Current Status of Information on the Induction of Mutations by Irradiation

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In order to understand the effect of irradiation on man's genes, it is necessary to have information that is not available at present and that, to some extent, may never be collected. However, there are several ways of estimating the magnitude of the inheritable bad effects that are caused by irradiation. Evans (*1*) divided a value that represented the average spontaneous mutation rate per generation at an average locus in man, 10^{-5}, by the estimated rate at which x-rays produce new mutations per roentgen (r) at the average locus, 3×10^{-8}. This gave a value of 300 r as the amount of irradiation that would double the spontaneous mutation rate. On the basis of this figure, Evans suggested that even if a few people were to receive relatively large doses of irradiation, it would not be of much effect in producing defects either in their children or in their remote descendants. Wright (*2*) has pointed out that Evans' estimate of the spontaneous mutation rate is likely to be far too high. By recalculating with the spontaneous mutation rate at one one-hundredth of that used by Evans, Wright found the effect of irradiation to be relatively great when it was compared with the spontaneous mutation rate.

Even if we could make an accurate estimate of the average mutation rate in man, this method would give an answer only *relative* to man's present genetic status. An evaluation of the absolute amount of radiation-induced genetic damage is dependent upon the estimation or knowledge of other facts, such as the manner of action of deleterious genes and the number of loci in man. Evans assumed (when he was discussing certain problems) that there are 10^5 loci, that 2.5×10^{-6} of all genes mutate to deleterious recessives each generation, and that there is an accumulation of 50 times as many mutants as occur each generation. These conditions would result in an average of one new deleterious mutant for every two persons, and the total accumulation of these mutants would be about 25 per person. Since it is known that brother-sister matings occur occasionally and since these appear to give normal children in most cases, an estimate of the number of mutants existing in man must not make this sort of child a too unlikely possibility. However, if there are about 25 deleterious recessive mutants per person, which would mean about 50 per married couple, then one-fourth of these, or about 12, would be present in both a brother and a sister. The chance that one of their offspring would not have any of these deleterious recessives in homozygous condition would be $(\frac{3}{4})^{12}$, or about 0.03. This is a far too small value to fit the facts and indicates that the assumptions made are not completely valid. Larger estimates of the number of deleterious mutants in man, such as the value of 60 suggested by Muller (*3*, p. 351), are obviously too high.

This article attempts to assess the effect of irradiation on man's genes by estimating the limits within which various pertinent values lie. These limiting values are then combined to give maximal and minimal estimates of the effect of irradiation on man. However, these estimates are constrained to reasonable values by reference to relevant observations.

Mutant loci in man. Man cannot be very different from any other mammal in factors such as gene number and the mechanics of gene action. It is known that mammals can be taken from large interbreeding populations and be bred in captivity from the progeny of a single pair, which indicates that individuals of these species are not carrying large numbers of deleterious recessive mutants. By extension from other mammals to man, it would appear that there is confirmation for the assumption that we are not carrying large numbers of deleterious recessives.

Within historical times, except in a small number of communities, man has probably kept matings between closely related persons sufficiently rare and matings with members outside the local in-group sufficiently frequent to warrant assuming at least a moderately large population size. In this case the deleterious mutants observed in man would occur at stable gene frequencies. By working with a small sample of first-cousin marriages, I estimated (*4*) that the average person is carrying only eight abnormal recessive genes. The term *abnormal* includes some genes that do not have an effect on viability and that may be balanced by genes that were not detected because they are lethal early in gestation. The number of deleterious mutants carried in the heterozygous state by the average person will be referred to as A. An estimate of A based on the observation of the children of related individuals approximates a total value, whether the genes are completely recessive or whether they have some effect in the heterozygous state. Since few genes (if any) are known to have an unfavorable effect in the heterozygous condition without being far more debilitating when they are homozygous, the average number of deleterious genes, whether simple recessives or partial dominants, cannot be very large.

Limits. We may choose the limits of 4 and 12 as bounding a reasonable estimate of A in man.

Whether the mutants at a locus cause death even

before birth or whether they do not affect the life-span but cause the individual to be sterile, the selective effect is roughly the same, for the frequency of the gene will be lowered in either case. A mutant that has a less-than-normal likelihood of being transmitted by a homozygous individual may be referred to as a *lethal* (I use this term in a broader sense than is usual). The processes of human society modify the lethality of many genes; for the purposes of this paper we assume that the sum of these modifications is about zero with respect to changes of gene frequency. If a lethal is not always effective, some of its homozygotes will be part of the breeding population. If the homozygotes leave very few offspring and are classed as lethal, or if they leave almost a normal number of offspring and are classed as viable, there will be little effect on our calculations. Mutants that reduce reproductive capacity to an intermediate value will bias calculations based on the assumption that all recessive lethals are fully efficient. The amount and direction of this bias is dependent upon the number of such mutants, their relative lethality, the proportion of them that is detected, and similar considerations. Our knowledge of such mutants is limited; for the purposes of this paper we must assume that they are sufficiently rare to have little influence on the calculations. Our estimate of A should be restricted to those deleterious mutants that have a strongly lethal tendency.

It would appear that some loci are not necessary for the life of an animal, for some viable *Drosophila* are homozygous for losses of genetic material. However, since almost all genetic losses that fail to kill homozygotes are so small that we can suspect them of being limited to a single gene, most genes appear to be necessary for life. If a gene is necessary for life, it will have mutant alleles that are lethal, even though the most frequent mutant form at the locus may be viable. Loci that do not form lethal mutants may affect appearance or physiology but not enough to cause death. *Limits.* It is reasonable to assume that at least 0.75 of all loci can form mutants that are lethal when homozygous.

The total number of loci in man is unknown, even the order of magnitude. It is generally agreed that there is evidence for assuming 5000 to 10,000 as the number of loci in *Drosophila,* and most students of the subject suggest that man's greater complexity requires that he have more genes than the fruit fly has. *Limits.* There is no particular reason to believe that 5000 loci are too few for man. An estimate of 100,000 loci is well above the maximum number usually proposed.

Spontaneous mutation rate in man. A number of recent papers have contained calculations of the mutation rate of various human loci and these have been toward the values of 10^{-4} or 10^{-5} per generation (*5*). However, the highest of these rates is probably in error, because the selection that seems to occur in favor of heterozygotes (*6, 7*) was neglected; and some of these rates may be questioned as being too high on other genetic grounds (*8*). Moreover, since the mutation rate is not calculated unless a condition is relatively common, these rates may be selected because they are particularly high (*2*).

Let us define a value v as the average rate at which mutations to deleterious alleles occur at the N loci capable of having such mutations. The mutation pressure, which is continually forming these alleles from the normal, will be balanced by selection at the frequency $\sqrt{v}$, which is known as the equilibrium frequency. If the population is in equilibrium, $A = N\sqrt{v}$. Unfortunately, if there is a wide variety of mutation rates this formula will not hold, for it assumes that v is the same for all loci. With just a small number of highly mutable loci the true value of v will be much higher than would be calculated from this formula. For example, given 10 recessive lethal loci, if one locus mutates to a recessive allele at a rate of 9.01×10^{-6} and nine each mutate at 0.11×10^{-6}, the average mutation rate will be 1×10^{-6}. The high-mutating locus would have a mutant equilibrium frequency in the population, $\sqrt{v}$, of 3×10^{-3}, and each of the low-mutating loci would have a mutant frequency of 0.33×10^{-3}. The total frequency of mutant alleles in this population would be 6×10^{-3}. If each of 10 loci had the same mutation rate, a total frequency of mutants at 6×10^{-3} would mean that each had a frequency of 6×10^{-4} and a mutation rate of 3.6×10^{-7}. This is only about one-third of that calculated for loci with differing mutation rates. *Limits.* It seems reasonable that if A and N are estimated, the apparent value of v will be between one-half and one-tenth of its true value.

Stern *et al.* (*9*) reported for *Drosophila* that a number of recessive lethals have a slight-to-moderate lethality in the heterozygous state. One may interpret their results as indicating that about one-third of the mutants are lethal to some heterozygotes (Stern *et al.* would replace "one-third" by "most"). The proportion of *Drosophila* mutants that has a deleterious effect on the heterozygotes is probably a bit greater than this, for the chance of finding a mutant that has a lethal effect on one-fourth of all heterozygotes is only three-fourths as great as the chance of finding a mutant that does not affect the viability of heterozygotes.

Muller (*10*) has discussed the possibility that there are many semidominant lethals in man and has referred to the work of Levit (*11*), who suggested that a number of man's ailments are inherited as poorly penetrant dominants. These human semidominants might have little selective effect, because they often act after the peak of the reproductive period. In *Drosophila,* the trial of metamorphosis may be an important factor in the youthful susceptibility of the species to heterozygous lethals, so that lethals may not be as deleterious to the heterozygote in man as they are in *Drosophila.* Statistically, the difference between assuming that genes are recessive in heterozygotes and that they are partially dominant is that the mutation rate must be higher in the latter case to

support a given equilibrium frequency. If the average human being carried as many as eight or 10 deleterious mutants in the heterozygous state, and if a moderately high proportion of these mutants were detectable as incompletely penetrant dominants that act before about the age of 50 years, then much larger numbers of them than are known should have been found by now.

The lethality that is caused by a gene may be denoted by the symbol s, the selective disadvantage. The value of s is 1.0 for lethal recessive genes and is omitted from formulas; for semidominant lethals, s equals the proportion of heterozygotes that are selected against because they carry the gene. *Limits.* It is reasonable to assume that the limits of the proportion of deleterious recessive genes that has some effect in the heterozygote are 0 and 0.30. Such genes cannot average more than 10 percent mortality among the heterozygous carriers by the age of parenthood.

Radiation-induced mutation rate. Although radiation-induced mutation rates have usually been studied only in mature sperm, the rate in oogonia and spermatogonia is the only value of practical importance, because of the short life-span of all other stages. Russell (*12*) tested mice for spermatogonial mutants at seven loci and found an average mutation rate of 2.5×10^{-7}/r. (This type of estimate is not subject to the error discussed in the preceding section and need not be corrected for differences in mutation rates.) Unfortunately, Russell's result does not accurately represent an over-all average, because the numbers of mutants at the various loci indicate that they mutate at widely differing rates. A choice of different loci might have resulted in a far different average rate. Moreover, a criterion for choosing these loci was that Russell already possessed a viable recessive mutant for each, which might have selected against loci with low mutation rates.

Isoalleles are minor differences from the standard form of the gene that can be detected only by special techniques, although some of them might have been found by Russell because of the methods that he has employed (*13*). Even if isoalleles are frequently formed, they are, by definition, of little importance to the vitality of the individual. On the whole, the mutations found by Russell do not include isoalleles but probably indicate the mutation rate toward the physiologically important alleles that would form at any locus. *Limits.* These data of Russell's indicate that the average induced mutation rate per locus is probably between 1×10^{-6} and 2×10^{-8}/r in the mouse, and it is reasonable to assume that this also describes the limits of the range for man.

Estimates of man's genetic make-up. Limits for a number of factors have been suggested in the foregoing sections. The major limiting condition is the observation that the average man is not carrying a large number of recessive and semidominant lethal genes. If the average number of deleterious mutants in man is as few as four, then either the mutation rate must be small or the number of loci must be small. If there are as many as 12 deleterious mutants, the mutation rate and the number of loci might be greater.

For a population in equilibrium, radiation damage will be least effective if the value of A is very high, the loci differ greatly but have a high average spontaneous mutation rate, and the number of loci at which mutants contribute to A is small. Choosing the limiting values at this end of the scale, the number of deleterious recessives (A) carried heterozygously in the average man is 12; there are about 5000 loci, of which only 0.75 can have lethal alleles; about 0.30 of the lethal loci are semidominant, killing 0.10 of the heterozygotes; and the mutation rate differs so greatly from locus to locus that the apparent value of v will be about one-tenth of the true value. With these figures, the number of loci at which lethals can occur is 3750. Of these, 2625 (N_1) will be recessive lethals and 1125 (N_2) will be semidominant lethals ($s = 0.1$). The apparent value of v can be calculated from $A = N_1\sqrt{v} + N_2 v/s$. This formula is solved with $\sqrt{v}$ equal to 0.0045 and v equal to 2.0×10^{-5}. The true rate of v might be about 2×10^{-4}.

This value is greater than was considered likely to be the rate of mutation in man. Small changes in some of the contributing factors might bring down the true value of v to 2×10^{-5}, which is probably still too high but not unreasonable. Reductions in the proportion of loci that are semidominant and in the ratio between the true and the apparent values of v are particularly indicated.

If we assume the lowest reasonable average rate of induced mutation, 2×10^{-8}/r, then 1 r of irradiation will induce only one one-thousandth as many mutations as occur spontaneously. To double the spontaneous mutation rate, gonads would have to be exposed to 1000 r. However, Russell's (*12*) controls clearly showed a low spontaneous mutation rate compared with the many mutations produced by irradiation. Animals irradiated with 600 r showed more than 20 times as many mutations as the controls. Allowing for the small numbers involved, the minimum effectiveness of 600 r is at least 6 times the spontaneous rate, and 100 r is the upper limit of the irradiation dose that doubles the spontaneous mutation rate. Therefore, estimates of the spontaneous and the radiation-induced mutation rates must not differ by a ratio of more than 100 : 1. With only 3750 sensitive loci, the average number of radiation-induced mutations per germ cell for an exposure of 100 r would be about 0.075, or about one in every 13 germ cells, if mutations are induced at an average rate of 2×10^{-7}/r. Thus, even this large dose of irradiation would have little effect on subsequent generations. Alternatively, if the natural irradiation received by the population of the earth were increased to the extent of adding an average of 1 r by the time that parenthood is achieved, new deleterious mutants would occur only once in every 1333 gametes. In either of these cases the damage to subsequent generations must be quite low and will not be important when it is compared

with the spontaneously occurring mutations in the population as a whole.

The data of Hertwig, as compiled by Russell (*12*), suggest that the sum of all lethal mutations at all loci in mice is as low as 6×10^{-6}/r for each gamete, or some value up to about 10 times this frequency. Even at 6×10^{-5} mutations/r there would be only one lethal in every 16,000 gametes after 1 r of irradiation, which is a lower rate than the lowest estimated here. It is possible that the discrepancy between Hertwig's data and the values calculated in this paper is the result of the small number of observations made by Hertwig.

The estimate of the maximum effectiveness of radiation damage is also affected by certain limiting factors. Natural radiation yields at least 3 r within 30 years (*1*), and it may yield 17.5 r during this period of time (*3*, p. 475). Taking the lesser of these rates, the maximum radiation-induced mutation rate per roentgen cannot be more than one-third of the spontaneous mutation rate (if other factors contribute to spontaneous mutation, it would be lower). If the radiation-induced rate is as high as 1×10^{-6}, the true spontaneous rate would be at least 3×10^{-6}. The apparent spontaneous rate might be as high as half of this, or 1.5×10^{-6}, and $\sqrt{v}$ would be 1.2×10^{-3}. N_1 would be about 3300 if A is equal to 4, and N_2 would constitute 0.30 of all deleterious mutants if 1600 semidominants exist. These 4900 sensitive loci would yield an average of 0.0049 mutations/r for each gamete, or about one mutant in every 200 gametes. A proportional decrease in the radiation-induced and spontaneous mutation rates would permit increased estimates of N but would result in even smaller proportions of the gametes carrying new mutations. However, an increase of A to a value as high as 12 would increase the size of N to 15,000, and after 1 r of irradiation the frequency of gametes carrying newly induced mutants would be about one in 70. There would be an increase in the amount of damage caused by irradiation, but no change would occur in the relative effectiveness of spontaneous and induced mutation. An irradiation dose of about 400 r (independently of the value of A) would be enough to increase the number of deleterious genes in each of the offspring of the irradiated person by 50 percent, and the number of deleterious genes carried in each gamete would be doubled. The assumption that almost one-third of all mutations have a semidominant lethality would mean that some of the immediate descendants of a heavily irradiated person would have a distinct likelihood of being impaired or killed because of the irradiation.

Conclusions. The present genetic status of man is that he probably is carrying a few deleterious mutants and that mutation is transforming more normal genes to abnormal ones at about the same rate that selection is causing abnormals to be lost. Many mutations are lethal and, if man-made irradiation increases the mutation rate, the result is sure to be deleterious. However, the radiation-induced mutation rate per roentgen seems to be bounded at between one-third and one one-hundredth of the spontaneous rate, and the spontaneous rate does not appear to be as high as some authors have recently suggested.

In terms of the absolute amount of damage done, as little as 1 r of irradiation may produce between one mutation in 1300 gametes and one mutation in 70 gametes. This is not a very wide range, considering how little we know about so many of the factors concerned. The narrowness of the range is the result of the action of two limiting features. The fact that the spontaneous mutation rate is known to be low despite the presence of a certain amount of irradiation in the atmosphere provides a maximum limit to the effectiveness of irradiation in producing mutations. The comparison of the progeny of control and irradiated animals provides the lower limit for the relative effectiveness of irradiation. The range thus being set, the points on the scale at which this range might be placed are limited by our knowledge that the average man is carrying some, but not many, deleterious recessive genes. Within these limits it is difficult to suggest that one part of the scale is better than another. The lower limits of the effectiveness of irradiation seem most likely because attempts to find radiation-induced mutants, and particularly the experiments of Hertwig, who tested for any sort of mutant within the entire genome, have been hearteningly meager in their successes.

Some of the values that have been imprecisely estimated here can be refined in the near future. Of particular importance is an extensive study of both the fertility and viability of the descendants of irradiated mammals. This will help us to determine whether or not many genes will be produced that decrease viability without being detectable as lethals. Studies of the children of related individuals will make up the other main source of information, because this will be one of our most fruitful ways to determine the actual value for man's current genetic structure. The comparison of spontaneous mutation in man with that in other mammals will also be of value.

What would happen to man if the mutation rate were permanently doubled by an accidental poisoning of the atmosphere by irradiation? It would be several generations before the accumulation of new mutations would amount to very much. The average number of deleterious mutations would increase, and the frequency with which persons bearing the same mutants would marry and have defective offspring would increase too. For completely recessive genes, the doubling of the mutation rate means that the frequency of the gene and of abnormal homozygotes in the population is increased as the square root of the mutation rate. A gene that had had a frequency of 0.00010 would eventually build up to a frequency of 0.00014. With such small changes, it would seem unlikely that a doubling of the mutation rate could pose a serious problem to the life of the species, and it might go almost unnoticed. Some of our current dysgenic practices that are countenanced because of custom, inertia, humanitarian practices, or foolishness are probably more serious to the species.

Lest anyone misinterpret these deliberations as

justification for rashness, some special warning should be given. The basic fact to remember at all times is that any irradiation is bad, and therefore irradiation should be used only if it can be assumed that the good will outweigh the bad. Certainly our descendants should be protected by our avoiding the irradiation of the gonads of any person until he is past the procreative age. Also, the society as a whole should be protected against a general increase in background irradiation. The existence of worse practices cannot be an excuse for perpetrating a bad one.

References and Notes

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News and Notes

Science News

The United Nations Educational, Scientific and Cultural Organization is sponsoring the establishment of an **International Computation Center** in Rome. The convention setting up the center will come into force when 10 states have ratified or formally accepted it. So far four countries—Belgium, Ceylon, Italy, and Japan—have deposited ratifications or instruments of unconditional acceptance. The convention has been signed by eight states: Egypt, Greece, Iraq, Israel, Liberia, Mexico, the Netherlands, and Turkey.

The projected center, a laboratory equipped with the best available mechanical devices for calculation, will have three main functions: scientific research, training of experts through a system of fellowships, and the provision of services to organizations and persons who, under certain conditions, will be authorized to request calculations required to solve unusually complex scientific, technical, administrative, or financial problems.

In cooperation with the Royal Australian Air Force, the U.S. Air Force is to operate an inland **meteorological research station** near Alice Springs, Australia. This station will supply information to scientists at the Woomera rocket range in South Australia, and at the new weapons-testing site at Maralinga, Australia, 50 mi north of the transcontinental railway, midway between Kingoonya and Leakin. Atomic clouds that form above the Maralinga range are expected to drift in the direction of the new station in central Australia.

Two species of imported parasitic flies may aid in **sugarcane borer control,** the U.S. Department of Agriculture reports. After 2 years of tests, research entomologists at the USDA Sugarcane Field Station, Houma, La., describe the parasites as "promising" for gaining partial control of the destructive sugarcane insect, and some Louisiana cane growers have imported and released the flies in their fields.

One of the flies—*Metagonistylum minense*—came originally from the Amazon; the other—*Lixophaga diatraeae*—from Cuba. Both attack the borer in the same way. They deposit their eggs near the entrances of holes made by the borers in the sugarcane stalks. The eggs hatch almost immediately into maggots that move into the holes and destroy the borers.

In cooperative research with the Louisiana Agricultural Experiment Station, USDA's Agricultural Research Service has successfully imported these flies from Trinidad and established them on at least four Louisiana sugarcane plantations. A year after their release on one plantation, the parasitic flies achieved 75 percent borer control. New generations of the flies had migrated as far as 2 mi from the original release point.

Investigators speak in terms of "partial" control, because they anticipate that, as with other parasitic insects, populations of these flies will tend to ebb and flow as they are influenced by host abundance and prevailing weather. However, even some help would be welcome to growers, who must pay about $9 an acre annually to have their cane dusted with insecticides for borer control. Dusting is justified if 7 shoots of cane in 100 ft of row are infested. If parasites could reduce the infestation to below 6 infested shoots per 100 ft of row, at least one and perhaps two of the seasonal dustings could be eliminated.

General Motors Research Laboratories Division and the Medical College of South Carolina have announced development of the **electrostethograph,** a device that makes it possible to study heart sounds that are inaudible through a stethoscope. The new machine utilizes both an oscilloscope and a direct-writing mechanism. The patient lies on a foam rubber mattress that absorbs any interference vibrations, and the recording is made through a small flat disc that is placed on the chest.

Yale University has announced the acquisition of the ***Codex Paneth,*** a 1378-page volume that is believed to have been the entire medical library of the University of Prague when it was founded in 1347. The work comprises 42 separate texts that represent