Throughout this worksheet, assume that the population is HUGE, so even a very small difference in fitness will matter. Also assume that newly introduced alleles will not be immediately lost to drift.

In West African populations, Cavalli-Sforza and Bodmer (1971) estimated relative fitness of different genotypes at the hemoglobin locus. (Example taken from Hartl and Clark textbook.) Hemoglobin S appears to protect against malaria in the heterozygote but causes sickle-cell anemia in the homozygote.

For the first two problems, consider only the two alleles A (normal) and S (sickle-cell trait). Expected counts were based on the allele frequencies in these populations.

Genotype	AA	AS	SS	Total
Observed count	25,374	5,482	67	30923
Expected count	25,607	5,065	251	30923
Ratio	0.9909	1.0823	0.2669	
Normalized to AS	0.9156	1.0000	0.2466	

1. (2 pts) If we assign a fitness of 1.0 to AS, what are the relative fitnesses of AA and SS based on these data? (Hint: Do this in two steps. First find out, for each genotype, the ratio of individuals observed to individuals expected. Then normalize to give AS a value of 1, adjusting the others proportionately.) *See above.*

2. (1 pt) What are the allele frequencies observed in these data?

   P(A)=0.9092, P(S)=0.0908.

3. (1 pt) What are the expected allele frequencies at the overdominant equilibrium? Do these seem to match the data? (You do not need to do a statistical test.)

   Equilibrium is t/(s+t). s=0.0844, t=0.7534, P(A)=0.8993. This is very close to the observed 0.9092. It's one of the most convincing demonstrations of an overdominant equilibrium in humans.

4. (2 pts) Suppose that only A existed in a large population. If you introduced a few copies of S, what would be the expected outcome? Give a numeric estimate of the allele frequencies after a long time.

   They would be at the equilbrium above, P(A)=0.8993, as long as S was not lost early on.

5. (2 pts) Suppose that A and S existed, at their equilibrium, in a large population. Suddenly, a medical breakthrough eliminated malaria, removing all disadvantage to the AA homozygote, but leaving the disadvantage of the SS homozygote. What would be the expected outcome after a long time? *S is now a bad recessive and should decline, increasingly slowly, until it reaches its mutation/selection equilibrium. I also accepted answers that said it would be lost. One student made the interesting point that the fitness of SS might decrease as well; likely it also protects against malaria, and any such advantage would be lost.*

   In the actual data, Cavalli-Sforza and Bodmer also observed a third, rarer allele, C. Here is their full table.

Genotype	AA	AS	SS	AC	SC	CC	Total
Observed count	25,374	5,482	67	1737	130	108	32,898
Expected count	25,615	4,967	307	1769	165	75	32,898
Normalized fitness	0.8975	1.0000	0.1977	0.8896	0.7139	1.3047	

6. (2 pts) What are the relative fitnesses, assigning a fitness of 1.0 to AS? BE SURE to do at least four digits after the decimal or you will lose some important distinctions. *See above.*

   In the following questions, you do not need to calculate equilibrium frequencies (they are quite tricky with three alleles). Just indicate the general direction things will go. Will the new allele tend to increase or decrease? Hint: when an allele is very rare, it exists almost solely in heterozygotes, and its future can be predicted by the fitness of the heterozygotes. The homozygous fitness of a very rare allele hardly matters.

7. (2 pts) Suppose that only A existed in a large population. If you introduced a few copies of C, what would be the expected outcome? *AA has a higher fitness than AC, so the most likely outcome is to fix A. People were skeptical of the small fitness difference, but in a large population it will generally be enough to overcome drift. Even if it is not, the likely outcome of drift is also loss of C as it is rare. Fixation of C is highly improbable.*

8. (2 pts) Suppose that only C existed in a large population. If you introduced a few copies of A, what would be the expected outcome? *A will almost surely be lost as AC is much worse than CC.*

9. (3 pts) Suppose that A and S existed, at their equilibrium, in a large population. If you introduced a few copies of C, what would be the expected outcome? *Most of the C will be in AC, and thus disfavored, but it's fairly tricky to show that the S's will not help C survive. The easiest approach is to note that at the equilibrium of AS the allele frequencies are around 90% A and 10% S. So the few C's will find themselves 90% in AC and 10% in SC. The mean fitness of those genotypes is less than the mean fitness of the population with only A and S, so C will be lost.*

10. (3 pts) Describe a situation in which, even in a large well-mixed population, natural selection will not produce the best possible outcome.

    There are many possible answers. This homework shows a dramatic one: if the starting frequency of the best allele is too low, in an underdominant system selection will fix the worse allele.

    You could also point to overdominance, early death of a favorable mutation due to drift, or unfavorable linkage (hitch-hiking).

    I was not as convinced by arguments about, for example, medical care removing selection. If selection is removed, the outcome IS the best possible outcome, as far as evolution can see.