EPIDEMIOLOGIC STUDIES OF CARCINOGENESIS BY IONIZING RADIATION

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1. Do we really need human epidemiologic data for pollutants?

In general, we should like to express our lack of sympathy for the expressed purpose of this Symposium, which is the planning of epidemiological studies for the evaluation of effects of major pollutants on humans. Carcinogenesis and leukemogenesis are two particularly worrisome long term effects which deserve consideration with respect to any pollutant. From our experience with ionizing radiation as a pollutant we have derived some lessons that we believe are extremely important to understand if society is to avoid paying a very high, probably unacceptable, price for the introduction of environmental pollutants. One such lesson centers around the prevalent notion that human epidemiological evidence concerning carcinogenesis should be required *before* technological promoters are willing to admit the serious potential hazards of a pollutant. Ionizing radiation is a classic example of this fallacious notion.

In our opinion it is *neither* appropriate *nor* good public health practice to demand human epidemiologic evidence to evaluate carcinogenic or leukemogenic hazard of a pollutant. First, in a civilized society, there *should never* exist an ideal set of human epidemiologic data. What epidemiologic data do become available are always subject to serious reservations with respect to equivalence of controls and exposed groups upon variables other than the specific pollutant variable under study. The net result is that controversy persists interminably. Peculiarly, but not unexpectedly in the face of promotional bias, the presumption is all too commonly made that, where uncertainty exists about the magnitude of effect, it is appropriate to continue the exposure of humans to the potential pollutant. It would indeed be sad if this Symposium helped contribute to this pernicious philosophy, which can only be described as that characteristic of a society bent upon ecocide in the name of ostensible technological progress.

In the case of radiation as a pollutant, we may consider some of the major epidemiological samples that have become available for study and relate the reservations that have been raised concerning acceptance of the results derived

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from the study of these samples. Approximately 100,000 survivors of Hiroshima and Nagasaki atomic bombing have been under followup study with respect to cancer and leukemia. Dosimetry reconstruction is difficult, at best, considering the nature of the event during which the radiation exposure occurred. Further, the associated possible injurious factors other than radiation were expected, in general, to be highly correlated with radiation exposure. Another large sample available for epidemiological study is the series of some 11,000 cases of ankylosing spondylitis in Great Britain, treated with X-irradiation. No satisfactory control series of spondylitics, untreated by X-rays, but otherwise equivalent, is available. Hence, questions can properly be raised about using the population at large as a reference sample. And the use of drugs for pain relief in addition to radiation therapy leads to the question of effects due to the drugs alone or to synergistic effects between drugs and radiation (see Collen and Friedman's contribution to this Symposium).

It can be pointed out that a vast experience with experimental animals of several species has proved cause and effect relationship between radiation exposure and carcinogenesis and leukemogenesis. Therefore, the real significance of the human studies is to ascertain comparability of dose response relationships for humans versus other species, rather than establishment of whether the observed association of radiation and cancer in these human population samples is *causal.*

We believe the appropriate approach to the study of leukemogenic or carcinogenic potential of pollutants is the study of dose response relationships in several mammalian species. And until or unless scaling laws are established among species, including humans, it should be *assumed,* for public health purposes, that the human is *at least* as sensitive as the *most* sensitive experimental species studied. In the ionizing radiation case, abundant experimental animal data have accumulated over the past quarter century demonstrating that radiation can provoke cancers of essentially all organs, provided the radiation is delivered to susceptible cells. Moreover, reasonable dose response data were available through such studies (Gofman and Tamplin [11]). Had these experimental animal data been utilized properly, the recent surprise concerning the higher than anticipated cancer hazard of ionizing radiation need not have occurred.

Having expressed our serious disapproval of the concept that human epidemiological studies should represent an approach to the study of pollutant effects, we should like to review here the treachery inherent in such studies, how they led to an earlier underestimate of the carcinogenic effect of radiation, and the residual uncertainties which still exist in assessment of the magnitude of the carcinogenic response to ionizing radiation in humans.

1.1. *Carcinogenesis and leukemogenesis in humans exposed to ionizing radiation.* Direct evidence that virtually all forms of human cancer can be induced by ionizing radiation has accumulated over several decades, often, however, with poor assessment of dose response relationships. By now, acute and chronic myelogenous leukemia, other acute leukemias, multiple myeloma, bone sarcoma,

skin carcinoma, lung cancer (bronchiogenic and other varieties), thyroid cancer, breast cancer, stomach cancer, pancreas cancer, malignant lymphoma, colon cancer, cerebral tumors, neuroblastoma, Wilms tumor, maxillary and other sinus carcinomas, and pharynx cancer have all been shown to be inducible in humans by ionizing radiation. (Gofman and Tamplin, [7]). One disease (presumed malignant), chronic lymphatic leukemia, does not, thus far, appear to be radiation-induced (Lewis [21]). The implications of this finding remain unclear. For those remaining varieties of human cancer, other than the ones just listed, no evidence indicates they are not radiation-inducible. Within the evidence available, fortunately limited, there are simply no adequate data concerning radiation-induction.

Recently we presented three generalizations concerning induction of human cancer and leukemia by ionizing radiation. (Gofman and Tamplin, [7], [9]). These generalizations follow:

GENERALIZATION 1. All forms of cancer, in all probability, can be increased by ionizing radiation, and the correct way to describe the phenomenon is either in terms of the dose required to double the spontaneous mortality rate for each cancer or, alternatively, of the increase in mortality rate of such cancers per rad of exposure.

GENERALIZATION 2. All forms of cancer show closely similar doubling doses and closely similar percentage increases in cancer mortality rate per rad.

GENERALIZATION 3. Youthful subjects require less radiation to increase the mortality rate by a specified fraction than do adults.

Others (Stewart and Kneale, [31]) had clearly stated the outlines of these generalizations based upon the irradiation of infants *in utero*. Court-Brown and Doll [3] had done so based upon irradiation of adults. Additional study (Gofman, Gofman, Tamplin, Kovich, [13]) provides no reason to suggest a change in any of these generalizations; rather, it provides supplementary support for the generalizations.

The second of these generalizations led us to predict that for every leukemia induced by ionizing radiation, the *sum* of the number of cancers induced would stand to leukemia *as does the sum of spontaneous cancer mortalities to leukemia mortality*. Since the sum of spontaneous cancer mortalities is some twenty times that of leukemia mortality (Table III) over a fair share of the human adult life span, we predicted the sum of cancer mortalities per unit of radiation would be twentyfold that of leukemia. This caused a furor in the "radiation community," since the International Commission on Radiological Protection (ICRP) [17] had predicted in 1966 only *one* cancer mortality per leukemia mortality from radiation (exclusive of thyroid carcinoma which shows a low mortality rate in the cases which do occur). The error in the ICRP estimate represents a classic illustration of the pitfalls in the epidemiologic approach that had been used. Leukemia happens to occur earlier, post-irradiation, than do other cancers. Thus, since the ICRP was studying population samples in the relatively early years post-irradiation, the cancer mortality was seriously underestimated.

Data are available for adults from the study of the irradiated ankylosing spondylitis cases in Great Britain [3]. These subjects were irradiated primarily in early adulthood and then followed for periods up to 27 years. This study provides a good basis for testing the prediction that the sum of cancer mortalities is some 20 times that of leukemia mortality following irradiation. It is obvious that such a comparison test requires that radiation dosages be equivalent for all sites compared, or that appropriate dosage corrections be made before comparison of cancer mortalities with leukemia mortality. The Court-Brown and Doll data are presented in Table II, including partial followup through 27 years.

TABLE I

INCREASE IN CHILDHOOD CANCER AND LEUKEMIA FROM *In Utero* RADIATION
Radiation delivered in the form of X-rays during diagnostic pelvimetry.
Estimated dose <2 rads.

Type of cancer	Radiation induced increase
Stewart-Kneale data (1968)	
Leukemia	50% increase over spontaneous mortality rate
Lymphosarcoma	50%
Cerebral tumors	50%
Neuroblastoma	50%
Wilms' tumor	60%
Other cancers	50%
MacMahon data (1962)	
Leukemia	50%
Central nervous system tumors	60%
Other cancers	40%

TABLE II

CHANGE IN RATE OF INDUCED MALIGNANT DISEASE WITH DURATION OF TIME SINCE EXPOSURE IN IRRADIATED ANKYLOSING SPONDYLITICS
(From data in Table VI of Court-Brown and Doll, 1965.)

Years after irradiation	Cases per 10,000 man-years at risk	
	Leukemia and aplastic anemia	Cancers at heavily irradiated sites
0–2	2.5	3.0
3–5	6.0	0.7
6–8	5.2	3.6
9–11	3.6	13.0
12–14	4.0	17.0
15–27	0.4	20.0
Total of expected cases in 10,000 persons in 27 years calculated from the rates given	67	369

TABLE III

RATIO OF SPONTANEOUS CANCER MORTALITY RATES TO LEUKEMIA MORTALITY RATES
(Derived from *U.S. Vital Statistics* for 1966.)

Males	Age group (years)	Ratio, $\left(\frac{\sum \text{Spontaneous cancer mortality rates}}{\sum \text{Leukemia mortality rates}}\right)$
	40–44	15.9
	45–49	22.9
	50–54	28.5
	55–59	28.7
	60–64	29.2
	65–69	29.1
	70–74	23.5

In these studies 40 per cent of the total bone marrow (the expected site of origin of the leukemias) is estimated to have received irradiation. The spondylitis treatment is directed to the spine, not to other bone sites containing marrow. The mean bone marrow dose is 880 rads (for spinal marrow).

The "heavily irradiated" sites in those studies represent the sites receiving spray irradiation incident to the planned spinal irradiation. Dolphin and Eve [4] estimated that these "heavily irradiated" sites received approximately seven per cent of the mean spinal marrow dose.

From Table II, the observed ($\sum$ Cancer Mortalities/Leukemia Mortality) = (369/67).

The $\sum$ Cancer Mortalities must be multiplied by (100/7), to correct dosage for "heavily irradiated" sites to be equivalent to that for the spinal marrow.

The Leukemia Mortality must be multiplied by 2.5 to correct for the fact that only approximately 40 per cent of the total bone marrow received irradiation.

Therefore, for true total body irradiation the *Corrected Ratio* for radiation-induced malignant diseases, ($\sum$ Cancer Mortalities/Leukemia Mortality) = $(369/67)(14/2.5) \cong 31$.

Since the spondylitis patients were irradiated in early adulthood, the period of followup is approximately in the 40 to 70 year age region. From *U.S. Vital Statistics*, 1966, we can derive the ratio, ($\sum$ Spontaneous Cancer Mortality Rates/$\sum$ Leukemia Mortality Rate) for this age range. These values are presented in Table III.

In the spondylitis patients, the sites designated as "heavily irradiated" include lung, stomach, colon, pharynx, esophagus, pancreas, lymphatic tissue. The major contributing sources to cancer mortality are, therefore, included. Possibly the ratio ($\sum$ Radiation-Induced Cancer Mortalities/$\sum$ Leukemia Mortality), determined here to be approximately 31 might be increased some if remaining tissue sites had been irradiated. The ratio ($\sum$ Spontaneous Cancer Mortality Rates/$\sum$ Leukemia Mortality Rate) is in the neighborhood of 20 to

30, for the relevant age range. Within the errors of such data as those for the spondylitis cases, the similarity of ratios for the spontaneous and the radiation-induced cases can be taken as strong support for Generalization 2 presented above, and as *grossly* at variance with the earlier ICRP prediction.

By now, however, this whole controversy has all but subsided. An ICRP Task Force (1969) has presented the Court-Brown and Doll data, together with the dose correction shown above (application of the Dolphin-Eve correction). Hamilton [15] stated that his own estimate of the ratio, ($\sum$ Radiation-Induced Cancer Mortalities/Radiation-Induced Leukemias), is within a factor of five of that of the authors, but he failed to take into account the dosage corrections which are, of course, absolutely essential in the treatment of the ankylosing spondylitis data. When the Hamilton estimate is appropriately corrected for the dose difference between bone marrow and the "heavily irradiated" sites (where cancers arise), his revised estimate would be *entirely* in accord with our own estimate. Mole [24] has recently published an estimate that the sum of radiation-induced cancer mortalities is "an order of magnitude" greater than radiation-induced leukemias. In a personal communication in 1970, Mole indicated to us that he had *not* applied the full Dolphin-Eve dosage correction, and this almost certainly explains the residual factor of two differences between his estimates and our own.

Thus, the so-called "radiation controversy," at least with respect to the ratio ($\sum$ Cancer Mortalities/$\sum$ Leukemia Mortality) for total body radiation, is essentially over. The controversy did pinpoint a valuable epidemiological pitfall, namely, the serious underestimate of cancer hazard from ionizing radiation resulting from the use, by standard setting bodies, of epidemiologic data for a time interval *before* the serious carcinogenic effects had developed. And the long observation periods required should alert us to the futility of hopes of learning of carcinogenic effects of new pollutants through human epidemiologic studies on a time scale that can be practically useful.

1.2. *Dose response relationships: ionizing radiation-induction of cancer and leukemia.* The ultimate objective, for a pollutant such as ionizing radiation, is an estimate of the human cost in premature death through cancer and leukemia, resulting from fairly chronic low or moderate dose irradiation. It is self evident that dose response relationships are required for such an estimate. Less immediately evident are some of the more subtle characteristics of the dose response relationships, characteristics which are crucially determinative of the magnitude of expected human cost.

One such characteristic is the time of onset of the carcinogenic response following exposure. Closely related is the duration of the response period in an exposed population. A second characteristic is the nature of the dose response curve over a wide range of doses. This becomes especially important because much of the available epidemiologic data covers a dose region higher than that anticipated for population exposure. Dose rate is an ancillary feature deserving

consideration. A third characteristic is the variation in dose response relationship as a function of *age at exposure.*

1.2.1. *Time of onset of carcinogenic response and its duration.* A valid parameter commonly employed to assess carcinogenic response to ionizing radiation is the *radiation-induced age specific mortality rate* from any particular malignancy or group of malignancies. It would be ideal if this parameter were readily available both from the experimental animal and human data, but this is not always the case. Following radiation exposure (of humans and experimental animals) there is a period of time which elapses before any provably induced mortality from cancer or leukemia is observed. In short lived mammals, like the laboratory rat, this period is on the order of magnitude of months; in the human, of years. Most workers have referred to this apparently silent period as a *latent period.* It is not at all certain that such a latent period is truly as long as has generally been suspected. What is more likely is that the dose response curve shows at first a gentle slope upward with time, followed by a more steep slope, and then followed by what may be called a "plateau" region (Figure 1a). In studies involving relatively few subjects, the low incidence in the gentle slope region can appear to be a period free of effects, and this may well be why the impression has arisen of a long latent period. In most of the data available for analysis, the quantitative features of this segment of the response versus time curve are poorly defined.

Of additional great importance would be knowledge concerning *duration* of the "plateau" region of the response versus time relationship. Unfortunately, the available data simply do not allow, for any particular malignancy, satisfactory construction of this curve to ascertain how long the "plateau" region persists. For chronic myelogenous leukemia [36] the data suggest that once the excess mortality rate from radiation is perceived, it persists year after year for some 10 to 15 years, whereupon the excess mortality rate drops toward a lower value. In that same study the radiation-induced excess acute leukemia mortality rate showed no significant decline from the peak (or "plateau") value even after 20 years beyond irradiation. In the study on patients with spondylitis treated by X-rays [3], the 15 to 27 year period post-irradiation showed a *higher* excess mortality rate than any earlier periods of observation. There is no evidence within that study, of a return toward spontaneous mortality rates from malignant disease for the irradiated subjects.

Both the Japanese studies and the spondylitis studies should, in the next ten years, provide very valuable clues concerning the *duration* of the plateau region of response. For the present, however, no valid data are available to determine plateau duration. Indeed, and regrettably, the data for experimental animals, with respect to this issue, are no better than the sparse human data. As will be noted in the subsequent discussion of estimating long term population effects of low or moderate dose radiation, the duration of the plateau region is an extremely crucial parameter in determining the human cost expected. Furthermore, the

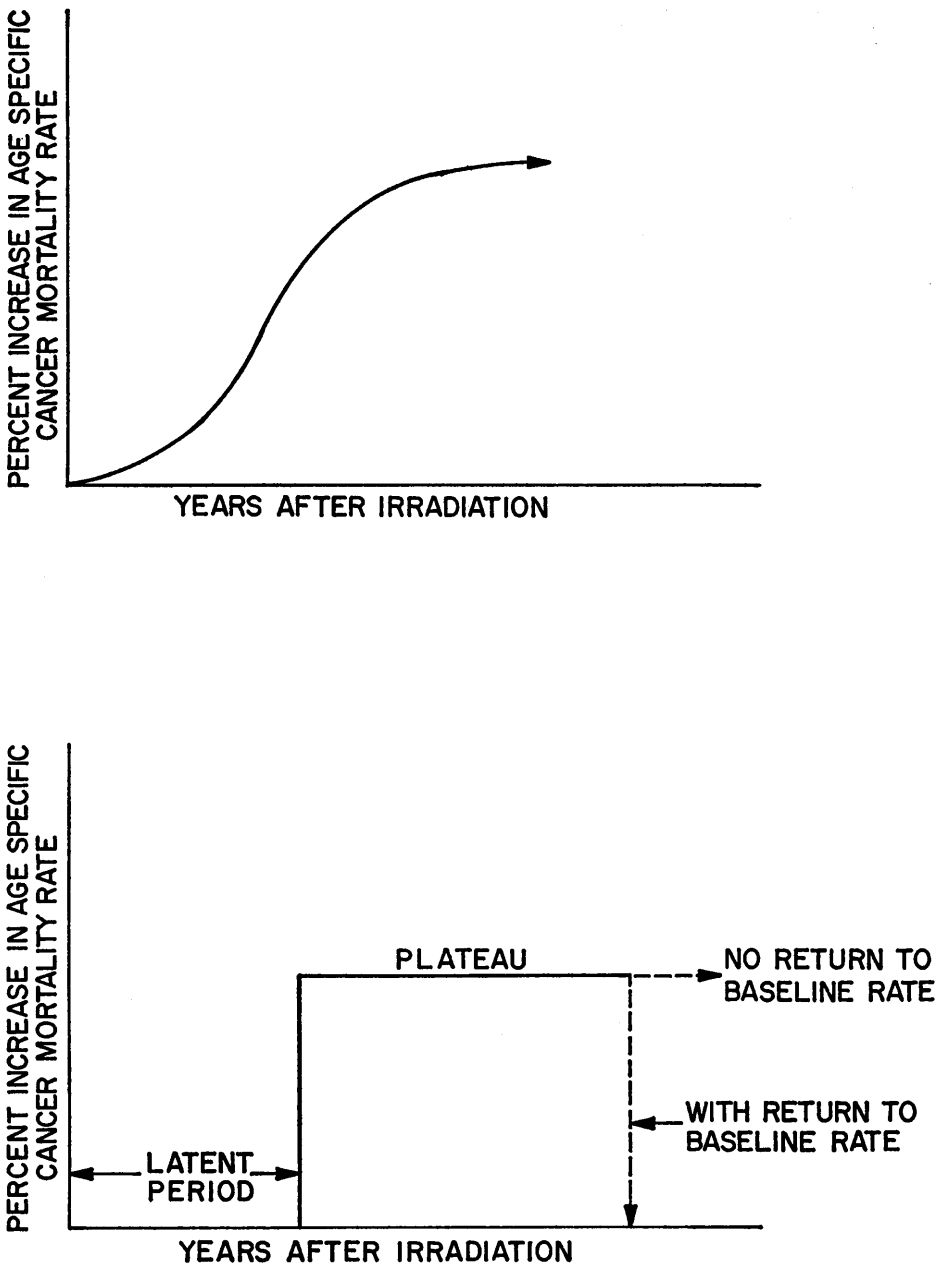

FIGURE 1

Dose response *versus* time curve; actual shown in upper panel, ideal shown in lower panel.

shape of the early part of the dose response curve (the so-called latent period region) is also an important parameter in determining the total magnitude of expected population cost.

In the absence of definitive data on these two issues, we shall idealize such dose response curves using simplifying assumptions which are in reasonable accord with what experience is available. Figure 1b presents such an idealized diagram describing the main features of the dose response relationship. The gently sloping part of the response curve is there replaced by an idealized "zero" response; followed by an abrupt rise to a flat plateau region. The duration of the flat plateau region is then available as a parameter for study, which is all that can be done at this time in the absence of definitive data.

In order to explore the consequences of variation in major parameters (length of "latent period" and duration of "plateau"), the following assumptions will be used:

ASSUMPTION 1. *A single latent period of five years for in utero irradiation is assumed to agree with the estimates of Stewart and Kneale* [30], [31].

ASSUMPTION 2. *A single latent period of* 15 *years is assumed for all forms of cancer for all irradiation beyond birth (except in the extreme case).*

Three general case types will be discussed, first, that with *no* return toward the spontaneous mortality rate (plateau, extending throughout the remaining life span for the population at risk); and second, that with an idealized abrupt return to spontaneous mortality rates after a 30 year plateau region. And third, an extreme case with a latency period of ten years (instead of 15 years) for all postnatal radiation and a plateau duration of 20 years. Both these changes have the effect of reducing the expected consequences of irradiation. We refer to such cases as "extreme" because it appears doubtful that the gently sloping part of the dose response curve is any shorter than ten years for the majority of radiation-induced malignancies (aside from leukemia, which *appears* shorter than all others), and second, because what evidence is available suggests that the plateau region is most likely to be *greater* than 20 years in duration.

It is essential to consider the manner of description of the radiation-induced excess age specific mortality rates. Commonly, results are presented either as excess cases per 1000 population at risk, or as the percentage increment in cancer mortality over the spontaneous age specific mortality rates. In some cases data are available for individual malignancies; in others, all cancers are presented as a sum. There is no theoretical reason for preference of absolute or percentage increments in age specific mortality rates. Both expressions suffer the defect that data derived from one population sample (for example, Japanese subjects) may not be directly applicable to another population sample (for example, United States subjects). We are far, far from having sufficient epidemiologic data to address such questions.

We have mentioned earlier the desirability of having age specific mortality rates for all ages of interest. We are far from that goal. Instead, available to us are radiation-excess mortality rates over a span of years of observation of exposed

population samples. Therefore, expressed either as absolute or per cent increment in mortalities, the data allow only an average value for this span of years. In the absence of further evidence, we are here treating the plateau region as a *fixed* percentage increment in cancer mortality per unit of radiation over the *entire plateau region*. Only extensive further data can definitively test the validity of this particular approach. In its favor is the conservative nature of this treatment for public health purposes. Let us consider the implications of this treatment. Since *spontaneous* age specific cancer mortality rates change with age (rising steeply with age beyond 20 years), the assumption of a *fixed* percentage increment for radiation-induced excess over the whole plateau implies that the *absolute* increase in age specific mortality rate induced by radiation also changes with age. Thus, if the plateau region represents a 50 per cent increase in mortality rate, there will be 1000 extra deaths per 10^6 persons per year where the spontaneous mortality rate is 2000 deaths per 10^6 persons per year. At a later age, with a spontaneous mortality rate of 4000 deaths per 10^6 persons per year, the *absolute* increment due to radiation would be 2000 deaths per 10^6 persons per year. Thus, a constant percentage increment in the plateau response region *implies* that absolute radiation-induced age-specific mortality rate increments will increase over a span of ages.

"Spontaneous" cancer mortality rates include all known and unknown causes of cancer. Therefore, in an epidemiologic study, radiation-induced cases resulting from natural radiation background plus medical radiation exposures are included in the "spontaneous" cancer mortality rates for the population sample under study. Thus, if calculations are presented concerning the percentage increase in cancer mortality rate per rad of *additional* exposure to such a population, the true "spontaneous" base rate must be lower than that which includes the radiation effect from such sources as medical or natural radiation. Therefore, the true radiation percentage increment per rad is actually larger than that presented. For calculational purposes this does not introduce any significant complications. However, if the effect per rad is high, then the observed per cent increment per rad is *stated* to be lower than it truly is, simply because the spontaneous rate already is inflated by that mortality due to natural plus medical (and other) radiation for the population sample under study.

1.2.2. *Dose response relationships over a range of doses.* One cannot be certain that the time aspects of the dose response relationship are identical over all dose ranges to be considered. Earlier impressions have been that the "latent period" (the gently sloping region described in Section 1.2.1.) might be longer at lower radiation doses. This speculation was weakly supported, if at all. The kind of study which led to this impression of a longer latent period at lower doses generally included small population samples at the lower doses, such that the expectancy of cancer at the low doses was often measured as a small fraction of one case [37]. Under these circumstances the probability of observing zero cases, in a small population sample, is very high. The *observation* of zero cases led to the false impression of a long latent period. In this manner the myth arose, concern-

ing "practical thresholds" at low doses, that low doses of radiation might not be carcinogenic simply because the latent period could exceed the life span of the exposed population. Finkel and co-workers [6] recently demolished this myth very effectively, based upon a study of some 3200 mice exposed to radium 226. They saw no evidence of a variation in latent period with dose and indicated that they believed no other investigators would see variation either if they had an *adequate* population sample in the low dose region.

In the absence of any evidence to the contrary we shall assume latent periods and duration of plateau to be *independent* of the dose range under consideration. We shall, further, consider the effects calculated in the plateau region of the idealized diagram of Figure 1b. The epidemiologic data available cover a wide range of doses of radiation, with much of the human data, at least up to recently, having been obtained at moderate or high doses. Our interest, for purposes of evaluation of radiation is, in general, for doses in the low to moderate range. It is, therefore, essential to know the nature of the dose response curve over a wide range of doses if the epidemiologic data are to be utilized for predictive purposes in the case of population exposures.

A priori, in such problems, there is no way to predict the nature of the dose response curve. In principle, three generalized dose response patterns, connecting observations at high doses with those to be anticipated at low doses are conceivable (see Figure 2).

Curve A may be taken as one representative curve of a family of curves that are convex upward. Clearly, curves of this family express pessimism in that they predict a higher response at low doses than would be anticipated from a linear dose response relationship, such as curve B. Curve C, on the other hand, is a representative of a family of curves concave upward. This curve may be considered the "optimistic" curve from the viewpoint of a radiation-associated technology. The optimism arises because there can be a low dose region where the excess mortality due to radiation may be extremely low.

Early in the history of study of radiation carcinogenesis data were available, for humans and experimental animals, only for the fairly high dose region, and the shape of the entire curve down to very low doses was unknown. During that period, most responsible scientists and radiation study groups such as the International Commission on Radiological Protection made the prudent assumption of a linear relationship of radiation dose versus excess cancer mortality rate (curve B). While this did represent a conservative approach consistent with sound public health principles, it must be emphasized that this was by no means the *most* conservative position. Any of the family of curves, represented by curve A (Figure 2) represents a *more* conservative relationship for connecting available high dose points with the low dose region. But all these considerations describe an era that is now past. Abundant new data, in humans and experimental animals, have now become available, permitting description of the dose response relationship over a wide range of doses. These new data all point unmistakably to the correctness of curve B, the linear relationship between

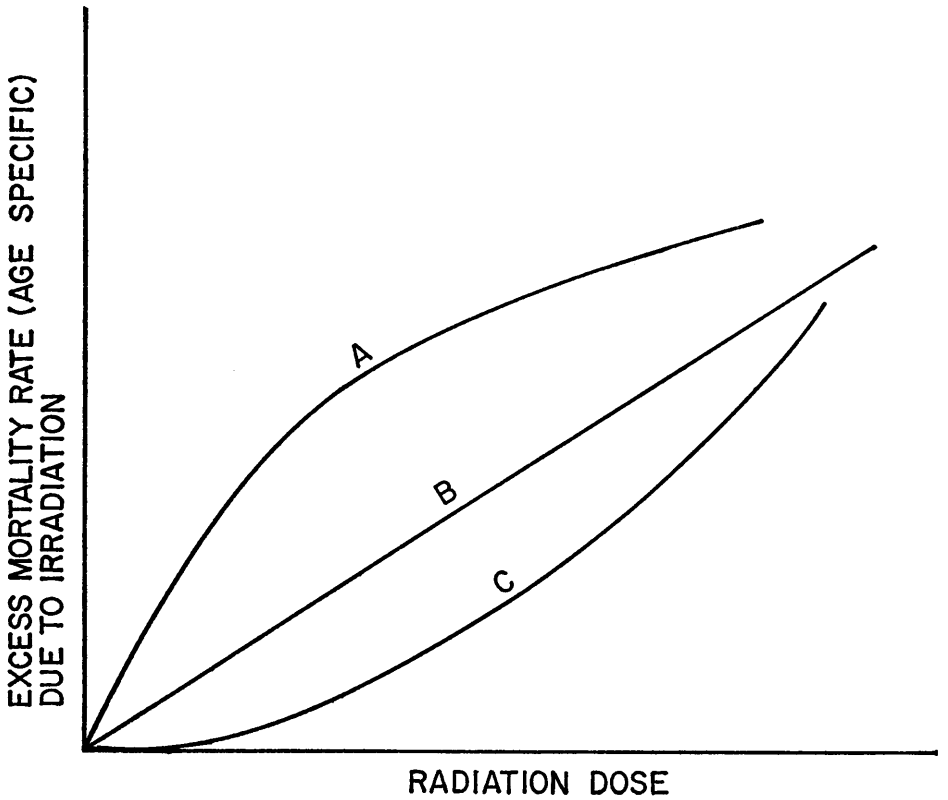

FIGURE 2

Three generalized dose response patterns: (A) higher response at low doses; (B) linear dose response relationship; and (C) low response at low doses.

excess cancer mortality and radiation dose, over a very wide range of doses for a variety of cancers and benign tumors. While one can understand the disappointment of radiation-industry promoters over the disappearance of the fondly regarded curve C, it is not possible to condone their lack of appreciation of the existence of all this new evidence.

Let us consider the specific new evidence that has appeared in recent years. (1) Shellabarger, Bond, Cronkite and Aponte [28] have demonstrated linearity both for breast adenocarcinoma and breast fibroadenoma development in rats exposed to X-rays or gamma rays down to total doses of 15 rads. (2) Upton and co-workers [34] have demonstrated linearity for mouse mortality from thymic lymphoma down to total doses of ten rads. Studies at lower doses are in progress. (3) Finkel, Biskis, and Jinkins [6] have demonstrated linearity for osteosarcoma development in the mouse with radium 226 injection over a wide range of doses. This is a landmark study, since it is refreshingly characterized by the experi-

mental design of providing an adequate number of experimental animals in the low dose region. The authors [7], [8] have pointed out the fallacious conclusions derived from the study of inadequate numbers of humans, exposed to radium 226, who developed osteosarcoma. (4) Hempelmann [16] has indicated linearity in the production of human thyroid adenomas by X-rays, including data points down to 20 rads total dose to the thyroid gland. (5) Beebe, Kato, and Land [1] have extended the leukemia studies in survivors of the Hiroshima-Nagasaki bombings. They have demonstrated linearity in the production of human leukemia with radiation dose, down to total doses of 20 rads. (6) Stewart and Kneale [31] have demonstrated linearity between cancer and leukemia induction in children during the first ten years of life and irradiation by X-rays *in utero* in the process of diagnostic obstetric radiography. Their observations covered the range of approximately 2.0 rads, thus providing direct human evidence in the extremely low dose region. (7) Mays and Spiess [29] have demonstrated linearity in the production of osteosarcoma both in human adults and children as a result of radium 224 injection. Their experimental data extend down to 90 rads estimated dose. These studies are grossly at variance with the claims of Evans [36] of a "threshold" for osteosarcoma in humans by alpha emitters at a dose of 1000 rads.

Taken overall, these recent and diverse publications leave very little reason to doubt a linear dose response relationship for cancer and leukemia induction by radiation. It has been an interesting phenomenon, indeed, to observe the antics of the promoters of radiation-associated technologies during the evolution of all these data. Starting with their hope that linearity would fail below 100 rads, they have been forced to retreat steadily to 50 rads, then 25 rads, and now they find themselves faced with linearity down to the region of a fraction of one rad. Hope springs eternal.

To be sure, for any particular set of data, one could always argue that *perhaps* there is a deviation from linearity somewhere below the dosage represented by the lowest experimental point. There exists, however, no rational support for such an assumption, since it would require a fundamental change in the mechanism of radiation carcinogenesis in the region below the linearity region. Further, such an assumption, in the *absence* of evidence supporting it, represents an unsound approach to the protection of the public health. The *in utero* data [31] extending down to approximately 0.3 rads, militate strongly against further serious consideration of nonlinearity in the very low dose region.

From the point of view of mechanism, linearity between radiation dose and carcinogenic response suggests that a single event phenomenon is involved in the production of the critical change which results in the development of cancer. If a single event produces the carcinogenic change over a wide range of doses, for a variety of cancers, for several mammalian species, there appears little reason to expect a fundamental change in such mechanism at still lower doses.

Since linearity appears well established for a variety of cancers, we shall here consider the dose response relationship, in the plateau region, as being linear for

every type of cancer and leukemia (Figure 3) for prediction purposes. The excess age specific mortality rate, for any cancer, can be expressed, for a linear dose response relationship, as a percentage increase per rad over the spontaneous mortality rate for that particular cancer. Such percentage increment is simply the slope of the linear plot of Figure 3. For illustrative purposes, assume the slope, for a particular cancer, were determined to be one per cent per rad. It follows then, for a linear relationship, that 100 rads will produce 100×1, or a 100 per cent increase in cancer mortality above the spontaneous cancer mortality rate. That dose which increases the spontaneous cancer mortality rate by 100 per cent is commonly *defined* as one doubling dose of radiation for production of that particular cancer. Thus, if a is the slope of the line in Figure 3, then the doubling dose is defined as $100/a$ (for this particular cancer). The doubling dose notation does *not* in any way imply a geometric progression in excess cancer mortality rate with increasing radiation dose. Rather, one doubling dose adds 100 per cent to the spontaneous age specific mortality rate, two doubling doses add 200 per cent, three doubling doses add 300 per cent, and so forth. It is simply a matter of convenience as to whether radiation carcinogenesis, for any particular cancer, is described as the per cent increment in cancer mortality rate per rad or as the

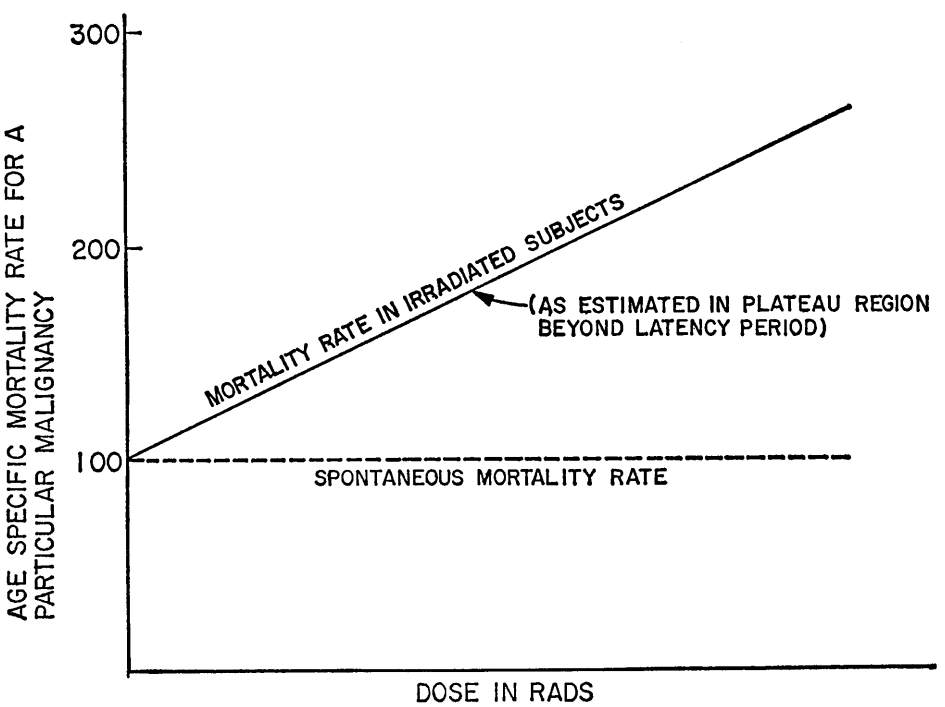

FIGURE 3

Linear dose response relationship in the plateau region where the age specific mortality rate is a percentage increase per rad.

dose in rads, the doubling dose, required to add an *excess* mortality rate equal to the spontaneous age specific rate. Nothing about the doubling dose notation infers or suggests that the doubling dose is the same for all forms of cancer. This is a matter for experimental evidence to decide. Before considering the question of variation of doubling dose with form of cancer induced, it is necessary to turn our attention to the variation in sensitivity to radiation carcinogenesis with age at irradiation.

1.2.3. *Variation in carcinogenic dose response relationship with age at radiation exposure.* Our considerations thus far have led us to description of radiation carcinogenesis as follows: (1) *dose response relationship, at a specified age, is linear* (Figure 3), *characterized by a particular percentage increment in cancer mortality per rad for a particular form of cancer;* and (2) *dose response relationships will be treated for the idealized "plateau" region of the curve of the response* versus *time after radiation exposure.*

For any particular cancer, occurring *at a specified age,* how does the slope of the dose response line vary with *age at irradiation?* It is clear that any refined effort to assess population response to continuous or intermittent radiation exposure required consideration of this particular question. To the best of our knowledge there exists no theory that provides the answer to this question. We must, therefore, have recourse to empirical data.

First, we have the data for *in utero* radiation provided by Stewart and Kneale [30], and MacMahon [22]. These data, presented in Table I, describe the increase in cancer and leukemia mortalities during the first ten years of life following irradiation *in utero.* Inspection of the data leads to a best estimate of a 50 per cent increase in mortality rates for a variety of cancers and for leukemia for radiation associated with diagnostic pelvimetry. The similarity in percentage increase in cancer mortality for diverse cancers and for leukemia, for such radiation, is striking. Stewart and Kneale [31] indicate that approximately four X-ray films lead to 100 per cent increase in such childhood cancers and leukemia mortality rates. During the period of accumulation of their evidence, each X-ray film represented less than 0.5 rad delivered to the infant *in utero.* Conservatively, therefore, one estimates that two films, or 1.0 rads, are required for an approximate 50 per cent increase either in cancer or leukemia mortality rates. (The true value may be somewhat higher than the conservative 50 per cent increase per rad.)

None of the Stewart studies address the issue of effects of *in utero* radiation upon the development of cancer or leukemia beyond the first ten years of life. Both from the Hempelmann studies [16] and the Hiroshima-Nagasaki studies (Jablon and Belsky, [19], involving the irradiation in early infancy, we have conclusive evidence that carcinogenesis extends far beyond the first ten years of life. It would be surprising, therefore, if such were not the case for *in utero* irradiation as well. In any event, our treatment of the data for estimating population exposure specifically explores the effect of various durations of the plateau response region. Utilizing the Stewart-Kneale and MacMahon data, we shall use

a 50 per cent increase in age specific cancer mortality rates per rad for irradiation received *in utero* and shall assume this value holds for all cancers and leukemias.

For infancy and childhood irradiation, there are two major sources of information: (a) data for thyroid cancer induction in U.S. children irradiated in early infancy; and (b) data for various cancers in Japanese subjects in Hiroshima and Nagasaki, who were between 0 and 9 years of age at the time of bombing.

For the thyroid cancers occurring in irradiated children, Pochin [26] provided an estimate that the absolute increment is one case per 10^6 persons per year per rad of exposure of the thyroid gland. Carroll, Hadden, Handy and Weeben [2] reported the spontaneous thyroid cancer rate as approximately five to ten cases per 10^6 persons per year in the age range 10–20 years. Combining these data, we have previously estimated 10 to 20 per cent increase in thyroid cancer per year per rad for irradiation in infancy. (Gofman and Tamplin, [9]).

Jablon and Belsky [19] have recently provided data for cancers (other than leukemia) in persons exposed to atom bombing at 0–9 years of age. For those receiving 100 rads or more, the cancer mortality rates (during the period 10 to 24 years beyond exposure) was 8.4 times that observed for persons receiving less than 10 rads. The mean dose for the (100 rad or more) group was not given, but it must lie between 100 and 200 rads. So, 100 to 200 rads represent 7.4 doubling doses ($8.4 - 1.0 = 7.4$). Therefore, the doubling dose for cancer production in these 0–9-year old children (at exposure) lies between 14 and 28 rads. This corresponds to a 3.5 to 7.0 per cent increase in cancer mortality rate per rad. The per cent increment in leukemia mortality rate per rad was even higher, as observed in a group of children 0 to 14 years of age at the time of bombing [19]. A variety of cancers were represented in the Jablon and Belsky data, but the limitations of numbers did not allow for treatment of individual types of cancers, (see also [20]).

From several sources, data are available concerning the percentage increase in specific site cancer mortality rates per rad for persons irradiated in early adulthood [32]. These include data for subjects receiving radiation under widely different conditions. Included are: (1) breast cancer (Nova Scotia women [23] receiving fluoroscopic radiation and Japanese survivors of atomic bombing); (2) thyroid cancer (Japanese survivors of atomic bombing); (3) lung cancer (spondylitis cases and Japanese survivors of atomic bombing); (4) leukemia (spondylitis cases and Japanese survivors of atomic bombing); (5) stomach cancer (spondylitis cases); (6) colon cancer (spondylitis cases); (7) pancreas cancer (spondylitis cases); (8) bone cancer (spondylitis cases); (9) lymphatic and other hematopoeitic organ cancer (10) miscellaneous cancers (spondylitis cases); and (11) pharynx cancer (spondylitis cases).

The range of values determined for percentage increase in cancer mortality rate per rad of exposure was between one and five per cent with an estimated best value of approximately two per cent per rad. Ideally, one would want to have these values determined for groups irradiated at a specified age, and one would

wish to be certain that the observations were strictly referable to the plateau region of the response *versus* time curve, rather than possibly including some data referable to the latent period. But such ideal data are unavailable. Hence, we shall use a two per cent increase in cancer mortality rate per rad as a "best" value, we shall consider that it applied to all cancers (the major ones are all represented in the data), and we shall relate this value to irradiation at approximately 20 to 30 years of age. As will be noted below, the overall data indicate the sensitivity to cancer induction when expressed as the per cent increase over spontaneous cancer mortality rates per rad of exposure, is a steeply declining function of age at irradiation. Therefore, it is entirely possible that the range of one to five per cent increase in cancer mortality rate per rad might be narrowed appreciably but for differences in age at irradiation for the young adult groups tabulated. Inaccuracies in dosimetry may also account for part of the range of values observed. In any event, the average value of two per cent per rad for irradiation in the age range of 20–30 years will be seen below to be consistent with trends noted over a very broad span of ages at irradiation.

Beebe, Kato and Land [1] have recently presented data for cancer mortalities during the 1962–1966 period for Hiroshima-Nagasaki survivors who were between 25 and 55 years of age at the time of bombing (1945). It appears quite clear, from their studies, that there is a *markedly* lower sensitivity for cancer induction per rad compared with that for younger subjects. These workers estimate a 20 per cent increase in cancer mortality risk per 100 rads, or 0.2 per cent per rad for this older group of subjects.

Summarizing all the evidence just described, we have the following estimates of sensitivity to radiation-induction of cancer and leukemia as a function of *age at irradiation:*

in utero	~50% increase in mortality rate per rad
0–9 years of age	3.5–20%
20–30 years of age	~2%
~50 years of age	~0.2%

There can be no doubt that risk of induction of excess cancer mortality rates per rad, described as per cent increase over spontaneous mortality rate, declines steeply with increasing age *at* irradiation. Within the totality of available epidemiologic evidence now available the estimates just listed provide about as much description of this declining function as is now possible. For purposes of estimation of the consequences of population exposure, these estimates can be reasonably approximated by the step function presented in Table IV. It can be shown that the precise values in the step function are *not* the dominant parameters that determine the consequences of population exposure. Of far greater importance is the *duration* of the plateau region of the response *versus* time curve.

TABLE IV

VARIATION IN CANCER INDUCTION PER RAD WITH AGE

These estimates represent a step function approximation in reasonable accord with the data points available in the text.

Age at irradiation (years)	Increase in cancer mortality rate *per rad* (in Plateau Region) (per cent)
In utero	50
0–5	10
6–10	8
11–15	6
16–20	4
21–30	2
31–40	1
41–50	0.5
51–60	0.25
61 and beyond	Assumed negligible

2. The carcinogenic consequences of population exposure to environmental ionizing radiation

The major parameters required to evaluate the consequences of population exposures to ionizing radiation have been identified in the foregoing discussion. That the epidemiologic data are far less than ideal for quantitative evaluation is undeniable. A humane society should consider itself fortunate that better data are *not* available.

The various sources of potential ionizing radiation exposure include natural radiation, radiation from weapons testing fallout, radiation from a variety of peaceful atomic energy programs, and radiation from diagnostic medical and dental exposure. Since the signing of the atmospheric test ban treaty, weapons testing fallout has become a small source, and should decline further, unless nonsignatories to that treaty increase weapons testing appreciably.

Peaceful atomic energy programs are currently *allowed* to deliver an average dose of 0.17 rads per year to the U.S. population. At present, so far as measurements allow dose estimates, it appears that such programs deliver only a small fraction of this "allowable" average dose. Nevertheless, with the burgeoning growth of the nuclear electric power industry plus numerous proposals for utilization of "peaceful" nuclear explosives (Project Plowshare) plus growing radioisotope utilization, the exposure to the population from the "peaceful" atom will undoubtedly grow. So long as 0.17 rads per year remains permissible by Federal Regulations, there is good reason to believe the full exposure may ultimately be reached. It is, therefore, of special importance to calculate the

cancer and leukemia expectation for such an average exposure to the U.S. population.

Medical and dental exposures to X-rays have resulted in a steadily increasing average population dose of ionizing radiation. Medical diagnostic X-ray exposure has recently been estimated to provide approximately 0.10 rads as an average population somatic tissue dose (Morgan [25]). We are in full accord with Morgan that advantage should be taken of modern technology to reduce such exposure drastically, especially since Morgan has estimated that a ten-fold reduction in average exposure could be accomplished without any loss in diagnostic X-ray information.

Natural radiation provides an average population exposure in the neighborhood of 0.125 rads per year. Such features as radioactivity content of building materials, radioactivity in rocks of the earth, and elevation above sea level account for variation in such natural doses among population subsamples. Through a strange system of logic, or better, illogic, it is commonplace for promoters of radiation-associated technologies to arrive at the wholly absurd conclusion that doses comparable to natural radiation cannot be carcinogenic because natural radiation "has always been with us."

The above sources of ionizing radiation represent primarily low Linear Energy Transfer (LET) radiation. Primarily the radiations are X-rays, gamma rays, and beta rays. Carcinogenic effect per rad will be essentially identical for all these radiation sources. One could estimate population consequences per millirad per year, for natural radiation exposures, for medical exposures, or for the 0.17 rads per year permitted as an average population exposure for peaceful atomic energy activities. Since the concern of this Symposium is with matters related to environmental pollution, it is particularly appropriate to estimate the consequences of the 0.17 rad per year average allowable population exposure. The U.S. Government [5] has decreed this much population pollution to be permissible (Federal Radiation Council, 1960). The scientific and lay communities should be especially interested in the carcinogenic consequences of this permissible pollution by ionizing radiation. It should be evident that the consequences of natural, medical, or weapons fallout exposures can be derived from the consequences of 0.17 rads per year by direct application of the linearity of dose *versus* response.

We have previously estimated the cancer plus leukemia consequences of exposure to 0.17 rads per year to be approximately 32,000 extra cancer plus leukemia deaths per year, at equilibrium, for the U.S. population at its current size of 2×10^8 persons, [10], [11]. That estimate was based upon the average two per cent increase in cancer mortality rate per year per rad of exposure observed for young adults, coupled with a 30 year duration of the plateau region. With the more extensive data available in the past year concerning sensitivity variation with age, a more refined estimate is now possible. Moreover, it is important to explore the implications of both a longer and shorter duration of the plateau region, as well as the implications of variation in "latent" period. As

we shall see, the estimate of 32,000 extra deaths per year is by no means overly conservative, since this number can rise several fold if it turns out that the plateau region extends throughout the life span of exposed populations.

2.1. *Cancer hazard for average population exposure (total body irradiation) at 0.17 rads per year.* Three general cases will be considered here, the case where the plateau persists indefinitely after latent period, where the plateau region persists 30 years with subsequent return to spontaneous cancer mortality rates, and the extreme case where the plateau region persists 20 years with a latent period of 10 years for post natal radiation (in contrast with 15 years for the first two cases).

CASE 1. *Plateau persists indefinitely after latent period.*

The calculation is based upon the consideration of the total per cent increment in radiation-induced cancer mortality rate at a particular specified age as made up of the sum of contributions from radiation received at ages less than the specified age. The procedure will be illustrated below.

For *in utero* irradiation we have stated above that a five year latent period will be assumed.

In Case 1 calculations, a 15 year latent period is assumed for all post natal irradiation.

Radiation received in any particular year of life begins to contribute to cancer mortality rate only after the latent period is over. Thus, radiation in the first year of life *starts* contributing to cancer mortality in the 16th year of life. Radiation in the 10th year of life starts contributing to cancer mortality in the 25th year of life.

For *in utero* irradiation at 0.17 rads per year, approximately 0.12 rads would be received in the course of a pregnancy. At 50 per cent increase in cancer mortality rate per rad, we calculate 50×0.12, or a six per cent increase in cancer mortality rate for the *in utero* radiation exposure. Now, since we have assumed a five year latent period for *in utero* radiation, there is obviously *zero* cancer mortality increment during the first four years of life. For the fifth year of life and beyond, however, the six per cent increment in cancer mortality rate would apply for each year that the plateau region persists. In Case 1, under consideration here, this would be for the remainder of the life span of the exposed population.

For irradiation in the first year of life (0.17 rads), the sensitivity factor to be taken from Table IV is ten per cent per rad. Thus, $10 \times 0.17 = 1.7$ per cent increase in cancer mortality rate. However, since we are taking the latent period for post natal irradiation to be 15 years, it follows that irradiation in the first year of life does not begin to add its increment in cancer mortality rate until the 16th year of life. For Case 1, this increment would be effective for all subsequent years for the exposed population, since indefinite persistence of the plateau is assumed.

Therefore, for the 16th year of life, there is six per cent from the *in utero* irradiation plus 1.7 per cent from irradiation in the first year of life, for a total

increment of 7.7 per cent in radiation-induced cancer mortality rate. For the 17th year of life, we have 6 per cent from *in utero* radiation, 1.7 per cent from 1st year irradiation, plus 1.7 per cent from the 2nd year irradiation, for a total of 9.4 per cent increment in cancer mortality rate from the irradiation received *in utero* plus the first two years of post natal life.

The increment in cancer mortality for irradiation in each subsequent year of life is calculated in the same manner as the product of the sensitivity factor from Table IV (for that year of life) by the 0.17 rads. The *total* increment in cancer mortality rate for any particular year of life is the *sum* of all contributions *to that year* from irradiation at earlier years, taking into account that no increment is derived until the latent period is over for that particular year's irradiation. In this manner, a value for total per cent increment in cancer mortality rate becomes available for every year of life, taking into account, appropriately, irradiation received at all earlier periods of life. For ease of comparison with *U.S. Vital Statistics*, these annual values are averaged for five year age intervals.

In assessing impact of irradiation upon the population, we can consider just the per cent increase in age specific cancer mortality rate. The values just calculated provide this result. Or, alternatively, and of possibly greater interest, is the absolute increase in number of cancer deaths per year at each age for the population at risk. We are now immediately in a position to make this estimate.

From *U.S. Vital Statistics*, the absolute number of spontaneous cancer deaths per year for each age interval is provided (1966 data used here). Now, let us suppose for a particular age that the combined increment due to all prior radiation is a 15 per cent increment in cancer mortality rate over the spontaneous cancer mortality rate. And let us suppose, further, that for this particular age, the spontaneous cancer mortality rate is 1000 cases per year. The radiation-induced increment is then (15/100) $\times$ (1000), or 150 radiation-induced cancer deaths for the population at this particular age.

In a similar manner, a tabulation of absolute numbers of radiation-induced cancers by age interval can be built up, separately for males and females. Finally, the total annual number of radiation-induced cancer fatalities can be calculated by summation over all age intervals for males plus females. This tabulation, for Case 1 calculations, is provided in Table V. The result, a prediction of some 104,000 annual additional cancer fatalities is more than three times worse than our earlier estimate. We are, of course, not at all surprised at this result, for we had indicated earlier that taking sensitivity as a function of age into account could make for a much more serious prediction. Additionally, Case 1 calculations consider the plateau region to extend indefinitely, whereas our earlier calculations were based upon a 30 year duration of plateau.

It can be further noted that if the real effect is as large as shown in Table V (and no reason exists to reject the Case 1 analysis), then the contribution of natural plus medical radiation must constitute a quite appreciable segment of the so-called "spontaneous" cancer mortality rates. One could consider a second iteration on the total calculation, correcting the "spontaneous" mortality rates

TABLE V

RADIATION-INDUCED CANCER MORTALITY BY AGE AND SEX

5 year latency for *in utero* radiation.
15 year latency for all other radiation.
Plateau constant after latency period.
Exposure: 0.17 rads/year.

Total spontaneous cancer mortality per year = 303,691 cases.
Total radiation-induced cancer mortality per year = 104,259 cases.
Per cent increase in cancer which would occur with 0.17 rads average annual exposure = 34.3 per cent.

Age interval	Per cent increase in cancer mortality rate	Annual spontaneous cancers (male)	Annual radiation induced cancers (male)	Annual spontaneous cancers (female)	Annual radiation induced cancers (female)
(Years)					
0–4	0	827	0	720	0
5–9	6	826	50	606	36
10–14	6	673	40	482	29
15–19	9.4	820	77	546	51
20–24	17.2	754	130	508	88
25–29	23.3	796	186	733	171
30–34	27.8	1,145	318	1,418	394
35–39	30.5	2,104	641	2,890	881
40–44	32.2	4,163	1,340	5,565	1,791
45–49	33.4	7,109	2,372	8,732	2,914
50–54	34.2	12,363	4,231	11,950	4,089
55–59	34.8	17,594	6,123	14,359	4,997
60–64	35.2	22,469	7,909	15,780	5,555
65–69	35.5	25,275	8,968	17,921	6,358
70–74	35.7	25,698	9,169	18,746	6,689
75–79	35.8	21,221	7,589	16,650	5,954
80–84	35.8	13,318	4,763	12,141	4,342
85 and beyond	35.8	7,793	2,787	8,996	3,217
Total		164,948	56,703	138,743	47,556

downward (by subtracting the contribution from natural plus medical radiation) and correcting the per cent increment per rad upward as a result of the lower true "spontaneous" mortality. These two effects would tend to balance out, so that the final calculations of population risk would not be seriously altered. It would, however, point up the major contribution of natural plus medical radiation to the existing cancer mortality rate, wholly aside from increments due to peaceful atomic energy programs.

CASE 2. *Plateau region persists 30 years, with subsequent return to spontaneous cancer mortality rates.*

It is possible that once the increased cancer risk due to irradiation is fully developed (the plateau region), such risk may not persist indefinitely. It is difficult to know, within presently available epidemiological data, how many

years the plateau lasts, if it does indeed only last a limited period for cancer. A calculation based upon a 30 year plateau period is provided here. In this calculation, the contribution of radiation received in any particular year of life is credited for 30 successive years, following the latent period. After this, the contribution of that particular radiation is cut off. Thus, for example, the per cent increment in cancer mortality rate from radiation received during the 1st year of life begins to be credited starting in the 16th year of life, and is credited for each subsequent year of life out to the 45th year of life. Beyond the 45th year of life, no crediting toward radiation-induced cancer mortality is given for irradiation in the first year of life. Similar calculations are made for irradiation in each subsequent year of life. Otherwise, procedures of calculation are similar to those for Case 1, Table V (five year latent period for *in utero* radiation; 15 year latent period for all post natal irradiation). The calculations for Case 2 are presented in Table VI.

TABLE VI

CASE 2: RADIATION-INDUCED CANCER MORTALITY BY AGE AND SEX

5-year latency period for *in utero* irradiation.
15-year latency period for all other irradiation.
Plateau: 30 years beyond latency period.
Exposure: 0.17 rads/year.

Total spontaneous cancer mortality per year = 303,691 cases.
Total radiation-induced cancer mortality per year = 74,013 cases.
Per cent increase in cancer which would occur with 0.17 rads average annual exposure = 24.4%.

Age interval (years)	Per cent increase in cancer mortality rate	Annual spontaneous cancers (male)	Annual radiation-induced cancers (male)	Annual spontaneous cancers (female)	Annual radiation-induced cancers (female)
0–4	0	827	0	720	0
5–9	6	826	50	606	36
10–14	6	673	40	482	29
15–19	9.4	820	77	546	51
20–24	17.2	754	130	508	87
25–29	23.3	796	185	733	171
30–34	27.8	1,145	318	1,418	394
35–39	24.5	2,104	515	2,890	708
40–44	26.2	4,163	1,091	5,565	1,458
45–49	26.0	7,109	1,863	8,732	2,288
50–54	25.4	12,363	3,140	11,950	3,035
55–59	24.9	17,594	4,381	14,359	3,575
60–64	24.6	22,469	5,527	15,780	3,882
65–69	24.4	25,275	6,167	17,921	4,373
70–74	24.6	25,698	6,322	18,746	4,612
75–79	24.4	21,221	5,178	16,650	4,063
80–84	24.5	13,318	3,263	12,141	2,975
85 and beyond	24.0	7,793	1,870	8,996	2,159
Total		164,948	40,117	138,743	33,896

It is evident, on comparison of Table V with Table VI, that reduction of the plateau duration provokes a marked drop in the expected mortalities (104,000 down to 74,000). However, both values are extremely high and should raise grave concern about the nature of the societal benefits that might be worth permitting population exposures as high as 0.17 rads per year as the average exposure. No comfort whatever is to be drawn from repeated assurances that abound from nuclear promoters to the effect that "we'll never give you the full allowable exposure" while at the same time they staunchly defend retaining such an allowable exposure. Good intentions are materially aided by codification into Federal Regulations.

The calculations should be especially illuminating to the sponsors of this Symposium addressing the issue of designing epidemiologic studies for the evaluation of societal impact of environmental pollutants. A quarter of a century into the atomic era, the epidemiologic data indicate that our permissible doses could lead to a public health calamity—a 25 to 35 per cent increase in annual cancer mortality rate. No evidence at this time militates against the most pessimistic calculation (Case 1). We have commented elsewhere that this late realization based upon epidemiologic data could all have been averted by judicious use of experimental animal data decades ago (Gofman and Tamplin [11]).

It is of interest to speculate upon possibilities that might have resulted in the Case 1 or Case 2 calculations leading to a serious overestimate of the cancer hazard. For example, one might consider the possibility that dosimetric or other errors had led to an overestimate of the percentage increment in cancer mortality rates per rad at all of the ages listed in Table IV. We believe it is unlikely that such an overestimate could be as much as two-fold. Moreover, one might also, under such circumstances, consider that the seriousness of the results is underestimated as a result of dosimetric errors.

CASE 3. *The extreme case: plateau region persists 20 years, latent period of 10 years; post natal irradiation.*

It is important to ascertain what the prospects for "optimism" may be with regard to carcinogenic consequences of population exposure to radiation. Therefore, we may consider the possibility that the duration of the plateau region of the response *versus* time relationship is materially shorter than 30 years. From the epidemiologic evidence available, admittedly still scanty, we would estimate that it is highly unlikely for plateau duration to be less than 20 years. (Radiation-induced cancers have been described occurring 30 to 40 years after exposure.) But since this should lessen greatly the expected consequences, we shall test here a 20 year duration for the plateau region. It is also evident that if the latent period were shorter than 15 years, the net carcinogenic effect would be reduced further, because the large per cent increments in cancer mortality rate for irradiation early in life would not be carried as far forward into the later age spans where the spontaneous cancer mortality rates are high and, hence, the products of per cent increment by spontaneous mortality rates are also high. The procedure of calculation is precisely the same as that employed for Case 1

and Case 2 except for the alterations in the two parameters, plateau duration and latent period for postnatal irradiation. The results are presented in Table VII. The final estimate for population exposure at an average of 0.17 rads per

TABLE VII

CASE 3: RADIATION-INDUCED CANCER MORTALITY BY AGE AND SEX

5 year latency period for *in utero* radiation.
10 year latency period for all other radiation.
Plateau: 20 years beyond latency period.
Exposure: 0.17 rads/year.

Total spontaneous cancer mortality per year = 303,691.
Total radiation induced cancer mortality per year = 9,428.
Per cent increase in cancer which would occur with 0.17 rads average annual exposure = 3.1%.

Age interval	Per cent increase in cancer mortality rate	Annual spontaneous cancers (male)	Annual radiation induced cancers (male)	Annual spontaneous cancers (female)	Annual radiation induced cancers (female)
(Years)					
0–4	0	827	0	720	0
5–9	6	826	50	606	36
10–14	9.4	673	63	482	45
15–19	17.2	820	141	546	94
20–24	23.3	754	176	508	118
25–29	21.8	796	173	733	160
30–34	21.1	1,145	241	1,418	299
35–39	15.0	2,104	315	2,890	434
40–44	10.2	4,163	425	5,565	568
45–49	6.6	7,109	471	8,732	576
50–54	4.6	12,363	566	11,950	550
55–59	3.3	17,594	577	14,359	474
60–64	2.2	22,469	503	15,780	347
65–69	1.6	25,275	402	17,921	287
70–74	1.2	25,698	311	18,746	225
75–79	1.0	21,221	212	16,650	167
80–84	1.0	13,318	133	12,141	121
85 and beyond	1.0	7,793	78	8,996	90
Total		164,948	4,837	138,743	4,591

year is 9428 extra cancer deaths per year. While this is a marked reduction compared with the estimates for Case 1 and Case 2, the seriousness of such radiation exposure levels is self-evident. We would doubt that a more "optimistic" set of parameters than those for the Case 3 calculation is likely to be justified.

3. Life shortening by radiation-induced cancer

A variety of pronouncements have greeted estimates of the serious carcinogenic hazard of population exposures to doses in the neighborhood of 0.17 rads

per year. One such we have dealt with above, namely, the statement that, after all, this dose is comparable in magnitude with natural radiation, which humans have endured on earth for the entire history of the species. No further comment is required. A second is that even though the calculated cancer deaths may indeed occur, they will occur so late in life as to be inconsequential. Grendon has championed this approach, readily provable to be false, [14]. A variant of this approach is that of Sagan [27] who has pointed out that, even if the calculated cancers did occur, the average life shortening for the exposed population would be very small. In fact, it has become fashionable of late to estimate the deleterious effect of environmental hazards in terms of average life shortening for the exposed population. We hear "Wouldn't people be willing to give up a few minutes, hours, or days of life span so we can all enjoy 'clean, cheap, and safe' nuclear electricity?" This approach to evaluation of life shortening is exceeded in its scientific fallacy only by its immorality in public deception.

If those who die prematurely of cancer due to irradiation are averaged in with those who do not, the *apparent* loss of life expectancy appears quite small. What *really* matters is the average loss of life expectancy for those who *do* develop radiation-induced cancer. Their loss of *decades* of life expectancy is not easily recompensed by a "loan" from those who do not become victims. The losses in life expectancy for the victims are readily estimated. If the victims of radiation-induced cancer had *not* been irradiated, there is *a priori* every reason to assume they would have experienced the usual life expectancy associated with their age group at victimization. Thus, from 1971 estimates, a man at age 25 years has a life expectancy of 45.5 years. If he dies at 25 years of age of radiation-induced cancer, he has lost 45.5 years of life expectancy. In Table VIII are presented the calculated losses of life expectancy by age group for the persons developing radiation-induced cancers, as well as the average loss of life expectancy for *all* the cases of radiation-induced cancers as a group. For males developing radiation-induced cancers, the average loss of life expectancy is 13.1 years. For females, the loss is 13.7 years. Such average losses hardly are in accord with Grendon's assertion that the radiation-induced cancers occur so late in life as to be inconsequential. For men in the age group of 65 to 69 years, the life expectancy (as of 1971) is 11.5 years. If these men lose their life through radiation-induced cancer at 67 years, they have lost 11.5 years. One wonders whether Grendon has checked with such members of the population to ascertain that these "old" people need not care about losing 11.5 years of life.

Let us return to the Sagan view of only a minor loss of life expectancy (hours or days). If the man-years of life expectancy are distributed into the *entire* U.S. male population of 95,919,000 men instead of into the 56,703 victims of radiation-induced cancer, the average loss of life expectancy is computed to be 2.8 days. This practice of hiding the serious loss in life expectancy for the victims of an environmental poison by averaging the loss over the larger group of nonvictims deserves strong condemnation. The sole effect of the practice is to obscure the real hazard of an environmental poison from the public, carried through on

TABLE VIII

LOSS OF LIFE EXPECTANCY FROM RADIATION-INDUCED CANCER
(Data from Table V)

Life expectancies are somewhat higher for females than males, so the use of male life expectancies here leads to a slight *underestimate* of the loss of life expectancy for females with radiation-induced cancers.

Note: The use of data from Table V (the Case 1 estimate) leads to the *lowest* estimate of loss of life expectancy. For Case 2 (Table VI) and Case 3 (Table VII), the radiation-induced excess cancer mortalities are more prominent at earlier ages. Hence, for either of these the life expectancy loss would be appreciably *higher* than the 13 year estimate for Case 1.

Age group (in years)	① Number of radiation-induced cancers	② Average Loss of life expectancy (years)	① × ② (Man-years of loss of expectancy)	③ Number of radiation-induced cancers	③ × ② Woman-years of loss of expectancy
0–4	0	66.1	0	0	0
5–9	50	62.0	3,100.0	36	2,232.0
10–14	40	57.2	2,288.0	29	1,658.8
15–19	77	52.5	4,042.5	51	2,677.5
20–24	130	47.8	6,214.0	88	4,206.4
25–29	186	43.2	8,035.2	171	7,387.2
30–34	318	38.6	12,274.8	394	15,208.4
35–39	641	34.0	21,794.0	881	29,954.0
40–44	1,340	29.5	39,530.0	1,791	52,834.5
45–49	2,372	25.3	60,011.6	2,914	73,724.2
50–54	4,231	21.3	90,120.3	4,089	87,095.7
55–59	6,123	17.7	108,377.1	4,997	88,446.9
60–64	7,909	14.4	113,889.6	5,555	79,992.0
65–69	8,968	11.5	103,132.0	6,358	73,117.0
70–74	9,169	9.1	83,437.9	6,689	60,869.9
75–79	7,589	6.9	52,364.1	5,954	41,082.6
80–84	4,763	5.1	24,291.3	4,342	22,144.2
85+	2,787	~3.0	8,361.0	3,217	9,651.0
Total	56,703		741,263.4	47,556	652,282.3

Average loss in life expectancy (males) $= \frac{741{,}263.4}{56{,}703}$, or 13.1 years.

Average loss in life expectancy (females) $= \frac{652{,}282.3}{47{,}556}$, or 13.7 years.

behalf of the promoters of the technology responsible for the distribution of the poison.

The ridiculous nature of this approach to calculation of loss of life expectancy would be obvious to everyone if we considered an issue like the death of young Americans in Vietnam. After all, when those Americans who are at home are averaged in with those who are killed in Vietnam, the *average* loss of life expectancy is small, the deaths are not tragic, for, on the average, everyone is just losing days from their life. The public would not stand for such nonsense. Why they

are so readily brainwashed by pseudoscientific evaluation of loss of life expectancy for environmental poisons escapes understanding.

4. Are there possible mitigating factors which could reduce the estimated hazard of population exposure?

We have considered above the crucial parameters, such as latent period and duration of carcinogenic response plateau, which can determine in a major way the magnitude of expected population cost. We must address a few other concepts, since the uninitiated may hear that such concepts provide a reasonable basis for expecting a lesser hazard. As will become evident, there is essentially no reason to expect any lessening of hazard. Among these concepts are: (a) a possible threshold, (b) a possible "practical" threshold, (c) protraction of radiation, and (d) repair of radiation injury.

4.1. *Thresholds: absolute and "practical."* In the discussions above it was demonstrated that abundant new data concerning the low dose region of radiation exposure indicate linearity of dose *versus* carcinogenic response over a wide range of doses. There really never has existed *any* acceptable evidence for an absolute threshold of exposure below which radiation carcinogenesis will not occur. It is to the credit of all radiation study groups that they have consistently rejected supposed evidence for radiation thresholds with respect to carcinogenesis. The linearity of dose *versus* response, now demonstrated down to very low doses, indicates there is no reason to expect any evidence for an absolute threshold ever to develop.

One total *non sequitur* has often been introduced into discussions concerning a possible threshold. That concerns the development of signs and symptoms of acute radiation sickness following radiation exposure. Everyone cognizant with this field has known for decades that acute radiation sickness is *not* linearly related to radiation dose, whereas carcinogenesis now appears definitely so related. The underlying mechanism in acute radiation sickness relates to whether or not cell *replacement* can operate rapidly enough to prevent such phenomena as mucosal ulceration or leukopenia. At radiation doses where cellular replacement *is* rapid enough, radiation sickness just does not occur. For carcinogenesis, not a shred of evidence has ever been adduced that cellular replacement can avert cancerous change.

The modification of the threshold concept to the "practical" threshold we have dealt with above. There is no basis for expecting any help from this concept.

4.2. *Protraction of radiation.* It is very commonly stated, with appallingly little evidence, if any, that if radiation is delivered slowly, the carcinogenic effect is lessened. A little later this was modified to the statement that protraction protects against carcinogenesis from low LET radiation (such as beta rays, X-rays, or gamma rays), but not high LET radiation (such as neutrons or alpha particles). A variety of experiments have been cited as direct demonstrations that protraction of radiation affords protection against carcinogenesis, [34].

Almost invariably such experiments contrast acute delivery of radiation *early* in life with protracted radiation extending from early in life through a significant part of the life span of the experimental animal. In some of the specific cases reported, the author has himself demonstrated a marked diminution in carcinogenicity of radiation with increasing age at irradiation [33]. In other studies, this point is entirely neglected. In the material presented throughout this communication the steep decline in carcinogenicity per rad with age in *humans* has been documented. Thus, the most probable interpretation of experiments contrasting acute versus protracted irradiation is simply that protraction provides part of the irradiation *at older* ages and, hence, cancer induction is lessened. All that this re-emphasizes is the extreme seriousness of radiation as a carcinogen early in life. Whether there truly exists *any* residual mitigation from radiation protraction is uncertain within present evidence. Certainly such bodies as the International Commission on Radiological Protection have acted with wisdom, from the public health viewpoint, in refusing to count upon protraction of radiation to lessen carcinogenic hazard.

We feel strongly that it would be appropriate to go further, for any environmental pollutant, and state the following principle: "If under any dosage rate schedule a pollutant shows a certain magnitude of toxic effect, that toxic effect should be assumed to be *at least as high* for any other dosage rate schedule, until and unless definitively proven otherwise."

Adherence to such a public health principle might reduce the danger from those individuals all too ready to spew forth clichés, such as, "Maybe the poison won't be so bad if we give it slowly."

In the carcinogenesis field there is one special circumstance that deserves special consideration here. This is the case, either in humans or experimental animals, of a cancer whose incidence does *not* increase spontaneously in a monotonic fashion with increasing age. While most of the familiar cancers of adult life do show monotonically increasing incidence rates with increasing age, this is not true for several human cancers that occur in childhood (for example, neuroblastoma, Wilms' tumor). Some of these childhood cancers show a peak incidence in the first decade of life and a declining incidence thereafter. There is every reason to suspect that certain cancers of experimental animals may have a similar age related incidence pattern.

Earlier in this communication we presented a generalization (Generalization 1) which stated "the correct way to describe the phenomenon (cancer induction by ionizing radiation) is either in terms of the dose required to double the spontaneous mortality rate for each cancer, or, alternatively, of the increase in mortality rate of such cancers per rad of exposure." Let us consider what might occur if one happened to do dose protraction *versus* acute radiation studies on a cancer having a peak incidence at one age period. If Generalization 1 is correct, then the results obtained by dose protraction could appear to be a lesser incidence of the cancer simply *because* of its spontaneous age incidence pattern, and be wholly unrelated to any "protection" resulting from slow delivery of the radiation. We

suspect that in time such an experiment will be done, and the results misinterpreted, to society's detriment.

4.3. *Repair of radiation injury.* Lastly, we must consider the phenomenon known as "repair." We hear commonly stated that DNA repair mechanisms exist and, hence, low dose radiation may not be as harmful as a carcinogen as had been suspected. No serious student of biology doubts the existence of DNA excision-repair or of such phenomena as light-stimulated thymine dimer repair. However, the *existence* of such phenomena by no means argues in any way for mitigation of radiation carcinogenesis. There is no evidence whatever that has been adduced relating such repair to ionizing radiation carcinogenesis.

When we observe the induction of cancer by ionizing radiation, we are, as yet, totally in the dark concerning the mechanism operative in production of the cancer. Whatever such mechanism may be it is entirely conceivable that a large part of the carcinogenic damage of radiation may get repaired. What we are *observing* is the net, unrepaired carcinogenic damage. The only conceivable way that any such hypothetical *carcinogenic* repair could help at low dose would be for *more efficient* repair to exist at low doses or slow delivery of dose than for high doses or rapid delivery of dose. If the *fraction* of unrepaired carcinogenic damage by radiation were independent of total dose and/or dose rate, then the very existence of any such repair mechanism would be wholly irrelevant as a possible mitigating factor for population consequences of low dose rate exposure. And since (a) we know of no such carcinogenic repair mechanism, and (b) nothing whatever is known about variation in efficiency of an unknown repair mechanism as a function of dose and dose rate, it should be clear that all this represents the sheerest of speculative fancy. The linearity of dose response in carcinogenesis by radiation argues strongly *against* repair of carcinogenic damage at low doses with decreasing repair at successively higher doses.

Injection of speculative fancy into a serious matter of public health protection is irresponsible. Relating DNA repair phenomena to mitigation of carcinogenic injury by radiation, in the absence of any demonstration that these phenomena are in any way related to each other, seems equally irresponsible.

5. A re-look at the purposes of this symposium after consideration of the potential population consequences of low dose radiation exposure

Do we really want to design epidemiologic studies to evaluate the population effects of pollutants, or potential pollutants, past, present, or future? Radiation, to paraphrase many nuclear enthusiasts, is one of the most intensively studied environmental poisons. Yet, for those who have had the patience to read through this communication, certain points, we hope, will stand out. Twenty-five years into the atomic era, and 75 years after Roentgen's discovery of the X-ray, we realize that, while the risk of cancer is high, certain parameters, still not possible to evaluate within present epidemiologic data, may make the cancer risk *more*

than three times higher than our pessimistic estimates of 1969. Are there rational humans who will be able to understand setting an allowable radiation guide for population exposure which may provoke a public health hazard one-third the magnitude of the entire cancer problem? We can only hope that the lessons of the radiation story will lead to a radical change in human approach to the questions of environmental pollutants.

Statisticians and epidemiologists, of course, are inclined to look forward to doing what statisticians and epidemiologists are professionally prepared to do. Unfortunately, this is true also about physicists, chemists, and engineers.

The purpose of this Symposium *implies* that, for the host of potential pollutants now being introduced into our environment, enough epidemiologic evidence will, in the course of time, accumulate so that the statisticians and epidemiologists can do their thing. This means that the statisticians and epidemiologists have capitulated *in toto* to the dictum that progress means we must expose humans to by product poisons of industry in the future as we have in the past. And *then* the effects will be studied. If our radiation experience is any guide at all concerning the time scale over which we will learn the effect of our folly, and there is every reason to believe for carcinogenesis or genetic injury that the time scales will be similar, then the chances for humans surviving this approach are slim indeed.

We think it might have been more important if this gathering of statisticians and epidemiologists had met instead to lend their talents and wisdom to a concerted human effort to work toward to total recycling economy, in which essentially zero pollution is the objective instead of the building up of a reservoir of epidemiologic evidence of the effects of pollutants on humans. Indeed, such a thrust might even lead to the revolutionary idea of "Why do some of these nonsensical activities labelled 'Progress' at all?"

6. Summary

Ionizing radiation is a potent leukemogen and carcinogen. The demand for epidemiologic evidence of human injury has resulted in a belated appreciation of the true magnitude of the serious carcinogenic hazard of population exposure to radiation. Even now, a quarter of century into the evaluation of the epidemiologic evidence, certain parameters of crucial character remain indeterminate. Should these parameters turn out to have unfavorable values, the seriousness of the hazard may truly be even larger than recent pessimistic estimates. We question, therefore, the wisdom of epidemiologic studies of *human* exposure for new potential carcinogens being introduced into our environment.

Refined estimates presented here suggest that our earlier estimate of 32,000 extra cancer deaths per year for exposure to the still permissible 0.17 rads per year (average for U.S. population from the "peaceful" atom) are not at all conservative. The true cancer risk may be closer to 100,000 extra deaths per

year, representing a 30 per cent increase over the current spontaneous cancer mortality. Fortunately, atomic energy programs have not *yet* progressed to a point where such allowable exposure are being experienced.

The National Council on Radiation Protection has recently stated that the current standards for radiation exposure are satisfactory (1971). We would not for one moment challenge the fact that the exposure standards are satisfactory to the membership of the National Council on Radiation Protection any more than we would challenge the concept that possession of 10,000 nuclear missiles is satisfactory for the Department of Defense. What escapes our understanding, however, is how one might go about evaluating the quantitative nature of the nebulous relationship between the interests of the membership of the NCRP and the public's interest in good health.

Medical uses of X-rays presently are a major source of population exposure and are undoubtedly responsible for a significant part of our currently experienced cancer mortality rate. Morgan's suggestions for feasible reduction in medical X-ray exposure, without loss of medical diagnostic information, deserve immediate action [25].

Natural radiation, while in large part not directly within our control, is comparable in responsibility to medical X-rays in the quantitative fraction of cancer mortality rate currently being experienced. No rational basis exists for the frequently heard suggestion that natural radiation can be used as a benchmark for estimation of "safe" exposures. Natural radiation must be estimated as possibly responsible for taking a toll of several tens of thousands of lives annually by premature cancer and leukemia in the USA alone. Here again we must agree with Morgan, that man may decide to look carefully at the radioactivity of certain "natural" building materials before using them for home construction.

Life expectancy loss experienced by those who will become the victims of *allowable* population radiation exposure will average more than 13 years. The assertions of "only a few days of loss of life" are arrived at by the absurd and dangerous practice of distribution of the man-years lost in life expectancy into the larger group of nonvictims of radiation carcinogenesis.

Epidemiologic investigations are extremely interesting and carry, for the investigators, the thrill experienced in solving murder mysteries and other challenging problems. We have extreme doubt that the planning of appropriate epidemiologic investigations for future environmental pollutants is likely to be any real contribution to the public health. There has to be a more rational approach to the question of potential environmental carcinogens—like not introducing them into the environment at all.

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Discussion

Question: David L. Levin, National Cancer Institute

In regard to the cancer/leukemia ratio and the extrapolation of risk down to low levels of irradiation, we have also looked at the Court-Brown and Doll data on spondylitics and the Hiroshima-Nagasaki data. We have found that the cancer/leukemia ratio, when adjusted for difference in dose to the target organs is indeed higher than often quoted. Also, we have made calculations on the lifetime risk of developing cancer from irradiation levels of 170 mrads based upon extrapolations from high dose situations (X-ray therapy and atom bomb) to low dose situations. Using different methodology than that described today, we computed risks to be of the same general level as those shown by Dr. Gofman. We are now continuing our calculations trying to improve our estimate based upon demographic studies.

Reply: J. Gofman

We are, of course, pleased to hear that Dr. Levin and his colleagues arrive at the same general conclusions as we do. This confirms our statement that the so called "radiation controversy" concerning cancer risk is over. Dr. Levin is certainly correct that there are other calculation methodologies. We have tried and presented several approaches. It turns out that, since we all have the same epidemiologic data at our disposal, the rules of arithmetic and algebra require that the same general conclusions will be reached.

Often the issue is confused by those who don't really disagree with the calculation of the cancer hazard. It is just that some people don't worry about adding 100,000 extra deaths per year from cancer. This is more a problem of central nervous system physiology and pathology than it is one of epidemiology.

Question: E. B. Hook, Birth Defects Institute, Albany Medical College

How do the calculations of a presumed increase in tumor incidence following an increase of 0.17 rads per year compare with the known "background" dose of radiation and known tumor incidence?

Reply: J. Gofman

As discussed in the presentation, we would calculate the tumor incidence due to natural background radiation would stand to that for 0.17 rads/year as does 0.125 rads per year to 0.17 rads/year. No one has experimentally or by an epidemiological study segregated the cancer cases due to natural background radiation from so-called "spontaneous" cancer cases. There is every reason to believe that background radiation accounts for its expected share of the total observed cancer mortality rate.

Question: E. Tompkins, Human Studies Branch, Environmental Protection Agency

Would you please explain your statement that there is no reason to believe that the number of films (as reported by Stewart and Kneale) is associated with disease of the mother.

How do you explain the difference in distribution of number of films by trimester?

Reply: J. Gofman

Let us consider first those women who received X-rays specifically for diagnostic obstetric radiography. This group constituted the bulk of the Stewart-Kneal sample. Within this group of women selected to receive diagnostic obstetric radiography, I know of no reason to believe the radiographer would take a number of films, to achieve pelvic dimension measurements, that would be correlated with pre-existing disease in the mother.

With respect to the difference in distribution of film number by trimester, this is not at all surprising. Films taken before the third trimester almost certainly were taken for an indication other than diagnostic pelvimetry. It is commonplace to find that the number of films required for one particular diagnostic purpose may differ from that required for another.

Question: Alexander Grendon, Donner Laboratory, University of California, Berkeley

You answered a previous question by saying that the component of the natural cancer incidence due to background radiation is also multiplied by added radiation. Doesn't this constitute a square law relation rather than the linear relation postulated by you?

Reply: J. Gofman

I have said nothing at all that suggests a square law relationship. I believe the difficulty, Mr. Grendon, resides in your interpretation of what I said. I said that when the cancer mortality increment per rad is expressed as a percentage of the "spontaneous" cancer mortality rate, the "spontaneous" rate incorporates the contribution of natural plus medical radiation. Such expression of the increment is simply a statement of *observation* in a particular population sample. For purposes of determining the real per cent increment per rad over nonradiation "spontaneous" cancer mortality rate, the appropriate procedure would be to subtract out the medical plus natural radiation contribution to the observed "spontaneous" rate. I believe this is adequately clarified in the text. I had no intention of suggesting that additional radiation multiplies the effect of background radiation.

Question: Unnamed discussant

Could you comment on the quality of the Hiroshima data on leukemia as compared to that of Dr. Stewart's data and that of Dr. MacMahon? Is it not true that the effects of trauma, dietary and medical care effects on the population exposed to the bomb radiation as compared to the controls and the subsequent heavy mortality by abortion and congenital defects among the exposed fetuses and infants make these results far more questionable than the studies of infants exposed in peace time to diagnostic X-rays?

Reply: J. Gofman

Yes, I prefer the Stewart and MacMahon data to the Hiroshima-Nagasaki data on leukemia in childhood following *in utero* radiation both for the reasons you cited and for other reasons.

Perhaps we should clarify for the audience what the issue is here. Recently Jablon [48] published data on subjects irradiated *in utero* in the Japanese atom bombings. Jablon indicated that for the exposure received by this population sample, the observed occurrence of childhood cancer and leukemia was far less than that to be expected from the Stewart or MacMahon data. I have several very serious reservations about the Japanese data.

(1) The bulk of the man-rads of exposure in the Japanese sample arises from those cases with very high exposures (100–200 rads). We are all familiar with the observations in experimental studies that, while the carcinogenic dose response relationship is linear over a large range, one does arrive at high doses where the carcinogenic response levels out and then drops drastically. Many refer to this as "the other side of the dose response curve." From the Stewart evidence, it appears that the doubling dose for *in utero* induction of leukemia and cancer is of the order of one rad. This would mean that the bulk of the man-rad exposure of the Japanese sample occurred in infants receiving 50 to 200 doubling doses. There is every reason to suspect that this would place them well over on the "other side of the dose response curve." Hence this factor alone should lead to a lesser carcinogenic/leukogenic response in the Japanese sample than anticipated based upon the Stewart evidence.

(2) The Japanese sample of infants exposed *in utero* was characterized by an enormous mortality during the first year of life. No data are provided concerning the nature of these mortalities. If the risk of subsequent mortality from cancer or leukemia is correlated with risk of mortality in the first year of life (and we know nothing of the existence or nature of such relationships), it is conceivable that the Japanese sample was depleted, by enormous first year mortality, of the most likely candidates for subsequent cancer or leukemia. The discussant, for example, pointed out the issues of dietary and medical care effects in the Japanese sample. This is certainly appropriate, and it is entirely possible that those with enough radiation injury to develop leukemia later may be especially susceptible to earlier death from malnutrition, for example. This effect would not have occurred in the Stewart or MacMahon population samples.

(3) The Jablon data on children exposed between 0 and 9 years of age at the time of bombing show a marked increase in carcinogenic and leukemogenic risk. It would be very surprising that the carcinogenic/leukemogenic risk in the Japanese *in utero* cases would be absent.

(4) I would take serious issue with Dr. John Totter's statement (in discussing Dr. Sternglass' paper this morning) that the Japanese data represent an unbiassed sample compared with the Stewart data. For the obvious reasons listed above, I would draw the opposite conclusion to that of Dr. Totter. In so doing, I agree with the discussant who raised this question.

Question: Prem S. Puri, Department of Statistics, Purdue University

You presented a table showing the mortality figures by age for individuals who were exposed to radiation at Hiroshima, Japan. Do you have some information on the possible radiation effects on the mortality of the descendants in the next generation of these individuals?

Reply: J. Gofman

I believe it is far too early to be able to comment on mortality effects among the descendants of the survivors of the atom bombing in Japan.

Question: J. Martin Brown, Stanford Medical Center

Is it not true that the data of Stewart, Kneale and of MacMahon show that the radiation induced excess over the spontaneous rate has disappeared eight to 10 years after the pelvic X-rays of the fetus? Won't this make a big difference to your calculation of the radiation induced incidence of cancer in view of its marked dependence on the length of the plateau period?

Reply: J. Gofman

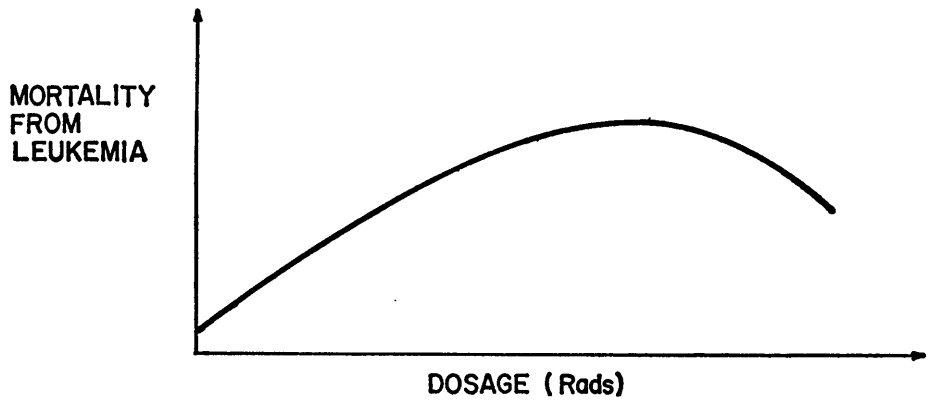
I do not believe that either the Stewart-Kneale or the MacMahon data really allow for one to draw the conclusion that the radiation induced excess disappears at eight to ten years or at any other time, for that matter. I do understand how that impression can have arisen, however. The overall mortality curves (spontaneous) for cancer show a peak at about the middle of the first decade of life and then a decline to a *relatively* low level until the early 20's of age when the upturn begins, due to the appearance of the various malignancies of adult life. In the Stewart-Kneale and MacMahon children the radiation induces the *same* kinds of cancers that occur spontaneously in the children. Since there is about a 50 per cent increase due to obstetric radiography in such cancers and leukemias over their spontaneous occurrence, it is not surprising that the radiation induced cases would show a peaking just as do the spontaneous cases. The decline from the peak among the radiation induced cases gives the *impression* that the radiation induced excess is disappearing. This, I would consider, is totally illusory.

If one could study this phenonmenon into later years (adulthood), radiation induced cases might rise in incidence as the spontaneous incidence rises, and, for all we know, this effect might persist throughout the lifetime of the exposed population. A *very* different study from those of Stewart-Kneale or MacMahon would be required to address this issue. Incidentally, for children irradiated between 0 and 9 years of age, the radiation induced cancers are *rising* in incidence 20 years post irradiation in the Japanese survivors, as would be expected from the rising spontaneous incidence with age increase.

But let us presume the *in utero* effect did decrease after 8 or 10 years. From Table V, the average increase in cancer mortality rate is calculated to be approximately 34 per cent of the spontaneous mortality rate. If the 6 per cent due to *in utero* irradiation is subtracted, the radiation induced rate would be approximately 28 per cent of the spontaneous mortality rate.

Question: B. G. Greenberg, School of Public Health, University of North Carolina, Chapel Hill

I wonder, Dr. Gofman, if the ordinate in your graph, mortality from, say, leukemia, has been adjusted for other deaths on a competitive risk basis. If not, the graph seems to imply that the best protection for a person who has been irradiated is to expose him to an additional overwhelming dose in order to bring his mortality risk down.



Reply: J. Gofman

Of course there would be an increasing mortality with increasing radiation dose for a whole variety of radiation induced causes of death. Among the survivors of the increased dose, the leukemia risk would still be a lower fraction of the total irradiated population than at lower doses. The competitive risk of other mortalities must be considered. If we wish to focus on keeping just leukemia mortality down, I would suggest that execution of the entire irradiated population sample by a firing squad would be even more effective than the supplemental radiation suggested by Dr. Greenberg. (See Figure 2, Curve A.)

Question: Thomas F. Budinger, Donner Laboratory, University of California, Berkeley

Dose rate effect has been shown for *carcinogenesis* [45], *survival* ([42], [41]), and *genetic mutations* [44]. Exposure in the range of 170 mrem distributed through one year is more than 10^6 times less dose rate than the dose rate of exposures from which Dr. Gofman draws his conclusions. Therefore, from a biophysical standpoint it is difficult to accept his figures as applicable to any anticipated population exposure. These studies as well as curvilinear dose response relationships in radiation carcinogenesis (for example, see [46],) suggest some repair mechanism is present. A reasonable assumption is that DNA and chromosomes are involved in somatic and genetic mutation. We now have ample biophysical data to show DNA breaks are repaired very efficiently by at least two cellular mechanisms (for example, see [43]). In fact, the history of radiation damage and successful or unsuccessful repair is readily seen by follow-

ing chromosome aberrations [40], [38]. Radiation insult repair is dependent on linear energy transfer [39] and for high LET exposures we would expect, and indeed find, linear dose effect response and little or no dose rate effect on DNA repair, chromosome aberrations, or carcinogenesis. Thus, only for high LET irradiation is a linear extrapolation valid. If we all were being exposed to neutrons or penetrating high Z charged particles, I would agree with Dr. Gofman's figures. Anticipated radiation exposures are low LET at low dose rates; thus, I do not see a public health threat as great as the threat of trace elements and other man-made contaminants.

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Reply: J. Gofman

I believe I have disposed of Dr. Budinger's major concerns in the body of this communication. A few of the specifics raised by Dr. Budinger are either *non sequiturs* or reflect such unsatisfactory public health principles that they deserve comment here.

(a) Dr. Budinger states that dose rate effect for carcinogenesis has been shown by Upton, [45]. This is simply not true. No studies of Upton are free of the criticism amply discussed in the text that the chronic exposures extend into later life of the experimental animal where sensitivity to carcinogenesis drops. Indeed, the studies of Upton, which Dr. Budinger quotes, are provably suspect on these grounds based upon Upton's own data. (This issue is thoroughly discussed in one of our earlier papers, Gofman and Tamplin [47].)

(b) Dr. Budinger comments that "exposure in the range of 170 mrem distributed throughout one year is more than 10^6 times less dose rate than the dose rate of exposures from which Dr. Gofman draws his conclusions. Therefore, from a biophysical standpoint it is difficult to accept his figures as applicable to any anticipated population exposure."

There *may* be sound grounds upon which our figures are unacceptable, but I truly am surprised that Dr. Budinger states "from a biophysical standpoint" it

is difficult to accept them. It becomes necessary to point out a few biophysical principles to Dr. Budinger.

First, the existence of a linear relationship between carcinogenic response and dose (see references in text) implies, *biophysically*, a single event phenomenon for radiation induction of cancer. This *biophysical* point should remove most of Dr. Budinger's concern.

Second, let us consider Dr. Budinger's factor of 10^6 in dose rate. Especially, let us consider the biophysics involved. Dr. Budinger would appear to be considering that 170 mrem delivered over the course of a year by environmental pollutants delivering low LET radiation to be oozed into tissue at a slow, smooth rate. Unfortunately, the biophysical reality is considerably different from the picture of Dr. Budinger.

Let us consider, biophysically, the delivery of 170 mrem to cells over one year versus delivery in a fraction of a second, as from an X-ray machine. We shall find that Dr. Budinger's factor of 10^6 melts away with great speed.

At 1 MEV or less, X-rays and gamma rays deliver energy to tissues through their photoelectric or Compton conversion to electrons. Therefore, the entire group of low LET radiations (X-rays, gamma rays, β particles) can be covered by consideration of β particle (electron) interaction with cells.

$$1 \text{ rad} = 100 \text{ ergs/gram} = 6.25 \times 10^7 \text{ MEV/gram.}$$

Let us consider 1 MEV β particles as representative.

This means 1 rad represents 6.25×10^7 β particles delivering their energy per gram of tissue.

The range in tissue for 1 MEV β particles is approximately 4000 microns.

For a cell of 20 micron diameter, a 1 MEV β particle traverses 200 cells, on the average. Therefore, 6.25×10^7 β particles traverse 1.25×10^{10} cells.

For cells of approximately 20 micron diameter, volume is approximately $4 \times 10^3 \mu^3$, and 1 gram of tissue represents approximately $10^{12} \mu^3$.

So there are $10^{12}/(4 \times 10^3) \cong 2.5 \times 10^8$ cells per gram of tissue cells.

If one rad represents traversal of 1.25×10^{10} cells, then each cell is traversed $(1.25 \times 10^{10})/(2.5 \times 10^8) = 50$ times.

Therefore for 170 mrads, each cell is traversed $(0.17)(50) = 8.5$ times on the average.

Each traversal of a cell by a single beta particle occurs in a time frame of a fraction of a second. Now, if we are to compare *equivalent doses*, 170 mrads, delivered instantaneously versus over the span of one year, for the same kind of radiation, for example, 1 MEV β particle (the same would be true for X-rays or gamma rays), it follows, obviously that the exact same number of β particles, on the average, must traverse the cells whether instantaneously or over the span of a year. For the instantaneous delivery, let us assume all the β particles (between 8 and 9 of them, average 8.5) all are delivered together exciting effects over a short interval, t (time frame, seconds or less). For the one year delivery, there will still be 8.5 β particles delivered per cell, and *each* β particle will exert effects

in precisely the same short time interval, t, except that the individual events will be separated from each other by a little over a month, on the average. Therefore, the "slow" delivery, so far as cellular events are concerned occupies (8.5 t) instead of t. Therefore, the maximum *real* difference in rate of delivery of energy to the cell is 8.5 fold. Thus, Dr. Budinger's "factor of 10^6," drops to a factor of 8.5, a drop of more than 100,000 fold. The interjection of the issue of about a month between events is a red herring. I do not believe that, for carcinogenic events occurring 5 to 25 years later, Dr. Budinger would argue that irradiation in September of a particular year would be much different from irradiation in May.

In all likelihood, even the factor of 8.5 fold is illusory. For a single cell, not all of the 8 or 9 events occur in the same region of the cell's volume. For a *particular* region within a cell receiving irradiation, 170 mrads may, therefore, represent the effect of only *one* β particle traversal, *not* the traversal of 8 or 9. So the *actual* time frame of events for the cellular level may be precisely the same at a particular sensitive site whether all the 170 mrads is delivered instantaneously or spread over one year. This would melt Dr. Budinger's factor of 10^6 down to a factor of *unity*, for the two regimes of irradiation. But we needn't quibble as to whether Dr. Budinger's concern is irrelevant by a factor of 100,000 or a factor of 1,000,000.

There are additional data, indeed available from Upton's work (A. C. Upton and G. E. Cosgrove, Jr. "Radiation-induced leukemia," *Experimental Leukemia*, (edited by M. A. Rich) New York Appleton-Century Crofts, 1968, pp. 131–158) which show conclusively, at least for thymic lymphoma in the mouse, that even at doses like 20 rads, there is no difference between "instantaneous" and "slow" delivery of radiation with respect to thymic lymphoma development. One of the good features of this experiment of Upton's is that the two regimes of irradiation, instantaneous and slow, were delivered at comparable age periods in the life span of the mouse, a feature *not* controlled in the vast majority of acute versus chronic irradiations. What Upton and Cosgrove showed was that there was *no* difference for thymic lymphoma incidence whether 200 rads total was delivered as 10 exposures, each of 20 rads (7 to 25 rads/min), spaced 30 days apart or whether delivered at 0.5 millirads/minute, which consumed the same approximate overall time period (approximately 300 days).

Using the same type of calculations as above, where 20 millirads represents one ionizing event (50 events per rad), the Upton data would indicate that one event per 40 minutes gave no different result, for thymic lymphoma induction, from 1000 events in *one* minute (20 rads in one minute $\cong$ 1000 events).

(c) Dr. Budinger brings up DNA repair and chromosome aberrations. These are very interesting phenomena that every knowledgeable scientist realizes do exist. But neither Dr. Budinger nor anyone else has suggested any relevance of these phenomena for the question of radiation dose rate and carcinogenesis. If Dr. Budinger knows the events in radiation carcinogenesis well enough to assert that DNA repair has anything to do with dose rate and cancer production, I

urge him strongly to publish these findings. At present, without such evidence, the mere mention of phrases like "DNA repair," or like "DNA and chromosomes are involved in somatic mutation" is about as useful in assessing the question of dose rate and carcinogenesis as are yesterday's stock market quotations. We wouldn't deny that the stock market quotations are interesting.

(d) Lastly, we must respond to Dr. Budinger's statement, "Anticipated radiation exposures are low LET at low dose rates; thus, I do not see a public health threat as great as the threat of trace elements and other man-made contaminants."

We have seen above that Dr. Budinger's factor of 10^6 in dose rate for low LET radiations melts away at least by 100,000 fold, when the biophysics is considered. But, whatever the magnitude of carcinogenic effect of ionizing radiation may be, it is difficult to understand the philosophy implied in Dr. Budinger's statement that other poisons may be worse. They may very well be. If one unnecessary poison kills 10,000 people per year while another kills 30,000 people per year, shall we exonerate the first unnecessary poison because it unhappily didn't reach the *top* of the best seller list?

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