29 November 1963, Volume 142, Number 3596 **SCIENCE**

# Evolutionary and Population Genetics

Active and intellectually stimulating research is going on in organismic as well as molecular genetics.

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A century ago Darwin was the dominant figure in biology, and his theory of evolution was the major achievement of biology of his time. It seems in the highest degree likely that our time will stand, in the history of biology, for the discovery of the molecular basis of heredity. With a dramatic suddenness the deoxyribonucleic acids were shown to be the principal bearers of the genetic information in most organisms, and the mechanisms of their self-reproduction or replication were, at least in principle, elucidated. These mechanisms happen to be beautifully simple ones; the four "letters" of the genetic "alphabet" can specify a virtual infinity of different genes, in a way analogous to the way the 26 letters of the Latin alphabet can make up any number of words, sentences, and ideas. Here is an example of a scientific discovery comparable to a work of art; the enterprise of science can, after all, yield results as beautiful as the inspiration of a poet.

It is both inevitable and good that the dazzling achievements of molecular genetics have attracted wide attention. It is probably also inevitable, but not so good, that a bandwagon effect has led some people—and not only immature students but some scientists who should have known better—to proclaim that molecular genetics is all that there is or should be to genetics. Genetics and biology must, however, deal not with one but with several levels of biological integration. Living matter is integrated on the molecular, chromosomal, cellular, individual, populational, and biotic-community levels. It is convenient to divide these levels into two classes—the molecular and the organismic.

The reductionist faith, that if we knew a lot about the lower-most level then all the phenomena of the higher integration levels would somehow explain themselves, is still the religion of some scientists, but it is really contrary to the aim and method of science. The organismic phenomena have to be studied as such, not deduced from the molecular phenomena. Man is an organism, not a molecule, although some diseases which afflict his flesh are molecular diseases. Mankind is a Mendelian population of a remarkable sort. Biology and genetics will not renounce, will not even postpone, their efforts to understand man and mankind, together with other organisms of other species—animal, plant, and microbe. If proof was needed, the 11th International Congress of Genetics showed that active and intellectually stimulating research is going on in organismic as well as in molecular genetics. And finally, it must be made crystal clear that organismic and molecular genetics are not divided by a wall; numerous problems straddle the division. Genetics as a science retains its logical unity despite its amazingly rapid growth. A new integration may, however, soon be called for.

The favorite materials of genetic research change. In genetics as a whole, *Drosophila* is no longer the queen of genetics—it seems to be relegated to the honorific obscurity of a queen mother. The most rewarding objects for study of molecular genetics are microorganisms, bacteria, and viruses, with *Neurospora* on the fringes. Even in population genetics, where *Drosophila* still wears its crown proudly, it is being challenged by an upstart—man. Many geneticists used to take it for granted that man is an unfavorable subject for genetic research, because, with people, experimental crosses cannot be arranged and, for such research, the length of a human generation is prohibitive. These defects are, however, compensated for by the availability in man of information not elsewhere available. The literatures of medicine, physiology, psychology, demography, and even sociology contain a wealth of data of interest to genetics. A great deal is known about the history of mankind, while history has recorded nothing about the doings of drosophilae. Last but not least, more people are interested in man than in anything else; money and effort not available for other studies are invested in studies on man.

## Studies in Human Populations

Human genetics is clearly one of the growing points of modern genetics. Owing especially to widespread utilization of biochemical and biophysical techniques, a steadily increasing number of genetic entities are being recognized and investigated. I reckon that the number of gene loci known to be represented by at least two alleles is now, or soon will be, of the same order in man as in *Drosophila melanogaster*, although their linkage and other relationships are, of course, much less well known. Many of these genes give mutant alleles responsible for the syndromes of diseases and malformations. They furnish abundant material for

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studies in medical genetics. A growing number of genes are, however, brought to light which are of great interest also to what may be called anthropological genetics. Many genes, particularly those which affect immunological traits and blood constituents, have two or more alleles that occur with reasonable frequency in at least some human populations.

The study of the incidence of such genes in human populations belongs to a borderline field between genetics and anthropology and is of equal interest to both. Human populations can be described at least as meaningfully in terms of the relative frequencies of alleles of various genes in their gene pools as in terms of the mean values of morphological characters. This characterization, together with the body and skeletal measurements of classical anthropology, is yielding new insights into the nature and the evolutionary relationships of human racial groups. Two generalizations have emerged.

First, the differences between races are mostly quantitative rather than qualitative; races differ often in gene frequencies rather than in the presence or absence of genes. This obviously controverts biological racism, which raises its ugly head in several countries. Men are entitled to equality of opportunity, although they are genetically all different; they must be judged according to their individual achievements, not according to the race or population from which they spring.

Second, the frequency variations and geographic gradients (clines) of different genes are by no means always correlated. The gene pools of a given pair of populations may be similar in the incidence of some genes but different in the incidence of others. The weakness or lack of correlations raises difficulties for recognizing, and especially delimiting, nameable racial groups. Some authors found these difficulties so formidable that they declared in all earnestness that human races do not exist at all! This misjudgment is due to a failure to realize that a race is both a biological phenomenon and a unit of classification. Mendelian populations which differ in the frequencies of some genetic variables are racially distinct, but it does not follow that all racially distinct populations must be given racial (or subspecific) names. Discovery of races is a biological problem, but naming them is a nomenclatorial problem. There is nothing arbitrary about the criteria for determining whether racial differences between two populations do or do not exist, but it is a matter of convenience and judgment to decide when and which racially distinct populations should or should not be given race names.

Classical geneticists preferred not to venture far from the solid ground of genetic entities analyzable in terms of discrete gene differences. Organismic evolutionary genetics and population genetics, as well as genetics applied to animal and plant breeding, are forced to deal largely with polygenic inheritance. This involves, before all else, more sophisticated operational approaches. The most powerful tool of the Mendelian-Morganian genetics is hybridization and analysis of hybrid generations in terms of the segregation ratios. Crossing and selection, followed by analysis in terms of means and variances, are emerging as equally indispensable tools of what is variously labeled biometrical, mathematical, or quantitative genetics. Contriving and perfecting these tools is one of the most important current endeavors in modern genetics. It is leading to a new understanding, and it may be hoped to a better control, of the genetic architecture of populations and of the selectional processes enacted in these populations.

## Genetic Variability

To a classical geneticist, most individuals of *Drosophila* were "wild-type," and a few were mutants. In man and other forms, some individuals were "normal" and others aberrant. Population genetics has, however, shown that the amount of genetic variability, at least in Mendelian populations of sexual and outbreeding forms, is so great that no two individuals, identical twins excepted, are ever genetically alike. And furthermore, the phenotypically expressed variability, detectable through observation of morphological or physiological traits, is only a small part of the total genetic variability. For much of the variability is concealed in heterozygous state, or in linked gene combinations styled "super-genes." This variability can be released to the phenotypic surface by breeding and selection, by homozygosis, and by crossing over.

A considerable part of the expressed, and an even greater part of the concealed, variability consists of variants that are in some degree unfavorable to the organism. This unfavorable, deleterious, ostensibly unadaptive part is designated the genetic load or the genetic burden of the population. Studies on genetic loads are being actively pursued. They are stimulated by the intrinsic interest of the subject; moreover, they are of fundamental importance for evolutionary genetics. They are also of practical importance, especially in connection with the problem, so much discussed because of its bearing on public health and even on politics, of the genetic damage inflicted on populations by exposure to ionizing radiations. A vastly greater problem concerns the alleged weakening of natural selection in man, which leads to a spread of socially undesirable genotypes. These studies have revealed a most interesting cleavage of attitudes among geneticists, a cleavage which goes deep down to two philosophical approaches to biology.

## Typological and Populational Approaches

That the world of life is an outcome of evolutionary development is now, more than a century after the appearance of Darwin's *On the Origin of Species*, quite generally recognized among biologists. Ingrained habits of thought nevertheless resist change. Two ways of thinking, the typological and the populational, show a remarkable endurance. Both have ancient and venerable antecedents. The typological approach can be traced from Parmenides and Plato, through Aristotelian and Thomist philosophy, to Linnaeus, Goethe, and Owen, and to some of the conceptualizations of systematics, genetics, and comparative morphology. It is basically un-evolutionistic, if not anti-evolutionistic. To be sure, few biologists would claim that the people whom they meet are only distorted representations of the ideal and unchanging archetype of man, or that the drosophilae we capture are imperfect images of the optimal Superdrosophila abiding in Platonic heaven. Many entertain, however, pretty definite ideas of what the Normal Man is or ought to be and talk about the wild-type *Drosophila* as if wild-type flies were genetically all identical. The populational approach is traceable from Anaximander and Heraclitus, through philosophers of the Enlightenment, to Darwin, and to the modern biological, or synthetic, theory of evolution. It considers change, variation, and diversity more interesting and important than stability or ideal optimal states.

The typological and populational approaches will probably continue to persist in genetics; perhaps they reflect two different intellectual constitutions. I would nevertheless like to indicate why the typological line of reasoning is, in my opinion, not adequate and not a valid approach to certain biological problems. An assumption which is unquestionably attractive because of its simplicity is that the unfixed genes in a Mendelian population are represented by two or more alleles, one of which confers on its possessors a fitness or selective value greater than any of the others. If this were so, then the prevalent form of selection would be a normalizing selection. Since this selection is not ideally efficient, some generations elapse between the origin of an unfavorable gene by mutation and its elimination by selection. Populations will carry genetic loads, which will then be mutational loads.

When an equilibrium between mutation and selection is reached, the numbers of deleterious alleles that arise and the numbers that are eliminated by selection in each generation will be approximately equal. Muller (*1*) has called the process of elimination "genetic death." It is important to keep in mind that genetic death does not always kill (*2*). Nonproduction of offspring, due to failure to find a mate or to sterility or a reduced fertility, all result in genetic death. Normalizing selection, and most other forms of selection, could, theoretically, take place even if all the progeny survived, without any death at all before the reproductive age. As pointed out by Haldane (*3*) as long ago as 1937, recurrent deleterious mutation should cause a loss to the population amounting to the aggregate mutation rate multiplied by a factor between 1 and 2, depending upon recessivity or dominance. Haldane's deduction is perfectly valid, but it should not be understood to mean that a fraction of the zygotes equal to the sum of mutation rates must necessarily die in every generation before reaching the reproductive age. Natural selection is a more subtle process than some biologists give it credit for being; the elimination of some components of the mutational load may occur by decreasing the birth rates rather than by increasing the death rates.

The mutational load reduces the fitness of the population. It persists in populations because the normalizing selection is counteracted by recurrent mutation. Theoretically, if mutation could be suppressed, then, given enough time and a constant environment, the population would tend to reach the asymptote of complete uniformity and homozygosis. Those who believe that the genetic load in human populations is exclusively or almost exclusively mutational load must, to be consistent, regard genetic uniformity beneficial and genetic heterogeneity inimical to the fitness of a population.

Typological thinking thus makes a kind of Platonic archetype of Man the eugenic ideal. The ideal mankind would be genetically as uniform as an asexual clone, composed of individuals as similar as identical twins, but in compensation endowed with the Optimal Genotype. It may be objected that in every human society there are too many different functions and vocations to be performed efficiently by a single genotype. This objection is not necessarily fatal to the typological ideal. A believer in such an ideal might logically answer that a really optimal genotype will make its carriers not only optimally adapted to perform some one function but also developmentally plastic and optimally trainable for any function. To be sure, most adherents of these views escape from under their logic before this "ideal" is reached, even in theory. I am not, however, belaboring a straw man; I have heard one of the greatest living geneticists arguing in all earnestness for this ideal.

Genetic analysis shows that, at least as a rule, it is not a single genotype but an array of genotypes that fit a Mendelian population to secure and to maintain its hold on its environments. This is precisely where genetic analysis negates typological approaches. Far from being a sad imperfection of nature, genetic diversity is an adaptive device. Heterozygotes for some genetic variants are fitter than either of the corresponding homozygotes. Such variants are kept in populations in the state of balanced polymorphism by the heterotic form of the balancing natural selection. It is an open issue how often the superior fitness of a heterozygote is due to interaction of a single pair of alleles (so-called single gene heterosis) and how often it is due to congruence of linked gene combinations (supergenes). The two situations lead to much the same observable results and, therefore, are hard to distinguish experimentally.

## Genetic Variation and Developmental Homeostasis

It must be always kept in mind that the environment which a population faces is rarely uniform in the laboratory and is probably never so in nature. Genetic diversity in complex and diversified environments may be maintained by the diversifying form of the balancing natural selection, even in the absence of heterosis in the heterozygotes. Other things being equal, populations which live in heterogeneous environments, and which have mastered many ecological niches, should be genetically more strongly diversified than the inhabitants of narrowly specialized or ecologically marginal habitats. There is some evidence that this is indeed a fairly general tendency. There are, however, at least two possible ways of adapting to environmental heterogeneity—genetic variation and developmental homeostasis (the ability to react adaptively to the whole range of environments which a population encounters). These two methods of adaptation are not mutually exclusive, and both are made use of in evolution. An interesting and challenging theoretical problem concerns the evolutionary strategies that can be used to achieve the optimum adaptive results under certain environmental conditions; whether evolution has actually followed the optimal strategies which we can devise on paper is, of course, a different matter.

The genetic variability found in living populations may be divided, very roughly, into two classes. First, there are hereditary diseases, malformations, and constitutional weaknesses—variants disadvantageous to the organism in homozygous and in heterozygous condition, in most or in all environments, constantly generated by the mutation pressure, and kept in check by the normalizing selection. Second, there is genetic diversity and polymorphism, adaptively advantageous because of heterosis or because of high fitness in some environments or ecological niches. Such diversity is kept up by various forms of balancing selection. One of the most important, and also most controversial, problems of organismic genetics is the relative magnitude of these classes of genetic variability.

It is here that the typological and the populational approaches are most clearly in opposition. However, the matter need not remain forever in the realm of philosophical predilections. Evidence is accumulating rapidly, especially in some species of *Drosophila* and in man, to show that neither the variability maintained by recurrent mutation nor that kept up by balancing natural selection are negligible. The mutational component is relatively greater in the concealed, and the balanced component in the phenotypically expressed, genetic variability. It is also very likely that the relative magnitudes of these components will be found to differ in different organisms, particularly in those with contrasting ecologies and diverse reproductive methods. The genetic population structure can hardly be the same in obligatorily outbreeding and in facultatively or obligatorily inbreeding forms. Here is a great, and as yet almost unexplored, field of study in comparative genetics. Comparative genetics is, surely, no less legitimate and no less promising a field than comparative anatomy or comparative physiology.

## Present State of Evolutionary Genetics

To characterize briefly the present state of evolutionary genetics is no easy task. It is fair, I think, to say that modern evolutionism has upheld Darwin's basic idea that the diversity of organisms is a product of evolution controlled by natural selection. To put it differently, the diversity of life is a response of the living matter to the diversity of environments on our planet. There are many environments, and many different ways of making a living in many of them. No organism can exploit all these opportunities; there are, instead, many different organisms to exploit the different opportunities.

The development of Darwin's idea has taken the form of the modern biological, or synthetic, theory of evolution. Its essential point is that evolutionary changes adaptive to the environment are constructed by natural selection from genetic raw materials—mutations—which at their origin are adaptively irrelevant. In other words, mutations do not arise only where and when they are needed for adaptive reconstructions of the genotype; they arise regardless of whether or not the living species stands in need of them. Most of them, in fact, contribute to the genetic load, or the genetic burden, which a species or a population carries. It is the action of natural selection, aided particularly by the Mendelian segregation and the gene recombination resulting from sexual reproduction, that compounds adaptively coherent genotypes from adaptively ambiguous raw materials. I like to stress that the action of natural selection is not like that of some mechanical sorting-out device, such as a sieve; it is, rather, a cybernetic regulatory mechanism, which makes the preceding genetic changes condition the succeeding ones. In the perspective of time, natural selection is a creative process which results in production not only of novelties but of adaptively meaningful novelties.

It would be wrong to say that the biological theory of evolution has gained universal acceptance among biologists or even among geneticists. This is perhaps unlikely to be achieved by any theory which is so extraordinarily rich in philosophic and humanistic implications. Its acceptance is nevertheless so wide that its opponents complain of inability to get a hearing for their views. On the other hand, the biological evolution theory has not congealed into a dogma. Far from that, the excitement of discovery is now as great as it has been at any time since Darwin; we know that what we know is very little, but we hopefully believe that methods and techniques now, or soon to be, available will enable us to know much more.

I neither can nor should attempt to give here even a cursory review of the open problems of genetic evolutionism. The conflict between the typological and the populational approach I have already mentioned in another connection. I shall mention two more issues which seem to me of outstanding interest. Let us take the view that the organic diversity is brought about by natural selection adapting life to fill out different environments. But how extensive are the genetic differences which underlie the visible ones? Some of the classicists of genetics believed that a single mutation may bring forth a new species. Except for Goldschmidt (*4*) with his systematic mutations, the "species" which they had in mind were not reproductively isolated Mendelian populations but, mostly, the so-called "elementary species," chiefly clones of apogamic plants. Morgan recognized that all mutants he observed belonged to the single species *Drosophila melanogaster.* Nevertheless, he and his associates tended to assume that species, at least closely related ones, differed in rather few genes. As recently as 1948, Sturtevant (*5*) argued that most genes are the same in the genetically studied species of *Drosophila.* Others assumed that even quite remote forms, as long as they possess enzymes with similar functions, have similar genes. The classical hypothesis postulates small numbers of mutational steps to account for evolutionary changes.

This view is, however, too simple to be credible. Its difficulties stem, in the first place, from the fact that whenever not only species but races, and even individual variants from the same population, are crossed, the segregations that are observed indicate numerous gene differences. The evidence for this became unequivocal, particularly after Mather (*6*) led the parade of studies on polygenic variability and its inheritance. The number of unfixed genes in Mendelian populations proved to be very large—in fact, so large as to be not exactly countable with the aid of any methods yet devised. There is no way of telling in how many genes individuals of the same species may differ, or what the average number of loci is for which they are heterozygous. I suspect that an estimate of the order of 100 for this average number is on the conservative side.

The splendid achievements of biochemical genetics have not so far been helpful in this matter; they have, rather, made the puzzle more puzzling. Take, for example, the fact that the hemoglobins are remarkably similar in all vertebrates, from fish to man. Ingram (*7*) estimates that 85 mutational steps would be sufficient to account for the difference between the alpha and the beta hemoglobin chains, differentiation of which took place presumably in our very remote ancestors. The alpha chains of human and gorilla hemoglobins differ in substitution of two amino acid residues, and could have been made different by only two mutations. Is this conservatism an exceptional situation, caused by the physiological importance of hemoglobin? Or may there be two or more classes of genes, some more mutable and others more stable? An interesting speculation of Wallace's (*8*) may perhaps point the way to answering these questions.

It should occasion an evolutionist no surprise to find that evolutionary concepts evolve. Our conceptualizations are not identical with those of Darwin, although there is an unbroken continuity between ours and his. Darwin emphasized differential mortality and survival as the mainsprings of natural selection, yet he was certainly aware of the importance of fecundity and care of the offspring. We stress the importance of reproductive success, admitting, of course, that survival is essential. Carriers of a genotype must survive to reproduce, and they must reproduce to survive in the next generation. The operationally cogent measure of Darwinian fitness, or adaptive or selective value, is the contribution which a genotype, or a class of genotypes, makes to the gene pool of the following generation in relation to the contributions of other genotypes. Sir Julian Huxley (*9*) has made impassioned pleas against this "geneticism." My apology for my geneticism is that I wish to measure natural selection instead of merely talking about it. Such measurements show, among other things, that the intensities of natural selection observable in nature and in experiments are often greater than evolutionists a generation ago would have dared to suppose.

## Understanding the Phenomena of Selection

The need to understand the phenomena of selection can hardly be exaggerated. Such understanding is important for improving domesticated animals and plants. It is perhaps even more important for understanding the biological evolution of mankind. Here a geneticist has to find the right course between the Scylla and Charybdis of two contrasting oversimplifications, both having wide currency, especially in the popular scientific literature. One is that "natural" selection no longer operates in civilized mankind, and that the human species is therefore headed toward genetic degradation and eventual breakdown. Its polar opposite is the assertion that the biological evolution of our species came to a standstill when culture appeared, and that the status of the gene pool of mankind is now wholly irrelevant to the new, strictly human, kind of evolution, which is evolution of culture.

Some of the misapprehensions can be disposed of rather easily. The selection which was going on when man was living in his supposedly "natural" state, however you may choose to define that elusive condition, is not the only "natural" selection. Surely we observe natural selection in operation when a child afflicted with a hereditary disease dies, or when an achondroplastic dwarf fails to find a marriage partner. Moreover, high mortality rates are not indispensable for natural selection; theoretically, natural selection could operate just as effectively in a population in which all the children born reach puberty, provided the carriers of different genotypes have different reproductive rates.

It may well be that some genotypes which acted as lethals in Stone Age man have a fitness above zero in Atomic Age man. I feel that insufficient attention has been given to the converse situations. Could it not be that some genotypes are worse off under civilized conditions than they were in a state of rustic simplicity? Neel (*10*) speculated that the genotypes responsible for diabetes melitus may belong to this class. And what about the genotypes which make their carriers likely to develop nervous disorders? However that may be, it is only "natural" that the relative fitness of different genotypes changes as environments change, and environments in which people live change both rapidly and radically. Theoretical discussions of these matters are plainly insufficient. Natural selection has been talked about for more than a century; we must now start measuring it, in man and in other organisms. As things stand at present, we have very few even approximate estimates of the Darwinian fitness of genetic variants in human populations. Such quantification is indispensable for understanding the status and the perspectives of the gene pool of our species. As it is now, all predictions and all eugenical utopias have at best only the status of educated guesses or personal opinions. In particular, it is of crucial importance to learn what part of the human variability is due to recurrent mutation and what part is maintained by balancing natural selection. Indeed, while the mutational genetic load should, as far as possible, be minimized, the balanced load is, in Mather's felicitous phrase, a "load" only in the sense in which the expenditures which a community makes to bring up and to educate its younger members are a "load" on that community.

And yet, the contention that man's biological evolution is now inconsequential and is replaced by cultural evolution is a dangerous illusion. To be sure, any sociologist who treats mankind as though it were nothing but an animal species brings only discredit to his science. Man is man, as well as an animal. The biological and the cultural changes have genetic consequences, and genetic processes may have repercussions in the evolution of culture. The greatest and most immediate biological danger which mankind faces comes not from the alleged suspension of natural selection but from the uncontrolled population growth, the so-called "population explosion." If mankind succeeds in solving the problem of population size, the problem of population quality may perhaps be dealt with through some of the same techniques, and—even more important—some of the same willingness to regulate one's behavior for the benefit of the generations yet unborn. If, on the other hand, mankind is unable to save itself from being suffocated in the population flood, it need hardly be concerned about its genetic quality.

Finally, one of the unsolved problems to which a geneticist will always return in his thinking is the possibility of a control of the evolutionary process by means of directed gene change. The discoveries of transformations and transductions in microorganisms perhaps give some substance to this dream. What tremendous possibilities its realization would open for the improvement of animals and plants and, before all else, for the control of the human gene pool is apparent to every geneticist. Skeptics warn us that this dream may remain just that—a dream. One thing, however, seems safe to say: genetics, both molecular and organismic, is now in a period of rapid development. Its development promises to lead to a better understanding of life and to a better understanding of man. To help man understand himself and his place in the universe may be the ultimate purpose of genetics, of biology, and perhaps of all science. In the immortal words of Sophocles, "Many wonders there be, but naught more wondrous than man."

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