cleus of the grandmother $r/+$ which exceptionally entered the germ track. If these $r/+$ eggs develop by pseudoparthenogenesis (autogamy)—a possibility known from *Solenobia*—the offspring is female and wild type. If occasionally a few such nuclei undergo normal meiosis and fertilization, the possible classes of daughters as well as sons appear in small and equal numbers. A repetition with the alleles r^9 and r^{39} gave only a few such cases in about 8,000 females tested; r^{39} females are almost sterile, r^9 females relatively fertile. All together, about 1 female in 20 was fertile. In many of these, the grandmaternal X chromosome was marked with *Bar*, but only once were *Bar* offspring obtained from non-*Bar rr* ♀ by the activation of the grandmaternal polar copulation nucleus. A few more such cases occurred with complications by previous crossing over, all together in less than 2 per cent of the fertile females.

[1] C. J. Lynch, *Genetics*, **4**, 501, 1919; T. H. Morgan, *Z. indukt. Vererbungs.*, **7**, 323, 1912; *Am. Naturalist*, **49**, 240, 1915.

[2] S. J. Counce, *Z. indukt. Vererbungs.*, **87**, 443, 1956 (3 parts).

[3] R. Goldschmidt and K. Katsuki, *Biol. Zentr.*, **47**, 45, 1927; **48**, 39, 685, 1928; **51**, 78, 1931.

[4] J. Seiler, *Arch. Julius Klaus-Stift. Vererbungsforsch.*, **28**, 40, 1953.

---

*SPECIAL PROBLEMS INHERENT IN THE STUDY OF HUMAN GENETICS WITH PARTICULAR REFERENCE TO THE EVALUATION OF RADIATION RISKS**

By James V. Neel

DEPARTMENT OF HUMAN GENETICS, UNIVERSITY OF MICHIGAN MEDICAL SCHOOL, ANN ARBOR, MICHIGAN

Read before the Academy April 22, 1957, by invitation of Committee on Arrangements for the Annual Meeting

Studies on man have contributed relatively little to the flowering of genetics which has characterized twentieth-century biological science. The reasons for this are well known: the length of the generation time in man, the impracticability of test matings, the difficulties in controlling environmental variables, the role of cultural overlay in molding and obscuring genetic predispositions. There are, in my opinion, numerous evidences today that despite these drawbacks, the study of human genetics has finally come of age, to the point where studies on man will yield results on a level of significance with those emerging from studies of other organisms well known to the geneticist. These results will emerge, not from looking to man for the qualities which have made *Drosophila* and *Neurospora* so useful to the geneticist, but, in part at least, from taking advantage of certain special attributes of man and the populations in which he gathers, attributes not shared by other organisms.

In considering the factors which have contributed to the coming of age of human genetics, it is convenient to distinguish between developments which are related to the "natural" evolution of the subject and other developments which are currently contributing to a somewhat "forced" evolution. As regards the "natural" evolution of human genetics, three contributory factors are outstanding. The first is

the recent rapid expansion of medical and biological knowledge, with the result that in the evaluation of a problem involving the genetics of man there can be brought to bear a set of techniques which far exceed those available for any other organism. The second is the development, during the last twenty years, of statistical techniques which enable a maximum of genetic information to be extracted from two-generation data, such as one must often be content with in human genetics. The third factor of importance in the recent "natural" evolution of human genetics is the changing content of medical practice, with the increasing control of contagious and parasitic diseases and the growing relative importance of congenital, constitutional, and degenerative diseases, to all of which genetic factors are so important.

As regards the "forced" evolution of human genetics, it is apparent that the very lively discussions of the past several years concerning the genetic problems created by increasing exposure to ionizing radiation have gone far to focus attention on the absolute necessity of acquiring as soon as possible a far better understanding of human genetics than we now possess. These same discussions have also stimulated many able geneticists to direct a greater portion of their creative energies toward human genetics than would otherwise have been the case, and to give serious consideration to the special problems of this field, a development from which the field cannot but benefit. The activities of the National Academy of Sciences Committee on Radiation Genetics are a notable example of this.

My assignment today is to review the special problems inherent in the study of human genetics. An exhaustive treatment of this subject would obviously be extremely time-consuming. Under the circumstances, I have chosen to restrict my remarks to the special problems which arise in connection with the subject of today's symposium, the evaluation of the genetic risks of increasing exposure to ionizing radiation.

In the evaluation of this problem there are certain types of information which are indispensable, in the sense of supplying the figures fed into mathematical treatments of the subject. These are (1) the spontaneous rate of mutation in man, be it on a per locus or a per gamete basis; (2) the induced mutation rate per locus or per gamete per unit of ionizing radiation; (3) the "accumulation factor," i.e., the ratio of deleterious mutations already present in the population to those arising spontaneously each generation through mutation; and (4) the manner of action of natural selection on past and contemporary human populations. Let us now consider briefly some of the special problems inherent in furthering our information concerning man in each of these four areas.

The Spontaneous Rate of Mutation of Human Genes. The spectrum of phenotypic effects resulting from gene mutation ranges from complete lethality to extremely minute effects, apparent only under special circumstances. Two of the standard techniques used in the study of mutation rates in sexually reproducing forms consist (1) in the use of a special strain of animals in which one or more chromosomes carry complex chromosomal rearrangements associated with so-called "marker" genes, of particular use in the detection of mutations associated with lethal effects, and (2) in the use of special strains homozygous for a number of recessive mutations involving known loci, of particular use in the detection of mutations at these specific loci. Neither of these techniques is available for man. One is therefore forced to

rely on the very simple device of counting the rate of appearance of a variety of mutant phenotypes in human populations and then computing the mutation rate, either on the basis of the gene replacement rate necessary to offset the reproductive disadvantage accruing to the phenotype or, in the case of dominantly inherited traits, on the basis of the proportion of sporadic cases. The former approach requires the assumption that the population is in genetic equilibrium or nearly so. In the case of phenotypes determined by recessive genes, the former approach also necessitates certain critical assumptions concerning the effect of the gene when heterozygous.

In order to avoid making such assumptions, which may introduce indeterminate errors, the tendency in recent studies on human mutation rates has been to concentrate on phenotypes determined by dominant genes and to base the estimate solely on the proportion of sporadic cases of the disease occurring in a given population over some arbitrary time interval. Now the situation is simpler, but still, before one can argue from the frequency of the trait in the population to the mutation rate, one must meet two important qualifications.

First, one must establish how frequently the phenotype in question is not the result of a germinal mutation. This may be difficult, but to fail to do so may introduce an error. A single specific example will suffice. Retinoblastoma is a type of cancer of the eye, developing at an early age, which in many family studies has been shown to behave as if due to a single dominant gene with a high degree of penetrance. Some years ago our group carried out a state-wide survey in Michigan, with reference to the frequency of occurrence of "sporadic" cases—i.e., individuals with no family history.[1] We then calculated a mutation rate on the assumption that each of these individuals represented a mutational event. We specified at the time that this estimate would be incorrect if some of these individuals owed their disease to nongenetic causes or to somatic mutations, but we had no evidence that this was the case. Subsequently, several studies have suggested that when the offspring of affected individuals who have reproduced are studied, there are fewer affected children than would be expected if all affected individuals owed their disease to germinal mutation.[2, 3] Our own estimate was consequently too high. This potential source of error is not serious, in the sense that the means of dealing with it are both clear and feasible, although temporarily, as in our case, the necessary data may not be at hand.

Second, for an estimate to be entirely valid, one must establish the fact that the mutant phenotype in question always results from mutation at the same locus. This is not possible in man at the present time, so that all studies to date may actually be measuring the sum of mutation at several loci. However, developments are in sight which will in some measure meet this problem. These are of two types. Studies on the linkage relationships of the gene(s) responsible for a given phenotype will reveal how many different loci may give rise to mutations resulting in that phenotype. For instance, elliptocytosis is a condition in which the erythrocytes are oval rather than round. Many extensive pedigrees are known in which the trait behaves as if due to a dominant gene. It has now been shown that in some of the pedigrees this gene behaves as if closely linked with the locus or loci responsible for the Rh serological reactions, while in other pedigrees there is no apparent linkage (see references in Morton[4]). The logical conclusion is that there are at least two genetic loci at which mutation may give rise to the ovalocytic trait. The second approach to a determination of the number of different loci at which there may

occur genes resulting in a given phenotype involves careful clinical studies of the trait. For instance, it has now been shown that there are really two types of hemophilia, both sex-linked in their inheritance, with the serum from an individual of one type able to correct the bleeding defect in the other type (see references in Graham,[5] Macfarlane,[6] Schulman and Currimbhoy[7]). One type is about four times as frequent as the other. Studies were carried out some ten to twenty years ago on the rate of mutation to the hemophilia gene.[8, 9] If the mutations resulting in these two types of hemophilia are ultimately shown to involve different loci, then the mutation-rate estimates resulting from these early studies must now be revised downward, to take into account the fact that two different loci are involved (cf. Graham[5]). As another example, diabetes insipidus, a condition characterized by the excretion of large quantities of very dilute urine, frequently behaves as if due to a sex-linked recessive gene. It has now been shown that in some pedigrees typical of sex-linked inheritance, the condition can be remedied by the administration of pitressin, an extract of the pituitary gland. In these pedigrees the primary defect would seem to be in the pituitary gland. In other pedigrees the condition does not respond to pitressin. Here the primary defect apparently resides in the renal tubule.[10] Clinical tools again allow us to differentiate two distinct types of the disease, a fact to be reckoned with if mutation-rate studies on this condition were contemplated.

Thus far, studies have been carried out on the rate of appearance through mutation of about a dozen different dominantly inherited phenotypes. The results are summarized in Table 1. It is an interesting fact that despite all the qualifications

TABLE I

ESTIMATES OF THE RATE OF APPEARANCE THROUGH MUTATION OF CERTAIN GENES IN MAN*

CHARACTER	POPULATION	MUTANT GENES PER 100,000 GAMETES	REFERENCE
		Autosomal Dominants	
Aniridia	Denmark	0.5	Møllenbach, 1947 Penrose, 1957
Chondrodystrophy	Denmark	4.3–4.9	Mørch, 1941
	Sweden	7	Böök, 1952
	Japan	9–14	Neel and Schull, unpublished
Dystrophia myotonica	Northern Ireland	0.8	Lynas, in press
Epiloia	England	0.8–1.2	Penrose, 1936
Marfan's syndrome	Northern Ireland	0.5	Lynas, unpublished
Microphthalmos without mental defect	Sweden	0.5	Sjögren and Larsson, 1949
Multiple polyposis of the colon	Michigan	1–3	Reed and Neel, 1955
Neurofibromatosis	Michigan	10	Crowe, Schull, and Neel, 1955
Pelger's nuclear anomaly	Germany	2.7	Nachtsheim, 1953
Retinoblastoma	England	1.4	Philip and Sorsby, 1944
	Michigan	2.3	Neel and Falls, 1951
	Germany	0.4	Vogel, 1954
Waardenburg's syndrome	Holland	0.4	Waardenburg, 1951
		Sex-Linked Recessives	
Hemophilia	England	2	Haldane, 1935, 1948
	Denmark	3.2	Andreassen, 1943
Pseudohypertrophic muscular dystrophy	Utah	10	Stephens and Tyler, 1951
	Northern Ireland	4.5–6.5	Stevenson, 1953
	Germany	4	Becker and Lenz, 1955
	England	4.3	Walton, 1955

* After J. V. Neel and W. J. Schull, *Human Heredity* (Chicago: University of Chicago Press, 1954); L. S. Penrose, in *Proceedings of the First International Congress of Human Genetics* (*Acta Genet. et Statist. Med.* [Suppl.], 6, 169–182, 1956); A. C. Stevenson, *World Health Organization Publ.* (in press).

I have erected, the average of these estimates, about 3×10^{-5}, is not very different from the average commonly quoted for *Drosophila*, about 2×10^{-5}. However, because of these very qualifications, as well as certain other methodological difficulties involving *Drosophila* as well as man, it would perhaps be wise to regard this as an interesting coincidence rather than as a demonstration of similarity, until such time as much more extensive data are available.

In certain considerations it is important to have an estimate of the "total" mutation rate, i.e., the average number of mutations per gamete. In order to convert figures on the rate of mutation at specific loci to a "total" mutation rate, one must make certain assumptions concerning the number of mutable loci present in man. This is an extremely thorny problem for *Drosophila* or *Neurospora*, and even worse for man. Nor does it seem that here we can anticipate rapid advances with respect to human material. For the present, human genetics, in problems involving gene number, will have to be guided by the findings in other animals. Fortunately, there is an approach to the question of "total" mutation rates which does not involve gene number per se. Recently, Morton, Crow, and Muller[11] have described a mathematical formulation which enables one to estimate the total mutation rate per gamete per generation on the basis of a comparison of certain attributes of the offspring born to consanguineous as contrasted to nonconsanguineous marriages. This is a technique which should be quite useful. Unfortunately, the data now available which could be fed into these equations are of limited validity. This is a situation which time will certainly rectify, since there is currently a great deal of interest all over the world in the outcome of consanguineous marriage.

There is one final point I should like to make concerning studies of spontaneous mutation rates. It is a well-established fact that mutations with very minor phenotypic effects far exceed in number the mutations with major effects, with which it is usually convenient to work in experimental material. Better techniques for evaluating both the frequency and the effects of these "small mutations" are urgently needed. A recent development in human genetics may point the way to approaching these small mutations. It now appears that the distinguishing feature between sickle cell and normal hemoglobin may be a simple amino acid substitution in a polypeptide chain.[12] This difference is determined by a single gene substitution. One may speculate that the rather marked effect on the properties of hemoglobin induced by this gene substitution in the case of sickle cell hemoglobin are due to the fact that this particular amino acid substitution is especially critical. The techniques are now available for analyzing the hemoglobin of different individuals, literally amino acid by amino acid. Such techniques promise to give much needed insight into the amount of concealed genetic variability in protein structure and, by inference, into the frequency of undetected mutation. Such mutation may be of importance either through a cumulative effect or as supplying a significant source of variation when environmental conditions change.

The Induced Mutation Rate per Locus per Unit of Ionizing Radiation. The difficulties in reaching conclusions concerning the sensitivity of human genes to ionizing radiation are readily apparent. There are a number of circumstances under which substantial groups of human beings have received relatively large amounts of radiation. However, in no instance is the amount of radiation sufficiently large that one can survey the population involved with respect to the rate of

appearance of specific new mutant phenotypes, with any reasonable expectation of detecting a difference between the progeny of irradiated and controls. Rather, the approach must be much less specific, involving changes in the vital statistics of the progeny, i.e., such end points as sex ratio, stillbirth and neonatal death rates, frequency of occurrence of malformation, age-corrected death rates, etc. The most ambitious attempt to date to come to grips with this problem has been the Academy-sponsored study on the children of the survivors of Hiroshima and Nagasaki.[13] This study was inconclusive, in the sense that while no clear-cut genetic effect of the atomic bombings could be demonstrated, neither, because of the magnitude of the "observational error," could effects of an extent comparable to those produced by the irradiation of experimental material be excluded. There is, however, a more positive and sometimes overlooked aspect of these studies. They permit us to set upper limits to the sensitivity of human genes to irradiation. Thus, one of the important developments in radiation genetics during the past decade has been the demonstration by Russell[14, 15] that the mutation yield per unit of radiation was some ten times greater for the mouse—the first mammal to be so studied—than for the fruit fly. It was conceivable that man was in turn conspicuously more sensitive to the mutagenic effects of radiation than the mouse. We believe that the findings in Japan tend to exclude this possibility. Other positive aspects of the Japanese studies are that they have been collected and recorded in such a fashion that the findings may for analytic purposes be combined with such other sets of pertinent data as may some day become available and that they yield normative data concerning such questions as the outcome of consanguineous marriage, which contribute to a better understanding of the population genetics of man.

Recent developments in tissue culture[16] hold real promise of a somewhat more direct approach to this question of the sensitivity of human genes to irradiation, albeit in somatic rather than in germinal cells. It is now possible to establish "clones" of tissue culture cells, all the cells in a given culture having been derived from a single ancestor cell. It thus becomes possible to irradiate suspensions of cells and then "plate them out," as it were, much as can be done with bacterial suspensions. Mutant clones can be detected by morphological or antigenic criteria, and mutation rates thus established.

The Accumulation Factor. The term "accumulation factor" has been used to designate the ratio of the number of deleterious genes which, on the average, are already present in the individual's gene complex to the number arising each generation in consequence of mutation. This figure serves as an important yardstick, both in estimating the strength of selective factors in the past and in providing a background against which increases in mutation rate must be viewed. One way of getting at this problem is the study of both the rate of death in, and the physical and mental characteristics of, the children resulting from consanguineous marriage. Böök[17] has recently presented the first unbiased, unselected, and carefully controlled data on this point; his limited material suggests that there is an average of a *minimum* of three detrimental autosomal recessive genes in heterozygous form per individual. On theoretical grounds, the true figure has been estimated to be considerably higher.[18–20] As noted earlier, there is much current interest in this topic, and important data will almost certainly be forthcoming in the near future.

A second approach to this problem consists in the methodical collection of data concerning the frequency of inherited diseases. An estimate obtained from such data will of course be a minimum estimate. At the present time, our information concerning the frequency of most inherited diseases is so poor as to make frequency estimates of this type of relatively little value. This is a situation which can certainly be rectified, although for many years in the future this approach will yield very *minimum* estimates. A third means of estimating the accumulation factor consists of the development of clinical techniques which will make it possible to detect gene effects which have in the past gone unnoted. There is increasing evidence that many so-called "recessive" genes have some manifestation when heterozygous. Individuals who possess undesirable genes which find no or very slight expression are sometimes designated as "genetic carriers." We are now able to detect, with greater or lesser degrees of accuracy, several dozen different carrier states (review in Falls and Neel[21]). Some of the most pertinent examples in this respect are drawn from the field of hematology, where the relative ease with which hematopoietic tissue and its products may be sampled has led to relatively rapid advances. While it is certainly not imminent that by subjecting an individual to a battery of tests we can come up with a precise statement concerning the number of "undesirable" genes he carries, it should at least be possible to evaluate the situation as regards quite a number of specific possibilities in the near future.

The Manner of Action of Natural Selection in Past and Contemporary Human Populations. Of all the gaps in the background knowledge necessary to a precise evaluation of the genetic risks of ionizing radiation, that gap which will some day be filled by information concerning the manner of action of natural selection looms in my mind the largest. Many current treatments of the problem assume that the combined efforts of the physician and the sanitary engineer, coupled with agricultural and transportation developments that render famine unlikely, have brought the processes of natural selection which have shaped the human race to a virtual standstill. It is difficult to discern a really sound basis for this rather sweeping opinion, since we know so little about the workings of natural selection in either primitive or contemporary populations. There can be no question of some important recent shifts as regards selective pressures. But whether these shifts are of a magnitude or type which actually mean that the human species is no longer capable of evolving to meet rapidly changing conditions, as some would maintain, is to me a very moot point indeed. There appear to be many opportunities to study natural selection at work today.[22] These range from studies on causes of individual fertility differences to the relationship between diet and health. Recent developments with respect to the abnormal human hemoglobins have provided a striking example of how the frequency of an apparently undesirable trait can be maintained through the mechanisms of balanced polymorphism. It is of the utmost importance to determine the degree to which the human species may be "buffered" against adverse genetic developments by such genetic systems.

Mathematical Models. Having discussed the principal types of information we need in order to evaluate the genetic risks of increasing exposure to ionizing radiation, I do not want to leave you with the impression that, if this information were available, we would have only to feed it into certain equations and the answers would emerge like sausages from the other end. Despite the brilliant contributions

of Wright, Fisher, Haldane, and, more recently, Kimura, to the mathematical theory of evolution, this subject is still in its early stages. Most statistical models in this field have dealt with events at a single locus represented in a population by two alleles, with one of the alleles bearing a fixed selective relationship to the other, or with a relatively simple departure from this situation. In truth, of course, genetic changes in populations in consequence of ionizing radiation are the result of events at many thousands of loci, each represented by multiple alleles, with the selective value of a particular gene a function of the genetic makeup of the organism at many other loci. As the fifth general development necessary to an evaluation of this problem, then, I would mention the development of a mathematical approach which goes far beyond present techniques in recognizing the complexity of the problem and which is evolved at all times to take advantage of present-day electronic computers.

Concluding Remarks. In concluding this very brief survey of some of the problems of human genetics, I would like to face squarely one practical issue. The most precious asset of mankind today is the germ plasm which has enabled him to develop the culture we all enjoy. If current developments—of which increasing exposure to ionizing radiation is only one—threaten the integrity of this germ plasm and are paving the way for the decline of our species, then here is a problem equal in magnitude to any with which we are currently confronted. I think it important to emphasize that the kind of data necessary to an intelligent evaluation of the problem will not issue from the investigations of a few scattered geneticists but will require a greatly expanded effort on both human and nonhuman material, involving many teams of highly trained personnel. The annual financial support of research in human genetics in this country today is probably well below the cost of a single large jet bomber. While I by no means believe that genetic disaster is just around the corner, there is no doubt that the problems with which we are confronted call for an order of magnitude of research effort far in excess of what in the past, in the field of biology, has seemed adequate.

* Contribution to the Symposium on Genetics and Radiation Hazards of the National Academy of Sciences, under the chairmanship of G. W. Beadle.

[1] H. F. Falls and J. V. Neel, *Arch. Ophthalmol. (Chicago)*, **46**, 367–389, 1951.

[2] F. Vogel, *Z. menschl. Vererbungs- u. Konstitutionslehre*, **32**, 308–336, 1954.

[3] D. P. Tucker, A. G. Steinberg, and D. G. Cogan, paper delivered at a joint meeting of the American Society of Human Genetics and the American Association of Physical Anthropologists, Ann Arbor, Michigan, April 12, 1957.

[4] N. E. Morton, *Am. J. Human Genet.*, **8**, 80–96, 1956.

[5] J. B. Graham, *Am. J. Human Genet.*, **8**, 63–79, 1956.

[6] R. G. Macfarlane, *Physiol. Rev.*, **36**, 479–502, 1956.

[7] I. Schulman and Z. Currimbhoy, *Ped. Clin. N.A.*, pp. 531–549, May, 1957.

[8] J. B. S. Haldane, *J. Genet.*, **31**, 317–326, 1935.

[9] J. B. S. Haldane, *Ann. Eugen.*, **13**, 262–271, 1947.

[10] H. Forssman, *Am. J. Human Genet.*, **7**, 21–27, 1955.

[11] N. E. Morton, J. F. Crow, and H. J. Muller, these PROCEEDINGS, **42**, 855–863, 1956.

[12] V. M. Ingram, *Nature*, **178**, 792–794, 1956; also *Proceedings of the Conference on Hemoglobin* (Washington, D.C.: National Research Council, 1957) (in press).

[13] J. V. Neel and W. J. Schull, *Natl. Research Council–Natl. Acad. Sci. Publ.* **461**, pp. xvi and 241, 1956.

[14] W. L. Russell, *Cold Spring Harbor Symposia Quant. Biol.*, **16**, 327–336, 1951.

[15] W. L. Russell, *Am. Naturalist*, **90**, 69–80, 1956.

[16] T. T. Puck and H. W. Fisher, *J. Exptl. Med.*, **104**, 427–433, 1956.
[17] J. A. Böök, *Ann. Human Genet.*, **21**, 191–221, 1957.
[18] R. D. Evans, *Science*, **109**, 299–304, 1949.
[19] H. J. Muller, *Am. J. Human Genet.*, **2**, 111–176, 1950.
[20] H. J. Muller, in *Radiation Biology*, ed. A. Hollaender (New York: McGraw-Hill Book Co. Inc., 1954), **1**, 351–453.
[21] H. F. Falls and J. V. Neel, *Eugen. Quart.*, **1**, 166–170, 1954.
[22] J. V. Neel, *Am. Anthropologist* (in press).

---

*THE SCOPE OF GENETICS**

BY CURT STERN

DEPARTMENT OF ZOÖLOGY, UNIVERSITY OF CALIFORNIA, BERKELEY, CALIFORNIA

"The experiments which will here be discussed took their origin from artificial fertilisations which have been carried out on ornamental plants in order to obtain new color variants." This opening sentence of Gregor Mendel's paper points to one of the humble origins of genetics: horticulture. Significantly, as late as 1901, it was the Royal Horticultural Society of London that sponsored the English translation of the then newly rediscovered classic. But the practical desires of the lovers of flowers were not the only incentives to the birth of genetics. All through the eighteenth and nineteenth centuries the species problem occupied the minds of biologists. On the one hand, Linnaeus had defined species in a way which lacked operational usefulness: There are as many species as there were diverse forms created at the beginning by the Infinite Being. On the other hand, Linnaeus and other plant hybridizers attempted to probe into the nature of species by experimental means. Were hybridizations between different species possible? Could they be induced artificially? Did they ever occur in nature? What kind of organism was a species hybrid? Was it sterile like the mule? If fertile, what kind of offspring did it produce?

In 1859, Darwin's *Origin of Species* proved to be the successful break through the confines of a static conception of species within which biology had accumulated so much of its unordered bulk of empirical facts. Then plant hybridization became a potential tool for progress in a new range. Mendel himself, who began his studies before the appearance of Darwin's book but wrote his report six years after that event, by then had recognized clearly the role of genetics in this respect. The detailed analysis of successive generations of hybrids "seems to be the only right way," he wrote, "by which we can finally reach the solution of a question the importance of which should not be underestimated in connection with the history of the evolution of organic forms."[1]

Genetics and evolution were indeed to become intimately and fruitfully associated with one another; but the scope of genetics was destined to embrace many other regions. From variations in color and form, and from the species problem and hybridization, the emphasis soon shifted to the permanent units which underlie the externally visible phenomena. Mendel's essential discovery had been the