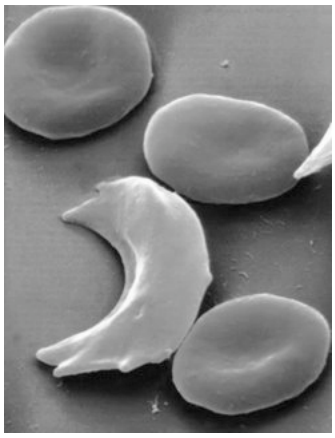
Evolution of Sickle Cell Disease

ERYTHROCYTE POLYMORPHISMS AND MALARIA

10 year old girl

- Goes to clinic with severe chest pain
- Many visits for joint pains & exhaustion
- Labeled a hypochondriac
- Blood count revealed low rbcs

Blood smear



Sickle Cell Disease

- 70 million Americans have Sickle Cell Disease
- 2 million are carriers of Sickle Cell Trait
- Most have SubSaharan African Ancestry
- 1 in 12 African Americans has Sickle Cell Trait

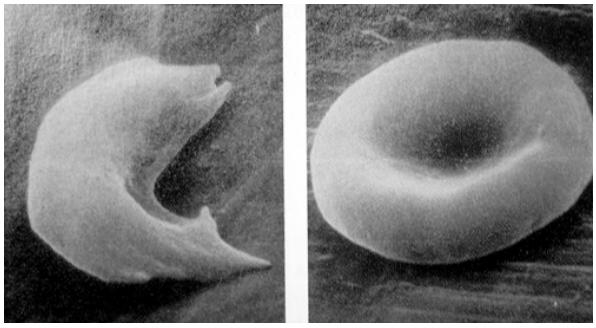
Sickle Cell Disease

- Catastrophic disease of children
- Attacks occur when oxygen levels in blood drop
- Red blood cells deform & assume sickle shape
- Sickle cells tend to trap other blood cells, cause "sludging".
- Severe sludging deprives tissues of oxygen and can kill muscle and bone.

Sickle cell disease – Why?

- Proximate hypothesis?
- Ultimate hypothesis?

Hemoglobin



Hemoglobin

- Oxygen transport –

Picks up oxygen from the pulmonary veins – drops off oxygen in tissues and capillary beds

- Contains iron
- Red blood cells

Mutation of Beta Hemoglobin

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183944_Translat  MVHLTPVEKSAVTAXWGKVNVDEVGGEALGRLLVVYPWTQRFFESFGD
29436_Translate  MVHLTPEEKSAVTALWGKVNVDEVGGEALGRLLVVYPWTQRFFESFGD
consensus        MVHLTP-EKSAVTAlWGKVNVDEVGGEALGRLLVVYPWTQRFFESFGD

183944_Translat  TPDAVMGNPKVKAHGKKVLGAFSDGLAHLDNLKGTFATLSELHCDKLH
29436_Translate  TPDAVMGNPKVKAHGKKVLGAFSDGLAHLDNLKGTFATLSELHCDKLH
consensus        TPDAVMGNPKVKAHGKKVLGAFSDGLAHLDNLKGTFATLSELHCDKLH

183944_Translat  PENFRLLGNVLVCVLAHHFGKEFTPPVQAAYQKVVAGVANALAHKYH
29436_Translate  PENFRLLGNVLVCVLAHHFGKEFTPPVQAAYQKVVAGVANALAHKYH
consensus        PENFRLLGNVLVCVLAHHFGKEFTPPVQAAYQKVVAGVANALAHKYH
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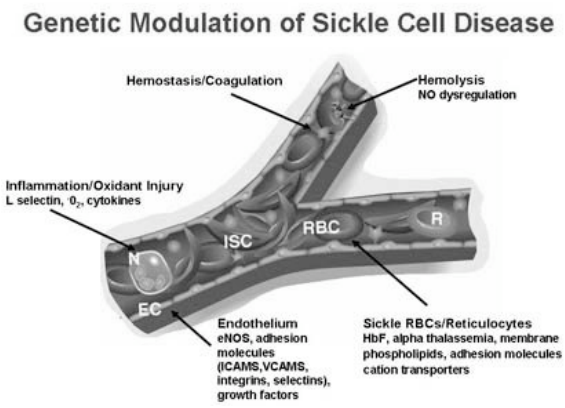
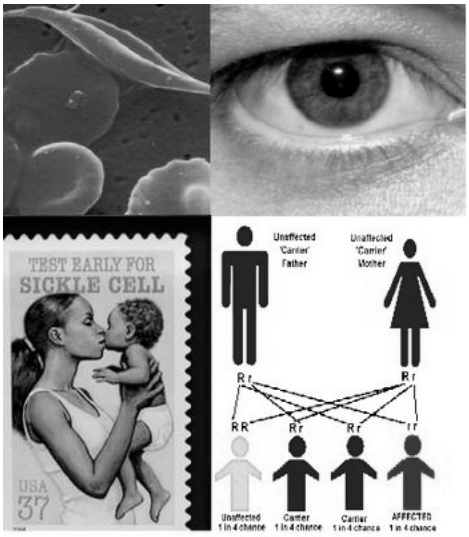
Blockage of circulation



Human Variation

- HbAA – homozygote "normal hemoglobin"
- HbAS – heterozygote sickle cell trait
- HbSS – homozygote sickle cell



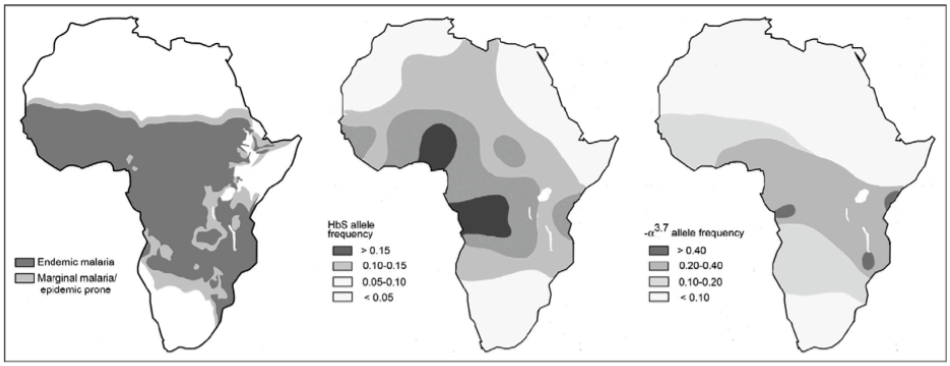
Inheritance

- Sickle Cell is inheritence is autosomal recessive
- Hb AA
- Hb AS – usually no symptoms
- Hb SS – manifests as sickle cell disease

Sickle Cell Disease

- High Mortality:
- Males with HbSS Age 42 years
- Females with HbSS Age 48 years
- Anemia
- Chest Pain
- Stroke
- Susceptibility to Bacterial Infections

Geography



Maps showing the correlation between the geographic incidence of malaria and the allele frequencies for HbS and α^{+}-thalassaemia in sub-Saharan Africa. Deletions of the $-\alpha^{3.7}$ type cause most α^{+}-thalassaemia in Africa. Reprinted by permission from Macmillan Publishers Ltd: *Nature Genetics* [68], copyright (2005).

Geography

- SCD occurs in places with malaria
- First described in southern Italy
- Then noticed in subsaharan Africa
- Sickle cell trait absent in places like Kenyan highlands where mosquito and malaria absent

Inheritance

- Sickle Cell is inheritence is autosomal recessive
- Hb AA
- **HB AS – BENEFIT IN MALARIA?**
- Hb SS – manifests as sickle cell disease

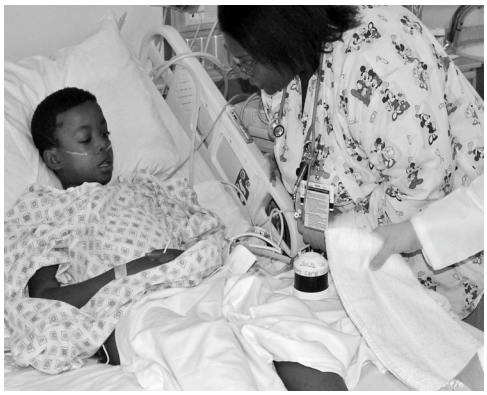
- Concept – balanced polymorphism
- Heterozygous advantage.

Another Case

- January 2006, a US family of 5 kids visit Nigeria
- Pre-trip: pediatrician gives antidiarrheals only
- No chemoprophylaxis
- 3 kids all given Fansidar for fever during trip.
- Kids felt better

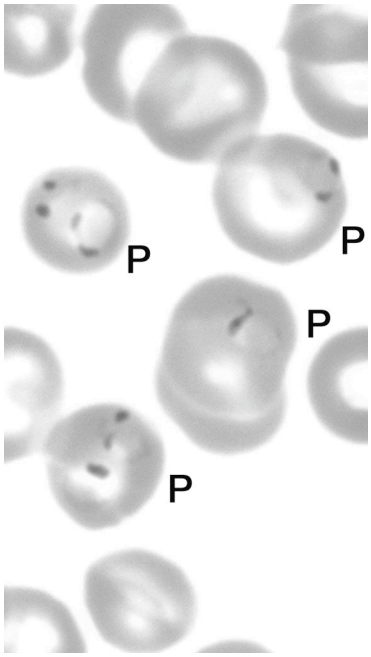
3 had return of fever in US

- Diagnosed with flu
- Given antibiotics at the local clinic
- Then they got sicker
- Mom notices 1 child is very weak and has yellow eyes!



Yellow Kid

- Yellow pupils
- Anemic
- Low Blood Sugar
- 1 in 20 rbcs parasitized
- Placed on Ventilator
- Transfused
- All 5 kids tested pos for falciparum malaria

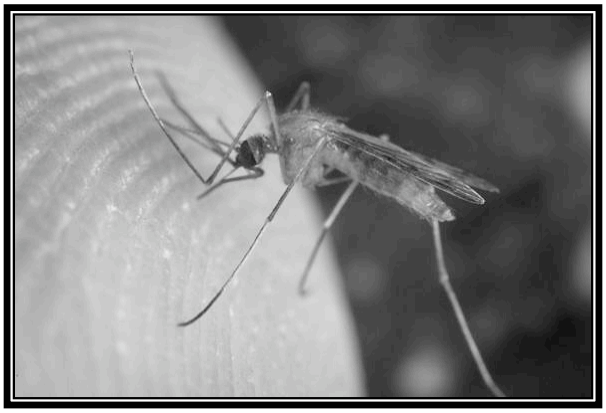


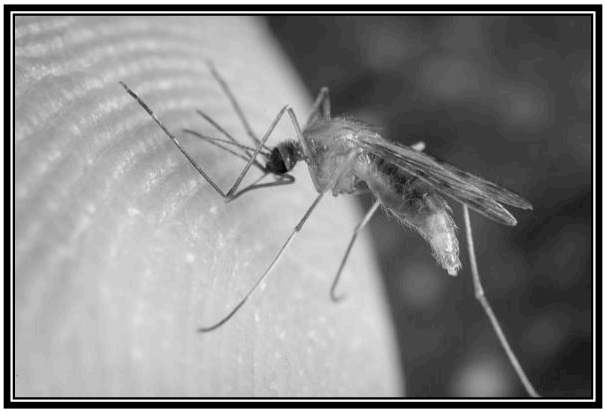
Malaria

- 400 million cases worldwide
- Malaria kills 1,500,000 yearly
- Young children and pregnant women
- Immunity partial, not durable
- 30,000 travelers: preventable illness

Malaria Vector & Pathogen

- Female Anopheles - Crepuscular hours.
- Congenital and transfusion - related cases
- Autochthonous: single mosquito transmits disease from 1 human to another





Severe Malaria

- Cerebral malaria: seizures, coma
- Severe anemia, red cells burst
- Hemoglobin in urine
- Fluid in lungs
- Loss of platelets
- Cardiovascular collapse and shock
- Blood becomes acidic

Malaria Pathogenesis

- Malaria parasites digest RBC proteins and use glucose to lactic acid as energy, thus hypoglycemia & acidosis.
- Injure RBC membrane: hemolysis, splenic clearance & anemia.
- Makes blood cells sticky - obstruct microcirculation
- Thrombocytopenia - splenic sequestration

Malaria benefit?

- Carriers of sickle cell trait have better survival from early bouts of malaria
- Could protection from malaria be selective force that maintains sickle cell rbc mutation in the population?

HbSS

- Full blown sickle cell disease
- Increased mortality from sickle cell attacks.
- In locations like Chicago, with no malaria, this genetic polymorphism would be subject to negative selection.
- What about in coastal Kenya?

HbAS

- Admitted to hospital less in malarious regions
- Die less often than HbAA in malarious regions
- Protect against severe malaria infection
- Infected rbcs sickle 40 times more readily than non infected cells
- Decreased parasite reproduction
- Increased clearance from the population.

Selection for HbAS

- Outweighs negative selection for HbSS
- Maintains HbS allele in population
- Frequency of allele is dependent on presence of malaria
- Balanced polymorphism

So how does HbAS protect against malaria?

- Evolutionary hypothesis can lead to insights into the proximate mechanisms of disease.
- Physiology and pathophysiology intersect…

Sickle Cell Anemia HbSS:

- Cells sickle – cause obstruction of microcirculation
- Anemia - Sickled cells have enhanced removal from circulation
- Increased phagocytosis of rbcs
- Increased oxidative stress on rbc membrane
- Spelenic sequestration of rbcs

Malaria: Sickle trait promotes removal of parasites!

- HbSS without malaria:
- Cells sickle – cause obstruction of microcirculation
- Anemia - Sickled cells have enhanced removal from circulation
- Increased phagocytosis Increased oxidative stress on rbc membrane
- Sequestration of abnormal rbcs

- HbAS and Malaria:
- Cells sickle – cause obstruction of microcirculation
- Anemia - Sickled cells have enhanced removal from circulation
- Increased phagocytosis
- Increased oxidative stress on rbc membrane
- Sequestration of abnormal rbcs

Other polymorphisms that may protect against malaria

Membrane proteins
Duffy blood-group negativity
Gerbich blood group negativity
Ovalocytosis as a result of deletions in the band 3 gene
Complement receptor proteins
RBC enzymes
Glucose-6-phosphate dehydrogenase deficiency
Pyruvate kinase deficiency
Haemoglobinopathies
Structural haemoglobin variants
Haemoglobin C
Haemoglobin E
Haemoglobin S
The thalassaemias
α-thalassaemia

Language

- Compare:
- Red blood cell defects and malaria

  Mol Biochem Parasitol. 2006 Oct;149(2):121-7. Epub 2006 Jun 9
- Erythrocyte variants and the nature of their malaria protective effect

  Cellular Microbiology 7 (6): 753-763 2005

Host defenses or pathogen virulence factors?

Genes that cause disease

- If they are common, they probably have some current or historical selective pressure that keeps them around
- Deleterious mutations occur at rates 1:50,000
- Some genes are very frequent e.g. 20% of population or more: raise questions

Factor V Leiden

- Most common hypercoagulable state that associated with Deep Vein Thrombosis
- Way too common to be a sporadic mutation – up to 20% in some populations
- Positive selective pressure promotes its persistence?
- What might that be?

Summary

- Malaria – sickle cell trait is a balanced polymorphism
- Genetic polymorphisms ask evolutionary question – what selective pressure or benefit keeps them in population
- Frequency of polymorphism is a clue