invited opinion
statistics report #1

The problem of low-dose radiation toxicity

IBERALL, A. S. *The problem of low-dose radiation toxicity.* Am. J. Physiol. 244 (Regulatory Integrative Comp. Physiol. 13): R7–R13, 1983.—This article deals with the problem of distinguishing the mortality effects in mammals of exposure to *added* low-level radiation exposure, from the effects of natural background radiation. In contrast to the recent 1980 conclusions of the Committee on the Biological Effects of Ionizing Radiations (BEIR III) (that there is no threshold), this article suggests an absolute threshold of about 500 rem (r), if the dose is distributed uniformly over the life span (e.g., at 5–10 r/yr for human beings). Although this conclusion had been implied in an earlier study (*Ann. NY Acad. Sci.* 147: 1–81, 1964), its validity was strengthened by the work of Raabe et al. (*Science* 208: 61–66, 1980). They demonstrated that a radiation exposure threshold in dogs was identifiable through the induction of cancers. From a policy point of view, the conclusions of the present article are intended to foster continuing political debate; from a scientific point of view, the aim is to highlight the basic physiological mechanism for the senescence process—the breakdown of cellular regulation, in particular organ systems, as a major source of mortality, in cases in which failure of the cardiovascular system has not already led to catastrophe.

cancer; dose response; lethality; low-level radiation; mortality; risk; threshold

THIS ARTICLE deals with the effects of low-level ionizing radiation. Although I feel very strongly about the analysis, I don't insist that it should guide public policy. Making policy is a political process. This report is merely a technical letter to the Editor.

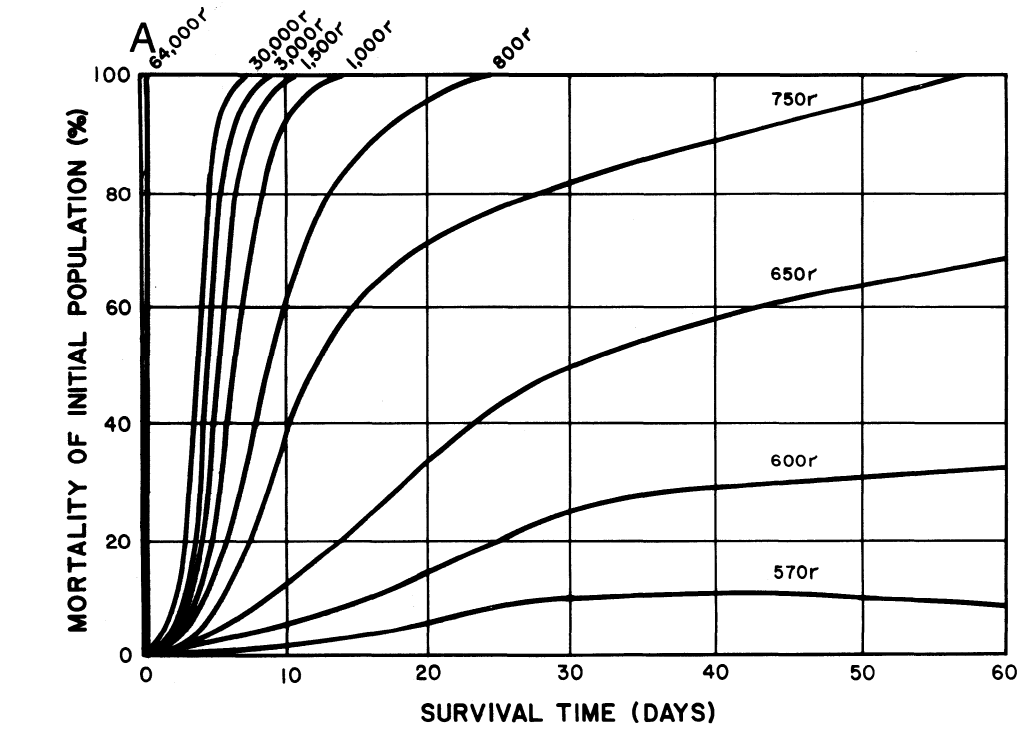
Eighteen years ago I did a study on radiation lethality for the Atomic Energy Commission (6). It was prompted by the United States Army's interest in the cumulative effects of radiation as a causative agent of death or debilitation in soldiers, who are initially healthy young men. The prevailing idea then [based on the work of Sacher (9) and of Blair (1)] was that radiation exposure at high doses caused death in some fraction of the population in proportion to the dosage, but there was full repair of radiation damage in the surviving fraction.

The radiation lethality literature at that time was confusing because investigators had developed a unitary model of a process that could not be unitary. (By "unitary" is meant a process involving a single cause.) To minimize confusion, it is necessary, at least, to differentiate between acute lethal dose and life-shortening dose. The first refers to the direct cause of rapidly occurring death, whereas the second pertains to long-term effects, in which death is delayed until the end of a nearly normal life span. These two processes could not stem from identical effects of radiation. This point will be made even stronger later when I discuss the so-called LD_{50-30}, that is, the lethal dose that kills 50% of the population in 30 days. (The choice of this time period has a considerable degree of arbitrariness.)

Another source of confusion about radiation effects, particularly at high dosages, is nonlinearity: changes in dosage do not result in proportional changes in the response. An appreciation for the inherent nonlinearity of radiation effects can be gained by comparing the difference between the magnitude of a lethal dose for a single "impulsive" or acute exposure and that for uniformly divided, multiple-dose "chronic" exposure. An impulsive dose of 600–700 r will kill a person quickly, whereas 5,000 r can be accumulated in smaller doses throughout a lifetime with only a moderate life-shortening effect.[1]

I approached the problem of the nonunitary nonlinear characteristics of radiation-induced disease by studying results expert observers had obtained. I found only five

[1] Whole-body radiation exposure is measured in roentgen units, or r. Other commonly used measures of radiation are physical units, or rads, and biologically equivalent units, or rems. These not-quite-identical units will be used interchangeably here and will be referred to simply as r.



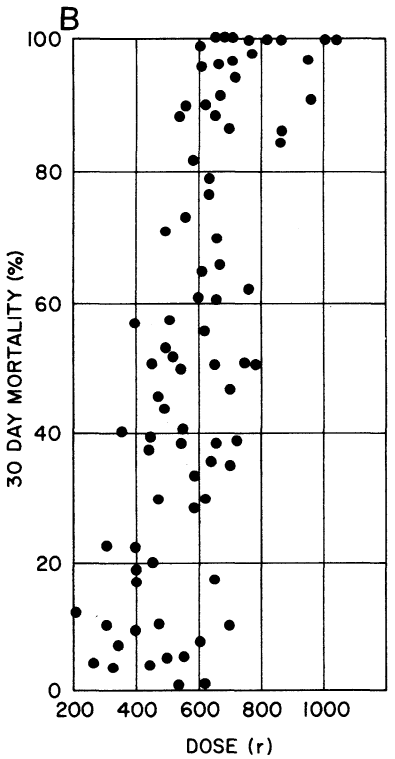


FIG. 1. Lethality of single large dose of radiation of mice. *A*: short-term mortality (fraction of an initial population killed) shown as survival time. *Curves* are structured around choice of LD_{50-30} of 650 r. [Redrawn from Iberall (6). That reference, a review and theoretical synthesis of various radiation lethality studies, lists about 20 sources of data.] *B*: experimental variation reported for 30-day mortality for mice [redrawn from Iberall (6)].

classes of effects: *1*) shortening of life span (delayed death); *2*) nearly immediate death; *3*) debilitation, similar to that of some diseases (partial or nearly complete recovery may occur); *4*) detectable, irreversible changes in some cells (e.g., cancer or cataracts); *5*) hereditary change.

A sixth category has been proposed for certain very special circumstances: there might be *beneficial* effects. To understand biologic responses to the challenge of radiation it seemed necessary to study each of these effects independently. Here I shall concentrate on the effects of radiation at lower doses—those associated with the long-term effects of shortening of life span [*1*) above].

Acute effects of single high doses [*2*) and *3*), above] will be considered only briefly. Such insults seem to be largely independent of species, for mammals, and cause different effects, the nature and courses of which are dependent on the point in the animal's life span at which the insult is received. The LD_{50-30} for a single lethal dose to mice or humans is about 650 ± 100 r, or 550 ± 100 r if calculated from data for all the mammalian species so far studied. The dose depends on age at time of exposure. An effective lethal dose for an older individual may be only half that of the lethal dose for a younger animal.

It is generally agreed that an acute dose of 25 r produces no detectable clinical effects. That the LD_{50-30} represents a transition from one unitary cause of death to another may be illustrated experimentally (typical results are shown in Fig. 1). There is large variation in lethality in mice between a dose of 570 r, in which a delayed death merely shortens a nearly normal life, and a dose of 800–1,000 r, in which death occurs quickly (Fig. 1*B*). The transition is shown for the entire life span of these naturally short-lived animals in Fig. 2. The results suggest that impulsive doses on the order of 100 r produce scarcely measurable life-shortening effects, but that discontinuity or break in mortality occurs in the vicinity of 600 r. The data of Fig. 3 show that there is at least one additional discontinuity at an even higher dose level (approx 20,000 r). The breakpoint near 600 r can be seen again.

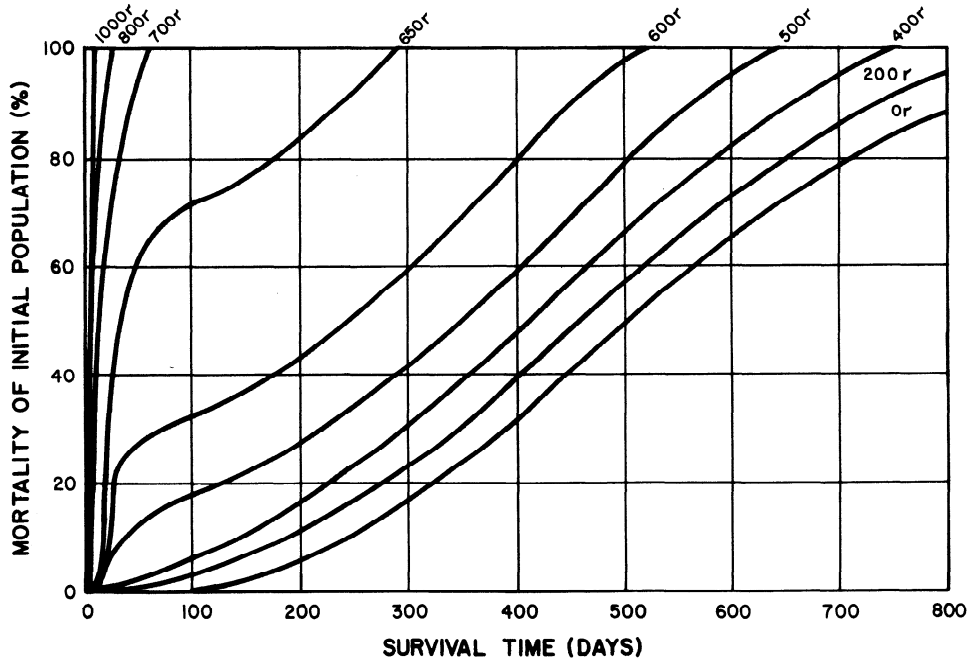


FIG. 2. Composite lethality of a single dose of radiation; mortality-survival time characteristics over entire life span of mice (6).

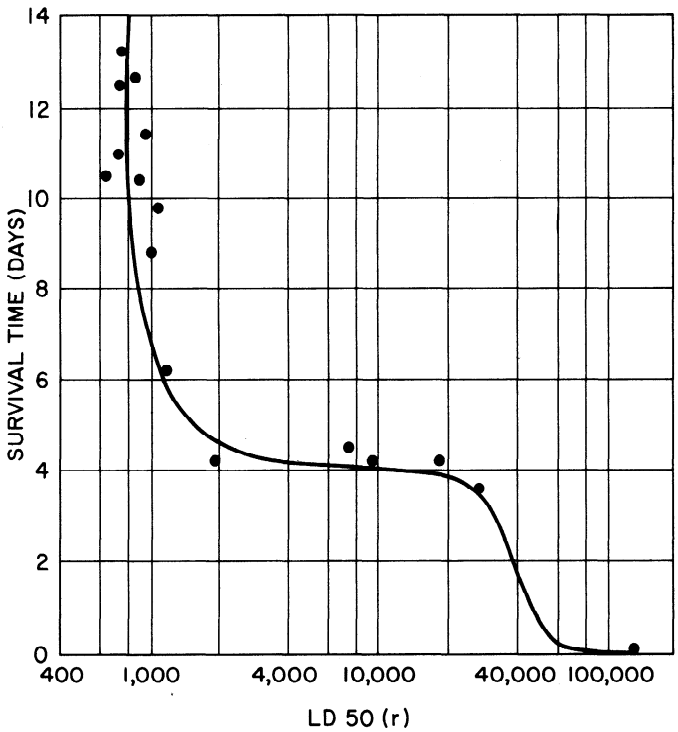


FIG. 3. Lethality of a single very large dose of radiation: very short-term survival time LD_{50} for mice. [Redrawn from Iberall (6); data source is Cronkite and Chapman (4).]

The lack of detectable effects acute doses under 100 r (i.e., below the discontinuity between immediate and delayed effects) also characterizes chronic exposures administered over the entire life span at cumulative levels up to about 800 r, which is equivalent to about 1 r/day in mice (Fig. 4). These results imply that a population of mice may receive doses of 1 r/day during an entire lifetime with no significant change in statistical mortality. Because among Class Mammalia there seems to be no species dependence of radiation effects, we can argue that equivalently, a population of human beings could receive up to 10 r/yr (0.2 r/wk) during entire lifetimes with no detectable effect on statistical mortality. These were the conclusions reached in my earlier report (6).

These results support the choice of the conventional radiological standards for human beings (6, 7). For example, the decision, in 1954, to reduce the standard for acceptable level of chronic radiation exposure from 0.7 r/wk (35 r/yr) to 0.3 r/wk (15 r/yr) was valid. The 1958 recommendation (7) of about 0.1 r/wk (5 r/yr) as the upper limit of safe chronic exposure had a more conservative tone but fits the data. A single acute dose of 100 r appeared to represent about the same negligible risk.

Data appearing after that initial study did not modify my opinion, until the appearance of the paper by Raabe et al. (8) in 1980. The message in the title, "Bone cancer from radium: canine dose response explains data for mice and humans," is one that I accept literally. That study raised a new point.

When I first reflected on the mortality statistics for the US population, I thought the chief causes of death were largely associated with organ failure, e.g., with cardiovascular causes of death. I had tentatively postulated that the organ system most susceptible to radiation-induced degradation was the reproductive system. But Sacher (9), a pioneer in radiation lethality research, had attempted to characterize more general mortality mechanisms. [See Strehler (11) for a comparison of various theories of mortality.] Sacher's work led to the development of a generalized homeostatic image of morbidity and mortality. This approach emphasizes the need to identify the major structural features that determine "absolute" organism deterioration, rather than those specific disease mechanisms that pathologists like to enter into death certificates.

The paper of Raabe et al. (8) changed my opinion about how we should view a terminal stage of radiation-

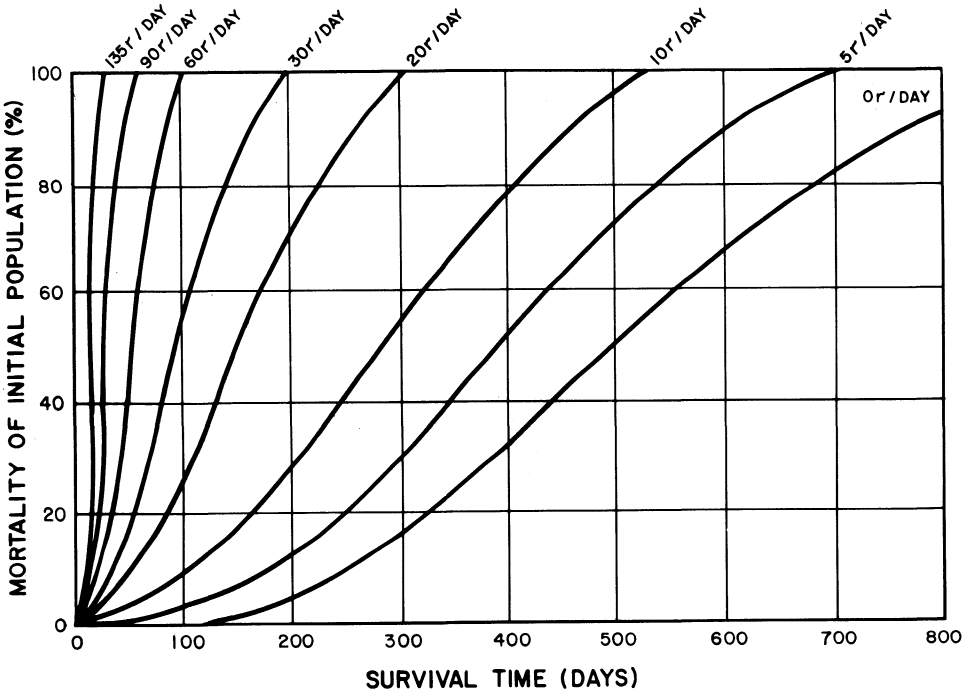


FIG. 4. Composite lethality of a constant rate (chronic) dosage of radiation. Mortality-survival time characteristics over entire life span of mice [redrawn from Iberall (6)].

induced mortality.[2] It suggested that the background radiation "noise" level is a real environment to which living systems are constantly exposed, and that whatever they do or experience—good or bad—reflects, in part, that background. Given that environment, some radiation-induced cancer occurring late in life is a transformation to be expected, as a structural change. That transformation to cell line neoplasms in organs is likely to occur because of a breakdown in the regulatory machinery at the cellular level. Cooper (3) offers an account of such breakdown, even involving "normal" genes. The effects of shifts of the radiation background (e.g., the effects of radiation environment on cancer incidence at any time of life) cannot now be specified, given the present state of limited knowledge about cancer. With respect to radiation effects, the radiologist R. Mole wrote (personal communication; July 1979):

> The idea of a progressive deterioration of the body's economy, a degeneration, perhaps as a consequence of multiple somatic mutation, or expressed as "non-specific aging," has now been abandoned by pretty well everyone. It is induction of cancer which is the main hazard and the only life-shortening factor at occupationally permissible levels of [radiation] exposure and below.

What then is the "threshold" (if any) of extra radiation exposure *below which that radiation will not induce additional cancer*? According to the data of Raabe and associates (8), it is about 0.1 r/day for dogs, which have an approximately 5,000-day life span (Fig. 5), when the radiation is concentrated in the skeleton. An equivalent threshold dosage for human beings would be about 5–10 r/yr. At this threshold the question of whether or not there are any additive effects of natural noise levels of radiation at its levels of 0.1-0.3 r/yr, would seem to be "no." In effect, this is a strong threshold. The cumulative dose-response curve does not go to zero but has an intercept. Note that these data say nothing about dose-response relationships for hereditary effects. I have not studied them and do not know what their "thresholds" (if any) are.

In 1980 the Committee on the Biological Effects of Ionizing Radiation (BEIR) of the National Academy of Sciences (USA) published a report (called BEIR III) (2) concerning the long-term somatic and genetic risks to large human populations exposed to low-level ionizing radiation. They assert that the natural background of about 0.1 r/yr is doubled by medical exposures and increased severalfold in a number of occupations. Their risk estimates involve a great deal of uncertainty (2):

> [The] most difficult task has been to estimate the carcinogenic risk of low-dose, low-LET, whole-body radiation. [We] recognized that the scientific basis for making such estimates is inadequate, but ... that policy decisions ... require a position on the probable cancer risk from low-dose ... radiation. [See footnote 3.]

[2] The reader should note that I do not claim that radiation effects are the only or chief determinants of mortality curves, at low levels of chronic exposure. Mortality curves may be shaped by an intrinsic senescence process having nothing whatever to do with background radiation. The discussion here concerns special circumstances in which radiation does have a detectable effect on mortality, as it might be separated out from intrinsic processes.

[3] LET is linear energy transfer. Not all radiation is equally effective in interaction with matter: X rays, γ-rays, and electrons have one sort of unit effectiveness for their rad energy; protons and fast neutrons have a higher effectiveness, etc. These differences are expressed by "increased quality" factors, which are multipliers used to represent equalization of effectiveness.

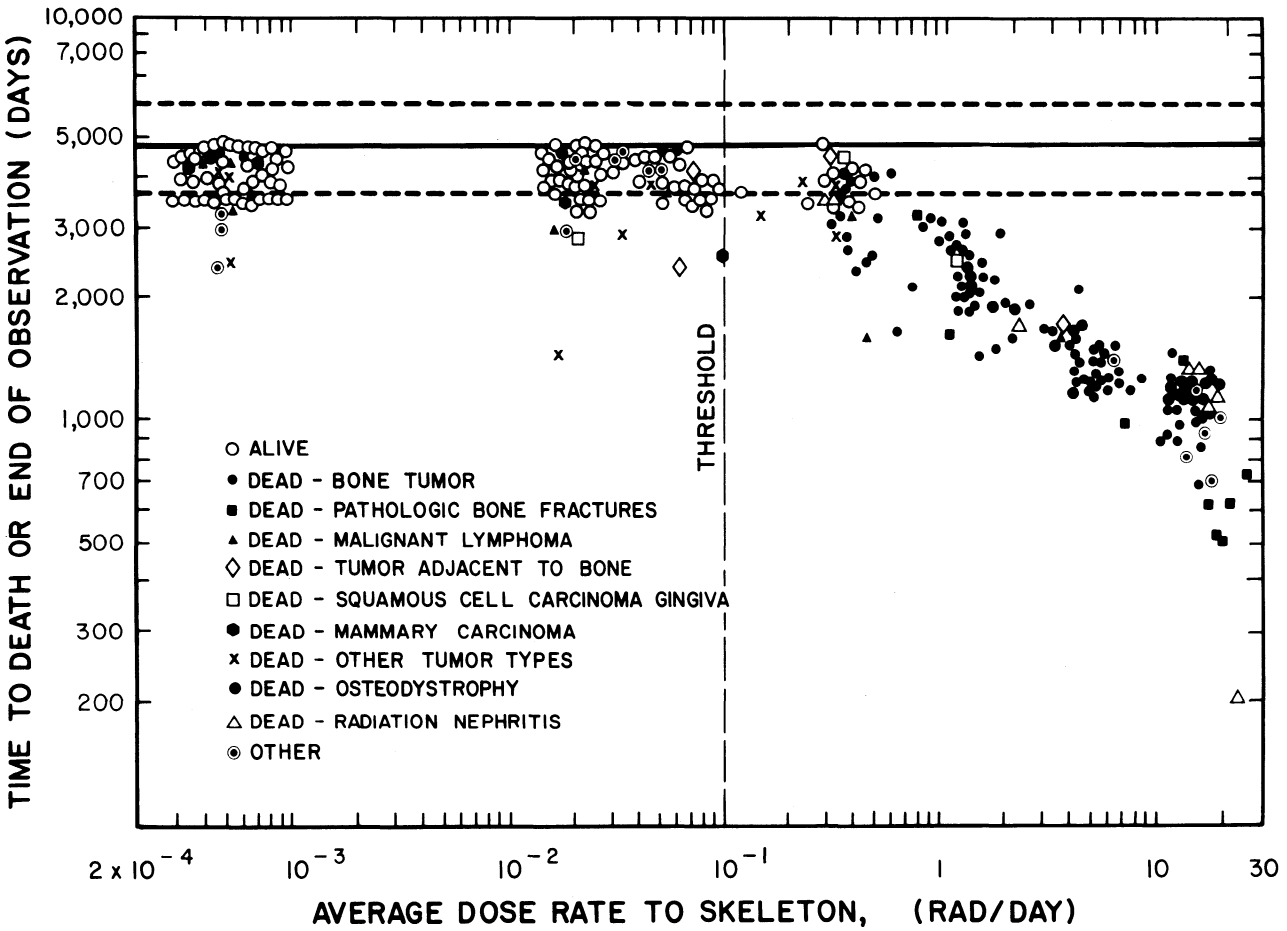
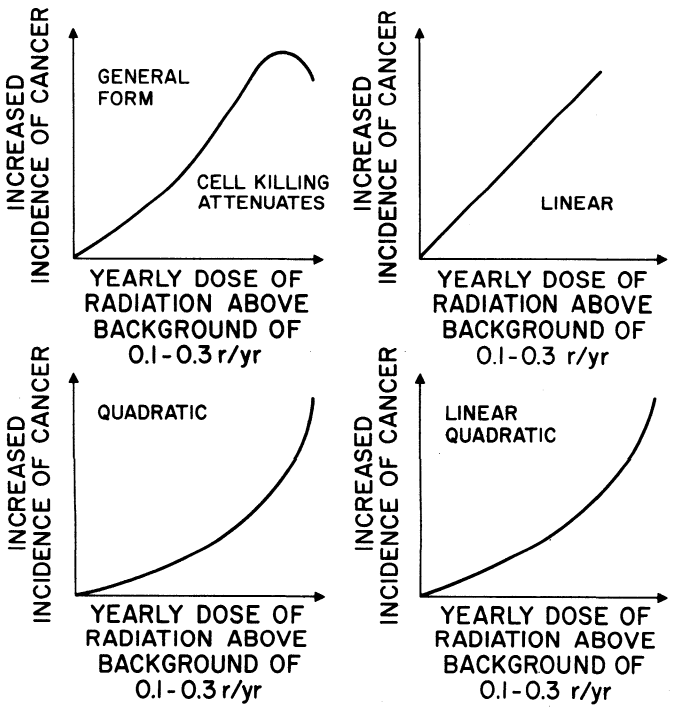


FIG. 5. Lethality at a constant rate (chronic) dosage of radiation. Survival time average dose rate (to skeleton) of beagles. Cause of death is characterized (8). (Curves are redrawn with permission.)

In assessing the somatic effects of radiation, cancers are considered to be the major delayed effects. Breast, thyroid, and lung cancers are the principal risks, exceeding leukemia. The BEIR Committee describes the risk as a dose-response curve, where the response is incidence of cancer. Risk is age dependent. In their estimation, a 10 r impulsive dose increases the risk over naturally occurring mortality by about 0.5–1.5%. Chronic exposure of 1 r/yr increases the risk 3–8%. Note that they define percentage increase above the natural rate in the following way: if the naturally occurring lifetime cancer risk is 16,000 cases per hundred thousand persons, or 16%, then a 1% increase because of an additional 10 r impulse of radiation exposure (for example) is 1% of 16,000, or 160 extra cases. It is important to realize that much of the technical focus of the report is on the shape of the dose-carcinogenic-response curve (Fig. 6).

The BEIR Committee does not know whether or not natural background dose rates of about 0.1 r/yr (X- or γ-rays, low-LET) are detrimental, nor do they expect effects to be identified in the forseeable future. On the other hand, for dose rates of a few r/yr, they claim that "a discernible carcinogenic effect could become manifest." Low-dose, low-LET radiation does not seem to have any somatic effects other than cancer. Radiation-induced genetic effects have not been demonstrated in humans at these levels of exposure. From data on animals, one expects that genetic effects would involve gene mutation and chromosomal aberrations. BEIR III estimates that 1 r of potential exposure in the population will result in 5–75 "additional serious genetic disorders per million liveborn offspring." At equilibrium, 1 r per generation would result in 60–1,000 serious genetic disorders per million liveborn offspring. However, to emphasize the limitations of the current understanding of the genetic effects of radiation, they point out that this risk is small "in relation to current estimates of the incidence of serious human disorders of genetic origin—roughly 10% of liveborn offspring."

Restricting discussion to somatic effects, it might be supposed—narrowly—that the difference between the views held by this author and those expressed in the National Academy report (2) might be a question of the numerical threshold of carcinogenic lethality. For example, I would say that an acute dose of 100 r (low-LET) is indistinguishable (or barely distinguishable) from the environmental noise, whereas BEIR III suggests that 10 r could produce a discriminable effect. Or, again, I would say that a chronic dosage of 5–10 r/yr is barely distinguishable from the background, whereas BEIR III would maintain that levels above about 0.1–0.3 r/yr could produce discriminable effects. But our differences are greater than that. There are basic philosophical differences underlying the two lines of thought.



ALTERNATIVE DOSE-RESPONSE CURVES FOR RADIATION INDUCTION OF CANCER

FIG. 6. Alternative dose rate-lethality response (via neoplasms) curves discussed by a National Academy report (2).

TABLE 1. *Leading causes of mortality: US 1960–1965*

Cause	Percent (of the 1% death rate)
Diseases of the heart and circulation	39
Cancer	16
Strokes	11
Flu, pneumonia	4
Accidents	6*
Infant diseases	2
Diabetes	2
Emphysema, bronchitis, asthma	2

Death rate: about 1% of the population/yr. *Half are automobile accidents.

I abandoned the attempt to determine an effective dose-response characterization when no defensible, unitary, linear description of radiation lethality could be found. I then turned to the statistical character of mortality curves and segregated them into different causal domains, one of which is life shortening by radiation-induced cancers. Within these independent domains an effective dose-response relationship is preserved. Such an approach to the analysis of data on radiation-induced cancer can be defended on the basis that multiple independent factors always contribute to mortality. The major causes of mortality in the US for the period 1960–1965 are shown in Table 1.

The general age-specific character of human mortality of a larger population is presented in Fig. 7.

As a matter of scientific, and also possibly public, policy it is reasonable to concentrate on those factors contributing the most to the death rate. Society itself, by reacting with relative indifference to low mortality levels, establishes what amounts to a "societal" noise level of risk (10). This level of acceptable risk may change as the values of the society change, but it is, nevertheless, a definite level. Considering the indifference of the American public to automobile accidents, it would seem that this level is about 20,000 deaths per year, or, more conservatively stated, at least 10,000 deaths per year can easily be overlooked if the risks of these deaths are perceived as being distributed homogeneously across the population. For a population of 200 million, this is a level of about 0.5–1% of the yearly death rate, or an absolute level of 0.005–0.01% of the population dying "extra" deaths.

Some support for the "societal noise" hypothesis may be found by examining the changes in death rate that have taken place in the United States between 1920 and 1960. Only causes and changes in the death rate of greater than 50 per hundred thousand (absolute changes of 0.05%) will be considered (Table 2). To a considerable extent, other causes of death that are already under 10 per hundred thousand (0.01%) are no longer viewed as matters of public concern, although they remain matters of individual and professional concern. Only a change of at least 50 new deaths per hundred thousand population is perceived as socially significant. Viewed from such a perspective, efforts directed toward effecting changes on

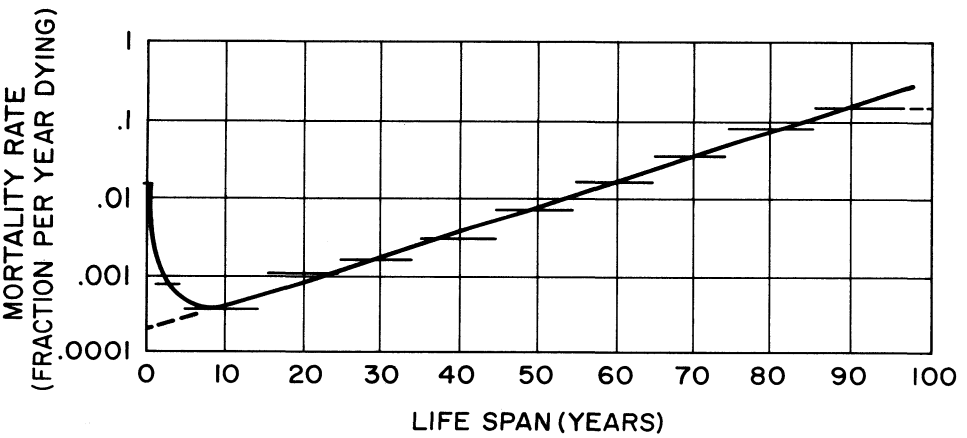


FIG. 7. Death rate for a human population (USA, 170) [series B181-192 (5)]. Barred data are average for each age interval.

TABLE 2. *Distribution and changes in rates of causes of death (US)*

Cause	Deaths/100,000 Population		Change	Probable Reason for Change
	1920	1960		
TB	113	6	−97	Medical treatment
Cancer	83	147	+64	Not yet understood
Heart	163	366	+203	Not yet understood
Kidney	82	7	−75	Medical treatment
Flu, pneumonia	207	37	−170	Medical treatment
GI tract	54	4	−50	Medical treatment
Unspecified individually	154	63	−91	Half, medical treatment
Children's diseases			(−80)	Medical treatment

the order of only 10 per hundred thousand (the noise level) in a cancer mortality rate which is currently at a level of 160 per hundred thousand, cannot be taken seriously. A more useful concern would be to find some explanation for the change in cancer mortality from 80 per hundred thousand in 1920 to the current (1970) 160 per hundred thousand. In light of the above arguments I don't believe that chronic total radiation exposure of 5–10 r/yr or less should be regarded as significant for increased risk of cancer mortality.

The National Academy report, contrary to the views expressed here, seems to reckon in terms of a peculiar measure, i.e., the percentage change in lifetime cancer risk of 160,000 cases per million persons. The total lifetime risk of lethality is, of course, one million cases per million persons, from all causes of death. When "extra" deaths are attributed to an increase in radiation-induced cancer, it might seem to suggest a corresponding diminution in the number of deaths arising from some other—possibly correlated—cause. Such is not the case. Each mechanism may be largely independent, with the major causes of death still being associated with the cardiovascular system. In addition, each cause seems to have its own normally fluctuating noise level.

The appearance of extra risk because of radiation is interpreted as a dose-response relation by the Academy report and regarded by them—and by others—as the identification of a scientific principle for the effects of radiation. But this conclusion seems unjustified; such an identification can be truly scientific only when a theory of cancer is developed, as well as a theory of mortality. The best one can do with their analysis, and with the analysis offered here, is to view them both as self-consistent, but also to note that they do not agree. They cannot both be equally rational. It is a matter of how to interpret statistical data. I do not believe that the report of the National Academy does it properly.

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