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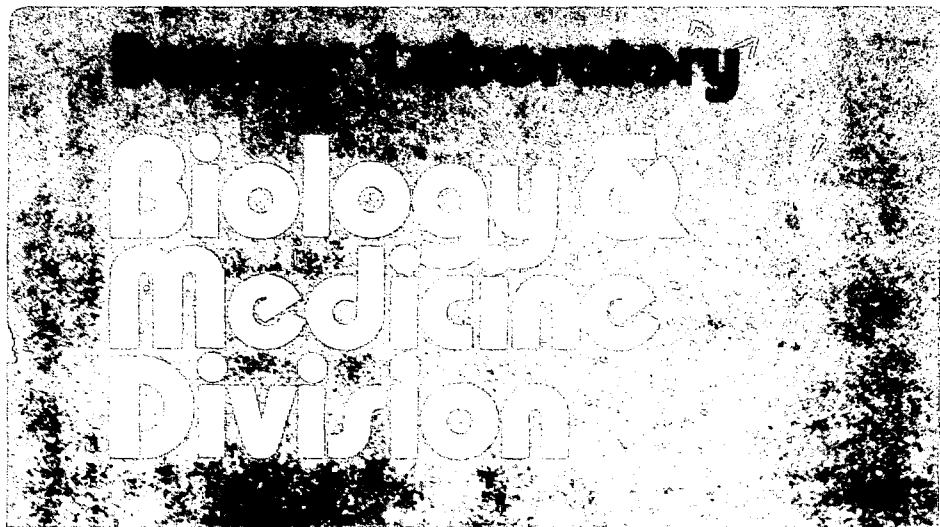
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THE BEIR-III CONTROVERSY

Jacob I. Fabrikant

June 1980

MASTER



INTRODUCTION

My assignment this evening is to try to give you some sort of general background to a controversy that arose during the preparation of the current Report [1] of the Committee on the Biological Effects of Ionizing Radiation of the National Academy of Sciences-National Research Council (the BEIR-III Report). To do this, I shall try to discuss with you how certain of the areas addressed by the present BEIR Committee have attempted to deal with the scientific basis for establishing appropriate radiation protection guides, and what effect this may have on decision-making for the regulation of societal activities concerned with the health effects in human populations exposed to low-level radiation. What I may consider important in these discussions, I speak only as an individual, and in no way do I speak for the BEIR Committee, or for any of its members, whose present deliberations are soon to become available. It would be difficult for me not to be somewhat biased and directed in favor of the substance of the BEIR Reports [1-3], since as an individual I have been sufficiently close to the ongoing scientific deliberations of agreement and disagreement as these have developed over the past 10 years.

I think the best thing for me to do is to review, very briefly, why we have advisory committees on radiation, and why the BEIR Committee, and its current Report [1], may be somewhat different than the others. To do this, I shall discuss what we know and what we do not know about the health effects of low-level radiation, particularly as these may highlight the controversy which has led to scientific dispute within the Committee. Further, I shall comment on how the risks of radiation-induced cancer in man may be estimated, the sources of the scientific and epidemiological data, and the dose-response models used, and the uncertainties which limit precision of estimation of excess risks from radiation. And finally, I should like to conjecture with you, and with my colleagues here this evening, on what lessons we have learned or should have learned from the BEIR-III Committee experience, and especially on what the implications might be of numerical risk estimation for radiation protection and public health policy.

WHY DO WE HAVE ADVISORY COMMITTEES ON RADIATION?

For more than half a century, responsible public awareness of the potential health effects of ionizing radiations, initially from medical and industrial exposure, then from nuclear weapons and weapons testing, and now from the production of nuclear energy, has called for expert scientific advice and guidance. And, advisory committees on radiation of international and national scientific composition have for these many years met and served faithfully and effectively to deliberate and to report on three important matters of societal concern: (1) to place into perspective the extent of harm to the health of man and his descendants to be expected in the present and in the future from those

societal activities involving ionizing radiations; (2) to develop quantitative indices of harm based on dose-response relationships in order to provide a scientific basis to be applied to concepts of acceptable risk and protection of human populations exposed to low-level radiation, and related primarily to somatic and genetic risks; (3) to identify the extent of radiation activities which could cause harm, to assess their relative importance, and to provide a framework on how to reduce unnecessary radiation exposure to human populations.

To a greater or lesser extent, each advisory committee on radiation--such as the UNSCEAR, the ICRP, the NCRP, and the BEIR Committee--have dealt with these matters. But significant differences occur in the scientific reports of these various bodies, and we should expect differences to occur, because of the charge, the scope, and the composition of each committee, and most important, because of public attitudes existing at the time of the deliberations of that particular committee, and at the time of the writing of that particular report. The BEIR Report [1] is different. However, the main difference is not so much from new data or new interpretations of existing data, but rather from a philosophical approach and appraisal of existing and future radiation protection resulting from an atmosphere of constantly changing societal conditions and public attitudes.

HOW IS THE BEIR REPORT [1] DIFFERENT?

The Report [1] of the Committee on the Biological Effects of Ionizing Radiation is the record of the deliberations of an expert scientific advisory committee of the National Academy of Sciences - National Research Council, and deals with the scientific basis of the health effects in human populations exposed to low levels of ionizing radiation. The current Report [1] broadly encompasses two areas. (1) It reviews the current scientific knowledge--epidemiological surveys and laboratory animal experiments--relevant to radiation exposure of human populations and to the delayed or late health effects of low-level radiation. (2) It evaluates and analyzes these late health effects--both somatic and genetic effects--in relation to the risks to health from exposure to low-level radiation. The Committee presently consists of 22 members, selected for their special expertise in areas of biology, biophysics, biostatistics, epidemiology, genetics, mathematics, medicine, physics, public health, and the radiological sciences. The reports [1-3] of the BEIR Committee have, in the past, become reference texts for the scientific basis for development of appropriate and practical radiation protection standards and for public health policy.

The 1972 BEIR-I Report [2] and the 1980 BEIR-III Report [1] may differ from one or more of the other radiation advisory committee reports of the UNSCEAR [4,5], the ICRP [6,7], the NCRP [8,9], and of other national councils and committees, in four important ways.

(1) The BEIR Report [1-3] is intended to be a readable, usable document for those societal activities concerned with radiation health. The conclusions, recommendations, and detailed appendices are purposefully written in a straightforward manner, to be read and understood by scientists, by physicians, and by congressmen alike.

(2) The BEIR Committee [1-3] does not set radiation standards or public health policy. However, the Committee's reports are purposefully presented so that they will be useful to those responsible for decision-making concerning regulatory programs and public health policy involving radiation in the United States. There is no intent to make the task any easier or to set a firm direction for those decision-makers who must consider the strengths and limitations of science and technology, and the relevant societal and economic conditions, in the development and execution of such regulatory programs. In this regard, the BEIR Reports [1-3] suggest that those responsible for setting radiation protection standards must always take into account societal needs at that time, so that such standards are established on levels of radiation exposure which are not necessarily absolutely safe, but rather those which are considered to be appropriately safe for existing circumstances at the time to fulfill society's needs, particularly in the areas of general population and occupational exposure from medical applications and from nuclear energy.

(3) The epidemiological surveys and laboratory animal data are carefully reviewed and assessed for their value in estimating numerical risk coefficients for the late health effects, and particularly cancer, in human populations exposed to low-level radiation. Therefore, the BEIR Report [1,2] uses a particularly practical format for decision-makers, namely, the numerical risk coefficients estimated are presented in probabilistic terms, within most likely upper and lower boundaries, derived solely from the scientific facts, the epidemiological data, and the scientific hypotheses and assumptions on which they are based.

(4) The BEIR Report [1-3] addresses the continued need to assess and evaluate the benefits from those activities involving radiation as well as the risks. In our resource-limited society, such benefit-risk assessment is essential for societal decision-making for establishing appropriate and achievable radiation protection standards. Decisions can and must be made on the value and costs of technological and societal programs for the reduction of risk by reducing the levels of radiation exposure. This would include societal choices centered, as well, on alternative methods involving nonradiation activities available through a comparison of the costs to human health and to the environment [3].

It was within this framework that the present BEIR-III Committee pursued its responsibilities from the beginning of 1977 to January 1979. At that time, there appeared to be a majority for support within the Subcommittee on Somatic Effects for the method to estimate

the cancer risk for low-dose, low-LET whole-body radiation. With what would have been a dissenting position on the part of some, and the recognition of a need to move on quickly to complete the Report, the Committee did not meet thereafter, and the current BEIR-III Report [1] was released on May 2nd, 1979. There would have been no reason to release the Report, in my opinion, if there had not been some assurance prior to that time that a reasonable, but not necessarily unanimous, consensus had been achieved within the Committee. However, it is since that time, since May 2nd, 1979, that the so-called BEIR-III "Controversy" surfaced for public admonition. In order for me to provide you with any understanding of the events as I have known them, I should like to begin here with some observations on radiation and health to help place matters into better perspective.

WHAT ARE THE IMPORTANT BIOLOGICAL EFFECTS OF LOW-LEVEL RADIATION?

My remarks here will be restricted primarily to those delayed or late health effects in humans following exposure to low-LET radiation, x-rays and to gamma rays from radioactive sources, and to a much lesser extent to high-LET neutron and alpha radiations, since these are the ionizing radiations most often encountered in the nuclear industry and in medicine. Briefly, low-level radiation can affect the cells and tissues of the body in three important ways. First, if the macromolecular lesion occurs in one or a few cells, such as those of the hematopoietic tissues, the irradiated cell can occasionally transform into a cancer cell, and after a period of time, there is an increased risk of cancer developing in the exposed individual. This biological effect is called carcinogenesis; and the health effect, cancer. Second, if the embryo or fetus are exposed during gestation, injury can occur to the proliferating and differentiating cells and tissues, leading to abnormal growth. This biological effect is called teratogenesis; and the health effect, developmental abnormality in the newborn. Third, if the macromolecular lesion occurs in the reproductive cell of the testis or the ovary, the hereditary genome of the germ cell can be altered, and the injury can be expressed in the descendants of the exposed individual. This biological effect is called mutagenesis; and the health effect, genetically-related ill-health.

There are a number of other biological effects of ionizing radiation, such as cataracts of the lens of the eye, or impairment of fertility, but these three important late effects--carcinogenesis, teratogenesis and mutagenesis--stand out as those of greatest concern. This is because a considerable amount of scientific information is known from epidemiological studies of exposed human populations and from laboratory animal experiments. Furthermore, we believe that exposure to ionizing radiations, even at low levels of dose, carries some risk of such deleterious effects. And, as the dose of radiation increases above low levels, the risk of these deleterious health effects increases in exposed human populations and from laboratory

animal experiments. Furthermore, we believe that any exposure to radiation, even at low levels of dose, carries some risk of such deleterious effects. And, as the dose of radiation increases above very low levels, the risk of these deleterious health effects increases in exposed human populations. It is these latter observations that have been central to the public concern about the potential health effects of low-level radiation, and to the task of estimating risks and of establishing standards for protection of the health of exposed populations. Indeed, all reports of expert advisory committees on radiation are in close agreement on the broad and substantive issues of such health effects.

WHAT DO WE KNOW ABOUT THE HEALTH EFFECTS OF LOW-LEVEL RADIATION?

A number of very important observations on the late health effects of low-level radiation have now convincingly emerged, and about which there is reasonably good general agreement. These observations are based primarily on careful evaluation of epidemiological surveys of exposed human populations, on extensive research in laboratory animals, on analysis of dose-response relationships of carcinogenic, teratogenic and genetic effects, and on known mechanisms of cell and tissue injury in vivo and in vitro.

(1) Cancer-induction is the most important late somatic effect of low-dose ionizing radiation. Solid cancers arising in the various organs and tissues of the body, such as the female breast and the thyroid gland, rather than leukemia, are the principal late effects in individuals exposed to radiation. These different organs and tissues appear to vary greatly in their relative susceptibility to cancer-induction by radiation. The most frequently occurring radiation-induced cancers in man include, in decreasing order of susceptibility: the female breast; the thyroid gland, especially in young children and in females; the hematopoietic tissues; the lung; certain organs of the gastrointestinal tract; and the bones. There are influences, however, of age at the time of irradiation, and at the time of expression of the disease, of sex, and of the radiation factors and types--LET and RBE--affecting the cancer risk.

(2) The effects of growth and development in the irradiated embryo and fetus are related to the gestational stage at which exposure occurs. It appears that a threshold level of radiation dose and dose rate may exist below which gross teratogenic effects will not be observed. However, these dose levels would vary greatly depending on the particular developmental abnormality and on the radiation types and qualities.

(3) Estimations of the radiation risks of genetically-related ill-health are based mainly on laboratory animal observations, primarily from laboratory mouse experiments, because of the paucity of

data on exposed human populations. Our knowledge of fundamental mechanisms of radiation injury at the genetic level is far more complete than, for example, of mechanisms of radiation carcinogenesis, thereby permitting greater assurance in extrapolating information on genetic mutagenesis from laboratory experiments to man. Mutagenic effects are related linearly to radiation dose even at very low levels of exposure. With new information on the broad spectrum and incidence of genetically-related ill-health in man, such as mental retardation and diabetes, the risk of radiation mutagenesis in man affecting future generations takes on new and special consideration.

WHAT DO WE NOT KNOW ABOUT THE HEALTH EFFECTS OF LOW-LEVEL RADIATION?

In spite of a thorough understanding of these late health effects in exposed human populations, there is still a considerable amount we do not know about the potential health hazards of low-level radiation.

(1) We do not know what the health effects are at dose rates as low as a few hundred millirem per year. It is probable that if any health effects do occur, and of this we are not certain, they will be masked by environmental or other competing factors that produce similar effects.

(2) The epidemiological data on exposed human populations are nevertheless highly uncertain in regard to the forms of the dose-response relationships for radiation-induced cancer in man. This is especially the case for low-level radiation. Therefore, it has been necessary to estimate human cancer risk at low radiation doses primarily from observations at relatively high doses, frequently greater than 100 rads and more. However, it is not known whether the cancer incidence observed at high-dose levels also applies to cancer-induction at low-dose levels.

(3) We do not have reliable methods at the present time of estimating the repair of injured cells and tissues of the body exposed to very low doses and dose rates. And further, we do not know how to identify those persons who may be particularly susceptible to radiation injury, perhaps on the basis of genetic predisposition.

(4) We have only very limited information on the precise radiation doses absorbed by the tissues and organs of individuals in irradiated populations exposed in the past. Furthermore, we do not know the complete cancer incidence in each study population, since new cases of cancer continue to appear with the passing of time. Accordingly, any estimation of excess cancer risk based on such limited dose-response information must necessarily be incomplete, until the entire study population has died from natural or other causes.

5) We do now know the role of competing environmental and other host factors--biological, chemical or physical factors--existing at the time of exposure, or following exposure, which may influence and affect the carcinogenic, teratogenic, or genetic effects of low-level radiation.

WHAT ARE THE UNCERTAINTIES IN THE DOSE-RESPONSE RELATIONSHIPS FOR RADIATION-INDUCED CANCER?

In our present BEIR-III Committee, during its earliest deliberations, a number of the members were concerned that in most epidemiological surveys, there was great uncertainty in regard to the shapes of the dose-response curves for cancer-induction by radiation in humans, and this was especially the case at low levels of dose. Estimates of the cancer risk at low doses appeared to depend more on what is assumed about the mathematical form of the dose-response function than on the available epidemiological data themselves. Accordingly, for the final report, in estimating the excess cancer risk from low-dose low-LET radiation, a majority of the BEIR-III Committee members chose to use a linear-quadratic (i.e., a quadratic function with a linear term in the low-dose region) dose-response model felt to be consistent with epidemiological and radiobiological data in preference to more extreme linear or pure quadratic dose-response models. In this regard, the current BEIR-III Report [1] differs substantially from the 1972 BEIR-I Report [2]. I should like to examine the deliberations of this difficult decision more closely.

In recent years, a general hypothesis for estimation of excess cancer risk in irradiated human populations, based on theoretical considerations, on extensive laboratory animal studies, and on limited epidemiological surveys, suggests various and complex dose-response relationships between radiation dose and observed cancer incidence [10-15]. Among the most widely considered models for cancer-induction by radiation, based on the available information and consistent with both knowledge and theory, takes the complex quadratic form: $I(D) = (\alpha_0 + \alpha_1 D + \alpha_2 D^2) \exp(-\beta_1 D - \beta_2 D^2)$, where I is the cancer incidence in the irradiated population at radiation dose D in rad, and α_0 , α_1 , α_2 , β_1 and β_2 are non-negative constants (Figure 1). This multicomponent dose-response curve contains (1) initial upward-curving linear and quadratic functions of dose, which represent the process of cancer-induction by radiation; and (2) a modifying exponential function of dose, which represents the competing effect of cell-killing at high doses. α_0 is the ordinate intercept at 0 dose, and defines the natural incidence of cancer in the population. α_1 is the initial slope of the curve at 0 dose, and defines the linear component in the low-dose range. α_2 is the curvature near 0 dose, and defines the upward-curving quadratic function of dose. β_1 and β_2 are the slopes of the downward-curving function in the high-dose range, and define the cell-killing function.

Analysis of a number of dose-incidence curves for cancer-induction in irradiated populations, both in humans and in animals, has demonstrated that for different radiation-induced cancers only certain of the parameter values of these constants can be theoretically determined. However, the extent of the variations in the shapes of the dose-response curves derived from the epidemiological or experimental data does not permit direct determination of any of these precise parameter values, or even of assuming their values, or of assuming any fixed relationship between two or more of these parameters. Furthermore, in the case of the epidemiological surveys, this complex general dose-response form cannot be universally applied. Therefore, it has become necessary to simplify the model by reducing the number of parameters which would have the least effect on the form of the dose-response relationship in the dose range of low-level radiation. Such simpler models, with increasing complexity, include the linear, the pure quadratic, the quadratic (with a linear term), and finally, the multicomponent quadratic form with a linear term and with an exponential modifier (Figure 2).

The BEIR-III Committee recognized three serious limitations constraining precise numerical estimation of excess cancer risks of low-level radiation in exposed human populations. First, we lack an understanding of the fundamental mechanisms of cancer-induction by radiation, particularly in man. Second, the dose-response data from epidemiological surveys are highly uncertain, particularly at low levels of dose. Third, experimental and theoretical considerations suggest that various and different dose-response relationships may exist for different radiation-induced cancers in exposed human populations. Nevertheless, the Committee also recognized that these limitations did not relieve decision-makers of the responsibility for guiding public health policy based on appropriate radiation protection standards. Accordingly, not only did the BEIR-III Committee consider it essential that quantitative risk estimation be calculated, based on the available epidemiological and radiobiological data, but that in addition, it was equally essential that precise explanations and qualifications of the assumptions, procedures, and limitations involved in the calculation of such risk estimates must be clearly provided in the report of the Committee. This has been done explicitly, but not without much discussion and disagreement among its members, in the current BEIR-III Report [1] containing the estimates of excess cancer risk. In its final analyses, the majority of the members of the Committee has preferred to emphasize that some experimental and human data, as well as theoretical considerations, suggest that for exposure to low-LET radiation, such as x-rays and gamma rays, at low doses, the linear model probably leads to overestimates of the risk of most radiation-induced cancers in man, but that the model can be used to define the upper limits of risk. Similarly, a majority of the members of the Committee believes that the pure quadratic model may be used to define the lower limits of risk from low-dose low-LET radiation. The Committee generally agrees, that for exposure to high-LET radiation,

such as neutrons and alpha particles, linear risk estimates for low doses are less likely to overestimate the risk and may, in fact, underestimate the risk.

WHAT IS THE CONTROVERSY OVER LOW-LEVEL RADIATION?

The estimation of the cancer risk of exposure to low-level radiation is said to be clouded by scientific dispute. In particular, there appears to be disagreement among some scientists as to the effects of very low levels of radiation, even as low as our natural radiation background. Some say this is the central issue of controversy within the BEIR-III Committee. While there is no precise definition of low-level exposure, many scientists would generally agree that low-level radiation is that which falls within the dose range considered permissible for occupational exposure. According to accepted standards [16], 5 rem per year to the whole body would be an allowable upper limit of low-level radiation dose for the individual radiation worker.

In this context, and with this as the boundary condition for occupational exposure, then it could very well be concluded that most of the estimated delayed cancer cases which may be associated with a so-called hypothetical nuclear reactor accident, or even after long periods of occupational exposure among radiation workers, for example, are therefore considered by some scientists to be caused by exposures well below these allowable occupational limits. Furthermore, if it is assumed that any extra radiation above natural background, however small, causes additional cancer, then if millions of people are exposed, some extra cancers will inevitably result. Other scientists strongly dispute this, and firmly believe that low-level radiation is nowhere near as dangerous as their adversarial colleagues would contend. Central to this dispute, it must be remembered that cancers induced by radiation are indistinguishable from those occurring naturally; hence, their existence can be inferred only on the basis of a statistical excess above the natural incidence. Since such health effects, if any, are so rarely seen under low-level radiation because the exposures are so small, the issue of this dispute may never be resolved--it may be beyond the abilities of this science and mathematics to decipher.

It is just this type of controversy that was at the root of the division within the present BEIR-III Committee. There is little doubt that the Committee's most difficult task has been to estimate the carcinogenic risk of low-dose low-LET whole-body radiation. Here, to the disquiet of some of the members of the Committee, emphasis was placed almost entirely on the limited number of human epidemiological studies, since it was felt by the majority of the members that little information from laboratory animal and biophysical studies could be applied directly to man. Therefore, as the earlier 1972 BEIR-I

Report [2] had done, some members of the present BEIR-III Committee considered it necessary to adopt a linear hypothesis of dose-response to estimate the cancer risk at very low-level radiation exposure where no human epidemiological data are available. Here, it is assumed the same proportional risks are present at low levels as at high levels of radiation. This position implied that even very small doses of radiation are carcinogenic, a finding that, for example, could force the Environmental Protection Agency to adopt stricter health standards to protect against occupational and general population exposure. Other members of the Committee did not accept this position, and believe this is an alarmist approach. When there is no human epidemiological evidence at low doses of low-LET radiation, these scientists prefer to assume that the risks of causing cancer are proportionally lower.

Let us look at some of the problems. In its deliberations, the BEIR-III Committee concluded two important observations. (1) It is not yet possible to make precise low-dose estimates for cancer-induction by radiation because the level of risk is so low that it cannot be observed directly in man. (2) There is great uncertainty as to the dose-response function most appropriate for extrapolating to the low-dose region. In studies of exposed animal and human populations, the shape of the dose-response relationships for cancer-induction at low doses may be practically impossible to ascertain statistically. This is because the population sample sizes required to estimate or test a small absolute cancer excess are extremely large; specifically, the required sample sizes are approximately inversely proportional to radiation dose, and if 1,000 exposed and 1,000 control persons are required in each group to test this cancer excess adequately at 100 rads, then about 100,000 in each population group are required at 10 rads, and about 10,000,000 in each group are required at 1 rad. Thus, it appears that experimental evidence and theoretical considerations are much more likely than empirical epidemiological data to guide the choice of a dose-response function for cancer-induction. In this dilemma and after much disagreement among some of its members, the majority of the members of the present BEIR-III Committee chose to adopt as a working model for low-LET radiation and carcinogenesis the quadratic (with linear term) dose-response form with an exponential term to account for the frequently observed turndown of the curve in the high-dose region. However, in applying this multicomponent model, only certain of its derivatives, including the linear, the linear-quadratic, i.e., the quadratic with linear term, and the pure quadratic functions, could prove practical for purposes of estimation of cancer risk (Figure 2).

It should be remembered that in the 1972 BEIR-I Report [2] the cancer risk estimates for whole-body radiation exposure were derived from linear model average excess cancer risk per rad observed at doses generally of a hundred or more rads. These estimates were generally criticized on the grounds that the increment in cancer risk per rad may well depend on radiation dose, and that the true cancer risk at

low doses may therefore be lower or higher than the linear model predicts [9]. In laboratory animal experiments, it has been shown, often with considerable statistical precision, that the dose-response curves for radiation-induced cancer can have a variety of shapes. As a general rule, the curve has a positive curvature for low-LET radiation, i.e., the slope of the curve increases with increasing dose. However, at high doses, the slope often decreases and may even become negative. Dose response curves may also vary with the kind of cancer, with animal species, and with dose rate. On the basis of the experimental evidence and current microdosimetric theory, therefore, the present BEIR-III Committee could quite reasonably adopt as the basis for its consideration of dose-response models the quadratic form with a linear term in the low-dose region, and with an exponential term for a negative slope in the high-dose region.

On the other hand, most of the members of the Committee recognized that, in large part, the available human data from the large body of epidemiological studies fail to suggest any specific dose-response model, and are not sufficient reliable to discriminate among a priori models suggested by the experimental and theoretical studies. However, there appears, at present, to be certain exceptions from the human experience. For example, cancer of the skin is not observed at low radiation doses [17], and dose-response relationships for the Nagasaki leukemia data appear to have positive curvature [18]. The incidence of breast cancer induced by radiation seems to be adequately described by a linear dose-response model (Figure 3) [11,19].

In the Committee's attempts to apply derivatives of the multi-component, linear-quadratic dose-response model to the epidemiological data, simplification was necessary to obtain statistically stable risk estimates in many cases. It is now well known that certain members of the BEIR-III Committee were passionately divided on this matter; some members of the Committee strongly favor the linear model, others favor the pure quadratic form. A further modification of the linear-quadratic form was assumed with the linear and quadratic components to be equivalent at some dose, which is consistent with the epidemiological data and the radiobiological evidence, and avoids dependence on either of the two extreme forms [14-16].

WHAT ARE THE UNCERTAINTIES IN ESTIMATION OF THE CARCINOGENIC RISK IN MAN OF LOW-LEVEL RADIATION?

The quantitative estimation of the carcinogenic risk of low-dose, low-LET radiation is subject to numerous uncertainties. The greatest of these concerns the shape of the dose-response curve. Others include the length of the latent period, the RBE for fast neutrons and alpha radiation relative to gamma and x-radiation, the period during which the radiation risk is expressed, the model used in projecting risk

beyond the period of observation, the effect of dose rate or dose fractionation, and the influence of differences in the natural incidence of specific types of cancer. In addition, uncertainties are introduced by the biological risk characteristics of humans. For example, the effect of age at irradiation, the influence of any disease for which the radiation was given therapeutically, and the influence of length of observation or follow-up of the study populations. The collective influence of these uncertainties is such as to deny great credibility to any estimates of human cancer risk that can be made for low-dose³, low-LET radiation. It is for these reasons, the present BEIR-III Committee decided that emphasis should be placed on the assumptions, procedures, and uncertainties involved in the estimation process and not on specific numerical estimates derived thereby.

WHAT ARE THE SOURCES OF EPIDEMIOLOGICAL DATA FOR THE ESTIMATION OF EXCESS CANCER RISK IN EXPOSED HUMAN POPULATIONS?

The tissues and organs about which we have the most reliable epidemiological data on radiation-induced cancer in man, obtained from a variety of sources from which corroborative risk coefficients have been estimated, include the bone marrow, the thyroid, the breast, and the lung. The data on bone and the digestive organs are, at best, preliminary, and do not approach the precision of the others. For several of these tissues and organs, risk estimates are obtained from very different epidemiological surveys, some followed for over 25 years, and with adequate control groups. There is impressive agreement when one considers the lack of precision inherent in the statistical analyses of the case-finding and cohort study populations, variability in ascertainment and clinical periods of observation, age, sex and racial structure, and different dose levels, and constraints on data from control groups.

By far, the most reliable and consistent data have been those of the risk of leukemia, which come from the Japanese atomic bomb survivors [18], the ankylosing spondylitis patients treated with x-ray therapy in England and Wales [20,21], the metropathia patients treated with radiotherapy for benign uterine bleeding [22], and the tinea capitis patients treated with radiation for ringworm of the scalp [23,24]. There is evidence of an age-dependence and a dose-dependence, a relatively short latent period of a matter of a few years, and a relatively short period of expression, some 10 years. This cancer is uniformly fatal.

The data on thyroid cancer are more complex. These surveys include the large series of children treated with radiation to the neck and mediastinum for enlarged thymus [25], children treated to the scalp for tinea capitis [23,24], and the Japanese atomic bomb survivors [18] and Marshall Islanders [26] exposed to nuclear

explosions. Here, there is an age-dependence and sex-dependence-- children and females appear more sensitive. Although the induction rate is high, the latent period is relatively short, and it is probable that no increased risk will be found in future follow-up of these study populations. In addition, most tumors are either thyroid nodules, or benign or treatable tumors, and only about 5 percent of the radiation-induced thyroid tumors are fatal.

In very recent years, much information has become available on radiation-induced breast cancer in women [13,19]. The surveys include primarily women with tuberculosis who received frequent fluoroscopic examinations for artificial pneumothorax [27], postpartum mastitis patients treated with radiotherapy [28], and the Japanese atomic bomb survivors in Hiroshima and Nagasaki [18]. Here, there is an age-dependence and dose-dependence, as well as a sex-dependency, and the latent period is long, some 20 to 30 years. Perhaps about half of these neoplasms are fatal.

Another relatively sensitive tissue, and a complex one as regards radiation dose involving parameters of the special physical and biological characteristics of the radiation quality, is the epithelial tissue of the bronchus and lung. These surveys include the Japanese atomic bomb survivors [18], the uranium miners in the United States and Canada [29,30], and the ankylosing spondylitis patients in England and Wales [20,21]. There is some evidence of age-dependence from the Japanese experience, and a relatively long latent period. This cancer is uniformly fatal.

The risk of radiation-induced bone sarcoma, based primarily on surveys of the radium and thorium patients who had received the radioactive substances for medical treatment, or ingested them in the course of their occupations [31,32], is low. For all other tumors arising in various organs and tissues of the body, values are extremely crude and estimates are, at best, preliminary.

There is now a large amount of epidemiological data from the various comprehensive surveys from a variety of sources; the most extensive, perhaps, include the Japanese atomic bomb survivors [18], the patients treated to the spine for ankylosing spondylitis [20,21], the metropathia patients [22] and the early radiologists [33]. These data indicate that leukemia is now no longer the major cancer induced by radiation, and that solid cancers are exceeding the relative incidence of radiation-induced leukemia [5]. That is, in view of the long latent period after some 30 years or more following radiation exposure, the risk of excess solid cancers may prove to be many times the risk of excess leukemia. But these risk estimates must remain very crude at the present time, since they do not take into account any lack of precision in certain of the epidemiological studies, particularly as regards radiation dose distribution, ascertainment, latency periods, and other important physical and biological parameters. The

BEIR [1,2], the UNSCEAR [4,5] and the ICRP [6,7] Reports have estimated the risk from low-LET whole-body exposure in different ways and based primarily on the large number of epidemiological surveys carefully followed, many of which now have adequate control study populations, a very crude figure of the total lifetime absolute risk of radiation-induced cancer deaths can be derived. This figure for all malignancies from low-LET radiation, delivered at low doses would be estimated to be less than about 100 excess cases per million persons exposed per rad. But, this figure could very well be an overestimate of the true risk, and the actual number of excess cancer cases may be much lower [1,5]. Although any such numerical estimate must be considered unreliable, it does provide a very rough figure for comparison with other estimates of avoidable risks, or voluntary risks, encountered in everyday life.

WHAT ARE THE RISK ESTIMATES OF RADIATION-INDUCED CANCER IN MAN?

The chief sources of epidemiological data used in the current BEIR-III Report [1] are the Japanese populations exposed to whole-body irradiation in Hiroshima and Nagasaki, the patients with ankylosing spondylitis and other patients who were exposed to partial body irradiation therapeutically, or to diagnostic x-rays and the various occupationally-exposed populations, such as uranium miners and radium dial painters. Most epidemiological data do not systematically cover the range of low to moderate radiation doses for which the Japanese atomic bomb survivor data appear to be fairly reliable. Analysis in terms of dose-response, therefore, necessarily rely greatly on the Japanese data. The substantial neutron component of dose in Hiroshima and its correlation with gamma dose limit the value of the more numerous Hiroshima data for the estimation of cancer risk from low-LET radiation. The Nagasaki data, for which the neutron component of dose is small, are less reliable for doses below 100 rads.

After much deliberation and a good deal of determined debate, the present BEIR-III Committee chose three exposure situations for illustrative computations of the lifetime cancer risk of low-dose, low-LET whole-body radiation: (1) a single exposure of representative (life-table) population to 10 rads; (2) a continuous, lifetime exposure of a representative (life-table) population to 1 rad per year; and (3) an exposure to 1 rad per year over several age intervals exemplifying conditions of occupational exposure. These three exposure situations were not chosen to reflect any circumstances that would normally occur, but embrace the areas of concern--general population and occupational exposure and single and continuous exposure.

Much dissatisfaction and disagreement attended the choice of these particular dose levels to be used for illustrative purposes. These were substantially different from the only exposure situation chosen

for the illustrative computation by the 1972 BEIR-I Committee, where 100 mrem per year was the level selected. Some members of the present BEIR-III Committee strongly felt that below these three dose levels, which were arbitrarily chosen for the current Report, the uncertainties of extrapolation to very low-dose levels were too great to justify any attempt at risk estimation. Other members felt just as strongly that risk estimates for cancer-induction by radiation could be reliably calculated at dose levels of 1 rad or even much less. These differences were never satisfactorily settled. The selected annual level of chronic exposure of 1 rad per year, although only one-fifth the maximal permissible dose for occupational exposure, is nevertheless consistent with the occupational exposure experience in the nuclear industry. The U.S. 1969-1971 life-table was used as the basis for the calculations. The expression time was taken as 25 years for leukemia and the remaining years of life for other cancers. Separate estimates were made for cancer mortality and for cancer incidence.

In the absence of any increased radiation exposure, among one million persons of life-table age and sex composition in the United States, about 164,000 persons would be expected to die from cancer, according to present cancer mortality rates. For a situation in which these one million persons are exposed to a single dose increment of 10 rads of low-LET radiation, the linear-quadratic model predicts increases of about 0.5 percent and 1.5 percent over the normal expectation of cancer mortality, according to the projection model used. For continuous lifetime exposure to 1 rad per year, the increase in cancer mortality, according to the linear-quadratic model, ranges from about 5 percent to 10 percent over the normal expectation, depending on the projection model. The upper and lower limits of these cancer mortality risk estimates suggest a very wide range or envelope of values which may differ by as much as an order of magnitude, or more. The uncertainty derives mainly from the dose-response models used, from the alternative absolute and relative projection models, and from the sampling variation in the source data. The lowest risk estimates--the lower bound of the envelope--are obtained from the pure quadratic model; the highest--the upper bound of the envelope--from the linear model; and the linear-quadratic model provides estimates intermediate between these two extremes.

To compare the cancer mortality risk estimates with those of the 1972 BEIR-I Report [2] and the 1977 UNSCEAR Report [5], it was most convenient to express them as cancer deaths per million persons per rad of continuous lifetime exposure. For continuous lifetime exposure to 1 rad per year the linear-quadratic dose-response model for low-LET radiation yields risk estimates considerably below the comparable linear-model estimates in the 1972 BEIR-I Report [2]. The difference mainly reflect changes in the assumptions made by the two BEIR Committees almost a decade apart. The present BEIR-III Committee preferred a linear-quadratic, rather than linear, dose-response model for low-LET radiation, and preferred not to assume a fixed relationship

between the effects of high-LET and low-LET radiation. Furthermore, the present risk estimates do not, as in the 1972 BEIR-I Report [2], carry through to the end of life very high relative-risk coefficients obtained with respect to childhood cancers induced in utero by radiation.

There was a good deal of reluctance by some Committee members to introduce cancer-incidence data--for the first time in any report--for purposes of risk estimation. Since cancer mortality data are considered far more reliable than comparable incidence data, cancer incidence risk estimates are less firm than mortality estimates. However, the Committee also recognized that the incidence of radiation-induced cancer provides a more complete expression of the total social cost than dose mortality. The present BEIR-III Committee used a variety of dose-response models and several data sources. For continuous lifetime exposure to 1 rad per year, for example, and based on the linear-quadratic model, the increased risks expressed as percent of the normal incidence of cancer in males were about 2 percent to 6 percent, depending on the projection model. The various dose-response models produced estimates that differed by more than an order of magnitude, whereas the different data sources gave broadly similar results. Risks for females were substantially higher than those for males, due primarily to the relative importance of radiation-induced thyroid and breast cancer.

Estimates of excess cancer risk for individual organs and tissues depend in large part on partial-body irradiation and use a much wider variety of epidemiological data sources. Except for leukemia and bone cancer, estimates for individual sites of cancer can be made only on the basis of the linear model, and all risk coefficients are estimated as the number of excess cancer cases per year per million persons exposed per rad. For leukemia, the linear-quadratic model yielded about 1.0 to 1.4 excess leukemia cases, for females and males, respectively. For solid cancers, linear-model estimates were, for example: for thyroid in males, about 2, and in females, about 6; for female breast, about 6; and for lung, about 3.5 to 4. These risk coefficients derive largely from epidemiological data in which exposure was at high doses, and these values may, in some cases, overestimate risk at low doses.

WHAT ARE THE IMPLICATIONS OF NUMERICAL RISK ESTIMATION FOR RADIATION PROTECTION AND PUBLIC HEALTH POLICY?

The present BEIR-III Committee has not highlighted any controversy over the health effects of low-level radiation. In its evaluation of the epidemiological surveys and the laboratory animal data, the Committee has carefully reviewed and assessed the value of all the available scientific evidence for estimating numerical risk coefficients for the health effects in human populations exposed to low-level radiation.

Such devices required scientific judgment and assumptions based on the available data only, and have necessarily and understandably led to some disagreement not only outside the Committee room, but among Committee members, as well. But such disputes and disagreements center not on the scientific facts and not on the existing epidemiological or experimental data, but rather on the assumptions, interpretations, and analyses of the available facts and data.

The present scientific evidence and the interpretation of available epidemiological data can draw very few firm conclusions on which to base scientific public health policy for radiation protection standards. The setting of any permissible radiation level or guide remains essentially an arbitrary procedure. Based on the radiation risk estimates derived, any lack of precision does not minimize either the need for setting responsible public health policies, nor the conclusion that such risks are extremely small when compared with those available of alternative options, and those normally accepted by society as the hazards of everyday life. When compared with the benefits that society has established as goals derived from the necessary activities of energy production and medical care, it is apparent that society must establish appropriate standards and seek appropriate controlling procedures which continue to assure that its needs and services are being met with the lowest possible risks.

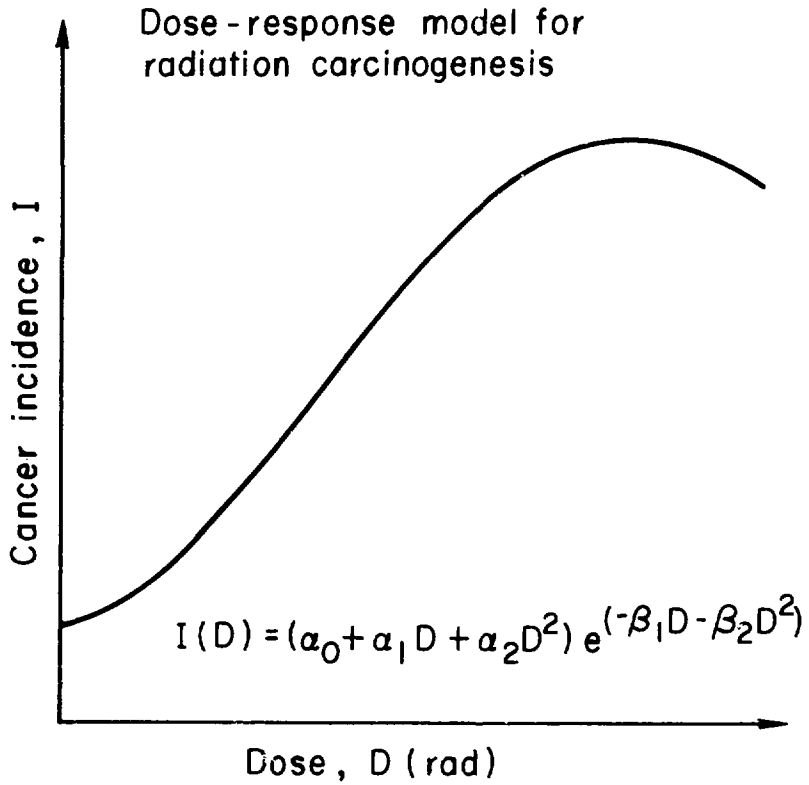
In a third century of inquiry, embodying among the most extensive and comprehensive scientific efforts on the health effects of an environmental agent, much of the practical information necessary for determination of radiation protection standards for public health policy is still lacking, and may remain so. It is now assumed that any exposure to radiation at low levels of dose carries some risk of deleterious health effects. However, how low this level may be, or the probability, or magnitude of the risk, still are not known. Radiation and the public health, when it involves the public health, becomes a broad societal problem and not solely a scientific one, and to be decided by society, most often by men and women of law and government. Our best scientific knowledge and our best scientific advice are essential for the protection of the public health, for the effective application of new technologies in medicine and industry, and for guidance in the production of nuclear energy. Unless man wishes to dispense with those activities which inevitably involve exposure to levels of ionizing radiations, he must recognize that some degree of risk to health, however small, exists. In the evaluation of such risks from radiation, it is necessary to limit the radiation exposure to a level at which the risk is acceptable both to the individual and to society. A pragmatic appraisal of how man wishes to continue to derive the benefits of health and happiness from such activities involving ionizing radiation, in times of everchanging conditions and public attitudes in our resource-limited society, is the task which lies before each expert advisory committee on the biological effects of ionizing radiation, now and in future years.

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SHAPES OF DOSE RESPONSE CURVES

