Overview

Since the late 19th century, there have been many important discoveries about the mechanisms of inheritance and evolution. These have occurred mainly as a result of three research developments:

1. the invention of more powerful microscopes and other precision research tools
2. the use of short lived organisms such as fruit flies and bacteria for breeding experiments
3. the rigorous application of the scientific method

We now understand that natural selection is just one of a number of processes that can lead to evolution. This knowledge has resulted in the development of a more complete understanding of genetic changes that is usually described as the **synthetic theory of evolution**. This is essentially a combination of Charles Darwin's concept of natural selection, Gregor Mendel's basic understanding of genetic inheritance, along with evolutionary theories developed since the early 20th century by **population geneticists** and more recently by molecular biologists.

Hardy- Weinberg Equilibrium Model

The biological sciences now generally define **evolution** as being the sum total of the genetically inherited changes in the individuals who are the members of a population's gene pool. It is clear that the effects of evolution are felt by individuals, but it is the population as a whole that actually evolves. Evolution is simply a change in frequencies of alleles in the gene pool of a population. For instance, let us assume that there is a trait that is determined by the inheritance of a gene with two alleles--B and b. If the parent generation has 92% B and 8% b and their offspring collectively have 90% B and 10% b, evolution has occurred between the generations. The entire population's gene pool has evolved in the direction of a higher frequency of the b allele--it was not just those individuals who inherited the b allele who evolved.

Godfrey Hardy
(1877-1947)

This definition of evolution was developed largely as a result of independent work in the early 20th century by **Godfrey Hardy**, an English mathematician, and **Wilhelm Weinberg**, a German physician. Through mathematical modeling based on probability, they concluded in 1908 that gene pool frequencies are inherently stable but that evolution should be expected in all populations virtually all of the time. They resolved this apparent paradox by analyzing the net effects of potential evolutionary mechanisms.

Wilhelm Weinberg
(1862-1937)

Hardy, Weinberg, and the population geneticists who followed them came to understand that evolution will not occur in a population if five conditions are met:

1. mutation is not occurring
2. natural selection is not occurring
3. the population is infinitely large
4. all mating is totally random
5. there is no migration in or out of the population

These conditions are the absence of the things that can cause evolution. In other words, if no mechanisms of evolution are acting on a population, evolution will not occur--the gene pool frequencies will remain unchanged. However, since it is highly unlikely that any of these five conditions, let alone all of them, will happen in the real world, evolution is the inevitable result.

Hardy and Weinberg went on to develop a simple equation that can be used to discover the probable genotype frequencies in a population and to track their changes from one generation to another. This has become known as the **Hardy-Weinberg equilibrium equation**. In this equation ($p^2 + 2pq + q^2 = 1$), p is defined as the frequency of the dominant allele and q as the frequency of the recessive allele for a trait controlled by a pair of alleles (A and a). In other words, p equals all of the alleles in individuals who are homozygous dominant (AA) and half of the alleles in people who are heterozygous (Aa) for this trait in a population. In mathematical terms, this is

$$p = AA + \tfrac{1}{2}Aa$$

Likewise, q equals all of the alleles in individuals who are homozygous recessive (aa) and the other half of the alleles in people who are heterozygous (Aa).

$$q = aa + \tfrac{1}{2}Aa$$

Because there are only two alleles in this case, the frequency of one plus the frequency of the other must equal 100%, which is to say

$$p + q = 1$$

Since this is logically true, then the following must also be correct:

$$p = 1 - q$$

There were only a few short steps from this knowledge for Hardy and Weinberg to realize that the chances of all possible combinations of alleles occurring randomly is

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

or more simply

$$p^2 + 2pq + q^2 = 1$$

In this equation, p^2 is the predicted frequency of homozygous dominant (AA) people in a population, $2pq$ is the predicted frequency of heterozygous (Aa) people, and q^2 is the predicted frequency of homozygous recessive (aa) ones.

From observations of phenotypes, it is usually only possible to know the frequency of homozygous recessive people, or q^2 in the equation, since they will not have the dominant trait. Those who express the trait in their phenotype could be either homozygous dominant (p^2) or heterozygous ($2pq$). The Hardy-Weinberg equation allows us to predict which ones they are. Since $p = 1 - q$ and q is known, it is possible to calculate p as well. Knowing p and q, it is a simple matter to plug these values into the Hardy-Weinberg equation ($p^2 + 2pq + q^2 = 1$). This then provides the predicted frequencies of all three genotypes for the selected trait within the population.

By comparing genotype frequencies from the next generation with those of the current generation in a population, one can also learn whether or not evolution has occurred and in what direction and rate for the selected trait. However, the Hardy-Weinberg equation cannot determine which of the various possible causes of evolution were responsible for the changes in gene pool frequencies.

Significance of the Hardy-Weinberg Equation

By the outset of the 20th century, geneticists were able to use Punnett squares to predict the probability of offspring genotypes for particular traits based on the known genotypes of their two parents when the traits followed simple Mendelian rules of dominance and recessiveness. The Hardy-Weinberg equation essentially allowed geneticists to do the same thing for entire populations.

It is important not to lose sight of the fact that gene pool frequencies are inherently stable. That is to say, they do not change by themselves. Despite the fact that evolution is a common occurrence in natural populations, allele frequencies will remain unaltered indefinitely unless evolutionary mechanisms such as mutation and natural selection cause them to change. Before Hardy and Weinberg, it was thought that dominant alleles must, over time, inevitably swamp recessive alleles out of existence. This incorrect theory was called "genophagy" (literally "gene eating"). According to this wrong idea, dominant alleles always increase in frequency from generation to generation. Hardy and Weinberg were able to demonstrate with their equation that dominant alleles can just as easily decrease in frequency.

Mutation

Mutations are alterations of genetic material. They occur frequently during DNA duplication in cell division. This should not be surprising considering the fact that mitosis and meiosis are essentially mechanical processes with millions of operations that must be precisely completed in order for duplicate DNA molecules to be created. There are four common categories of mutations:

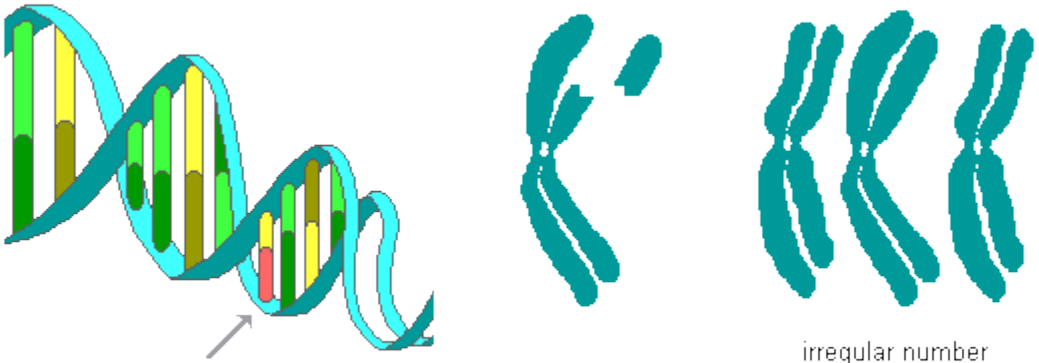
1. DNA base substitutions and deletions
2. unequal crossing-over and related structural modifications of chromosomes
3. partial or complete gene duplication
4. irregular numbers of chromosomes

Substitutions and deletions of single bases are common. For example, an adenine can be accidently substituted for a guanine. Such small errors in copying DNA are referred to as **point mutations**. There is a self correcting mechanism in DNA replication that repairs these small errors, but it does not always find every one of them.

Structural modifications of chromosomes generally occur as a consequence of the crossing-over process during cell division. Normally, there is an equal exchange of end sections of homologous chromosomes. Occasionally, there is a reunion of an end section onto a chromosome that is not homologous. Likewise, there can be an orphaned end section that does not reattach to any chromosome. The genes on such orphans are functionally lost.

Sometimes, an extra copy of an entire gene is produced when a DNA molecule is replicated. This is an important source of genetic variation for a species because spare copies of genes can mutate and change their function over time thereby producing a new variation that natural selection can favor or reject. Large-scale evolutionary changes in a species line generally occur in this way.

Irregular numbers of chromosomes can occur as a consequence of errors in meiosis and the combining of parental chromosomes at the time of conception. Such is the case when there are three instead of two autosomes for pair 21. This specific error is characteristic of Down syndrome.



In order for a mutation to be inherited, it must occur in the genetic material of a sex cell. Estimates of the frequency of mutations in human sex cells generally are about 1 per 10,000-1,000,000 for any specific gene. Since humans have approximately 20,000-25,000 genes, it is to be expected that most sex cells contain at least one gene mutation of some sort. In other words, mutations are probably common occurrences even in healthy people. Most probably do not confer a significant advantage or disadvantage because they are point mutations that occur in non-gene coding regions of DNA molecules. They are relatively neutral in their effect. However, some

mutations are extremely serious and can result in death before birth, when an individual is still in the embryonic or early fetal stages of development.

Mutations can occur naturally as a result of occasional errors in DNA replication. They also can be caused by exposure to radiation, alcohol, lead, lithium, organic mercury, and some other chemicals. Viruses and other microorganisms may also be responsible for them. Mutations appear to be **spontaneous** in most instances. That does not mean that they occur without cause but, rather, that the specific cause is almost always unknown. Subsequently, it is usually very difficult for lawyers to prove in a court of law that a mutagen is responsible for causing a specific mutation in people. With the aid of expert scientific testimony, they can often demonstrate that the mutagen can cause a particular kind of mutation. However, that is not the same thing as proving that a plaintiff's mutation was caused by that mutagen instead of some others.

The great diversity of life forms that have been identified in the fossil record is evidence that there has been an accumulation of mutations producing a more or less constant supply of both small and large variations upon which natural selection has operated for billions of years. Mutation has been the essential prerequisite for the evolution of life.

In order for a mutation to be subject to natural selection, it must be expressed in the phenotype of an individual. Selection favors mutations that result in adaptive phenotypes and eliminates non-adaptive ones. Even when mutations produce recessive alleles that are seldom expressed in phenotypes, they become part of a vast reservoir of hidden variability that can show up in future generations. Such potentially harmful recessive alleles add to the genetic load of a population.

Natural Selection

In Charles Darwin's 1859 seminal book, *On the Origin of Species*, he tried to answer the question of how species originate. He saw a paradox. On the one hand, all living organisms attempt to perpetuate their kind by producing many more offspring than are necessary to maintain their numbers. Yet, the actual size of natural populations usually remains relatively constant over time. How could this be? Darwin's answer was that many of the offspring do not survive to reproduce. This phenomenon can be illustrated by considering the common housefly (*Musca domestica*). Females lay up to 500 eggs at a time. The eggs hatch into larvae which go through several molting stages and then transform into pupae. Thirty-six hours after emerging from pupae, females are receptive for mating. Adult flies live 15-30 days, during which time, females lay eggs repeatedly though they mate only once. Over a 4-5 month period, the descendents of a single mating pair of house flies potentially could number 19^{20}. If that actually occurred, we very quickly would be up to our armpits in fly bodies all over the planet and the piles would grow at a rapidly increasing rate. Fortunately, most fly eggs, larvae, and pupae are killed by other insects and microscopic parasites. This keeps the total fly population more or less constant over time. Darwin surmised that the environment operated in a selective way, reducing the number of poorer-adapted variants of a species while increasing the proportion of better-adapted ones. This process became known as natural selection.

Darwin correctly understood that natural selection is usually the most powerful mechanism of evolution. However, he did not fully comprehend how it operates. This was due to the fact that he was largely ignorant of the mechanisms of genetics. That knowledge mostly came after his time. We now know that natural selection's effect on individuals depends on their phenotypes which in turn are determined mostly by their genotypes. The environment ultimately selects individuals with the best suited genotypes to survive to reproduce. Those individuals who have more surviving offspring pass on more of their genes to the next generation. As a consequence, the gene pool frequencies shift in the direction of their more adaptive alleles. However, the alleles that provide an advantage now may not in the future as new environmental stresses appear. Natural selection acts as a constantly changing template in its selection of winners and losers. This introduces chance into the equation. It is largely a matter of luck in having the right combination of genes at the right time to survive as the environment changes. Extinction occurs if those genes are not present.

For natural selection to cause evolution, it must select for or against one or more of the genotypes for a trait. In the case of a trait that is determined by a single gene with two alleles, there are five combinations of genotypes that nature can select:

1. either homozygote (AA or aa but not both)
2. both homozygotes (AA and aa)
3. either homozygote and the heterozygote (AA and Aa or aa and Aa)
4. the heterozygote (Aa)
5. all alleles (AA, Aa, and aa)

Selection Against One of The Homozygotes

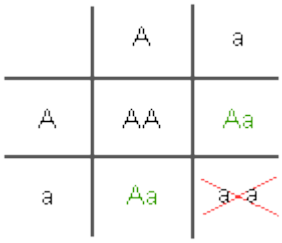
For traits that are controlled by a single gene that has two alleles, selection against one of the homozygotes (AA or aa) will result in a progressive decrease in the allele of which that unsuccessful homozygote consists. For example, if aa is completely selected against while AA and Aa are selected for, there will be only four possible successful mating patterns (as shown in the table below).

Selection against one of the homozygotes (aa)			
Possible parent mating patterns	Expected offspring genotypes		
	AA	Aa	aa
AA X AA	4		
AA X Aa	2	2	
Aa X AA	2	2	
Aa X Aa	1	2	1
Total	9 (56%)	6 (38%)	1 (6%)

Within one generation, the frequency of homozygous recessive (aa) children will drop dramatically. There will be a progressive decrease in the frequency of the "a" allele and a corresponding increase in the "A" allele every generation in which aa genotypes are selected against (as illustrated in the table below). This has been referred to as directional selection because of the shift in gene pool frequencies towards the advantageous allele.

Evolutionary trend resulting from complete selection against homozygous recessive (aa) individuals			
Allele	Generation		
	1	2	3
A	50%	67%	75%
a	50%	33%	25%

However, the recessive allele (a) will not completely disappear since it is still passed on by heterozygous (Aa) parents to the half of their children who are likely to also be heterozygous.



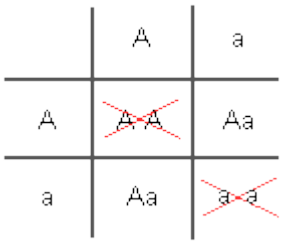
For the vast majority of human genes, the pressure of natural selection is usually far more gentle. As a consequence, the resulting evolution is so slow as to be difficult to detect in only a few generations. In the case of recessive traits such as albinism, homozygous recessive individuals are only at a slight selective disadvantage. They usually live to adulthood and reproduce. In some other genetically inherited recessive conditions, such as juvenile onset diabetes, the selection has been more severe. In the past, those who inherited it usually died in childhood before passing it on to the next generation. As a result, the frequency of this recessive allele was progressively reduced. This has all changed, however, since the discovery of insulin in 1921. Diabetes is no longer the killer of children it once was, and diabetic children grow up to have children with a higher than average chance of inheriting this disease.

In the mid 1990's, a striking example of intense selection against one of the homozygotes for a trait came to light. This stemmed from the discovery that some people do not get AIDS even if they are repeatedly exposed to the HIV virus that is responsible for this usually fatal disease. The people who are immune have inherited two copies of a rare mutant gene known as CCR5-delta 32 -- they are homozygous. Those who are heterozygous apparently have a partial immunity or at least a delay in the onset of AIDS. Approximately 10% of Europeans now have the CCR5-delta 32 gene variant, but it is extremely rare or absent in other populations of the world. There is a surprising connection in this story. The CCR5-delta 32 gene also provides immunity to a deadly disease of bacterial origin, bubonic plague. People who are homozygous for the CCR5-delta 32 gene variant are completely immune, while heterozygotes have partial immunity. It is very likely that this life-saving

allele occurs as a random mutation and that it was selected for by the devastating black plague epidemics that swept over Europe beginning in the 14th century. During the first wave of plague, between 1347 and 1350, one fourth to one third of all Europeans died from this disease. Natural selection favored those who by chance had inherited the CCR5-delta 32 gene variant. Repeated waves of plague over the next three centuries resulted in an increase in the frequency of CCR5-delta 32 in the European population.

Selection Against Both Homozygotes

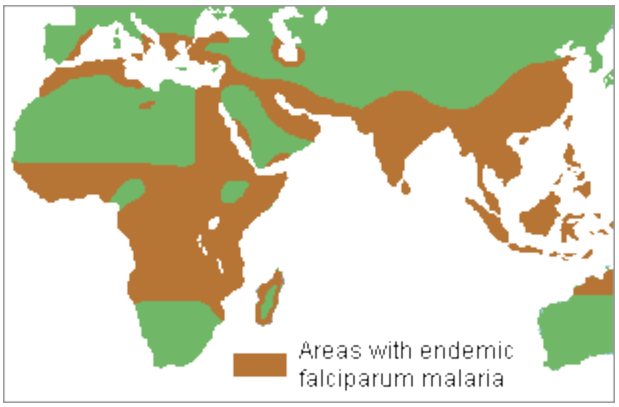
If there is complete selection against both homozygotes (AA and aa) in childhood, the only possible mating will be between heterozygous individuals (Aa) and, in turn, only heterozygotes will live up to reproduce.



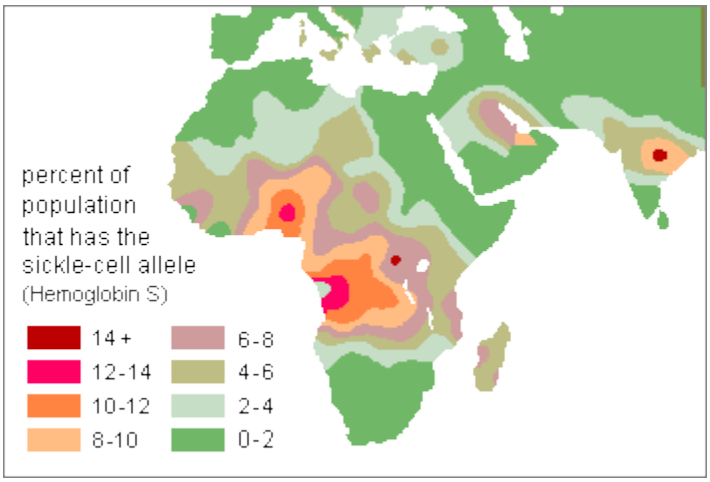
Extreme environmental conditions selecting only for heterozygous individuals can result in a **balanced polymorphism** in one generation. That is to say, the frequency of the two alleles (A and a) can each reach 50% and remain at that level so long as there is this sort of harsh natural selection. This has been referred to as stabilizing selection, or balancing selection, because there is not a shift in the gene pool frequencies towards one of the alleles.

Selection against both homozygotes (AA and aa)			
Possible parent mating patterns	Expected offspring genotypes		
	AA	Aa	aa
Aa X Aa	~~1~~	2	~~1~~
Total	0 (0%)	2 (100%)	0 (0%)

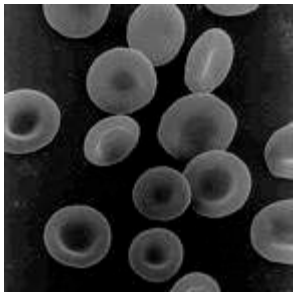
An example of nature selecting against both homozygotes was found in Central Africa. This is an area in which malaria has long been a serious problem. While 10% of the world's human population is infected by malaria, 90% of the cases are in sub-Saharan Africa. It is the major cause of death there. Children and pregnant women are especially vulnerable. An African child dies of malaria every 30 seconds on average. Malaria is caused by several related parasitic microorganisms (*plasmodia*) that feed on red blood cells. The microorganisms are transmitted from person to person by mosquitoes when they suck blood from their victims. People who produce normal red cells are good hosts and easily get the disease, which is debilitating and ultimately often results in death.



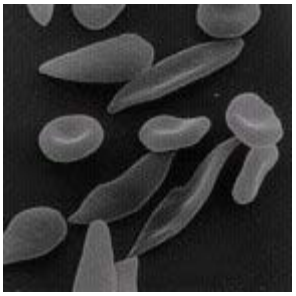
There is a high frequency of an inherited condition known as **sickle-cell trait** in African malarial zones. Homozygous recessive sicklers (aa) have resistance to **falciparum malaria** because their misshapen, deflated red cells are poor hosts. Unfortunately, these individuals usually die in childhood from **sickle-cell anemia** and related health problems. About 100,000 people around the world succumb to it every year. However, that is far fewer than the 1,500,000 who die from malaria.



People who are heterozygous (Aa) for sickle-cell trait also have moderately good resistance to malaria because some of their red cells are misshapen and deflated, but they rarely develop the severe life threatening anemia and related problems typical of homozygous (aa) sicklers. Those who are homozygous dominant (AA) produce normal red blood cells, which makes them excellent hosts for malaria. Therefore, in falciparum malarial environments, nature selects for heterozygous sicklers. At the same time, it selects against homozygous sicklers and people who produce normal red blood cells.



Normal human red cells



Deflated red cells from a human with sickle-cell anemia

The sickling allele was not produced by natural selection. It apparently pops up periodically as a random mutation. Unless it is selected for, its frequency remains very low within a population's gene pool because it results in a selective disadvantage for those who inherit it. The presence of widespread falciparum malaria changes the situation. The otherwise harmful sickling allele provides an advantage for heterozygous individuals.

Selection favoring the sickling allele is an example of biocultural evolution. Human culture altered the environment, which resulted in factors that were advantageous to both the malarial microorganisms and the mosquitoes that transmit them between people. The sequence of events apparently began about 2000 years ago with the introduction into Africa of Southeast Asian root and tree crops that were adapted to the humid tropics. This resulted in an agricultural revolution and a subsequent human population explosion in sub-Saharan Africa. Slash-and-burn forest clearance for preparing agricultural fields altered the natural environment in a way that selected for the Gambiae group of *anopheles* mosquito's that are largely responsible for spreading malaria. At the same time, the progressively increased density of humans made it easier for mosquitoes to find hosts and to inadvertently spread malaria. The more people who acquired malaria, the more likely it was for mosquitoes to transmit the malaria *plasmodia* to new hosts. Subsequently, the sickling allele became increasingly valuable as a population defense against the devastating effects of malaria. This natural selection by malaria in sub-Saharan Africa was not so complete as to result in a balanced polymorphism in just one generation. In fact, after nearly 2,000 years of selecting for the sickle-cell allele, it is not often found to be above 20% in any major African population.

Sickle-cell trait is very rare in North America with a single exception--African Americans. One in 12 of them carry the allele for sickle-cell trait and about 80,000 have sickle-cell anemia or other related clinical symptoms. One in 375 African American children is homozygous recessive for it. This is not surprising because most African Americans have ancestors who came from the malarial zones of West and Central Africa.

Several other genetically inherited conditions may provide a degree of immunity to malaria in regions of the world in which sickle-cell trait is rare. Thalassemia and glucose-6-phosphate dehydrogenase deficiency (G6PD) may be in this category. They occur especially among people in South Asia and around the Mediterranean Basin. Both of these conditions result in severe anemia. As in the case of sickle-cell trait, this anemia apparently makes the victims poor hosts for the

malaria plasmodia. It is likely that all three of these inherited blood abnormalities are biological solutions to the problem of surviving the harsh natural selection caused by malaria.

Selection Against The Heterozygote And One Of The Homozygotes

If natural selection is against an allele in both homozygous and heterozygous genotypes, the rate of change in gene pool frequencies will usually be much more rapid. In fact, it can result in the elimination of an allele in only one generation. For example, if both aa and Aa genotype individuals fail to reproduce, then only AA people will contribute their genes to the next generation--the descendents will only inherit "A" alleles. This is an extreme form of directional selection.

Selection against the heterozygote and one of the homozygotes (Aa and aa)			
Possible parent mating patterns	Expected offspring genotypes		
	AA	Aa	aa
AA X AA	4		
Total	4 (100%)	0 (0%)	0 (0%)

There are at least 5,000 genetically inherited human abnormalities and diseases. Apparently, many, if not most, of them are caused by recessive alleles. Usually, these alleles are carried without symptoms by heterozygous (Aa) individuals and are only selected out of the gene pool when homozygous recessive (aa) children are born. In order for humanity to be quickly rid of these diseases, there would have to be selection against both the heterozygous and the homozygous recessive individuals. However, this extreme form of natural selection is very rare.

Genetic testing and counseling is now often aimed at discouraging heterozygous carriers of harmful recessive alleles from reproducing. Sickle-cell trait and Tay-Sachs disease have been the main focus of this health campaign in North America. It has been particularly effective among the Ashkenazi (Eastern European) Jewish population in the United States. While they have a very high frequency of the allele for Tay-Sachs disease, the number of their children now born with it is low due to hard personal decisions that many Jews make based on genetic testing and education. By choosing not to have children, people who carry the recessive allele do not pass it on. The attempt at eliminating sickle-cell trait has been somewhat less successful among African Americans.

Selection Against The Heterozygote

When natural selection is only against heterozygotes, there will be four successful mating patterns (as shown in the table below). These will normally result in half of the children being heterozygous (Aa).

Selection against the heterozygotes (Aa)			
Possible parent mating patterns	Expected offspring genotypes		
	AA	Aa	aa
AA X AA	4		
AA X aa		4	
aa X AA		4	
aa X aa			4
Total	4 (25%)	8 (50%)	4 (25%)

However, if natural selection eliminates heterozygotes in childhood, the adult reproducing population will be genetically polarized. Half will normally be homozygous dominant (AA) and half will be homozygous recessive (aa) (as shown in the table below). This has been referred to as disruptive selection because both extremes are favored.

Selection against the heterozygotes (Aa)			
Possible parent mating patterns	Expected offspring genotypes		
	AA	Aa	aa
AA X AA	4		
AA X aa		~~(4)~~	
aa X AA		~~(4)~~	
aa X aa			4
Total	4 (50%)	0	4 (50%)

Selection Against All Genotypes

When nature completely selects against all genotypes (AA, Aa, aa), the result is that neither of the two alleles will appear in the next generation. More importantly, extinction of the population will occur since all genotypes are at a selective disadvantage.

Complications of Natural Selection

In all of the natural selection examples given so far, it has been assumed that there are only two alleles of each gene. However, some traits are controlled by many more alleles. In addition, simple Mendelian rules of dominance do not always hold, especially in the case of polygenic traits. It must be assumed that the way in which nature selects for or against such traits can be more complex than described here.

Through culture created technology, modern humans have been able to alter selective pressure for or against certain genes. This is mainly a consequence of two actions that are having a profound impact on our human gene pool. We have very likely increased the rate of mutation by inadvertently releasing many mutagenic chemicals and radiation into our environment. At the same time, modern medicine has reduced discrimination against harmful disease causing genes by developing cures for what previously had been fatal conditions. In the past, these genes were generally weeded out of our gene pool by natural selection killing off those who carried them. A form of eye cancer in young children, known as **retinoblastoma,** provides an example of this phenomenon. It is a rare disease, affecting only about 4 out of every million babies. Since it is a dominant trait, both homozygous dominant and heterozygous genotypes result in retinoblastoma. Prior to the development of surgical procedures to treat this cancer, it was virtually always fatal. Its victims died before they could pass it on to another generation. Most new cases were probably the result of extremely rare mutations in sex cells. With adequate treatment, 70% of the patients can now survive retinoblastoma and can transmit it to at least 50% of their offspring. As a result of preventing children from suffering and dying from a horrible disease, we have increased the likelihood that more children will be born with it. This will make us ever more dependent on new costly medical treatment procedures. Is this wrong? Most of us would say of course not. Morally we cannot do otherwise. We can not let children die if we can prevent it. However, it does create a growing dilemma for humanity. We potentially are building up an ever larger genetic load of harmful genes because we have hindered nature's ability to eliminate them from our gene pool.

Small Population Size Effects

Genetic Drift

In small, reproductively isolated populations, special circumstances exist that can produce rapid changes in gene frequencies totally independent of mutation, recombination, and natural selection. These changes are due solely to chance factors. The smaller the population, the more susceptible it is to such random changes. This phenomenon is known as genetic drift.

In order to get a better understanding of the potential effect of population size on evolution, it is useful to carry out a simple coin flipping experiment. The expectation is that heads will turn up 50% of the time because there are only two sides to a coin--heads and tails. If you flip a coin 10 times, it may or may not result in 5 heads.

 **Coin flipping experiment**. Take a coin out of your pocket. Flip it 10 times and record the results.

Repeat the experiment twice. Calculate the percentage of times the coin came up heads in each of your three experiments and, finally, in all of your experiments combined. What did you learn?

The more times that you flip your coin, the more likely it will approach the expected 50% heads. If you do it an infinite number of times, it will be 50%. In other words, when a sample is very small,

the probable outcome may not occur. As the sample increases in size, it will get progressively closer to it.

This kind of deviation from the expected outcome with small samples also occurs in genetic inheritance when breeding populations are very small. For example, when women and their mates are both heterozygous (Aa) for a trait, we would expect that 25% of their children will be homozygous recessive (aa). By chance, however, a particular couple might not have any children with this genotype (as shown below in the Punnett square on the right).

expected

	A	a
A	AA	Aa
a	Aa	aa

genotypes of children
25% *AA*
50% Aa
25% aa

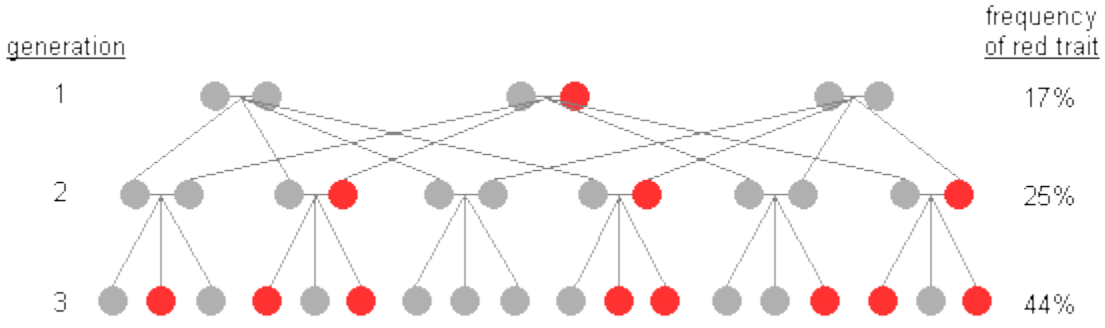
chance deviation

	A	a
A	AA	Aa
a	Aa	~~a a~~

genotypes of children
33.3% *AA*
66.7% Aa
0.0% aa

Unless other families have an unpredictably large number of homozygous recessive (aa) children for this trait to counter the deviation, the population's gene pool frequencies will change in the direction of having fewer recessive alleles--genetic drift will occur.

The net effect of genetic drift on a small population's gene pool can be rapid evolution, as illustrated in the hypothetical inheritance patterns shown below. Note that the red trait dramatically increases in frequency from generation to generation. It is important to remember that this can occur independent of natural selection or any other evolutionary mechanism.



Rapid genetic drift over three generations

Such distorting statistical anomalies occur regularly. In small populations, they can have a rapid, significant effect on gene pool frequencies of subsequent generations. In large populations,

however, they are commonly neutralized by other families having children with countering genotypes.

Since genetic drift is measurably effective only in small populations, it must have played a major role in the early stages of human evolution when our populations were tiny. However, even in large societies, such as the United States today, there are small, culturally isolated communities like the Amish and Dunkers of rural Pennsylvania and the Midwest that are mostly closed breeding groups. In such sub-populations, genetic drift is still an important evolutionary mechanism.

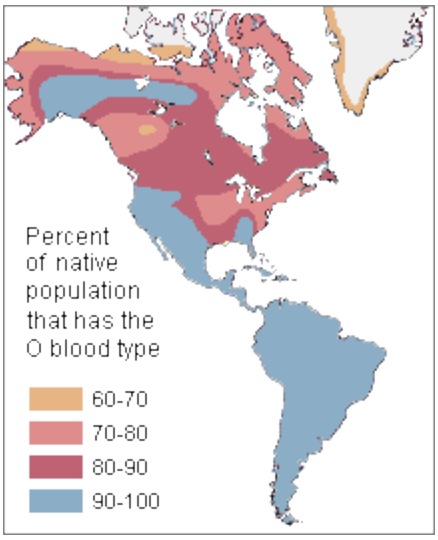
Founder Principle

Another important small population effect is known as the founder principle or founder effect. This occurs when a small amount of people have many descendants surviving after a number of generations. The result for a population is often high frequencies of specific genetic traits inherited from the few common ancestors who first had them.

In the Lake Maracaibo region of northwest Venezuela, for instance, there is an extraordinarily high frequency of a severe genetically inherited degenerative nerve disorder known as **Huntington's disease**. Approximately 150 people in the area during the 1990's had this rare fatal condition and many others were at high risk for developing it. This disease usually does not strike until early middle age, after people have had their children. However, Huntington's can occur much earlier. About 10% of its victims develop symptoms when they are younger than 20 years old. There is no cure for this disease, but there has been a test for its genetic marker available since 1993.

All of the Lake Maracaibo region Huntington's disease victims trace their ancestry to a woman named Maria Concepción Soto who moved into the area in the 19th century. She had an unusually large number of descendants and was therefore the "founder" of what is now a population of about 20,000 people with a high risk of having this unpleasant genetically inherited trait.

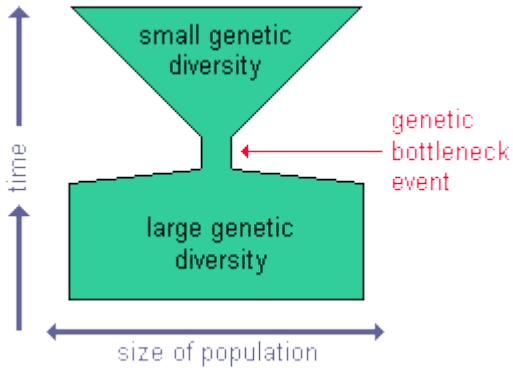
Another example of the founder effect has been discovered among the 16-18,000 Old Order Amish people of Lancaster County, Pennsylvania. They are descended from a few dozen individuals belonging to an Anabaptist sect in Germany who migrated to Pennsylvania during the early 1700's. Over the last 40 years of the 20th century, 61 babies with an extremely rare fatal genetic disorder known as microcephaly were born to 23 Amish families. All of these families are descendants of a single Amish couple nine generations ago. They were the founders of the population with the genes for microcephaly today.



It is also possible to find the results of the founder effect even though the original ancestors are unknown. For example, South and Central American Indians were nearly 100% type O for the ABO blood system and 100% positive for the Rh blood system. Since nothing in nature seems to strongly select for or against blood types, it is likely that most of these people are descended from a small band of closely related "founders" who also shared these traits. They migrated into the region from the north, probably by the end of the last Ice Age.

Bottleneck Effect

In many species, there have been catastrophic periods caused by rapid dramatic changes in natural selection, during which most individuals died without passing on their genes. The few survivors of these evolutionary "bottlenecks" then were reproductively very successful, resulting in large populations in subsequent generations. The consequence of this bottleneck effect is the extraordinary reduction in genetic diversity of a species since most variability is lost at the time of the bottleneck.



Gene Flow

Evolution can also occur as a result of genes being transferred from one population to another. This gene flow occurs when there is migration. The loss or addition of people can easily change gene pool

frequencies even if there are no other evolutionary mechanisms operating. For instance, if all red haired people were to leave Scotland, the next generation there would likely have very few people with this trait. The Scottish population would have evolved as would the populations into which the red haired people migrated.

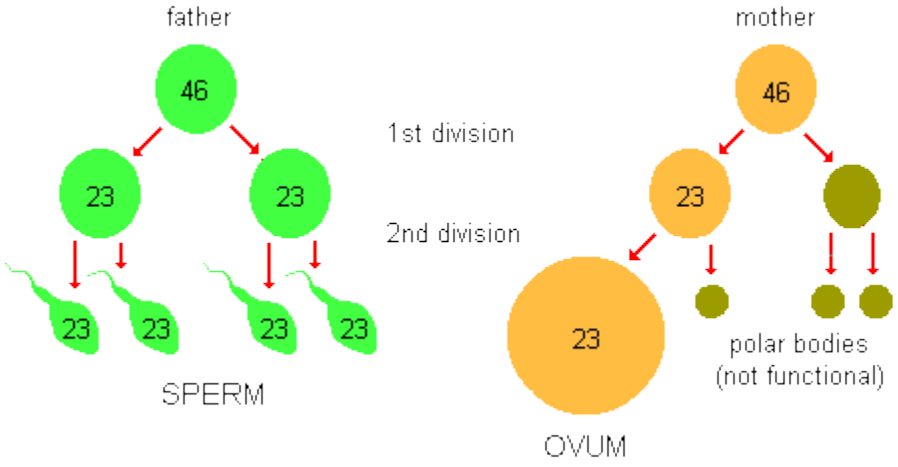
Gene flow can also occur without migration. When people travel to another area and successfully mate with people in the population there, a transfer of genes occurs between the populations even though the traveler returns home. For example, when U.S. soldiers had children in Southeast Asia with Vietnamese women during the war there in the 1960's and early 1970's, they altered the gene pool frequencies of the Vietnamese population.

Genes may occasionally also flow between species. For instance, bacterial DNA may be transferred to animals or plants. This apparently rare form of gene flow has been documented for some species of insects, but it has not been conclusively demonstrated for humans.

Recombination

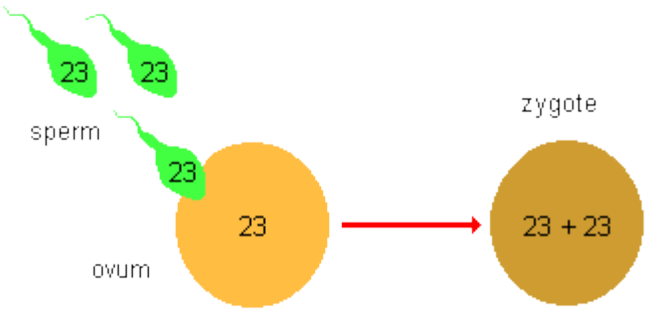
Natural selection is usually the most powerful mechanism or process causing evolution to occur, however, it only selects among the existing variation already in a population. It does not create new genetic varieties or new combinations of varieties. One of the sources of those new combinations of genes is recombination. It is responsible for producing genetic combinations not found in earlier generations.

Sperm and ova are radically different from somatic cells in the number of chromosomes that they contain. Both male and female sex cells normally get only half of the pair of parent chromosomes (23 for humans). Which half goes to any one sex cell is a matter of chance.



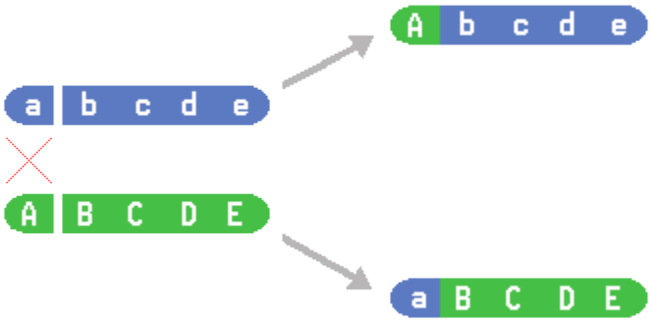
Net effect of the meiosis process in terms of chromosome numbers

At conception, a single sperm and an ovum combine their chromosomes to produce a zygote with the normal full set of 46, but with a new combination of chromosomes distinct from either parent.



Sperm and ovum combining their chromosomes in a new zygote

New combinations of existing genes are produced at the beginning of meiosis when the ends of chromosomes break and reattach, usually on their homologous chromosome. This crossing-over process results in an unlinking and recombination of parental genes. In the example below, one end of each chromosome of this homologous pair is exchanged along with the genes that they contain. The next generation inherits chromosomes with partially new sequences of alleles.



Crossing-over

The consequence of this recombination is the production of sperm and ova that can potentially add even greater diversity to a population's gene pool. However, it does not result in new alleles. Subsequently, recombination by itself does not cause evolution to occur. Rather, it is a contributing mechanism that works with natural selection by creating combinations of genes that nature selects for or against.

Non-Random Mating

In all human populations, people usually select mates non-randomly for traits that are easily observable. Cultural values and social rules primarily guide mate selection. Most commonly, mating is with similar people in respect to traits such as skin color, stature, and personality. Animal breeders do essentially the same thing when they intentionally try to improve varieties or create new ones by carefully making sure that mating is not random. When they select mates for their animals based on desired traits, farmers hope to increase the frequency of those traits in future generations. In so far as the discriminated traits are genetically inherited, evolution is usually a

consequence. However, the results are not always what farmers expect. The reasons why will be explained shortly. Even without the intervention of farmers, most animals select mates carefully--they do not mate randomly.

In order to understand the effect of non-random mating patterns, it is useful to first examine the results of random mating. As Hardy and Weinberg demonstrated in the early 20th century, the gene pool of a population that is mating randomly and is not subject to any other evolutionary process will not change--it will remain in equilibrium. If mating is entirely random, there will be nine possible mating patterns for a trait that is controlled by two alleles (A and a).

AA X AA	Aa X AA	aa X AA
AA X Aa	Aa X Aa	aa X Aa
AA X aa	Aa X aa	aa X aa

In a population which has 50% of each of these two alleles, the expected offspring genotype frequencies with random mating will be 25% homozygous dominant (AA), 25% homozygous recessive (aa), and 50% heterozygous (Aa), as shown in the table below. They will remain in this ratio every generation that random mating continues and no other evolutionary mechanism is operating.

Random Mating			
Possible parent mating patterns	Expected offspring genotypes		
	AA	Aa	aa
AA X AA	4		
AA X Aa	2	2	
AA X aa		4	
Aa X AA	2	2	
Aa X Aa	1	2	1
Aa X aa		2	2
aa X AA		4	
aa X Aa		2	2
aa X aa			4
Total	9 (25%)	18 (50%)	9 (25%)

The number of children are what would be expected by chance if each mating pair has 4 children.

You can work this out yourself by creating a Punnett Square for each set of parents.

Positive Assortative Mating

The most common non-random mating pattern among humans is one in which individuals mate with others who are like themselves phenotypically for selected traits. This is referred to as positive assortative mating. The term "assortative" refers to classifying and selecting characteristics. An example of positive assortative selection would be tall slender people mating only with tall slender

people. Taken to the extreme, positive assortative mating results in only three possible mating patterns with respect to genotypes for traits that are controlled by two autosomal alleles--homozygous dominant with homozygous dominant (AA X AA), heterozygous with heterozygous (Aa X Aa), and homozygous recessive with homozygous recessive (aa X aa).

The net effect of positive assortative mating is a progressive increase in the number of homozygous genotypes (AA and aa) and a corresponding decrease in the number of heterozygous (Aa) ones in a population, as shown in the table below. Each generation that there is positive assortative mating, this polarizing trend will continue in the population.

Positive Assortative Mating			
Possible parent mating patterns	Expected offspring genotypes		
	AA	Aa	aa
AA X AA	4		
Aa X Aa	1	2	1
aa X aa			4
Total	5 (42%)	2 (17%)	5 (42%)

Negative Assortative Mating

The least common non-random mating pattern among humans is one in which people only select mates who are phenotypically different from themselves for selective traits. This is referred to as negative assortative mating. It would occur, for instance, if people who have the Rh negative blood type only mate with those who are Rh positive.

In terms of genotypes, there are six possible negative assortative mating patterns for traits that are controlled by two autosomal alleles, as shown in the table below. The net effect is a progressive increase in the frequency of heterozygous genotypes (Aa) and a corresponding decrease in homozygous (AA and aa) ones in a population. In other words, negative assortative mating has the opposite effect as positive assortative mating.

Negative Assortative Mating			
Possible parent mating patterns	Expected offspring genotypes		
	AA	Aa	aa
AA X Aa	2	2	
AA X aa		4	
Aa X AA	2	2	
Aa X aa		2	2
aa X AA		4	
aa X Aa		2	2
Total	4 (17%)	16 (67%)	4 (17%)

Evolutionary Consequences of Non-random Mating

Like recombination, non-random mating can act as an ancillary process for natural selection to cause evolution to occur. Any departure from random mating upsets the equilibrium distribution of genotypes in a population. This will occur whether mate selection is positive or negative assortative. A single generation of random mating will restore genetic equilibrium if no other evolutionary mechanism is operating on the population. However, this does not result in a return to the distribution of population genotypes that existed prior to the period of non-random mating. A comparison of the 2nd and 5th generations in the table below illustrates this fact.

Effects of non-random mating on a population's gene pool					
Generation	Parent mating pattern	Offspring genotype frequencies			Effect on genotype frequencies
		AA	Aa	aa	
1	random	50%	30%	20%	equilibrium
2	random	50%	30%	20%	equilibrium
3	negative assortative	45%	40%	15%	change
4	negative assortative	40%	50%	10%	change
5	random	40%	50%	10%	equilibrium
6	random	40%	50%	10%	equilibrium
7	positive assortative	43%	45%	12%	change
8	positive assortative	48%	34%	18%	change

NOTE: genotype frequencies in an actual population may differ somewhat from those in this table, but the direction of change from generation to generation will be the same.

Plant and animal breeders usually employ controlled positive assortative mating to increase the frequency of desirable traits and to reduce genetic variation in a population. In effect, they try to guide the direction of evolution by preventing some individuals from mating and encouraging others to do so. By doing this, farmers, in a sense are acting in the place of nature in selecting winners and losers in the competition for survival. This method has been used to develop purebred varieties of laboratory mice, dogs, horses, and farm animals. The amount of time it takes for this process can be much shorter than one might imagine. If brothers and sisters are mated together every generation, it will only take 20 generations for all individuals in a family line to share 98+% of the same alleles—they essentially will be clones, and breeding results will be close to those resulting from self-fertilization. Commercially sold laboratory research mice have been mated brother to sister for 50-100 generations or more. The downside of this practice is that positive assortative mating results in an increase in homozygosity of harmful alleles if they are present in the gene pool. The high frequency of hip dysplasia, epilepsy, and immune-system malfunctions in some dog varieties are primarily a result of inbreeding. The reduction in viability and subsequent loss of reproductive potential of purebred varieties has been referred to as **inbreeding depression**. In contrast, animals that have been crossbred with mates from very different genetic lines are more likely to have lower frequencies of homozygous recessive conditions. Subsequently, they are liable to be more viable. This phenomenon has been referred to as **hybrid vigor** or **heterosis**.

Human mating rarely is as consistently positive assortative as is the case with purebred domesticated animals. As a consequence, inbreeding depression is rarely a problem except for some reproductively isolated small societies and subcultures. The Old Order Amish are an example. This relatively small population centered in Pennsylvania and Ohio has been self-isolated by their religious beliefs and lifestyle for nearly three centuries. They mostly select mates from within their own communities, which results in positive assortative effects on their gene pool. The Amish population has a comparatively high frequency of Ellis-van Creveld syndrome , which is a genetically inherited disorder characterized by dwarfism, extra fingers, and malformations of the arms, wrists, and heart. The majority of the known cases in the world of this rare syndrome have been found among the Amish, and 7% of them carry the responsible recessive autosomal allele.

Consanguineous Mating

Consanguineous mating, or inbreeding, is the sexual union of closely related individuals, such as brothers, sisters, or cousins. It is an extreme form of positive assortative mating since close relatives usually are genetically more similar than are unrelated people who share a few traits. When siblings mate together, it is in effect positive assortative mating for many genetic traits. Half of the alleles of brothers and sisters are likely to be shared. If they mate together, their children would be expected to have a quarter of those alleles in common. Therefore, when consanguineous mating occurs, the result is significantly less genetic diversity among the descendants than if the parents had mated with someone who was not closely related but was like them in terms of selected traits such as skin color or stature.

It has long been assumed by the general public in western nations that children of inbred parents inevitably have a high probability of inheriting mental retardation and other serious genetic defects. This is not necessarily true. If a harmful allele is present in a family, it will show up at a

higher than normal rate among inbred children. If inbreeding continues to be the common mating pattern in a family line, it is likely that homozygosity will increase in frequency and the family will experience a progressive rise in the genetic load of the deleterious allele. On the other hand, if the allele is not present in the family line, inbred offspring are not likely to have a higher than normal risk of inheriting a mutation for it. Inbreeding also could potentially increase the odds of a child inheriting desirable traits. If the family genetic line has alleles that contribute to advantageous characteristics, such as intelligence, health, or what their culture defines as beauty, they are more likely to show up in children resulting from inbreeding if the parents have these characteristics. Consanguineous mating also may be an advantage for women who are Rh negative because it would increase the chances that their children would be Rh negative. As a consequence, there would be a lower risk of erythroblastosis fetalis in the children. You will learn more about this potentially fatal condition and its connection with Rh blood types in the next tutorial of this series.

The closer two mates are in generational distance from their common ancestor, the greater the likelihood of positive assortative effects on the genomes of their children. Based on statistical data for 38 populations in South Asia, Africa, Europe, and South America, it has been determined that the increased risk for "significant birth defects" among the offspring of first cousins is only 1.7-2.8% above the risk for the general population. The predicted risk for the children of brothers and sisters or parents and their children is 6.8-11.2% above that of the general population. Based on these numbers, it would seem that while the risk is high for very close biological relatives, it is relatively low for first cousins and more distant kinsmen. In fact, there is a high probability that the children of first cousins will not have significant birth defects. In addition, there does not appear to be a statistically significant increase in the frequency of gross chromosomal anomalies, such as trisomy-21 (Down syndrome), in the children of consanguineous unions.

While first cousin marriages are extremely rare in North America, Europe and East Asia, they are very common in some parts of the world due to long existing cultural traditions. Roughly a third of the marriages in rural India are between first cousins. In the Arabian Peninsula, the rate is 50% or higher. In both areas, there are ongoing nationwide educational campaigns to discourage first cousin marriages. The hope is that if they are successful in reducing the number of such unions, it will cut medical costs for the nations. So far there has been some success in changing the marriage patterns of more educated urban Saudis and Indians, but there have been little inroads into rural areas where most first cousin marriages occur.

A recent statistical study of 165 years of genealogies for 160,000 couples in Iceland has shown somewhat surprising results. Married couples who were third cousins (they shared a great-great-grandparent) had more offspring than did couples who were less closely related. In other words, marrying third cousins resulted in greater reproductive success. However, couples who were first or second cousins had fewer offspring and those children died at a younger age.

Summary

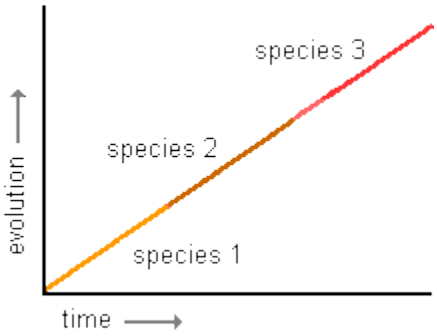
We have seen in this and previous sections of the tutorial that evolution can result from any of four main processes operating independently or together. In addition, there are two ancillary contributing processes.

Main processes	Ancillary processes
1. mutation	1. recombination
2. genetic drift	2. non-random mating
3. natural selection	
4. gene flow	

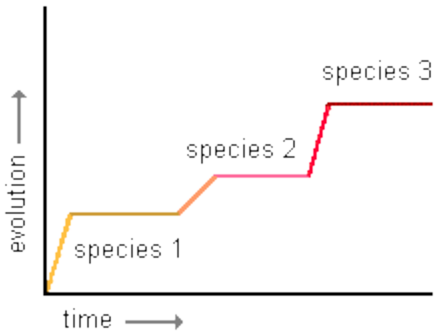
Mutation is the ultimate source of new genetic varieties in a species. However, gene flow can be responsible for the introduction of new alleles into a population. Generally the most rapid and dramatic evolution is due to natural selection. Recombination and non-random mating can change the frequencies of genotypes which in turn can be selected for or against by nature. Genetic drift can also result in rapid evolution of the gene pools of very small, reproductively isolated populations. It is highly likely that our ancestors lived in such small populations for 99+% of the last 2.5 million years during which our genus *Homo* was evolving. Subsequently, genetic drift and other small population size effects must have frequently been a major factor in our evolution along with natural selection.

Micro and Macro Evolution

Throughout most of the 20th century, researchers developing the synthetic theory of evolution primarily focused on **microevolution**, which is slight genetic change over a few generations in a population. Until the 1970's, it was generally thought that these changes from generation to generation indicated that past species evolved gradually into other species over millions of years. This model of long term gradual change is usually referred to as **gradualism** or phyletic gradualism. It is essentially the 19th century Darwinian idea that species evolve slowly at a more or less steady rate. A natural consequence of this sort of **macroevolution** would be the slow progressive change of one species into the next in a line, as shown by the graph on the right.



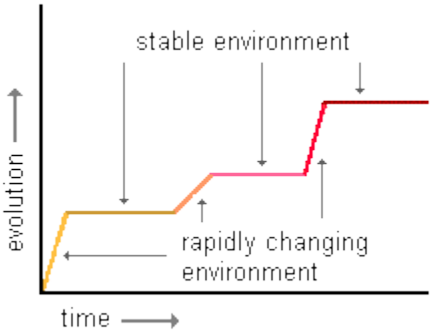
Gradualism



Punctuated equilibrium

Beginning in the early 1970's, this model was challenged by Stephen J. Gould, Niles Eldredge, and other leading paleontologists. They asserted that there is sufficient fossil evidence to show that some species remained essentially the same for millions of years and then underwent short periods of very rapid, major change. Gould suggested that a more accurate model in such species lines would be **punctuated equilibrium** (illustrated by the graph on the left).

The punctuated, or rapid change periods, were presumably the result of major environmental changes in such things as predation pressure, food supply and climate. During these times, natural selection can favor varieties that were previously at a comparative disadvantage. The result can be an accelerated rate of change in gene pool frequencies in the direction of the varieties that become the most favored by the new environmental conditions. It would be expected that long severe droughts, major volcanic eruptions, and the beginning and ending of ice ages would be likely triggers for rapid evolution.



Long periods of stability and short episodes of change

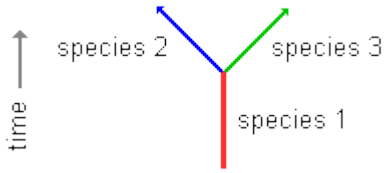
Random mutations provide variations that help a species survive. Mutations in regulator genes in particular can quickly result in radically new variations in the organization of the body and its important structures. As a consequence, changes in these genes can result in a greater likelihood that at least some individuals will have variations that will allow them to survive during times of extinction level events. In this situation, subsequent generations would be significantly changed from the generations before the period of severe natural selection. In other words, regulator genes probably play an important part in the rapid change phases of punctuated evolution.

It is now quite apparent that the evolutionary history of life on this planet is extremely complicated. Different species have evolved at different rates and those rates have changed through time in response to complex patterns of interaction with other species and other environmental factors. In addition, it is clear that most species lines have already become extinct as a result of their inability to adapt to changed conditions.

Origin of Species

Where do new species come from? That is a key question that the biological sciences have been asking for more than 200 years. Charles Darwin gave us part of the answer in his explanation of natural selection. The remainder came as a result of Gregor Mendel's experiments with basic genetic inheritance and the 20th century discoveries of the other natural processes that can cause evolution. We now know that evolution can occur in two different patterns--adaptive radiation into

multiple species results in **cladogenesis** and successive speciation within a single evolutionary line results in **anagenesis** .



Adaptive radiation
resulting in cladogenesis

Successive speciation
within a single species line
resulting in anagenesis

Adaptive radiation is the progressive diversification of a species into two or more species as groups adapt to different environments. Natural selection is usually the principle mechanism driving adaptive radiation. The initial step is the separation of a species into distinct breeding populations. This usually happens as a result of geographic or social isolation. Over time, the gene pools of the isolated populations diverge from each other by gradually acquiring different mutations and sometimes as a result of random genetic drift. When the populations are in dissimilar environments, environmental stresses are often not the same. As a result, nature selects for different traits existing within the gene pools of the populations. Over time, the populations genetically diverge enough so that they can no longer reproduce with each other. At this point, they have become separate species and usually continue to diverge in subsequent generations. In intermediate stages, the two newly or about to be separated species may be able to interbreed and produce children, but most of them are likely to be sterile. This is the case with the offspring of horses and donkeys--i.e., mules. Eventually, however, species genetically diverge so much that they are unable to produce any children. This is the case with sheep and cattle.

The evolution of species by successive speciation occurs within a single evolutionary line without the branching of adaptive radiation. This takes place when the members of a species consist of a single breeding population for many generations. Descendant generations experience continuous spontaneous mutations and new directions of natural selection as the environment changes. This results in progressive changes in the gene pool frequencies of the population. At any one time, all members of the population are the same species. However, as generations subsequently replace each other, the gene pool is transformed--i.e., it evolves. Eventually, the changes are great enough that if descendants could go back in time to mate with their distant ancestors, the genetic differences would prevent them from producing fertile offspring. In other words, they would be different species.

In the real world, the patterns of evolution can be very complex and changing. Both adaptive radiation and successive speciation can go on simultaneously.

Origin of Life

It may seem strange that the question of the ultimate origin of life on earth was not discussed at the beginning of this tutorial. It was an intended omission. The focus has been on the processes by which living things change through time, not on how life first came about. These are separate issues. A consideration of ultimate origins bridges into the realm of religion for many people. Regardless of whether you believe that life began spontaneously as a result of natural processes or was due to divine intervention, it is sobering to realize that science is close to being able to create life out of non-living substances. In fact, most of the initial steps have already been taken. The video linked below shows just how close we are to creating living organisms.