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W. L. Russell

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MAMMALIAN RADIATION GENETICS

W. L. Russell

INTRODUCTION

This symposium is concerned with the basic aspects of radiation effects. When we turn to the genetic effects of radiation in mammals, there are so few aspects on which there is any information that the problem of sorting out the fundamental findings has hardly arisen. In this paper it will, therefore, be possible to survey most of what is known and pass on to a consideration of what is needed next. Since one of the purposes of this symposium is an interchange of views between investigators in different fields, an attempt will be made to avoid technical details.

Among the practical needs in mammalian radiation genetics is a pressing one for more data on which to base estimates of the genetic hazards of radiation in man. The present paper will be concerned largely with this problem. Our own work is directed primarily in this direction, our objective being to uncover some of the basic facts in at least one mammal—the mouse. Before discussing the experimental work, however, it seems desirable to consider some of the general features of the genetic hazard of radiation.

NATURE OF THE GENETIC HAZARD OF RADIATION

Among the hazards of exposure to radiation, the genetic effects are of importance because of several unique features.

1. There is usually no healing of the damage. Some types of damage to the genetic material, for example the breaking of a chromosome, may, under certain conditions, heal. Others, for example "cell lethal" muta-

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tions, are by their nature prevented from passing on to any descendants. However, from effects that are actually hereditary, in the sense of becoming manifest in the next or subsequent generations, the only chance of healing lies in the remote possibility of reverse mutation.

2. The damage is transmitted to descendants. This is, of course, implicit in the term "genetic." Nevertheless, it is sometimes forgotten. Arguments to the effect that we should be phlegmatic about the effects of small doses of radiation, because the total damage is probably no worse than that resulting from various other insults to the organism which man tolerates or even enjoys, ignore the fact that among commonly tolerated insults radiation is the only one known to affect descendant generations.

3. The damage is hidden for a long time before it becomes manifest. Hereditary effects obviously require at least one generation to express themselves. For the large class of recessive mutations, many generations would, on the average, be required in a large, more or less random-breeding population. This class of mutations is particularly insidious in the sense that, even when a particular recessive mutation is finally revealed, it is usually only a very small fraction of the total effect that has become manifest, the rest still being hidden in individuals heterozygous for the mutation.

4. There is no threshold dose. In other words, genetic changes may be expected at any dose, no matter how small. There is a large body of experimental evidence of various kinds which supports this contention and some actual confirming data from doses as low as 25 r in Drosophila [Spencer and Stern (21)]. It is true that Caspari and Stern (2) have presented data which could be interpreted as indicating that the linear relationship between gene mutations and dose does not hold at low doses, but, as the authors themselves point out, other interpretations are possible. It should also be mentioned that, although the difference in mutation rate between controls and experimentals (given 52.5 r chronic exposure) is not statistically significant in these data, this should not be allowed to obscure the fact that the rate observed in the experimentals is higher.

In drawing up safety measures against genetic effects of radiation in human populations, serious attention must be given to point 4. If there is no threshold dose, then a so-called "tolerance" dose cannot be one which produces no genetic effect, but only one which does not add a "serious" increase to the effects that already occur as a result of natural radiation and other causes. The problem of estimating the genetic hazard of radiation, therefore, resolves into two main questions: (i) What is the increase in mutation rate per dose? (ii) How great an increase can be tolerated?

The first question is relatively simple, although the designing of practical experiments to answer it may not be easy.

The second question is highly complex. In the first place, it involves human values. Even if we postpone a consideration of these by changing the question to "What are the effects of a given increase in mutation rate?", the problem is still a tremendous one. Muller has, in his paper (p. 322), already pointed out some of the many unknowns: the relative numbers of the various types of genes, their degrees of dominance, and so forth. Other aspects, particularly effects at the population level, present a major challenge to statistical geneticists. The problem is not entirely novel to them. The same complex of variables—mutation and selection pressures, population size, coefficients of inbreeding, etc.—has been considered in dealing with the problems of evolution and improvement in domestic plants and animals. In the present state of knowledge of these variables, the diversity of theoretical possibilities that can be derived from a consideration of them is almost overwhelming. An excellent example of this diversity is provided by Wright (23) in his speculations on the effects which an increased mutation rate might have on just one single character of a population, namely, its reproductive rate.

Wright calculated that, with regard to completely recessive mutations that affect reproduction in the population solely by depressing the reproductive value of the mutants themselves, a somewhat optimistic view can be taken on the chances of survival of the human population. He points out, however, that this is not the only way in which the reproductive value of the population could be affected. If the mutants were of inferior quality (for example, with lowered intelligence or character), they could constitute a drag on the population as a whole in its ability to utilize its resources and thus bring about a further reduction in the reproductive value which, with high mutation rates, could conceivably lead to collapse rather than to a new equilibrium. If the mutants were inferior and not <u>less</u> fertile than the non-mutants, then the population would tend towards collapse with even the slightest mutation rate. A systematic increase in mutation rate would speed up the process. Finally, if the mutants were inferior but <u>more</u> fertile than the non-mutants, such a runaway process would be enormously enhanced.

Wright suggests still another line of possibilities. For example, it could be imagined that with social and economic changes resulting from the increased number of mutants, the relative reproductive values of mutants and non-mutants might change too, and even reverse their order, thus, in the last case given above, leading to a new equilibrium instead of collapse.

It is apparent that the question of how great an increase in mutation rate can be tolerated in the human population is exceedingly difficult to answer even when consideration is limited to a single, quantitatively measurable end effect: the reproductive rate. The difficulty of estimating theo-

retically the combined effects of the complex of variables emphasizes the need for experimental work in population genetics, such as that being done on Drosophila by Wallace (22), in order to collect empirical data. In mammals there is still much to be done, in fact almost everything, on the preliminary problem of measuring the radiation-induced mutation rate. In the next section, some of our present experiments and the results of earlier investigations are outlined and discussed.

EXPERIMENTAL WORK

Gene Mutations

Mutations produced by x-rays have been reported in mice by Snell (15) and Hertwig (7, 9, 10), but the data are not adequate for a reliable estimate of mutation rate. The difficulties encountered in trying to measure mutation rates in mice, as compared with Drosophila, are very great and not, as is often supposed, due solely to the slower reproductive rate of mice and to the greater space and labor required to raise them. In Drosophila, the most reliable and most easily determinable mutation rates are those based on lethal mutations on the X-chromosome. These rates are obtained by a well-known method, devised by Muller, which makes use of sex-linked genes, acting as markers and chromosome inversions which suppress crossing over. Neither of these being, as yet, available in the mouse, Muller's method cannot be used. Sex-linked lethals could be detected by observing a disturbed sex ratio in the offspring of daughters of irradiated males, but this would be far more tedious and relatively uncertain unless further extensive tests were made.

It would be out of place here to consider in detail the possible ways of measuring mutation rates in other whole groups of genes. For our present research at Oak Ridge they have been rejected in favor of a method for obtaining mutation rates at specific loci. This consists essentially of mating irradiated wild-type mice, and non-irradiated controls, to a strain homozygous for as many known recessive genes as can be managed practicably. A mutation at any of the loci represented by the recessives will then be detected in the first generation. The method has not been suggested before, for mice, presumably because of the relatively large number of animals needed. It was calculated, however, that, with the facilities offered by the Atomic Energy Commission, reliable mutation rates might be obtained in a reasonable time if they were not lower, or much lower, than the Drosophila rates.

The method has several advantages. All mutations are detected in the first generation, whereas methods for obtaining autosomal recessive vis-

ible mutations as a group require at least three generations and then recover only a portion of the total. The mutants can be recognized at a glance, in contrast to the detailed examination, by highly trained observers, necessary when searching for mutations at all loci.

Another advantage of the method lies in the fact that the type of information obtained by it should be suitable for a meaningful comparison with results from Drosophila. Data on the rate of mutation of visibles at all loci would, for example, be less favorable because the number of mutants detected is dependent on the minuteness of examination of the anatomy and physiology of the organism, and it would be hard to determine comparable levels for this in species as widely different as fruit flies and mice. It is important to have data that can be compared because the total information on mutation in mice is bound to lag behind that for Drosophila. The estimating of human hazards will, for a long time, be dependent on some extrapolation from fruit flies to men, and this will be less conjectural if at least one meaningful cross-reference point is established between Drosophila and a mammal.

It is encouraging to know that, as work on specific loci in the mouse proceeds, Muller and his collaborators are making large contributions to data of this kind in Drosophila. In addition to increasing the reliability of the Drosophila side of the comparison, these data will be of help in evaluating the results obtained in the mouse. Thus, the extent of variation found in the induced rates of the many loci being tested in Drosophila will have a bearing on the confidence with which general conclusions can be drawn from the average rate obtained for the seven loci under examination in the mouse.

Muller's data are also likely to prove of great aid in the planning of further experiments on mice. The Drosophila results will include induced mutation rates at the specific loci in eggs as well as in sperm, and in immature as well as mature gametes. Observations are also being made to determine what proportion of the mutations is associated with detectable chromosomal aberrations. Information on some of these factors may be obtained in the mouse, but, as it is a major task to collect enough data for a reliable over-all rate, there can be only limited sub-division of the data or repetition of the experiment under other conditions. The Drosophila results on these and other factors should show which are likely to be the important ones to test.

It is too early yet to draw conclusions from the results being obtained at Oak Ridge.* A pilot experiment was undertaken while the stocks of

* Russell, W. L., X-ray-induced mutations in mice, Cold Spring Harbor Symposia Quant. Biol., XVI, 1951 (in press).

mice were being built up to the size necessary for the large-scale program. The findings from this experiment have settled many of the problems, particularly effects on fertility, involved in an economical operation of the large project. On the basis of mutation rates in Drosophila, few, if any, mutations at the chosen loci were expected in the pilot experiment. Some possible ones were, however, observed, and two of these have already been confirmed by breeding tests. Since more data should be available before long, it would be premature to report the mutation rate calculated from the present figures. The results do indicate that the large-scale program should yield enough mutations to give a reliable figure on the induced rate. The anxiety involved in having to depend primarily on Drosophila data in the planning of this large project with mice is thus somewhat reduced.

Chromosome Aberrations

Much is already known about the induction by x-rays of chromosomal aberrations in the mouse. The pioneer work was done by Snell (14, 15), Snell and Ames (20), and Hertwig (5, 6, 8). Their results, which have been published in detail and have been reviewed by others [for example, Lea (11)], will be presented briefly here in order to provide a background for a few comments about their bearing on the genetic hazards of radiation in man.

When mice are exposed to a heavy dose (for example, in the neighborhood of the median lethal dose) of x-rays and then mated to non-irradiated animals, it can be shown that the offspring conceived shortly after irradiation fall into at least four distinct groups. One group dies in early embryonic stages. The death of this group is presumably due to chromosomal aberrations ("dominant lethals") some of which, as shown by Brenneke (1), result in cytologically visible abnormalities in the nuclei of cells in the early cleavage stages. The remaining three groups are born alive and all appear normal, but only one group proves to have normal fertility, the other two being sterile and semisterile, respectively. It is probable that there are other groups, including stillborn and living abnormal animals, but these seem to be relatively rare.

Since the fertile and the semisterile groups breed, they can be tested genetically. The fertile animals, when outcrossed to normal animals, produce normal, fertile offspring. The semisteriles, when outcrossed, yield three main types of progeny. The first type is comprised of embryos that die at various stages in development. The loss of these accounts for the reduced litter size, about one-half normal, by which the semisteriles were first recognized. The other two types, which occur in equal numbers, prove to be semisterile and normal fertile. On further testing of these, they turn out to be like the semisteriles and fertiles obtained in the first

generation following irradiation. Thus, the semisterility is passed on as a "dominant" to one-half of the viable offspring of semisterile animals.

Snell suggested that the semisterile animals carried a reciprocal translocation which was inherited by their semisterile offspring. He thus accounted for the dying embryos as having unbalanced chromosome complements and for the normal fertile offspring as being balanced and not carrying the translocation. In one case, Snell (17, 18) was able to confirm this interpretation by linkage tests.

With the above brief historical outline as a background, we can turn to some later findings and a discussion of the results.

The results of Lorenz et al. (12), who detected no semisterility in the offspring of mice exposed to gamma rays from a radium source, have been widely quoted by authors concerned with human hazards, with the implication that they are at variance with the findings of Snell and Hertwig and that the explanation may lie in a difference between the effects of chronic and of acute radiation. Hertwig (6), however, had shown that the incidence of semisterility is high only in offspring conceived within a short period (about 4 weeks) following irradiation, that is, as a result of irradiating mature sex cells. If the experimental procedure of Lorenz et al., as given in the earlier report of Deringer et al. (3), is examined with this in mind, it is found that the exposed females were not bred until a month after removal from the radiation field, and that although exposed males were bred immediately after removal it is not stated whether the offspring tested for fertility came from the first or subsequent litters. In all, 42 offspring of exposed males were tested. Even if it is assumed that all of these were conceived shortly after removal from the radiation field, the total dose received in postspermatogonial stages was still not very high. From the rates obtained by Snell and Hertwig, it could have been predicted that perhaps 1 of the 42 offspring would have been expected to show semisterility. There is, therefore, no conflict between the two sets of results. The question of dependence of effect on intensity of radiation is not yet answered, but since the effect with which we are concerned applies only, or mainly, to mature gametes, it seems probable that, as in Drosophila, intensity may be less important than total dose.

Additional data on the incidence of sterility and semisterility in the offspring of irradiated males have been obtained by us. They will be presented in a separate paper for publication elsewhere, but they should perhaps be given in summary here to show that they agree closely with the results of Snell and Hertwig. The animals tested, 22 males and 15 females, were offspring of males exposed to 250-kvp x-rays at an intensity of approximately 80 r per min and for doses of 500, 750, or 1000 r. They were conceived within from 2 to 30 days after irradiation of the father. Their fertility was adequately tested, and the status of those classified as

semisteriles has been further checked in descendant generations. The results obtained are compared with those of Snell (15) and Hertwig (8), for similar dose ranges, in Table 1. Averaging the effects over wide dose

TABLE 1

INCIDENCE OF STERILITY AND SEMISTERILITY IN OFFSPRING (MALE AND FEMALE COMBINED) OR IRRADIATED MALES

Investigator	Dose to ♂ Parent, r	Offspring			
		Percentage			Total Number
		Sterile	Semi-sterile	Fertile	
Snell	400—1200 (mostly 600—800)	5.8	31.4	62.8	121
Hertwig	500—1000 (mean 764)	11.5	25.3	63.2	182
Russell	500—1000 (mean 669)	8.1	27.0	64.9	37

ranges is, of course, a poor procedure, but over the ranges given here is presumably justifiable for the purpose of a rough comparison; and, in any case, Snell does not tabulate his results in a way that can be used to calculate the incidence for each dose.

The high rate of induction of reciprocal translocations by radiation in the mouse is, therefore, supported by three independent investigations and is not refuted by the results of Lorenz et al.

It is noteworthy that this rate is far higher than in the fruit fly. The yield from an acute dose of about 600 r in the mouse is comparable to that from 5000 r in Drosophila melanogaster. The difference between the two species is presumably due to the larger number of chromosomes or amount of chromatin in the mouse. It is, therefore, reasonable to guess that the rate in man would be as high as that in the mouse or even higher. If the hazard from this were not controllable, it would be serious. Fortunately, as has already been pointed out, Hertwig's work shows that the incidence of semisterility is high only in offspring sired shortly after irradiation, namely, before the beginning of the sterile period that follows within a few weeks after the giving of high acute doses. In the progeny conceived after the end of the sterile period, the incidence of sterility and semisterility did not differ significantly from that in the controls. Applying these results to man, the important practical conclusion can, therefore, be drawn that the probability of passing on certain types of chromosomal aberrations to the next generation will be greatly reduced if individuals exposed to high doses of radiation refrain from begetting offspring for a period of perhaps 2 or 3 months after exposure.

Another problem concerning translocations that is of practical importance in man is the determination of the exact times of death of the aneuploids, or unbalanced chromosomal types, which result from the matings of semisterile with normal individuals and which apparently perish while still in embryonic stages. The death of an advanced fetus would obviously constitute more of a hazard to the mother than the loss of an early embryo. In the mouse, there seems to be considerable variation in the time of death, but from the work done so far, including the study by Otis (13), who also made a careful comparison of normal mouse and human developmental stages, it may be tentatively concluded that most deaths would occur before the seventh week of human pregancy. It must be remembered, however, that the number of semisterile lines in the mouse that has been examined for this characteristic is not yet large.

There are many other aspects to the problem of induced chromosomal aberrations in mice which require further study. For example, in two out of eleven semisterile lines being tested at Oak Ridge, the viable progeny of outcrosses of semisterile with normal do not fit the simple ratio of one-half semisterile and one-half fertile. Both these lines are producing some completely sterile descendants, and one is yielding individuals whose fertility is apparently well below that of characteristic semisteriles. It is not yet clear what the pattern of inheritance is in these lines.

The possible effects of translocations in individuals homozygous for them also need to be investigated further. The few cases obtained so far are apparently completely normal phenotypically. This indicates, as Hertwig (8) pointed out, that position effect may be relatively unimportant in the mouse as compared with Drosophila.

Very little is known about the induction of chromosomal aberrations in mammals by radiations other than x-rays. Snell and Aebersold (19) and Snell (16) made a few experiments with neutrons. Dosage comparisons are difficult, but it appears that neutrons may be more effective than x-rays in the production of both dominant lethals and reciprocal translocations.

ESTIMATES OF THE GENETIC HAZARD OF RADIATION

In spite of the lack of knowledge regarding radiation-induced mutation rates in mammals, several estimates of the genetic hazards of radiation in man have been published. These are based primarily on the induced rates in Drosophila. A common scale for measuring the hazard is the dose of roentgens that would produce a rate as high as the spontaneous rate. For this, a knowledge of the spontaneous rate in man is required also. Here, again, little information is available. For these reasons, most, if

not all, geneticists would agree that current estimates of even the basic factor in the human genetic hazard, namely, the increase in mutation rate, are little better than guesses. Nevertheless, such guesses have to be made, whether explicitly or implicitly, because of the necessity for practical decisions, involving perhaps serious consequences, about the protection of people against exposure to radiation.

Several groups concerned with the safeguarding of personnel have, for some time, assumed that the mutation rate in man would be doubled by a dose of about 30—50 r. Two estimates differing widely from this figure in opposite directions have been suggested by Evans (4) and Wright (23). A brief consideration of these estimates will serve to bring out a few more of the problems involved in calculating the genetic hazard.

Evans takes $10^{-5}/3 \times 10^{-8} = 300$, in round figures, as the dose of roentgens required to double the natural rate of gene mutations per generation in man. The denominator in this expression is the induced rate for sex-linked lethal mutations in Drosophila, per roentgen per locus, averaged over all loci in the X-chromosome. Evans accepts this as applying to all chromosomes in man. The numerator, 10^{-5}, is assumed by Evans to be the rate for comparable spontaneous mutations per locus and generation in man. He bases this figure on the rates for hemophilia and epiloia.

Wright criticizes Evans on the following grounds. If the spontaneous rate of lethal mutation per locus per generation in Drosophila is 10^{-6}, and if Drosophila has only one-tenth as many loci as man, both of which figures are accepted by Evans, then the spontaneous rate per gamete per generation in Drosophila is only one-hundredth of what is assumed by Evans for man. Wright argues that it is likely that Drosophila and man would have acquired about the same spontaneous mutation rate per gamete per generation, in so far as this is adjustable in the course of evolution, or that the rate would be lower in man, where there is less wastage of offspring between fertilization and maturity. Even if the spontaneous rate per gamete and generation in man is taken to be as high as that in Drosophila, this figure is still only one-hundredth of that assumed by Evans, or holding the other factors constant, 10^{-7} per locus per generation. Wright points out that there is no incompatibility between rates of the order of 10^{-5} for hemophilia and epiloia and a rate of 10^{-7} for the average of all loci.

If, as Wright claims is possible, the average spontaneous mutation rate per locus in man is only one-hundredth of that assumed by Evans, and if the other factors assumed by Evans are correct, then the dose required to double the rate of mutation in man is also only one-hundredth of that calculated by Evans, namely, 3 r. Both this figure and the 300 r obtained by Evans are based on the rate of induced mutation in irradiated sperm.

Irradiation of early germ cell stages would, on the basis of results in Drosophila, be perhaps only from one-half to one-fifth as effective.

Regardless of the evolutionary considerations raised by Wright, it seems to the present author that the product of the figures assumed by Evans for number of loci and spontaneous recessive lethal mutation rate in man is too high. A consideration of the effect it would have on the offspring of first-cousin matings, for example, will show that it can hardly agree with the facts. The value taken by Evans for the average spontaneous rate of mutation to recessive lethals per locus and generation in man has already been given and is $a = 10^{-5}$. He accepts the view that N, the number of loci in man, probably lies between 10^4 and 10^5. His figure for a minimum estimate of the accumulation factor is m = 50. Accordingly, the average number of recessive lethals per gamete would be aNm = between 5 and 50. Individuals would, therefore, on the average, be heterozygous for from 10 to 100 lethals, and the two common grandparents of first cousins would together be heterozygous for from 20 to 200. The probability that a particular gene heterozygous in one of the common grandparents will not become homozygous in an offspring of first-cousin mating in 63/64. Ignoring linkage, and lethals common to the two grandparents, the probability that the child of a first-cousin mating will not be homozygous for any of the 20—200 lethals heterozygous in the grandparents is, sufficiently accurate for our purpose, $(63/64)^{20}$ to $(63/64)^{200}$, or 0.73—0.043. Thus, according to the limiting values assumed by Evans, the percentage of death as a result of consanguinity in the offspring of matings of first cousins who have average grandparents would be from 27 to 96 per cent.

There are very few data available on the results of first-cousin matings in human populations, but 96 per cent death as a result of the consanguinity must surely be too high. Even 27 per cent death from this cause seems too large, particularly if consideration is given to the fact that, in Drosophila, the rate of occurrence of mutations with markedly deleterious effects is at least twice that of lethals. Applying this ratio to man would mean that, calculating from the lower limit given by Evans, there would be a total of 61 per cent death or markedly depressed viability.

The effect of consanguinity would, furthermore, be even greater if, as seems probable, the accumulation factor is higher than the estimate of 50, which was, in fact, taken by Evans as a minimum value.

If a significant proportion of the lethals, assumed to be recessive in the above discussion, had a selective disadvantage in the heterozygote which was sufficient to lower the accumulation factor below 50, then the above calculations would no longer hold. In this case, however, the effect of these genes in heterozygous condition would, on the basis of Evans'

values for spontaneous mutation rate and number of loci, depress viability to such an extent that it would be doubtful whether the population could survive.

Thus, irrespective of whether the lethal mutations are completely recessive or have adverse effects in the heteroxygotes, it would seem that the product of the values for spontaneous mutation rate and number of loci, as assumed by Evans, is too large. As there is no reason to reject Evans' range of values for the number of loci, it appears that his figure for the spontaneous mutation rate must be too high. This agrees with the view expressed by Wright, at least as far as indicating that the number of roentgens required to double the natural rate of mutation in man is lower than that calculated by Evans.

In the above treatment, as well as in that of Wright, it has been assumed that the value of 10^{-5} was meant by Evans to apply to the spontaneous rate of mutation to recessive lethals per locus and generation in man. Evans certainly attaches this meaning to it, for in his calculation of the ratio of spontaneous to induced mutations he divides it by the induced rate for recessive lethals per locus per roentgen. In other parts of his paper, however, he mentions it as if it referred to the mutation rate of all recessives. Most authors have taken this to be about 6 times the rate to lethals. If Evans did mean the figure of 10^{-5} to apply to all recessives, then his value for the ratio of spontaneous to induced mutations, or the number of roentgens required to double the natural rate of mutation, should be divided by 6. This would bring it in line with the commonly accepted figure mentioned at the beginning of this section.

There are, then various reasons for thinking that the number of roentgens required to double the natural rate of mutation per generation in man is not as high as the 300 r estimtaed by Evans, and there is at least one argument, that advanced by Wright, for thinking that it may be as low as 3 r.

It would be out of place here to attempt to discuss all the published calculations of the genetic hazards of radiation. The above examples were chosen to illustrate some of the difficulties encountered and the wide range of current estimates. It should be noted that the difficult problem, mentioned earlier in this paper, of evaluating the effect of a given increase in mutation rate was not considered here. The sole objective under discussion was an estimate of the increase in rate following a given exposure to radiation. It has been shown that a wide range of answers to this limited question is possible according to the interpretations placed on the available data which, at the present time are comprised mainly of the induced and spontaneous mutation rates in Drosophila together with the spontaneous rates of a few genes in man. It is apparent that one of the pressing needs

in the estimation of human hazards is for basic information on mutation rates in mammals.

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DISCUSSION

Muller:

I should like to re-emphasize Russell's remarks on translocation effects, produced when mature sperm are radiated. If the sperm used in the fertility studies are obtained after the sterile period, no translocation effects are seen. It is evident that the translocation effects have disappeared because of death of the involved sperm, and it should be re-emphasized that genic mutations almost certainly exist but were not capable of demonstration under the circumstances of the experiments done to date.