PRESENTATION OF THE U. S. A. NATIONAL ACADEMY OF SCIENCES REPORT ON THE EFFECTS OF IONIZING RADIATION (BEIR REPORT). 2. GENETIC EFFECTS

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Abstract

Information for assessing the magnitude of the human genetic risk from radiation still comes almost entirely from nonhuman sources, mainly the mouse. The Committee recommended that estimates for low dosages be made on the assumption of a linear relationship between the effects at the lowest doses where reliable measurements exist and the effect at zero dose. This was chosen as a plausible assumption for some effects (mutation and chromosome breakage) and as a conservative procedure for others (nondisjunction and chromosome loss).

The Committee considered four bases for risk estimation. In order of reliability these are: (1) The risk relative to natural background radiation, (2) The risk relative to specific genetic conditions, (3) The risk relative to current incidence of serious disabilities, and (4) The risk in terms of overall ill health.

The Original BEAR Report

The current report is a follow-up of the original report of the National Academy of Sciences Committee on the Biological Effects of Atomic Radiations (BEAR).[1] This Committee, along with a corresponding group in Britain working at the same time and not entirely independently, introduced the idea of regulating the *average* dose to the population.

The BEAR Committee recommended that man-made radiation be kept at such a level that the *average* individual in the population receive less than 10 r before the mean age of reproduction, a period of time taken to be 30 years. Moderate variation in exposure from person to person was not regarded as very important as long as the population average is kept low for the reason that the damage is to later generations. The concern is not so much that of the individual for his own children, for which the risk is slight, but of society for an overall disease and disability rate in future generations. Prior to this report, the main emphasis had been on the protection of the person receiving the radiation. The individual dose limit was set so as to be well below that for which there is any observable harm. The BEAR Genetics Committee emphasized the linear, non-threshold concept for genetic effects and its implication that there is no "safe" dose, a concept that had been discussed earlier by the NCRP.

The general principles guiding the Committee were: (1) Mutations, spontaneous or induced, are much more often harmful than beneficial. This is to be expected on the grounds that mutations, being random events, are more likely to make well regulated systems worse rather than improving them. It has also been

observed experimentally that mutations whose effects are large enough to be visible are almost always harmful. (2) Any amount of radiation, however small, that reaches the reproductive cells entails some genetic risk. (3) The number of mutations produced is directly proportional to the dose, so that linear interpolation from high dose data provides a valid estimate for low dose effects. (4) The effect is independent of the rate at which the dose is administered or of the spacing of the total amount. The last of these has turned out to be wrong, as will be discussed later.

With these principles, the number of mutations is the simple product of the number of genes in the population *times* the dose *times* the mutation rate per gene per unit dose. For the last quantity, mouse data were becoming available at the time of the BEAR study, and the effects were considerably higher than those in Drosophila, which had constituted the main quantitative evidence before this time. But there was no estimate of the number of genes in any mammal. There wasn't any very good evidence in Drosophila either. Some Drosophilists suggested that the bands on the salivary gland chromosomes might correspond to genes and that counting them might give an estimate of the number of genes; but this generally was regarded as naive. A more indirect way was to estimate the ratio of the total mutation rate to the specific locus rate, but this had its problems because of the difficulty in measuring the total mutation rate. This ratio was taken to be about 10,000 and the risk estimates therefore were for a hypothetical organism whose mutation rate is that of the mouse and whose gene number is that of Drosophila.

H. J. Muller strongly advocated the principle that each mutant must ultimately be eliminated from the population, and therefore for each mutation there must eventually be one gene extinction, or "genetic death". The Committee included this kind of calculation in its report, but with mixed enthusiasm. Some thought it to be the only way of trying to assess the *total* impact of mutation. Others thought the problem of finding the correspondence between gene extinctions and tangible measures of human suffering and frustration to be completely insoluble, and therefore the method essentially worthless. The Committee also estimated the mutation rate doubling dose and applied this to the estimated mutational component of human disease and disability.

What Has Been Learned Since?

What has been learned in the nearly two decades since the BEAR Committee met? An enormous amount by any standards! The BEAR Report was written early enough to miss both the molecular revolution and the development of human cytogenetics. I don't believe the letters "DNA" appear anywhere in the Genetics Report, and the chromosome number is given as 48.

We now know the chemical basis of the gene with an amount of detail that would have been utterly unbelievable in the 1950's. The chemical basis of mutation is deeply understood and the systems of mutation repair, especially of UV damage, are models of clarity and beauty. The human species has joined Tradescantia, maize, and Drosophila in becoming cytologically respectable.

With such deep fundamental knowledge one might expect that estimation of radiation risks would be correspondingly more precise. Yet, there remain large gaps, the most serious being (1) the almost complete absence of information on radiation mutagenesis from human sources, and (2) our inability to determine the relationship between an increase in the mutation rate and the effect on human welfare in the future. In some ways the situation seems worse than it did in the 1950's because researches in the meantime have brought out complexities that were not suspected at that time. It can no longer be assumed that the number of mutations is independent of the dose rate or of fractionation.

Furthermore, we are more cognizant of differences in different kinds of cells, between the sexes, and among different organisms.

How Valid Are Mouse Data?

Since we still don't have any reliable human radiation data we still have to rely on other organisms, particularly the mouse. The BEIR Report[2] and the United Nations Report (UNSCEAR)[3] do this. Is there any reason to believe that mouse rates are equivalent to man? I should like to present some data, recently assembled by Abrahamson, Bender, Conger, and Wolff[4], that should add to our confidence in extrapolation from other organisms to man. They plotted the mutation rate per rad per locus as a function of the amount of DNA in the haploid genome. The results for Escherichia, yeast, Neurospora, Drosophila, mouse, tomato and barley, on a log-log plot, fall very close to a straight line at a 45 degree angle to the axes. The amounts of DNA in these species ranges over a factor of 1000; so do the mutation rates, ranging from 10^{-9}/rad for *E. coli* to 10^{-6}/rad for barley. Yet, the ratio is nearly constant. The human species has about 20 percent more DNA per cell than the mouse, so placing ourselves at the appropriate place on the line gives a single-locus mutation rate of 2.6 X 10^{-7}/rad. This is the value for high dose-rates; chronic radiation would produce effects 1/3 to 1/4 as high.

Is there any way to make sense out of this remarkable observation? There is perhaps one way. We must remember that what is constant when normalized for the amount of DNA is the *per locus* rate, not the genome rate.

It is known that in bacteria the genome is a continuous string of DNA and that there are roughly 3000 genes. There is now good evidence from Drosophila that the number of gene loci is equal to the number of salivary gland chromosome bands -- just as the more naive geneticists used to think. The evidence comes from the work of Judd and his colleagues[5] who for several years collected all mutants that were located in a small region of the X chromosome that could be delimited by a deletion. They now seem to have found all the gene loci in this area, since for some time all the new mutants have been mapped at one of the previous sites. These lethal, or in a few cases, visible, mutants fall into 16 distinct groups, as defined by a complementation test. It is also true that there are exactly 16 salivary chromosome bands in this region. Unless this is a fantastic numerical coincidence, the simple idea that the number of genes is equal to the number of chromomeres appears to be correct. There is supporting evidence from other Drosophila chromosome regions.

The number of salivary gland chromosome bands is a little over 5000. Thus, the Drosophila has only about twice as many genes as *E. coli*. Yet, the amount of DNA per cell is an order of magnitude higher. There is also good evidence that the Drosophila chromosome is a continuous strand of DNA -- some 20 Angstroms in diamter and about a centimeter long! Thus, it looks as if a Drosophila gene is at least ten times as long as a bacterial gene.

If we accept this inference, then as organisms get larger and more complex, they don't get many more genes, but rather, the genes get longer. If this is true, the gene in higher organisms presents a larger target for radiation. Perhaps this is the explanation of the puzzling results of Abrahamson *et al.*

In any case, whether the explanation is correct or not, the fact that the data from these diverse organisms lies so close to the line adds to our confidence in extrapolating to man from the mouse.

Risk Estimates

All quantitative estimates that the BEIR Genetics Committee used were derived from mouse low dose-rate data. No correction was made for the larger amount of DNA in the human cell, although this would have made only a trivial difference (about 20 percent) among much larger uncertainties. Cytogenetic estimates were usually made directly as if humans were mice, although adjustments were made in those cases where there was some reason to think humans are different.

Estimates of genetic disease other than cytogenetic was done by estimating the relative risk for one rem. This is the proportion by which the mutation rate is increased by one rem; its reciprocal is the doubling dose. This was estimated by taking the specific locus rate for mice, averaged over the two sexes, as the radiation induced rate. The spontaneous rate was estimated directly from human spontaneous mutation rate studies. From this we derive 1/200 to 1/20 as the relative risk of one rem -- or 20 to 200 as the doubling dose.

For any category of disease the Committee attempted to estimate the *mutational component* of its incidence. Conceptually, we think of the disease incidence as divided into two discrete compartments, one of which has an incidence directly proportional to the mutation rate and the other whose incidence is independent of the mutation rate. (Nobody thinks that this is a correct picture of the true situation, but it seemed to us to be a reasonable model for the purpose of risk assessment.) For conditions that are caused by dominant or X-linked mutations, the mutational component as defined above is very nearly one. For congenital anomalies and constitutional diseases the fraction is taken to be from 5 to 50 percent.

The Committee recommended four bases for risk estimates: (1) The risk relative to the natural background radiation; (2) The risk for specific genetic conditions; (3) The risk for severe malformation and disease; and, (4) The risk in terms of overall ill health.

These are in decreasing order of robustness and accuracy and increasing order of social relevance. Unfortunately, the closer we come to estimating tangible human dangers, the more uncertain the estimates become.

1. The Risk Relative to That From Natural Background Radiation.

Of course, this is not a risk estimate at all; but it may be very useful as a policy guide, nonetheless. The idea is this: The human species has lived with this amount of radiation throughout its evolutionary history. Although we don't think this has been good for us, nevertheless we have managed to survive, even thrive. Most people don't take background radiation levels into account when they decide where to work or live; in other words, the risk is comparable to other risks that are commonly, usually unthinkingly, accepted. As the Report says: "If the genetically significant exposure is kept well below this amount, we are assured that the additional consequences will neither differ in kind from those which we have experienced throughout human history nor exceed them in quantity."

2. The Risk For Specific Genetic Conditions.

The basis for this estimate is the radiation-induced rate for mice, averaged over both sexes. For chronic radiation of spermatogonia in males and oocytes in females, the average is taken to be .25 X 10^{-7} per rad. Using the incidence of dominant and X-linked diseases and making informed guesses as to the persistance of these genes in the population, the human risks were estimated.

3. The Risk Relative to the Current Incidence of Serious Disabilities.

With a 20-200 rem doubling dose, an exposure of 5 rem per generation (170

mrem per year) would cause an eventual increase of from 2.5 to 25 percent in the burden of disease that owes its incidence to mutation. About one percent of children have a dominant or X-linked disease or disability, and this incidence is essentially proportional to the mutation rate. Recessive diseases are rarer and their incidence is only very indirectly related to the mutation rate. Disease of more complex etiology -- congenital anomalies, anomalies expressed later in life, constitutional and degenerative diseases -- are partly genetic, but there is great uncertainty as to how directly their incidence reflects the mutation rate. It is unlikely that more than half the incidence has this cause. Some would estimate it as low as 5 percent. The estimates are summarized in Table 1, which is taken from the BEIR Report.

Table 1. Estimated effect of 5 rem per generation on a population of one million. This includes conditions for which there is some evidence of a genetic component.

Disease classification	Current incidence	Effect of 5 rem per generation	
		First generation	Equilibrium
Dominant diseases	10,000	50-500	250-2500
Chromosomal and recessive diseases	10,000	Relatively slight	Very slow increase
Congenital anomalies	15,000	5-500	50-5000
Anomalies expressed later	10,000		
Constitutional and degenerative diseases	15,000		
TOTAL	60,000	60-1000	300-7500

4. The Risk in Terms of Ill Health.

In addition to the categories above, we have illnesses of many sorts, ranging from so mild as to constitute only a minor inconvenience to severely incapacitating and fatal. The mutational component can only be guessed. Dominant genes probably play a smaller part in this than they do in the conditions in Table 1. Rather arbitrarily we took 20 percent as the mutational component. This leads to an estimate, at equilibrium, of an increase in all disease of between .5 percent and 5 percent if the population were exposed to 5 rem per generation. The Committee also suggested how a dollar value might be placed on a rem through this estimate.

One factor that is left out of these calculations, and which we have no way of assessing, is what appears to be the majority of mutants in Drosophila -- namely, mutants with a very mild effect on viability. These mutants show very little recessiveness, so their impact is partly in the first generation after the mutation occurs and is spread over the next 50 to 100 generations. Extensive mouse experiments offer no evidence for any measurable contribution from such mutants. The Committee had this admonition: "We remind all who may use our estimates as a basis for policy decisions that these estimates are an attempt to take into account only known tangible effects of radiation, and that there may well be intangible effects in addition whose cumulative impact may be appreciable, although not novel."

As regards public policy toward radiation protection, the Committee had this to say: "It seems clear that the genetically significant radiation exposure from fallout, from nuclear power developments, and from occupational exposure (treated as a part of the over-all population average) is now very small relative to that from natural radiation. There is no reason to think that the dose commitment for the development of nuclear power in the next few

decades should be more than about a millirem annually. The 1956 report and the guides that grew out of it were the result of an effort to balance genetic risks against the needs of society. It now appears that these needs can be met with very much less than the 170 mrem per year of the current Radiation Protection Guides. Accordingly, the 170 mrem seems to provide an unnecessarily large cushion.

Likewise, we believe that the currently much higher level of radiation from medical sources (mainly diagnostic) should be examined in view of the same concept. If it can be reduced further without impairing essential medical services, then the present level is unnecessarily high."

References

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