Quantitative Inferences concerning the Genetic Effects of Radiation on Human Beings

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IN 1927 H. J. MULLER showed that the natural rate of appearance of new mutations in the fruit fly could be increased by irradiation with X-rays (*22*). Similarly, mutations have been produced in many other organisms, including plants such as corn, barley, and beans, by acute and by chronic irradiation. These observations have stimulated much speculation with regard to their applicability to mammalian forms and especially to man.

Lorenz and Heston (*20*) found that mice bred from five to six generations while continuously exposed, 24 hours a day, to 1.1 r and 0.11 r of radium gamma radiation[1] showed no damage to chromosomes, as evidenced by normal litter size and apparently normal life span. Deringer *et al.* (*7*) exposed mice chronically 8 or 24 hours a day to 8.8 r or 4.4 r. Total accumulated doses were for females 770 r and 880 r, and for males 1,100 r. No evidence for the production of visible genetic changes was obtained in the immediate offspring of mice thus irradiated. No evidence was found for the production of chromosome translocations in tests of the offspring of male mice exposed to a total dose of 1,100 r at the rate of 8.8 r given for 8 hours a day, nor in the offspring of female mice which received a total dose of 770 r at the rate of 8.8 r given 24 hours a day.

Hertwig (*14, 15*) demonstrated the production of four recessive gene mutations. Of these, two were produced in the offspring of male mice mated immediately after irradiation (irradiation of mature sperm), and resulted in retarded growth. The second two were produced in offspring of male mice mated after recovery from a period of temporary sterility following irradiation (irradiation of spermatogonia, or sperm-forming cells). They produced anemia and oligodactylism.

The acute dose in Hertwig's cases was 1,500 r of X-rays to the testes (*10*), the rest of the body being shielded to prevent death from whole body irradiation. The mutations were discovered by breeding the sons of the irradiated males to their own daughters. If the entire body had been irradiated at the dosage rate used locally in this experiment it would have received more than twice a lethal dose. Snell (*26*) found that about one-third of the progeny of mice whose testes were exposed to acute doses of about 600 r produced litters of reduced size. This condition of hereditary "semisterility" is believed to be caused by chromosome breakage and translocation (a class of *chromosomal* mutations [*10*]), not by *gene* mutation.

The importance of genetic changes in human beings justifies an attempt to extrapolate to man (*5, 8*) the abundant genetic data on the fruit fly, *Drosophila melanogaster,* and on plants. Catcheside especially has made commendable contributions toward quantitative estimations of the possible genetic effects on human beings of irradiation.

In *Drosophila melanogaster* which has only four pairs of chromosomes, genetic studies have led to the conclusion that the number of individual genes in each long chromosome is of the order of 1,000. We may take the set of chromosomes to include some 3,000 positions for genes. In man the total number of genes per gamete is unknown, but since there are 24 chromosomes, with a total length perhaps 10 to 12 times that of the four chromosomes of *Drosophila melanogaster,* the total number of genes in man is very likely greater than 5,000, and probably lies between 10^4 and 10^5. Recent estimates suggest a value of $(3 \pm 1) \times 10^4$ genes per gamete in man (*28*).

Spontaneous Gene Mutations

In all organisms so far studied, there is a spontaneous gene mutation rate which has an average value such that the probability of mutation is of the order of 10^{-5} to 10^{-6} per gene per generation and appears to be independent of the average life span. Also in man the observed spontaneous mutation rate is about 10^{-5} per generation for hemophilia (*13*) and for epiloia (*11*).[2] Thus in long-lived organisms the gene

[1] One roentgen (r) of X radiation or of gamma radiation produces ionization in tissues to an average extent of about 1.6 ion-pairs per cubic micron, or 1.6×10^{12} ion-pairs per gram of tissue.

[2] These two diseases happen to be well suited to the calculation of mutation rates, and no reason is known for suspecting that the rates found should be any higher or lower than for genes whose mutation rates are now unknown. It is, of course, possible that these measured mutation rates in man are automatically selected samples of genes which are relatively more mutable than the average of all genes in man. The decision must obviously await the accumulation of quantitative data on other mutations in man. It is interesting to note that a value of about 10^{-3} per gene per generation was found (*23*) in the Italian population of Rochester, New York, for the mutation causing thalassemia, a disease which appears to be found predominantly in persons of Mediterranean derivation.

material appears to be somewhat more stable, per unit of time. The range of numerical values is easily explained on quantum mechanical grounds (*25*). Apparently, the chemical activation energy, for an isomeric change in the configuration of the molecule or molecules comprising the gene, is slightly greater for the genes of long-lived animals. Small differences in this activation energy (which is of the order of 1 to 2 electron volts) can account for differences of several millionfold in the mean life of a gene configuration. Thus the observation that the average spontaneous mutation rate is of the order of 10^{-5} per gene per generation, regardless of life span, is experimentally and theoretically acceptable.

If there are N genes per gamete, and if the average probability of a spontaneous recessive mutation is $a = 10^{-5}$ per gene per generation, then aN is the mean number of new recessive mutations per gamete per generation. It has been estimated (*5*) that seriously deleterious and lethal mutations constitute perhaps one-quarter or less of the spontaneous mutations, and that minor recessive mutations predominate. In the long run, the extremely unfavorable mutations leading to hereditary abnormalities are almost wiped out by natural selection. The recessive mutations become distributed in the population of succeeding generations, and appear in an individual only if both parents carry the same recessive mutation.

The generation time for man is about 25 years, or 40 generations in 1,000 years. Thus there has been a long accumulation of recessive mutations, and each individual carries far more mutated genes than have arisen through mutation in his own generation. Because of relatively recent social changes such as the industrial revolution, the human population is not in genetic equilibrium (*12*). The persistence (*12, 16*) of any particular recessive mutation in the population will depend on the degree of inbreeding in the population, loss of particularly unfit mutants by natural selection, loss by reverse mutations or second mutations of the same gene, and interbreeding of semi-isolated population groups. Because genetic equilibrium between mutation and selection cannot be assumed for the slightly deleterious mutants, it seems reasonable to assume, somewhat arbitrarily, that at least $m = 50$ times as many recessive mutations have been accumulated in the population as are produced by spontaneous mutation in each generation. Then if aN is the spontaneous mutation rate per generation, and m is the accumulation factor, the average number of recessive mutant genes per germ cell of each member of the population may be written as $n = m \cdot aN$. Assuming, tentatively, that $m = 50$, we have $n = 50 \cdot aN$.

If a particular sperm cell contains n_1 recessive mutations distributed randomly among N genes, then the chance that a particular designated gene carries a recessive modification is n_1/N. Similarly if an ovum carries n_2 recessives, the chance that the same designated gene carries a recessive mutation is n_2/N. The chance of coincidence, in the union of these two gametes, is then $(n_1/N)(n_2/N)$ for the particular designated gene. Because there are N genes altogether in each gamete, the chance of observing a coincidence of any two recessives in any of these N genes is then $(n_1/N)(n_2/N)N = n_1n_2/N$. Then the statistical chance of the occurrence of a hereditary abnormality or anomaly due to the coincidence of two recessive mutations is $C_0 = n_1n_2/N$. If we assume $n_1 = n_2 = maN = (50 \times 10^{-5})N$, and that N is as large as 10^5, then $C_0 = (2.5 \times 10^{-7})N = 0.025$ is the estimated fraction of all births[3] in which some sort of recessive modification may be expected to appear visibly in the progeny.

Radiation-induced Gene Mutations

The mutations that can be induced by X-rays, gamma-rays, or ultraviolet light in a variety of organisms are not novel types of changes, but are similar to the mutations that occur spontaneously. The number of mutations produced is simply increased by the irradiation. Radiation-induced recessive mutations can be identical with spontaneous mutations in an unirradiated individual. A gene mutation that has occurred spontaneously or that has been produced by radiation (e.g., $a \rightarrow a'$), can return to the original, or "wild type" ($a' \rightarrow a$), spontaneously or as a result of irradiation of the progeny, although the statistical chance of this happening is low.

Although most of the spontaneous and the radiation-induced mutations are undesirable, a few are advantageous. For example, the present high commercial yields of penicillin are due in part to the exclusive use of high yield strains of *Penicillium,* selected from a large number of radiation-induced mutants of the naturally occurring parent mold (*1–3, 6, 17, 24*). Of course, this high yield is beneficial to *us,* but it has not been proved rigorously that it is beneficial to the *Penicillium.*

In *Drosophila melanogaster,* gene mutations in the X-chromosome of mature sperm have (*5*) an average induction rate of about $b_X = 3 \times 10^{-8}$ per gene per roentgen. The mutation induction rate at a particular gene locus varies by as much as a factor of 5 in either direction from this average value. Most of the

[3] It has been estimated that 22 percent of all human conceptions terminate in nonviable offspring (*28*). This includes all causes of death of the foetus, of which an undetermined but presumably small fraction are genetic causes.

measurements have been accomplished by the use of genetic techniques especially applicable to the observation of sex-linked lethals, but enough has been done on sex-linked visible recessives to suggest that the results are similar. Presumably about the same average numerical value will also apply to gene mutations in the other chromosomes, although present genetic techniques have led to numerical results only for genes located along the X-chromosome in irradiated sperm.

There are measurable differences in the mutation induction rate in sperm of *Drosophila melanogaster* which have been irradiated at various stages in the process of spermatogenesis. When immature sperm are irradiated at the early spermatogonial stage, the number of visible sex-linked mutations eventually produced is only about one-half as great as is found following the same irradiation dose given to mature sperm. The effective ratio of the radiation sensitivity of immature to mature sperm is even smaller (ratio of about 1:5) for sex-linked lethal mutations. These effects probably arise because many of the altered spermatogonia, or immature sperm, fail to survive through the process of spermatogenesis and hence never become available as mature sperm (*10*).

At radiation rates of 0.6 r/hr and greater, the number of sex-linked mutations induced in mature sperm of *Drosophila melanogaster* appears to be independent of dose rate (*19*), or quantum energy, and to be linear (*27*) with total irradiation dosage from 25 r to at least 1,000 r. The assumption is usually made that this constant mutation induction rate per roentgen will hold even at very low dosage rates. Recently, however, experiments have been completed (*4*) at the very low dosage rate of 2.5 r/day. Mature sperm of the Canton Special strain of *Drosophila melanogaster,* stored in the spermathecae of females of the Muller-5 strain, were irradiated with radium gamma-rays at a rate of 2.5 r/day for 21 days, at the end of which time the sperm had accumulated a total dose of 52.5 r. The progeny resulting from subsequent fertilization by these aged and irradiated sperm showed an unexpectedly small number of mutations, and indeed was not significantly different statistically from that of unirradiated controls. The number of sperm tested was such that the probability is less than one percent that the result is merely a chance deviation from the rule of proportionality between total dosage and the number of induced mutations. The possibility therefore exists that the genetic effects per roentgen may be less at very low dosage rates than the effects previously observed at higher dosage rates, where repair or recovery of the gene material has not been observed. Further experiments at low dosage rates are needed to answer this question, since it has an important bearing on the "point-hit theory" of radiation effects and on the extrapolation of data to the case of men who are occupationally exposed to radiation at very low dosage rates.

In more recent studies (*27*) of the Canton Special strain of *Drosophila melanogaster* it required a dose of about 50 r to mature sperm in order to double the number of new sex-linked visible and lethal mutations. In these observations the spontaneous mutation rate for sex-linked lethals is 0.0010, while the induced rate is 0.00002 per r. Writing N_X for the number of gene loci on the X-chromosome, we have $a_X N_X / b_X N_X = 0.0010/0.00002 = 50$ r to double the spontaneous mutation rate. If N_X is about 1,000, the spontaneous mutation rate would be about $a_X = 10^{-6}$ per gene per generation, and the induced mutation rate would be about $b_X = 2 \times 10^{-8}$ per gene per roentgen, for this strain under the particular cultural conditions of this experiment.

Quantitative observations of the rate of induction of mutations by radiation have been made in a variety of organisms, including *Drosophila,* tobacco mosaic virus, and bacteria. The results are remarkably similar. Because such widely different organisms as *Drosophila,* virus, and bacteria exhibit substantially the same rate of induced mutation per roentgen, it is usually assumed that about the same average numerical value, $b = 3 \times 10^{-8}$ per gene per roentgen, may also hold for induced mutations in mature germ cells in man.

In man, mature sperm have a fertile life span of about seven weeks (*10*) but the relative sensitivity of sperm and eggs at various developmental stages is unknown. We may represent the time average of the relative radiation sensitivity of immature sperm and eggs in man by k, as compared with the relative sensitivity $k = 1$ for mature gametes. For low level radiation continued over a time which is long compared with seven weeks, k may be significantly less than unity for the male, but substantially unity for the female. If these factors could be evaluated numerically for man, then in the equations and computations which are to follow one would replace the radiation sensitivity, b per gene per roentgen, by the smaller quantities $k_1 b$ for males and $k_2 b$ for females. Because of the large uncertainty in the currently available numerical estimates of k, we would hardly be justified in carrying this refinement into the calculations. So in what follows we shall use the maximum values $k_1 = k_2 = 1$, thereby assuming that immature sperm and eggs have as great a radiation sensitivity as mature gametes. We will therefore overestimate the genetic effects of chronic irradiation, insofar as this particular factor is concerned.

Ratio of Induced to Spontaneous Mutations

It is interesting to note that cosmic radiation and local gamma radiation, totaling about 0.3 mr per day, are entirely inadequate to account for the natural spontaneous gene mutation rate. Even in a long-lived organism such as man, the dosage from natural sources of radiation amounts to only about 0.1 r per year, less than 3 r between birth and the average childbearing age. Such a small amount of radiation would give only about $3b = 9 \times 10^{-8}$ mutations per gene per generation, whereas the few observed spontaneous human rates of $a = 10^{-5}$ per gene per generation are more than 100 times as large.

We see that a total dosage of the order of $aN/kbN = 10^{-5}/3 \times 10^{-8} = 300$ r per generation is required to bring the induced rate up to equality with the natural rate of mutation per generation. Thus an average dosage of about 300 r per individual per generation would be required to double the natural rate of appearance of new gene mutations per generation. If we chose a lower numerical value for the spontaneous mutation rate, say $a = 3 \times 10^{-6}$, the rate-doubling dose a/b would become about 100 r, provided $k = 1$.

A radiation worker whose whole-body dosage, and hence gonadal dosage, is limited to 0.1 r per working day, as is now the practice in the United States, could at most receive 0.5 r in a five-day week, or 25 r a year, or 250 r in a 10-year working period before childbearing. Actually, the daily average radiation dose per worker will fall far below this maximum because on many days an individual's dose will be much less than the maximum permitted value of 0.1 r. For example, the average daily dose at installations like the Hanford Engineer Works and the Oak Ridge National Laboratory is about 0.005 r. Only rarely does any individual receive the maximum 0.1 r dose. Thus the average 10-year dose, at 0.005 r per day, is only about 20 r for these groups.

In the notation introduced earlier, we may write that the number n_1 of recessive mutants transmitted in an individual's germ cells will be the sum of the accumulated naturally occurring mutants, maN, plus the induced mutants, $kbDN$, where D is the dose in roentgens which this individual receives before he has children. Thus:

$$n_1 = maN + kbDN$$

Writing $n_0 = maN$ for the naturally occurring mutants, and f_1 for the ratio of the new total n_1 to the unirradiated total n_0, we have:

$$f_1 = n_1/n_0 = (maN + kbDN)/maN = 1 + \frac{kbD}{ma}$$

If the numerical values developed earlier turn out to be approximately correct for man, then with $b = 3 \times 10^{-8}$ per gene per r, $a = 10^{-5}$ per gene per generation, an accumulation factor of $m = 50$, and the relative radiation sensitivity of immature to mature gametes $k = 1$, we have:

$$f_1 = 1 + (6 \times 10^{-5})D$$

Thus a radiation worker who received $D = 250$ r before having children will have $f_1 = 1 + 0.015$, and $n_1 = 1.015n_0$, or 1.5 percent more mutants than if unirradiated. If he then has children by an unrelated and unirradiated spouse ($n_2 = n_0$), the statistical chance of an inherited anomaly due to recessive gene mutations is: $C = n_1n_2/N = (1.015n_0)n_0/N = 1.015C_0$, or only 1.5 percent greater than the normal chance C_0.

The occurrence of inherited anomalies in the first generation offspring due to *dominant* mutations induced in one parent by radiation is more difficult to estimate numerically because of the lack of numerical data, but may be the more important hazard. Here the accumulation factor, m', will be smaller and will depend more strongly on the degree of unfitness conferred by the particular mutant. The degree of dominance (or "penetrance") of the mutant will affect its visibility as well as its accumulation. For the sake of estimating an order of magnitude, we might make some rough assumptions. If the ratio of induced to spontaneous dominant mutations, (b'/a') is the same as (b/a) for recessive mutations, and if the penetrance is taken at its maximum value of unity, and the fitness taken such that the accumulation is about $m' = 3$, then the ratio, f' of induced to spontaneous dominant mutant genes per gamete would be very approximately:

$$f' = (m'a'N + kb'DN)/m'a'N$$
$$= 1 + kb'D/m'a' \approx 1 + k(b/a)D/m'$$
$$1 + 1 \times (3 \times 10^{-8}/10^{-5})D/3 \approx 1 + 10^{-3}D,$$

or about 1.25 for $D = 250$ r. That is, if the penetrance is unity, then the statistical chance of the appearance of a dominant anomaly in the first generation offspring would be increased by about 25 percent over the chance of the same anomaly's occurring spontaneously. It is interesting to note that the medical literature already contains reports of over 2,250 cases of women whose ovaries were treated with X-rays (mostly 50 to 100 r, for various gynecological conditions) and that no anomalies definitely attributable to radiation have been observed in their subsequent offspring (*9, 10, 18, 21*). The offspring would show dominants, if present, and male offspring would show sex-linked recessives, if present. However, other recessives would not be visible in the first generation offspring.

The natural rate of congenital anomalies C_0 is small, and is already influenced by such factors as

nutrition, consanguineous marriages, and socio-economic shifts. Therefore, many eugenists and geneticists feel that no significant eugenic harm would be done by the additional factor of radiation, provided that radiation doses to the general population were confined to values that would not more than double C_0 within the foreseeable future. Whereas we see that the effects in the first generation progeny are small, we must also consider the accumulated effects of recessive mutations over, say, 2,000 years. Because the induced mutations are similar to the natural mutations, and because genetic equilibrium cannot be assumed, we should use the same accumulation factor, m, for the ratio of the accumulated induced mutations present after many generations to the new induced mutations per generation. Dealing now with population averages, and assuming equal average irradiation for both sexes, we have after many generations:

$$\begin{aligned} n_1 = n_2 &= maN + mkbD_1N \\ &= n_0(1 + kbD_1/a) \end{aligned}$$

where D_1 is the average, over all individuals of both sexes, of the number of roentgens to the gonads per generation up to the end of the childbearing period. If we require that the congenital anomalies be no more than doubled, then

$$2 = \frac{C}{C_0} = \frac{\frac{n_1 n_2}{N}}{\frac{n_0 n_0}{N}} = \left(1 + \frac{kbD_1}{a}\right)^2$$

hence: $$1 + kbD_1/a = \sqrt{2}.$$

It is to be noted that this general result, for the condition after many generations, is independent of the accumulation factor m, and that the genetically permissible average dose D_1 depends only on the average spontaneous mutation rate a, and the average induced mutation rate b. Again assuming $a = 10^{-5}$ per gene per generation, $k = 1$, and $b = 3 \times 10^{-8}$ per gene per roentgen, we find:

$$\begin{aligned} D_1 &= (\sqrt{2} - 1)(a/kb) \\ &= 0.414 \times 10^{-5}/3 \times 10^{-8} \\ &= 140 \text{ roentgens.} \end{aligned}$$

Since the dose D_1 deals with population averages (both men and women) and is the mean dose per head, $D_1 = 140$ r could be realized by 100 percent of the population receiving 140 r, or 50 percent receiving 280 r, or 10 percent receiving 1400 r, etc. If, for example, as many as five percent of the total population received an average dose of 280 r before childbearing, then the average dose to the entire population would be $0.05 \times 280 = 14$ r, and the eventual fractional increase (after, say, 2,000 years) in congenital anomalies due to radiation could be expected to be about:

$$\begin{aligned} C/C_0 &= (1 + 3 \times 10^{-8} \times 14/10^{-5})^2 \\ &= (1 + 0.041)^2 \\ &= 1.08 \end{aligned}$$

or only eight percent greater than the spontaneous rate in a similar unirradiated population. If we assume a smaller value for the spontaneous mutation rate, say, $a = 3 \times 10^{-6}$, then for $C/C_0 = 2$, the average dose per head per generation becomes $D_1 = 42$ r, while an average dose of $D_1 = 14$ r would give only $C/C_0 = (1 + 0.14)^2 = 1.30$, or 30 percent greater than the spontaneous rate in a similar unirradiated population.

Conventional equilibrium theory. In a statistically large population, it is well known (e.g., Hogben, *16*, p. 195) that if s is the fractional reduction of net fertility in individuals who are homozygous with respect to a particular recessive mutant, then when genetic equilibrium between selection pressure and mutation pressure is reached, the gene frequency of this recessive will be $\sqrt{a/s}$. Thus in our notation, $ma = \sqrt{a/s}$, or $m = \sqrt{1/as}$ for spontaneous mutations, while $ma + mbkD = \sqrt{a + bkD)/s}$ for the sum of the spontaneous and the induced mutations. However, if the selection coefficient, s, is small, as is probable for many of the minor recessive mutations, then constant conditions over a period of many thousand generations are required before genetic equilibrium with respect to such genes is closely approached (e.g., Hogben, *16*, p. 143). Even so, this standard treatment in the existing mathematical theory of genetics neglects reverse mutations or second mutations of the same gene, inbreeding, statistical fluctuations in partially isolated population groups of finite size (*29*), and population shifts which result in interbreeding between population groups.

It may be worth while to note what could be deduced for human populations, if it were permissible to assume genetic equilibrium. The effective accumulation factor $m = 1/\sqrt{as}$ for minor recessive mutations might then be of the order of magnitude of 1,000 or more after many thousand generations of constant conditions. This would reduce our estimate of the first generation effects by a factor of $1{,}000/50 = 20$ or more, and suggests that our estimate of $m = 50$ for the nonequilibrium case may even be unduly conservative. After thousands of generations of exposure to D_1r per generation, the new equilibrium mutant gene frequency per gene locus would be $\sqrt{(a + kbD_1/s}$, and the ratio C/C_0 of birth anomalies in irradiated and unirradiated populations would become $(a + kbD_1)/a = (1 + kbD_1/a)$, instead of the square of this quantity, as derived for the nonequilibrium case. Thus again, the numerical estimates made on the nonequilibrium,

or square-law model, appear to lie well on the conservative side.

Many simplifications of known genetic facts have had to be made in arriving at these numerical values but the analytical form and the general order of magnitude of the results should not have been altered thereby. Certainly the gradual accretion of knowledge in cytogenetics will permit future refinements in such calculations. Although one cannot be dogmatic where extrapolations of data are involved, it does seem highly improbable that any detectable increase in hereditary abnormalities will result, even after many generations, from daily radiation doses up to 0.1 r per day given to a small fraction of the population.

To review the genetic concepts and experiments most pertinent to the question of mutations induced by radiation: For a variety of organisms, the probability of a spontaneous gene mutation is of the order of 10^{-5} to 10^{-6} per gene per generation, and is substantially independent of the life span. Experiments on several types of organisms have shown that irradiation can produce gene mutations. These induced mutations are not novel types, but appear to be entirely similar to those which occur spontaneously. When the irradiation is carried out at a rate of 0.6 roentgens per hour, or higher, the average probability of inducing a gene mutation is about 3×10^{-8} per gene per roentgen. The spontaneous mutation rate is therefore very much higher than could be expected as a result of the cosmic radiation and local gamma radiation (0.3 mr/day) and is therefore due to other causes than irradiation. When the irradiation of experimental organisms is carried out at a low rate (order of 1 to 8 roentgens per day) no induced mutations have yet been observed in the organisms studied (fruit fly, mouse). This suggests that the effective average radiation sensitivity of immature sperm and eggs may be less than the sensitivity of mature sperm and eggs. Dominant mutations may become visible in the first generation offspring. Recessive mutations may appear only in homozygous individuals of a later generation, and therefore recessive mutations accumulate in the population as a result of both spontaneous and induced mutations. From the appropriate mathematical theory, and the experimental data now available, it seems safe enough to conclude that no detectable increase in hereditary abnormalities is likely to result, even after many generations, if a small fraction of the population receives daily radiation doses up to 0.1 roentgen per day.

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