THE GENETIC EFFECTS OF HIGH ENERGY IRRADIATION OF HUMAN POPULATIONS

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How much, of what, is happening to how many people? A consideration of the effects of radiation on exposed individuals —and their descendants.

HUMAN POPULATIONS are now being subjected to increases in high-energy radiation, through the explosion of A-bombs and H-bombs, and through the widespread medical use of X-rays.

The genetic effects of such exposures have recently been the subject of some public discussions. Since the matter is of public concern, and is also of considerable complexity, it seems desirable to elaborate somewhat on previous comments.

Two types of radiation hazard may be distinguished—those to the exposed individuals, and those to their descendants.

The present discussion is based on the latter class of effects—the genetic results, which will come to expression in the descendants of the exposed individuals.

It is not to be inferred that the direct effects on exposed individuals are negligible. In particular, there is evidence that irradiation does increase the incidence of leukemia and other malignant growths. These are difficult to estimate quantitatively, and there may perhaps be a dosage threshold, such that low doses of the sort here considered are ineffective. However, no such threshold has been demonstrated, and the safest course at present is to suppose that it does not exist—i.e., that even at very low doses there is a real, though small, hazard to the exposed individual.

The genetic effects of irradiation arise through effects *on the germ cells of exposed individuals. These germ* cells, like the other cells of the body, contain numerous separate hereditary elements, or *genes*, which are responsible for the inherited properties of individuals. The genes in any one individual are of many different kinds, but each particular kind is ordinarily transmitted unchanged from one generation to the next. On rare occasions, however, a gene may *mutate*—i.e., undergo a change to a new kind of gene, which is then transmitted to the following generations in the new, changed, form. The genetic interest in high-energy irradiation arises from the fact that it increases the frequency of such mutations.

As previously formulated, the basic facts here are:

(1) High-energy irradiation produces mutations.
(2) The frequency of induced mutations is directly proportional to the dosage of irradiation. There is almost certainly no threshold value below which irradiation is ineffective.
(3) The effects of successive exposures are cumulative.
(4) The effects are permanent in the descendants of the affected genes. There is no recovery.
(5) The overwhelming majority of these mutations is deleterious; that is, they seriously affect the efficiency of individuals in later generations in which they come to expression. These deleterious effects may lead to early death or to any of a wide variety of defects, often gross ones.
(6) There is a store of such undesirable genes already present in any population. What irradiation does is to add to this store.

A further elaboration of these facts falls naturally under two major headings. First, what are the quantitative relations between irradiation dosage and genetic damage? Second, to what dosages are people being exposed? Unfortunately, both of these questions are inherently difficult to answer, and only very rough approximations are possible. No scientist interested in exact quantitative results would touch the subject, were it not that its social significance leaves us no alternative. We must, like it or not, try to get some sort of idea as to how much, of what, is happening to how many people.

Irradiation and mutation

The quantitative determination of the relation between irradiation and mutation requires careful and elaborately controlled experiments, which must be carried out on a very large scale. It is quite impossible to get significant data directly concerning man, so we are forced to turn to other organisms, and it is also clear that our criteria for mutations in other organisms leave out of account some of the more important kinds that are to be expected in man—more especially those having to do with behavior. The most satisfactory data concern the small fly, Drosophila, and were collected by Spencer and Stern. Their data lead to the conclusion that 1 standard "Roentgen unit" of irradiation (written *1 r) will induce 1 lethal mutation per 10,000 treated germ*-cells of Drosophila (sperm cells, in this experiment).

It has recently been suggested that there is a much greater effect in mice, and presumably in people, but I cannot agree that this evidence is convincing. It would seem safest to assume—and it must be recognized that this *is* only an assumption—that the rate in man is roughly the same as that in Drosophila. In any case there appears to be no reason to suppose that man has a lower response to irradiation.

The above rate refers to lethal mutations. In general, according to the usual scheme, such a mutated gene has no effects on an individual that carries it—unless one of the same kind was received from each parent. (It may be estimated that, in man, something like 3 percent of the mutant genes will be expressed in males who received them only from their mothers; i. e., will be "sex-linked"). The result would be that an induced mutation of this type would not usually come to expression until numerous generations had passed. However, Stern et al have recently shown that, in Drosophila, even the individuals with only a single "dose" of a lethal mutation have, on the average, about a 4 percent impairment of efficiency, so the undesirable effects from these genes must be supposed to begin appearing in the generations immediately following irradiation.

Time and mutation

Some of the induced mutations will also be substantially the same as (in genetical terminology, will be allelic to) some of those already present in the population; these may come to expression before there is intermarriage among the descendants of a single exposed individual. This consideration does not lead to any change in the probable average amount of damage due to induced mutations, but it does lead to a decrease in the estimate of the probable average time interval between exposure to radiation and the expression of the effect of the induced mutations.

There are other, non-lethal, types of mutations that are induced by irradiation. The measurement of their frequencies is difficult, and it may be doubted whether *their frequency, relative to that of lethals, will be the* same in man as it is in Drosophila. In the latter organism the evidence is that non-lethal mutations leading to the production of clearly distinct changes in the structure of viable individuals are distinctly less frequent than lethals; mutations leading only to a somewhat lowered efficiency of the individual are roughly twice as frequent as lethals.

On the whole, then, it seems a reasonable guess that the rate of induction of lethals in Drosophila may be used as a very rough index of the probable rate of induction of undesirable mutations in man—an index that is more likely to be too low than too high. This rate—1 in 10,000 germ-cells per r unit—will be used here without attempting any corrections.

The physical measurement of radiation has been developed to a high degree of refinement. But the estimation of the effective doses received by man is a complex matter, and at best can yield only approximate values. We are all of us receiving radiation in small amounts all the time, from cosmic radiation and from naturally occurring radioactive elements in the ground, in the walls and floors of rooms, in the air, and in our bodies. Further, the amount of this radiation varies from time to time and from place to place. We can, at most, get an approximate average value for irradiation per unit time. Since altitude is an important variable in the cosmic ray component of this normal "background" radiation, I have given two values—one for approximately sea-level, and one for an elevation of 6000 feet.

Fall-out from bombs

It is especially difficult to arrive at a value for the increase in irradiation due to fall-out from the bombs, since this varies erratically from one place to another, since the activity from any one explosion rapidly decreases with time, and since the effectiveness of a radioactive element will be greater if it happens to become incorporated in the tissues of the body. It is for these reasons, rather than because of any policy of secrecy, that it is very difficult to obtain from the published accounts any very satisfactory figure for the average increase in background. The value I have taken from AEC reports appears to represent an estimate for an average locality in the United States in Sept. 1954.

In the following table I have included (from the summary by Plough, 1952, *Nucleonics* Vol. 10) some figures for dosages resulting from a few types of X-ray exposures to which people are sometimes exposed in medical practice. These again are averages, and there is much variation in the output of different machines. There is some scattering of radiation in any X-ray treatment, so that areas other than those intentionally treated will get some effect. The amount of such scattering is difficult to estimate. Accordingly I have included in the table only those treatments involving areas close to the ovaries or testes, and have not included the two exposures to which the largest numbers of people are subject—dental and chest examinations.

Irradiation, in r-units

Background, at sea level	— 0.1 per year	3.0 per generation
Background, at 6000 feet	— 0.15 per year	4.5 per generation
Increase in background due to bomb fall-out	— 0.0035 per year	0.1 per generation
X-ray examinations—		
lumbar, spine, anterior-posterior	— 1.5	per treatment
lumbar, spine, lateral	— 5.7	per treatment
pregnancy, anterior-posterior	— 3.6	per treatment
pregnancy, lateral	— 9.0	per treatment
gastro-intestinal fluoroscopy	— 10 to 20 per minute	
Irradiation of ovaries to induce fertility	— 200 or more	
Recommended maximum permissible for radiological workers	— 0.3 per week	15 per year
Average, Oak Ridge and Hanford workers, 1949	— 0.2 per year	

From a genetical point of view, what we are interested in is the product of the dosage received multiplied by the mutation rate per unit dose. In other words, what will be the frequency of deleterious mutations resulting from the various radiation sources to which people are subjected?

Considering first the natural background, 3.0 to 4.5 r per generation would yield from 3 to 4.5 mutations per 10,000 germ cells. This is probably less than the amount of mutation that would be present if it were possible to screen people from all irradiation of any kind. In Drosophila only a small fraction of the normal mutation rate is due to natural background irradiation; but the proportion due to that cause in man is presumably much larger because the length of a generation is hundreds of times greater, and the total background irradiation per generation is greater by the same factor, whereas the number of mutations not due to irradiation is probably proportional more nearly to the number of cell-generations than to time—and man and Drosophila do not differ greatly in this factor.

Incidentally, many discussions of irradiation and mutation emphasize the natural rate, and start with an attempt to determine the amount of irradiation necessary to double this rate. This seems to me a wrong approach, since the natural rate is not known and will not be easy to determine, and since the induced mutations are added to the natural ones and the two types do not have any fixed proportionality. The natural mutation rate is no more relevant than is the death rate from bacterial infection.

Natural background radiation

The natural background radiation is something that is always present, and discussion of whether it is a good thing or a bad one is pointless, since nothing can be done about it. The other sources here listed, however, are man-made, and it is legitimate to inquire what they may be expected to do to human populations.

If the increase due to bomb fall-out persists at current levels it may be expected to give about 1 deleterious mutation per 100,000 germ cells per generation—or, since each individual arises from two germ cells, 1 per 50,000 conceptions.

It may seem that this is a negligible proportion, and it should be emphasized that it is such a low number that no individual should be particularly disturbed about the probability that his immediate descendants will be affected.

But, according to the Population Division of the United Nations, there are something like 3,900,000 births per year in the United States, and about 90 million per year in the world. This means that, if the increase in irradiation due to fall-out continues at the estimated present rate, it will lead to the functioning of about 78 mutated germ cells every year in the United States; and, if the same level of irradiation occurs in the rest of the world, of about 1800 per year in the population of the world. These will go on arising at this rate, year after year, as long as the irradiation continues and the number of births stays in this same range.

Another calculation may be made that is of some interest. The Pacific tests of 1954 apparently gave an average total of about .0035 r for any one locality in the United States. It may be estimated that the people now living in the United States will produce, during their lifetimes, over 100 million offspring; i. e., over 200 million of their germ cells will ultimately function. The estimate then is that 70 of these offspring will carry deleterious genes induced by this one series of tests.

A conservative estimate

It may still seem that these numbers are too small to be seriously considered, but there are several points to be made. I have made every effort to be conservative; the numbers given should be considered minimal ones—the true value could possibly be 100 times greater. And there is a possibility that the irradiation of the germ-cells may sometimes be much greater than is here estimated, if there is a heavy fall-out, especially if some of the radioactive elements become incorporated in the tissues. Finally, from a humanitarian point of view, any increase at all in the number of individuals that are defective either mentally or physically is not to be lightly dismissed.

In any case, it is inexcusable to state, as has been done, that no hazard exists. One might agree that the hazard is slight when weighed against the possible benefits; and I would agree that the hazard to any one individual remote from the site of an explosion is so small as to be disregarded. But the fact remains that there *is* a hazard, and that it may become a significant one in terms of large populations.

The "maximum permissible" exposure has been set by the International Commission on Radiological Protection, evidently on the basis of probable effects on exposed individuals themselves, without regard to genetic effects. If one imagines a situation where an entire population should be exposed to this amount of irradiation continuously, the dose per generation would add up to about 450 r—corresponding to about 4.5 percent of all germ cells undergoing mutation—i. e., every year about one-third of a million infants would be born with newly-arisen deleterious mutations, in the United States alone.

This is an amount that some authorities believe might endanger the survival of the race if it were repeated in every generation, and even if the race survived its members would probably decrease in efficiency. It does not seem likely that any such general level of irradiation will be reached—unless possibly in the event of all-out atomic warfare—but to describe an exposure this large as "permissible" is misleading, to say the least, when one thinks in terms of populations.

The "maximum permissible" exposure will become a matter for careful consideration if nuclear reactors come to be widely used as power sources, since under those conditions also there will be an increase in the background radiation. The amount and character of such increases will depend in part on the type of reactors used, and on the details of their design and operation—and it is a matter of public concern that this factor, as well as economic ones, be taken into account in a program for the non-military development of atomic energy.

The figures for the medical uses of X-rays run higher than those we have been considering, and there can be no doubt that in much of the world this is a far more effective cause of mutation than is radioactive fall-out. The published dosage values are in some respects misleading, since many irradiations—especially among the more drastic therapeutic ones—are most often given to patients who are unlikely to have any further children. But in such cases as the pregnancy examinations here listed it must be remembered that not only the mother's ovaries but also the germ-cells of the child are being exposed. If all members of the population were to receive even 1 r-unit just before birth, as would be possible here, the expected result would be that about one in 5000 of the next generation would carry a new mutation due to the treatment. In the case of the irradiation of the ovaries of a sterile woman to induce fertility it may be calculated that the resulting child has at least 1 chance in 50 of carrying a new mutation due to the treatment.

Medical use of X-rays

In general, the conclusion seems warranted that the medical use of X-rays is dangerous, and should be applied with caution and with full realization of the genetic hazards involved. In any given case the potential gains should be weighed against the potential damage; and in order to do this intelligently it is necessary to get as good an estimate as possible for the weight to be assigned to each side of the balance.

The medical use and the fall-out danger are different not only in the amounts of irradiation involved, but also in some ethical respects. An individual does not usually have to submit to an X-ray examination, or treatment, and when he does so the irradiation is administered for his own personal advantage. But we are all of us submitted, willy-nilly, to fall-out, and while it may be argued that some of this is for our ultimate advantage, it must be recognized that we get fall-out from Russian bombs as well, and that the rest of the world gets it from Russian and American bombs alike.

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