INDUCTION OF MUTATIONS IN MAMMALS BY IONIZING RADIATION

by

Leo Szilard

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Our purpose here is to describe a project aimed at determining the magnitude of the mutagenic effect of ionizing radiation in mammals, such as mice. For the purposes of this project, we must distinguish between mutations which have been inherited by a given generation of a population, and mutations which have been acquired by that generation. The acquired mutations may have spontaneously arisen in the animal during its embryonic development or after birth, and they may have been induced by exposing the animal to ionizing radiation, either during its embryonic development or after birth.

The proposed project is limited to the study of recessive lethal mutations which are carried by an X chromosome, i.e., it is limited to the so-called sex linked recessive lethals.

Both the acquired and the inherited sex linked recessive lethals should manifest themselves in a reduction of the proportion of males in the brood, at birth. This effect may be expected, however, to be very small. Thus, for example, if

½% of the X chromosomes in the ova carry an inherited or acquired sex linked recessive lethal, then the proportion of the males in their brood would thereby be reduced only by $\frac{1.7}{1000}$. Rather than to rely on this effect, we shall adopt a method of study which appears to be more promising. Our method can provide us with reliable information concerning the abundance of the sex linked recessive lethals that have been inherited by the female population. This may be seen as follows:

Let us consider a population of 10,000 female mice and assume, for the sake of argument, that a small proportion of these females, say 1%, have inherited a sex linked recessive lethal. In a sample of 10,000 female mice there would, then, be about 100 females who have inherited a sex linked recessive lethal.

A female mouse which has inherited a sex linked recessive lethal will, on the average, have 33 males in a brood of 100. Accordingly, we should expect to find in our sample of 10,000 females, about 50 females who have 33, or less than 33, males in a brood of 100.

The rest of the female mice which have not inherited a sex linked recessive lethal will, on the average, have 50 males in a brood of 100. In our sample of 10,000 females, there will be about 9,900 females who have not inherited a sex linked recessive lethal and, on the basis of simple statistical

considerations, we should expect to find among them about 7 females who have 33, or less than 33, males in a brood of 100.

If we have a sufficiently large sample of female mice available, we may determine what proportion of these mice have inherited a sex linked recessive lethal, by proceeding as follows:

We breed each female mouse until its brood totals 100. The sex of each new born mouse is determined and, with the exceptions stated below, that mouse is then killed.

In each case when we find that a female has a low proportion of males in its brood, we may suspect that an inherited sex linked recessive lethal is responsible. In order to determine whether this is, in fact, the case, we preserve 5 or 6 females out of the last litter and each of these we breed until it has a brood of 100. If any one of these 5 or 6 females has a low proportion of males in its brood, then this would confirm that an inherited sex linked recessive lethal was, in fact, responsible.

Mutation Rate and the Inherited Load of Mutations

We may study the spontaneous mutations which result in sex linked recessive lethals by applying to a natural mouse population our method of counting the number of females who have inherited a sex linked recessive lethal. A sample of 10,000 females should be sufficient for this purpose.

By counting the females who have inherited a sex linked recessive lethal we determine the inherited load of sex linked recessive lethal mutations. There exists a simple relationship between this load and the rate per generation at which an X chromosome acquires a recessive lethal through spontaneous mutation.

Let us designate with μ_m the probability that such a mutation should occur in one generation during the passage of an X chromosome through the male, and designate with μ_f the probability that it should occur in one generation during the passage of an X chromosome through the female. Since a male who had inherited an X chromosome carrying a recessive lethal would not be viable, the probability that an X chromosome in the sperm of the adult male of average age carries a recessive lethal is given by μ_m. If ε designates the probability that a female, born to adult parents of average age, inherits a sex linked recessive lethal, then the probability that an ovum of an adult female of average age contains an X chromosome which carries a recessive lethal is given by $\frac{\varepsilon + 2\mu_f}{2}$.

It follows that if we mate an adult female of average age with an adult male of average age, we may write for ε, the probability that a female offspring will inherit a sex linked recessive lethal,

$$\varepsilon = \frac{\varepsilon + 2\mu_f}{2} + \mu_m$$

or $$\varepsilon = 2(\mu_f + \mu_m)$$

and this may also be written in the form

$$\varepsilon = 4\bar{\mu}; \text{ where } \bar{\mu} = \frac{\mu_f + \mu_m}{2}$$

Thus, in the case of sex linked recessive lethals, there exists a simple relationship between the inherited load of mutations and the rate per generation at which such mutations arise.

We have such a clear relationship between the inherited load of recessive lethal mutations and the rate per generation at which such mutations arise only for the class of the sex linked recessive lethals. Once we go outside of this class we cannot derive such a relationship because, outside of this class, it is not known how long the recessive lethal mutations persist.

Radiation Induced Mutations

We now turn to the induction of sex linked recessive lethal mutations by ionizing radiation. Let us first consider, for the sake of argument, an experiment in which we start out with a natural population of 10,000 females and an equal number of males. Let us expose the females to a certain X-ray dose d_f and designate with x_f the probability that an X chromosome contained in an ovum carries a radiation-induced recessive lethal mutation. Similarly, let us expose the males to a certain, either equal or

different, X-ray dose d_m and let us designate by x_m the probability that an X chromosome contained in a spermatozoa carries a radiation-induced recessive lethal.

Let us now mate adult females of an average age with adult males of an average age and keep one female from the first litter ~~of each female~~, while the rest of the brood is killed. We would thus end up with 10,000 female mice in the second generation. The probability that a female mouse of this second generation has inherited a sex linked recessive lethal is then given by

$$P_1 = x_m + x_f + \varepsilon$$

This number P_1 can be experimentally determined by breeding each female until it has a brood of 100 and determining the proportion of the males in the brood of each mouse in the manner described above.

If ε has been determined for a natural mouse population, then P_1 will now determine $(x_m + x_f)$. This sum is the probability that exposure of the mouse population to ionizing radiation produces a sex linked recessive lethal mutation in an X chromosome which will be passed on to the offspring.

The same result can be obtained at lesser cost if we start out in the first generation with a smaller sample of a natural population, say 1,000 females and 1,000 males. After exposure of the male and female population, we mate adult females

of average age with adult males of average age and obtain one or two litters from each female. From the litters of each female we keep 10 females and kill the rest of the brood. In this manner we end up with 10,000 female mice in the second generation. Each of these second generation females we now breed until it has a brood of 100 and, we pick out the females who have a low proportion of males in their brood. This permits us to determine, in the manner described above, which of the females of the second generation have inherited a sex linked recessive lethal.

Because we are using here a small sample of females in the first generation, the spontaneous sex linked lethals inherited by these females would introduce a sampling error into our result. In order to avoid such a sampling error, we eliminate from the tabulation of our data any second generation female who has inherited a sex linked recessive lethal, if any of her 9 sisters have also inherited a recessive sex linked lethal. The remaining females of the second generation who have inherited a sex linked recessive lethal (and whose sisters have not) must have inherited a sex linked recessive lethal which either has spontaneously arisen in one of her parents or was induced in one of her parents by the exposure to the ionizing radiation. Therefore, the probability that a female mouse retained in the tabulation of our data has inherited a sex linked recessive lethal is given by

$$P_2 = x_m + x_f + \mu_m + \mu_f$$

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* * * * * *

Let us, now, assume that we expose both the male and female population to the same dose of ionizing radiation, d. We may then experimentally determine by the methods described above the dose d = D, for which we have

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This dose, D, would induce as many sex linked recessive lethal mutations as would spontaneously arise in one generation and we may, therefore, refer to it as the "doubling dose."

The same dose, D, would also induce as many recessive lethal mutations carried by some other chromosome than the X chromosome as would spontaneously arise in one generation on that other chromosome. It follows that if a population were exposed, generation after generation, to the doubling dose, D, in the mutational equilibrium, which would be gradually approached, the load of inherited mutations would be twice as great as the load of inherited spontaneous mutations. If we know how big the

doubling dose is, we may then assess the genetic damage suffered by a population which, generation after generation, is exposed to some dose d of ionizing radiation.

Naturally, our primary interest would be to find the doubling dose, D, not for mice, but for man. The question in what manner one might attempt to deduce the doubling dose for man from experimental results obtained with mice goes beyond the scope of this presentation.

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different, X-ray dose d_m and let us designate by x_m the probability that an X chromosome contained in a spermatozoa carries a radiation-induced recessive lethal.

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$$P_1 = x_m + x_f + \varepsilon$$

This number P_1 can be experimentally determined by breeding each female until it has a brood of 100 and determining the proportion of the males in the brood of each mouse in the manner described above.

If ε has been determined for a natural mouse population, then P_1 will now determine $(x_m + x_f)$. This sum is the probability that exposure of the mouse population to ionizing radiation produces a sex linked recessive lethal mutation in an X chromosome which will be passed on to offspring.

The same result could be obtained at lesser cost if we start out in the first generation with a smaller sample of a natural population, say 1,000 females and 1,000 males. After exposure of the male and female population, we mate adult females

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In each case when we find that a female has a low proportion of males in its brood, we may suspect that an inherited sex linked recessive lethal is responsible. In order to determine whether this is, in fact, the case, we preserve 5 or 6 females out of the last litter and each of these we breed until it has a brood of 100. If any one of these 5 or 6 females has a low proportion of males in its brood, then this would confirm that an inherited sex linked recessive lethal was, in fact, responsible.

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Let us designate with μ_m the probability that such a mutation should occur during the passage of an X chromosome through the male, in one generation, and designate with μ_f the probability that it should occur during the passage of an X chromosome through the female, in one generation. Since a male who had inherited an X chromosome carrying a recessive lethal would not be viable, the probability that an X chromosome in the sperm of the adult male of average age carries a recessive lethal is given by μ_m. If ε designates the probability that a female, born to adult parents of average age, inherits a sex linked recessive lethal, then the probability that an ovum of an adult female of average age contains an X chromosome ~~carrying~~ which carries a recessive lethal is given by $\frac{\varepsilon + 2\mu_f}{2}$.

It follows that if we mate an adult female of average age with an adult male of average age, we may write for ε, the probability that a female offspring will inherit a sex linked recessive lethal,

lethal, $\mathcal{E} = \frac{\mathcal{E} + 2\mu_f}{2} + \mu_m$

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$\mathcal{E} = 4\bar{\mu}$; where $\bar{\mu} = \frac{\mu_f + \mu_m}{2}$

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We now turn to the induction of sex linked recessive lethal mutations by ionizing radiation. Let us first consider, for the sake of argument, an experiment in which we start out with a natural population of 10,000 females and an equal number of males ~~mice~~. Let us expose the females to a certain X-ray dose d_f and designate with X_f the probability that an X chromosome contained in an ovum carries a radiation-induced recessive lethal mutation. Similarly, let

us expose the males to a certain, either equal or different, X-ray dose d_m and let us designate by χ_m the probability that an X chromosome contained in a spermatozoa carries a radiation-induced recessive lethal.

Let us now mate adult females of an average age with adult males of an average age and keeps. One female from the first litter of each female ~~mouse is then kept~~, while the rest of the brood is killed. We would thus end up with 10,000 female mice in the second generation. The probability that a female mouse of the is second generation has inherited a sex linked recessive lethal is then given by

$$P_1 = \chi_m + \chi_f + \varepsilon$$

This number P_1 can be experimentally determined ~~in the manner described above~~, by breeding each female until it has a brood of 100 and determining the proportion of the males in the brood of each mouse, in the manner described above.

If ε has been determined for a natural mouse population, then P_1 will now determine $(\chi_m + \chi_f)$. This sum is the probability that exposure of the mouse population to ionizing radiation produces a sex linked recessive lethal mutation in an X chromosome which will be passed on to offspring.

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Because we are using here a small sample of females mice in the first generation, the spontaneous sex linked lethals inherited by the females mice of the first generation would introduce a sampling error into our research result. In order to avoid such a sampling error, we eliminate from the our tabulation of the results our data any second generation female who has inherited a sex linked recessive lethal, and all the sisters, if any of her 9 sisters have also inherited a recessive sex linked lethal. The remaining females mice of the second generation which have inherited a sex linked recessive lethal (and whose sisters have not) and which are retained in our tabulation will, then, must have inherited a sex linked recessive lethal which either has spontaneously arisen in one or the other of her parents or was induced in one or the other of her parents by the exposure to the ionizing radiation. Therefore, the probability that a female mouse retained in the tabulation of our data has inherited a sex linked recessive lethal is given by

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This manuscript was prepared while the author served as consultant to ....

FIRST DRAFT

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If a population is exposed, generation after generation, to the same dose of ionizing radiation, a new mutation equilibrium will gradually establish itself. If the dose of ionizing radiation given each generation induces as many mutations as would spontaneously arise per generation, then in the mutation equilibrium the mutation load of the exposed population would be twice as high as the mutation load of the unexposed parental population. Therefore, we shall designate this particular dose as the "doubling dose". If we knew the "doubling dose", we would be in a much better position to assess the genetic damage that a population would suffer if exposed, generation after generation, to a given dose of ionizing radiation.

The mutagenic effect of ionizing radiation in mice has been extensively studied by observing the number of mutations which a given dose of ionizing radiation may produce at a number of non-genetic loci. It is not possible, however, to conclude from such observation the "doubling dose" for mice, even though it may be possible to determine the mutation load carried by these loci in an unexposed population. The persistence of mutations at such genetic loci is not known and, therefore, it is not possible to deduce the mutation load from the mutation rate, or vice versa. There exists one class of mutations, however, where the mutation load can be computed from the mutation rate: the class of the sex linked lethal mutations.

In this case, the probability that at the time of conception either the one or the other of the two sex chromosomes of a female carries a recessive lethal is four times as high as the average probability that a sex chromosome acquires a recessive lethal in one generation. The term "average" is used here because the probability that a sex chromosome acquires a recessive lethal may be different if the sex chromosome passes through a male and if the sex chromosome passes through a female. Accordingly, in the case of recessive sex linked lethals, we may say that the probability that a sex chromosome carries a recessive lethal at the time of conception of the female (i.e., the load of recessive lethals of a sex chromosome at the time of conception) is twice as high as the average probability that a sex chromosome acquires a recessive lethal in one generation. Therefore, we may determine the doubling dose by counting the number of sex linked recessive mutations induced by a given dose of ionizing radiation and comparing this number with the load of recessive sex linked mutations carried by the unexposed parental population.

In the following we describe an experiment that is designed to determine quantitively the mutagenic effect of ionizing radiation in mice by counting the number of sex linked recessive lethal mutations induced by a given dose of radiation. This may be done as follows:

We expose a population of, say, twenty thousand mice to ionizing radiation (generation No. 1). We then breed the ten thousand females contained in this population and obtain from each one litter. This litter is destroyed, with the exception of one female mouse. We thus obtain ten thousand female mice (2nd generation) and each of these we breed for about one year, breeding each mouse until it has a brood of one hundred. Let us assume now, for the sake of argument, that one per cent of the female mice of the second generation (about one hundred mice) carried a sex linked recessive lethal immediately following conception. Among the offspring of these mice, the male to female ratio will be one to two and, accordingly, about fifty will have about thirty-three,or less than thirty-three, male offspring in a brood of one hundred. The remaining females of the second generation, close to ten thousand, will have a male to female ratio in their offspring of one to one, and simple statistical considerations show that only about seven out of ten thousand will have thirty-three, or less than thirty-three, males in a brood of on e hundred.

It may be seen from this that by counting the female mice of the second generation who have an abnormally low male to female ratio in their broods, it is possible to assess the number of females of the second generation who carry a sex linked recessive lethal immediately after their conception. In order to make the determina-

tion more precise, it is necessary to test, in the case of each female mouse which has an abnormally low ratio of male to female in its brood, whether this abnormality is, in fact, due to a sex linked recessive lethal inherited by the female. For the sake of carrying out such a test, it is necessary to preserve, out of the broods which show an abnormally low male to female ratio, five or six females taken from the last few litters. If the abnormally low male to female ratio in a brood of the third generation was due to a sex linked recessive lethal inherited by a female of the second generation, then we may expect that at least one of the five or six females preserved will show a similar low male to female ratio in her brood.

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