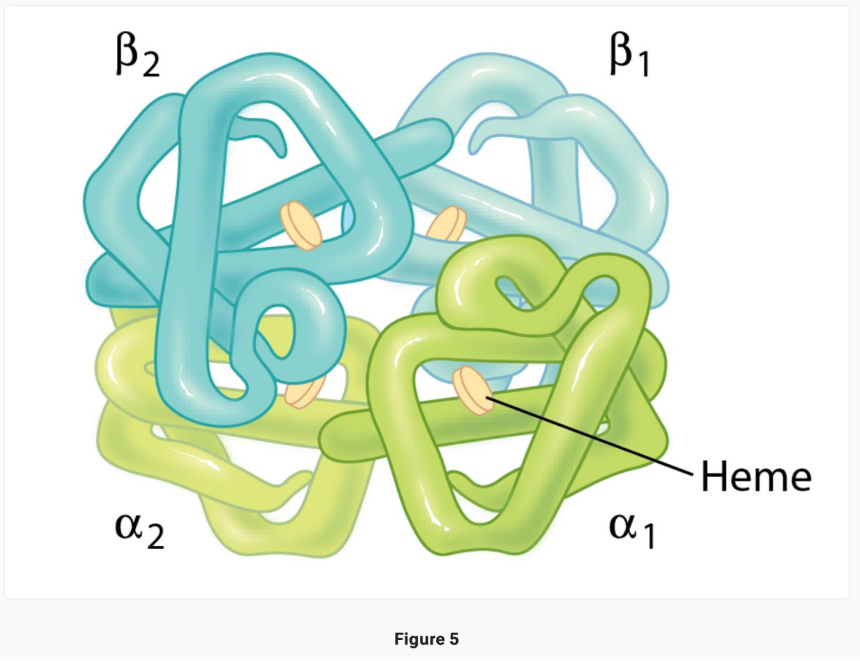


Figure 5

Four globin chains meet together to make one hemoglobin molecule

- Hemoglobin contains heme + globin
- Heme – carries the oxygen
- Globin chains – proteins that provide a home for heme
- Two types of globin chains important for this lecture → alpha and beta
- There are more but that's for another lecture!

Structure of Heme – Do Not Memorize!

UNC SCHOOL OF MEDICINE

- **Heme**
  - Protoporphyrin IX
  - Four nitrogen bonds
  - Iron molecule
    - Ingested in our diet
    - Reversibly binds oxygen (O2) and carbon dioxide (CO2)
  - Four heme molecules per hemoglobin

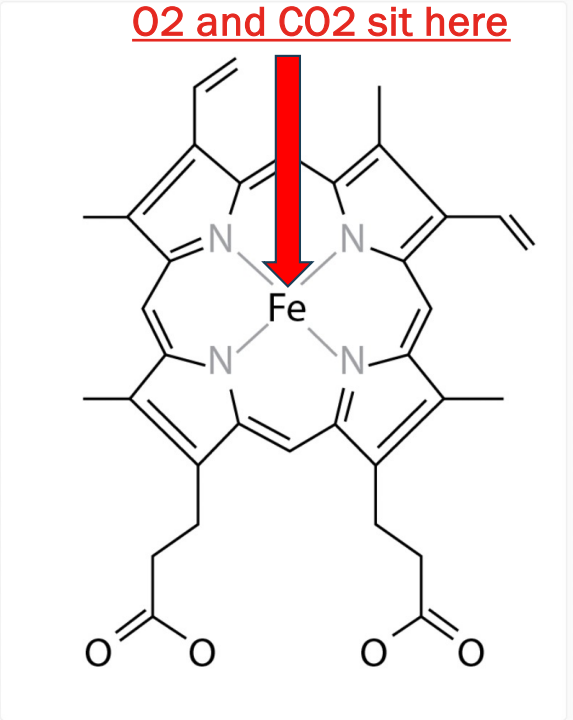


Figure 4

Back to our question: What is Anemia?

UNC SCHOOL OF MEDICINE

- **Anemia** – decreased red blood cells → Decreased hemoglobin → Decreased ability to carry oxygen throughout the body
- Signs and Symptoms – related to low oxygen in tissues
  - Shortness of breath
  - Fatigue
  - Dizziness
  - Rapid heart rate
  - Conjunctival pallor
  - Dry skin and nails

There are many different types of anemias

UNC SCHOOL OF MEDICINE

Table 1

Anemias Classified by Cause

Cause	Anemia
Blood loss	Just one anemia here: anemia of blood loss!
Decreased production	Iron-deficiency anemia Anemia of chronic disease Megaloblastic anemia Aplastic anemia Sideroblastic anemia
Increased destruction	Hereditary spherocytosis Glucose-6-phosphate dehydrogenase deficiency Sickle cell anemia Thalassemia Autoimmune hemolytic anemia Microangiopathic hemolytic anemia

Another Way to Classify Anemias: RBC Size

UNC SCHOOL OF MEDICINE

Table 2

Anemias Classified by Morphology

RBC Size	Anemia
Microcytic	Iron-deficiency anemia Thalassemia Sideroblastic anemia (sometimes due to lead poisoning)
Normocytic	Hereditary spherocytosis Anemia of blood loss Glucose-6-phosphate dehydrogenase deficiency Autoimmune hemolytic anemia Aplastic anemia Anemia of chronic disease (less commonly microcytic) Sickle cell anemia Microangiopathic hemolytic anemia
Macrocytic	Megaloblastic anemia Nonmegaloblastic anemia (eg, alcohol-related)

Iron Deficiency

UNC SCHOOL OF MEDICINE

- Most common nutritional deficiency worldwide
  - Iron comes from our diet → leafy green vegetables and meat
- Most common cause of anemia
- Lack of iron inhibits formation of hemoglobin → decreased number of effective red blood cells

Iron Deficiency Anemia

UNC SCHOOL OF MEDICINE

- Definition: Body lacks sufficient iron to produce enough healthy red blood cells
- Most commonly seen in:
  - Persons who menstruate
    - Losing blood every month
  - Pregnant people
    - Need more iron to keep up with growing fetus
  - Patients with chronic blood loss (ex. Colon cancer)
    - Losing blood through gastrointestinal system
  - Children <5 years old
    - Cow's milk makes it harder for the body to absorb iron

Iron deficiency anemia: Pathophysiology

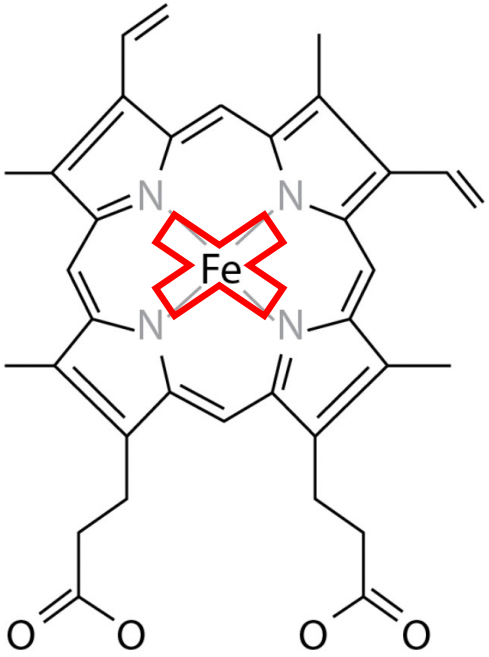


Figure 4

- Heme synthesis occurs via a biochemical pathway in which the final step involves iron being inserted into the heme ring
- Without adequate levels of iron, iron is not inserted into the heme ring
- Leads to decreased hemoglobin and eventually decreased RBCs → ANEMIA

Iron Deficiency Anemia: Pathology

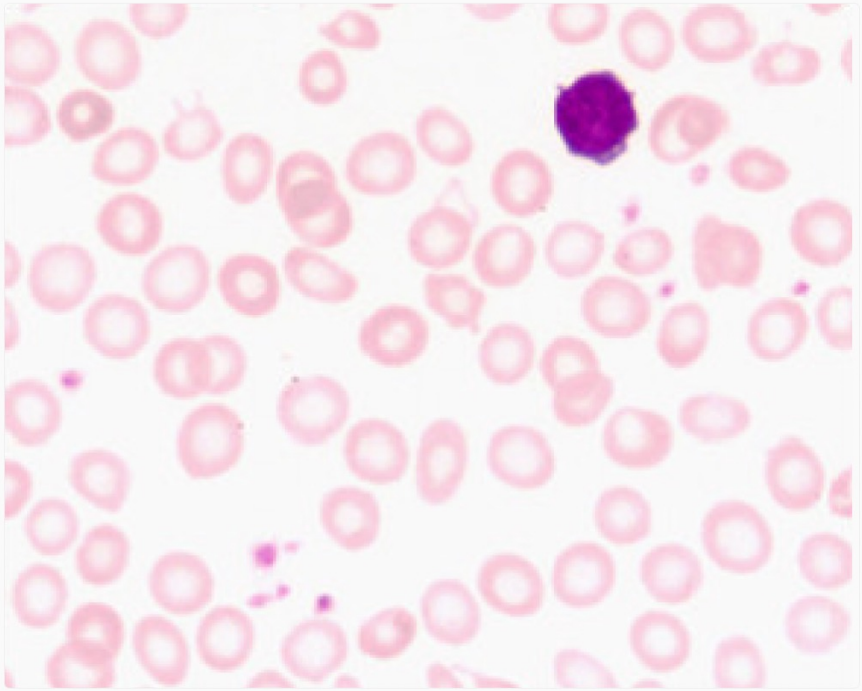


Figure 1

- RBCs are small or “microcytic”
- RBCs contain less hemoglobin ”hypochromic”

There are many different types of anemias

UNC SCHOOL OF MEDICINE

Table 1

Anemias Classified by Cause

Cause	Anemia
Blood loss	Just one anemia here: anemia of blood loss!
Decreased production	Iron-deficiency anemia Anemia of chronic disease Megaloblastic anemia Aplastic anemia Sideroblastic anemia
Increased destruction	Hereditary spherocytosis Glucose-6-phosphate dehydrogenase deficiency Sickle cell anemia Thalassemia Autoimmune hemolytic anemia Microangiopathic hemolytic anemia

Another Way to Classify Anemias: RBC Size

UNC SCHOOL OF MEDICINE

Table 2

Anemias Classified by Morphology	
RBC Size	**Anemia**
Microcytic	Iron-deficiency anemia Thalassemia Sideroblastic anemia (sometimes due to lead poisoning)
Normocytic	Hereditary spherocytosis Anemia of blood loss Glucose-6-phosphate dehydrogenase deficiency Autoimmune hemolytic anemia Aplastic anemia Anemia of chronic disease (less commonly microcytic) Sickle cell anemia Microangiopathic hemolytic anemia
Macrocytic	Megaloblastic anemia Nonmegaloblastic anemia (eg, alcohol-related)

- Iron Deficiency Anemia is typically a “Microcytic, Hypochromic Anemia”

Iron Deficiency Anemia: Physical Exam Findings

Figure 2

Conjunctival pallor

Figure 3

Koilonychia – fingernails bend upward in a concave, spoon-like shape

Iron Deficiency Anemia: Physical Exam Findings

UNC SCHOOL OF MEDICINE

- **Fatigue**
- **Pallor:** Especially visible in palmar creases, conjunctivae, and mucous membranes
  - **Conjunctival pallor** – reliable sign of anemia
- **Tachycardia**
- **Pica** - craving non-food substances like ice, clay, dirt

Iron Deficiency Anemia: Management

UNC SCHOOL OF MEDICINE

- Iron Supplementation is the mainstay of treatment
  - Usually oral iron
  - Severe cases may require transfusion and/or intravenous iron
- Identify the underlying cause
  - Why is the patient experiencing heavy menstrual bleeding?
    - Give oral contraceptives
  - Is the patient bleeding from the gastrointestinal system? If so, then is it from an ulcer? Cancer?
    - Get an endoscopy and colonoscopy
  - Is the child drinking too much cow's milk?
    - Limit cow's milk intake

There are many different types of anemias

UNC SCHOOL OF MEDICINE

Table 1

Anemias Classified by Cause	
Cause	**Anemia**
Blood loss	Just one anemia here: anemia of blood loss!
Decreased production	Iron-deficiency anemia Anemia of chronic disease Megaloblastic anemia Aplastic anemia Sideroblastic anemia
Increased destruction	Hereditary spherocytosis Glucose-6-phosphate dehydrogenase deficiency Sickle cell anemia Thalassemia Autoimmune hemolytic anemia Microangiopathic hemolytic anemia

Sickle Cell Disease (SCD): Epidemiology

UNC SCHOOL OF MEDICINE

- Inherited disorder of hemoglobin
- Affects millions of people worldwide
- Most common inherited blood disorder in the United States
  - Found in 1:3000 people
- 8% of Black people in US are carriers for sickle cell trait (one abnormal gene)

Figure 1

SCD Pathophysiology: Recall: Structure of Hemoglobin

UNC SCHOOL OF MEDICINE

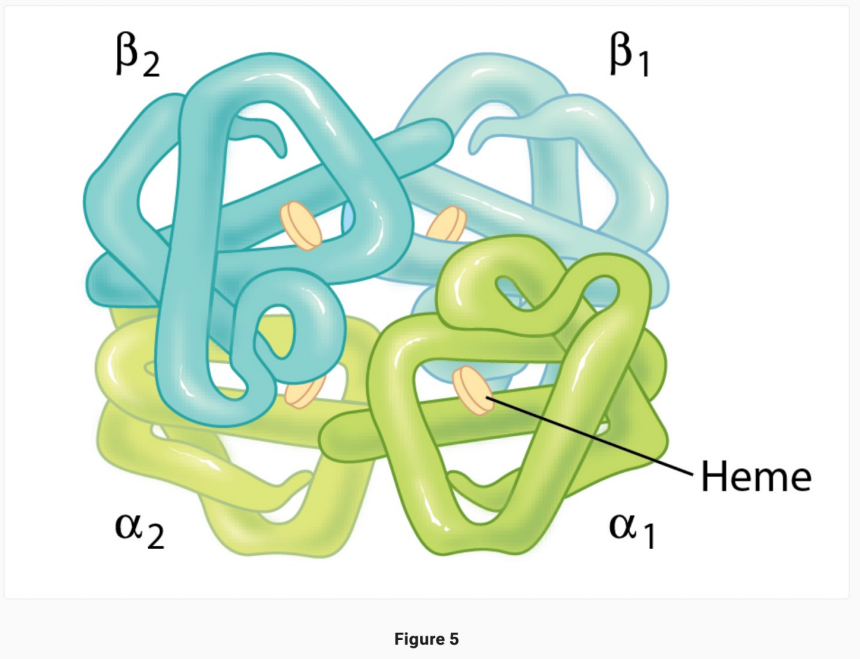


Figure 5

Four globin chains meet together to make one hemoglobin molecule

- Two beta globin chains and two alpha globin chains
- Heme sits tightly in the middle of each of the four chains
- Any changes to the chains can cause problems forming hemoglobin

Sickle Cell Disease: Pathophysiology

UNC SCHOOL OF MEDICINE

- Caused by a change to the DNA (point mutation) in the beta globin gene
- The mutation changes the amino acid from a glutamate to valine
- Valine does not like water!
- The valine in the beta globin chain hides from water within the RBC → especially in low oxygen states
- Changes the formation of the beta globin chain

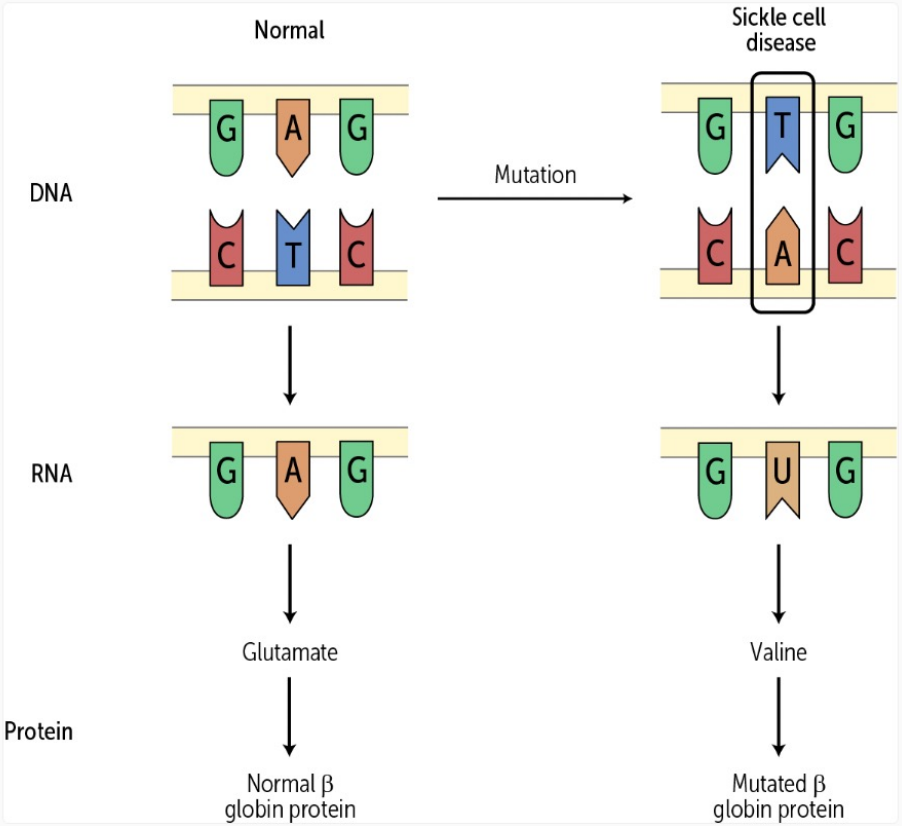
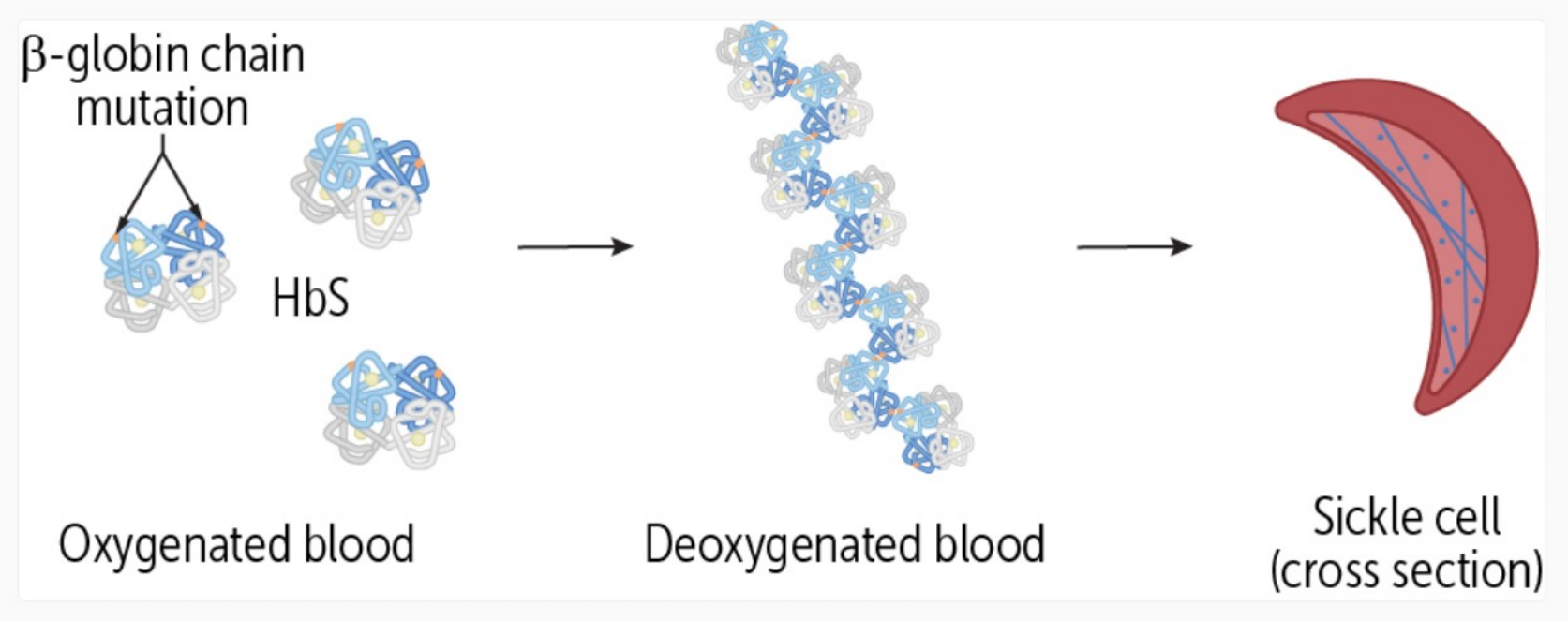
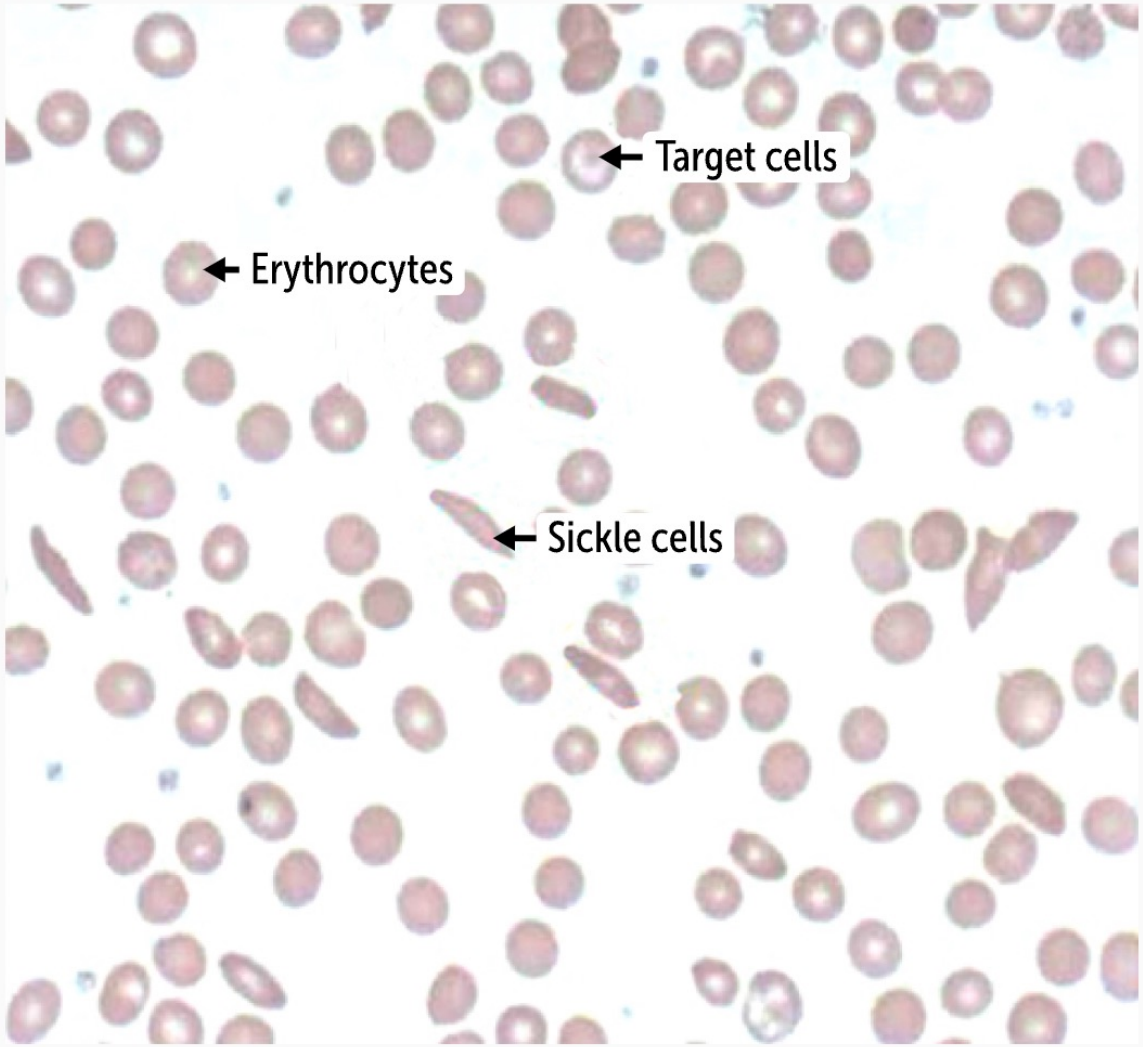


Figure 3

Sickle Cell Disease: Pathophysiology



The abnormal beta globin chains within hemoglobin crosslink up so that the valine can hide → RBC "sickles" due to rigid crosslinked hemoglobin.



QUIZ

Sickle Cell Disease: Pathophysiology

UNC SCHOOL OF MEDICINE

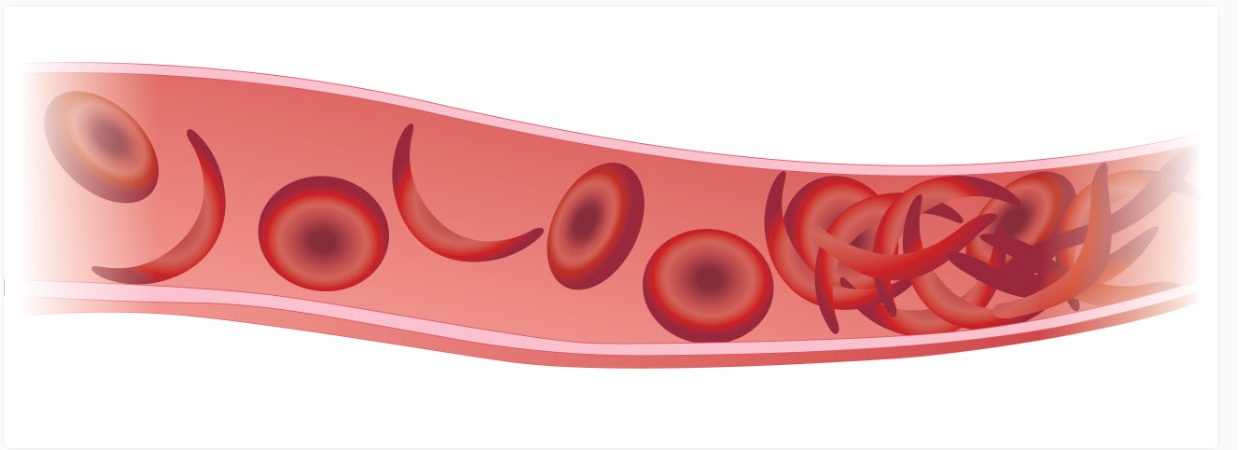


Figure 5

- Vaso-occlusive disease → decreased flexibility of RBCs → ischemia, infarction, pain
- Increased RBC destruction → anemia

Sickle Cell Disease: Inheritance

UNC SCHOOL OF MEDICINE

- Autosomal recessive
- Requires two abnormal copies of the beta globin gene (one from each parent)
- Sickle cell trait – one abnormal copy of the beta globin gene
  - Can have sickling during extended low oxygen states (ex. Exercise)

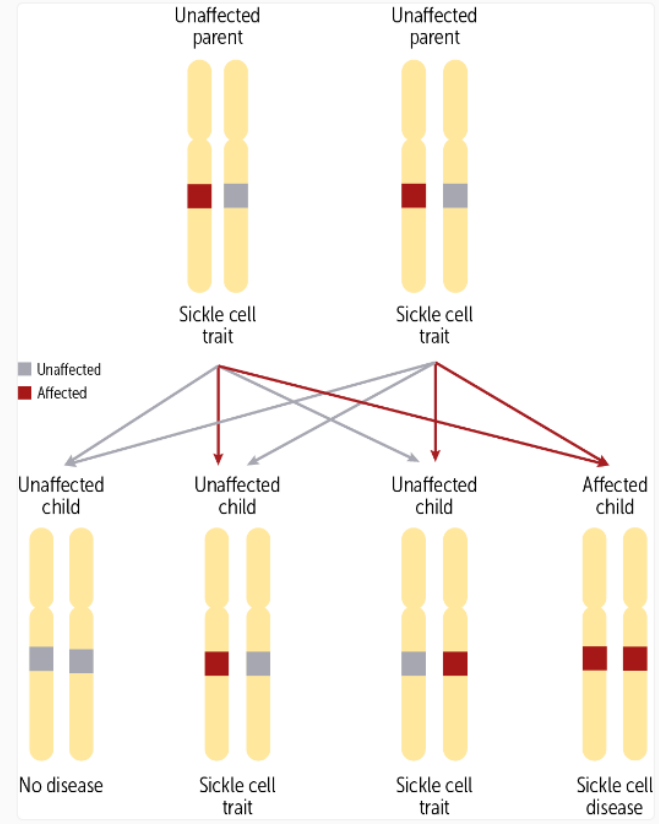


Figure 2

Sickle Cell Disease: Presentation

UNC SCHOOL OF MEDICINE

- General symptoms of anemia
- Episodes of sharp localized pain → vaso-occlusive disease complications
  - Asplenia
    - Repeated splenic infarctions causes spleen
    - Susceptible to certain infections
  - Acute chest syndrome
    - Clogged vessels in the lungs
    - Chest pain, shortness of breath, fever, decreased oxygen in the blood
    - Significant cause of hospitalization and mortality
    - Usually precipitated by an infection
  - Strokes
    - Due to occlusion of arteries in the brain
  - Dactylitis
    - Pain in bones of the hands and feet
  - Priapism
    - Painful erections in men due to occlusion of penile arteries

Sickle Cell Disease: Diagnosis

UNC SCHOOL OF MEDICINE

- Anemia on complete blood count
- Peripheral smear with sickled red blood cells
- Hemoglobin electrophoresis will show abnormal hemoglobin localization

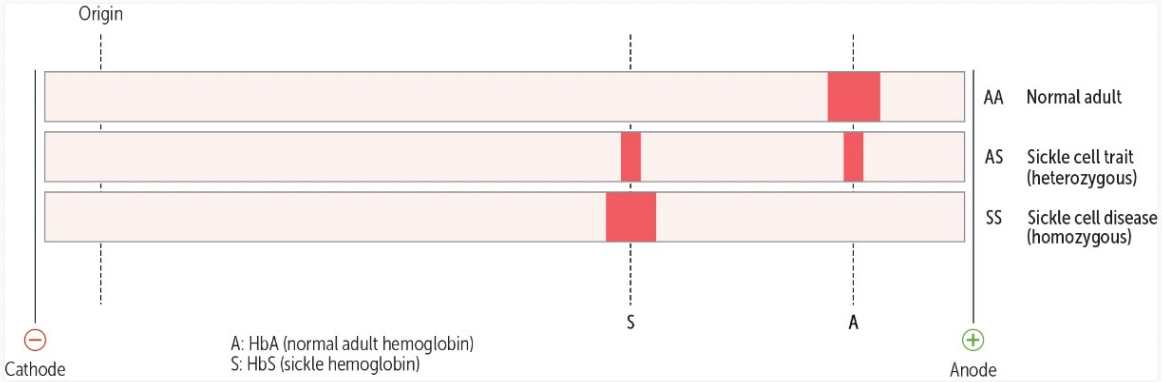


Figure 8

Sickle Cell Disease: Management

UNC SCHOOL OF MEDICINE

- **Prevent infection** from functional asplenia → vaccinate patients
- **Prevent pain crises** → stop smoking, avoid excess alcohol, stay well hydrated, avoid overly strenuous exercise
- **Hydroxyurea** → medication that increases a different type of hemoglobin that will not sickle
- **Treat anemia** → RBC transfusions
- **Treat acute pain episodes** → pain medication, RBC exchange transfusions
- **Cure** → Hematopoietic Stem Cell Transplant

Sickle Cell Disease: Gene Therapy

UNC SCHOOL OF MEDICINE

- Two FDA approved gene therapies for sickle cell disease
- **Casgevy (exagamglogene)**
  - Uses gene editing technology (CRISPR) to modify patient's stem cells to increase the production of a different type of globin chain instead of the beta globin chain
  - Fetal hemoglobin → two alpha chains and two gamma chains
  - Prevents sickling
- **Lyfgenia (lovotibeglogene)**
  - Uses a viral envelop to deliver a healthy copy of the beta-globin gene to a patient's stem cells
  - Stem cells can now produce RBCs with healthy hemoglobin
- Transformative for patients treated
  - Prevents severe vaso-occlusive crises
- Still a disparity in who can afford the treatment

Why is Sickle Cell Disease More Prevalent in the Black community?

UNC SCHOOL OF MEDICINE

- Likely evolutionary – geographic distribution of the sickle cell mutation in Africa correlates to areas where malaria infections are highly prevalent

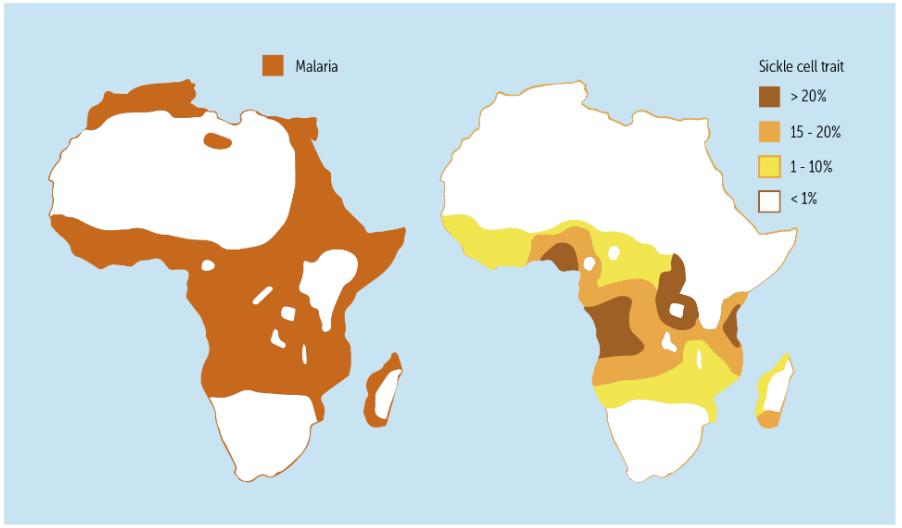


Figure 4

Why is Sickle Cell Disease More Prevalent in the Black community?

UNC SCHOOL OF MEDICINE

- Patients with SCD have some protection against malaria (common mosquito born illness in Africa).
- We aren't 100% sure why this happens.
- One theory is the parasite that causes malaria will decrease oxygenation within the RBC it infects.
- This will cause the cell to sickle and then be cleared by the spleen, limiting the parasite's ability to reproduce and infect the host.

The Stigma Surrounding Sickle Cell Disease

UNC SCHOOL OF MEDICINE

- **Definition:** Negative stereotypes, discrimination, or prejudice experienced by people with SCD
- **Impact:** Leads to social isolation, delayed care, and worse health outcomes

The Stigma Surrounding Sickle Cell Disease: Sources

UNC SCHOOL OF MEDICINE

- **Healthcare system:**
  - Mislabeling patients as “drug-seeking” during pain crises
  - Under-treatment of pain due to bias or mistrust
- **Community & society:**
  - Lack of awareness → misconceptions about contagiousness or lifestyle causes
  - Discrimination in school, work, relationships
- **Internalized stigma:**
  - Feelings of shame or guilt about the illness

The Stigma Surrounding Sickle Cell Disease: Consequences

UNC SCHOOL OF MEDICINE

- Delayed presentation to hospital during crises
- Avoidance of care (leading to more complications)
- Mental health burden: anxiety, depression
- Decreased quality of life

What can we do?

UNC SCHOOL OF MEDICINE

- **Education:** Raise awareness in schools, workplaces, and communities
- **Provider training:** Reduce bias, improve pain management practices
- **Support networks:** Patient advocacy groups, peer support programs
- **Policy change:** Protect against discrimination in employment & insurance

What about sickle cell trait?

UNC SCHOOL OF MEDICINE

Equity Issues Related to Sickle Cell Trait (SCT) and Associated Harms.*

Equity Issue	Harms
Mandatory testing of members of the U.S. military, sometimes accompanied by public identification of people with SCT	Members of the military with SCT may be treated differently from their peers; may face stigma, which could affect promotions; and may have their health information made public.
Mandatory testing of NCAA athletes in all divisions, with no waiver option	Athletes with SCT may be treated differently from their peers (e.g., they may have different training regimens). Testing costs money, and training may be delayed while programs await test results. Athletes may receive inadequate education about SCT.
Use of the phrase "exercise collapse associated with sickle cell trait" (ECAST)	There is a potential for anchoring bias, misdiagnosis, and inadequate treatment in cases of exertion-associated adverse events. SCT is treated as if it were a disease.
Requirements that hematopoietic stem-cell donors donate bone marrow and not peripheral-blood stem cells for transplantation	Although both approaches are safe overall, bone marrow collection is associated with a higher risk of complications.
Use of SCT as a cause of death for people who die in police custody	SCT can be used as a cover for abuse of Black people by law-enforcement officers, leading to a lack of accountability and justice.

* Information is from Ebert et al.,[2] Baker et al.,[3] and LaForgia and Valentino-DeVries.[4] NCAA denotes National Collegiate Athletic Association.

Further Reading:

- Carney BJ, Achebe MO, Haspel RL. **Sickle Cell Trait, Inequity, and the Need for Change.** *N Engl J Med*. 2024;391(21):1972-1974. doi:10.1056/NEJMp2408196

- Ortega RP. **Gaps remain in college sports' 15-year-old sickle cell policy.** *Science*. 2025;389(6763):864-865. doi:10.1126/science.aeb7968

Summary

UNC SCHOOL OF MEDICINE

- Hemoglobin carries oxygen around the body
- Anemia is defined as a decrease in red blood mass
- There are many causes of anemia
- Iron deficiency anemia is the most common cause of anemia
- Sickle cell disease is the most common inherited anemia
- Sickle cell disease is caused by a point mutation in the beta globin chain leading to crosslinking of hemoglobin inside the red cell

Questions?

UNC SCHOOL OF MEDICINE

- Thank you!