Sickle cell refers to an allele that affects the β-chain of hemoglobin.

- The allele, $S$, confers resistance to malaria.
- But there is a pleiotropic effect of the allele when homozygous that causes severe anemia.

Actually, there are 3 alleles at the β locus:

- $A$ - "normal", susceptible to malaria when $AA$.
- $S$ - "sickle-cell".
- $C$ - recessive, gives high resistance when homozygous.

**Fitnesses of genotypes given below**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Fitness</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>$AA$</td>
<td>0.9</td>
<td>Susceptible</td>
</tr>
<tr>
<td>$AS^+$</td>
<td>1.0</td>
<td>Resistant</td>
</tr>
<tr>
<td>$SS$</td>
<td>0.2</td>
<td>Anemia</td>
</tr>
<tr>
<td>$AC$</td>
<td>0.9</td>
<td>Susceptible</td>
</tr>
<tr>
<td>$SC$</td>
<td>0.7</td>
<td>Anemia</td>
</tr>
<tr>
<td>$CC^+$</td>
<td>1.3</td>
<td>Highly resistant</td>
</tr>
</tbody>
</table>

**Note:** Overdominance for fitness

**Note:** Highest fitness

From Templeton, A. R.
When Bantu-speaking peoples of Africa expanded into West-Central Africa, malaria was not a problem. However, with their introduction of slash-and-burn agriculture they established a "new" environment ripe for malaria.

**Initial (Before Slash-and-Burn) Allele Freqs.**

- $A$, near unity
- $S$, very rare
- $C$, very rare

Let

- $p = \text{freq of } A$
- $q = \text{freq of } S$
- $r = \text{freq of } C$

Now, remember our ol' friend, $\Delta q$?

- For two alleles we had

$$\Delta q = q' - q = \frac{8[p w_{12} + q w_{22}]}{\overline{w}} - q$$

where $\overline{w} = p^2 w_{11} + pq w_{12} + q^2 w_{22}$

- Expanding to 3 alleles gives

$$\Delta q = (q' - q) = \frac{8[p w_{A2} + q w_{S2} + r w_{C2}]}{\overline{w}} - q$$
Simplifying from the previous page, we get

\[ \Delta \theta = \frac{2}{\bar{w}} \left[ \rho W_{AA} + 2\bar{q} W_{AS} + \bar{q}^2 W_{SS} \right. \\
+ \left. 2 \bar{q} r W_{AC} + r^2 W_{CC} + 2 \bar{q} r W_{AC} \right] \]

where \( \bar{w} = \rho \bar{w}_{AA} + 2\bar{q} \bar{w}_{AS} + \bar{q}^2 \bar{w}_{SS} \)

\[ + 2 \bar{q} r \bar{w}_{AC} + r^2 \bar{w}_{CC} + 2 \bar{q} r \bar{w}_{AC} \]

Now: let \( q_s = \rho W_{AS} + \bar{q} W_{SS} + r W_{AC} - \bar{w} \)

And think of \( q_s \) as the \textit{Ave Excess of the S Allele}

- And note that \( q_s \) gives the difference in \textit{Fitness} between a \textit{gamete} bearing \textit{S} and the \textit{population mean}

Given this definition of \( q_s \), we get

\[ \Delta \theta = \frac{2}{\bar{w}} q_s \]

Note that \( \Delta \theta = 0 \) when \( q_s = 0 \)

Also note that the direction of \( \Delta \theta (+ \text{ or } -) \) depends only on the sign of \( q_s \)

Similarly:

\[ \Delta p = \frac{p}{\bar{w}} q_A \]

\[ \Delta r = \frac{r}{\bar{w}} q_c \]

\[ q_A = \rho W_{AA} + \bar{q} W_{AS} + r W_{AC} - \bar{w} \]

\[ q_c = \rho W_{AC} + \bar{q} W_{SC} + r W_{CC} - \bar{w} \]
From prev.: $\Delta g_8 = \frac{g_8^2}{\frac{13}{6}} \Delta g_s$

$$\Delta r = \frac{r}{13} \Delta g_e$$

For our initial gene freq. before Slash-and-Burn $p = 1; \delta = 0, r = 0$

we get

$$\bar{w} = p^2 w_{AA} + 2 p \delta w_{AS} + \delta^2 w_{SS}$$

$$= 1 \left[ 0.9 \right] + 0 + 0$$

$$+ 2 \delta r w_{Sc} + r^2 w_{cc} + 2 p \delta r w_{Ac}$$

$$= 0 + 0 + 0 + 0$$

AND

$$q_8 = P w_{AS} + \delta w_{SS} + r w_{Sc} - \bar{w}$$

$$= 1 \left[ 1.0 \right] + 0 + 0$$

$$= 0.1$$

Hence $\Delta g_8 > 0$, and the $S$ allele should $\uparrow$ when rare.
Consider now the $c$ allele

$$\Delta r = \frac{r}{w} A_c$$

*Under the same initial conditions* $(p=0.21, q=0.20, r=0.20)$

$$\bar{w} = 0.9 \text{ (as shown prev page)}$$

$$A_c = pWac + qWsc + rWcc - \bar{w}$$

$$= 1[0.9] + 0 + 0 - 0.9$$

$$= 0.9 - 0.9 = 0$$

**Hence: the response to malaria was**

1) Rapid increase in $S$

2) No change in $c$ [even though the $CC$ genotype is most fit!]

**Thus dominance in the $S$ allele and recessiveness in $c$ plays a critical role!**

*At equilibrium* $(\Delta p = \Delta q = \Delta r = 0)$

1) $p \approx 0.89$

2) $q \approx 0.11$

3) $G_S = (0.89)(1.0) + (0.11)(0.2) + (0.00)(0.7) - 0.91$

$$= 0$$

4) $G_c = (0.89)(1.0) + (0.11)(0.7) + (0.00)(1.3) - 0.91$

$$= -0.03$$

**Hence $c$ can't increase in the polymorphic population**
HENCE (and this is the take-home message)

The course and end point of selection requires knowledge of

1) Starting conditions

and 2) Dominance

Is this (ie 1 & 2 above) enough?

... Suppose we allow some inbreeding?

i) Let \( \hat{f} \) = be the prob of a \( s \)-bearing gamete joining with another \( s \)-bearing gamete which is IBD (identical by descent)

Then \((1-\hat{f})\hat{g} = \text{prob of two } s \text{ alleles which are not IBD.}\)

Thus

\[
Q_d = (1-\hat{f})pW_{ss} + [\hat{f} + (1-\hat{f})\hat{g}]W_{ss} + (1-\hat{f})\hat{r}W_{sc} - \bar{w}
\]

\[
Q_c = (1-\hat{f})pW_{ac} + (1-\hat{f})\hat{g}W_{sc} + [\hat{f} + (1-\hat{f})\hat{r}]W_{cc} - \bar{w}
\]

ie. the allele originated in the same recent ancestor, say grandma.
Now suppose we allow slight inbreeding: \( f = 0.05 \).

Then, for \( p^2; 1; q^2; r \neq 0 \):

\[
A_s = (1-f)pW_{As} + [f+(1-f)q]W_{As} + (1-f)rW_{Sc} - \bar{w}
\]

\[
= (0.95)(1)(1.0) + [0.05]0.2 + (0.95)(0)(0.7) - 0.9
\]

\[
= 0.06 \quad \text{Hence } A_s > 0; \text{ } s \uparrow \text{ when rare}
\]

\[
A_c = (1-f)pW_{Ac} + (1-f)qW_{Sc} + [f+(1-f)r]W_{Ac} - \bar{w}
\]

\[
= (0.95)(1)(1) + (0.95)(0)(0.7) + [0.05+0.7](1.3) - 0.9
\]

\[
= 0.02 \quad \text{Hence } A_c > 0; \text{ } c \uparrow \text{ when rare}
\]

Thus inbreeding would allow for the \( c \) allele to increase, whereas outbreeding would not.

**Hence:** In addition to starting conditions and dominance relationships, we need to know breeding system to predict the course and endpoint of selection.

**What is the endpoint for \( f = 0.05 \)?**

As \( c \uparrow \), \( A_s \) & \( A_c \) acquire negative values.

And the \( c \) allele is fixed at \( r = 1.0 \).