

In this unit, we'll look in detail at the mechanisms of evolution at the population level using the principles of Mendelian genetics. We'll start by deriving the Hardy-Weinberg equilibrium equations and discussing the conditions under which evolution does not occur, then continue with a more qualitative discussion of the mechanisms by which it does occur. We'll look in particular detail at some of the more subtle and complex features of natural selection.

Notes for this chapter:

1. You should be able to work problems 1-5 and 7 at the end of chapter 5 in the text.
2. Skip "Adding selection to H-W analysis: the calculation of genotype frequencies" pp. 123-128

Topic outline:

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- II. The Hardy-Weinberg equilibrium*
 - A. The H-W equilibrium describes how allele frequencies change over time under a set of simplifying assumptions*
 - B. Numerical example of H-W*
 - C. Generalizing H-W : symbolic/algebraic representation*
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 - E. Applying H-W: is a population in H-W equilibrium?*
- III. The effect of selection on allele frequencies*
 - A. Selection acts when genotypes differ in fitness*
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 - C. The CCR5- Δ 32 allele revisited*
- IV. Patterns of selection: the genetics of a locus can affect evolution*
 - A. Recessive vs. dominant alleles*
 - B. Selection on heterozygotes*
 - C. Frequency-dependent selection*
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- V. Mutation*
 - A. Mutation as an evolutionary force*
 - B. Mutation-selection balance*
 - C. Cystic fibrosis revisited*

I. Introduction to population genetics:

- A. Population genetics is the branch of evolutionary biology that examines, in detail, how/why allele frequencies change in populations over time
 1. remember this is one definition of evolution
- B. Much of the work of population geneticists involves developing mathematical

models of how genes and alleles should “behave”

1. Models are based on
 - a. principles of Mendelian (and modern molecular) genetics
 - b. processes like natural selection, mutation, migration, etc.
2. Note that the development of these models was key to the Modern Synthesis

C. Examples of the kinds of questions population genetics helps to answer (sometimes with surprising results) include:

1. We know that individuals homozygous for the CCR5- Δ 32 allele are much more resistant to HIV than are other individuals – will the AIDS epidemic cause that allele to become more frequent in human populations?
2. In the early 1900's, a strong eugenics movement developed in the U.S.
 - a. proponents were geneticists and others concerned with potential “weakening” of U.S. “genetic stock” via breeding with genetically “inferior” individuals
 - b. this included individuals
 - i. suffering from “genetic diseases” such as “feble-mindedness”
 - ii. individuals exhibiting “moral weakness” (e.g., homelessness, out-of-wedlock births, etc.)
 - iii. individuals from various racial/ethnic stocks (including, e.g., individuals from Eastern Europe)
 - c. result was, among other things
 - i. immigration quotas
 - ii. compulsory sterilization programs
 - d. question: assuming that the genetic assumptions behind compulsory sterilization programs were met (i.e., “undesirable traits” were the result of genes following simple Mendelian principles), would compulsory sterilization actually result in a decrease of undesirable traits?

3. Cystic fibrosis is among the most common serious genetic diseases among humans of European ancestry
 - a. CF is an autosomal recessive disease that affects ~1 in 2500 births
 - b. for most of human history, CF has been lethal, killing people before they reached reproductive age
 - c. in spite of that, frequency of CF carriers is as much as 4% in some populations – why is the frequency so high?

II. The Hardy-Weinberg equilibrium:

- A. The H-W equilibrium describes how allele frequencies change over time under a set of simplifying assumptions
 1. H-W is an example of a **null model**: it describes how a biological system will work in the absence of whatever process we're interested in (in our case, evolution by natural selection)
 2. Seems paradoxical – but remember that many processes are always operating in biological systems. By understanding how systems will behave in the absence of a particular process, we can better understand how they behave in the presence of that process.
 3. Specifically, the H-W equilibrium describes what happens to allele and genotype frequencies in populations under a set of conditions that preclude evolution by natural selection or other mechanisms: (pp. 117+)
 - a. No selection:
 - i. all genotypes survive at an equal rate and
 - ii. contribute equal numbers of gametes to the gene pool for the next generation
 - b. No mutation:
 - i. no new alleles are added to the population
 - ii. no mutation of one existing allele to another existing allele (e.g., A to a, a to A)

- c. No migration:
 - i. no new alleles are added via the migration of new individuals to the population
 - ii. no existing alleles are “removed” via the migration of individuals out of the population
 - d. Infinite population size: random events don’t cause the loss (or reduction in frequency) of alleles
 - e. Random mating:
 - i. alleles combine according to their frequency in the population, not according to choice
 - ii. note that the text is wrong here: some forms of non-random mating do result in change in allele frequency as well as change in genotype frequency
- B. Numerical example of H-W: to illustrate how H-W works, we’ll follow the alleles in a hypothetical population through one “cycle” from gametes in generation 1 to gametes in generation 2 (figs. 5.1-5.3)
1. Start with hypothetical population:
 - a. one gene, 2 alleles A and a
 - b. 60% = .60 of gametes have A allele
 - c. 40% = .40 of gametes have a
 - d. note that frequency of A + frequency of a = 100% = 1
 - e. note that with 1 gene and 2 alleles, we can get 3 possible genotypes:
 - i. AA
 - ii. Aa
 - iii. aa
 2. Calculate the frequency of each genotype under the assumptions we listed above
 - a. most important here = random mating: the chances of any allele

combining with any other allele to form offspring is strictly a function of allele frequency

- b. easy way to calculate = use Punnett square incorporating allele frequency:

	sperm	
eggs	.60 A	.40 a
.60 A	.36 AA	.24 Aa
.40 a	.24 Aa	.16 aa

- c. summarize and double-check by making sure genotype frequencies add up to 1 = 100%:

i. $.36 AA + .48 Aa + .16 aa = 1$

3. Calculate the frequency of alleles in the new generation given the genotypes calculated above (= calculate the frequency of A and a these genotypes will produce when they mate) – simplest method = counting alleles:

- a. assume 100 individuals @ 2 alleles (or 2 gametes) each = 200 alleles total in the population
- b. count the alleles in each genotype (= count the gametes each genotype will produce): e.g. for A

# of ind. of each genotype	# of A alleles per individual	total # of A alleles
36 AA	2	72
48 Aa	1	48
16 aa	0	0
total # of A		120

- c. calculate the frequency: $120 A / 200 \text{ alleles total} = .60 = 60\%$
- d. check calculation by calculating the frequency of a and checking to be sure $A + a = 1$:

# of ind. of each genotype	# of a alleles per individual	total # of a alleles
36 AA	0	0
48 Aa	1	48
16 aa	2	32
total # of A		80

- i. $80 a / 200 \text{ alleles total} = .40 = 40\%$
- ii. $.60 + .40 = 1$: calculations are correct

4. Result:

- a. we started with .60 A and .40 a and got the same allele frequencies in the second generation
 - i. allele frequencies haven't changed over time
 - ii. so no evolution has occurred
- b. this means that our genotype frequencies will also stay the same over time (when random mating occurs, we'll get the same combinations of alleles and consequently the same frequencies of offspring)

C. Generalizing H-W : symbolic/algebraic representation allows us to generalize the results of our numerical example to any population that meets the basic H-W conditions

- 1. Assume a single gene (locus) with two alleles, represented A1 and A2
 - a. use capital letters and numbers so no confusion with dominant and recessive (the general case also covers codominance, etc.)

- b. these alleles can result in 3 genotypes:
 - i. A1A1
 - ii. A1A2
 - iii. A2A2
- 2. Represent allele and genotype frequencies symbolically:
 - a. allele frequencies:
 - i. p = frequency of A1
 - ii. q = frequency of A2
 - b. genotype frequencies:
 - i. P = frequency of A1A1
 - ii. Q = frequency of A1A2
 - iii. R = frequency of A2A2
 - c. note that:
 - i. **$p + q = 1$** (so $p = 1 - q$)
 - ii. **$P + Q + R = 1$**
- 3. As before, calculate genotype frequencies from allele frequencies using Punnett square:
 - a.

	sperm	
eggs	p A1	q A2
p A1	p^2 A1A1	pq A1A2
q A2	pq A1A2	q^2 A2A2

- b. summarize genotype frequencies: under H-W conditions
 - i. P (= frequency of A1A1) = p^2
 - ii. Q (= frequency of A1A2) = $2pq$
 - iii. R (= frequency of A2A2) = q^2

c. Note that:

i. $p^2 + 2pq + q^2 = (p + q)^2 = 1$

ii. only under H-W does $P = p^2$, $Q = 2pq$ and $R = q^2$

4. Calculate allele frequencies in the new generation as before

a. calculate total # alleles in the population:

i. total # individuals = $p^2 + 2pq + q^2 = (p + q)^2$

ii. each individual has 2 alleles, so total # alleles = $2(p + q)^2$

b. calculate frequency of A1 by “counting alleles” as before:

i.

# of ind. of each genotype	# of A1 alleles per individual	total # of A1 alleles
p^2 A1A1	2	$2p^2$
$2pq$ A1A2	1	$2pq$
q^2 A2A2	0	0
total # of A1		$2p^2 + 2pq$

ii. frequency of A1 = number of A1 / total alleles in the population:

$$2p^2 + 2pq / 2(p + q)^2$$

iii. simplify:

a) $2p(p + q) / 2(p + q)^2 = p / (p + q) = p / 1 = p$

b) so frequency of A1 = p

c. similarly, the frequency of A2 will = q (verify on your own)

d. and, as in our numerical example, we have no change in allele frequency and no change in genotype frequency over time

5. A simpler way to calculate allele frequencies is to use the generalization that, in any population:

a. $p = P + \frac{1}{2} Q$: reasoning is that

i. every P individual produces all p gametes

- ii. every Q individual produces $\frac{1}{2}$ p gametes and $\frac{1}{2}$ q gametes
 - b. $q = R + \frac{1}{2} Q$ (same reasoning)
 - c. so (**this is important!**), for any population, if you can identify the genotypes, you can calculate allele frequencies:
 - i. identify genotypes
 - ii. calculate genotype frequency = total # of each genotype/total # in population
 - iii. use equations above:
 - a) $p = P + \frac{1}{2} Q$
 - b) $q = R + \frac{1}{2} Q$
- D. Summarizing the major findings of H-W
1. Given a population with genotype frequencies $A_1A_1 = P$, $A_1A_2 = Q$ and $A_2A_2=R$, then
 - a. $p = \text{frequency of } A_1 = P + \frac{1}{2} Q$
 - b. $q = \text{frequency of } A_2 = R + \frac{1}{2} Q$
 2. The conditions of the H-W equilibrium are
 - a. no selection
 - b. no mutation
 - c. no migration
 - d. infinite population size
 - e. random mating
 3. When the conditions of H-W are met, then:
 - a. the population will be in equilibrium
 - b. allele frequencies will not change over time (no evolution will occur)
 - c. genotype frequencies will not change over time
 4. When a population is in H-W equilibrium, given allele frequencies $p = A_1$ and $q = A_2$, then the genotype frequencies will be
 - a. $P = p^2$

- b. $Q = 2pq$
- c. $R = q^2$
- 5. Note also that, in theory, as soon as the conditions of H-W occur in a population, H-W equilibrium will
 - a. be achieved in one generation and
 - b. will be maintained as long as the conditions are maintained
- E. Applying H-W: is a population in H-W equilibrium?
 1. Remember that, if a population is in H-W equilibrium, then $P = p^2$, $Q = 2pq$ and $R = q^2$
 2. If we can identify genotypes, we can use the above to test whether or not the population is in equilibrium
 3. General procedure:
 - a. measure genotype frequencies (measure P, Q, R)
 - b. use P, Q, and R to calculate p and q: remember, for any population
 - i. $p = P + \frac{1}{2} Q$
 - ii. $q = R + \frac{1}{2} Q$
 - c. check to see if $P = p^2$, $Q = 2pq$ and $R = q^2$
 4. Example:
 - a. given a population of flowers:
 - i. assume flower color is determined by a single gene with two alleles and incomplete dominance:
 - a) A1 = red allele
 - b) A2 = white allele
 - c) A1A1 individuals have red flowers
 - d) A1A2 individuals have pink flowers
 - e) A2A2 individuals have white flowers

- ii. in a random sample of plants, you find
 - a) 32 plants with red flowers
 - b) 96 plants with pink flowers
 - c) 72 plants with white flowers
 - b. calculate the genotype frequencies
 - i. total # of plants = $32 + 96 + 72 = 200$
 - ii. $P = A_1A_1$ red flowers = $32/200 = .16$
 - iii. $Q = A_1A_2$ = pink flowers = $96/200 = .48$
 - iv. $R = A_2A_2$ = white flowers = $72/200 = .36$
 - v. check to be sure frequencies add up to 1: $.16 + .48 + .36 = 1$
 - c. use genotype frequencies to calculate allele frequencies:
 - i. $p = P + \frac{1}{2} Q = .16 + \frac{1}{2} (.48) = .16 + .24 = .40$
 - ii. $q = R + \frac{1}{2} Q = .36 + \frac{1}{2} (.48) = .36 + .24 = .60$
 - iii. check to be sure $p + q = 1$
 - d. test to see if population is in H-W:
 - i. does $P = p^2$?
 - a) $p = .40$
 - b) $p^2 = .16 = P$: yes, population is in H-W
 - ii. double check: does $R = q^2$ (or does $Q = 2pq$)?
 - a) $q = .60$
 - b) $q^2 = .36 = R$: yes, population is in H-W
5. Example 2: given same kind of plants as above
- a. in a random sample of plants you found 20 with red flowers, 20 with pink flowers, and 60 with white flowers
 - b. calculate genotype frequencies:
 - i. total # flowers = $20 + 20 + 60 = 100$
 - ii. $P = A_1A_1$ = white flowers = $.20$
 - iii. $Q = A_1A_2$ = pink flowers = $.20$
 - iv. $R = A_2A_2$ = white flowers = $.60$

- c. calculate allele frequencies:
 - i. $p = P + \frac{1}{2} Q = .20 + \frac{1}{2} (.20) = .30$
 - ii. $q = R + \frac{1}{2} Q = .60 + \frac{1}{2} (.20) = .70$
 - iii. $p + q = .30 + .70 = 1$
 - d. test:
 - i. does $P = p^2$?
 - a) $p^2 = .09$; $P = .20$:
 - b) no, population is not in H-W equilibrium
 - ii. check: does $Q = 2pq$?
 - a) $2pq = 2(.3)(.7) = .42$; $Q = .20$
 - b) no, population is not in H-W equilibrium
6. Work sample problems on your own
- a. problem #2 from end of chapter
 - b. additional problems at end of notes
- F. Summary:
1. The H-W equilibrium equations are a null model – they tell us what will happen to allele frequencies in populations over time in the absence of a variety of processes, including evolution by natural selection
 2. The conditions under which the H-W equilibrium will occur are very unlikely to be met in natural populations
 3. If we can identify appropriate genotypes in a population, we can tell whether or not a population is in H-W equilibrium
 4. If the population is NOT in H-W, we can conclude that one or more conditions of H-W are not being met – and can begin to figure out which ones and why
 5. The H-W equations are a starting point that population geneticists can use to model what will happen in natural populations when the H-W conditions are not being met – this is what we'll consider over the next few chapters

III. The effect of selection on allele frequencies

A. Selection acts when genotypes differ in fitness:

1. selection happens when some phenotypes produce more offspring than do others in a population – which can happen when, e.g.,
 - a. some phenotypes live longer (and so reproduce more)
 - b. some phenotypes are more attractive to mates
 - c. some phenotypes produce more offspring
2. Selection will only lead to evolutionary change when the differences among phenotypes (i.e., the characteristics that allow some phenotypes to produce more offspring than others) are heritable – that is, there must be a difference in the fitness of the genotypes
3. In reality, all phenotypes (and therefore fitness) are the result of both genetic and environmental influences – but for the purposes of this discussion, we'll simplify matters and assume that fitness is strictly a function of genotype
4. Question: does selection affect H-W equilibrium? Short answer = yes!

B. Selection changes allele frequencies over time = leads to evolutionary change

1. numerical example (figs. 5.9, 5.10)
 - a. Assume population of mice with random mating, etc.
 - i. One locus (gene) affects survival
 - ii. two alleles, with frequencies
 - a) $B_1 = .60 = p$
 - b) $B_2 = .40 = q$
 - iii. population consists initially of 1000 zygotes: so genotype frequencies will be (given random mating)
 - a) $B_1B_1 = 360 = P$
 - b) $B_1B_2 = 480 = Q$
 - c) $B_2B_2 = 160 = R$

- b. Now assume that individuals differ in their rates of survival
 - i. 100% of B1B1 individuals survive
 - ii. 75% of B1B2 individuals survive
 - iii. 50% of B2B2 individuals survive
 - c. Calculate number of adults in population:
 - i. 100% of 360 B1B1 = 360 B1B1 adults
 - ii. 75% of 480 B1B2 = 360 B1B2 adults
 - iii. 50% of 160 B2B2 = 80 B2B2 adults
 - iv. total # of adults = 800
 - d. Calculate new genotype frequencies:
 - i. $360 \text{ B1B1 adults} / 800 \text{ total} = .45 \text{ B1B1} = P$
 - ii. $360 \text{ B1B2 adults} / 800 \text{ total} = .45 \text{ B1B2} = Q$
 - iii. $80 \text{ B2B2 adults} / 800 \text{ total} = .10 \text{ B2B2} = R$
 - e. What will be the allele frequencies in the next generation?
 - i. $p = B1 = P + \frac{1}{2} Q = .45 + \frac{1}{2} (.45) = .675$
 - ii. $q = B2 = R + \frac{1}{2} Q = .10 + \frac{1}{2} (.45) = .325$
 - f. so we have had a change in allele frequency: evolution has occurred
 - a) p was .60; now is .675
 - b) q was .40; now is .325
 - g. note that this example uses fairly strong selection – but analyses with weaker selection show same general pattern: favored alleles increase in frequency over time (fig 5.11)
2. Empirical example: laboratory natural selection experiment on *Drosophila* (fig. 5.10)
- a. started with population with two Adh alleles (F and S) – Adh codes for the enzyme that breaks down ethanol
 - b. maintained populations as follows:
 - i. two control populations on normal food
 - ii. two experimental populations on food spiked with ethanol

- iii. in all populations, breeders selected at random from surviving adults
(so no artificial selection added)
 - c. results: tracked frequency of F and S alleles in each population over time
(fig 5.11):
 - i. no long-term, consistent change in allele frequencies in control
populations
 - ii. experimental populations both showed rapid, consistent decline in S
(and increase in F)
 - iii. clearly, evolution is happening
 - d. Can we attribute change to selection rather than violation of some other
assumption?
 - i. only difference between experimental and control populations was
amount of ethanol in food = a difference in environment
 - a) consistent with basic selection theory: fitness of genotypes
depends on their environment
 - ii. Adh extracted from F homozygotes breaks down ethanol at twice the
rate of Adh from S homozygotes: so we have a difference in enzyme
function that is consistent with the selection hypothesis
- C. The CCR5- Δ 32 allele revisited: will the AIDS epidemic cause an increase in
frequency of this allele?
- 1. Intuitively, seems logical that an allele that increases resistance would
increase in frequency during an epidemic – however, analysis based on H-W
model suggests otherwise (fig. 5.13):
 - 2. Investigators used three scenarios to model the effect of AIDS on allele
frequency (fig. 5.13):
 - a. Scenario 1: high frequency of the beneficial allele + strong selection
favoring the allele
 - i. frequency = .20 = highest reported for any population (Ashkenazi
Jews)

- ii. infection and mortality rates highest reported = sub-Saharan Africa
- iii. under these conditions, allele is virtually fixed (frequency = ~ 100%) at the end of 40 generations (~ 1000 years)
- iv. note that this combination of conditions doesn't occur anywhere:
 - a) allele is virtually absent in sub-Saharan African populations, where selection is strongest
 - b) infection and mortality rates in Europe are very low, where allele frequency is highest
- b. Scenario 2: high frequency of beneficial allele + low infection and mortality rates (= weak selection)
 - i. this is the situation in European populations
 - ii. result = virtually no change in allele frequency in 40 generations
 - iii. reason = selection is too weak to cause appreciable change in such a short period of time (note that 40 generations is virtually instantaneous in evolutionary time)
- c. Scenario 3: low frequency of beneficial allele + high infection and mortality rates (= strong selection)
 - i. this is the situation in many sub-Saharan African countries
 - ii. result = virtually no change in allele frequency in 40 generations
 - iii. reason = most copies of the allele are present in heterozygotes, who get infected and die – they don't generate enough homozygotes for selection to favor
- 3. Summarize:
 - a. in terms of AIDS epidemic, we can't expect the frequency of this allele to increase appreciably in the near term
 - b. in general, selection will have major effects
 - i. over long periods of time even when frequency of favored allele is low and selection is weak
 - ii. over short periods of time only when frequency of favored allele is

high and selection is relatively strong

IV. Patterns of selection: the genetics of a locus can affect evolution. Here we look at three slightly more complex questions: Does it matter whether the alleles selection acts on are dominant or recessive? What happens when selection acts on heterozygotes rather than homozygotes? What happens when the direction of selection changes over time?

A. Recessive vs. dominant alleles

1. Empirical example: selection in *Tribolium* beetles

- a. beetles have a lethal recessive allele for the L gene:
 - i. gene has two alleles: + and l
 - ii. + is dominant
 - iii. +/+ and +/l are phenotypically normal
 - iv. l/l individuals don't survive
- b. investigator (Dawson) started two experimental populations using heterozygotes as founders
 - i. initial frequency of + and l were .50
 - ii. because l is lethal, expected frequency of l to decline to 0 and + to increase to 1
- c. results (fig. 5.14): matched prediction, but with important "twist"
 - i. initially, frequency of l declined rapidly (and + increased rapidly)
 - ii. but, over time, rate of change declined: between generations 10 and 12, got no change in the frequency of either allele
 - iii. after 12 generations, l wasn't completely eliminated and + wasn't fixed

2. H-W principles explain what's going on:

- a. when selection acts against homozygous recessives, frequency of the recessive allele declines
- b. When allele becomes extremely rare, even strong selection won't make much difference in its frequency
 - i. homozygous recessive phenotype will be very rare

- ii. most of the (rare) recessive alleles will be present in heterozygotes
 - iii. because heterozygotes are phenotypically dominant, selection doesn't act against them
 - c. Note that, because lethal recessives can be "hidden" in heterozygotes, it's virtually impossible to eliminate recessive phenotypes completely
3. Conclusions about selection on dominants vs. recessives:
- a. Selection will act to increase the frequency of the favorable allele (and ultimately to fix it), regardless of whether it is dominant or recessive – however, there are a few differences in the details
 - b. Selection acting against recessives:
 - i. When recessive alleles are common and selection acts strongly against them (as in, e.g., lethal recessives), evolution will be fairly rapid (and recessive allele will decline in frequency).
 - ii. When recessive alleles are rare, even strong selection against them won't cause major changes in frequency
 - iii. Because lethal recessive alleles can "hide" in heterozygotes, they are virtually impossible to eliminate
 - c. Selection acting against dominants
 - i. When dominant allele is lethal, it will be eliminated in a single generation
 - ii. When dominant allele is not lethal and initially present at relatively high frequency, the rate of selection will be slow initially, then rapid
- B. Selection on heterozygotes: what happens when the fitness of the heterozygotes is different from the fitness of one of the homozygotes?
1. **Heterozygote superiority = heterosis = overdominance:** fitness of the heterozygote is greater than that of either homozygote
- a. classic e.g. = sickle-cell anemia
 - i. homozygous recessive trait
 - ii. in homozygous recessive individuals:

- a) point mutation in one hemoglobin chain alters hemoglobin function
- b) specifically, hemoglobin changes shape and causes RBC to “sickle”
- c) Sickled cells have two effects:
 - i) anemia because sickled cells are phagocytized by immune system cells
 - ii) pain because sickled cells get trapped in capillary beds
- iii. in heterozygotes, sickling occurs when partial pressure of oxygen inside RBC’s drops – so anemia is less than for homozygous recessives
- iv. where malaria is common, heterozygotes have greater fitness than either homozygote:
 - a) homozygous dominant individuals are susceptible to malaria and die before reaching reproductive age
 - b) heterozygous individuals are more resistant to malaria:
 - i) parasite completes part of its lifecycle inside RBCs, where it consumes oxygen
 - ii) so presence of parasites causes partial pressure to drop and sickling to occur
 - iii) once RBC’s sickle, they’re phagocytized by immune cells – and parasites are removed
- v. result is that the deleterious recessive allele is maintained because of selection favoring heterozygote
- b. generalizations about heterozygote superiority:
 - i. result = alleles will reach equilibrium at frequencies other than those predicted by H-W
 - ii. because selection is favoring heterozygotes, both alleles will be maintained over time – instead of one allele being fixed and one eliminated (selection is maintaining genetic variability)

- iii. because both alleles are actively maintained over time, all three genotypes will be actively maintained over time
 - a) general term for population with multiple phenotypes = **balanced polymorphism**
 - b) heterosis = one mechanism that can produce this pattern (there are others)
- 2. Heterozygote inferiority = **underdominance** = heterozygotes have lower fitness than do either homozygote – a bit more complex
 - a. because heterozygotes have low fitness, most matings will take place among homozygotes
 - b. whichever allele (dominant or recessive doesn't matter) is most common in a population will be selectively favored and will be fixed
 - c. do thought experiment: imagine population with two alleles A and a; selection acts against heterozygotes (assume no heterozygotes survive to adulthood)
 - i. if A is more common than a, population will have high frequency of AA and lower frequency of aa
 - ii. assume random mating:
 - a) because they're more common, AA individuals will most likely mate with AA
 - b) because they're rare, aa individuals are more likely to mate with AA than with aa
 - c) because most aa mate with AA, they produce heterozygous offspring
 - iii. so, most a alleles will be found in heterozygotes and eliminated – A will be fixed
 - iv. same will happen if a more common than A
 - d. Note that fixation only depends on initial frequency, not on dominance or recessiveness:

- i. general outcome will be that some populations will have only dominants and some will have only recessives
- ii. so, although underdominance reduces genetic variability within populations, it will maintain variability among populations

C. Frequency-dependent selection: what happens if the direction of selection changes over time?

1. Scale-eating fish

a. background:

- i. *Perissodus microlepis* = fish from Lake Tanganyika
- ii. feeds on the scales of other fish – comes up from behind and bites off scales
- iii. fish occurs in two forms:
 - a) “right-handed” have mouths twisted to right, and attack target fish on the left flank
 - b) “left-handed” have mouths twisted to left, and attack on the right flank
- iv. to a first approximation, handedness is determined by a single gene with two alleles; right is dominant over left

b. investigator (Hori) hypothesized that selection should “change direction”

over time: whichever form was most rare should be favored over whichever was common (= negative frequency-dependent selection):

- i. reasoning was that target fish, which are generally highly vigilant anyway, would learn to become more vigilant for attacks from whichever side was used by most common form
- ii. consequently, rare form would have a feeding advantage over common form, giving them higher fitness
- iii. as rare forms became more common, their advantage would decline as target fish became more vigilant for attacks from their preferred side – giving selective advantage to the other form

- c. Hori tested his hypothesis several ways:
 - i. used H-W principles to calculate expected allele and phenotype frequencies and compared them to actual frequencies in the population:
 - a) expected average phenotype frequency of .5 for each form
 - b) but also expected slight fluctuations: rare forms should become more common (frequency should increase above .5), then decline as the other form is favored, etc.
 - c) result matched prediction: fig. 5.20
 - ii. tested whether frequencies fluctuated around .5 at random, or were maintained there by selection:
 - a) if selection favors rare forms, should find that rare forms are breeding more than common forms
 - b) collected breeding individuals in three different years, and always found that the most abundant handedness of the breeders was the opposite of the population as a whole (when “lefties” were abundant, “righties” were doing most of the breeding).
 - iii. tested proposed mechanism of selection by examining bite wounds on target fish in two different years -- one when “lefties” common and one when “righties” common:
 - a) remember, hypothesis proposes that rare forms have feeding advantage because target species are more vigilant for common form
 - b) in both years, found more bite marks inflicted by rare form than by common form
2. Rare-male mating advantage:
 - a. in at least some species (including some *Drosophila*), females prefer to mate with rare males
 - b. result is the same as above: phenotype frequencies will fluctuate around

some equilibrium

3. Summarizing effects of frequency-dependent selection:
 - a. even in a given environment, the “direction” of selection can change over time (i.e., selection does not always favor the same genotype, even when environmental conditions don’t change)
 - b. frequency-dependent selection allele and genotype frequencies to deviate from H-W predictions
 - c. negative frequency dependence (selection favoring rare individuals) has the same effect as does heterosis:
 - i. because fitnesses change over time, both alleles are maintained in the population over time – selection does not fix one and eliminate the other
 - ii. so this is another mechanism that leads to balanced polymorphism
 - d. note that when mating preference depends on phenotype frequency, non-random mating CAN, in fact, cause a change in allele frequency over time
- D. On your own: read the section on eugenics and compulsory sterilization and answer the question: why, aside from the obvious human rights problems, is compulsory sterilization a foolish idea?

V. Mutation

A. Mutation as an evolutionary force

1. As we’ve already noted, mutation is ultimately the origin of the genetic variation that selection acts on – it provides the raw material for evolution.
2. By itself, though (i.e., in the absence of selection for or against the mutant allele), does mutation cause evolutionary change?
 - a. We can use H-W principles to demonstrate that, even at the high end of known mutation rates (i.e., one mutation per 10,000 gametes per generation), mutation alone will have virtually no effect over a few generations.
 - b. Over many generations, though, the effect can be substantial

- c. so, answer is:
 - i. yes, mutation can cause substantial changes in allele frequencies over time, but does so slowly at best
 - ii. at the mutation rates characteristic of most genes in most organisms, mutation alone is a weak mechanism of change at best
 3. Mutation becomes a more potent mechanism of evolutionary change in conjunction with selection – when selection favors new mutant alleles, substantial changes in allele frequency will occur much more rapidly than via mutation alone.
- B. Mutation-selection balance
1. As far as we've been able to tell so far, most mutations are at least mildly deleterious, so selection acts to eliminate them.
 2. Yet, deleterious alleles remain in populations at frequencies higher than predicted by H-W – why?
 3. Reason is that mutation is an ongoing process, so new deleterious alleles are always being created
 - a. if alleles are being created by mutation at the same rate they're eliminated by selection, the allele will achieve an equilibrium frequency
 - b. we can calculate the equilibrium frequency with a simple equation:
 - i. $q^* = F/s$ where
 - a) q^* = the equilibrium frequency of the mutant allele
 - b) F = the mutation rate (the rate at which the new allele is created)
 - c) s = the selection coefficient = a number between 0 and 1 that measures the strength of selection acting against the allele
 - ii. equation simply shows what we'd expect:
 - a) when mutation rates are low and selection against the allele is high, the equilibrium frequency will be low
 - b) when mutation rates are high and selection is relatively weak, the equilibrium frequency will be high

4. We can use this equation to test whether or not a particular allele is being maintained because of mutation-selection balance – e.g., spinal muscular atrophy
 - a. autosomal recessive disease caused by deleterious mutations in a gene on chromosome 5
 - b. investigators (Wirth and colleagues) determined that
 - i. allele frequency is about 0.01 (one mutation per hundred gametes) in the Caucasian population
 - ii. selection coefficient is about .9 – the disease is almost lethal
 - c. use the equation to figure out what mutation rate would be required to balance such strong selection and give us an equilibrium frequency of 0.01:
 - i. substitute known figures of 0.01 and .9 for q^* and s , respectively
 - ii. solve for F : mutation rate would have to be about 0.9×10^{-4}
 - d. Wirth et al. then examined chromosomes of individuals with spinal muscular atrophy, their parents and other family members to determine the actual mutation rate:
 - i. found a rate of 1.1×10^{-4}
 - ii. very close to that predicted by mutation-selection equation
 - iii. so concluded that deleterious mutant alleles are maintained by a balance between mutation and selection

C. Cystic fibrosis revisited

1. CF is caused by recessive loss-of-function mutations in the CFTR (cystic fibrosis transmembrane conductance regulator) gene
 - a. CFTR is a cell surface protein expressed in mucus membrane linings
 - b. acts as, among other things, a chloride channel (inability to regulate chloride concentrations causes many of the problems associated with CF)
 - c. gene also plays a role in allowing cells of lung lining to ingest and destroy *Pseudomonas aeruginosa* bacteria

- i. inability to destroy bacteris means individuals homozygous for mutant CFTRs have chronic *P. aeruginosa* lung infections
 - ii. ultimately leads to severe lung damage and early death
2. Selection against loss-of-function mutations in CFTR is strong:
 - a. until recently, very few individuals with CF lived to reproductive age
 - b. many of those who do survive are sterile
3. In spite of strong selection, allele remains present at frequencies higher than predicted by H-W (about 0.02 among people of European ancestry) – is mutation-selection balance the reason?
 - a. assume selection coefficient of 1 (homozygotes never reproduce)
 - b. use equation to determine the mutation rate that would be required to produce equilibrium frequency of about 0.02
 - c. result = mutation rate of 4×10^{-4}
 - i. actual mutation rate seems to be about 6.7×10^{-7}
 - ii. this is substantially lower than would be required for mutation-selection balance
 - iii. so something else is going on
4. Is CF maintained by heterozygote superiority?
 - a. Piers et al. have suggested that CF heterozygotes are resistant to typhoid fever and therefore exhibit heterozygote superiority
 - b. hypothesis is that typhoid bacteria (*Salmonella typhi*) use CFTR protein as a point of entry into cells:
 - i. homozygous wild-type individuals will be susceptible to typhoid
 - ii. homozygous mutant individuals will have CF
 - iii. heterozygotes will be resistant to typhoid and not have CF
 - c. tested hypothesis by constructing mouse cells with 3 different CFTR genotypes using wild type and most common mutant CFTR allele, then exposing cells to *S. typhi* – results were pretty dramatic (fig. 5.26):
 - i. +/- cells had 569,000 bacteria per gram of cells

- ii. +/-mutant cells had 77,500 bacteria per gram of cells = 86% less than homozygotes
- iii. mutant/mutant cells had 1.3 bacteria per gram of cells = virtually no infiltration
- d. strongly suggests that CF, like sickle-cell anemia, is maintained by heterozyote superiority

VI. Summary/conclusions:

- A. The H-W equations provide a null model for examining changes in allele frequencies in populations over time
- B. Selection causes allele frequencies to change over time – it is a mechanism of evolutionary change
- C. The results of selection can be surprising and complex:
 - 1. When selection favors an individual allele, that allele will increase in frequency to fixation, but the details of the process depend on
 - a. the frequency of alleles in the population
 - b. the strength of selection
 - c. whether the allele is dominant or recessive
 - 2. Selection acting on heterozygotes maintains genetic diversity in populations:
 - a. heterosis results in balanced polymorphism within populations
 - b. selection acting against heterozygotes will reduce variation within populations, but maintain variation among populations
 - 3. The direction of selection can change over time – negative frequency dependent selection is another mechanism that results in balanced polymorphism
- D. Mutation is an important component of evolutionary change
 - 1. it is the raw material of evolutionary change
 - 2. alone, it causes change very very slowly
 - 3. in conjunction with selection, it can lead to substantial change relatively rapidly

4. mutation-selection balance helps explain the persistence of deleterious alleles in populations over time

Additional Hardy-Weinberg problems

The MN blood group in humans is determined by a single gene with two co-dominant alleles (M and N); three phenotypes (M, MN, and N) are produced by three genotypes (MM, MN, and NN respectively). Phenotypes can be determined by testing with antisera. Determine whether or not each of the populations below are in Hardy-Weinberg equilibrium.

Population	Type M	Type MN	Type N
African-American	79	138	61
European-American	1787	3039	1303
Native American	123	72	10