Mutations, selection, and isolates.

When a mutation arises in an isolate, it cannot in the first generation be the subject of selection (unless it is a simple dominant). It can disappear by chance, but it can, also by chance, pass into the next generation. In the latter case it is still free from selection, and this is also the case in the following generation, as marriages between brothers and sisters do not take place among human beings. In the third generation, too, it is practically free, as it is extremely seldom that aunts and uncles marry their nephews and nieces. Only in the fourth generation, following a marriage between cousins, can the mutation be subject to selection. The genes may then unite to form homozygotes.

It should however, be remembered that if the cousins, who are heterozygotes in the fourth generation, are of the same sex, the mutation cannot conceivably be subject to selection after a marriage between cousins. If there are two heterozygotes, the probability of this is $\frac{1}{2}$, and if there are three, $\frac{1}{4}$. All this means that, to start with, mutations are not subject to selection. Only after heterozygosis has reached a certain extent do character-bearers appear who are thus subject.

If the selection is absolute, so that every character-bearer is prevented from propagating, a state of balance will set in at a minimum heterozygous frequency, which is determined by the mutation frequency. If we assume a population where the gene is absent to begin with and where a certain mutation frequency appears combined with absolute selection, the heterozygous frequency will slowly rise to the state of balance. If we assume that mutations cease after this has been reached, the heterozygous frequency will slowly decrease and asymptotically approach 0, though this process will, of course, be extremely gradual.

Now, the position of the least heterozygous limit depends not only on the mutation frequency but also on the intensity of the selection, and on the processes present in the population, namely the size of the isolates, assortative mating, and inmarriage. It is, of course, different in different modes of inheritance.

Let us assume that the state of balance lies at a frequency of character-bearers of $1: N$. If the character is monohybrid-recessive and the gene has the frequency $r$, we get:
Therefore, The frequency of heterozygotes, $2^{rd}$, will be:

If $n$ is a large number, the expression will be approximately.

In polyhybrid recessivity, when the different genes have the frequencies $r_1, r_2, r_3, \ldots, r_n$, the state of balance lies at
If $r_1, r_2, r_3, \ldots, r_n$, i.e. every $dx = d$, we get:

The heterozygous frequency will then be:

If $n$ is a large number but $n$ is not, we get:

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In polyhybrid dominance, when the dominant gene has the frequencies $d_1, d_2, d_3, \ldots, d_n$, and the recessive gene the frequencies $r_1, r_2, r_3, \ldots, r_n$, the state of balance will lie at:
If $d_1 = d_2 = d_3 = \ldots d_n$, we get:

The heterozygous proportion at the least heterozygote limit will be:

If we know the frequency of the character-bearers to be subject to selection, we can use these formulæ to calculate the frequency of the genes and of the heterozygotes in the different hereditary mechanisms.

We have previously stated that, at a certain mutation frequency and a certain selection, a state of balance must gradually set in, when the number of individuals eliminated by selection corresponds to the number of mutations in monohybrid dominance and double mutation frequency in monohybrid recessivity. Let us assume that for some reason this state of balance is upset. The gene is assumed to have the frequency $r$. The mutation frequency is . Selection eliminates $k$ of the character-bearers, $r_2$. In this situation a change from generation to generation takes place. The difference between two consecutive generations is:

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Seeing that the process approaches the state of balance asymptotically, it will go on infinitely. We can then assume that the time represented by one generation is infinitely small; the difference between two
generations can thus be taken as the derivative with respect to time for a function expressing the course of the process. Thus:

By integration we get:

\[ r'0 \text{ is the gene frequency found in the primary generation, } r'1 \text{ is the gene frequency at the state of balance, and } r \text{ is a value between these, for which we will compute the time. It must be remembered that the equation cannot be used when } r'0 \text{ approaches } r'1. \]

We have assumed that the time one generation represents is very small in relation to the time elapsing before the state of balance is reached; this is not the case for extremely small differences from the state of balance. We have then no right to consider the discontinuous function to be continuous. For the rest, the equation shows that if \( r'0 \) deviates from \( r'1 \), but \( r'1 = r \), i.e. the value we are looking for is the frequency at balance between selection and the mutation, \( n \) will be . This means that the state of balance is only reached at infinity. It is therefore of interest to calculate the time which elapses before the state of balance is half reached, i.e. till that frequency which is the mean of the primary value and the frequency at balance. Assume that \( r'0 = cr'1 \) and thus:

We then get:

If \( k = 1 \), i.e. if there is total selection, and if we get:

and,

If \( k = 1 \) and we get:

We can with the help of these expressions calculate the number of generations needed for a change from a certain frequency of character-bearers to another frequency. We have previously asserted that the frequency of very rare monohybrid characters in a number of Western European countries may possibly have decreased to half that of about 50 years ago, on account of isolate-breaking. It will take infinite time before the state of balance is again achieved. It may, however, be of interest to calculate the time it takes to halve the distance between
the present frequency and the frequency of the state of balance. If
the original frequency is \( r_2 = 2 \) and the present frequency is \( r_2 \)
— halfway between them is:

We require, further, a value for the mutation frequency. Haldane
has made approximate, and naturally extremely uncertain calculations,
giving as a result a mutation frequency of \( 1: 105 \). If we assume total
selection, we find with the help of formula 84 a that, after 123 generations,
the difference has been levelled out by half: this if we reckon
25 years to a generation, would correspond to 3000 years. The calculation
gives a notion of how slowly the mutation frequency levels out
a deviation from the state of balance.
Haldane (1939 and 1940) has carried out a similar calculation, starting
from the view that there is in a population a certain amount of
inmarriage greater than would be expected in panmixia, and that
the state of balance prevailing in this situation is changed by a change
of the inmarriage frequency. The calculations he made give figures
of the same order of magnitude.
We have above discussed mutation frequency and selection assuming
that the processes take place in very large populations and for long
periods of time. Actually, of course, the populations are limited; not
only this, they are divided up into isolates of moderate size. The frequency
that genes arising through mutation have in the isolates will,
as a matter of fact, be very much conditioned by chance. If a heterozygote
results from mutation, the probability that the gene will disappear
and not be represented in the next generation is one quarter if
each marriage has, on an average, two children who reach sexual
maturity. In addition to this, the heterozygote in question may for
some reason be sterile, or not contract a marriage. In actual fact, the
gene runs a risk of disappearing by chance at the transition to each
new generation, but it may also happen to increase in frequency. In
small populations there is also the possibility that the gene increases

in frequency to such an extent as to give homozygosis; this means
that its allelomorph disappears at random. Processes of this kind
can probably play an important part for animals and plants. The first
to point out this possibility was Hagedoorn (1921). Subsequently
Sewall Wright (1921, 1930, 1931, 1932, 1934, 1935) and R. A. Fisher
(1928, 1930, 1931) analysed the problem mathematically from several
aspects. Dobzhansky (1937) has discussed the problem against the background of empirical investigations, and reviewed the literature in this field.

As regards man, there is hardly reason to reckon with random increase of mutations, giving rise to homozygosis, within isolates in civilized populations. On the other hand, there is no doubt that the opposite possibility—a random disappearance of mutations—is of importance; we must therefore take into account that certain genes are completely lacking in certain isolates, and have a larger or smaller frequency in others—that is to say, that that situation arises which the author earlier on assumed to obtain for genes of certain rare defects. But it can hardly be of interest to review in this connexion the mathematical expositions that have been made. Those who are interested are referred to the literature quoted, above all to the work of Dobzhansky.