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Genetic Loads in Natural Populations

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In every age there have been those who believed that mankind manages its affairs badly and that it faces a bleak future. Ours is the "age of anxiety," and fears are probably more widespread than they used to be. Certainly the fears go deeper. Even the gloomiest prophets of old held that, no matter what disasters may come, human nature will continue to be pretty much what it has always been. But the prophets of today believe that human nature itself is endangered, since the biological endowment of mankind is in decay.

The prophets of today may be right. The human race may be a failure. Man has become powerful enough to destroy himself. However, we should not accept the dire prophecies without careful scrutiny. The situation may not be beyond repair. It may also not be amiss to note that our understanding of human nature, and of the natures of other forms of life, is not quite sufficient to formulate a reliable prognosis. Many biologists hope that a better understanding might be helpful, and that it could be achieved through investigation of the natures of living species which are more accessible to such investigation than that of the human species is. But these hopes collide head-on with the not unreasonable doubt whether much light can be shed on the nature of man by studying anything other than man himself.

Anaximander of Miletos proclaimed, some 2500 years ago, that man was biologically unique. Anaximander thought that all living creatures except man arose by spontaneous generation from mud warmed by sun rays. Man alone developed by transformation from other organisms. The issue is still joined. Having examined all the biases, pitfalls, and sources of error, a human geneticist recently proved that man is, after all, not an overgrown *Drosophila* fly, and not even an overgrown mouse. We concur in his conclusion. Biologists have at times made themselves ridiculous by talking about man as though he were nothing but an animal. Man's human properties make him biologically unique. Even different species of *Drosophila* are not alike in their biological natures. It would be odd indeed if man had no genetic peculiarities.

The incontrovertible fact is, however, that in many ways man does resemble other life. Man is a sexually reproducing, outbreeding species. So are mice and most drosophilae. This imposes profound similarities on human, drosophiline, and murine biological natures. It is as unreasonable to overlook these similarities as it is to ignore man's uniqueness. Among the inevitable consequences of being a sexual, diploid, and outbreeding species is that man, as well as *Drosophila,* is burdened with loads of deleterious mutants. Under some circumstances, these mutants produce hereditary diseases, malformations, and constitutional weaknesses in their carriers.

Origin

It is not my purpose here to set forth in any detail the story of the origin of the mutational loads. However, the essentials are simple enough. Mutations are alterations of the hereditary materials which occur presumably in every living species. We do not know just why most mutations arise, and to conceal our ignorance, we call them "spontaneous." Thus far, genetics has found no effective means to diminish the frequency of the occurrence of spontaneous mutants. But it has discovered ways to increase their frequencies by high-energy radiations and by other mutagens. This is unfortunate, because increased frequency of mutations in the human population may endanger man's biological future.

Most mutations are more or less injurious to the organism. It is not hard to see why this should be so. The injurious character of most mutants is not an attestation of inherent perverseness of nature. A change in a gene is expected to be injurious for the same reason for which random rearrangement of wires in a radio set would spoil it more often than improve it. Moreover, most mutations which we observe today have occurred many times before we started to look for them, and the ones which were useful instead of detrimental have become established like the correct wiring in the radio set.

Magnitude

Data more precise than those now available are needed concerning the frequencies of mutations in different organisms, from *Drosophila* to mouse to man. But such data alone would not tell us as much as we should know about the genetic economy of the respective species, just as figures on the import of raw materials from abroad would not alone be sufficient to understand the economic life of a country. One must find out what happens to the mutants after they invade the collective genetic endowment, the gene pool, of a population. Here we enter a field very little explored and possibly fraught with surprises.

Table 1 gives an idea concerning approximate magnitude of the load of mutations borne by natural populations of a species of *Drosophila* native in western United States and in Mexico (*1*). It may be noted parenthetically that even such crude approximations would have seemed impossible of attainment until recently, and that they are now available for only some species of *Drosophila.*

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Comparable data for man are not yet within the range of what is possible. They could be obtained in corn and in a few other organisms, but this has not yet been done.

Table 1 discloses a startling situation. Between a fourth and a third of each of the chromosomes investigated are lethal or semilethal to homozygotes; that is, they kill all or most of their carriers if they are present in duplicate. Among the chromosomes free of lethals and semilethals, from 40 to 95 percent are subvital when homozygous; that is, they cause relatively milder hereditary diseases or impairments of the organism's vitality. From 4 to 18 percent of the chromosomes do not kill their homozygous carriers physically but kill them genetically; either the males, or the females, or, rarely, both sexes are completely sterile. It may be noted that genetically caused sterility among flies, like that among human beings, is often not accompanied by any noticeable impairment of body vigor. A genetic death does not always produce a cadaver.

It should be kept in mind that flies, like men, are diploid; a fly has the second, the third, and the fourth chromosome each represented twice. It can be shown by simple calculation from the data in Table 1 that the genetic endowment of 85 percent of individual flies includes one or more chromosomes which would kill their carriers if these chromosomes were present in double dose. More than half of the flies carry at least one chromosome which in homozygous condition would make either the females or the males sterile. Finally, all except a quite negligible minority of the flies carry one or more, mostly several, chromosomes which would incapacitate the homozygotes in various ways and in varying degrees short of semilethality. Since man, like *Drosophila*, is a sexually reproducing species, there is every reason to think that our load of mutations is hardly lighter than that of *Drosophila*; it may even be heavier.

Table 1. Percentages of the chromosomes in natural populations of *Drosophila pseudoobscura* which produce certain effects when in double dose (*1*).

Effects in homozygotes	Second chromosome	Third chromosome	Fourth chromosome
Lethal or semilethal	33	25	26
Subvital	93	41	95
Supervital	0.1	0.7	0.1
Female sterility	11	14	4
Male sterility	18	11	12

Effect on Fitness

If our genetic endowment is as replete with potentially morbid genetic factors as that of *Drosophila* is, this may seem to bear out the gloomiest forebodings of the decay of human nature. However, the remarkable fact is that the species of *Drosophila* whose genetic endowment is in this seemingly alarming condition is very successful in nature; it is certainly not a species approaching extinction. Moreover, it is a species living under "natural" conditions, not one grown effete because it has been pampered by civilized living. Apparently equally great loads of mutations, which would be staggering in the homozygous condition, have been found also in the few other flourishing species of *Drosophila* that have been examined in this respect. Strange as it may seem, the only known species which carries a markedly smaller load is *Drosophila prosaltans,* a rare, ecologically specialized form, which occurs spotwise in the American tropics without anywhere being the dominant species (*2*). Mention of the brilliant work of Wallace (*3*) is also relevant at this point. His experimental populations of *Drosophila* which acquired very heavy mutational loads owing to exposure to gamma rays of radium failed to show anything like a proportional reduction of their fitness.

The existence of populations seemingly saturated with injurious mutants, and yet highly successful in the struggle for life, is not as baffling as it may appear. Since heterozygous carriers of destructive recessive genes may be highly fit, the breeding structure of populations of some species sedulously provides to compensate for the load of detrimental recessive mutants by making most individuals in the populations heterozygous. Theoretically, a highly fit population may be obtained in either one of the following two extreme ways. First, the population may consist entirely of homozygotes for genetic factors which condition satisfactory fitness. Second, every chromosome in a highly fit population may be lethal in double dose, and yet it may yield high adaptedness in heterozygous combinations with all other chromosomes contained in the gene pool of the population. Of course, these extreme situations are rare in nature, if they occur at all; most populations will probably be found to have various intermediate structures. There is no way at present to tell what genetic architectures will be encountered in man or in various other organisms. This is an almost unexplored field. Although there are many difficulties in the way of such investigation, there is as much reason to study comparative genetics as there is to study comparative anatomy and comparative physiology.

The central problem posed by the existence of genetic loads in natural populations may be stated thus: What are the effects of these loads on the fitness of their carriers, given the breeding structure which the species normally has? A fearful mass of diseases and malformations would certainly appear if brother-sister mating were the normal means of reproduction in populations of *Drosophila* and of man. But incest is probably rare in most *Drosophila,* and even rarer in man. Outbreeding being the norm, the heterozygous carriers of harmful recessives are at least tolerably well off.

What may be called the classical hypothesis of genetic population structure holds that the genetic load is nothing but an unavoidable evil. The adaptively desirable condition is envisaged as homozygosis for genes giving high fitness. The genetic load results from a less than perfect efficiency of natural selection. Some generations elapse between the origin and the eventual elimination of a mutant from a population. The greater the load, the worse off the population. If mutation ceased to occur, populations would eventually throw off the load, would become homozygous, and would thereby gain in fitness.

There is every reason to think that the classical hypothesis is valid to some extent. It is obvious that mutants which cause dominant hereditary diseases, malformations, or diminished vigor detract from the fitness of their carriers. Furthermore, many recessive mutants which are lethal or strongly morbid when they are homozygous are debilitating to some extent also when they are heterozygous. Complete recessivity is not as common as genetics textbooks lead us to believe. Wright and I (*4*) inferred that recessive lethal mutants found in natural populations of *Drosophila pseudoobscura* cause slight but perceptible decreases of vigor when they are heterozygous. In 1952, this was demonstrated by Cordeiro (*5, 6*) and by Prout (*7*) for lethals in natural populations of *Drosophila willistoni,* by Stern and collaborators (*8*) for newly arisen lethal mutants in *Drosophila melanogaster,* and by Wallace (*9*) for lethals in irradiated populations of the same species.

Whether the classical hypothesis gives a valid account of the dynamics of natural populations may, however, be questioned. This would be correct only if there were no adaptively ambivalent mutants, deleterious under some conditions but favorable under others. Consider again the astonishing fact that almost every chromosome found in natural populations of *Drosophila pseudoob-*

scura is to some extent damaging in double dose. One may, to be sure, take refuge in saying that almost every chromosome normally contains several harmful recessive mutants which natural selection has not had time to eliminate. But to say this is to extend the term *recessive mutant* to a degree which makes it actually meaningless. What would a *Drosophila* and a man be like if they did not carry such recessive mutants? Perhaps they would be a superfly and a superman, but the fact is that such prodigies have never existed on earth. The species *Drosophila pseudoobscura* and *Homo sapiens* have been molded in the process of evolution as Mendelian populations which carry mutational loads. The adaptive norm of a sexual species has always consisted of individuals which carried in heterozygous condition genetic variants which would be destructive in double dose (*2*). The possibility must be considered that some degree of heterozygosis for mutants deleterious in homozygous condition may not be incompatible with high fitness in sexually reproducing species. This assumption is the essence of the balance hypothesis of population structure.

The mathematical theory of population genetics long ago demonstrated that if a heterozygote for a pair of genetic factors has an adaptive value higher than both homozygotes, then natural selection will maintain both factors in the population indefinitely. This is called balanced polymorphism, and it will also occur if the homozygotes are badly incapacitated or even lethally affected. Indeed, evidence has accumulated that balanced polymorphism is important in natural populations of *Drosophila*. There is some evidence (*10*) that balanced polymorphism also occurs in human populations, although there is no way at present to determine how widespread it is. The sturdiest *Drosophila* flies and sturdiest men may be products of hybrid vigor or heterosis. Farmers have good evidence that this is the case in highest yielding corn.

Illustrations

The evidence obviously cannot be set forth here in full, but some illustrations may be in order. Natural populations of many species of *Drosophila* vary in what may seem to be a tantalizingly recondite trait, the arrangement of genes in their chromosomes. In a part of central Brazil, an individual of *Drosophila willistoni* is heterozygous, on the average, for nine inversions in its chromosomes (*11*). Experiments with this and some other species of *Drosophila* have shown that inversion heterozygotes are in most environments superior in fitness to homozygotes. In Californian *Drosophila pseudoobscura* the relative fitness of carriers of certain chromosomal inversions is exquisitely sensitive to changes in the environment. The adaptive value of a certain heterozygote is more than twice that of a homozygote at 25°C, but if the temperature is lowered by only 9°, to 16°, the two become equal within the limits of experimental discrimination (*12*). In *Drosophila tropicalis* from one locality in Honduras, about 90 percent of the adult flies are heterozygotes for a certain chromosomal inversion (*13*). Since, among the eggs which these flies deposit, the homo- and heterozygotes are about equally frequent, it follows that most homozygotes die before they reach the adult stage. This might seem to be an appallingly inefficient situation for a population in nature to be in, and yet this population appears to be quite prosperous.

Table 1 shows that, although most chromosomes in *Drosophila pseudoobscura* are clearly deleterious in double dose, a small minority, less than 1 percent, are supervital. Flies homozygous for a supervital chromosome are more viable in the experimental environment than is an average fly which carries two different chromosomes. Here, one might think, we have found some normal chromosomes, unspoiled by mutation. Experiments of Spassky, Pavlovsky, Levene, and myself (*14*) have shown that this is not so. The supervital homozygotes are narrow environmental specialists. They retain their vigor only in a small range of environments, and their fitness deteriorates, often drastically, when the environment is changed.

Nor is it true, as has been surmised, that, in a given environment, normal and supervital chromosomes will be better in heterozygotes than the subvital chromosomes will be. This surmise was a reasonable one to make in view of the demonstration that recessive lethals tend on the average to be deleterious in heterozygotes. Experiments failed to vindicate the surmise. Heterozygotes which carry two different subvital chromosomes, or two different supervital, or one subvital and one supervital, are on the average equal in fitness. The key word in the last sentence is *average,* because different combinations of chromosomes do not have equal fitness. This is what agriculturists call "specific combining ability"; two inbred lines of corn, both lacking vigor, may give a vigorous and high-yielding hybrid. It may be noted at this point that by no means all chromosomes which are lethal in double dose are deleterious in heterozygotes, although they are so on the average. Stern and his collaborators (*8*), as well as Cordeiro (*5*) and Wallace (*9*), all found some recessive lethals which were heterotic in compounds with certain other chromosomes.

A part of the genetic load consists, then, of genetic variants which give hybrid vigor in single dose and yet are debilitating in double dose. These variants belong unmistakably to the genetic burden or "load" which the population carries, insofar as they weaken, incapacitate, or even kill the homozygotes. However, from the standpoint of population dynamics, there is an important difference between such variants and variants which are harmful or at least neutral in heterozygotes. The supply of the latter is maintained in the populations by the pressure of the mutation process; the frequency of the former is regulated chiefly by natural selection. Perhaps one should distinguish an unconditionally deleterious mutational load and a balanced load of mutations.

The discovery of the balanced load may seem to contradict the statement at the beginning of this paper, that most mutations are injurious to their carriers. There is no contradiction. Newly arisen mutants are much more likely to be unconditionally deleterious than are the mutants which have persisted in the populations for many generations. The simplifying assumption that newly arisen mutants, particularly those induced by exposure to high-energy radiations, merely add a qualitatively similar increment to the existing genetic load is no longer tenable. The genetic load which a sexual population carries is a compromise struck by natural selection between the adaptive requirements of the species and the mutation pressure. Many mutations which arise spontaneously, and *a fortiori,* mutations induced by mutagens not usually encountered by the species, do not pass the scrutiny of natural selection.

Conclusion

Any increase of mutation rates in human populations would add an increment to the store of human misery. If anything, radiation-induced mutants are more destructive than the spontaneous ones. As far as genetic effects are concerned, the only safe dose of high-energy radiation is no radiation. But beyond this, perhaps the most important lesson which the work on genetics of natural populations has taught us is one of humility. A satisfactory theory of population dynamics is not yet available. More data are needed on practically every aspect of populations genetics.

The genetic forces which impinge on human nature are not sufficiently understood for us to judge whether this nature is endangered, and if so to appraise how great the danger really is. Populations of various organisms will have to be studied. Of course, man is one of them. But it can hardly be overstressed that different organisms are most favorable for investigation of different aspects of population genetics, and that progress would be obstructed or side-tracked by undue concentration. The way towards understanding of biological aspects of human nature may lead through such lowly creatures as mice, drosophila, and even viruses.

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Heidelberg Natural Radiocarbon Measurements I

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Radiocarbon age determinations made at the University of Heidelberg in the period between March 1954 and July 1956 are described in this article (*1*). Tables 1, 2, and 3 contain various calibration measurements; Tables 4 and 5, the age determinations. Proportional counting of carbon dioxide with a gas pressure of roughly 1 atmosphere was used in making the measurements.

The carbon-14 content of a sample was compared with that of an arbitrary recent standard. Our standard is based on wood of the 19th century—that is, on wood that grew before the dilution of carbon-14 in the atmosphere by the industrial combustion of coal and oil (see subsequent paragraphs). For the calculations, a value of 5568 years (*2*) was used for the half-life of carbon-14.

The error given (*3*) is the statistical fluctuation of the carbon-14 measurement; it does not take into account variations resulting from other causes such as small fluctuations in the carbon-14 content of different plants of the same age, the uncertainty of the half-life, and others. These other variations have not been investigated thoroughly enough, and it is difficult to estimate them exactly. Most of the systematic errors are either common to all carbon-14 measurements (uncertainty in the half-life of C^{14}), or at least to all measurements made by the same laboratory (different standards for recent carbon), and radiocarbon dates can easily be corrected for them if new information should prove that correction is necessary.

Because these errors are relatively small, they are unimportant for older samples. However, some of the younger samples have a statistical error of less than 100 years; in these cases, we propose that ± 100 years be taken as the error if the figures are to be compared with historical dates, to allow for the afore-mentioned uncertainties.

The determinations listed in this article are numbered as follows: the first number following the letter H (Heidelberg) refers to the position in our sample list, and the second (after the hyphen) is the number of the specific determination.

Fossil organic material was usually treated only with hot, diluted acid, primarily to remove carbonates, but in addition, some samples were also treated with diluted alkali to remove humic acids.

The datings based on bone and antler seem to be unreliable. Even the organic fraction of bone frequently gives lower dates than the archeologic relationships allow. By "organic fraction" is meant the proteinic emulsion that is obtained after the finely ground bone has been dissolved in acid and purified by dialysis. The calcareous fraction of bone and antler (that is, the carbon dioxide generated by treatment with acid) shows even larger deviations from the true age, amounting to up to several thousand years in the case of old bones. Contamination by ground water seems plausible, considering the high carbon-14 content in the dissolved bicarbonate. The hard waters that we investigated (*4*) showed an apparent age of only 1000 to 3000 years.

We also consider it possible that the organic fraction has been contaminated by ground water. The C^{14}-active carbon dioxide in ground water is derived from the humus layer on the surface, and it is by no means impossible that sufficient organic material (*5*) to cause contamination is transferred by the water from this source and absorbed by the proteins in the bone. One cannot remove these absorbed substances from bone as easily as one can from wood, where the cellulose, which is for the most part insoluble, is treated with hot acids and bases and separated by filtering. Proteins, on the other hand, if treated in the same way, would themselves be dissolved. In the special case when the organic and calcareous fractions of a bone give the same age, the age can be accepted as correct, for it is very improbable that both fractions have undergone exactly the same amount of contamination.

Calibration Measurements

A series of carbon-14 determinations of wood dated exactly by dendrochronology has been made. With the age known, the loss of sample activity by radioactivity decay could be eliminated. Thus, after correction, each measurement gives a value for the activity of "recent carbon"—that is, the quantity A_0 in the decay law $A/A_0 = \exp.\ (-t/\tau)$ on which the calculation of radiocarbon ages is based (A is the measured activity of a sample today, t is the age of the sample, and τ is the mean life of carbon-14). The A_0 used in calculating the age values given is the mean of a preliminary set of measurements of this type. Further measurements shifted the mean slightly, but for practical reasons we have kept our original value of A_0 as a more or less arbitrary standard.

Table 1 contains the individual cali-

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