The Effects on Populations of Exposure to Low Levels of Ionizing Radiation: 1980

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The Effects on Populations of Exposure to Low Levels of Ionizing Radiation: 1980

COMMITTEE ON THE BIOLOGICAL EFFECTS OF IONIZING RADIATIONS,
Division of Medical Sciences
Assembly of Life Sciences
National Research Council,

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Washington, D.C. 1980

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July 22, 1980

Mr. Douglas Costle
Administrator
Environmental Protection Agency
401 M Street, S.W.
Washington, D.C. 20460

Dear Mr. Costle:

I am pleased to transmit the report "The Effects on Populations of Exposure to Low Levels of Ionizing Radiation" prepared under contract 68-01-4301 with EPA's Office of Radiation Programs.

The report, familiarly known as BEIR III (after its authoring Committee on the Biological Effects of Ionizing Radiations), has had a troubled history. In May 1979, a version of the report was publicly released. But when it was learned that a significant number of committee members believed that the somatic effects section of the report did not adequately reflect the full range of committee opinion generated by the admittedly incomplete data base, further distribution was discontinued.

It is not unusual for scientists to disagree on the interpretation of data. Generally, the sparser and less reliable the data base, the more opportunity for disagreement. In this case, there are sufficient data concerning the effects of exposure to high doses of ionizing radiation, but little reliable information concerning the consequences of exposure to lower doses, especially those low doses to which a human population might be exposed. Upon the issue of how one may extrapolate from the high doses to the low, scientific argument turned on the question of how one may validly extrapolate from the measured effects of high doses to the most probable effects of low doses.

The BEIR III report exhibits the range of opinion concerning how this extrapolation may be performed. Many committee members believe that the data best support a linear quadratic model for estimating risk; others, however, believe that the linear or pure quadratic models provided better estimates. The report presents all of these views, in balanced fashion. The committee as a whole, despite individual preferences, has agreed that the report treats each of the possible interpretations in a fair manner. Two members have not found it possible to endorse the report. The dissenting statement by Dr. Radford espouses the linear model; that by Dr. Rossi favors the pure

quadratic model. Both models are included. The polarity of these two views best illustrates the degree to which scientists disagree on this subject in absence of sufficient evidence to compel conclusion.

We believe that the report will be helpful to the EPA and other agencies as they reassess radiation protection standards. It provides the scientific bases upon which standards may be decided after nonscientific social values have been taken into account. If social values dictate a conservative approach, the report's linear model risk estimates may serve as a guide. If one wishes to accept scientists' best judgment while recognizing that the data simply will not permit definitive conclusions, one may select risk estimates using the linear quadratic model as a guide. Other considerations may lead to use of the pure quadratic risk estimates.

We regret that the transmittal of this report has been delayed so long. The Academy believes that the delay was necessary to permit time for restating the report so as to display all of the valid opinions rather than distribute a report that might create the false impression of a clear consensus where none exists.

Sincerely yours,

PHILIP HANDLER
President, National Academy of Sciences

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Statement Concerning the Current Version of Cancer Risk Assessment in the Report of the Advisory Committee on the Biological Effects of Ionizing Radiations (BEIR III Committee)

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Professor of Environmental Epidemiology
Graduate School of Public Health, University of Pittsburgh

Chairman, BEIR III Committee *and*
Chairman, Subcommittee on Somatic Effects

The present version of the report of the Advisory Committee on the Biological Effects of Ionizing Radiations (the BEIR III Report) is a modification of the draft report approved by the Academy in April 1979 and released at a press conference at the Academy on May 2, 1979. Subsequent modifications of this approved draft have been prepared by a group appointed by Dr. Philip Handler, President of the Academy, consisting of six members of the somatic effects subcommittee and one member of the genetic effects subcommittee. The modifications involve principally the section of the report summarizing cancer risk estimates (the third and final section of Chapter V) and some of the conclusions that flow from this section. Cancer is a somatic effect of radiation, that is an effect on the body cells of individuals exposed, as distinct from effects on the germ cells or genetic effects. Thus, the sections at issue have been the responsibility of the subcommittee on somatic effects of the full BEIR III Committee. This subcommittee originally consisted of seventeen members whose names are given in the front of the report. This number has been reduced to fifteen by the deaths of Dr. Benjamin Trumble in November 1977 and Dr. Cyril Comar in June 1979.

The material prepared by the subcommittee on somatic effects was written largely during 1977–1978, with occasional one or two-day meetings of the subcommittee to review draft material as it was prepared. It is important to note that the last meeting of the full subcommittee was held on December 15, 1978, a one-day meeting. The new material incorporated in the report since May 1979 has, therefore, not been approved by the subcommittee as a whole except by the process of asking for comments by mail. Perhaps because completion of the BEIR III report has been delayed for such a long time, few members of the subcommittee have responded. Nevertheless, the present version of the report includes very major change from the earlier draft and from the BEIR I report of 1972. That is the decision to adopt the so-called linear-quadratic model (excess cancer risk = $aD + bD^2$, where a and b are constants and D is radiation dose) as the basis for calculating risk at low doses of low LET radiation for all cancers, and not just leukemia as in the previous draft. In addition, risk estimates calculated from a model in which the excess cancer was assumed to be proportional to the dose squared (the so-called pure quadratic model, excess risk = bD^2) were also included. The effect of adopting the linear-quadratic model is to reduce the risk estimates at low doses somewhat. The pure quadratic model implies a very low risk at low doses.

The decision to use the *linear* (straight line) no-threshold model (excess cancer risk = aD), which implies a risk directly proportional to dose at all levels, for all radiation types and for all cancers except leukemia was the result of a vote taken in a meeting of the subcommittee in October 1977. This vote has never been rescinded by action of the whole subcommittee, and thus as chairman of the subcommittee, I cannot consider that the present version is in accord with the perceptions of at least several of its members.

The most serious consequence of this alteration in the conclusions of the earlier draft, however, is that all of the discussions and evaluations of the data on cancer risks that took place among subcommittee members as the draft material for the report accumulated during 1978, did so on the basis that the linear model would be applied. In this regard the subcommittee was adhering to a principle adopted by the BEIR I Committee, and as an expedient measure, in view of the limited amount of time available, I had felt that we would not spend our time reviewing in detail the scientific basis for those conclusions which agreed with the BEIR I report. In short, the requirement to complete the report in 1978 imposed by the Academy staff meant that the extent of discussions of fundamental issues had to be limited, particularly for matters that had been thoroughly presented in BEIR I. Thus, a detailed and critical discussion by the subcommittee of the

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scientific basis of deciding whether one or another dose-response model was applicable to cancer risks was not undertaken.

One exception to the above statement was the data from the Japanese A-bomb survivors. The results of the follow-up of cancer experience through 1974 in this important study population had been made available to subcommittee members in page proof by Dr. Gilbert Beebe in 1977, but in this form it was used primarily to provide an important source of data for the individual cancer risk sections being prepared by several members of the subcommittee and now found in Appendix A of Chapter V. Bound copies of this report (Life Span Study Report 8, Technical Report RERF TR 1-77) were distributed by the Academy staff in mid-1978. The significance of this distribution was that for the first time all the members of the subcommittee had, in an easily readable form, the latest information concerning cancer risk in this population. At about the same time we obtained the Oak Ridge calculations of factors by which kerma doses could be converted to specific tissue doses for both gamma ray and neutron exposures in the two cities. Subsequently, a large amount of time during the remaining few meetings of the subcommittee was spent in discussion of cancer data from this report in terms of the tissue dose-response relationships that could be inferred from the data as presented. Since such a process amounts at best to fitting theoretical lines to data points, in these discussions the subcommittee did not address the fundamental scientific basis of any of the models proposed to fit the Japanese data.

In my view, new data, obtained since the BEIR I report in 1972, strongly supported the decision of the BEIR I committee to adopt the linear no-threshold model for cancer induction by radiation. 1) New human studies were available giving stronger evidence of effects in the 10 to 50 rad range, and these studies generally gave about the same risk of excess cancer per unit dose as the higher dose data had. 2) The range of exposure patterns to low LET radiation included more studies of multiple small doses which could be compared to effects of single doses. 3) Studies of individuals especially susceptible to cancer induction by radiation and other carcinogens were being expanded (e.g., see Chapter II, the section entitled "Cell Mutation or Transformation"), and there was a possibility that these susceptible populations might be fairly large and not identifiable in advance. This possibility suggested at least that cancer risk estimates at low doses for this population subset could be somewhat higher than would be inferred from studies of unselected populations. 4) Studies of oncogenic transformations of human and animal cells in culture had been greatly expanded, with startling new results that challenged many of the traditional radiobiologic concepts that had formed a scientific basis for

extrapolation of effects of higher doses of low LET radiation into the low dose range. These results suggested, for example, that DNA repair did not necessarily imply that low doses of low LET radiation would be less carcinogenic per unit dose than high doses. 5) Finally, new evidence of cytogenetic changes observed in populations living in areas of high background radiation exposure had been obtained. At my suggestion this last evidence was not considered extensively by the subcommittee, primarily for the same reason they were not by the BEIR I Committee; that is, the significance of these changes observed in circulating lymphocytes in terms of human disease had not yet been defined. But these observations indicated that effects of radiation exposure at doses and dose rates moderately above background could be detected.

All of the above considerations indicated not only that the decision of the present subcommittee to reaffirm the applicability of the linear no-threshold dose response relationship was the correct one, but also that such a decision was not so conservative as had been thought at the time of the BEIR I report. That is, the cancer risk estimates for exposure to low doses based on the straight line extrapolation could be somewhat lower than might be found eventually to apply, especially to susceptible subsets of the population. Such an underestimation of risk, the subcommittee agreed, would be unlikely for low LET radiation, but the view that the linear extrapolation greatly overestimated the risk of low LET radiation at low doses appeared to me to be equally unwarranted. For high LET radiation, such as alpha radiation, the straight line extrapolation could underestimate the risk at low doses, but the evidence was not strong that such underestimation was very significant except in its theoretical inferences.

I now proceed to consider in some detail the scientific evidence pertinent to estimates of cancer risk in human populations from low doses of radiation. Of special importance are two questions that have divided the subcommittee. First, what is the experimental evidence to support the linear no-threshold dose-response relationship of cancer induction? Second, to what extent are the data from the Japanese A-bomb survivors concordant with all other human studies, and also consistent with linear or other dose-response models? A problem related to this last question is the degree of concordance of results from the two cities, Hiroshima and Nagasaki, and from comparison between the two cities the appropriate inferences to draw about the relative effectiveness of the neutron component of exposure in Hiroshima. (The type of bomb exploded in the two cities differed: both resulted in exposure to gamma radiation, but the Hiroshima bomb had a significant fraction of the radiation exposure from neutrons.)

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Some general comments are in order at this point. First, there was *no* disagreement among the members of the somatic effects subcommittee to accept the linear no-threshold dose-response relationship to define *genetic* effects of radiation at low doses, a position firmly taken by the BEIR III subcommittee on genetic effects (Chapter IV) in agreement with the BEIR I report. Based especially on the mouse studies of William L. Russell,[1,2] a member of the subcommittee on genetic effects for both BEIR I and BEIR III, the subcommittee did recommend that for low LET radiation exposure at low dose rates, the mutational risk per unit dose for radiation of the male testis is probably less by a factor of three at low dose rates than for equivalent doses given at a higher rate.

In the present version of the report, there is an inconsistency between the conclusions of the two subcommittees with regard to the appropriate dose-response relationship to be applied for genetic and carcinogenic effects of radiation. Consistency in evaluating these two effects of radiation is reasonable because there is now wide agreement among the scientific community studying cancer (for a summary of the evidence see *Origins of Human Cancer*[3]) that a necessary condition for induction of cancer is production of one or more mutations in the DNA of one or more cells in a tissue. This mutational change in somatic cells as a condition for carcinogenesis is the foundation of the use of short-term testing of mutations produced by environmental agents as a screening test for carcinogenic potency.[4]

The entire process of carcinogenesis is a complex one, however, and an initiating event, such as a somatic cell mutation, is not the only condition required for cancer to arise, whereas a mutation in a germ cell that retains its viability is the sole condition of a transmitted hereditary defect. For this reason one might anticipate that the dose-response relationship for cancer induction could differ in certain ways from that of genetic mutation. But it is important to note that the differences in the two processes arise because of host factors or other biological factors in cancer expression that are essentially *independent of the initiating event or events*, thus not necessarily related either in space or time to the dose of radiation. If, therefore, one argues from the above-mentioned difference that the dose-response curve for cancer induction should differ from that for genetic effects, such argument cannot be based on biophysical principles that relate to the initiating mutational event. Indeed, because we suspect that many unrelated biological factors influence the probability of subsequent development of human cancer after exposure to radiation (see Chapter II, the section entitled "Host Factors in Radiation Carcinogenesis"), it is far from obvious in which way one would postulate that the dose-response curve should be modified at low doses. If evidence existed that a significantly large group were especially susceptible because of differences in

some of the host factors related to carcinogenesis, we would expect that any cancer initiator such as radiation could be more effective per unit dose at low doses than at high doses, where all or most of the susceptible group could already have cancer induced.

The fact that we do not yet understand all the factors governing cancer development in man was an important reason why the subcommittee unanimously agreed to depend primarily on studies of human populations to define cancer risk from radiation exposure. The number of studies available is impressive, about 50 investigating cancer at various sites from irradiation for various reasons. In a few instances the results are negative, as one might expect on statistical grounds, or because epidemiologic criteria such as a suitable control population were difficult to meet. Yet, the remarkable fact is that the cancer risk estimates derived from a majority of the studies, involving widely different ethnic groups irradiated in different ways for different reasons, show a considerable agreement (see Chapter V, Appendix A), at least in the higher range of radiation doses where it has been possible to detect clear effects. The cancer mortality data from the Nagasaki A-bomb survivors are perceived by some members of the subcommittee as an exception, and this point will be discussed in detail below.

EXPERIMENTAL BASIS FOR DOSE-RESPONSE MODELS

The present version of the report has departed to some extent from the subcommittee decision to depend primarily on human studies for cancer risk estimates, in that adoption of the linear-quadratic dose-response model as the primary model to use for extrapolation of low dose effects of low LET radiation has been strongly influenced by data obtained on laboratory animals, which usually show cancer dose-response relationships curvilinear upward within, say, 200 rad. This influence is understandable if one considers that the human evidence of cancer risk is sparse for low radiation doses, but there are many reasons why animal studies are of limited value, and indeed may be misleading, with regard to dose-response information for human cancers.

These reasons include: 1) Animal cancers at particular sites may differ morphologically and in growth characteristics from human tumors at the same site, and for this reason initiating and promoting processes could be quantitatively different. 2) The strains of experimental animals used for nearly all research are highly inbred, and for each strain susceptibility to cancer induction is likely to be more homogeneous than in man. Human

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populations have variable genetic makeup and it is known that genetic factors influence cancer susceptibility.[5] This variability would have the effect of making the response at low doses greater per unit dose than at higher doses where the proportion of cancer-sensitive groups affected would be less. 3) The life span of most species such as rodents widely used for experimental studies of cancer is short, generally two to three years, and the latent period between exposure to radiation and onset of increased cancer incidence is proportionately a larger fraction of the life span in these species than in man. 4) Because animals used for lifetime studies of cancer development are kept in artificial surroundings, on a fixed nutritional regimen, and protected from intercurrent infections such as from viruses, exposure to a wide range of cancer-promoting or other factors which could modify cancer expression is thereby kept to a minimum. Such exposure is considered to be the almost daily lot of human existence, and may be an important contributor to the very marked influence of age on incidence of most cancers in man.[6] One consequence of this artificial environment of experimental animals is that for any single chemical or physical agent under study to lead to frank cancer, both initiating and promoting factors must be provided by the carcinogen; in the parlance of cancer research, the agent tested must be a complete carcinogen. There are two important consequences of this condition: first, the latent period may be inversely related to dose,[7] and second, one would expect that the cancer rate would more likely be proportional to the square of the dose, rather than to the first power of dose anticipated if only random initiating events were required for cancers to appear. Both these reasons, as well as the longer latent period in proportion to the short life span of these animals, lead to the dose-response curve at any time after the onset of excess cancer being likely to be strongly curvilinear upward. That is, low doses will appear to be less effective per unit dose than higher doses, even if the probability of cancer initiation were random and followed a linear, no-threshold relationship. It is significant that in human studies of radiogenic cancer where an effect of dose on latent period was looked for (Appendix A), the inverse dependence of latent period on radiation dose appears to be slight at most, consistent with the idea that the promoting step of radiation carcinogenesis in man is independent of the initiating event.

For the above reasons, therefore, I believe it is unwise to rely on dose-response data for cancer induction in experimental animals to support use of any particular dose-response model for human risk estimates from radiation exposure at low doses.

In the above discussion it is evident that the step of cancer initiation by radiation is an important element in quantitative understanding of risks

of radiation exposure. Because this process is believed to be a cellular phenomenon, albeit influenced by tissue and host factors, quantitative assessment of dose-response relationships for the process of oncogenic transformation of cells has been actively pursued both in theoretical terms and experimentally, especially since the BEIR I report. One of the most widely discussed theoretical concepts in recent years has been the Kellerer-Rossi theory of dual radiation action.[8] The essence of this theory is found in Chapter II in the section entitled "Physical Aspects of the Biologic Effects of Ionizing Radiation."

It is important to note at the outset the fundamental assumption underlying the theory, which is that *pairs* of sublesions, produced by radiation in critical sites in the cell, combine to form lesions which are eventually expressed as a permanent change in the cell, such as a mutation or oncogenic transformation. This assumption is an extension of the theory of Lea,[9] developed to account for effects of gamma and neutron radiation in producing gross chromosomal aberrations. In this particular case the assumption that two breaks (or sublesions) are required to produce the effect is very plausible. For chromosomal aberrations in human lymphocytes a dose-squared dependence of effects has been observed for low LET radiation,[10,11] consistent with Lea's theory. To extend the assumption of two sublesions being required for other effects of radiation than gross chromosomal aberrations requires that experimental evidence of an effect proportional to the dose-squared be observed for such effects. This experimental evidence, as referenced, is derived from studies of chromatid aberrations in *Tradescantia*, the spiderwort plant,[12] effects on bacterial spores,[13] and radiation induced life-shortening in animals.[14] (This last effect of radiation would be expected to involve non-stochastic processes, in sharp contrast to cancer induction; moreover, the subcommittee has concluded on the basis of available human data, that no non-specific life-shortening effect of radiation has been observed in man.) This array of evidence is far from convincing justification of the assumption that two sublesions are required to produce lesions in the DNA of mammalian cells that may lead, for example, to oncogenic transformation, unless such transformation is consistently associated with gross chromosomal aberrations.

If we follow the Kellerer-Rossi formalism, nevertheless, on the further assumption that the sublesions interact to produce a lesion over a range of about 1 mμ in the cell, then the frequency of effects, $E = K(\zeta D + D^2)$, where K is an arbitrary constant and zeta is a variable dependent on the frequency distribution of specific energies produced by single events. The Kellerer-Rossi theory, therefore, leads to a linear-quadratic dependence of effect on dose, a conclusion that is obvious from the fundamental

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assumption that pairs of sublesions are a necessary condition of ultimate effects. The theory has been applied to the problem of the relative biological effectiveness of different types of radiation at low doses, in which case both K and ζ are variables which are used to fit the experimental data. Experiments of Cox et al.,[15] in which mutation of HF19 human fibroblasts and V79 Chinese hamster cells by various radiations encompassing a wide range of LET was examined, were analyzed by Goodhead in terms of the Kellerer-Rossi theory.[16] Goodhead showed that the RBE values predicted on the Kellerer-Rossi theory were at considerable variance from those observed, and it was apparent that no consistent set of values for K and ζ in relation to LET could be derived from the data, nor were the derived "constants" consistent for similar effects in the two species. Goodhead also pointed out that ζ, which is equivalent to the dose at which the linear and quadratic terms are equal and which thus defines the dose range over which a simple linear fit to data is generally adequate, is very markedly affected by the diameter of the "interaction site," the locus within which the pairs of sublesions are presumed to produce the lesion. For an interaction diameter of 1 mμ, Goodhead's calculations indicate a value of ζ of about 30 rad for Co-60 gamma rays, and about 100 rad for 250 kVp x-rays. For a more likely interaction diameter of 0.4 mμ for cell transformation effects, the corresponding values are about 400 rad for both types of radiation. These latter values are so high that one would conclude that over the range of doses up to 200 rad, the Kellerer-Rossi theory actually *supports* application of the linear no-threshold dose-response relationship for oncogenic transformation.

But even more significant than these theoretical considerations are the results of recent studies of oncogenic transformation in mammalian cells by low doses of x-rays. Borek and Hall first showed[17] in hamster embryo cells that split doses of 210 kVp x-rays were more effective in producing transformations, and this result has been confirmed for doses below 100 rad in mouse $10T^1/_2$ cells[18] and in A31-11 mouse BALB/3T3 fibroblasts.[19] Little and his colleagues[20] have pointed out the complexity of the role of DNA repair in these results, and have concluded from studies in which a phorbol promoter or a protease inhibitor has also been added to mouse $10T^1/_2$ fibroblast cultures that the DNA lesions and repair process associated with cell killing and cell transformation are different. This observation is especially important because the Kellerer-Rossi theory has been mainly applied to studies of cell killing. Little[21] also has postulated that rapid DNA repair mechanisms are error-prone, and result in transformations. A slower, at least partially error-correcting repair process is also present, but if the cell undergoes DNA replication before this latter repair can occur, then the DNA alteration becomes "fixed" or

"stabilized" in a heritable form after one cell division. This change becomes expressed as a transformation after a number of subsequent cell divisions, the number influenced by whether the cells are exposed to other non-transforming chemicals or agents during this stage. These results emphasize the importance of exposure to other agents affecting cell proliferation in fixation and expression of transformational damage, a concept in accord with much evidence concerning non-specific factors in promotion of human cancer.

Work on this aspect of oncogenic transformation of cells is progressing rapidly and can be expected to yield important new insights into the relationship between transformations produced by low doses of all types of radiation and the process of carcinogenesis in animals and man. But the important point here is that the data in hand show clearly that biological factors such as DNA repair mechanisms and exposure to other non-transforming agents markedly modify the probability of an oncogenic transformation, and the simple view that repair of initial damage produced by low LET radiation at low dose rates will inevitably reduce the subsequent probability of cancer induction when compared to the same dose given at high dose rates, is clearly untenable.

For both these biological reasons as well as the theoretical points made, for example, by Goodhead, I believe the Kellerer-Rossi theory is quite unacceptable as having any relevance to dose-response relationships for human cancer. Indeed, the cell transformation data suggest that the linear no-threshold dose-response curve as a basis for extrapolating carcinogenic effects from high to low doses of low LET radiation could even somewhat *underestimate* the low-dose risk, as Miller and Hall[18] and Borek[22] have emphasized.

DOSE-RESPONSE DATA FROM EPIDEMIOLOGIC STUDIES OF HUMAN POPULATIONS

The above practical and theoretical problems thus refute the idea that experimental evidence provides any basis for deciding on the particular forms of the dose-response relationship in human radiation carcinogenesis. This situation means that we must rely on epidemiologic evidence to estimate risks at low doses of low LET radiation, as the subcommittee had concluded early in its deliberations. Unfortunately, as the third section of Chapter V points out, good dose-response data in human populations of large enough size to provide statistically reliable risk estimates in the range of doses less than 50 rad are very limited. Such data are needed if extrapolation to lower doses is to have any precision, or even

to determine whether the simplest extrapolation curve, the linear no-threshold model adopted by the subcommittee to estimate cancer risks from low LET radiation, is reasonable or not. As the above comments indicate, use of the linear extrapolation can hardly be considered to provide an "extreme" estimate of low-dose risk.

The only population study that does provide dose-response data of this type is that of the Japanese A-bomb survivors. It is not generally recognized that the strength of the Japanese data in epidemiologic terms lies in data obtained for low doses, less than 100 rad kerma. The major part of the number of survivors with significant exposures are in the two dose groups, 10-49 rad kerma, or a mean *tissue* dose of about 11 rad, and 50-99 rad kerma, or a mean *tissue* dose of about 35 rad. For doses greater than 200 rad kerma, about 120 rad mean tissue dose, the numbers of survivors included in the Life Span Study October 1, 1950, and who were over age 20 at the time of the bombing (the group in which nearly all cancer deaths had occurred between 1950 and 1974) were only 942 in Hiroshima and 684 in Nagasaki, numbers that are small enough that if the dose is fractionated further into three dose categories, as has been done in RERF Report 8, the results are likely to lead to statistically unstable estimates of excess cancer risk, especially in Nagasaki. Thus, it is fair to say that in the long run, a principal value of data obtained from this study population will be to permit estimation of cancer risk from acute exposures in a range of 10-35 rad mean tissue dose.

The fact that the A-bomb survivors are the only large group with a wide range of whole body radiation exposure makes them singularly important in dose-response evaluation of the carcinogenic effect of radiation in man. There was general agreement for this position among the subcommittee members, and it was the reason that extensive debate concerning interpretation of the follow-up data through 1974 from RERF Report 8, took place up to the final meeting of the subcommittee.

The areas of discussion revolved especially around interpretation of the Nagasaki data to evaluate effects of low LET radiation. Because the Hiroshima bomb led to a significant neutron exposure whose effect was difficult to assess independently, the Nagasaki data thus became the basis for defining low LET radiation effects. Unfortunately, the Nagasaki study population is much smaller than the Hiroshima group, and is especially small in the zero dose category, the accepted control population for the exposed populations. A better control population can be developed by combining the zero dose group and those exposed to 1-9 rad kerma (mean tissue dose about 1.8 rad), an approach which has been widely used to improve the analysis by investigators reporting results from these studies. Regardless of the control base selected, however, the data from Nagasaki

inevitably show quite large statistical error ranges, especially at the higher doses.

Another important issue has been the relative importance of cancer mortality data from the death certificate study compared to the results obtained from the Tumor Registries in the two cities. The results of the dose-response analysis for both cities and for these two data sources are shown for all cancers except leukemia and bone cancer in Figures V-6 and V-7 of Chapter V. The mortality data in Figure V-6 are for the period 1955-1974, while the incidence data are for 1959-1970. The total number of cancer cases in the two instances is about the same, thus the statistical power of analysis of results from the incidence and mortality studies is also about the same.

The mortality data shown in Figure V-6 suggest from the fitted regression lines that the radiation effect in Nagasaki was much less than in Hiroshima, thus implying that the neutron component in Hiroshima may have been of major importance. But it is clear from analysis of the individual data points that a major difference accounting for the low slope of the Nagasaki dose-response is the single point at about 120 rad (200-299 rad kerma). This point shows a quite high cancer rate in Hiroshima and low in Nagasaki. The data points for *both* cities are low for the point at about 160 rad. At the request of the subcommittee Dr. Charles Land ran the correlation for the data below 100 rad (5 data points) and found that the results gave a reasonable linear fit with a difference in slope between the two cities consistent with a constant RBE of about 5 for the neutron component.

While I do not suggest that this type of mathematical manipulation provides a great deal of help in establishing firm conclusions, I do believe that it is important to understand that the apparent difference in response for the two cities indicated by the regression slope in Figure V-6 arises because of differences observed at *high* doses, where the Nagasaki data especially are less reliable on statistical grounds, rather than because of differences at low doses, where the data are somewhat more robust. Moreover, to attribute the difference entirely to a high neutron effectiveness in cancer induction implies that an especially high RBE applies to high doses only, a conclusion entirely at variance with current views of the effect of dose on the RBE of neutrons.

The results of the data from the Tumor Registries, Figure V-7, show a marked difference for the Nagasaki dose-response compared to Figure V-6, and a concordance between the two cities that suggests a constant RBE for neutrons of about 5. It should be noted that the tumor incidence dose-response data depend on the same denominator base of the Life Span Study population as do the mortality data. One problem with the

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Tumor Registry data, however, is the fact that they have not yet been "evaluated," that is, it has not been determined whether out-migration from the cities, which would lose cases and therefore provide a lower estimate of risk, is randomly distributed by dose categories, and thus would not affect the slope of the dose-response curve. A random distribution by dose category of loss to follow-up from out-migration occurred in the women studied for breast cancer incidence in the two cities.[23] The loss by out-migration was only 16%, despite the fact that the study population included in 1950 a large number of young women who might be expected to move because of marriage.[24] The Tumor Registry data have the advantage, however, that a high percentage of the cases have either histologic or autopsy confirmation of the cancer diagnosis, and the Nagasaki Registry particularly is believed to be quite complete for the area around the city (Moriyama, I., personal communication to the subcommittee, 1978).

On the other hand, the death certificate data have an important deficiency in that major radiogenic cancers are significantly under-reported. Breast cancer in women is markedly under-reported because breast cancer has a relatively long survival time and thus death is often recorded as from another cause, and thyroid cancer is usually not fatal. Thus in both cases these highly important radiogenic cancers are not well reported in death certificates. Autopsy studies have also confirmed that in the study population lung cancer is misdiagnosed on death certificates in over half the cases, with over 1/3 of cases not even coded as cancer.[25] Thus, three of the major cancers induced by radiation are not accurately represented in the mortality data from death certificates, and for this reason, the advantage of complete ascertainment of death records for the study group is largely lost. While it is unlikely that such under-reporting of cases could by itself alter the dose-response curve, it could have the effect of making the range of uncertainty at any dose greater.

In the final analysis, there are inadequacies for both the death certificate and Tumor Registry data, but when they are all taken together a reasonable concordance appears. For all cases except the Nagasaki mortality data, the linear no-threshold dose-response curve appears to be an adequate description of the results, although as the voluminous discussion and tortured mathematics of the third section of Chapter V attest, it is possible to fit a number of other curves to the data about as well as the linear fit. The Nagasaki mortality data *are* consistent with the rest of the results except for the two data points at high doses in Figure V-6. But the chief point to be made at this stage is that mathematical constructs based on the Japanese data do not really contribute to decisions about the appropriateness of any particular dose-response relationship. The data for

all cancers are as yet too imprecise, and thus adoption of a particular dose-response relationship remains an arbitrary choice.

The dose-response data for leukemia mortality from 1950-1974 in Nagasaki are based on only 22 deaths for those exposed above 10 rad kerma, and as anyone familiar with analysis of dose-response is aware, it is impossible to do much more than say that a significant effect of exposure exists with such a limited number of cases. Certainly these data are totally inadequate to define the dose-response curve. Cases from the leukemia registry results presented in RERF Report 8 are more numerous, and suggest a curvilinear dose-response relationship for both cities consistent with a constant RBE for neutrons of about 10.

In the present version of the report, the Leukemia Registry data have been used as a "guide" to define the linear and quadratic coefficients (a and b above) to be used in the linear-quadratic model applied to *all* cancers. In other words, mathematical adjustments to the coefficients, necessary because the results of fitting the theoretical curves to the Japanese mortality data led to unreasonable figures (all the coefficients derived from mortality "appeared out of line with the incidence estimates"), were based on the leukemia "guide." On biological grounds the idea that dose-response relationships for solid tumors must be similar to leukemia is far from reasonable. First, of course, is the markedly different time course for induction of radiation-induced leukemias compared to the much more quantitatively important solid tumors. This fact suggests a major difference in the factors involved in carcinogenesis, which by inference could affect the dose-response relationship. Second is the observation, thoroughly discussed within the full subcommittee, that leukemias are the only human cancers in which distinct chromosomal abnormalities are consistently associated with the disease. In the case of chronic granulocytic leukemia, quantitatively a very important type of leukemia induced by radiation, the great majority of cases ($\sim$85%) have the Philadelphia chromosome abnormality present in the leukemic cells, and there is agreement among cytologists and hematologists that the abnormality is causally related to the disease.[26]

In contrast, consistent visible chromosomal abnormalities in the early stages of solid tumors have not been found. The implication is that the somatic mutations in these tumors either involve point mutations or chromosomal changes small enough not to appear as readily visible translocations, deletions, or other abnormalities, or they are not associated with any particular chromosome site. The importance in radiobiological terms of the association of specific chromosomal abnormalities with leukemia is that such abnormalities are well-known to be two-break events, and thus a dose-squared dependence for at least part of

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the induced leukemias has a biological rationale. This is the main reason I accepted the linear-quadratic model for leukemia in the April 1979 draft. Cytologic differences between leukemia and solid tumors such as those mentioned above, support the view that the dose-response curves may not be the same for all cancer types. This is an idea that Harald Rossi and I both felt was an important contribution of the BEIR III Report; now of course in the present version it has been eliminated. In sum, the approach taken to "adjust" constants to provide risk estimates for solid tumors based on the leukemia "guide" is arbitrary and in my view not scientifically justified. The leukemia tail is still wagging the radiogenic cancer dog.

An important question is the extent to which the Japanese data are consistent with the data from all the other studies described in Chapter V, Appendix A, when expressed as an excess risk of cancer incidence per rad per million person years, and roughly age-adjusted. In general, the concordance is excellent for the major cancers where several data sets exist such as breast, thyroid and lung cancer. Other sites show various degrees of agreement. But the most important comparison is for *total cancer incidence* coefficients derived for each sex from the Nagasaki Tumor Registry data. From data presented in the April 1979 draft, these are found to be about 2/3 as great as the sum-of-sites coefficients summarized in Table V-14. This degree of concordance of results from human studies of a great range of exposure conditions, ethnic makeup and basis for radiation exposure is truly remarkable. The relatively small difference could be accounted for in part by underascertainment of cases in the Nagasaki data, and by a somewhat lesser susceptibility to cancer induction by radiation in Japanese as compared with occidental populations, a reasonable conclusion because of the somewhat lower total cancer rates in Japan compared with the U.S. The fact that the total excess cancer incidence rate per unit dose in the Nagasaki A-bomb survivors is quantitatively similar to the total excess incidence derived on the linear hypothesis from the aggregation of all the other available human studies lends strong support to application of the risk coefficients from the data in Table V-14 for deriving cancer risk estimates from whole-body exposure to low LET radiation.

With regard to concordance of dose-response relationships between the Japanese data and other sources, most of the other studies do not have a sufficient range of doses or sufficient numbers to permit comparison with the Japanese data. For female breast cancer incidence vs dose, Figure A-1 (Appendix A) shows good agreement of the three western studies cited compared with the data from the A-bomb survivors. (In this case the data for both Hiroshima and Nagasaki give a good fit to the linear no-threshold relationship, with no evidence of an RBE for neutrons greater than 1.) For

thyroid cancer Hempelmann's data in children[27] do not agree closely with those of Colman[28] but taken together they are consistent with the linear model over a reasonably wide dose range. The lowest dose point at about 7 rad provided by Modan's results from examination of thyroid cancer in 10,900 Israeli children given scalp irradiation for tinea capitis[29] fits reasonably well with the linear extrapolation for the other two studies (see Appendix A). The lung cancer data for underground miners suggest that the dose-response curve from exposure to alpha radiation could be curvilinear downward, that is, low doses may be somewhat more effective in cancer induction per unit dose than high doses, a concept in accord with the idea that high LET radiation may show cell-killing effects at relatively low doses that would progressively reduce the cancer risk/rem as dose increased.

Some members of the subcommittee believe that the "sum-of-sites" method, used by the BEIR I Committee to estimate total cancer risks, overestimates risks somewhat, because out of the numerous epidemiologic studies of radiation-induced cancer at individual sites presented in Appendix A, some would be expected by chance to yield higher than the true estimates, since in any study observed and expected cases have an inherent statistical variability. For this reason selection of only positive results would bias the risk estimates upward. To some extent this problem has been dealt with for several minor cancers by pooling risk estimates for them and striking a balance between high and low estimates, these sites being particularly susceptible to the above problem because risk estimates for them often were derived from a single study. But for two of the most important contributors to the total cancer incidence risk, thyroid and female breast cancers, there are several studies available for each that show excellent agreement, and thus the uncertainty of the risk coefficients is small, and no selection of high values has occurred. For lung cancer there are also several studies, but only two involving low LET radiation, the Nagasaki Tumor Registry and British ankylosing spondylitis studies. These two studies show reasonable concordance, and are also concordant with the studies of the underground miners on the basis, derived independently from dosimetric and radiobiologic principles, that exposure to one Working Level Month is equivalent to a dose of 6 rem to the basal cell layers of the proximal bronchial epithelium.

The only sites contributing significantly to the total in Table V-14 where the above argument could have some merit are those for the digestive tract: esophagus, stomach and intestines, primarily large bowel. Even in these cases there is reasonable concordance among the studies available, and the likelihood that selection of data has biased the risk estimates upward is not great. But this reason for rejecting use of the "summed sites"

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approach to defining cancer incidence risks from whole-body exposure obscures two important points. First is that ionizing radiation is the only known human cancer-producing agent that has been found to increase the risk of cancer in nearly all the parenchymatous or epithelial tissues of the body (see Appendix A). Indeed it is a reasonable conclusion that at high enough doses, it should be possible to demonstrate a carcinogenic effect of radiation on *any* human tissue. Therefore one may conclude that in human studies where a small excess of cancer is found at a particular dose of radiation but is borderline in statistical significance, it is prudent to consider the effect may be real rather than to dismiss the study as negative.

Second, as the follow-up time of the human study populations in which many organs were irradiated is extended, evidence of excess cancers at many of the minor sites has emerged slowly over time because the excess is set against the usual variability of cancer arising from other causes. Thus "statistically significant" excess cancer in the irradiated population may not occur for those sites where a lesser radiation effect is present until many total cases at that site have accumulated. This phenomenon has been obvious from the successive follow-up reports of the Japanese A-bomb survivors, where the bulk of the cases are observed at relatively low doses. For this reason we must consider *any* quantitative risk estimates, positive or negative, as tentative and could underestimate the risk until a lifetime follow-up is completed. For the above two reasons the idea that Table V-14 risk coefficients are biased upward by an effect of selection of positive results totally ignores the combined strength of the evidence presented in Appendix A.

Another point raised by use of Table V-14 for estimating cancer risks is that it gives cancer incidence rates rather than cancer mortality. The decision to define cancer risks in terms of incidence rather than mortality was adopted early by the subcommittee and constituted a significant change from the BEIR I report. This decision was based in part on the awareness that cancers of the thyroid and female breast are now major radiation-induced cancers, and for these two sites mortality data give an inadequate indication of risk. This change from BEIR I was also based on the consideration by the subcommittee that any radiation-induced cancer produces a major psychological, social and economic cost to the individual affected, whether or not the cancer is ultimately the cause of death. Thus the idea that cancer deaths alone are the proper measure of radiation impact was rejected. Since the BEIR I report, new information was available which permitted better estimation of excess cancer incidence from radiation exposure to the thyroid and female breast; for other cancers there is little incidence data except from the Japanese Tumor Registries, but

because most of the other important radiogenic cancers including leukemia are eventually fatal, mortality gives a reasonable estimate of incidence. For this reason, the other coefficients in Table V-14 have been derived from mortality data.

Because cancer incidence risk estimates are those intended by the subcommittee, the amount of emphasis in the current version of the third section of Chapter V on discussion of cancer mortality data is unwarranted, and indeed the procedure of "indirect conversion of mortality estimates to incidence estimates" is clearly inappropriate for cancer of the thyroid and female breast. In my view the best basis for cancer incidence risk estimates from radiation exposure is Table V-14, because it draws on all the evidence available from Appendix A, much of it obtained in American or British study populations and on this basis more immediately applicable to risk estimates intended to be applied to the U.S. population. As pointed out above, it is supported well by the Nagasaki total cancer incidence data. These risk estimates applied to the 1969-1971 U.S. life table population are presented in Table V-30 of Chapter V, but it should be noted that this table does not include the risk for leukemia and bone cancer incidence. To determine total cancer risk the data from Table V-30 must have added the data from Table V-16, where leukemia and bone cancer incidence are derived using the linear-quadratic model agreed by the subcommittee as appropriate for leukemia only (bone cancer is such a minor cancer that it contributes trivially to total cancer risk regardless of the model used). Failure to provide a single estimate of risk of *total* cancer incidence is another deficiency of the present version of the third section of Chapter V. Table V-30 gives a range of risk calculations for each sex according to the various exposure regimens. This range reflects our uncertainty about the appropriate model by which current estimates of risk are projected forward to a lifetime cumulative risk. The two projection models used are the so-called absolute and relative risk models (see Chapter II, the section entitled "Epidemiologic Studies as the Basis of Risk Estimates for Effects of Ionizing Radiation"). It is evident that these two projection methods give total risk estimates that differ by a factor of about 3 for the projections of total population exposures. There was general agreement among the subcommittee members that at least this degree of uncertainty applied to the estimates of lifetime risk in these instances. For the occupationally exposed groups the two projections agree reasonably well.

In Table 1, I have combined Table V-30 with Table V-16 to give the best estimate of total excess cancer incidence derived for the exposure conditions used in the third section of Chapter V.

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TABLE 1 Estimates of Total Lifetime Excess Cancer Incidence from Exposure to Low LET Radiation—Projections Based on 1969-1971 U.S. Life-Table Population of One Million Persons at Start of Exposure, According to Absolute-Risk and Relative-Risk Projection Models. Data Taken from Tables V-30 and V-16 of Chapter V

	Absolute-Risk Projection		Relative-Risk Projection	
	Male	Female	Male	Female
1. *Single exposure to 10 rad* to 1,000,000 persons of all ages				
Expected lifetime cancers without radiation	285,000	260,000	285,000	260,000
Excess cancers induced by radiation	2,600	5,500	8,800	16,200
2. *Continuous exposure to 1 rad/yr* to 1,000,000 persons at outset				
a. *Lifetime exposure from birth*				
Expected lifetime cancers without radiation	283,000	285,000	283,000	285,000
Excess cancers induced by radiation	16,200	37,600	31,100	185,200
b. *Exposure ages 20-65*				
Expected lifetime cancers without radiation	292,000	300,000	292,000	300,000
Excess cancers induced by radiation	11,100	25,400	15,000	49,500
c. *Exposure ages 35-65*				
Expected lifetime cancers without radiation	296,000	296,000	296,000	296,000
Excess cancers induced by radiation	6,800	14,700	7,600	17,500
d. *Exposure ages 50-65*				
Expected lifetime cancers without radiation	295,000	269,000	295,000	269,000
Excess cancers induced by radiation	3,100	6,300	3,100	6,300

among radiation workers would ever be exposed either to a single dose of 10 rad or to continuous doses of 1 rad per year. The numbers of radiation-induced cancers appear to be large in most instances, but it is important to note that except possibly for the case of lifetime exposure to one rad/year, even with these unrealistically high exposures it would be very difficult to detect by epidemiologic methods that the excess cancers had occurred except for those particular sites which are especially sensitive to cancer induction by radiation.

On the linear hypothesis, the data for the single exposure to 10 rad can be converted to conventional "risk per rad" estimates by dividing by ten. This yields a range of 260 to 880 cases per rad per million exposed for males, and 550 to 1620 cases per rad per million exposed for females. If we adopt an intermediate value as more likely to obtain (that is, the relative risk model will only partially be found to be correct), the risk per rad for cancer induction is about 500 cases per million for males and 1000 cases per million for females. These values are higher than the risk estimates from BEIR I, in part because incidence is considered instead of mortality, and in part because the new data indicate somewhat higher lifetime risk than was evident in 1972.

If one applies total cancer risk estimates obtained from the life table projections for a single exposure in Table 1 to the Japanese A-bomb Life Span Study population by use of the linear hypothesis and the same method as was done to produce the estimates in Table 1, some important limitations of the Japanese A-bomb follow-up study become clearer. The Life Span Study population has a greater proportion of younger people than the 1969–1971 U.S. life table population, a circumstance that means the total radiation-induced cancers anticipated per number exposed will be somewhat greater than predicted from the model applied to single dose exposure in Table 1. Nevertheless some approximate conclusions are justified. First is that the number of excess cancers observed to the present follow-up in 1974 constitutes only about one-third of those that eventually will be expected if the time for expression of excess cancer risk is the lifetime of those exposed over the age of ten. In other words, the follow-up period for the Life Span Study group is still too short to define total cancer risks adequately. Second, even on the upper limit assumption that the lifetime *relative* risk model applies, no statistically significant excess of all cancers will ever be observed in the two lowest dose categories of the study population in Nagasaki, that is at mean tissue doses of 2 rad and 10.8 rad. For Hiroshima the same statement can be made for the lowest dose category (mean tissue dose 1.7 rad) regardless of the RBE assumed for neutrons within any reasonable range. For the next dose category, 10–49 rad kerma or a mean tissue dose of 10 rad, if a statistically significant ex-

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cess of total cancers is observed in Hiroshima compared to the zero dose group, such an observation will be consistent with an RBE for neutrons greater than one, but because the mean tissue dose from neutrons is only one rad in this group, the reliability of any numerical estimate of RBE derived from this excess will always be weak indeed. For the next dose category, 50-99 rad kerma or a mean tissue dose of about 34 rad in each city, a significant lifetime excess of total cancers will be easy to demonstrate in Hiroshima, but for Nagasaki the smaller sample size will probably mean that the statistical significance of the excess will be marginal if the lifetime relative-risk model is found eventually not to hold.

This application of the current total cancer risk estimates to the A-bomb survivor populations again emphasizes the caution that must be applied in interpreting the data for excess cancer risk in this study group, especially at low doses. Another implication of the above analysis is that an excess risk of cancers at particular sites which are sensitive to radiation and have a high natural rate will always be easier to demonstrate, especially in Nagasaki, than will an excess for all cancers, because the inclusion of a large number of cancer types with low or zero radiation sensitivity increases the random "noise" in the data. The above phenomenon is already obvious in the analysis of breast cancer incidence up to the present. In sum, the fact that the Japanese data at any follow-up state may not be strong enough in statistical terms to show a significant effect of low doses on total cancer risk does not prove that effects are not present; the excess cancer risk may be better evaluated by looking at particular cancer sites.

With regard to the appropriate RBE for high LET radiation and its dependence on dose, the data for alpha radiation compared with x-rays or gamma rays give reasonable RBE values of about 10 to 20 for lung and liver cancer (Appendix A). Comparisons of the Hiroshima-Nagasaki results do not allow any definitive statement with regard to the RBE of neutrons for the following reasons: First, the rates for total cancer incidence from the zero dose (control) populations are substantially higher in Hiroshima than in Nagasaki, and thus the assumption that the neutron component is the sole factor accounting for differences in cancer dose-response is untenable. Second, at low doses, where the results are most important, excess cancer rates are not yet statistically strong enough to provide an appropriate estimate of the contribution of neutrons and in some instances are likely never to be strong enough (see above). Third, neutron and gamma ray exposures were highly correlated for Hiroshima, and in the low dose range *tissue* doses for neutrons were only about 1/10 those for gamma radiation, thus random differences in results greatly magnify the imputed neutron effects at low doses. Fourth, the dosimetry for gamma rays and

neutrons is estimated to be good only to ±30%, thus any consistent dosimetry errors could also greatly affect the analysis of neutron effects in the comparison.

It should be pointed out that the assumption that the RBE for high LET compared to low LET radiation increases as the dose decreases does not necessarily imply that the dose-response curve for low LET radiation must be curvilinear upward at low doses. It is equally possible that the dose-response curve for high LET radiation is curvilinear downward. The point is that if we assume a fixed RBE independent of dose, we may underestimate somewhat the risk of low doses of high LET radiation and overestimate somewhat the risk of low doses of low LET radiation. But the available human epidemiologic data do not indicate to me that this degree of over- or under-estimation is very great, that is, more than a factor of 2. When we consider that cancer risk estimates may eventually have to take account of a significant subfraction of the population whose radiogenic cancer risk can be expected to be higher than the population at large, any conservatism arising from assumptions that may overestimate the risk by a small amount is justified at this time.

Pertinent to this question of the relative effectiveness of high LET radiation at low doses are the results of chromosome aberration studies in populations living in or otherwise exposed to high background radiation. In those situations where exposure has been especially to radon-222 the alpha radiation can account for these essentially two-break effects on the chromosomes.[30,31] In the Brazilian population living in a village on monazite sands, chromosome abnormalities were found elevated compared to a control group not so exposed.[32] In this case, it was postulated that alpha radiation from the Pb-212 daughter of Rn-220 reached the lungs or blood, and this exposure rather than the high background of gamma rays accounted for this effect. On the other hand, the dose-related chromosomal aberrations observed by Evans et al.[33] in nuclear shipyard workers exposed to relatively low cumulative doses were from exposures to "almost exclusively gamma radiation." It is of interest that 5 rad of acute x or gamma radiation has produced in human lymphocytes significant chromosomal aberrations.[34,35] Luchnik and Sevankaev[35] also observed an anomalous "plateau" of effect at intermediate gamma doses, very similar to that observed for cell transformations by Miller and Hall,[18] an effect which means that extrapolations from doses of 50 to 400 rad would underestimate the effect at the lowest doses. The production of chromosomal aberrations at low doses cannot be considered pathogenic for any disease as yet, as mentioned above, but these observations indicate that caution is warranted in any assumptions about the relative

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SUMMARY AND CONCLUSIONS

It is evident that adoption by the somatic effects subcommittee of the linear no-threshold dose-response model for defining radiation-induced cancer risks remains empirical at this time. There is no adequate theoretical model of human carcinogenesis that permits derivation of a dose-response relationship from first principles. The fact that radiation-induced cancer risk estimates from a large number of human studies with great variability of ethnic, cultural, and other environmental factors capable of influencing the results are as consistent as they are when compared on the basis of the linear extrapolation, suggests that radiation acts by increasing the probability of an initiating event, a somatic mutation. Other environmental factors which can modify the subsequent chance of neoplasia are sufficiently widely and randomly distributed in all human populations that the excess cancer risk is defined primarily by the probability of oncogenic cell transformation by radiation exposure. If such a transformation involves a radiation-induced point mutation or other small modification in the cell genome, then on classic target theory the linear no-threshold dose-response curve is entirely appropriate. Until we know more about the process of cancer development in man, we cannot go further with this problem.

The new evidence concerning cellular mechanisms of radiation carcinogenesis available since the BEIR I report represents in my view a major change in emphasis from the past. Whereas biophysical considerations, of which the Kellerer-Rossi theory is an example, have previously dominated the field and played an important role in concepts of effects of low doses of the different types of radiation, it is apparent that much more prominent now are biological variables that can involve the conversion of an initiating event induced by radiation into a fixed or heritable cell transformation, and the subsequent host factors that determine the probability of developing cancer. These biological factors include DNA repair processes and cellular mechanisms that modify them, the action of promoting agents and conditions that affect cell proliferation, the influence of viral infection on transformed cell DNA, immune processes affecting survival of transformed cells, and the effect of age on replication characteristics of the transformed cell or cells.

The above comments appear to be quite straightforward, and I believe

were the consensus of the somatic effects subcommittee during the period when the subcommittee was continuing to meet. Contrast this position with that adopted in the third section of Chapter V of the present version. The basis of the ratio of the linear and quadratic coefficients (a/b, in the equation $E = aD + bD^2$) is the leukemia registry data from the Japanese A-bomb survivors, data which do show a definite curvilinearity of dose-response. In addition the RBE assumed for neutrons is taken from the fit of the data to the leukemia results. Thus leukemia, a human cancer with cellular characteristics and time course after irradiation differing markedly from other radiogenic cancer types, is taken as the paradigm governing a number of important inferences for *all* radiation-induced cancers. These factors derived from leukemia are then used to fit the observed data for cancer *mortality*, which as has been discussed above are deficient in important ways for major radiation-sensitive solid tumors. Mortality data are then converted to incidence data by applying factors of cancer mortality by site shown in Table V-15. This approach studiously avoids using the Japanese Tumor Registry data for total cancer incidence which for both Nagasaki and Hiroshima (with adjustment of an RBE for neutrons of about 5) are in excellent agreement with the incidence data derived for individual sites from the extensive international studies described in Appendix A, and summarized in Table V-14.

The roundabout approach taken above in the present version in effect discards all the human studies of radiation-induced cancer except the Japanese data in defining cancer risk from low LET radiation. It also has the effect of reducing the cancer risk estimates sufficiently that it is possible for the conclusion to be drawn that the BEIR III cancer mortality risk estimates are about the same as were derived in BEIR I. This conclusion ignores, of course, the important step of changing to cancer incidence as a basis of defining risk, and also ignores the considerable body of supportive data, especially for cancers of the thyroid and female breast, which indicate that as the follow-up of human study populations has been extended, evidence of cancer risk is increasing, the doses at which effects have been observed have progressively decreased, and the number of different human cancers in which radiation exposure has shown an effect has been extended. The present version of the third section of Chapter V has failed to make these important points, and thus has not provided, in my view, an adequate up-to-date scientific assessment of risk which was the purpose for which the BEIR III Committee was established.

The fact that the human epidemiologic data which are relevant to the dose-response issue are generally consistent with the linear no-threshold dose-response model remains the principal basis for use of this model. It should be emphasized that every effort in presenting epidemiologic evi-

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dence of cancer induction by radiation should be as carefully and rigorously done as possible to take account of the dilution effect of non-radiosensitive cancers, age-specific adjustments, effects of confounding variables and the influence of latent period. In Appendix A, and for the Japanese data in Figs. V-6 and V-7, efforts have been made to achieve this aim. The graph of Japanese data presented in Dr. Harald Rossi's dissenting report has not been corrected for age, which is a major correction for cancer evaluation because of the sharp effects of age on cancer rates; the Nagasaki Life Span Study population is younger than the Hiroshima population and the age distribution varies by dose category. In addition the period 1950–1954 has been included by Dr. Rossi for all cancers, when we know that for all cancers except leukemia no excess risk is likely to have occurred during this period. It is time to recognize that epidemiology is a rigorous discipline requiring special attention to detail that characterizes any science.

Finally, I would like to take this opportunity to thank those members of the full committee who have worked hard to produce those parts of the current version that provide a scientific basis for assessing somatic and genetic risks. It is regrettable that the results of their hard work have been so long delayed in being released for general use.

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Separate Statement
Critique of BEIR III

HARALD H. ROSSI

SUMMARY

The first report of the Committee on the Biological Effects of Ionizing Radiations (BEIR I) has profoundly influenced governmental regulations and the public attitude towards radiation. It is to be expected that the impact of the current report (BEIR III) will be equally significant. The Committee drafting that report has thus been faced with a heavy responsibility because its findings are likely to affect national energy policy and the practice of medicine. In both of these areas overestimates as well as underestimates of the radiation hazard could result in serious detriment.

This is especially important with regard to the risk of radiogenic cancer which is frequently considered to be the major hazard of ionizing radiation. This critique deals with this subject only.

BEIR III represents an advance over BEIR I in a number of respects:

I. The uncertainties of risk estimates are stated more explicitly and it is stressed that the so-called "linear hypothesis" is likely to result in overestimates of the hazard from low-LET radiation.

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This has led directly or indirectly to further improvements.

II. It is acknowledged that it is probable that the cancer risk rises with absorbed dose at a rate that is higher than linear and the preferred mathematical model conforms with this postulate.

III. Extrapolations to single whole body doses of less than 10 rads are eschewed.

IV. It is stated that the effects of annual radiation doses of the order of 100 mrads (low LET) are unknown and that it is unlikely that they can be demonstrated.

V. It is recognized that RBE is an important factor and it is frequently assumed that it increases with decreasing level of effect. In most instances data from Hiroshima and Nagasaki are not pooled on the assumptions of equal effectiveness.

BEIR III is however deficient in two major respects:

I. Many of the risk estimates provided are still based on the "linear hypothesis" despite continuing and mounting contrary evidence from radiobiology and epidemiology (much of it quoted in BEIR III). Even though these figures are given somewhat less prominence, they are likely to assume primary importance for standard-setting bodies which, for the sake of prudence, are likely to adopt the highest estimates.

II. BEIR III fails to present explicitly data that indicate risk factors that are less than the lowest given in its report. This does not only again tend to support excessive risk estimates for low LET radiation, but may also lead to, perhaps even more important, underestimates of neutron hazards.

DETAILED COMMENTS

The inadequacies of the epidemiological information on radiogenic cancer in man permit a wide variety of interpolations and extrapolations of data that are often uncertain, if only in the statistical sense. The deduction of the most likely risk estimates can, however, be facilitated by considerations of theoretical or experimental findings of radiobiology which make certain models more—and sometimes much more—plausible.

Theoretical considerations permit definitive conclusions on the dose-effect relation for individual (autonomous) cells, but at this time they cannot be employed with any assurance to determine this relation for

the complicated process of radiation carcinogenesis. They do, however, lead to the conclusion that the RBE of high- relative to low-LET radiations should increase with decreasing level of effect to values which are very substantial and that this should be so not only for autonomous cells, but also for interacting cell systems.

Experimental observations on higher organisms have confirmed this expectation. In line with theoretical predictions, the RBE generally increases with decreasing neutron dose, D_N, according to

$$\text{RBE} = K(D_N)^{-1/2}.$$

In a number of systems K has been found to be about 45 if D_N is expressed in rads and the neutrons have energies comparable to the mean energy of the fission spectrum (~ 0.5 MeV). RBE values in excess of 100 have been observed at neutron doses of the order of 100 mrads which are thus equivalent to gamma ray doses of the order of 10 rads.

While experimental radiobiology is in accord with theoretical predictions regarding the dose-RBE relation, it also discloses a wide variety of dose-effect relations for carcinogenesis. Some of these even show a reduction of the natural incidence at moderate doses of low-LET radiation (and even for high-LET radiations). This is only observed when the natural incidence is high; however, statistical limitations would not permit a clear indication of this effect when the natural incidence is low. In most (but not all) instances, the curvature of the relation for low-LET radiation is positive indicating that in addition to any linear dependence on low doses (regardless of sign), there are positive quadratic and perhaps higher order terms in dose at intermediate doses. At high doses, a reduction or even a reversal of slope is often observed.

In summary, radiobiological considerations lead to the expectation that if cancer incidence is related only to terms that are linear and/or quadratic in dose, only a rough approximation may be attainable in many instances. In such approximations the relative magnitude of linear and quadratic terms is likely to differ depending on the type of neoplasm involved and a summation for all neoplasms could have a particularly complicated shape. It would, however, also be expected that, in general, linear extrapolations from doses of several hundred rads lead to an overestimate of the effects of doses of the order of 10 rads. It would furthermore be expected that because of the dose dependent RBE, the shape of any dose-effect relations is not the same for gamma and neutron radiations and in particular that they not *both* be linear above gamma ray doses in excess of about 10 rads or neutron doses that are 100 times less.

BEIR III employs three approaches to the analysis of epidemiological

s of radiation carcinogenesis. They do, however, that the RBE of high- relative to low-LET radia- ith decreasing level of effect to values which are at this should be so not only for autonomous cting cell systems.

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data on radiation carcinogenesis: They involve the "summed sites" method, the mortality (LSS) data for Japanese atomic-bomb survivors and the Nagasaki tumor registry data.

The "summed sites" treatment is based on estimates of the incidence of cancers in individual organs as given in Appendix A. The input data are derived from many sources, most of which involve irradiations with doses in excess of 100 rads. The Japanese data employed are essentially all from Hiroshima with assigned RBE values that vary between sites but are independent of dose for any of them. With the exception of leukemia, the "linear hypothesis" is employed throughout. This treatment evidently conflicts with radiobiological knowledge on several counts. There are further objections to these data largely obtained from diseased individuals of different ethnic backgrounds. For example, the spondylitic population was exposed to very high doses and these were applied only to tissues in or near the spine. This poses problems in the assessment of the "average" dose. If the leukemogenic effect of large doses depends on the square of the x-ray dose (as in fact assumed in BEIR III) and if 40% of the bone marrow (that located in or near the spine) is irradiated with a dose, D_x, with the remainder receiving essentially zero dose, the *effective* dose is not the mean 0.4 D_x, but instead 0.63 D_x. Such discrepancies become even more pronounced if the irradiated fraction of a tissue or organ becomes smaller.

In the absence of other information, these estimates might be considered as crude upper limits of the true risk for individual organs. However, the utilization of their sum in the methods employed to determine the overall cancer risk is one of the principal deficiencies of the BEIR III report. As was to be expected, it results in a substantially larger risk coefficient than those obtained by other methods and this inflated estimate may well be adopted by standard setting bodies who, in the interest of caution, may select the highest estimate provided.

The LSS data are generally considered to be the most reliable source of information on radiogenic cancer in the Japanese cities. They also permit a straightforward assessment of the cancer risk for a period of almost 30 yr following irradiation of a normal (albeit ethnically distinct) population. BEIR III provides this information for leukemia and all other cancers separately. Although this division may be necessary for the risk calculations, it masks the true dose effect relation of the over-all cancer impact for which the statistical fluctuations are substantially less. Figure 1 is a plot of cancer mortality per person year as a fraction of total kerma at Hiroshima and Nagasaki. These curves are not corrected for sex or age, but it may be assumed that such corrections could introduce only minor changes.

It appears that at Nagasaki it is impossible to detect an excess cancer

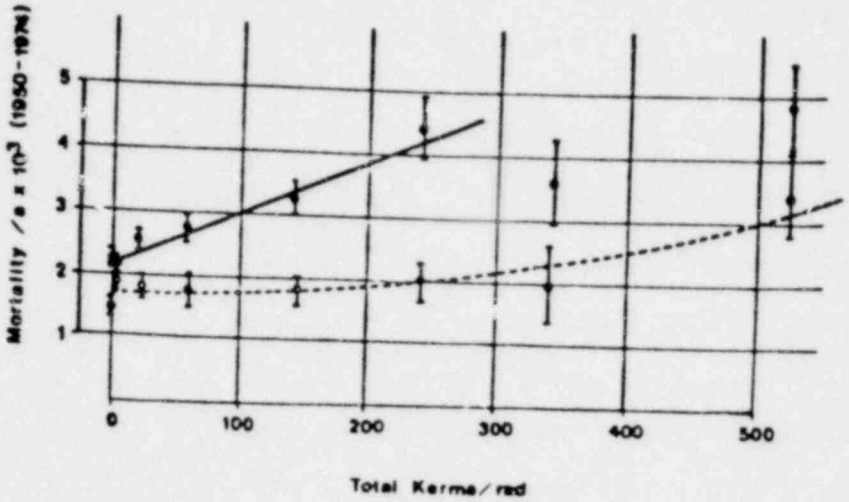


FIGURE 1 Average for the period 1950-1974 of the mortality from all malignant neoplasms per person year versus total free-in-air tissue kerma at Hiroshima (closed circles) and Nagasaki (open circles). The bars represent ± 1 standard deviation.

incidence at kerma values of less than about 300 rads although the populations exposed in each of the low dose intervals were about 1,000 or more. It is also evident that in line with other radiobiological information, the RBE of neutrons was very high. It should be borne in mind that at a given kerma at Hiroshima, only roughly 10% of the total absorbed dose to deep lying organs was due to neutrons. At high kerma, the Hiroshima data exhibit fluctuations which may be due to a variety of reasons, but the low kerma data can be approximated by

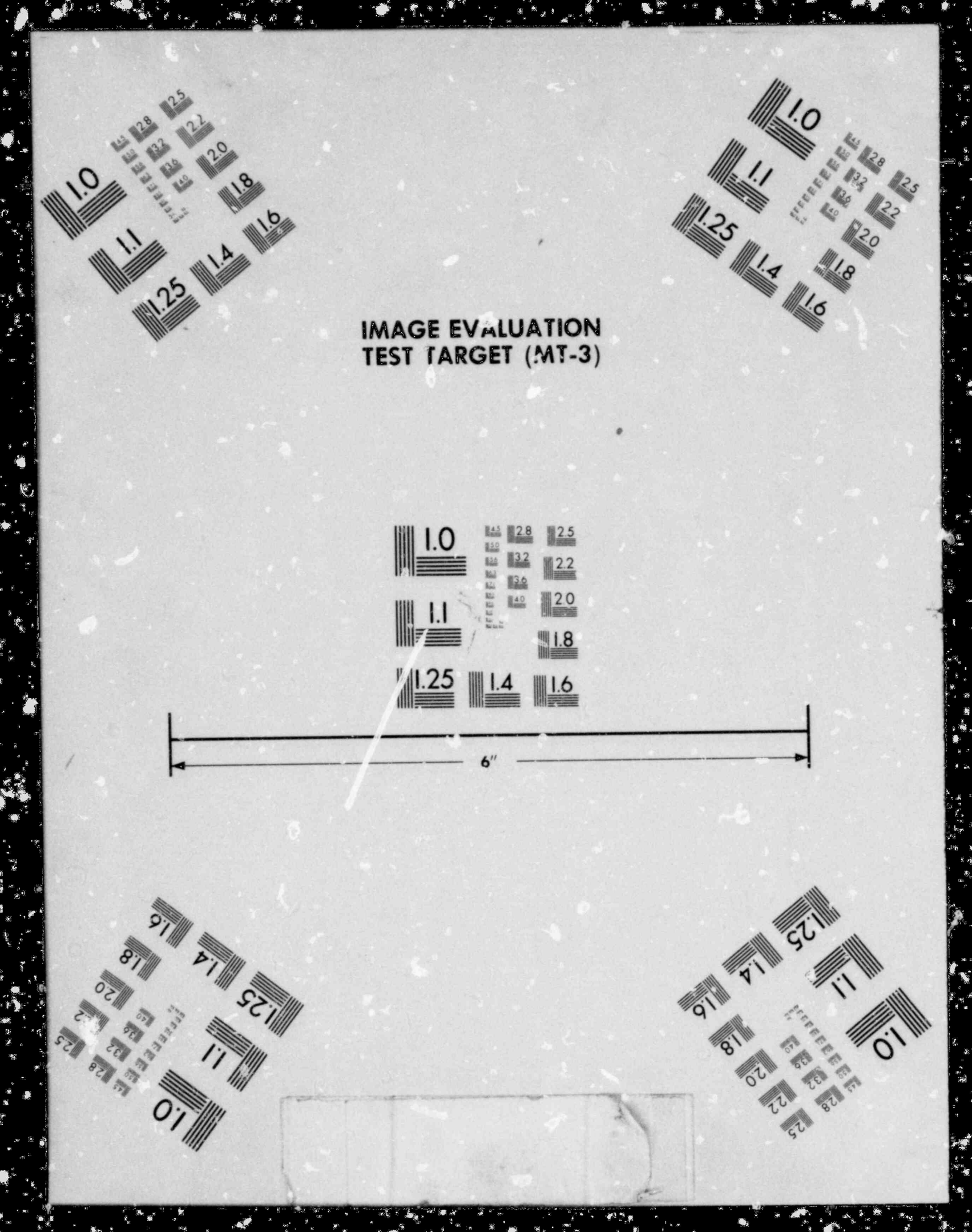
$$M_{Hi} = 2.2 \times 10^{-3} + 8 \times 10^{-6} (K_{Hi}/\text{rad}),$$

while the Nagasaki data conform to

$$M_{Na} = 1.8 \times 10^{-3} + 5 \times 10^{-9} (K_{Na}/\text{rad})^2.$$

Here M is the mortality due to all malignant neoplasms per person year, K the total free-in-air tissue kerma and the subscripts stand for the two cities.

Because of the high RBE of neutrons and their virtual absence at Nagasaki, it may be assumed that at low doses, all cancers were induced by neutrons at Hiroshima and by gamma radiation at Nagasaki. Em-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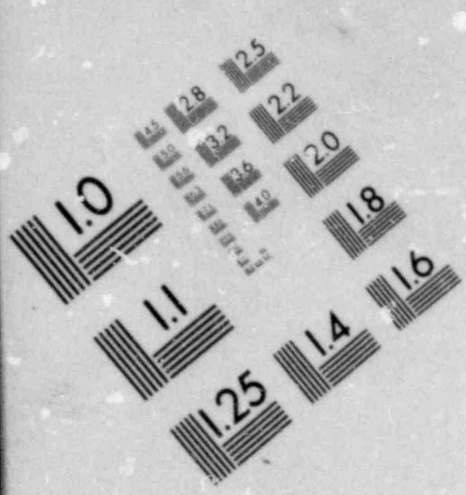

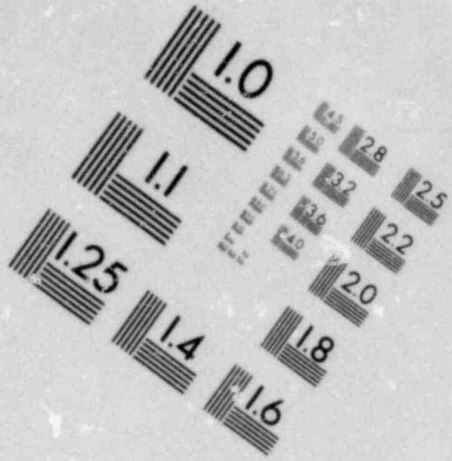

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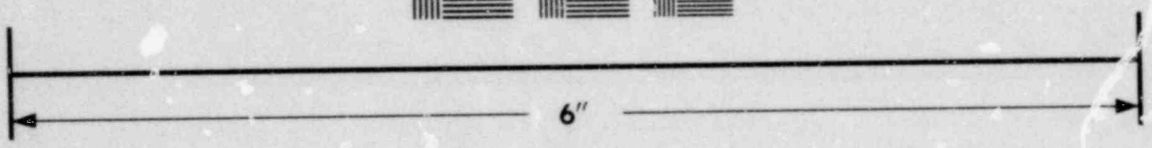

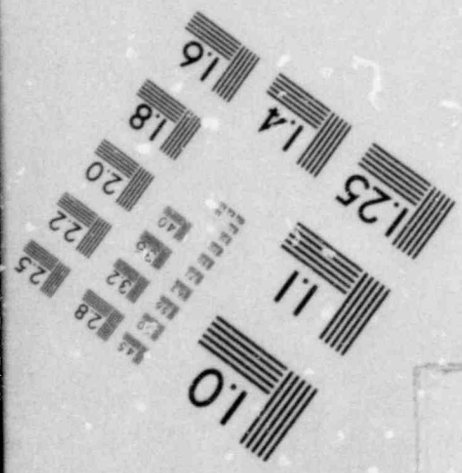

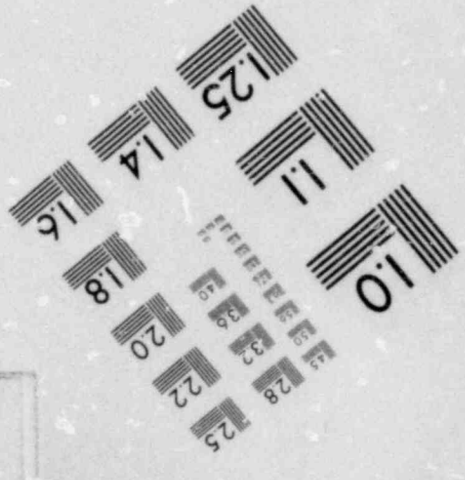

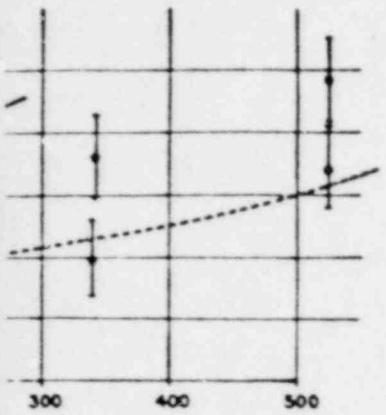

4 of the mortality from all malignant tissue kerma at Hiroshima (closed circles) 1 standard deviation.

n about 300 rads although the dose intervals were about 1,000 with other radiobiological infor- igh. It should be borne in mind only roughly 10% of the total due to neutrons. At high kerma, which may be due to a variety of approximated by

$< 10^{-6} (K_{H_i}/\text{rad})$,

$< 10^{-9} (K_{N_a}/\text{rad})^2$.

nant neoplasms per person year, the subscripts stand for the two

is and their virtual absence at doses, all cancers were induced ma radiation at Nagasaki. Em-

ploying the dose versus kerma relations given in BEIR III one obtains approximately

$$M_N = 1.3 \times 10^{-4} (D_N/\text{rad})$$

and

$$M_\gamma = 1.7 \times 10^{-8} (D_\gamma/\text{rad})^2.$$

Neither of these relations (and especially not the second) should be applied to absorbed doses that are less than about 10 rads. The estimate for gamma radiations is lower than any given in BEIR III. The neutron estimate is higher than any values that might be inferred from this report.

The failure to explicitly provide the information in Figure 1 and to derive the above estimates is another major deficiency of BEIR III. Discussions within Committee did not produce substantive reasons for rejecting the validity of this analysis and while there may well be reasons for considering other approaches, it is apparent that this analysis is of considerable significance.

The so-called L-L estimate for these data is not only scientifically contraindicated, but also lacks any foundation in the absence of a sensible linear component for Nagasaki. Efforts to approximate this curve by a linear and a quadratic dose term yield a negative sign for the former. In principle, there is no reason why this should not be so and mortality data for lung cancer at Nagasaki point in this direction. The statistical evidence for this possibility is nevertheless much too weak to provide significant support for the assertion that the natural cancer mortality was reduced by small doses. On the other hand, the LQ-L analysis is based on the relative magnitude of linear and quadratic terms as derived from *leukemia* incidence data from the *tumor registry* and this is being justified by the objective of introducing a linear term into data in which linearity cannot be found.

The mixing of data from the LSS series and the tumor registries is also inappropriate because they appear to be discordant. The reasons for this are not clear at this time. Although the LSS data are generally considered to be more reliable and cancer mortality may be deemed to be more relevant than cancer incidence, BEIR III quite properly decided not to ignore the registry data especially since they indicate higher risk factors. Analysis in terms of all three models can be justified including that by the L-L model since the Nagasaki data are best fitted by a linear rela-

tion. However the implied dose independence of RBE casts further doubt on the validity of the registry data.

The arguments presented here lead to the conclusion that the most plausible estimate of the cancer risk from low-LET radiation is lower than any of the ones given in BEIR III. As a corollary BEIR III may motivate potentially dangerous underestimates of the hazards of high-LET radiation.

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Comments on Certain Divisive Issues Noted in BEIR III

EDWARD W. WEBSTER*

This commentary is not intended as a dissent from the principal findings of the Committee, but rather to illuminate some of the issues on which the Report notes divisions of opinion within the Committee.

Probably the most important charge to the Committee was to estimate the increased risk of cancer likely to be incurred as a result of low doses of low-LET radiation delivered to the whole body. A linear-quadratic dose/effect relationship, defensible in the light of current radiobiologic findings, has been adopted by most of the Committee members as a reasonable basis for prediction of the risks of radiation-induced cancer. While subscribing to this important change in scientific viewpoint of the BEIR III Committee compared to that of BEIR I (1972), I must express a number of caveats regarding the actual forms of the dose/effect relationships utilized in the BEIR III risk estimates. I recognize, however, that the three estimates of mortality from solid cancer are not inconsistent with the Nagasaki mortality data.

Dissenting statements prepared by individual members of a National Research Council committee are not subject to the normal review processes of the National Academy of Sciences; nor are they subject to committee or staff editing or review. They appear exactly as the dissenting committee members prepare them. The NAS-NRC neither endorses nor takes responsibility for the content of the statements.

* Dr. Ingram subscribes to this statement. Dr. Mays also subscribes to this statement, with the addition of the paragraph that appears at the end of the statement.

1. On page 187 it is noted that in the linear-quadratic relation fitted to the Nagasaki solid cancer mortality data (Figure V-6), the slope of the linear component is about 0.4 excess cancer per million per year per rad. This slope depends on the assumption that the linear term and the square-law term are equal for a gamma dose of 1/0.0086 or 116 rads. This particular linear-quadratic relation was rejected by some Committee members on two main bases: a) the RBE is about 91 for a neutron dose of 1 rad; b) the ratio of solid cancer to leukemia for gamma rays is 0.4 whereas the British ankylosing spondylitis study for high doses of x-rays suggests a ratio of about 5. The relationship was thereupon adjusted to include the RBE for the leukemia LQ model: viz. 23. This arbitrary change caused the slope of the linear component of the LQ relationship to be increased from 0.4 to 1.4; that is, by a factor of 3.5. The solid cancer risk estimates finally propounded in Table V-19 and which are the "preferred" estimates, are based on this larger slope. It is important to note that a) the recent study of leukemia in the A-bomb survivors by Ishimaru et al.[1] estimated the RBE for 1 rad of fission neutrons at 48, based on a quadratic model for gamma response; this is similar to the value of 45 proposed by Rossi on more general grounds;[2] and b) there is no obvious reason why the ratio of solid cancer to leukemia should be 5:1, particularly in the low dose range. The ratio will depend on the specific shapes of the leukemia and solid cancer dose/response curves. Thus in the animal studies by Ullrich et al.[3] the ratio of the incidence of 3 solid tumors (ovarian, pituitary, and Harderian) to the incidence of thymic leukemia varied from 2.4 at 100 rads to 0.8 at 25 rads and 0.1 at 10 rads. The ratio was more nearly constant for neutrons. Moreover it is noted on p. 209 that the solid tumor/leukemia ratio is "very sensitive to the age distribution of the subjects under study and to the duration of followup." For example, the work of Stewart and Kneale[4] on *in utero* exposure indicates a ratio of 28/25 or 1.1. Thus, if the Hiroshima/Nagasaki mortality data is not adjusted for RBE in this arbitrary fashion, the "preferred" risk estimates presented in Table V-19 would fall by a factor of about 3.

2. In the Report, the arguments on p. 187 summarized above were also employed to change the slope of the *linear* dose/effect relation employed for risk estimation. Whereas the slope of the best-fitting line for gamma radiation data shown in Figure V-6 and Table V-9 was 1.40, the actual slope employed in Tables V-11 and V-20 was 3.47, an increase by a factor of about 2.5. Thus the linear model estimates of cancer mortality presented are higher than those suggested by the Hiroshima-Nagasaki study by this factor.

3. In the Report, the arguments on p. 187 were also used to change

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the coefficient of the *quadratic* relationship from 0.0047 (Table V-9) to 0.0184 (Table V-11 and V-21), an increase by a factor of 3.9. Again therefore the estimates of excess solid cancer mortality presented for the quadratic (square-law) model are higher by this factor than would be deduced *a priori* from the Hiroshima-Nagasaki data above.

4. The Report fails to state explicitly that the linear risk estimate for excess cancer *incidence* derived from Table V-10 (sum of the individual site risks) is grossly incompatible with the *linear* estimate for excess cancer *mortality* derived from the Hiroshima-Nagasaki study (Figure V-6). The average incidence risk from Table V-14 is 18 cases per million per year per rad, which is about *13 times greater* than the 1.40 fatal cancer cases deduced from the Japanese study, or about 7 times greater than the incidence risk derived from the Japanese study using the expansion factors in Table V-15. This great difference seriously challenges the credibility of the linear risk estimates based on the "summed sites" approach of Table V-30. This writer believes that these values not only have "considerable upward bias" as stated in the Report, but cannot be seriously considered in the light of the Japanese experience.

5. It is stated on page 179 that "the data [for the site-specific estimates in Appendix A] are reasonably firm for only a few organs." One of the important organs to which this applies is the lung, irradiated by low-LET radiation. The risk estimates for lung derived in Appendix A are almost entirely dependent on the epidemiological studies of miners exposed to high-LET radiation in the form of alpha radiation from radon inhalation and on the lung cancer incidence in Hiroshima. The assumption of the rather low RBE values of 10 for alpha irradiation and 5 for fast neutron irradiation exaggerates the effect of low levels of low-LET radiation. More importantly the lung section fails to note that the Nagasaki mortality data (low-LET radiation) show a *deficit* of lung cancer cases at doses up to 100 rads and this is also reflected in the Tumor Registry incidence data for low gamma ray doses.[5] The risk estimate for lung cancer from low-LET radiation is almost wholly dependent on the high dose (200 rad) ankylosing spondylitis study and is likely to be considerably less at low doses.

Additional comment by Dr. Mays: "I support the thoughtful comments of Dr. Edward W. Webster, and am particularly concerned that the risk coefficient derived from the sum of individual site risks exceeds by a factor of about 13 that derived directly from the A-bomb life-span mortality data. I feel that the latter is more likely to be appropriate and that future efforts by the Scientific Community should be directed toward resolving this discrepancy."

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Exhibit 2

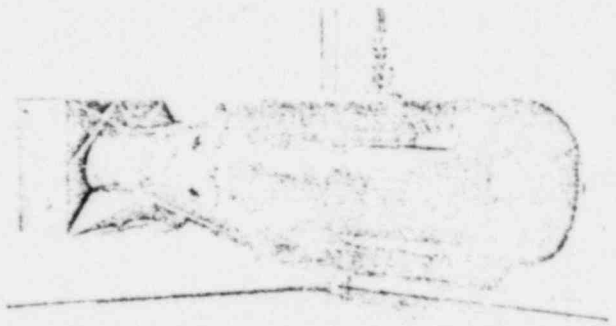
New A-Bomb Studies Alter Radiation Estimates

The basis of 15 years of radiation research may be in error; radiation toxicity may be understated

Some of the most important data on the effects of nuclear radiation on humans may be wrong, according to new research being done at the Lawrence Livermore weapons laboratory in California and the Oak Ridge National Laboratory in Tennessee. The new findings are far from welcome, as one consultant in this work says, for all the revisions "are moving in the wrong direction"—a direction that will worry the advocates of nuclear power. Government physicists have recalculated the data on the radiation fields created by the atomic blasts at Hiroshima and Nagasaki and produced some unexpected results. Their statistics show that most of the cancer caused by those bombs came from low LET gamma rays,* suggesting that this common type of radiation is more hazardous than had been assumed before.

The impetus for the revision comes primarily from Livermore, where physicists William Loewe and Edgar Mendelsohn last year used a computer to reconstruct the two explosions. Their findings are being checked and complemented by a group at Oak Ridge led by George Kerr. He began work on a similar project in 1977, shelved it, and then returned to the task in earnest when Loewe's data became known. Dean Kaul of Science Applications, Inc., in Chicago also carried out some early calculations that sparked interest in the issue. Kerr, Kaul, and Jess Marcum of Research and Development Associates in Santa Monica, California, have been funded by the Defense Nuclear Agency to explore the problem and check some of the old assumptions which have not yet been reexamined.

Although they differ in some of the details they stress, all of these scientists agree that the accepted figures for high LET (neutron) radiation at Hiroshima are grossly overstated. For example, the neutron radiation at a distance of 1180 meters from the epicenter of the blast appears to have been overestimated by a factor of 6 to 10. Since the effects on human health remain the same, one must conclude that the gamma rays were more toxic than had been thought.



U.S. Air Force

Did it produce neutrons or mostly gamma rays?

Duplicate of the bomb that hit Hiroshima

If this research proves correct—and it has survived a few peer challenges already—it will necessitate the rewriting of many basic documents on the hazards of radiation, including the first attempt to define such risks published in 1980 by the National Academy of Sciences. That study, the work of the Committee on the Biological Effects of Ionizing Radiation (the BEIR report), was fraught with controversy on this very question.

Although much of the BEIR report was released to the press in May 1979, the Academy decided to recall and rewrite it because of dissension among the authors. Some of them, led by Columbia University biophysicist Harald Rossi, argued that the paper overstated the cancer-causing effects of low LET radiation. Their arguments leaned heavily on Japanese data and particularly on the thesis that many of the cancers in Hiroshima were produced by high LET neutron radiation.

Using the old Hiroshima radiation data as evidence, Rossi argued that the BEIR committee should lower the cancer risk estimates published in an earlier BEIR report in 1972. Instead, the committee raised the risk estimates. Rossi considered this an alarmist move and withdrew his support from the document. In the end, the Academy felt compelled to write a report that effectively split the difference between Rossi's point of view and that of his chief adversary, the committee chairman, Edward Radford, an epidemiologist at the University of Pittsburgh. The risk estimates in the final report of July 1980 were not as high as Radford argued they should be nor even as high as those in the 1972 report. Neither Radford nor Rossi endorsed the document.

Rossi concedes that the Livermore calculations may do away with the evidence for his theory that neutrons were responsible for the high cancer incidence in Hiroshima. But he does not expect to alter his general view that the hazards of radiation are exaggerated. Radford, in contrast, says the new Hiroshima data vindicate his position and invalidate Rossi's. Furthermore, Radford considers the BEIR 1980 report obsolete and expects that the probabilities it gives for the risk of dying of cancer after exposure to gamma radiation will be doubled. Likewise, he thinks the probabilities for contracting any form of cancer after irradiation will be quadrupled.

The importance of the new research is that it completely changes the scheme of radiation doses that people are supposed to have received in Japan, particularly in Hiroshima. Until now, it was thought that the Hiroshima blast was unique in that it produced a large field of fast neutrons, a high LET form of radiation. Neutron radiation is considered more dangerous than low LET radiation, a category that includes x-rays, electrons, and gamma rays. Its singular presence in Hiroshima was said to make the cancer risk found there anomalous. Most of the radiation people encounter is not of this kind. The wastes from nuclear reactors, for example, emit gamma rays. Thus, a

*The terms "low LET" and "high LET" (for linear energy transfer) refer to the physical quality of the ray. Low LET radiation loses relatively little energy as it travels along its course, and includes electrons, gamma rays, and x-rays. High LET radiation loses energy more rapidly as it travels, and includes beams of neutrons and protons.

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number of scientists have always considered Hiroshima a special high-risk case, and in studying the peacetime hazards of radiation, they have discounted some of the cancer data from that city.

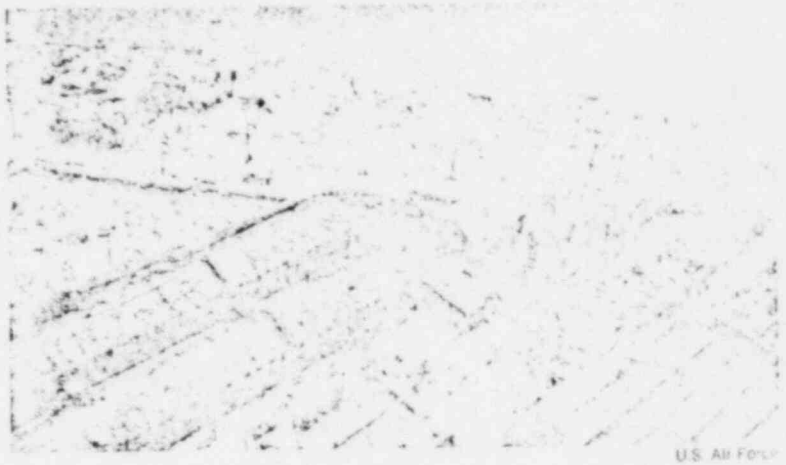
As it happens, the cancer mortality data from Hiroshima are the most valuable in the world. Unlike the data from Nagasaki, they are abundant enough to reveal a clear relationship between doses of radiation received and ill effects. That relationship is defined by a linear equation: an increase in dose above the natural background radiation correlates with a proportional increase in ill effects. The pattern suggests that any increase in radiation, no matter how small, directly increases the risk of getting cancer. The mortality data from Nagasaki are sketchier, making them susceptible to a variety of interpretations. The significant point is that if the new bomb calculations are accurate, the data from Nagasaki and Hiroshima can be combined and treated as a single, coherent pattern of response to low LET radiation. It is too early to say precisely what that pattern will look like, because now the doses must be recalculated for each radiation victim. But most of the researchers who spoke to *Science* said the new data would probably increase the risk estimates for gamma radiation.

Radford, an advocate of this point of view, claims that the argument over Hiroshima and its mortality data has been a distraction from the main body of scientific evidence. He says the 1980 BEIR report miscalculated in emphasizing mortality data so heavily, for death certificates do not give a very accurate reading of the number of cancers or even cancer deaths in a community. Radford thinks it was a mistake to pay so much attention to Rossi's theory about deaths in Hiroshima, for he claims the theory is contradicted by "90 percent" of the epidemiological data on record. He is pleased that the Hiroshima data may now look consistent with all the rest.

"The implications are far reaching for health regulation and nuclear power in this country in general," says David Auton, a physicist in the office of targets and damage assessment of the Defense Nuclear Agency. His office is funding the research at Oak Ridge that may confirm the new dose estimates. As he describes the situation, the health physics community faces a nasty dilemma, if the new bomb data are accurate. On one hand, the standard-setters may adhere to Rossi's principle, which maintains that many of the cancers produced in Hiroshima were caused by fast neutrons. But the number of neutrons thought to have been present is now so small that one must account for their effects by increasing the estimate of their potency. The resultant killing power of neutrons is "incredible," Auton says. Industrial safety rules would have to be revised, reducing exposure limits for neutron radiation to one-tenth of the present limits. For critical jobs, companies would have to employ ten times as many people. On the other hand, the health physics community could cling to the Rossi principle [illegible] that nearly all the cancers in Hiroshima were produced by gamma rays, not neutrons. That news will not be welcome either.

Auton wishes frankly that someone else were funding this research, which he thinks is important for future health and energy policy. His office is doing it because "nobody else was interested." The controversy has been brewing for at least 4 years, for that is how long it has been since a government consultant first raised serious questions about the validity of the Hiroshima data. According to Auton, however, it was just 5 months ago that he was approached by Harold Wyckoff, chairman of a special committee assigned to study this question for the National Council on Radiation Protection and Measurements. It is a private organization that collects and publishes radiation risk information. Since no other agency would fund the research, Auton says, he agreed to have the Defense Department pick up the tab for work being done at Oak Ridge, and thus come up with some answers for Wyckoff. The funding began about a month ago.

"This work is of marginal interest to us and we really can't afford to spend very much money studying civil effects," Auton says, but it is important to resolve the uncertainties. It might make more sense for the Department of Energy or the Nuclear Regulatory Commission to pay for this work, and "the electric power people really should be interested," according to Auton. It is important that the new research be credible. Auton agrees that it would be best if the sponsor were an independent group not associated with the weapons program or the nuclear industry.



U.S. Air Force

Hiroshima, 1945

Some concrete buildings survived the blast.

Arthur Upton, the former director of the National Cancer Institute and an expert in radiobiology, has followed this controversy closely since he learned of the new bomb data last fall. It is an important issue, he says, and should be the subject of more research, sponsored by a neutral scientific organization such as the joint U.S.–Japanese Radiation Effects Research Foundation. If the new dose estimates are correct, Upton says, "I am not sure one can substantiate the Rossi thesis." It may remain important for radiobiology, for there are differences in the way that plants and animals respond in the laboratory to high and low LET radiation. Upton agrees with Radford that the new data greatly strengthen the argument that there is no "safe" level of exposure to radiation, in that every incremental bit of exposure increases the chances of injury.

One of the curious aspects of this research is the manner in which it was published. The record serves as a compelling argument for declassifying as much as possible of what is done at government labs, for many of the assumptions in this case might have been challenged sooner had the underlying data been available for scrutiny.

The Rosetta stone of Japanese radiation dosimetry is known as T65D, which stands for tentative dose estimates compiled in 1965. The figures were assembled by physicist John Auxier of Oak

Ridge in a painstaking analysis of measurements made during and after the Japanese blasts, interviews with the bombardiers, and a test explosion in the Nevada desert. Some of his work was classified because it described in detail the makeup and radioactive output of the Little Boy (Hiroshima) and Fat Man (Nagasaki) bombs. Auxier's methods of computing the doses, which underlie 15 years of research on health effects in Japan, were never described in detail. In 1977, however, the government published a quasi-technical narrative by Auxier (*Ichiban*, Energy Research and Development Administration, TID 27080) giving some additional information on Auxier's methods.

As questions about these figures arose in the late 1970's, the National Council on Radiation Protection (NCRP) asked Auxier to justify his estimates with more supporting information. After working on this project for several months, Auxier explained that he could not reproduce all the data because some had been lost. He explained to *Science* that when Oak Ridge was reorganized in 1972, he was moved from one place to another, and his old classified files were left behind in his laboratory. Auxier says that the records division at Oak Ridge made a mistake in shipping the files: the valuable data were sent to the shredder.

The NCRP continued to ask for confirmation of the T65D numbers because they had become important in the debate on the hazards of radiation and because new data were becoming available. In 1976, the Los Alamos Scientific Laboratory in New Mexico, a weapons design center, released an estimate of the radioactive output of the Hiroshima bomb for the first time. The figures were not published, but given in a private letter to C. P. Knowles of Research and Development Associates, who was trying to help the Defense Nuclear Agency pin down the precise explosive power of the Fat Man bomb. This is one of the key uncertainties in the record; some say the blast equaled the power of 12.5 kilotons of TNT, and others say it may have been as potent as 15 kilotons. Several people in the weapons and biophysics communities soon obtained copies of the letter, including Kerr at Oak Ridge and Kaul at Science Applications. Using the new data and computer techniques not available when Auxier did his research, Kaul and Kerr in separate projects came up with numbers that were at odds with the T65D results.

Kerr's laboratory is the best equipped and best funded for this expensive computer work, Kaul says, and for that reason it has been given the primary responsibility for reviewing the old numbers. Kerr's task is complicated by the fact that he is in a sense Auxier's successor at Oak Ridge and works just down the hall from this senior official whose work he has been asked to review.

Auxier, meanwhile, says that his data are the best available, not likely to be changed much by the work of latter-day

Technology Transfer Reappraised

Transfer of technology from industrialized countries to developing countries emerged in the 1970's as a highly charged issue in the so-called North-South dialogue. Less-developed countries protested that control of technology by the industrialized North keeps them in a state of technological dependence.

A report* just issued by the Organization for Economic Cooperation and Development (OECD) in Paris questions major assumptions on which the technology transfer debate has been conducted. It argues that technology transfer has been mutually beneficial for industrialized and for developing countries, or at least some of them.

The report notes that technology transfer has helped a group of "industrializing" developing countries to participate, on stronger terms, in the world trading system. These include Brazil, Mexico, South Korea, Taiwan, Hong Kong, and Singapore.

The report's main challenge to the notion of technological dependence is its assertion that "technological monopolies are temporary," that change is propelled by a "technology cycle." New technology introduced in one country is transferred under tight control first to other developed countries and then to less-developed countries. As licensing and sale of the technology spreads, it becomes standardized.

Proof that this process is working is seen in the rise in imports by industrial countries of manufactured goods from developing countries. Moreover, some industrializing countries are themselves exporting technology, mostly in the form of turnkey plants and equipment.

Feedback from technology transfer also affects industrial countries. The impact has been most conspicuous in the decline of traditional industries, notably clothing, footwear, and light manufacturing, that have faced offshore competition. Loss of jobs has created a protectionist backlash that includes criticism of technology transfer. But, says the report, technology transfer has benefited the United States and other OECD countries by creating export markets for their capital-goods industries during a period of slow growth.

By focusing on the industrializing countries, the report offers a selective view of the problems facing developing countries. It does note in passing that for the poorest countries, the cost of imported oil, trade deficits, and foreign debt make the outlook bleak. Even for the industrializing countries, the burden of energy costs, deficits, and debt have "led to pessimism regarding future financing of development."

The report was prepared by the staff of OECD, which is essentially a club of governments of western industrial nations plus Japan. OECD serves as a data gathering and intergovernmental policy-planning organization. It is, therefore, not surprising that the report assesses technology transfer mainly from the sellers' point of view.

In broad terms, what the report's authors say is occurring is a major restructuring of the international industrial system. For the industrial countries an "adaptive strategy" is counseled. With a two-way trade in industrial products now established, the North can retain its comparative advantage only by keeping its "innovatory capacity" at a high level. Pressure to transfer R & D activities to developing countries will build as their scientific infrastructures strengthen. The report borrows from Lewis Carroll to observe that industrial countries must "keep running to stay in the same place."—JOHN WALSH

*"North/South: Technology, Transfers, The Adjustments Ahead," Organization for Economic Cooperation and Development, Paris, 1981. 512.

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revisionists. His judgment is widely respected. As the grand old man in this field, he is in a position to influence funding decisions on new research. Auxier told *Science* there is no need for an independent review of the discrepancies between his data and Kerr's, expressing an opinion which may have made it difficult to get the present review started. Auton, the Defense Nuclear Agency official who makes the funding decisions, says that he has great respect for Auxier's work, a respect based as much on Auxier's standing in the community as on his ability to "drag out corroborative data."

Kerr has never published any of his work outside the laboratory, he says, because he prefers to be "timid" about it. Earlier controversies have taught him to move cautiously in matters as important as this, and he still thinks there could be some weaknesses in the new bomb data.

This stalemate existed for several years until the summer of 1980 when Loewe decided to rework the calculations. He started the project because the old Hiroshima data and Rossi's recent warnings about the potency of neutrons worried people in the lab. Livermore scientists are involved in weapons research and are frequently exposed to neutron radiation. They wanted to know more about the dangers. Loewe's investigation, completed last October, found both the Hiroshima data and Rossi's principle to be unsubstantiated. Loewe argues that there is no evidence showing that neutrons were present in significant quantities in Hiroshima.

Loewe, Kerr, Auxier, and others in this controversy will present their arguments at a meeting sponsored by the Radiation Research Society on 31 May in Minneapolis. Auton calls it "the beginning of an important dialogue," one which he probably will not be able to attend because the new Administration has reduced the bureaucracy's travel allowances. But Auton hopes the meeting will lead to a general and independent review of the issues. "If the weapons folks" make it a strictly internal project, he says, "I just have a concern that nobody will believe the results."

—ELIOT MARSHALL

Science Adviser Post Has Nominee in View

The job, turned down by several candidates, may now be offered to a man who is not a member of the science establishment

The choice of science adviser to President Reagan has been narrowed down to a single candidate: George A. (Jay) Keyworth, a 41-year-old physicist from the Los Alamos Scientific Laboratory. Although the job had not formally been offered to Keyworth as of this writing, Administration officials expect an announcement by the end of May, but caution that something could still go awry even at this late stage of the selection process.

When Keyworth's name came up as a potential candidate late in April, it drew a mixture of surprise and unease from the scientific establishment. The surprise stems from the fact that Keyworth is virtually unknown outside his field. And the unease is related to the fact that his candidacy was being vigorously supported by Edward Teller, the so-called "father of the hydrogen bomb," and Harold Agnew, president of General Atomics and former director of Los Alamos. Both are well known for their hawkish defense views.

Those who know Keyworth describe him as smart and personable. His research has been concerned mostly with nuclear structure and low-energy nuclear reactions, and for the past 3 years he has directed the physics division at Los Alamos. One scientific colleague, Arthur Kerman of MIT, describes Keyworth as

Outsider causes unease

Candidate George Keyworth

"a very good scientist who is a lot broader than his background would indicate."

His background does not, however, include service on the usual round of government science committees. Hence he has little experience with federal science policy and has made few links to the scientific establishment. "He doesn't provide any channel between the national (scientific) community and the White House," complains one veteran of science and government affairs.

Such concerns are abruptly dismissed by Keyworth's supporters. Although he "lacks obvious credentials, that doesn't mean he will not do a superb job," says one. Agnew scoffs that "he has all the right credentials—all he doesn't have is 20 years membership in the club." In a telephone interview with *Science*, Agnew also said that he thinks much of the unease about Keyworth is simply due to the fact that he is an outsider—"If you get a bunch of chickens together and you put in a new rooster, they start clucking and running around," he remarks.

As for Keyworth's shortage of links to the scientific establishment, Agnew says that "defense will be the thrust of this Administration, and somebody who has the respect of the people in the defense labs is needed." He adds: "For the past four years, you have had a geologist in charge, and the defense community has suffered."

How did somebody from outside the traditional ranks of candidates for science adviser get selected? Keyworth says he was approached about the job early in April, and "it came as a surprise to me." The post was formally offered in March to Arthur Bueche, head of research and development at General Electric, but he was forced to turn it down for personal reasons. Several other people were subsequently sounded out about

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New A-Bomb Data Shown to Radiation Experts

Conference goers are impressed with the revised picture of Hiroshima, but foresee little change in risk estimates

Minneapolis. Physicist William Loewe spoke at the annual meeting of the Radiation Research Society here on 31 May and gave the first public presentation of the work he and Edgar Mendelsohn have done at the Lawrence Livermore National Laboratory. They have drastically revised the estimates of radioactive fallout from the Hiroshima and Nagasaki atomic bombs. The most important single finding they reported was that no neutron radiation of any statistical significance was present at Hiroshima, suggesting that nearly all the bomb-related cancers were produced by gamma rays. If correct, this means there are no good human data for judging the toxicity of neutron radiation.

The audience was receptive, and several old hands said they found Loewe's work impressive. No general consensus was reached on whether or not Loewe's data should replace the old estimates of atomic radiation prepared in 1965 by John Auxier of the Oak Ridge National Laboratory.

Most of the participants agreed on one thing, however: they were unhappy with the way the news of the possible revision was reported, and they were annoyed by the interpretation given by University of Pittsburgh epidemiologist Edward Radford, who has said that it may be necessary to double or quadruple the risk figures for getting cancer after exposure to radiation (*Science*, 22 May, page 909). Speaker after speaker echoed the theme sounded early in the meeting, that not enough work has been done to permit a conclusion such as the one Radford reached. Harold Wyckoff, chairman of a task force created in 1976 expressly to review this problem for the National Council on Radiation Protection and Measurements (NCRP), said, "I would strongly disagree with anyone using this data to determine risk coefficients." It is too early to do that, he said.

Loewe agreed that it would be wrong to draw broad conclusions based on his preliminary work, but he did tell the Minneapolis *Tribune* that he thought the new data will have a negligible impact on risk figures. Others, such as Warren Sinclair, president of the NCRP and an organizer of the meeting, were stronger in their denunciation of Radford, suggesting that the new Livermore data may even make radiation look less harmful than before.

If the sponsors of the meeting were unhappy with the way Loewe's work was presented to the public, other members were as unhappy with the way the information had been circulated (or not circulated) within the community. Perhaps the most outspoken was Seymour Jablon, the National Academy of Sciences' staff officer for joint U.S.–Japanese research on late effects of atomic radiation. He is a veteran observer.

Jablon rose during the general discussion to make three points. The NCRP has known since 1976 that there might be flaws in the Japanese data, he pointed out. "Meanwhile, the EPA is busy setting [occupational radiation] standards; other people interested in standards have been making noises. It really is urgent that we get on with this job. . . . Given the unique experience at Hiroshima and Nagasaki and the tens of millions of dollars which have been spent trying to accumulate the human biological data, it really is appalling to think that we stand here, 36 years later, debating orders of magnitude in the doses." He pleaded with federal officials present to give aid to complete the research quickly and shore up the $100 million investment in Japanese data.

> "Given the unique experience at Hiroshima . . . it really is appalling to think that we stand here 36 years later, debating orders of magnitude in the doses," Seymour Jablon said.

Second, Jablon said, "I think it's going to be absolutely necessary in this murky situation that any dosimetry system that is finally decided upon be reasonable in terms of biological influences that we know about. . . . And since the problem is of wider scope than merely physics, perhaps it would be advisable to consider adding some biological expertise to the [NCRP] task force."

Third, Jablon said, "I think that the way this whole problem developed is very unfortunate. Most of us, certainly I, heard about the problem . . . by word of mouth. The next thing was to receive pieces of paper which were not for publication, quotation, or citation. . . . I am told the Japanese Diet is about to have a debate on the subject, and still there is nothing published that one can point to and rebut or accept or whatever."

NCRP President Sinclair responded by saying that there was already one biologist on the NCRP task force, and that he would consider adding more when an attempt is made to extrapolate health effects from the bomb data. One of the physicists who has been at work on the problem the longest, George Kerr of Oak Ridge National Laboratory, said that he thought the data had not been published sooner because they were not strong enough to stand up to peer review. (Two relevant papers have now been submitted to *Health Physics* as technical notes: "Revised dose estimates at Hiroshima and Nagasaki," by Loewe and Mendelsohn, and "Implications of new Hiroshima and Nagasaki dose estimates: Cancer risks and neutron RBE," by Tore Straume and R. Lowry Dobson.)

Radford, who is not a member of the Radiation Research Society, skipped the meeting. He expressed disappointment, however, at the attitude that "we can't say anything until we have everything in hand," as he described it. According to Radford, that attitude can be used to delay reaching any conclusion: "It's what the tobacco industry did for years with the epidemiological evidence relating cancer to smoking. They just said,

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"Well, that last study wasn't perfect, so we'll ignore it."

The net effect of the new research, Radford insists, is not hard to summarize: the radiation data for the two cities of Hiroshima and Nagasaki are now likely to come out looking very similar. "You can state that as a general principle," says Radford, "and I do state it. That being the case, they confirm the fact that it was primarily gamma rays that produced the cancers, and that the neutrons, for all practical purposes, contributed so little that they're not important."

Radford believes that the Livermore data strengthen his argument that a linear no-threshold model is the correct one for describing the carcinogenic effects of exposure to low levels of radiation. And if this is correct, he says, the risk estimates published by the National Academy of Sciences in its 1980 report on the Biological Effects of Ionizing Radiation (BEIR) should be restated. He thinks the risks for contracting fatal cancer from radiation should be doubled. He would fix the risk at 250 to 500 excess deaths per rad of increased radiation per 1 million people, not 100 to 250 deaths, as he says BEIR and other documents have fixed it. Radford would also like to see the risks stated in terms of cancer incidence, not mortality, so as to recognize that real injury is done by cancers which do not necessarily kill. Including these figures, Radford says, would make it necessary to further raise the main risk coefficient used in the BEIR report.

Loewe did not discuss Radford's interpretation at the meeting, except to say that he could not understand how such views could be supported. Loewe said he did not see how one could draw a straight line through the old or new radiation effects data. Indeed, two scientists from Livermore who have been working in conjunction with Loewe, Tore Straume and R. Lowry Dobson, presented a paper suggesting that the new bomb data may lower the risk estimates for low doses of gamma radiation. They, too, were skeptical of all that Radford had said.

So many variables have been cited in this controversy that it may be worthwhile explaining just which data belong to whom. Radford, first of all, has done no new research on this issue. He is an epidemiologist with strong opinions on the subject, and he has seized upon Loewe's work as fresh evidence to support his view that many documents understate the hazards of low-level radiation. Radford also says that in defending this outlook he is working against the professional bias of health physicists, which, he claims, is to minimize the dangers of radiation.

Harald Rossi is a Columbia University biophysicist who challenged Radford's views as alarmist when both were serving on the BEIR committee. (Radford was the chairman.) Rossi argued that the hazards of gamma radiation were exaggerated, and he cited the Japanese bomb data to support his case. As part of this thesis, Rossi put forward the idea that many of the fatal cancers at Hiroshima had been caused by neutrons, not gamma rays. Neutron radiation is found rarely in nature, and as a practical matter it is of concern only to people exposed to nuclear weapons and the innards of operating nuclear plants. Rossi's work prompted the NCRP to send out a special advisory to weapons laboratories warning them that their safety standards might be inadequate because neutrons might be more dangerous than had been thought. That was 3 years ago.

Loewe and Mendelsohn were swept into this debate in 1979 because they worked at Livermore, a weapons lab, and were concerned about the NCRP advisory. Livermore did not change its safety standards, but it did finance some computer work by Loewe and Mendelsohn, who attacked the evidence for Rossi's thesis. Their calculations, now made public, do not demonstrate that neutrons are safe. They simply show that neutrons were so scarce in the Japanese blasts that one cannot measure their effects with accuracy. At the same time, the Livermore work significantly *increases* the estimate of gamma radiation in Hiroshima and slightly *decreases* the gamma radiation in Nagasaki.

Using this data, Dobson and Straume have made preliminary new estimates of the toxicity of gamma and neutron radiation. Their paper concludes, among other things, that if one uses the total cancer deaths as a guide, low doses of gamma radiation look less harmful than before. (Other statistical guides produce different results.) They also suggest that it may still be possible to blame the small number of neutrons in Hiroshima for many of the cancer fatalities. Asked about this part of the Straume-Dobson paper, Rossi said he considered it just "an interesting exercise," no more. He believes that if the Livermore data are correct, they will make it impossible to say anything conclusive about neutrons in Hiroshima.

An important caveat applies to all of the recent work on radiation in Japan: it does not include corrections for changes in the shielding provided by buildings or by body tissue. According to Jess Marcum, a contractor for Oak Ridge for a review of the data, significant revisions of the Livermore dose estimates may be necessary before one can reach a conclusion on toxicity. Marcum says he has spent about 1 month researching shielding by buildings and has discovered that the estimates of gamma doses in many cases will have to be lowered. In the area of interest, 1000 to 1700 meters from the epicenter of the blast, Marcum calculates that indoor gamma ray doses will have to be reduced by a little more than 60 percent. The net effect, he believes, will be to make gamma doses for individuals in Hiroshima about the same as in the old estimates produced at Oak Ridge in 1965, while the Nagasaki doses will be lower than the 1965 figures.

According to Jess Marcum, significant revisions of the Livermore dose estimates may be necessary before one can reach a conclusion about toxicity.

In addition, George Kerr of Oak Ridge is recalculating the shielding effect of body tissue for certain "target" organs such as the breast, thyroid, colon, and so on. Marcum reports second hand (Kerr is in Europe) that the net effect of this final adjustment may be to produce no change in the leukemia risk factors for the two cities, but to increase slightly the risk for breast cancer, bringing the latter into agreement with U.S. medical data on breast cancer caused by x-rays. If true, this is an "extraordinary conclusion," Marcum says, because it will give credibility to the research done by Loewe, Marcum, and Kerr, as well as to the Japanese epidemiological data.

One of the few things that is clear in all this is that Livermore's research has irreversibly toppled the status quo. It also seems clear that the federal government would be well advised to finance the work necessary to bring a new estimate of radiation dosimetry into focus as quickly as possible.—ELIOT MARSHALL

UNITED STATES OF AMERICA
NUCLEAR REGULATORY COMMISSION

BEFORE THE ATOMIC SAFETY AND LICENSING BOARD

In the Matter of	)	
	)	
CLEVELAND ELECTRIC ILLUMINATING COMPANY, et al.	)	Docket Nos. 50-440 50-441
	)	
(Perry Nuclear Power Plant, Units 1 and 2)	)	

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