HERMANN JOSEPH MULLER

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The first half of the present century has witnessed the gradual transition of genetics from the Cinderella status of Mendelism to the all-pervasiveness of molecular biology. The climax came with the momentous announcements of 1953, the opening of a new era. Yet, for those who had followed the developments of the theory of the gene, that climax was the expected outcome of a simple and beautiful idea: the gene as the basis of life and its corollary, life as the potentiality for evolution by natural selection. This idea Muller stated clearly in 1921. Yet he had already adumbrated it in 1910, when still an undergraduate (Carlson, 1967). The whole of his later work is, in essence, a development of this idea. Towards probing it he concentrated his powerful imagination, his inexhaustible technical dexterity, his methodological rigor, and his concern for humanity.

The present note—a token of admiration, gratitude and affection to the memory of a great teacher—is not biographical and it is not a review of the immense technical, experimental and theoretical contribution of Muller to most areas of genetics. It is limited to a consideration of Muller's idea of the gene as the basis of life and the part this idea played as the foundation for contemporary genetics. The magnitude of the debt is not generally realised.

Muller's profound interest in the properties of the gene as the initiator and organizer of life naturally led him to ask questions about the future of man, the highest consequence of those properties. The expansion of Muller's interest in this direction was gradual, and was spurred by the implications of radiation genetics—which he had fathered—and later by those of the atomic age. As far back as 1931 Muller's attitude was clear: "It is too late to protest that the choice of our own genes was determined by the sheer caprices of a generation now dead. But it is not too late for us to make sacrifices to the end that the children of tomorrow will start life with the best equipment of genes that can be gathered for them. . . . But it must also be remembered that a prime condition for an intelligent and moral choice of genes is an intelligent and moral organization of society."

In the last twenty years or so the evolutionary future of man and its guidance by man himself became a profound concern for Muller. It culminated in his detailed proposal for voluntary germinal selection, which has evoked, not unexpectedly, violent and most scathing reactions. Derision had already greeted his first statement, 47 years ago, that life as we know it and its evolution are the inevitable consequences of the properties of the gene. This we take now for granted. Forty-seven years hence our descendants may well take voluntary germinal selection for granted.

THE GENE AS THE BASIS OF LIFE

Seven papers spanning the period 1921 to 1965 give a general picture of the gradual refinement of this basic idea, of the inferences from it and of the incorporation in it of new knowledge as it became available. But the idea was already in embryo in Muller's mind as far back as 1913 (p. 11 of *Studies in Genetics, the Selected Papers of H. J. Muller*). These seven papers are: "Variation due to change in the individual gene": presented in 1921 at the Symposium on "The Origin of Variations" in a meeting of the American Society of Naturalists; "Mutation" presented in the same year at the International Congress of Eugenics; "The gene as the basis of life" presented in 1926 at the Symposium on "The gene" at the Congress of Plant Sciences; "Position effect and gene divisibility" (with Raffel) prepared in 1938 but published in *Genetics* only in 1940; "An analysis of the process of structural change in chromosomes of Drosophila" presented in 1939 at the International Congress of Genetics; "The gene" delivered in 1945 as the Pilgrim Trust Lecture of The Royal Society, and "The gene material as the initiator and the organizing basis of life" the delivery of which at the Mendel Centennial of the Genetics Society in September 1965 was prevented by Muller's illness.

Six of these seven papers are found in full or in excerpts in *Studies in Genetics, the Selected Papers of H. J. Muller* (Indiana University Press, Bloomington, Indiana, 1962). In the following notes the page references are to the pages in that collection. The seventh paper was published in the *American Naturalist*, 1966, **100,** 493–517. This 1966 paper looks far into the future, but is also retrospective and valedictory. In it Muller connects his earlier ideas and contributions to the developments since 1953. It makes as exciting a reading as the prophetic paper of 1921 and shows how thoroughly Muller, past his mid-70s and a very sick man, kept up with the formidable advances of the last decade. A long letter of 18 April 1966, addressed jointly to Drs. Atwood and Spiegelman (to whom I am indebted for a copy), comments on their recent work with Ritossa on the molecular genetics of "bobbed" and of the "minutes" in *Drosophila.* It is a striking example of how fertile and alert his mind still was in his last year of life.

The 1921 paper "Variation due to change in the individual gene" (pp. 175–188) starts with a forceful statement about the material nature of genes:

besides . . . proteins, carbohydrates, lipoids, and extractives . . . there are within the cell *thousands* of distinct substances—the "genes" . . . [which] . . . play a fundamental role in determining the nature of all cell substances, cell structures and cell activities.

The most distinctive characteristic of each of these ultra-microscopic particles is its property . . . [to react] . . . in such a way as to convert some of the common surrounding material into an end-product identical . . . with the original gene itself. [This is striking enough and] it is difficult to understand by what strange coincidence of chemistry a gene can happen to have just that very special series of . . . effects . . . which produces—of all possible end-products—just this particular one, which is identical with its own complex structure. But the most remarkable feature of the situation is not this oft-noted autocatalytic action in itself—it is the fact that, when the structure of the genes becomes changed through some "chance variation," the catalytic property of the gene may become correspondingly changed, in such a way as to leave it still *auto*catalytic. . . . What sort of structure must the gene possess to permit it to mutate in this way? . . . it must depend on some general feature of gene construction—common to all genes —which gives each one a *general* autocatalytic power—a "carte blanche"—to build material of whatever specific sort it itself happens to be composed of. Given, now, any material . . . having this one unusual characteristic, and evolution would automatically follow . . .

By innumerable successive steps such gene material would come to be increasingly complex and adapted to further its own replication.

After having highlighted what we now call replication and replication of variants, the 1921 paper goes on to emphasize something that only in the last few years has been taken up again: the specificity of synapsis which we now interpret in terms of complementary base sequences.

As in the case of autocatalytic forces, so here the attractive forces of the gene are somehow exactly adjusted to react in relation to more material of the same complicated kind. Moreover, when the gene mutates, the forces become readjusted so that they may now attract material of the new kind . . . the synaptic property of the gene . . . is dependent . . . on some general principle of its make-up, that causes whatever specific structure it has to be auto-attractive (and autocatalytic). . . . If the two phenomena are thus really dependent on a common principle in the make-up of the gene, progress made in the study of one should help in the solution of the other.

Again it is only in the last few years that this attack has been taken up vigorously in the general areas of molecular heterozygosis, DNA repair, gene conversion, integration of viral or episomal genomes, etc.

A further section of the 1921 paper deals with the attack on the nature of the gene by the study of mutation. The "remoteness of the gene-cause from its character-effect" should not lead to confusing loss of a character with loss of a gene. The reason why mutations are much more apt to cause an apparent loss in character than a gain is the nicely adjusted train of processes leading to a character so that . . . "any change in the genes—no matter whether *loss, gain, substitution or rearrangement*—(italics mine) is more likely to throw the mechanism out of gear . . ."

That mutation is ordinarily an extremely localized change in a gene, is shown by the fact that it ordinarily affects only one out of the thousands of different genes and that in a diploid cell it affects only one of the two identical genes present. The paper goes on to stress the importance of rigorous methods of analysis—at that time not yet available, but provided mainly by Muller himself in the following six years—for the study of mutation and of factors affecting it. Among these, Muller was to show in 1927 that X-rays are mutagenic.

The last part of the paper makes a plea for what had to wait for 20 years. It compares, astonishingly for that time, properties of bacteriophages (d'Herelle bodies) and genes, and says, referring to previously mentioned difficulties of a chemical attack on the gene: "Perhaps we may be able to grind genes in a mortar . . . after all. Must we geneticists become bacteriologists, physiological chemists and physicists, simultaneously with being zoologists and bontanists? Let us hope so."

All the statements of this remarkable 1921 paper seem today perfectly obvious. How far ahead of time they were can be gathered from the following episode, reported by Muller. The very distinguished paleontologist Henry Fairchild Osborn, was in the Chair. At the end of the meeting he commented "I'm glad you have a sense of humour, Muller."

The other 1921 paper "Mutation" (pp. 221–227) first clears up the terminological confusion and distinguishes between the cases of rare segregational gametes due to structural heterozygosis, as in De Vries' work on Oenothera and Muller's own case of balanced lethals, the cases of abnormal distribution to chromosomes and the remainder, "alterations of the gene." Then it goes on to give a number of statements—some summarized below—regarding changes of the genes: (*a*) most genes are exceedingly stable (half-life comparable to that of radium atoms); (*b*) changes are not exclusively losses, as shown by reverse mutation; (*c*) mutability and preferential direction of mutation may be changed through mutation; (*d*) mutation does not ordinarily affect simultaneously two or more loci and usually involves only one of the two homologues in a diploid cell; and (*e*) "Normal" (wild type) alleles in a species tend to be more often dominant than the mutants arising from them, and most mutants are deleterious.

In this paper—delivered to the Congress of Eugenics—we find a first mention of the problem of increasing genetic load in man as a consequence of relaxed selection and reduced inbreeding. In 1921, we must remember, the theory of population genetics consisted of not much more than the Hardy-Weinberg formula.

The 1926 paper, "The gene as the basis of life," deals first with estimates of gene numbers and size, then with the problem of whether the gene is compound, i.e. made up of several identical parts, as suggested by Demerec's work. It comes to the conclusion, from studies of the pattern of mosaics in *Drosophila melanogaster,* that this is unlikely to be the case but concedes that the matter was not settled. It took another five years to bear out Muller's conclusion.

The part of all-embracing interest in this paper is that dealing with the origin of life and its evolution (pp. 196–204). The essence is that reproduction

> did *not* exist before the property distinctive of the gene existed—namely, before that peculiar form of specific autocatalysis existed which is compatible with change in composition (mutation). The gene, then, arose coincidentally with growth and "life" itself, if our argument be correct. We shall further conclude that at the time of its inception this mutable autocatalytic system was extremely simple, as compared with forms of protoplasm that have as yet been analysed, consisting of little or nothing else, in fact, than what may be called the gene. [And further] . . . those features of gene structure which are responsible for its primary autocatalysis . . . must still be the same as in the immemorial ages past. . . . When we take this point of view . . . we escape our logical difficulty concerning the origin of present-day protoplasm, with its intricately interlocked parts that all act to further the growth and exact reproduction of the whole. For the origination of this system came about gradually, step after tested step. . . . In this process those mutant genes whose by-products (end-products other than their own material, not originally necessary for "life") were most useful, in further reproduction differentially survived, multiplied and mutated again. On this view . . . the protoplasm was, after all, only a by-product, originally, of the action of the gene material; its function . . . lies only in its fostering the genes, and the primary secrets common to all life lie further back, in the gene material itself.

This is a more profound way of expressing the concept which Samuel Butler put as "the hen is only an egg's way of making another egg."

An interesting footnote to this paper might be read as an anticipation of messenger-RNA. It says that the gene material need not be enzymatic. Its copies, in their reactions with the "protoplasm," may be produced as fast as they are used up and eventually lead to the production or modification of the real enzymes. Admittedly, I may be reading beyond what was really meant.

The 1938 (published 1940) paper by Raffel & Muller, "Position effect and gene divisibility etc.," followed the fruitful years after the demonstration of X-ray mutagenesis, part of which Muller spent at the Institute of Genetics in Moscow, where he had many very good collaborators. Radiation genetics had yielded a wealth of results bearing on mutation, allelism, chromosome rearrangements, position effects, refinements in location of genes and the first biophysical attacks on the nature of the gene. This is the era in which Muller and Timofeef-Ressovsky were instrumental in rousing the first interest of physicists—such as Jordan, Zimmer, Delbrück and Schroedinger—in genetics.

The importance of the 1938 paper—containing a formidable amount of experimental results—lies in the fact that the problems of the divisibility of the genetic material and the meaning of the ultimate units of heredity were stated clearly here for the first time. . . . "This . . . raises questions concerning the limits of what have been called 'genes,' and the propriety of assuming that 'genes' as conceived according to our different hypothetical criteria are necessarily coextensive."

The same general conclusion was drawn in the paper, published a few months earlier, "An analysis of the process of structural change" (pp. 409–422).

> . . . we must be careful not to take it for granted that the chromonemal internodes demarcated by different criteria would necessarily coincide with one another. X-ray breakage, for example, might be possible at more points than crossing-over breakage, or vice versa, and the points of crossing-over in turn may be different from the limits set by ultra-violet mutation or from the boundaries pertaining to certain types of gene-functioning and there might be still different limits prescribed for the smallest amount capable of exerting auto-synthesis or auto-attraction. . . . we should have . . . different kinds of "genes" according to the definition which we chose to follow.

It took 12 further years before I named the "mutational site," and 15 further years before Benzer named the "cistron" and the "recon."

Even though both the papers published in 1940—no doubt as a consequence of the times—were lacking the confidence usual in Muller's other writings, they contained all that was needed in the way of clear statement of the problems for further probes on the divisibility of the genetic material. I for one was certainly inspired by them. It would be interesting to know what influence, if any, they had on Lewis's and Benzer's thinking.

The 1945 Royal Society Pilgrim Trust Lecture "The Gene" (pp. 205–208) shows unmistakably a return of the old confidence and optimism. It is a synthesis of all that mattered up to that time. In it there is the remarkable suggestion, deduced from the properties of the gene material, that a process of crossing-over should occur even in bacteria and viruses, and that the transforming principle of Avery, Macleod & McCarthy was in fact chromosomes, or chromosome parts, which penetrated the affected bacterium and were integrated by some kind of crossing over.

We come now to the paper "The gene material as the initiator and the organizing basis of life" (*American Naturalist* 1966, **100,** 493–517), prepared for the 1965 Mendel Centennial meeting of the Genetics Society of America. Here, in the masterly historical introduction, is the point that at the time of Muller's early papers

> it had long been known that continued life . . . requires genetic material—we

> will here call it gene material—but it had not yet been proposed *that this by itself had constituted the earliest ancestors of organisms* (italics mine) . . . many biologists . . . tended to think of the gene material as having differentiated later within the protoplasm or as having arisen separately and combined in a symbiotic relation with the protoplasm.

In a reply to earlier criticism of this idea (*Bulletin of the Atomic Scientists,* Oct. 1964, pp. 36–37) Muller had stated tersely: "So let us not confuse the beginnings and essentials of life, self-replication and mutation, with those later developments: metabolism, protoplasm and cellular life in general."

Further on in the 1966 paper Muller hails "the breakthrough of genetics into biochemistry, or of biochemistry into genetics—whichever one prefers to term it" and the solution of the problem, which he had so clearly emphasized for three decades, of a structure endowing the genetic material with its unique and "truly fateful faculties—those of reproducing itself *and* its mutants, and of influencing other materials—the three faculties which, when in combination, underlie the possibility of all biological evolution."

He goes on to consider the recent experimental and paleochemical findings which make almost inescapable the idea that something like present-day gene material—that is a nucleic acid—was the initiator of life and life of increasing complexity was organized by it in the course of evolution. A main question remains the transition from proto-polynucleotides, capable just of replication and mutation, and polynucleotides capable of coding for proteins which favoured the preservation and multiplication of those polynucleotides.

Then follows a discussion of all the basic questions of the evolution of present-day nucleic acid-protein interrelations: degeneracy (which he prefers to call "synonymy"), the egg-and-hen problem of nucleic acids synthesis requiring protein, and protein synthesis requiring nucleic acids, the problem of the enormous amounts of nucleic acids in higher organisms and that of the evolution of lower and lower mutation rates. There is enough in this paper to stimulate the thinking and work of generations of biologists. The conclusion is as terse and simple as the 1921 paper: "The 'stripped down' definition of a living thing here offered may be paraphrased: *that which possesses the potentiality of evolving by natural selection.*"

The Future of Man

The papers from 1921, or even 1912, to 1966 on the properties of the gene material draw the grandiose picture of evolution by mutation, "step by tested step" from a primitive polynucleotide, just managing to replicate by using abiotic building blocks and whatever help inorganic catalysts could give, the whole way to man.

The steps depicted are from adsorption of nonspecific coats, to selecting these coats and gradually tailor-making them to help in replication, including them within a membrane together with the polynucleotide, the first cell, protein synthesis as we know it today, functional and reciprocal interlocking of genes and "protoplasm," multicellularity, differentiation, the evolution of a finite life-span, the development of integrated control systems, the central nervous system up to man with his cultural heredity and his conscious potentiality of taking his future in his own hands.

Such a vision, already sketched in Muller's youth, and made more precise and meaningful as the years and the knowledge accumulated, could not stop there. Muller's concern about the future of man had both the negative aspect of containing the genetic damage of man's own making—radiation, relaxed selection, relaxed inbreeding—and the positive aspect derived from that grandiose picture of evolution.

We must distinguish here between the purely scientific work and Muller's challenge to human society to decide "What genetic course will man steer?" (Address to the 3rd International Congress of Human Genetics, Chicago, 10 Sept. 1966).

I am not competent to evaluate in detail the problems of genetic load, of balanced polymorphism, of one-gene heterosis, of the dysgenic effects of medical advances and, in general, of the rapidly changing structure of society. Some documented conclusions of Muller on all of these matters have provoked heated discussions, not entirely dispassionate. One thing is clear: Muller has played a decisive part in making mankind conscious of the dangers to future generations of ionizing radiations. For what has been achieved in international agreement in this respect, little as it is, we are primarily indebted to him.

What I should like to consider here is the challenge implicit in the title of the Address mentioned above—and in many other writings of Muller since 1935—a challenge which is the direct extrapolation of the idea of the gene as the basis of life. Muller's argument, inadequately as I can summarize it, is that the tendencies to cooperation, to brotherly love, to parental, grandparental and community care, to sacrifice oneself for one's fellow's sake—in short all the tendencies which make human society—have some genetic basis which has evolved similarly to the genetic basis of any other biological feature. But where the evolution of these most human of human features differs is in the strength of positive feedback which genetics and culture have had. Social rewards and punishments, in respect of these cooperative features, have enormously reinforced other methods of natural selection and the genetic trend in its turn has speeded up the cultural trend.

There are two problems here. One is purely negative: modern society has now reached such a level of cooperative organization that individuals genetically less well endowed than the average in respect of these "social" features are less strongly discriminated against by natural and social selection than in the past. There is, therefore, a possibility of slowed down pace, stasis or even retrogression in the rate of genetic change of mankind's more human characteristics. There is also the consideration that the rate of genetic advance must be now very slow compared with the rate of cultural improvement. Cultural innovations spread at a fantastic speed to the whole of mankind, compared to the spread of genotypes favoring them.

Finally, the modern structure of society, with its merging of previously partially isolated populations, also acts in the direction of less effective selection against antisocial genotypes. All told, it looks as if we had reached or approached a point at which further genetic improvement in the mentioned directions would no longer be automatic.

The other problem is positive. Man has now the power of speeding up his own evolution in desired directions. The question is: which directions are desirable and who is to decide? Muller's suggestion is to replace the present secrecy, in the cases of artificial insemination, by the availability of sperm—stored for long after their death—from donors whose physical, intellectual and biographical features are made known. The selection is, therefore, voluntary and exercised by the couple concerned on the basis of the available information. Muller was convinced that a system like this, involving only a minor change in a practice which produces already some 10,000 children a year in the U.S., would give such appreciable results in a short time that couples for which it was not necessary would also gradually resort to it.

With his characteristic trust in mankind at large, Muller was also convinced that voluntary germinal selection of this kind would operate in the right direction for two reasons. First, in the early stages at least, couples resorting to it without necessity would, *ipso facto,* be above average precisely in those most human of human features for which selection is relaxed. Second, their choice of the sperm on the basis of the divulged features of the donors would also, on the average, be made in the right direction.

Muller's plan for voluntary germinal selection has been received by reactions most of which range from plain derision to violent denunciation. Whatever the practical merits of the proposal—and the danger of its being distorted for political or "racist" purposes should not be overlooked—the genetic course which mankind will choose to take is something that must be debated. If the grand picture of evolution drawn by Muller can be extrapolated, the expectation is that man will take a hand in shaping his own genetic future.

Notes

The list of Muller's works up to 1961 is at the end of *Studies in Genetics, the Selected Papers of H. J. Muller,* Indiana University Press, Bloomington, Indiana (1962)

Biographical data are in E. A. Carlson, 1967: The legacy of Hermann Joseph Muller: 1890–1967, *Can. J. Genet. & Cytol.* **9**: 437–48.

A Biographical Memoir, with complete list of papers, will appear in Vol. 15 of the *Biographical Memoirs of Fellows of The Royal Society.*