LOW DOSE RADIATION, CHROMOSOMES, AND CANCER

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We shall confine our remarks today to the somatic effects of radiation, that is, to those effects of radiation upon the generation of humans receiving such irradiation. Further, our focus will be upon two well-known effects of ionizing radiation upon humans; namely, cancer production and leukemia. One of us, Dr. Arthur Tamplin, has recently considered such other effects as genetic alteration, fetal mortality, and neo-natal deaths. (1)

Thus, if any comments made indicate serious concern on our part about allowable radiation standards for man, then that concern can only be amplified by considerations of the additional burden of genetic disorders in future generations, fetal deaths, and neo-natal deaths resulting from irradiation.

In 1964 at a Plowshare Symposium one of us indicated that the data requisite to provide a groundwork for a reasonable set of radiation standards for man simply were inadequate.(2) If we may quote Dr. Brian MacMahon, Professor of Epidemiology at Harvard, writing in the journal, "Ca - A Cancer Journal for Clinicians" in 1969 (3):

"While a great deal more is known now than was known 20 years ago, it must be admitted that we still do not have most of the data that would be required for an informed judgment on the maximum limits of exposure advisable for individuals or populations".

Thus, five years later, in 1969, Professor MacMahon is saying that our situation is not appreciably better than it was stated to be in 1964. Wholly aside from any opinion, a hard look at what data do exist leads us to have grave concern over a burgeoning program for the use of nuclear power for electricity and for other purposes, with an allowable dose to the population-at-large of 0.17 Rads of total body exposure to ionizing radiation per year. A valid scientific justification for this "allowable" dose has never been presented, other than the general indication that the risk to the population so exposed is believed to be small compared with the benefits to be derived from the orderly development of atomic energy for peaceful purposes.

We should like to emphasize here and now, lest the words be twisted, that the population has not received anywhere near 0.17 Rads per year from atomic energy activities thus far. Nevertheless, the industry is only now getting going and the 0.17 Rads per year is on the Federal Statute books as allowable.

Several questions need to be addressed here:

(1) What would have to be the case in order to make it true that the current guides to allowable population exposure will not lead to disaster.

(2) Why the possible effects of such a dose to the population may have falsely appeared to be very small.

(3) What the hard data available suggest the most likely risk to be.

(4) What research efforts are in progress in our own laboratory to evaluate the relevant questions in this area of dose versus effect.

Let us start with considerations of the first question, "What would have to be the true situation so that current guidelines do not promote a disaster". In Figure 1 are shown two possible relationships between dose of a biological insult and its effect upon the biological organism insulted.

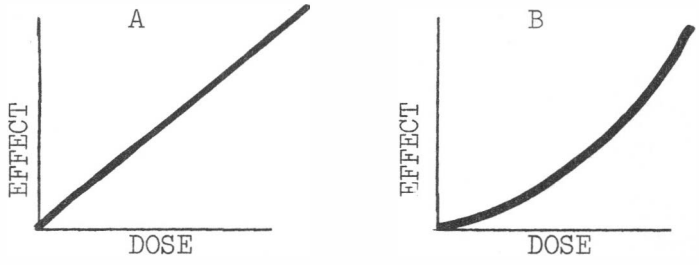

Figure 1

Let us consider radiation as the biological insult and the production of cancer plus leukemia in man to be the effect. Unfortunately, all the hard data concerning dose-effect relationship in man are for total doses above 100 Rads. Our estimates, therefore, of the effect per rad are, to be conservative, based upon a linear extrapolation from high dosages down to very low dosages. In essence, this means we utilize Curve (A) of Figure 1 and we assign a cancer-producing risk per rad as the same value whatever the total dose of radiation may be.

If our current radiation standards for the population-at-large remain where they now are by law, we would urge each of you to hope fervently and daily that curve (B) describes reality rather than curve (a). At present we simply don't know this answer.

There does exist a second possible way that the real situation might turn out more favorable than curve A. This has to do with the response of the biological system to fractionation of the radiation dosage. Some biological systems can repair themselves, at least in part, following irradiation, so that the sum of two doses separated in time has a lesser effect than the same total dose delivered at one time. Since most of the probable ways that human populations will receive irradiation in the course of peaceful exploitation of atomic energy will show fractionation with respect to time, we would urge you, additionally, to hope fervently that when data do become available (which they are not at this time), they will demonstrate a large protective effect of fractionation.

Next, we may turn to the second major question, "Why the possible effects of a dose such as is currently allowable may have falsely appeared to be extremely small".

First, there has existed a great interest in the genetic effects of radiation. Perhaps an over-focus upon genetic effects may have obscured the true relationship between radiation and production of cancer and leukemia. It has been estimated that, for a single gene locus, radiation may produce mutations with a frequency of approximately 1 per 10^7 per Rad. This is, of course, an extremely small risk per Rad. But is it in any way relevant for the problem at hand? There exists no evidence that the changing of one specific gene with a frequency of 1 per 10^7 per Rad is in any manner descriptive of the way radiation induces leukemia or cancer. Indeed, the evidence points away from this description. Thus assumption of a possible mechanism and the resultant smallness of the expected risk may well have led to complacency.

There is a second way that even the observed human dose-effect relationships may have led to complacency. Let us consider leukemia production in humans by radiation. There is no doubt in anyone's mind that, at least for doses above 100 Rads total, the risk is expressed as:

1 to 2 cases per 10^6 exposed persons per year per Rad, and that this rate, once the latency period is over, goes on for many years, ultimately declining. (3) Now, 1 or 2 cases of leukemia per million people per year sounds small. Indeed many have hastened to add that spontaneously leukemia occurs with a frequency of some 60 cases per million persons per year, -- a relatively rare disease. So 1 or 2 cases per million per year is small compared to 60 per million per year, which is itself small. As we shall see this approach represents a major error in thinking of implications. Alternate ways of viewing these data are imperative.

1 Rad → a leukemia increase of 1 or 2 per 10^6/year.

Spontaneously, leukemia occurs at 60 per 10^6/year.

Therefore, 1 Rad increases the leukemia incidence rate between 1.6 and 3.3%. Or, we can say that the doubling dose for leukemia is between 30 and 60 Rads.

What about other forms of cancer? Are they describable by a fractional increase in occurrence rate per Rad, and if so, how do such fractions compare with those for leukemia? Data do now exist for several human cancers induced by radiation. Estimates are available from U.S. data and from the Atomic Bomb Casualty Commission studies in Japan. (4)(5) The Japanese data show an approximate doubling dose of radiation of 100 Rads for thyroid carcinoma, or approximately 1% increase per Rad. The U.S. data show a risk of approximately 1 case of thyroid cancer per 10^6 persons per year per Rad. The spontaneous incidence rate reported by Carroll et al (8) for thyroid cancer is $\sim$ 5-10 per 10^6 persons per year in the age range 10-20 years. This combined with a risk of 1 per 10^6 persons per year per Rad leads to an estimate of 5-10 Rads as the doubling dose for thyroid cancer in children in the U.S. Thus the range, using both Japanese and U.S. data is between 5 and 100 Rads as the doubling dose for thyroid cancer, or between 1 and 20% increase in incidence per Rad. As a best estimate we will use the mean of the Japanese-U.S. data range. Hence, 1 Rad leads to a 2% increase in incidence rate, or 50 Rads is the doubling dose for thyroid cancer.

Next, consider lung cancer. Estimates are available from the A.B.C.C. for Japan and from the experience of uranium miners in the U.S.A. (5)(6). The Japanese data indicate an approximate doubling of the lung

cancer incidence rate for 100 Rads of exposure, or a 1% increase in incidence rate per Rad. The uranium miner data are complicated by two factors; (a) dosimetry is poorly known, and (b) many of the workers are still in the latency period. This latter leads to underestimation of the risk per Rad. What estimates have been made suggest the doubling dose to be between 250 and 500 Rads. If the correction for latency is introduced, and a factor of two is used for this, the estimate would be 125 to 250 Rads as the doubling dose. The range, therefore, including the Japanese plus the U.S. data is between 100 and 250 Rads as the doubling dose for lung cancer. Let us use 175 Rads as a best estimate here for the doubling dose for lung cancer, or 0.6% increase in incidence rate per Rad.

Breast cancer has been found to be radiation-induced in the Japanese studies (5). The estimated doubling dose is approximately 100 Rads for breast cancer, or 1% increase in incidence rate per Rad.

We can summarize these data as follows:

Disease	Doubling Dose	% increase in frequency per Rad
Leukemia	30-60 Rads	1.6 - 3.3%
Thyroid Cancer	~ 50 Rads	~ 2%
Breast Cancer	~100 Rads	~ 1%
Lung Cancer	~175 Rads	~ 0.6%

For such widely divergent organ systems, there is an amazingly small range for the estimated doubling dose. To the extent that latency has prevented full expression for some of these, the doubling dose has been overestimated. We know from other data that bone cancer and skin cancer have definitely been produced by radiation. With further study, the A.B.C.C. data will provide estimates of doubling doses for induction of cancer at other major remaining sites by radiation. At present the only malignant disease reputedly not induced by radiation is lymphatic leukemia. Even this may be in doubt since malignant lymphoma, a highly related disorder, is radiation-induced.

In view of the widely diverse forms of human cancers and leukemia showing such striking similarity in the risk of radiation induction, it does not appear at all rash to estimate that all forms of cancer will probably show a doubling dose close to those already observed. Using the central values for those already proved, we have as the estimate for all cancers:

$$\left\{\begin{array}{l} \text{100 Rads as the doubling dose} \\ \text{1\% increase in incidence rate per Rad.} \end{array}\right.$$

Now let us go on to our third question, "What do the hard data available suggest the likely risk to be associated with an allowable population exposure of 0.17 Rads per year?

If everyone received 0.17 Rads per year from birth to age 30 years, the integrated exposure (above background) would be 5 Rads per person. If the risk for all forms of cancer + leukemia is an increase of 1% in incidence rate per Rad, we have $5 \times 1 = 5\%$ increase in incidence rate.

For a population of 2×10^8 persons in the U.S.A. $\frac{1}{2}$ can roughly be estimated to be over 30 years of age. In this group, irradiated from birth, the latency period might, on the average, be expected to be over by $\sim$ 35 years of age.

The spontaneous cancer incidence is $280/10^5$ persons/year

$5\% \times 280 = 14.0$, 14 additional cancer cases per year per 10^5 persons, or

<u>14,000 additional cancer cases per year</u> in the U.S.A., considering <u>only</u> those over 30 years of age.

If we say that latency plus lower accumulated dosage provides a smaller number of additional cases in the under 30 year group, it would certainly not be an overestimate to add

2,000 cases for the under 30 year group.

Additionally, MacMahon estimates that in-utero human irradiation increases the risk of childhood cancer plus leukemia (3). The estimates are 2-3 Rads of in-utero radiation leads to an approximately 40% increase in such cancers. This in turn, suggests between 5 and 10 Rads to be the in-utero doubling dose for subsequent childhood leukemia plus cancer. Let us be conservative and use 10 Rads as the doubling dose, thus underestimating risk, if anything. 10 Rads as doubling dose means a 10% increase in risk per Rad. Therefore, 0.17 Rads (the guideline dosage) in-utero means a 1.7% increase in risk during childhood years for leukemia plus cancer. If we use 5×10^7 persons in the risk category ($\frac{1}{2}$ of those under 30 years of age) and a cancer incidence of 100 per 100,000 per year, we have

$1.7 \times 5 \times 10^2 = \sim 850$ additional cases/year of cancer plus leukemia from in-utero irradiation, expressed later.

Now $14000 + 2000 + 850 \simeq \underline{17000}$ additional cases of cancer per year in the U.S.A. if everyone received the currently allowable guideline dosage. This is equivalent to the mortality rate for one recent year of the Vietnam war! It would appear that this is rather a high price to consider as compatible with the benefits to be derived from the orderly development of atomic energy.

What Should Be Done

In the absence of (a) evidence that the dose-effect curve for cancer in man has a true threshold or is curvilinear, and (b) evidence that fractionation of dose protects appreciably, it would appear that the only sensible thing to do right now is to reduce the Federal Radiation Council dose allowable to the population-at-large by at least a factor of 10, -- to a figure of 0.017 Rads per year, or even less, for peaceful uses of atomic energy. We are well aware that this suggestion recommends that man-made radiation exposure be limited to a small fraction (0.1 or less) of natural background sources.

Several arguments might be raised against this proposal by some advocates of peaceful uses of the atom. But this proposal is not against peaceful uses of the atom: Rather, it is a proposal for the use of common sense discretion in atomic energy development.

Argument 1. "We don't deliver nor do we plan to deliver 0.17 Rads per year to the population-at-large from peaceful uses of atomic energy". We should certainly hope not! But, if it be true that we can develop atomic energy for electric power and other uses with a much lower delivery of radiation to the population-at-large, that is indeed excellent news. Let us immediately codify this into law so that no one can possibly be confused by a high allowable figure and a concomitant statement that we will stay well below that figure. Industry urgently needs a real standard that will hold up over time, since a later revision downward can lead to excruciatingly costly retrofits in a developed industrial application.

It is far better to lower the guidelines now and do our engineering design accordingly. If we are fortunate enough later to find either a curvilinear dose-effect relationship and/or protection by fractionation, it will be easy enough to raise the guidelines and allow more radiation. In this way we can avoid irreversible injury to a whole generation of humans while we find out the true facts.

Argument 2. "We live in 'a sea of radioactivity' and man has for time immemorial been exposed to ionizing radiation". Well, let us look at this closely. A reasonable value for average radiation due to natural causes is approximately 0.1 Rad/year. At 30 years of age, the average man has received 30 X 0.1 = 3.0 Rads of radiation from natural sources. (Higher in some locations).

If we now apply our factor of 1% increase in cancer incidence rate per Rad, we have

3.0 X 1 = $\sim$ 3% of the spontaneous cancer rate is due to natural radiation. We doubt that many persons informed in this field would be prepared to argue that 3% of "spontaneous" cancer plus leukemia is not due to natural radiation.

So, this argument concerning the sea of radioactivity falls of its own weight.

Argument 3. "It may take 10 or 20 years to determine whether or not there is protection either from curvilinear dose-effect relationship

or fractionation". That is perfectly correct. However, this militates in favor of reducing the allowable dosages rather than against reducing them. If it will take 10 or 20 years to determine this issue, why should we take the high risk of producing extensive irreversible injury in the interim?

Economic Aspects

The human impact of the misery of 17,000 additional cancer cases per year should transcend any other considerations. Nevertheless some economic considerations are important. It would certainly not be an overestimate that each additional case of cancer costs the community, public plus private, at least $10,000 (including patient care, lost work, lost taxes, welfare to dependent families), -- probably the economic cost is far higher.

17,000 x 10,000 = 170 million dollars/year.

We submit it is far better to appropriate $170,000,000 additional per year to learn the engineering and biology requisite to conduct the development of nuclear electricity and related peaceful uses of the atom under reduced allowable dose standards for the population. If we stay with the present guidelines we may very well pay the same amount of money or more plus a fantastic cost in human misery and premature deaths.

Lastly, what research efforts are in progress to answer some of the key questions in the area of dose versus effect?

If alteration of a single gene locus per Rad shows much too low a frequency to explain the increased cancer-leukemia risk per Rad, where could the true mechanism lie? We believe the chances are extremely good that it resides in the possible effect of radiation in altering the chromosome constitution of human cells. We should cite two major points now.

(1) 1 Rad of radiation has been demonstrated (at total doses down to 25 Rads) to produce a surprisingly high frequency of microscopically visible changes in the chromosomes of human cells. Estimates range from visible chromosomal injuries in 1 cell out of 30 per Rad to 1 cell per 1000 per Rad. But which of these chromosomal alterations, if any, are consequential for leukemia or cancer production? We must now turn to our 2nd major point.

(2) In work of the past few years some of us have demonstrated that there is, with high consistency, an excess of one particular chromosome known as the E-16 chromosome in human cells that show malignant behavior. (7). These studies have now been extended and show this excess to be prominent in all 18 of 18 malignant cell lines in tissue culture and in 11 out of 11 cases of human cancer studied directly. Two apparent exceptions are the diseases known as chronic myelogenous leukemia and Burkitt's lymphoma. Even for these two rare apparent exceptions, it is possible that they are really still consistent with the other cases, but it would take us afield to consider this in detail here. Many more cases of cancer need to be studied and are being studied in our laboratory. At this time, however, our finding of the highly consistent E-16 chromosome excess in cancer leads us to suspect that mechanisms which can damage cell reproduction so as to lead to cells with such an E-16 excess may represent a central pathway to cancer.

Our colleague, Minkler, is now engaged in an effort to determine the following parameters for human cells in culture:

(a) Can ionizing radiation alter human cells to produce cells with an excess of E-16 chromosomes? (We already know that one cancer-producing virus, the so-called SV40 virus, does so)

(b) If radiation does do this, what are the quantitative dynamics, such as

1. Effect per Rad delivered?
2. Effect of fractionation?
3. Effect of total dose on the effect per Rad?

Closing Remarks:

Unfortunately there is a recent tendency to create an apparent "adversary" position between so-called "environmentalists" and "those in favor of technical progress". This, we believe, is dangerous nonsense. We feel certain that the Atomic Energy Commission, the scientific and engineering community, and the electrical power industry are as concerned as we are to keep the environment safe for human

habitation and to bring society the earliest possible benefits of the peaceful atom. And because we are certain of this, we urge all these groups to join us in seeking an early revision downward by at least a factor of ten in the Federal Radiation Council guidelines for allowable exposure to the population-at-large.

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