Sports Hematology Issues

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Learning objectives

- Describe the epidemiology, clinical presentation, diagnosis, and management of :
  - Physiologic anemia
  - Iron Deficiency
  - Foot strike hemolysis
  - Sickle cell trait/sickle cell anemia

Question:

- 21 yo female track athlete presents for consultation after screening labs showed a hematocrit of 32. The most common cause of low hematocrit in athletes is:

a) iron deficiency anemia
b) dilutional pseudoanemia
c) sickle cell trait
d) laboratory error

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Dilutional Pseudoanemia

- Most common cause of "anemia" in athletes [1]
- Hemoglobin concentration is lower than the usually defined limits of normal [1]
- Red cell mass is actually unchanged or even expanded
  - Not decreased as it is in most true anemias [2-4]

1. Shaskey DJ. *Sports Med* 2000;29(1):27-38
2. Wells CL. *Eur J Appl Physiol* 1982;48:41-9
3. Dill DB. *Med Sci Sports* 1974;6:1-7
4. Weight LM. *Eur J Appl Physiol* 1991;62:358-62

Dilutional Pseudoanemia

- Plasma volume expansion has a larger percentage increase compared to red cell mass expansion [1]
- Plasma volume expansion may be 6-25% greater than baseline [2]
  - Pathophysiology poorly understood
  - Occurs within 3 hours following acute exercise
  - Degree of expansion correlates with amount and intensity of exercise [3]

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1. Shaskey DJ. *Sports Med* 2000;29(1):27-38
2. Balaban EP. *Clin Sports Med* 1992;11(2):313-25
3. Eichner ER. *Physician Sports Med* 1986;14(9):122-30

Dilutional Pseudoanemia

- Favorable adaptation to exercise [1]
  - Decreased viscosity allows for greater cardiac output
  - Greater overall oxygen delivery despite lower hemoglobin concentration
- Causes a mild anemia at best
- Should not affect MCV, Ferritin, RDW, or haptoglobin
- No associated symptoms
- Should normalize in 3-5 days if training stops

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1. Pate R. *Physician Sports Med* 1983;11:115

Case 1.

- 19 yo female nordic skier presents with fatigue, impared ability to train.
- No change in training volume/intensity
- Lives at 4500 ft. Trains at 7800 ft. No change.
- Normal menstrual cycles
- PE: WNL
- Labs: Hb 13.8, Hct 39, ferritin 19
- **What do you do?**

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Iron Deficiency

- Iron plays a key role in sports performance
- Iron deficiency is most prevalent nutritional deficiency in the US
  - 20% menstruating females
  - Iron deficiency with anemia prevalent in 1-3% of population
  - Up to 82% female athletes have ferritin <25 µ/L [1]

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Iron Deficiency in Athletes

- Where is the iron loss?
  - Nutritional Deficits
  - Blood Loss- menstrual, GI, GU
  - Iron regulatory hormones
  - Malabsorption

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Celiac disease and anemia

- Multiple mechanisms
  - Reduced absorption of supplemental iron
  - Malabsorption of B12/folic acid
  - Component of anemia of chronic disease
  - GI blood loss through intestinal inflammatory changes- unclear

Hepcidin (AKA LEAP-1 or HAMP)

- Key hormonal negative regulator of intestinal iron absorption
- Increases with inflammatory stimuli (cytokine IL-6) or elevated iron (acute phase reactant)
- Peaks 3-6 hours after exercise
  - Increased in low energy availability
- Reduces intestinal iron absorption
- Hepcidin levels are lower in the morning, increase throughout the day
  - Consider timing of meals

Sandstrom et al April 2017 Clin J Sport Med

Iron Deficiency in Athletes

- Laboratory evaluation:
  - CBC
  - Serum Iron, TIBC, and Ferritin
- Microcytic anemia with low ferritin (<10 µ/L) and low serum iron
  - Elevated TIBC
  - Low iron saturation (Fe/TIBC <15%)
- Nonathletic source must be adequately ruled out

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Sim M, et al. Iron considerations for the athlete: a narrative review. Eur J Appl Physiol. 2019

Iron-Deficiency Anemia

- Treatment
  - Adequate dietary intake in foods with Fe
    - Recommended Dietary Allowance
      - Women 14-18: 15 mg/day
      - Women 19-50: 18 mg/day
  - Consumption of foods that enhance Fe absorption
    - Foods with ascorbic acid (eg. orange juice)
  - Fe supplementation
    - Ferrous sulfate, ferrous bisglycinate
    - 6-12 months to replete stores
- Expect to see improved Hgb/Hct within 12 weeks of tx

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McClung JP. Iron status and the female athlete. *Journal of Trace Elements in Medicine and Biology*, Vol 26, Issues 2-3, June 2012, 124-6
Robertson JA, Ray TR. Hematologic Problems in Athletes. Netter's Sports Medicine. 2010. Chpt 26. 209-211
Shaskey DJ, Green GA. Sports Haematology. *Sports Med* 2000;29(1):27-38.

Non-anemic Iron Deficiency

- Controversial- ferritin low, Hgb/HCT normal
- Rat model- may lead to exercise dysfunction via muscle enzymatic disruption [1]
- Impact on sports performance is controversial
  - Early studies show no correlation between IDNA and performance
  - Some research suggests impact on endurance activities in those with IDNA
  - Early management prevents development of IDA

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1. Finch CA. *J Clin Invest* 1976;58:447-53
2. Newhouse IJ. *MSSE* 1989;21:263-8
3. Celsing F. *MSSE* 1986;18:156-61
4. Matter M. *Clin Sci* 1987;72:415-22
5. Dellavalle DM, Haas JD. Med Sci Sports Exerc. 2012 Aug;44(8):1552-9.6.
6. Dellavalle DM, Haas JD. Med Sci Sports Exerc. 2013 Nov 5. [Epub ahead of print]

Serum Ferritin	Supplementation Plan (ferrous sulfate)	Supplementation Plan (ferrous bisglycinate)
<12 ug/L	Supplement with: • 100-150 mg/day of elemental iron (ex: 500-750mg/day of ferrous sulfate) Continue to reassess every 12 weeks (iron deficient with or without anemia).	Supplement with: • 50 mg/day of elemental iron Continue to reassess every 12 weeks (iron deficient with or without anemia).
12-20 ug/L	Supplement with: • 65-130 mg/day of elemental iron (325-650 mg/day ferrous sulfate) Continue to reassess every 12 weeks (iron deficient with or without anemia)	Supplement with: • 25-50 mg/day of elemental iron Continue to reassess every 12 weeks (iron deficient with or without anemia).
21-35 ug/L	Supplement with: • 25-65 mg/day of elemental iron (125-325 mg/day ferrous sulfate) Continue to reassess every 12 weeks (iron deficient with or without anemia).	Supplement with: • 25 mg/day of elemental iron Continue to reassess every 12 weeks (iron deficient with or without anemia).
>35 ug/L[4,5,7]	**Previously Deficient:** • Maintain current dose until 3 months of normal tests (>35 ug/L)	**Previously Deficient:** • Maintain current dose until 3 months of normal tests (>35 ug/L)

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Patient-oriented approach

- With symptoms, evaluate:
  - CBC (MCV- low)
  - Ferritin- low
  - Serum Iron (low) and TIBC (high)
  - Consider hemoglobin electrophoresis to rule out thalassemia or sickle cell disease
  - If iron deficiency found, rule out GI or GU blood loss before supplementation

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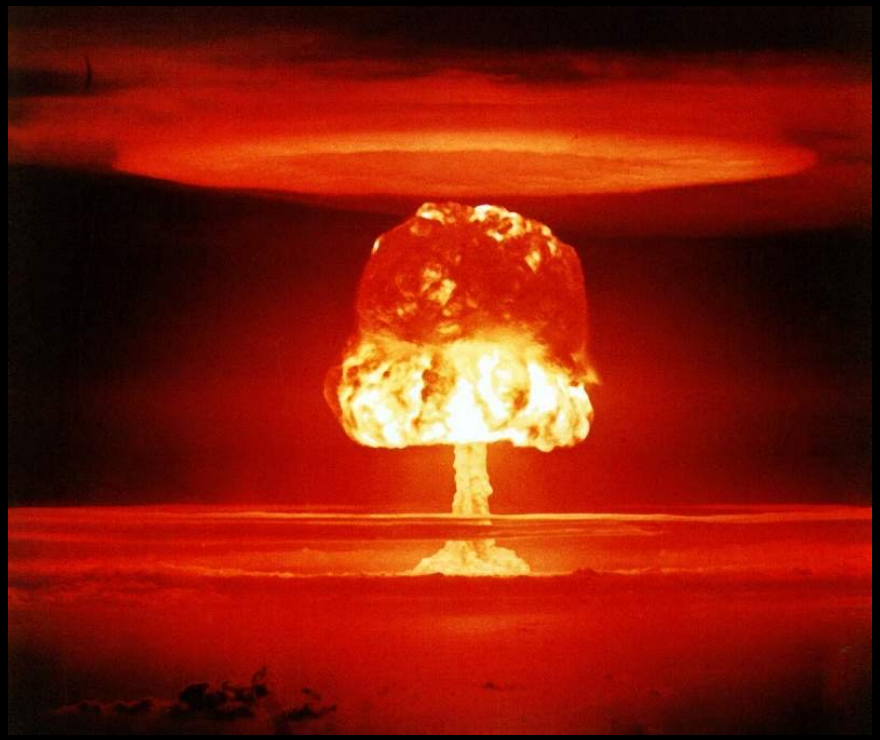
Shaskey DJ. *Sports Med* 2000;29(1):27-38

Hemolysis



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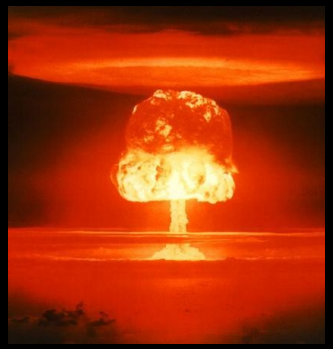
Hemolysis

- Described in 1881 in a soldier who had repeated attacks of hemoglobinuria after marching [1]
- Intravascular hemolysis linked to mechanical trauma ("footstrike hemolysis") [2]
- Elite endurance runners most susceptible, but has been described in swimmers, triathletes, and aerobic dancers [3-5]

1. Fleischer R. Berl Klin Wochenschr 1881;18:691
2. Shaskey DJ. *Sports Med* 2000;29(1):27-38
3. O' Toole ML. *MSSE* 1988;20:272-5
4. Selby BG. *Am J Med* 1986;81:791-4
5. Schwellnus MP. *Physician Sports Med* 1989;17(8):55-67



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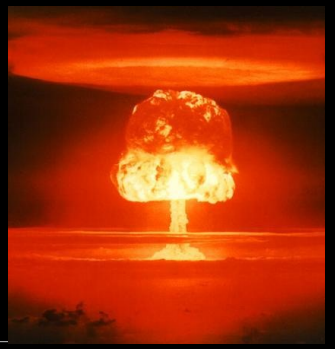
Hemolysis

- Anemia is macrocytic with increased reticulocyte count
  - Selective destruction of older, smaller RBCs
- Hemoglobinuria may be present
- If hemolysis is suspected, labs should be obtained within hours of a workout
  - Serum **haptoglobin** will be reduced
    - Scavenger for free iron- binds hemoglobin
    - Circulating haptoglobin is used faster than production



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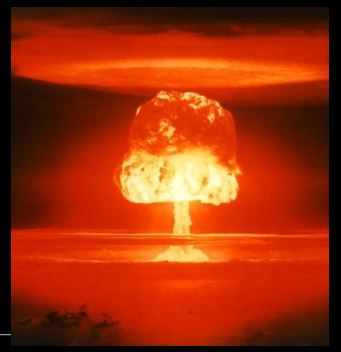
Shaskey DJ. *Sports Med* 2000;29(1):27-38

Hemolysis

- Clinically significant hemolysis resulting in hemoglobinuria and anemia is rare[1]

- Hemolysis significant to cause anemia should prompt work-up to exclude inherited membrane defects
  - Hereditary spherocytosis
  - Paroxysmal nocturnal hemoglobinuria [1]

1. Balaban EP. *Clin Sports Med* 1992;11(2):313-25



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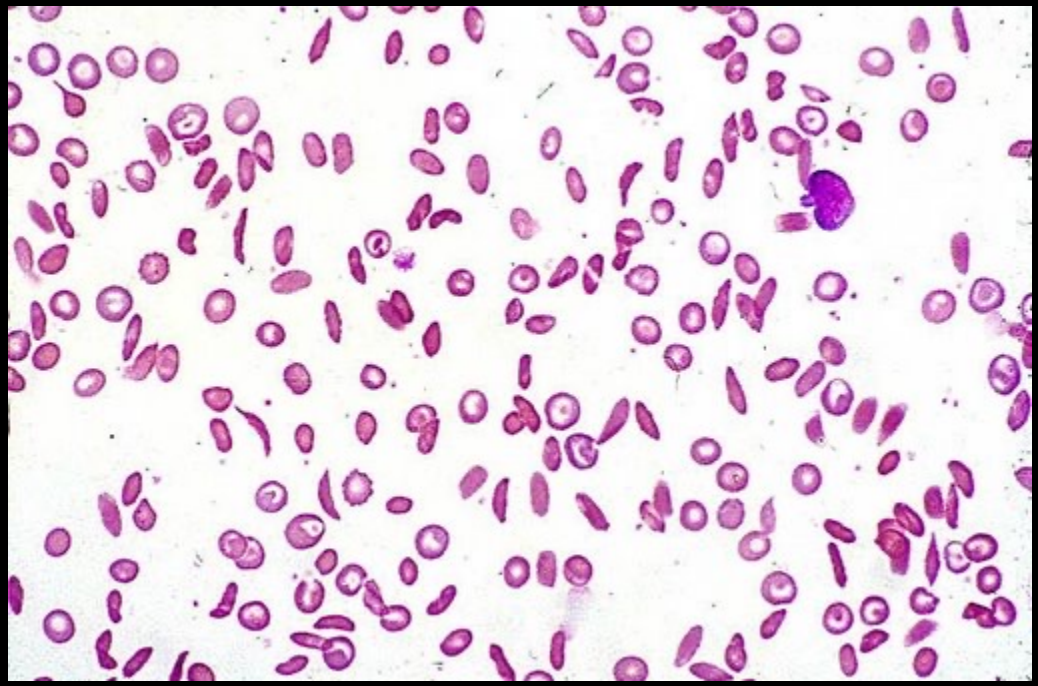
Sports Related Anemias

Type	Frequency	MCV	Haptoglobin	Ferritin
Dilutional Pseudoanemia	**Common**	Normal	Normal	Normal
Iron Deficiency	**Common**	**Low**	Normal	**Low**
Athletic Hemolysis	Rare	**High**	**Low**	Normal

Shaskey DJ. *Sports Med* 2000;29(1):27-38

Sickle cell



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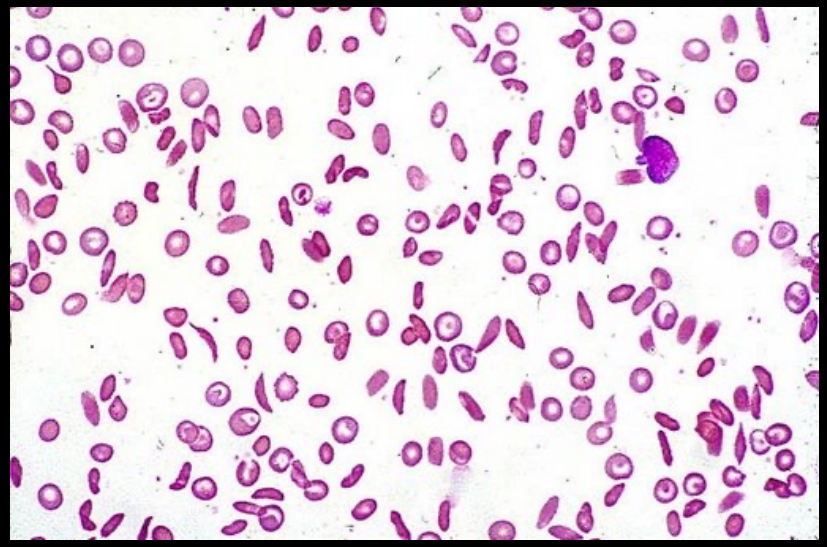
Definition

Sickle Cell **Disease**:

- Genetic hemoglobinopathy
- Results in deformation, increased rigidity, and destruction of RBCs
- Vasoocclusive and pro-inflammatory disease process
- Chronic multi-organ system disease
- Severe morbidity and mortality



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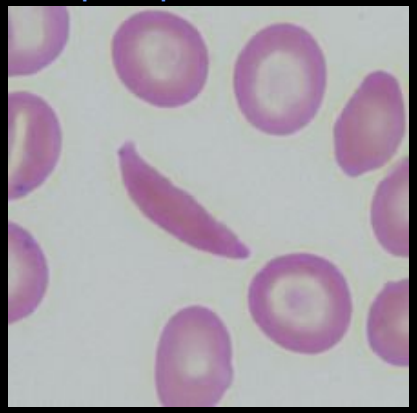

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Madigan and Malik, *Expert Rev in Mol Med* 8: (9) 1-18, 2006

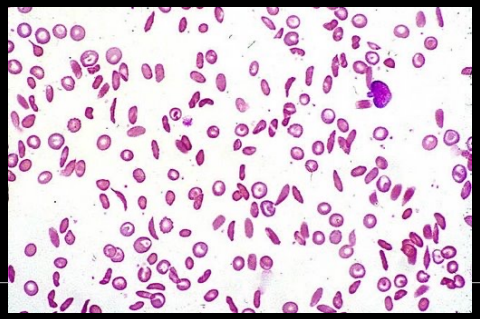
Sickle Cell TRAIT

- Sickle Cell **Trait**:

  - Controversial
  - Usually asymptomatic and without anemia
  - Pathology usually limited to renal and splenic vascular beds

Sickle Cell Mutation:

- β-globin gene (chromosome 11q) mutation
  - $\alpha_2\beta_2$ = normal hemoglobin
  - $\alpha_2\beta S$ = heterozygote = Sickle trait
  - $\alpha_2 S_2$ = homozygous recessive = Sickle cell disease
- Autosomal recessive genetic disease
  - Mutations represent different regional genetic characteristics
  - Severity of STC mutation is variable and may confer different risk to an individual athlete



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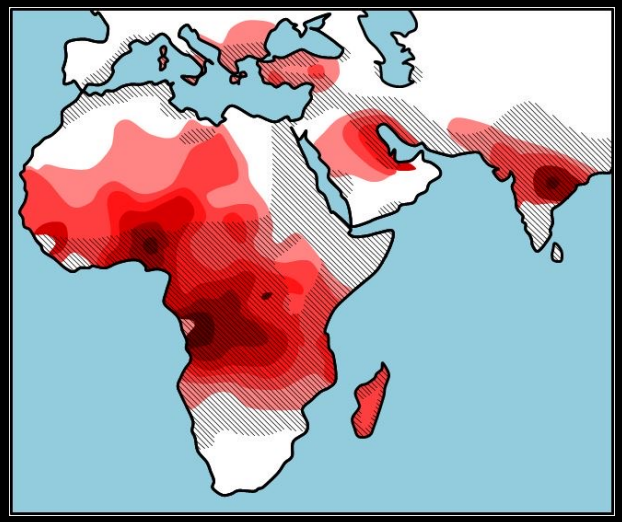
Asplund, O'Connor, Sports Health 2016

Epidemiology

Worldwide:

- Areas of Prevalence
  - Sub-Saharan Africa
    - SCT frequency 10-40%
    - Highest rates in Ghana,
    - Nigeria, Uganda
    - SCD frequence </= 2%



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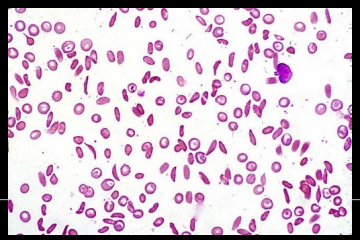
USA:

- Sickle cell trait = 2 .5 - 3 million (1 in 12) African Americans
- Sickle cell disease = 72,000 (1/500 African American births)



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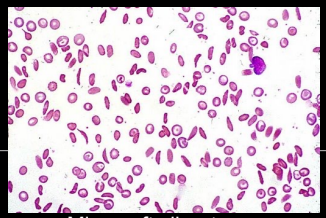
Clinical Presentation

Sickle Cell Trait:

- Increased risk of:
  - UTI in women
  - Hematuria (4X risk)
  - Hyposthenuria
  - Splenic sequestration / infarction at high altitude (>10,000 ft)
  - Exertional Heat Illness / Sudden Death (37 X increased risk in DI football players)



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Sickle Cell Trait in Military/Sport

- 1970 Four Deaths in Military Recruits
  - 4 more with exertional rhabdomyolsis
- 1974 Colorado football player died
- 1970-1985 Several collapses and deaths in military
- Air Force temporarily banned SCT applicants

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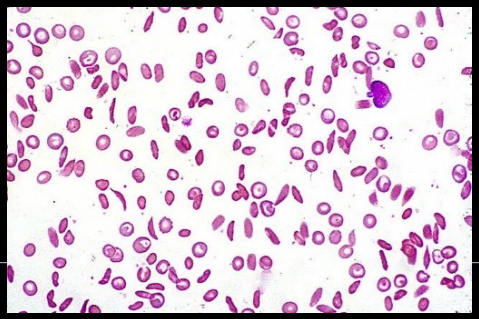
Pathophysiology

- Oxygen displaced from HbS:
  - Strenuous exercise
  - Lactic acidosis
  - Increased tissue temperatures
  - Dehydration
  - Decreased blood volume secondary to muscle demands

- Sickling leads to vascular obstruction -> ischemic rhabdomyolysis

NEJM 1985;312(25):1623-31
Curr Sports Med Rep 2007;6(3)134-135
Am J Hematol 2000;63:205-11



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ECAST

- Exertional collapse associated with SCT
  - Risk factors
  - Clinical features
  - management

ECAST

- Risk factors:
  - Heat
  - Altitude
  - Early season (deconditioned athletes)
  - High intensity training
    - Repeated sprints
    - Fast tempo multi-station drills
    - Near maximal exertion

ECAST

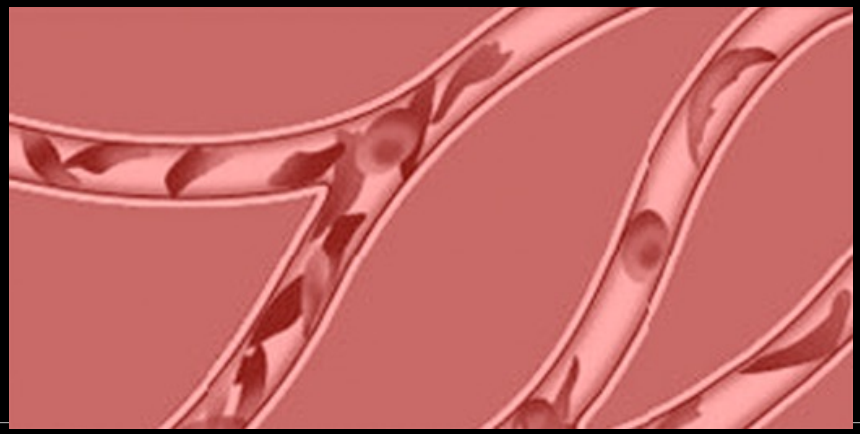
- Clinical features:
  - Athlete has muscle pain and weakness
  - Muscles may look/feel normal
    - Differs from cramps (no locked up muscles)
  - Athlete slumps to ground but usually can communicate
    - Differs from cardiac arrest
  - Tachypnea is present secondary to lactic acidosis, but athlete moves air well
    - Differs from acute asthma attack
  - Rectal temp <103
    - Differs from heat stroke

ECAST

- Management
  - ABCs
  - Cool if appropriate
  - Oxygen
  - IV access
  - Attach AED
  - ED transport if not rapidly improving

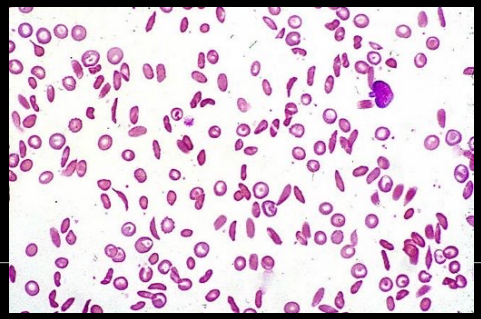
NCAA Sickle Cell testing

- Conducted on all US newborns
- Required for all NCAA athletes now (or sign a waiver)
  - All athletes allowed to compete



Precautions for SCT athletes

- "Universal Precautions"
- Acclimatize gradually
- Monitor hydration
  - Avoid diuretics
  - Consider testing urine concentrating ability in first AM void
- Modify workouts, condition gradually
  - Avoid sprints or repeats over 500m, and timed runs over ½ mile



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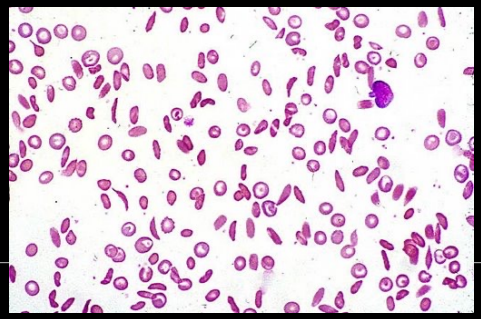
Precautions for SCT athletes

- No participation during illness
- Avoid or acclimatize to altitude
- If cramping, heat illness or unusual symptoms
  - IV fluids, supplemental O_2, cooling
  - If no improvement, transport to ED



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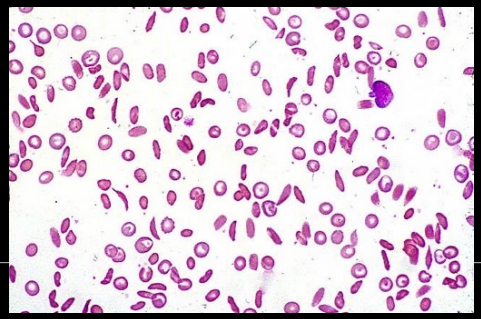
Precautions and Screening

- Does it help?
  - No prospective data in sports
- After military implemented protocols, number of cases reduced
  - 1982-1986 compared with 1977-1981
  - Rate dropped from 32 to 14 per 100,000



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Semin Hematol 1994;31(3):181-225

Summary

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  - Iron Deficiency
  - Foot strike hemolysis
  - Sickle cell trait/sickle cell anemia

Thank you

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