Heredity, Environment, and Evolution

Th. Dobzhansky
Department of Zoology, Columbia University, New York City

THE SAVAGE ONSLAUGHT on genetics by Lysenko and his partisans has had one useful result—and only one—that is, a great intensification of interest in genetics and evolution, not only among scientists but among educated people in general. Therefore, this is a propitious time for an attempt to restate some of the basic concepts of modern genetics and of evolution theory. It goes without saying that these concepts differ from those current in the past, and it is a safe prediction that they will continue to evolve unless the sciences of genetics and evolution are destroyed everywhere as they have been in Russia. Furthermore, the concepts vary somewhat, although to a minor extent, from one geneticist to another. The responsibility for the formulations offered here rests, of course, with the writer.

Genetics has been defined by Bateson as a study "of the phenomena of heredity and variation; in other words . . . the physiology of descent." Heredity, variation, and descent are aspects of the same basic phenomenon, although superficially they may seem distinct or even antagonistic. It is a matter of observation that children resemble parents, and this resemblance is ascribed to heredity. The resemblance is, however, not absolute, either between parents and children or among sibs. This is called variation. When we find, through observation or inference, that the organisms living now came from ancestors different from them we speak of evolution or descent.

A man may resemble his mother in some respects or "traits," his father in other traits, and be unlike either in still others. It looks as if what is inherited is not a general likeness but rather resemblance in different particular traits. In common as well as in scientific parlance, such human traits as skin color, eye color, hair form, and head shape are considered hereditary. No abstruse analysis is needed, however, to show that a "trait" is merely an abstraction useful for purposes of description, and as such cannot be inherited. An individual arises from the union of an egg contributed by the mother with a spermatozoon contributed by the father. These sex cells have no eyes, no hair, and no skin color. But a fertilized egg does develop, by means of a long series of very complex transformations and through many successive stages, into an organism which has eyes of a certain color, hair of a certain form, a more or less pigmented skin, etc. Furthermore, the traits or characteristics of an individual organism at any stage of its development are related to, and are to a certain extent predictable from, a knowledge of the traits of its parents and other ancestors. It is evident that what is inherited is a dynamic pattern of developmental processes which charts the course of the transformations of the body from fertilization to birth, to adulthood, and to death.

This charting, however, does not amount to anything like complete determinism. It is well known that the course of development is influenced by the environment. Therefore the outcome of development at any stage is a function of both the heredity of the developing individual and the environment in which the process has taken place. Heredity does not determine traits; it determines, according to the somewhat awkward expression proposed by the Danish biologist Raunkaier, the "norm of reaction" of the organism to the environment.

Different environments evoke different reactions in organisms with similar heredities; different heredities engender different reactions in organisms which develop in similar environments. It is therefore obviously necessary to distinguish the outcome of development from its cause. Johannsen proposed to designate the former as the *phenotype* and the latter as the *genotype*. The phenotype comprises all external and internal structures and functions of the organism. It can be studied and described by morphological, anatomical, and physiological methods. The genotype of an individual is the sum total of its hereditary properties. Examination of the pedigree, or of the progeny, or both, is needed to study the genotype. The phenotype of an individual changes continuously as the development proceeds, and, in fact, never becomes fixed. A series of photographs of a person taken at different times, from birth to maturity, old age, and death, illustrates the changeability of the phenotype. The genotype is relatively stable; the nature of this stability will be discussed.

It is a widespread misapprehension that hereditary traits are independent of the environment, and that traits subject to environmental modification are *ipso facto* not hereditary. On the contrary, no organic form or function can develop except as a response of a certain genotype to a certain environment. The so-

called "nature-nurture" (genotype-environment) problem is not to distinguish which traits are genotypic and which are environmental, for all traits are genotypic and environmental. The problem is to what extent the actually observed variability in individuals of a species (such as man) is caused by the available variety of genotypes, and by the existing variety of environments. In this sense, the relative importance of genotype and of environment is quite different for different traits. For example, the blood group to which a man belongs seems to be fixed by his heredity; no method of changing the blood antigens is known at present. The skin color depends both on the genotype and on the exposure of the skin to a certain part of the ultraviolet spectrum. Man's behavior is supposed to conform to circumstances, i.e., to the environment. But it is easy to show that behavior is influenced also by the genotype. For example, a man with a black skin (a genotypic trait) will, in a "color conscious" society (environment), evince a different behavior (phenotype) from a man with a light skin. The fact that in different social environments these men's behavior might be alike, or reversed, does not make the behavior independent of the genotype.

The relative importance of genotype and of environment in the determination of the developmental pattern is not unalterable. If the environment becomes standardized, the variability of genotypes increases in importance. Environmental agents become more influential when they grow stronger or more diversified, or when the organisms on which they act are genotypically uniform or nearly so. Now, man creates new environments and is therefore potentially able to augment or diminish the rigidity of genotypic determination. It is clear that the development of an individual is an orderly sequence of physiological and, ultimately, physicochemical reactions in which the genotype and the environment are involved. If a detailed knowledge of these reactions were available, the phenotype would be under our control to a much greater extent that it is now. As Goldschmidt has pointed out, any change in the phenotype produced by a variation of the genotype could, in principle, be produced by environmental influences as well. Although this presupposes a more nearly perfect knowledge of development than is actually available, the principle is valid. Medical treatment of hereditary disease or, indeed, of any other disease consists essentially in placing the patient in environments so contrived that his genotype reacts by engendering a phenotype which is regarded as desirable. Medicine and pedagogy are, from the standpoint of genetics, sciences of management of the human phenotype. Heredity is often spoken of as "destiny." It is destiny largely in proportion to our biological ignorance.

The foremost problem of genetics has been to investigate the structure and the operation of the genotype in individual and in evolutionary development. To date, the greatest discovery in this field has been that made by Mendel. Mendel demonstrated that the genotype is not a diffuse continuum, which it was believed to be before Mendel (the "blood" theory of heredity), but a sum of discrete particles, now called genes. The rules of the transmission of genes from parents to offspring have been established by means of a certain powerful analytical tool, invented by Mendel and perfected by his successors. This tool is hybridization of varieties of plants or animals which differ in some known respects; the distribution in the offspring of the traits in which the parents differed is followed one by one, and is recorded quantitatively. The rules discovered by Mendel enable biologists to make sense of a great mass of otherwise chaotic data; they also enable geneticists to devise new experiments and to predict their outcome. The gene theory has been established without the genes' having been seen under the microscope, just as chemical reactions have been understood in terms of molecules and atoms without molecules and atoms' having been seen.

The next step was made by the combined efforts of many brilliant men, among whom Weismann and Morgan were most important. This was the demonstration that the genes, or most of them, are carried in the microscopically visible chromosomes. The gene ceased to be merely a symbol; it became also a material particle. But the structure and the method of action of the gene still remained conjectural. The next advance, due again to collective achievement of numerous workers, among whom Muller has been most prominent, is now in process of accomplishment. Although many loose parts of the story still remain to be tied together, it seems most probable that the gene is a single molecule of nucleoprotein, or a part of a supermolecule, the chromosome. Some genes occur, however, in the cytoplasm also. There has developed, moreover, a most intriguing zone transitional between, first, cytoplasmic genes, which are necessary parts of a cell of a given species, second, viruslike symbionts which may or may not be present, and, finally, parasitic viruses which are transmitted from individual to individual not by heredity but by infection. A chromosome proves to be not a fortuitous assemblage of independent genes, but an organized system; the precise nature of the interrelations of the genes carried in the same chromosome is, however, still problematic. Whatever it may prove to be, heredity is a process enacted primarily on a molecular level inside the cells, and secondarily magnified to those macroscopic dimensions in which we are accustomed to observe the outcome of heredity.

A human egg cell is estimated to weigh about one millionth of a gram. The increase in weight from egg to adult is, accordingly, some fifty billion fold. The source of the material for this enormous growth is not far to seek. It is the food and water consumed and assimilated by the organism. The development of any organism involves, then, transformation of materials withdrawn from the environment into a likeness of the assimilating organism and of its ancestors. Heredity is a process whereby the organism reproduces itself by consuming a part of its environment. This is especially obvious when we observe living things giving rise to progeny. But self-reproduction takes place in any living body. Experiments with isotopes have shown an amazing lack of permanence of most of the adult mammalian body; many body constituents are periodically broken down and reconstructed anew from food materials. Heredity is, fundamentally, self-reproduction.

The units of self-reproduction are genes. Construction of their own copies is the most important and possibly the only function which the genes perform. Just what the chemical processes are whereby a copy of a gene appears next to it is unknown. It is possible that a gene first synthesizes its negative image, which next gives rise to a positive. Or the gene molecule may undergo transformations whose end result is two such molecules. In any case, the process of self-reproduction may be symbolized thus:

$$A + B = 2A + C$$

where A is the gene, B the materials from which the copy is made, and C the by-products or waste products. The essence of the process is that two gene molecules are formed where only one was present before. Whatever the chemistry may prove to be, the process is cyclic, and it is this cyclic nature that makes heredity possible.

The allegation that geneticists regard the genes as isolated from the rest of the body and from the environment is absurd. It has been known for about half a century that the chromosomes, and hence the genes, are reduplicated between the consecutive cell divisions. The genes are probably chemically the most active cell constituents. The genes change all the time, but the basic fact is that the changes are cyclic: they lead to self-reproduction. This is the modern meaning of the Weismannian distinction—which has been misinterpreted by geneticists as well as by philosophers—between the germ plasm and the somatoplasm. The germ plasm is the genic materials which reproduce themselves; the somatoplasm is produced in the process of gene self-reproduction. The "stability" of the genes is peculiarly dynamic—they change to produce their own copies. Self-reproduction is the fundamental quality of life that distinguishes it from inanimate nature. This explains the apparently paradoxical nature of life: life changes the environment and is changed by the environment, and yet it preserves an inner continuity which is, in fact, its basic property.

Every organism can exist in a certain range of environments and can subsist on a certain range of food materials. This means that a gene, A, is able to reproduce itself not only from a material, B, but also from other materials, denoted B^1, B^2, B^3, etc. The results of the self-reproducing processes are, then:

$$A + B^1 = 2A + C^1$$
$$A + B^2 = 2A + C^2$$
$$A + B^3 = 2A + C^3.$$

In other words, with rare exceptions, a gene either forms a faithful copy of itself or fails to reproduce altogether. Variations in the environment give variations in the products (phenotypes) C^1, C^2, C^3, etc., and not in gene A. This accounts for the paradox of variability of the phenotype and stability of the genotype which makes heredity possible. The so-called acquired characters are not inherited because the phenotype, C, is a product of the reproduction of the genotype, A, and not vice versa.

The genes are, nevertheless, not unchangeable. In fact, they can be changed quite readily: The genic materials can be burned, or we can poison the genes. Since the chemical basis of the genes is in all likelihood nucleoprotein, they should be capable of undergoing many kinds of changes. The problem is not whether genes can be changed but what is the outcome of a change. It seems that the property of the gene-molecule which makes self-reproduction possible is based on some as yet unknown chemical structure which can be lost very easily. By way of analogy, one can say that a gene is a very delicate mechanism, random changes in which are more likely to spoil it than to permit its continued functioning, and far more likely to spoil it than to improve it.

As a consequence, three kinds of changes in the genes can be visualized: (1) Changes that make the gene unable to reproduce itself. Such a gene is no longer a gene; it is dead. This is doubtless the most frequent kind of change, which leads to losses of genes. (2) Changes that permit self-reproduction to occur, but that are not incorporated in the reproduction process. In other words, the copy formed is like the original, or ancestral gene structure, and not like the new one. Such changes are ephemeral, and are not detected by genetic methods. They do not infringe upon the dynamic stability of the gene as it has been defined here. Stanley was able to produce and to demonstrate such changes in the tobacco virus by

chemical methods. (3) Changes that allow self-reproduction to continue and that are reproduced, or copied, in the daughter genes. Such changes are permanent and stable, in the same sense in which the ancestral gene structure was called stable. These are the mutations of genetics.

Several environmental agents that speed up the mutation process are known: x-rays, ultraviolet radiation, high temperature, and certain chemicals. The effects of these agents are, however, unspecific, in the sense that they enhance the probability of occurrence of mutations of all kinds (although not necessarily to the same extent). In the last analysis, every mutation is caused by environmental influences, and there is no theoretical reason why geneticists could not eventually learn to induce at will specific mutations in specific genes. Such a feat may already be within our grasp in the type transformation of pneumococcus bacteria. But the interpretation of these transformations is not yet quite clear and, undeniably, complete control of the mutation process is still not in sight.

The relations between mutations and the environment will now be considered from a different point of view—that of relative reproductive efficiency of the unchanged and mutated genes, and of organisms carrying them. We have seen that a gene encroaches on the environment and transforms a part of it (food) into copies of itself. The efficiency of this process may be described in terms of the number of copies (progeny) created per unit of time. The greater the surviving progeny of an organism, the better this organism may be said to be adapted to a certain environment. The process of differential perpetuation of different genes and genotypes is Darwinian natural selection. With respect to adaptedness, or fitness, three types of mutations may be distinguished.

(1) The adaptedness of the mutant is lower than that of the ancestral form in all existing or attainable environments. If a mutant leaves fewer surviving descendants per unit of time than does the ancestral form, the number of individuals of the former will decrease relative to the number of the latter. No matter how small may be the disadvantage of the mutant, the end result of the process will usually be extinction of the mutant. Inasmuch as the outcome of selection is in this case elimination of the mutant and preservation of the orginal type of gene or organism, this form of selection is a conservative force. It has been called by Schmalhausen "stabilizing selection," because it preserves the existing type of organization.

(2) The adaptedness of the mutant is higher than that of the ancestral form in all environments the species occupies or can reach. The outcome of the process of natural selection will here be the converse of the preceding case: the ancestral type will become extinct, and the environment will be monopolized by the mutant. An evolutionary change will have taken place, because a previously existent type is replaced by a new one.

(3) The adaptedness of the mutant is higher than that of the ancestral type in some environments, but lower in other environments. The process of natural selection will in this case lead to elimination of neither the mutant nor the original type. Instead, the outcome of selection will be establishment of an equilibrium state, at which both the old and the new types of organization will continue to exist. The numbers and relative frequencies of the two types will depend upon the abundance of the two kinds of environments in the world and upon the absolute reproductive efficiencies of the two types of organisms involved. The outcome of natural selection will thus be a diversification of the organisms existing in the universe. Two types will occur where only one lived before the change took place. This is the dynamic form of natural selection.

Evolution of living matter is compounded of changes of the kinds just described. Evolution is utilitarian in the sense that organisms change in the process of becoming adapted to their environments. The adaptation is brought about by natural selection which, in turn, is the outcome of differential perpetuation of different genotypes. Differential perpetuation is often styled "competition" and "struggle for life." Both expressions are metaphors, and have often been misconstrued. Imagine two species of bacteria or two genetic types of the same species of bacteria which multiply in the same test tube with nutrient broth. They are "competing" with each other in the sense that the more food one of them consumes, the less is left for the other. But the bacteria do not devour each other. When two species or varieties of grass occur in the same meadow they "struggle" with each other, in the sense that there is only a limited amount of space available for their growth. But this struggle does not involve anything like fighting in the human sense. *Competition* and *struggle* are emotionally loaded words, which are best avoided in discussions of causes of evolution.

No less misleading is the expression "survival of the fittest," which Herbert Spencer unfortunately coined to describe the operation of natural selection, and which became associated with something like the image of the Nietzschean superman. Now, *fitness* in the evolutionary sense, or *adaptive value,* as it is better called, does not necessarily connote even a superior ability of an individual to survive, and a lack of fitness in this sense is not synonymous with weakness or frailty. A superior adaptive value of one genotype over an-

other simply means that the carriers of the former leave, on the average, more surviving progeny than do the carriers of another genotype in the same environment. This superiority may result from the fact that individuals of one genetic type are stronger and more resistant to environmental hazards, and live longer than individuals of other genetic types. Or one type may be more sexually active or more fecund than another. Individual vigor and fecundity are not necessarily correlated, and a superior fecundity may compensate or even overcompensate for deficient vigor. This has indeed been observed in an experiment of the writer on some *Drosophila* flies, in which natural selection favored the spread of a type actually inferior to another type in viability between the egg and the adult stage, the second type being discriminated against by natural selection.

The processes of mutation and natural selection have been described here as though they involved changes of individual genes. This may be strictly true only in some viruses, which have been styled "naked genes" because they seem to consist of a single molecular species. In organisms other than viruses, the genotype is an integrated system of many kinds ("loci") of genes. Estimates of the numbers of gene loci in higher organisms are of the order of thousands or tens of thousands. Most or all of these loci change from time to time by mutation, and are represented in populations of a species by different variants ("alleles"). The constellation of gene alleles that an individual has consists of genes it has inherited from its ancestors or acquired by mutation of the inherited genes. The genes do not determine parts of the body, organs, traits, or even independent physiological processes. The entire genotypic system defines the matrix of the development of the organism as a whole. The development is apparently epigenetic, not preformistic, although preformism appeals to the thinking of many biologists, and many overtly or covertly preformistic theories are still current in biology. In any case, it is generally agreed that the adaptive value of a genotype in an environment is a property of the genotype as a whole, and not a simple sum of the values of its constituent genes. A gene, *A*, may be deleterious in combination with *B*, neutral with *C*, and useful with *D*.

Mendel showed that the variety of genotypes created in the process of sexual reproduction is staggeringly great. If a species has n genes, each represented by X variants (alleles), the number of genotypes possible in such species is X^n. With n of the order even as low as 1000, the number of possible genotypes is immense. Sexual reproduction is an unbelievably efficient trial and error mechanism because it creates countless new genotypes to be tested by natural selection. Because of the high efficiency of sex in the performance of this biological function, sexual reproduction has become established in most organisms as the normal method of propagation. Natural selection has evolved and perfected sex because it proved to be a basic adaptation which makes other adaptations more readily available. One of the most ridiculous features of the "dialectical" theory of Lysenko is his belief that the magic of sex "invigorates" the organism; his rejection of the gene theory has landed Lysenko in primitive animism. He fails to understand that it is the relative stability of genes that makes life possible, but that the stability is combined with a remarkable freedom in the creation of new genotypes in the process of sexual reproduction. The conservatism of heredity is balanced by the creativeness of sex.

The relationships between environment and evolution are subtle enough to make them often misunderstood. Evolution is controlled by the environment on two levels, and yet the environment cannot be said to impose changes on living species. The first level is that of mutation. The second is that of natural selection. The most accurate, although metaphorical, way of describing the dependence between evolution and environment is to say that environment provides the challenges to which organisms may or may not respond by adaptive modifications.

Mutations are, in the last analysis, physicochemical alterations in the genes or chromosomes; hence they cannot be wholly independent of the environment. And yet mutations are described as random and undirected changes. These adjectives mean that mutations arise regardless of whether or not the organism needs them for purposes of adaptation, and irrespective of whether the change may or may not be useful in some existing or possible environment. To suppose otherwise is to believe in magic. But the kinds of mutation that occur in any one gene are a function of the structure of that gene. Now, every gene is a product of a historical development extending from the dawn of life to our day. This development has been under the control of natural selection, hence of the environment. The structure of a gene is a distillate of its history, and the mutations that may occur in a gene are determined by the succession of environments in which that gene and its ancestors existed since the beginnings of life. The environment prevailing at the time mutation takes place is only a component of the environmental complex that determines the mutation.

Between the occurrence of mutation and the realization of an evolutionary change in a living population is interposed the domain of processes of population dynamics. The most important process in that domain is natural selection. The superiority of one genotype over others in adaptedness is clearly a func-

tion of the environment in which the process of selection is enacted. Nevertheless, natural selection involves a unique kind of interaction between the organism and the environment, the outcome of which depends upon both interacting variables. Similar environments therefore do not necessarily produce similar organic types. For example, deserts in different parts of the world are inhabited by many remarkably parallel adaptive types of animals and plants. The similarity of cacti in American deserts and certain euphorbias in South Africa is impressive. And yet, some of these adaptive types are missing in some deserts where the environment seems propitious for them. Their absence in appropriate environments is really no more surprising than the fact that human civilizations which have developed in similar environments are so often different. Organic evolution, like the genesis and development of human civilizations, is irreversible and unrepeatable. In the case of organic evolution, we now begin to discern the reason for this. A mutation is, in general, reversible and recurrent; in other words, the gene A mutates from time to time to a, but a mutates back to A with an equal or different frequency. If the gene A is adaptive in summer, for example, and a adaptive in winter, the selection favoring A during one season may be undone during the next season. But when many genes have mutated, and when natural selection has established a new and harmonious genotype including these mutants, the probability of reversion or of repetition of the process becomes negligible. Evolution becomes irreversible and unrepeatable as it ceases to be a physiological process and becomes a historical process.

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The Role of Lipids and Lipoproteins in Atherosclerosis

John W. Gofman, Frank Lindgren, Harold Elliott, William Mantz, John Hewitt, Beverly Strisower, and Virgil Herring

Division of Medical Physics, Donner Laboratory, and the *Radiation Laboratory, University of California,*[1] *Berkeley,* and

Thomas P. Lyon, *San Jose, California*

ATHEROSCLEROSIS is generally considered to be the major disease of this era. Its consequences in the coronary, cerebral, and peripheral arteries, in the form of occlusive phenomena, are responsible for more death and disability than any other disease. In spite of much study and research there is still no agreement concerning the sequence of pathogenetic events, etiology, or treatment of atherosclerosis. The not-too-rare occurrence of coronary artery occlusions (almost always a consequence of atherosclerosis) in young men from 20 to 40 years of age testifies to the fallacy of the idea, still prevalent, that atherosclerosis is a problem of the aged or senile. For the male it is a real threat in the prime of life. The absence of the disease at autopsy in many persons who have survived to be octogenarians is eloquent evidence that atherosclerosis should be regarded as a disease and not as an inevitable consequence of aging.

For many years it has been known that cholesterol (and its esters), phospholipids, and fatty acids are prominent components of early atheromatous lesions, whereas secondary pathological processes supervening may alter the relative preponderance of certain of these substances in late lesions. Some workers have indicted exogenous (dietary) cholesterol for the production of the disease, while others have denied the significance of this source of cholesterol, on the basis that large quantities of cholesterol may be endogenously synthesized from such precursors as water and acetate. The suggestion has also been made that atherosclerosis is the result of the chylomicronemia which follows meals. No agreement has been in sight,

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