RERF update RERF

News & Views from the US–Japan Radiation Effects Research Foundation

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RERF's Hiroshima Immunology Laboratory Celebrates Second Lustrum

This year, the Immunology Laboratory of Hiroshima's Radiobiology Department celebrates its tenth anniversary. It was established in July 1981 as part of the former Pathology Department at the proposal of RERF Chief of Research **Kelly Clifton** (presently at the University of Wisconsin–Madison). Current Chief of Radiobiology **Mitoshi Akiyama**, then at the Virginia Mason Research Center in Seattle, was invited to direct it. The initial objectives of the laboratory were to study the use of monoclonal antibodies for early detection of cancers in atomic bomb survivors, to perform research on the effects of radiation on the immune system of survivors, and to develop immunological techniques for application in other fields of research ongoing at RERF. Given budgetary factors and advice from the Scientific Council, the last two objectives were emphasized.

J TAKAYAMA

The Radiobiology Department research scientists: seated from left, Yoichiro Kusunoki, Yuko Hirai, Mitoshi Akiyama, Nori Nakamura, and Tomonori Hayashi. Standing, from left: Shigeko Umeki, Toshio Seyama, Terumi Mizuno, and Takashi Itoh.

"The laboratory has been very successful, and it can claim a history of high research quality and productivity," commented RERF Chairman **Itsuzo Shigematsu**.

One of the laboratory's early discoveries was the existence of impaired T-cell activity in survivors, tens of years after their exposure. In 1983, somatic mutation studies were

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Selected publications from the Immunology Laboratory

Peripheral lymphocyte response to PHA and T cell population among atomic bomb survivors. M Akiyama, M Yamakido, K Kobuke, DS Doc, HB Hamilton, AA Awa, H Kato. *Radiat Res* 93:572–80, 1983.

Monoclonal antibodies to human squamous cell carcinoma of the lung and their application to tumor diagnosis. S Kyoizumi, M Akiyama, N Kohno, K Kobuke, M Hakoda, SL Jones, M Yamakido. *Cancer Res* 45:3274–81, 1985.

Age-related alteration in the composition of immunocompetent blood cells in atomic bomb survivors. Y Kusunoki, M Akiyama, S Kyoizumi, ET Bloom, T Makinodan. *Int J Radiat Biol* 53:189–98, 1988.

Increased somatic cell mutant frequency in atomic bomb survivors. M Hakoda, M Akiyama, S Kyoizumi, AA Awa, M Yamakido, M Otake. *Mutat Res* 201:39–48, 1988.

Age and dose related alteration of in vitro mixed lymphocyte culture response of blood lymphocytes from A-bomb survivors. M Akiyama, OL Zhou, Y Kusunoki, S Kyoizumi, N Kohno, S Akiba, RR Delongchamp. *Radiat Res* 117:26–34, 1989.

Molecular analyses of in vivo HPRT *mutant T cells from atomic bomb survivors.* M Hakoda, Y Hirai, S Kyoizumi, M Akiyama. *Environ Mol Mutagen* 13:25–33, 1989.

Detection of somatic mutations at the glycophorin-A *locus in erythrocytes of atomic bomb survivors using a single beam flow sorter.* S Kyoizumi, N Nakamura, M Hakoda, AA Awa, MA Bean, RH Jensen, M Akiyama. *Cancer Res* 49:581–8, 1989.

Cloning of phenotypically different human lymphocytes originating from a single stem cell. M Hakoda, Y Hirai, H Shimba, Y Kusunoki, S Kyoizumi, Y Kodama, M Akiyama. *J Exp Med* 169:1265–76, 1989.

Spontaneous loss and alteration of antigen receptor expression in mature CD4⁺ T cells. S Kyoizumi, M Akiyama, Y Hirai, Y Kusunoki, K Tanabe, S Umeki. *J Exp Med* 171:1981–99, 1990.

Is interindividual variation of cellular radiosensitivity real or artifactual? N Nakamura, R Sposto, J Kushiro, M Akiyama. *Radiat Res* 125:326–30, 1991.

The 'Sanctification of Hiroshima'

by JW Thiessen
RERF Vice Chairman & Update Editor-in-Chief

One of the joys of working here is the chance to interact with the many eminent scientists visiting RERF. Most recently, we had the pleasure of receiving **Alvin** and **Gene Weinberg**, from Oak Ridge, Tennessee, who came to visit both Hiroshima and Nagasaki. Weinberg, of course, is well known for his activities in the field of nuclear energy, and especially for his analyses concerning the impact of energy technologies in its different dimensions. Although now officially retired, he is still very active as a speaker and, for example, as the chairman of the Dosimetry Subcommittee of the National Academy of Sciences's Advisory Committee for RERF.

Weinberg's interest in matters philosophical has given rise to some fascinating ideas and terminology. It was Weinberg who first coined the term "big science," and another of his many ideas is what he has called "the sanctification of Hiroshima," on which I wish to elaborate a little in this column.

Inspired by the outpouring of emotions on the occasion of the 40th anniversary of "Hiroshima," Weinberg observed that such anniversaries are not just commemorations of historical events, but bear resemblance to the observance of major religious holidays. Weinberg considers that an extremely important phenomenon, as it is only through the sanctification of Hiroshima that the world may continue to accept the absolute necessity of avoiding nuclear holocaust. Otherwise, the event would become mere historical information, one of the lessons of history likely to be forgotten in the long term.

JW THIESSEN

Gene and Alvin Weinberg visiting Peace Park in Hiroshima.

When Weinberg first wrote about this (in the *Bulletin of the Atomic Scientists* 41(11):34, December 1985), we were in the era of "mutually assured destruction"—with some justification abbreviated to MAD. The world has seen a rapid metamorphosis in the meantime, and the nuclear threat has suddenly changed character altogether. At least for the foreseeable future, MAD has gone, but nuclear terrorism, ie, the threat of individualized destruction rather than massive attack, is on the horizon and coming closer. It appears to me that the sanctification of Hiroshima, in this context, is of much lesser relevance than it was before. Hiroshima may now act as the prototype, the example for further action, instead of as the deterrent or preventative against future use. It seems to me that it is rather unlikely that a Saddam Hussein would be terribly impressed by the lessons of Hiroshima—whether in a historical or a sanctified sense—other than to support his own odious ambitions.

From a more local perspective, however, the sanctification of Hiroshima is continuing and strengthening. Hiroshima has, of course, by now fully adopted its identity as a symbol, rather than just as the name of a city

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Immunology Laboratory

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started using the lymphocyte-colony *HPRT* locus assay and an erythrocyte flow-cytometric assay of the *GPA* locus, originally developed by **RH Jensen** at Lawrence Livermore National Laboratory in the United States.

After reorganization of the Pathology Department into the Radiobiology Department (with Immunology, Cell Biology, and Pathology laboratories), a pioneering study was started on *ras*-gene expression in stored thyroid cancer autopsy samples, in collaboration with RERF's Nagasaki Laboratory.

Human lymphocyte cultures not only provided unique opportunities for initiating a new study on individual variations in cellular radiosensitivity (by the Cell Biology Laboratory), but also gave rise to the development of another flow-cytometric assay: the lymphocyte T-cell receptor (TCR) mutation assay, and to the evaluation of the frequencies of lymphocyte precursors responsible for specific antigens. In 1989, a third flow-cytometric mutation assay for the lymphocyte *HLA-A* locus was developed.

During the most recent years, monoclonal antibodies against human HPRT protein were developed, and a PCR-assisted HLA Class II allele typing technique was designed and tested. In addition, the lymphocyte TCR assay was tested on various other categories of radiation-exposed individuals, such as patients who were exposed to ionizing radiation for cancer treatment, injected with Thorotrast, or treated with iodine-131 for malignant thyroid disease.

In establishing links between modern immunological technology and radiobiology at RERF, the laboratory has introduced quantitative approaches to radiation effects measurement that have excellent potential for establishing, via "biological dosimetry," a screening method for identifying high-risk individuals in the Ukraine, Byelorussia, and the Russian Republic after the Chernobyl accident.

As Akiyama explained, "Additional plans include determining if highly exposed survivors have a limited immunological response capability to certain foreign antigens. We also plan to develop additional assay systems for quantitative measurement of somatic mutations in blood cells, using PCR and flow cytometry."

During the 10-year history of the laboratory, more than 40 original papers have been published in refereed scientific journals (see sidebar on page 1 for selected titles), and many others have appeared in local journals. The laboratory also has played an increasingly important role as a training ground for young scientists from Japan and abroad, and has participated in collaborative research projects with other laboratories worldwide.

"The laboratory will doubtless continue on its now well-established path," remarked RERF Vice Chairman **JW Thiessen**. "We wish Dr Akiyama and his enthusiastic staff the very best, and good luck."

The pages of *Update* will reflect the activity of the Immunology Laboratory in the years to come. ❑

RBE and Dose-response Functions

Is it necessary to introduce the concept of relative biological effectiveness?

by Dale L Preston and Richard Sposto, RERF
Department of Statistics

Since the radiation doses received by atomic bomb survivors include both gamma and neutron doses, questions related to the impact of neutrons on risk estimates derived from the atomic bomb survivor data are of continuing interest. These questions are often discussed in terms of the relative biological effectiveness (RBE) of neutrons. During the discussion following the session on the revised atomic bomb dosimetry system (DS86) held at the Ninth International Congress on Radiation Research in Toronto last July, many questions addressed the issue of RBE estimates derived from the RERF Life Span Study data.

H Rossi and **M Zaider** (*RERF Update* 3(1):2–3, 1991) discussed recent analyses of experimental data on RBE and commented on the possibility that intercity differences in the dose response for the chromosome aberration data might be explained by RBE values much higher than those currently in use for radiation protection purposes. Here we will outline several issues related to characterizing and estimating RBE. In addition, we suggest that directly considering the dose response as an explicit function of both the gamma and neutron components of dose (which we will call the bivariate dose-response function) without introducing the concept of RBE leads to a better understanding of the joint effects of gamma rays and neutrons and how well these effects can be estimated.

In the BEIR V report (*Health Effects of Exposure to Low Levels of Ionizing Radiation: BEIR V*. Washington, DC, National Academy Press, 1990), the RBE is defined as the "biological potency of one radiation as compared to another to produce the same biological endpoint." Thus if $f^*(\cdot)$ is the dose-response function for the reference radiation, eg, gamma radiation, and $f(\cdot)$ is the dose-response function for the radiation of interest, eg, neutrons or a mixture of gamma rays and neutrons, the RBE is defined as D^*/D, where D^* is that dose of the reference radiation such that

$$f^*(D^*) = f(D)\,.$$

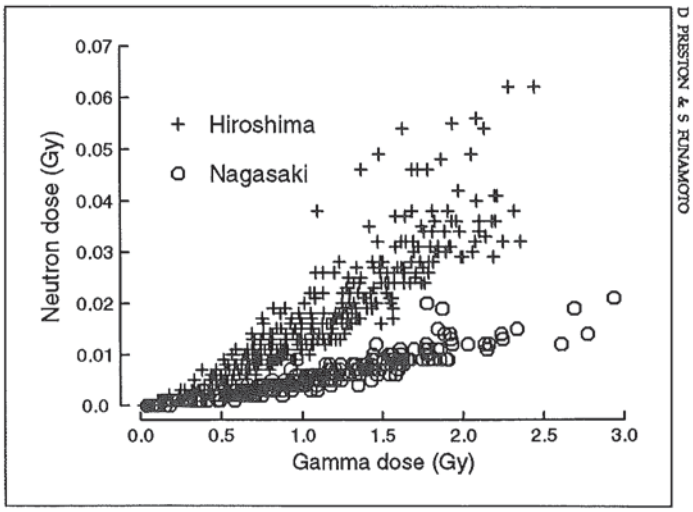
Although this definition is straightforward, it leads to complex expressions for the RBE. As an example, we can consider the RBE for neutrons relative to gamma rays assuming a linear-quadratic-linear (L-Q-L) bivariate dose-response function of the form

$$f(d_g, d_n) = \alpha_1 d_g + \alpha_2 d_g^2 + \beta d_n\,,$$

where d_g and d_n are the gamma and neutron doses. It is not difficult to determine that the RBE of a pure neutron dose, d_n, is given by the following function of d_n and the parameters of the dose-response function:

$$\frac{\sqrt{\alpha_1^2 + 4\alpha_2\beta d_n} - \alpha_1}{2\alpha_2 d_n}\,.$$

Since the dose-response parameters are not known, they are either estimated from the data or are defined in terms of values obtained from other studies of radiation-exposed populations or experimental data. Discussions of RBE are often focused on the "limiting RBE" of neutrons because this quantity is of direct interest in assessing the effect of low-dose exposures. This can be defined as the limiting value of the above function as d_n goes to 0. It can be shown that this value is the ratio of the neutron parameter to the linear gamma parameter, ie, β/α_1.



Gamma and neutron contributions to individual marrow dose estimates by city for a sample of members of the Adult Health Study.

There are several things to note about RBE functions. First, even for relatively simple dose-response functions, the RBE function varies with dose in a complex manner. Second, the RBE function depends on the outcome considered. For example, the RBE function for leukemia incidence is likely to differ from that for chromosome aberrations. Third, to some extent, the RBE function also depends on how the outcome is characterized. For example, the chromosome aberration data can be described in terms of Poisson counts of the number of aberrant chromosomes per cell or in terms of the proportion of cells with at least one aberration. These alternative descriptions of the outcome can lead to different dose-response functions and hence to different RBE functions. Although the bivariate dose-response function is also not invariant across outcomes or the characterization of outcomes, it seems to us that the introduction of the RBE concept as a function of primary interest does not lead to a simplification of the problem. Rather, it unnecessarily adds to the complexity.

Thus, while RBE functions and limiting RBE may be important for some purposes, it is better to view the RBE function as a by-product of the more basic and intuitive bivariate dose response for gamma and neutron radiation. In accordance with this view, we feel that it is important to place more emphasis on inference (and the limitations of inference) on the nature of the dose-response function than on the more abstract, and generally secondary, notion of the RBE function.

Working with the bivariate dose-response function in the RERF data has several advantages. Most importantly, dose-response functions of interest can be estimated directly using standard statistical methods, which allows us to test hypotheses and compute confidence intervals for the parameters of the dose-response function. Thus, these

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RBE and Dose Response

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models provide a direct estimate of the effect of primary interest in these data, ie, the effect of low-LET gamma radiation (given by α_1). It is also possible, by working with suitable parameterizations, to obtain direct estimates and bounds for parameters such as the limiting RBE of neutrons. For example, the L-Q-L model described above can be rewritten as

$$\alpha_1(d_g + \alpha_2^* d_g^2 + \beta^* d_n) ,$$

where $\alpha_2^* = \frac{\alpha_2}{\alpha_1}$ and $\beta^* = \frac{\beta}{\alpha_1}$. In this model, β^* is the limiting RBE of neutrons as noted above.

As shown in the figure, although the neutron contribution to the total dose is different for Hiroshima and Nagasaki, within each city the gamma and neutron doses for individual survivors are highly correlated, which implies that precise joint estimation of both intercity differences in the dose response and the parameters of the bivariate dose-response function (or the RBE function) is not possible. In statistical terms, these parameters are said to be confounded. Because of the high degree of confounding in the Life Span Study, most of the information about joint effects of gamma and neutron radiation is derived from the fact that the composition of the total dose differs for the two cities. Recognizing this has led many investigators to estimate RBE from RERF data by choosing an RBE function that causes city differences in the dose response to disappear. However, in order to produce estimates of gamma and neutron effects and to sidestep the problems of confounding, it is necessary to assume either that there is no city difference in the excess risk or that the magnitude of this city difference is known. It is also not generally recognized that whether or not there are city differences in the excess risks can depend on how the radiation effect is modeled. In particular, if the background rates (ie, rates in the unexposed) depend on city, the existence of a city difference in the radiation effect depends on whether this effect is modeled in relative or absolute terms. This is an important point since, although background rates for chromosome aberrations are similar for Hiroshima and Nagasaki, there are significant city differences in the background rates for many types of cancer, including leukemia. For this reason, it is necessary to consider how to describe the potential effect of city on the dose response. It seems reasonable to model these effects multiplicatively, ie,

$$f^*(d_g, d_n, c) = f(d_g, d_n)\, \rho(c) \ .$$

In this case, if the parameters of the bivariate dose-response function are estimated directly, the fact that the nature of city effects on the excess risk can depend on the form of the risk model does not affect the estimates of the parameters in $f(d_g,d_n)$.

In addition, in most studies in which investigators have examined RBE in terms of city differences, they have assumed a constant RBE. However, this assumption is appropriate only if both the gamma and neutron dose-response functions are linear at very low doses. If one wants to allow for nonconstant RBE it is much simpler to estimate the bivariate dose response directly with or without an assumption of no city difference in the dose response. Similarly, if one is interested in the applicability of specific RBE functions, eg, those of **DC Lloyd** et al (*Int J Radiat Biol* 29(2):169–82, 1976), to the RERF data, this can be done using formal statistical tests comparing estimated dose-response parameters with those arising from the model of interest. Preston et al (RERF TR 7-88) have used this approach with the RERF chromosome aberration data.

Our point here is not that we must give up all attempts to estimate RBE from the LSS data, but rather that efforts to do this in terms of city differences are misguided.

Because of their reliance on indirect methods, most discussions of neutron RBE based on the LSS data do not consider in detail uncertainties in the estimates. As noted above, one of the strengths of working directly with the dose-response function is that we can obtain a better idea of how well, or perhaps more appropriately, how poorly the LSS data allow us to characterize the separate effects of gamma and neutron radiation. Since the RBE is simply a function of the parameters of the dose-response function, if we cannot estimate the bivariate dose response with much precision then we clearly cannot estimate the RBE function with much precision.

Here we have discussed the relationship between the dose response and RBE functions and have noted that the bivariate dose-response function is a more fundamental concept than the RBE function. We also have noted some problems inherent in efforts to estimate the RBE or RBE function by means of city differences in the dose-response functions for the A-bomb survivor data. We suggest that there is a need to place greater emphasis on estimating the bivariate dose response in the LSS, and that by doing so one can obtain a better understanding of the effects of both gamma and neutron radiation and of the precision with which these effects can be estimated from the RERF data. ❑

Perspectives

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that played a role in Japan's recent history. This particularly strikes foreign visitors, who are genuinely surprised that Hiroshima is indeed a booming town, very much alive, with no clouds of doom hanging over it. The area of the Peace Park—even, I dare say, the A-bomb Dome itself—looks "new," organized, smooth, fully supported by modern technology. Clearly, we are not talking any more about merely recalling a past event. We have gone beyond that and are now establishing a monument to a memory, a religious sanctuary in Weinberg's sense.

With the 50th anniversary approaching rapidly, there is a discussion going on within the government to erect another visible memorial to the victims of the atomic bombings, in both Hiroshima and in Nagasaki, to be in place in 1995. These memorial centers are meant to serve as sources of information on the effects of the A-bomb in general, and those of radiation in particular, for the edification of other radiation-exposed people, eg, those affected by nuclear accidents such as at Chernobyl. RERF, it is said, would play a role in this context, maybe as the scientific core. It seems to me that such a role for RERF, seemingly attractive, may well turn out to become counterproductive to our efforts to perform research in an objective, purely scientific fashion. The centers, as they are thought of, may well become embroiled in politics and quasi-science, supervised as they may be by doubtless well-meaning, but unscientific people, more interested in the sanctification of Hiroshima than in the cause of science and the importance of objectively determined facts. In the final analysis, whatever one may think about the need to sanctify Hiroshima, religion and science are notoriously unsuitable bedfellows, and there will be a need to make (and express) a distinction between the two. ❑

'Little Boy' Replica Used in Analysis of Neutron RBE

The author summarizes the results of a collaborative study designed to help determine a radiobiological basis for evaluating the biological effectiveness of neutrons.

by Akio A Awa, RERF
Department of Genetics

As the single most important source of direct data on radiation-induced effects in humans, the atomic bomb survivor data are a major anchor for radiation risk estimates. Although neutrons are now believed to have contributed a smaller fraction of the dose at Hiroshima than previously thought, the high level of biological effectiveness observed experimentally for neutrons in general makes greater knowledge of their effectiveness in Hiroshima useful for adequate interpretation of A-bomb dose-response relationships.

A unique opportunity to approach this important issue experimentally arose when, for the first time, a replica of the Hiroshima device ("Little Boy," or LBR) was assembled at Los Alamos National Laboratory to operate as a nuclear reactor so that careful dosimetry of leakage radiation could be carried out under controlled experimental conditions. The neutron energy characteristics (including lineal energy) measured at a distance 0.74 m from LBR were remarkably similar to those calculated for the Hiroshima bomb at 1 to 2 km from the hypocenter (PP Whalen, in: *US–Japan Joint Reassessment of Atomic Bomb Radiation Dosimetry in Hiroshima and Nagasaki. Final Report*, Vol 1, pp 37–65, 1987, Hiroshima, RERF), and so they were considered suitable for use in radiobiological experiments to determine the effectiveness of actual Hiroshima neutrons.

Owing to the general interest in neutron RBE, a collaborative cytogenetic study was conducted as an interlaboratory effort by Lawrence Livermore National Laboratory, Los Alamos National Laboratory, the Oak Ridge Associated Universities, and RERF.

Chromosome aberration frequencies (mostly dicentrics and rings) were measured in human blood lymphocytes exposed in vitro to graded doses of LBR radiation (97% neutrons, 3% gamma rays). Vials of blood, obtained from two healthy males, suspended in air at distances up to 2.1 m from the center of the LBR uranium core, received doses ranging from 0.02 to 2.92 Gy. Three experiments, including six sets of exposures, were carried out with LBR located inside the building, and one experiment (two sets of exposures) outside. Four different LBR power levels were used, 11, 25, 50, and 100 W, as well as two exposure durations, 20 and 30 min. Exposures were initiated within 30 min of blood collection. The blood samples thus irradiated were cultured at 37°C in 5% CO_2 for 48 hours in a culture medium consisting of RPMI 1640 with Hepes buffer, fetal bovine serum, heparin, and phytohemagglutinin. Cells were harvested between 44 and 68 hours, following a 4-hour colcemid block. More than 98% of metaphases analyzed were in their first in vitro cell division.

Without knowing the exposure status of the chromosome preparations, a staff member from each laboratory independently scored the induced chromosome aberrations, ie, dicentrics and rings.

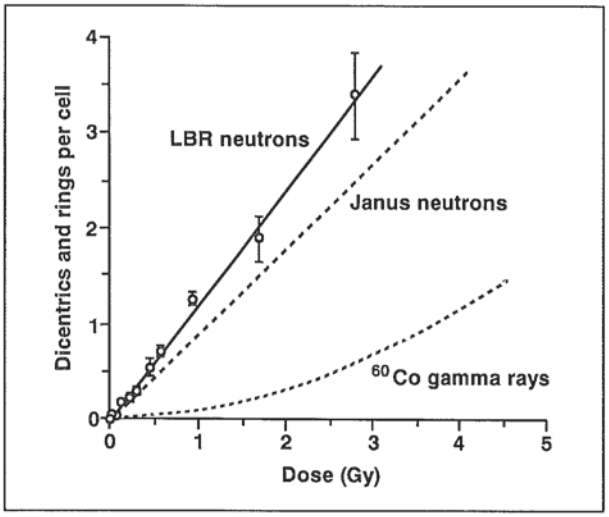

Figure 1. The LBR neutron data are plotted for pure neutrons only. The data points represent the mean frequencies of dicentrics (including rings and double the number of tricentrics) in pooled results from the three collaborating laboratories. For comparison, the dashed curves are for 0.85-MeV mean energy fission neutrons from the Janus reactor and for cobalt-60 gamma rays.

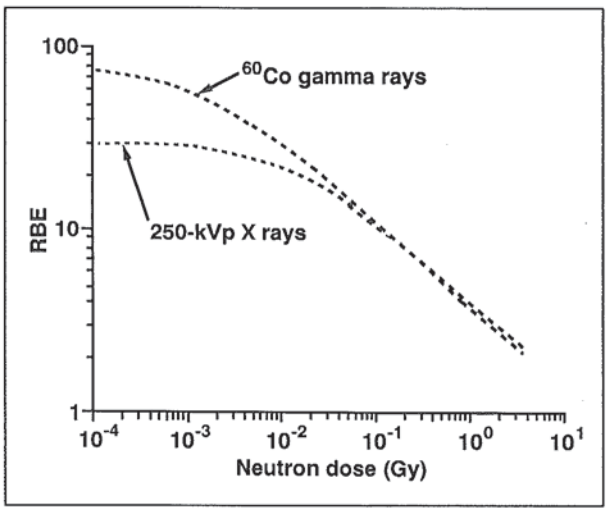

Figure 2. RBE curves for LBR neutrons obtained by using relevant coefficients from fitted curves from data for cobalt-60 gamma rays and 250-kVp X rays.

Interlaboratory comparisons suggested a tendency for LLNL results to be slightly lower and ORAU results slightly higher than the means of the pooled data from the three laboratories. RERF results were very close to the pooled means. However, none of the suggested interlaboratory differences are statistically significant; less than 5% of the data points are more

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Members of Collaborating Team:

Lawrence Livermore National Laboratory: ***AV Carrano, JL Minkler, T Straume,*** and ***RL Dobson*** (deceased).

Los Alamos National Laboratory: ***LM Deaven.***

Oak Ridge Associated Universities: ***LG Littlefield.***

Radiation Effects Research Foundation: ***AA Awa.***

News Briefs

✓ Ceremonies Mark 46th Anniversary of Atomic Bombings

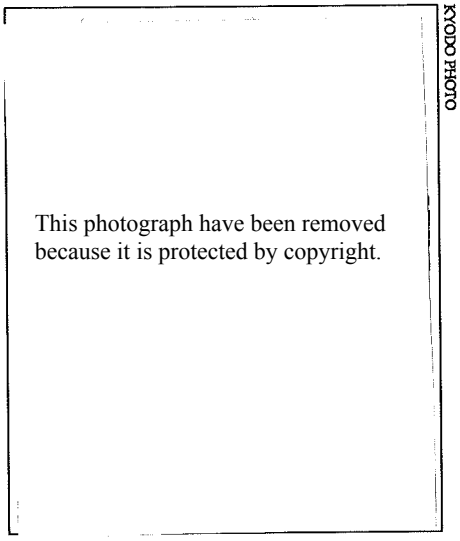
Early August brought tens of thousands to Hiroshima and Nagasaki for the yearly commemoration activities on 6 and 9 August. The ceremonies honor those who perished as a result of the world's first use of nuclear weapons in 1945 and renew the cities' pledges to promote world peace.

In Hiroshima, a crowd of about 55,000 people listened to Mayor **Takashi Hiraoka**'s peace declaration in which for the first time the city of Hiroshima officially addressed Japan's wartime role.

"Japan inflicted great suffering and despair on the peoples of Asia and the Pacific during its reign of colonial domination and war. There can be no excuse for these actions," stated Hiraoka. "...Remembering all too well the horror of this war starting with the attack on Pearl Harbor and ending with the atomic bombings of Hiroshima and Nagasaki, we are determined anew to work for world peace."

Three days later, about 25,000 people gathered in Nagasaki where Mayor **Hitoshi Motoshima** renewed his call for the Japanese government to enact a relief law to cover foreign and Japanese survivors of the atomic bombings. In 1989, speaking on behalf of Nagasaki, Motoshima apologized for Japan's colonization of Korea and China and its inhumane treatment of people in those countries.

Japanese Prime Minister **Toshiki Kaifu**, who attended the Hiroshima ceremony, pledged that the government will carry out further relief measures for atomic bomb survivors.



KYODO PHOTO

A scene from this year's memorial service in Nagasaki's Peace Park.

✓ IAEA Chernobyl Report Now Available

Update readers interested in a more detailed account of the year-long International Chernobyl Project can obtain a copy of the overview report (ISBN 92-0-129291-8) from the International Atomic Energy Agency, Division of Publications, Wagramerstrasse 5, PO Box 100, A-1400 Vienna, Austria.

✓ RERF Hiroshima Laboratory Hosting Brazilian Trainee

The Hiroshima International Council for Medical Care of the Radiation-exposed is sponsoring a three-month training period at RERF for Brazilian physician **Aparecido Cruz**, coordinator of the Cytogenetics Laboratory at the Fundação Leide des Neves Ferreira in Goiãna. In that city in September 1987, 300 persons were contaminated by a cesium-137 source that was removed from an improperly discarded medical therapy unit. Cruz will receive training in cytogenetic techniques that can be used for dose verification and biological monitoring.

✓ Japanese Physicians Consult with Atomic Bomb Survivors Living in North America

The eighth team of medical consultants traveled to Hawaii, Seattle, and Los Angeles in June to meet with survivors who now reside overseas. Supported by the Japanese Ministry of Health and Welfare, the Hiroshima Prefecture Medical Association and RERF collaborated to send two teams, which this year included Clinical Studies Associate Department Chief **Hideo Sasaki** and Division of Internal

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'Little Boy' and RBE

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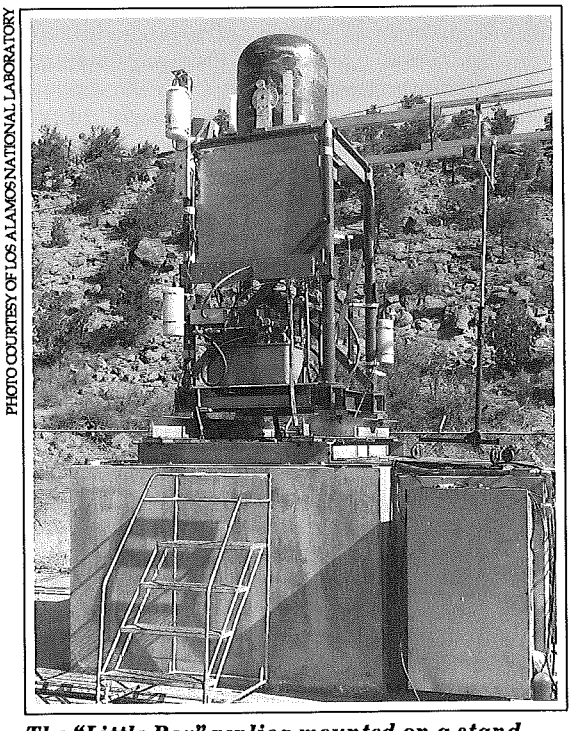


PHOTO COURTESY OF LOS ALAMOS NATIONAL LABORATORY

The "Little Boy" replica mounted on a stand with security skirts in place at the Critical Assembly Facility, Los Alamos National Laboratory.

than two standard residuals from the curve fitted to the pooled results. No significant differences were found among blood donors, power levels, or experiments, inside or outside the building (at 5% level of significance by analysis of variance).

As shown in Figure 1 on page 5, the dose-response curve for dicentric induction by LBR is linear. For comparison, a curve for Janus fission neutrons (AV Carrano, *Radiat Res* 63:403, 1975) and one for cobalt-60 gamma rays (LG Littlefield et al, in: *Medical Management of Radiation Accidents*, Boca Raton, Fla, CRC Press, 1990) are also shown in this figure. LBR neutrons produced 1.18 dicentrics per cell per gray. They were more effective than the high-energy fission neutrons ($\bar{E} \cong 1$ MeV) commonly used in radiobiology. Thus the slope of the curve for LBR neutrons ($\bar{E}$ = 0.21 MeV) is substantially greater than that for the Janus fission neutrons ($\bar{E}$ = 0.85 MeV). The ratio of slopes is 1.37. The LBR neutron curve contrasts markedly in both shape and slope with the linear-quadratic curve for gamma rays. Figure 2 on page 5 shows that the maximum RBE of Hiroshima neutrons at low doses is estimated to b 60 to 80 using cobalt-60 gamma-ra radiation as the comparison and 20 to 30 using 250-kVp X rays as the comparison.

The RBE value decreases as the dose increases. At a 0.1-Gy neutron dose, it is greatly decreased to an RBE range of 10–15, both for cobalt-60 gamma rays and 250-kVp X rays.

These findings indicate that neutrons emitted from the type of weapon detonated over Hiroshima are highly effective in producing biological damage—substantially more effective than the fission neutrons generally used in radiation biology, thus providing a radiobiological basis for more accurately evaluating the importance of neutrons in the Hiroshima atomic bomb data.

A more detailed report by Tore Straume, the present coordinator of this collaborative study, will appear in the journal *Radiation Research*. ❑

Binational Research Institute Presaged by Darling

by Hiroshi Maki, ABCC Associate Director, and JNIH Hiroshima Branch Laboratory Director, 1948–75

George B Darling was appointed director of ABCC in 1957. No sooner did Dr and Mrs Darling arrive in Japan than the couple was invited to the annual meeting of the Nihon Society of Radiology (in Sapporo) through the courtesy of **Masanori Nakaidzumi**, former dean, Faculty of Medicine, University of Tokyo. For Darling to have met, on the occasion, a great many distinguished radiologists from the universities and research institutes in Japan must have helped ABCC in many ways in the years to come. Although the trip was for only a week, it offered the two an opportunity to savor the country and its people.

Community relations strengthened

The early directors of ABCC were all very concerned about the feelings of the community toward ABCC. Darling, in particular, attached great importance to the feeling of the study participants, exposed or nonexposed. He appreciated their understanding and cooperation and always took heed of their well-being. I believe that he had a deep understanding of the customs and feelings of the Japanese. This could be seen from the interest he had in upholding the solemnity of the autopsy room. He held memorial services for the autopsied to show his respect and he visited the homes of the aged study participants to celebrate their longevity.

Time and again, Darling appealed to the government offices, universities, institutes, and public hospitals in Hiroshima and Nagasaki for their cooperation in the ABCC–JNIH collaborative studies, and he welcomed their suggestions. He earned greater acceptance from the Japanese, which, I believe, was the fruit of his ceaseless efforts.

Perhaps due to Darling's enthusiasm for the JNIH–ABCC program, the Darlings stayed in Japan for about 15 years. There is no doubt that Darling's long tenure provided continuity and improved US–Japan relations. The Darlings were interested in Japanese culture and traveled extensively throughout the country. Darling enjoyed *haiku* poetry, and Mrs Darling had a great interest in the tea ceremony and pottery.

Resources in Japan promoted

I greatly admired the efforts Dr Darling made to arrange for the transfer of the ABCC pathology specimens—including those collected in the earlier years—from the Armed Forces Institute of Pathology in Washington to the A-bomb Medical Records and Specimens Center of Hiroshima University and to Nagasaki University.

He also worked hard to obtain funds from the US government to build hospitals for Hiroshima and Nagasaki universities.

Maki at RERF's 15th anniversary in 1990.

In the introduction to the 1967–68 annual report, Darling wrote that, pending the 20th anniversary of ABCC, it would be timely for the Japanese and American governments to officially review ABCC. He expressed hope that the appropriate authorities of the US government would invite the views of the Japanese government on program priorities, administrative structure, staffing, and the financing of ABCC. Darling was also a proponent of a new joint agreement to ensure the continuation of scientifically promising studies for another 20 years. He suggested that ABCC be reorganized as a juridical person under Japanese law and that responsibility for professional direction, staffing, and financial support be redistributed. As it turned out, Darling's concepts provided the basis for establishing the Radiation Effects Research Foundation in 1975.

In 1972, Darling retired and returned to the US. He was succeeded by **LeRoy R Allen.**

✣ ✣ ✣

As ABCC director, George Darling's accomplishments can be highlighted by summarizing some of the honors he received during his long years of service.

• *November 1968:* The Darlings were invited to Their Majesties' Autumn Garden Party at the Akasaka Palace Gardens, Tokyo.

• *November 1967:* Upon the commemoration of the Japan Medical Association's 20th anniversary, Darling was presented with the association's Supreme Award for distinguished services in enhancing international exchange in the field of medicine.

• *November 1967:* Darling was awarded the Gold Medal of Merit of the Japan Red Cross Society for outstanding services.

MAX DESFORS

Darling, left, and the author in June 1970, five years before the establishment of the Radiation Effects Research Foundation.

• *December 1965:* Darling received a letter of commendation from the Hiroshima Medical Society for his contributions to the medical profession and to the community during his tenure.

• *November 1961:* Hiroshima Mayor **Hamai** presented a certificate of appreciation to ABCC for generously contributing to the purchase of X-ray equipment for the A-bomb Survivor Welfare Center.

• *October 1961:* After completing the new inpatient ward, Hiroshima University President **Tatsuo Morito** officially commended Darling for ABCC's support. ❑

Better US–Japan Understanding Cultivated

by Kenji Joji, ABCC–RERF Translation Section Chief, 1953–89

No one has left as indelible an imprint on the long history of ABCC as **George B Darling**. As ABCC's director, he demonstrated uncommon leadership, skill, and diplomacy in conducting a unique binational scientific investigation, and contributed to the welfare of humanity and to closer friendship and understanding between the United States and Japan.

The author, far right, interpreting for George B Darling in 1963 at a Buddhist ceremony held for families of the deceased who had been autopsied as part of the ABCC–RERF pathology program, which was conducted from 1955–88.

Reappraisal of ABCC mission

In the early 1950s, serious questions were raised concerning the feasibility of continuing ABCC's research program, despite a consensus in the scientific community that decades of study would be required to answer the unresolved questions regarding the late effects of radiation on human beings.

Addressing this need, **R Keith Cannan**, chairman of the Division of Medical Sciences, National Research Council, convened in October 1955 a meeting of NAS–NRC consultants to review the research design of ABCC. This meeting led to the recommendation that a Unified Study Program based on a fixed population be created. An Ad Hoc Committee for Reappraisal of the ABCC Program was thus created, headed by **Thomas Francis Jr,** professor of epidemiology, University of Michigan. The Francis Committee's recommendations became the blueprint of the future research program at ABCC–RERF.

Cannan was well aware of the political climate in Japan following the signing of the US–Japan Peace Treaty, of the possible repercussions of the enactment of the Atomic Bomb Survivors Medical Treatment Law, and of the need for both scientific and diplomatic leadership and wisdom in implementing the Francis Committee's recommendations. In 1957, Darling was appointed director of ABCC.

Darling is remembered by a colleague as being a staunch advocate of the ABCC nursing staff. Seated to Darling's left is Chiyoko Watanabe, chief of ABCC nursing from 1953–78.

Linked by language

Realizing that ABCC's research program could not be smoothly and effectively conducted without the cooperation of the local communities, the scientific community, and the government agencies concerned, in July 1957 Darling directed that all technical reports be published in a bilingual format and that all forms used in research also be bilingual.

In the same vein, in the next year he successfully arranged with the Hiroshima Prefectural Medical Association to establish an ABCC Section in the *Journal of the Hiroshima Medical Association* so ABCC's research achievements could be published in the open literature in Japan.

Ties with US institutions forged

Later in 1958, Cannan arranged to provide the needed continuity in program supervision for ABCC: the ABCC Department of Medicine through association with **Paul Beeson**, Department of Medicine, Yale University; the ABCC Department of Statistics through **Gilbert Beebe**, Follow Up Agency, NAS–NRC; and the ABCC Department of Pathology through **Sidney Madden**, Department of Pathology, University of California at Los Angeles.

Thanks to the spirit of binational cooperation and collaboration painstakingly created by Dr Darling and his staff, the Unified Study Program became and continued to be scientifically productive, and thus gained internationally greater recognition and a strong endorsement from the Japanese Advisory Council to ABCC, the NAS–NRC Advisory Committee on ABCC, and the US Atomic Energy Commission that it be continued on a long-term basis despite the aggravating financial situation in the United States, which at the time provided most of the operational funds.

When Darling retired after more than 15 years of meritorious service as director of ABCC, he returned to the US having laid the cornerstone of the new, truly binational organization he had envisioned. ❑

Notes

Is There Bias in the Life Span Study Death Data?

Cancer mortality

Recently, Sir **Richard Doll** (Radcliffe Infirmary, Oxford, England) raised the possibility of bias in the cancer death data in the Life Span Study, which are based on the reference to cancer in Part I of the death certificates (ie, on the indication of cancer as the proximate cause of death). He wondered how often cancer is given as the contributory cause of death, ie, referred to in Part II. At his request, RERF evaluated this issue, and results are contained in Table 1.

It is striking that the frequency of cancer on Part II is extremely low when the underlying cause is not cancer. It is also interesting to note that the frequency of cancer on Part II, when cancer is not referred to on Part I, is closely similar in all dose groups (in fact, it is slightly higher in the two higher dose groups, based on very small numbers).

Sir Richard agrees that these results preclude any possibility of bias from this source, but remarks that cancer tends to be given as the preferred cause of death in our study population—and possibly in the whole of Japan—more often than in the United Kingdom, whenever a decedent has been affected by it.

Noncancer mortality

Regarding the dose response of noncancer mortality in the LSS (Y Shimizu et al, RERF TR 2-91, in press) as reported in the last issue of *Update*, **Iwao M Moriyama** (International Institute for Vital Registration and Statistics, Bethesda, Md) brought to our attention the problem of trying to select a single cause of death when many diseases and conditions are contributing to death, as is often the case with the elderly population. As a possible solution to this problem, he suggested looking at all deaths attributed to noncancer causes partitioned by whether cancer was mentioned on the death certificate.

The data analyzed at Sir Richard's request (right panel of Table 1) do not support the notion that cancer reported in Part II of the death certificates for noncancer deaths might account for the dose response observed in noncancer mortality. The data presented in Table 2, gathered at Moriyama's suggestion, also indicate the very low frequency (less than 0.2%) of cancer mentioned in Part I of the death certificate for those deaths attributed to noncancer causes. The frequency is not dose-related. These results also seem to exclude the possibility of a bias in the handling of multiple-cause deaths as the explanation of the observed noncancer dose response in mortality. ❑

Table 1. Frequency of cancer mentioned in Part II of the death certificates, Life Span Study, 1950–85

Kerma (Gy)	Underlying cause of death (Part I)			
	Cancer		Noncancer	
	Total no.	Cancer on Part II	Total no.	Cancer on Part II
0	4,419	116 (2.6%)	17,551	125 (0.7%)
0.01–0.09	3,818	129 (3.4%)	14,765	107 (0.7%)
1.00–1.99	271	10 (3.7%)	626	7 (1.1%)
≥2.00	168	9 (5.4%)	322	3 (0.9%)
	χ^2 = 7.51, df = 3, p = .057		χ^2 = 1.57, df = 3, p = .67	

Table 2. Frequency of cancer or noncancer mentioned in Part I of the death certificates, Life Span Study, 1950–85

Kerma (Gy)	Underlying cause of death (Part I)			
	Cancer		Noncancer	
	Total no.	Noncancer on Part I	Total no.	Cancer on Part I
0	4,419	1,241 (28.1%)	17,551	30 (0.2%)
0.01–0.99	3,818	1,037 (27.2%)	14,765	24 (0.2%)
1.00–1.99	271	66 (24.4%)	626	0 (0.0%)
≥2.00	168	56 (33.3%)	322	1 (0.3%)
	χ^2 = 5.05, df = 3, p = .17		χ^2 = 1.49, df = 3, p = .69	

Life Span Study Data on Disk

Due to unexpected difficulties in producing the printed version of LSS Report 11, Part 3, release of the data on disk will be delayed. We apologize for any inconvenience this may cause our readers.

News Briefs

continued from page 6

Medicine Chief **Kazuo Nerishi**. A total of 532 *hibakusha* were seen, including 48 children of survivors. This year's consultations attracted 61 new participants.

✓ Research Staff News

Department of Epidemiology: **Yukiko Shimizu** was promoted to senior scientist on 1 October, and **Yasuhiko Yoshimoto** was promoted to associate senior scientist.

Department of Statistics: Visiting Research Fellow **Yamin Gao,** Laboratory of Industrial Hygiene, Beijing, will investigate aspects of modeling cancer risk during his one-year stay at RERF.

✓ Highlights of the RERF Lecture Program

On 8 July, **Niel Wald**, University of Pittsburgh, lectured on automated chromosome analysis.

Marc Goodman of the University of Hawaii Cancer Research Center discussed cancer studies in that state on 24 July.

Shimizu

In Nagasaki on 30 July, **Shiquan Sun** spoke about studies of occupational radiogenic cancer in the People's Republic of China.

On 21 August, RERF Epidemiology Chief **Kiyohiko Mabuchi**, RERF Statistics Chief **Dale Preston,** and **Elaine Ron,** research scientist, spoke about solid tumor incidence in the A-bomb survivors, 1958–87.

TM Fliedner, University of Ulm, Germany, discussed present concepts for radiation accident management on 22 August.

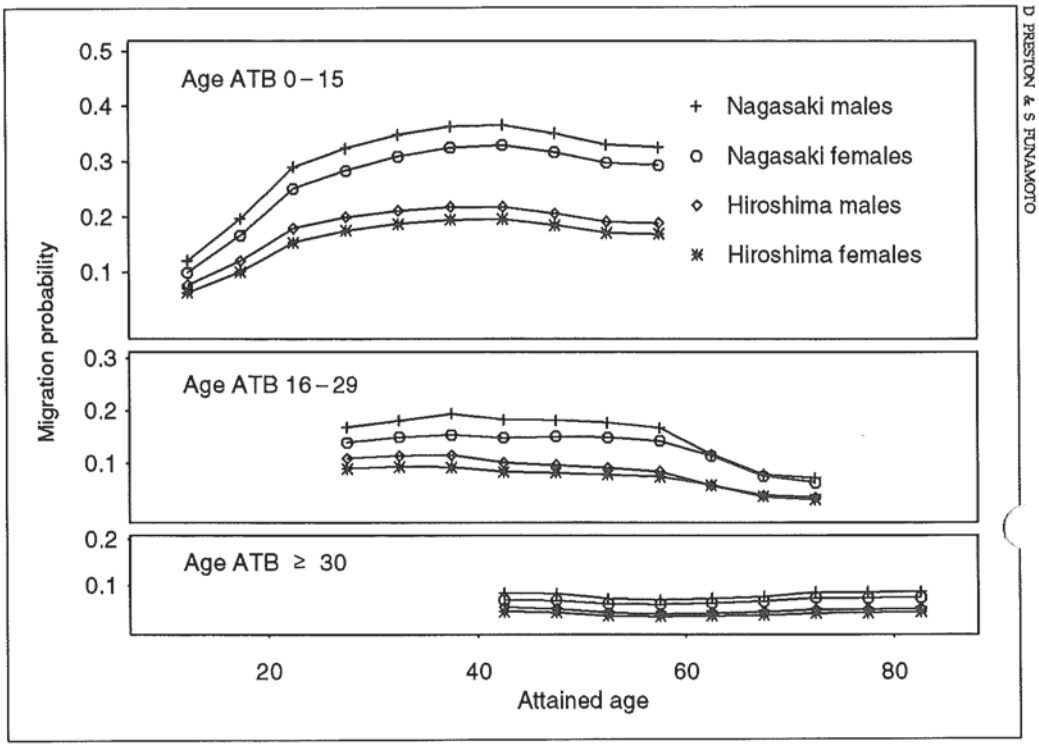
On 30 August, **Alvin M Weinberg** of the Institute of Energy Analysis, Oak Ridge, Tenn, lectured on the future of nuclear energy and the role of RERF research.

On 26 September **Marie-Louise Johnson** of Benedictine Hospital, Kingston, NY, spoke about environmental and genetic factors in cutaneous malignancy.

Dwayne Reed, Kuakini Medical Center, Honolulu, Hawaii, discussed "the stroke paradox" on 16 October. ❑

Facts & Figures

Migration Probability in the Adult Health Study



Because of the nature of the Japanese family registration system (known as the *koseki*), information on mortality among members of the Life Span Study cohort is virtually complete. However, this is not the case for other outcomes of interest. In particular, in analyses of the cancer incidence data from the Hiroshima and Nagasaki tumor registries, it is necessary to allow for the effect of migration on the number of cases reported.

The accompanying figures present the estimated migration probabilities for members of the Adult Health Study by time, age at the time of the bombings (ATB), sex, and city. These estimates were derived from models which allow people to leave and return to the area, and they are based upon contacting information obtained by the staff of RERF's Adult Health Study and the Contacting Section.

From these figures, it can be seen that younger survivors are more likely to migrate than older survivors, that men are more likely to migrate than women, and that Nagasaki residents have higher migration rates than Hiroshima residents. The estimates shown in these plots were used as the basis of an adjustment for migration in the recently completed analyses of the Life Span Study cancer incidence data. The ideas underlying this adjustment will be discussed in a forthcoming Commentary and Review Series report. ❑

Book Review

A Review of Forty-Five Years' Study of Hiroshima and Nagasaki Atomic Bomb Survivors, edited by K Yokoro et al, *J Radiat Res* (Tokyo) (Suppl) 32, 412 pp, 1991, ¥8000 (including overseas postage and handling). Distributed by Business Center for Academic Societies, 16-3 Hongo 6-chome, Bunkyo-ku, Tokyo, 113 Japan.

A little more than 15 years ago, a supplement of the (Japanese) *Journal of Radiation Research* covered 30 years of atomic bomb survivor research in 164 pages. The present volume is more than three times larger than the 1975 publication. Both editions cover the material in three sections on dosimetry, biological effects, and future research. The 1991 version adds an extensive and very useful "Summary and Conclusions" chapter.

In the last 15 years, far-reaching new data have been collected, all well covered in the new volume. The section on dosimetry concentrates now entirely on DS86, of course, rather than on T65D, the main subject in the earlier publication, and it occupies a generous 153 pages. A lot of attention is devoted to the discrepancies between DS86 kerma estimates and the values derived from neutron-induced radioactivity measurements and gamma thermoluminescence studies in ceramic materials. This points out that future work will be needed to find the cause of what appears to be a systematic error in DS86, particularly significant in Hiroshima, but, beyond that, potentially important for the narrowing of uncertainties in radiation risk estimates in general.

The section on biological effects (221 pages) covers a wide variety of (mostly) cancers, some not or less extensively covered in the earlier volume. It is this and the next section that have the largest percentage of RERF contributors. In the volume as a whole, 26 out of 42 papers are from RERF scientists or from scientists associated with RERF. The remaining 16 papers are from the Atomic Disease institutes in Hiroshima and Nagasaki (5 and 2, respectively), Hiroshima University (4), and from four other research institutes in Japan (2 from Kanazawa University and 1 each from the others).

As an overview of research performed in a number of institutions, this publication is an excellent source of information. Some of the data are already obsolete, such as those on noncancer effects, which recently have been updated using DS86 (Y Shimizu et al, *RERF Update* 3(2):3–4, 1991). An upcoming RERF publication on cancer incidence using tumor registry data will update and give additional information on many of the subjects covered in the biological-effects section. Nevertheless, for people interested in an overview rather than an up-to-the-minute summary, this volume is a very worthwhile book to have.

—JW Thiessen

Recent Scientific Publications

Approved Technical Reports

Detection of a length polymorphism in the 5′ flanking region of the human β-globin gene in a Japanese population with denaturing gradient gel electrophoresis. N Takahashi, K Hiyama, M Kodaira, C Satoh. **RERF TR 7-91.**

An analysis of the ATTTT repeat polymorphism located approximately 1,400 base pairs upstream from the β-globin structural gene was carried out by denaturing gradient gel electrophoresis (DGGE) of RNA:DNA duplexes. Genomic or cloned DNAs were digested with restriction enzymes and hybridized with P-32-labeled RNA probes, and resulting RNA:DNA duplexes were examined by DGGE. A difference in the number of repeat units was recognized by differences in duplex mobility on the DGGE gel. In this study of 81 unrelated Japanese from Hiroshima, a sequence heteromorphism was observed at this site. Alleles with 5 and 6 repeats of the ATTTT unit, which had already been reported, were found in polymorphic proportions. In addition, two unreported alleles, one having 7 repeats and the other having an A-to-G nucleotide substitution in the fifth repeat, were detected. Family study data showed that the segregation of these four types of variants is consistent with an autosomal codominant mode of inheritance. This study also demonstrated that DGGE of RNA:DNA duplexes is a sensitive tool for detecting variations in DNA.

Radon concentrations in residential housing in Hiroshima and Nagasaki. T Aoyama, EP Radford, H Yonehara, H Kato, M Sakanoue. **RERF TR 8-91.**

A survey of indoor radon (Rn-222) concentrations in Hiroshima and Nagasaki was carried out to assess the variability of exposure expected among atomic bomb (A-bomb) survivors. Two hundred dwellings (100 from each city), chiefly of members of the Life Span Study population, were selected for this survey. We used two types of alpha-track detector: a Terradex detector type SF and a bare-track detector improved by Yonehara et al. Comparative measurements showed that although there was an adequate correlation between the values obtained using the two detectors, the geometric mean value for the bare-track detector was 45% lower than that for the Terradex detector. This difference was considered to be due to differences in the calibration methods and sensitivities of the detectors to thoron (Rn-220).

The geometric mean values of the radon concentrations for 193 locations in Hiroshima and 192 locations in Nagasaki measured by Terradex SF detectors were 51.8 Bq/m^3 and 26.5 Bq/m^3, respectively. The large difference is attributable to the different geological environments of the two cities.

Correlating factors with the indoor radon concentrations were also studied. The geometric mean concentration was significantly higher in wooden houses with mud walls than in other types of house. This tendency was especially remarkable in Hiroshima.

The difference between the estimated dose equivalents for exposure to radon progeny in dwellings in Hiroshima and Nagasaki over the last 30 years might amount to 0.8 Sv; however, no statistically significant difference was observed in lung cancer mortality in the low-dose range in either city. Nevertheless, the indoor radon concentrations estimated in this survey could have a significant influence on the dose-response relationship for A-bomb exposure.

Differential effects of atomic bomb irradiation in inducing major leukemia types: Analyses of open-city cases including the Life Span Study cohort based upon updated diagnostic systems and the Dosimetry System 1986. M Tomonaga, T Matsuo, RL Carter, JM Bennett, K Kuriyama, F Imanaka, S Kusumi, K Mabuchi, A Kuramoto, N Kamada, M Ichimaru, AV Pisciotta, SC Finch. **RERF TR 9-91.**

From 1945 through 1980, 766 cases of leukemia were reported to the Atomic Bomb Casualty Commission and its successor, the Radiation Effects Research Foundation, among the open-city sample of atomic bomb survivors who were within 9 km of the hypocenters at the time of the bombings (ATB). Only 249 of these cases occurred among the Life Span Study (LSS) cohort. In this paper, we use data from the additional 517 cases from the leukemia registry together with the LSS cohort data to study the effects of atomic bomb irradiation on major leukemia types. All available hematological specimens of registered leukemia cases were reviewed. The French-American-British classification and other improved diagnostic methods were used to reclassify cases into 21 categories, including new disease entities such as adult T-cell leukemia (ATL). These categories were then grouped into four major types for analysis: (1) acute lymphoid leukemia (ALL), (2) acute myeloid leukemia (AML) including myelodysplastic syndromes (MDS), (3) chronic myeloid leukemia (CML), and (4) other types including ATL (OTHER). Analyses of radiation effects were based on the updated Dosimetry System 1986 (DS86).

Incidence rates of all four leukemia types increased with increasing exposure level. The effects of radiation exposure were significantly greater on the incidence of ALL and CML than on that of AML and OTHER. Exposures of 50 mGy and probably as low as 16 mGy apparently produced excess cases of ALL and CML, whereas exposures of 50 mGy and probably at least 229 mGy were required to produce excesses in AML. This differential effect disappeared in time as incidence rates returned to (or toward) background levels.

In the two lowest dose categories (1–49 and 50–499 mGy), estimated incidence either remained constant or increased slightly as the population of survivors aged. In the two highest dose categories (500–1,499 and ≥1,500 mGy), however, estimated incidence rates of all types declined. An excess of AML and ALL, but not CML and OTHER, remained through the final study period (1976–80) in the ≥1,500-mGy dose category.

Among unexposed persons, the estimated risk of CML in Nagasaki relative to Hiroshima was significantly less than that of AML, whereas that of OTHER types was significantly greater, because ATL cases occurred only in Nagasaki. The city effect on background rates appeared to explain the generally higher incidence of leukemia (except for ATL) in Hiroshima.

Also in unexposed persons, incidence in older groups (16–35 years ATB, ≥36 years ATB) relative to the youngest group (0–15 years ATB) was less for ALL than AML, but greater for CML and OTHER types than for AML. The risk of ALL remained relatively constant with age ATB whereas that of AML, and to a greater extent CML and OTHER, increased with age ATB.

The time to onset of ALL, AML, and CML declined with increasing dose. The rate of decline, however, was greater for ALL and CML than for AML. The resulting differences at high doses reflect shorter incubation times for atomic bomb-induced ALL and CML than for AML.

Skin cancer incidence among atomic bomb survivors in Nagasaki based on the DS86 dosimetry system. N Sadamori, M Otake, T Honda. **RERF TR 10-91.**

The effects of exposure to ionizing radiation on the incidence of skin cancer in a cohort of A-bomb survivors in the Nagasaki Life Span Study extended (LSS-E85) sample were investigated using the Dosimetry System 1986 (DS86). Among a total of 25,942 survivors at risk whose DS86 dose estimates were available, 47 cases of skin cancer including malignant melanoma were confirmed from the Nagasaki Tumor Registry during the period from 1 April 1958 to 31 December 1985. The dose-response relationship of skin cancer based on an additive relative risk model showed linearity without threshold, not a linear-quadratic curve. The excess relative risk (ERR) of 2.2/Gy in the LSS-E85 sample was highly significant (95% confidence limits: 0.5 to 5.0/Gy). On the other hand, the ERR of 3.1/Gy in the AHS sample was also significant (95% confidence limits: 0.6 to 20.3/Gy). When dose equivalents based on a relative biological effectiveness of neutrons of 10 were used, the ERR in the former sample decreased to 2.0/Sv (0.7–4.5), and the risk in the latter group also declined, to 2.7/Sv (0.6–17.8). The ERR did not differ significantly between males and females in the LSS-E85 and AHS samples, but a highly significant increase was observed for the ERR of age at exposure and time trend since exposure. The ERR of skin cancer cases including and excluding four malignant melanoma cases for the LSS-E85 sample (there were no malignant melanoma cases in the AHS sample) showed almost the same linear dose response.

continued on next page

Recent Scientific Publications

Approved Research Protocols

A comparative study of vertebral fracture prevalence in Japan, Hawaii, and the US mainland. S Fujiwara, PD Ross, LJ Melton III, R Sposto, JW Davis, RD Wasnich, H Sasaki, K Kodama. **RERF RP 3-91.**

This study is intended to determine if differences in the frequency of vertebral fractures exist among three populations (native Japanese in Hiroshima, Japanese-Americans in Hawaii, and Caucasians in Rochester, Minnesota, US) and to investigate the risk factors of vertebral fracture. We will apply uniform, objective diagnostic criteria in order to compare fracture prevalence among the three populations. In addition to determining the prevalence of fractures in each population, we should also be able to identify potential confounding variables or risk factors for vertebral fractures. The results of these analyses may be useful in planning life-style or therapeutic interventions to prevent fractures.

Mail survey on epidemiologic factors in the Life Span Study extended (LSS-E85) sample, 1991. S Akiba, Y Shibata, F Kasagi, K Shimaoka, CE Land, M Yamada, K Mabuchi. **RERF RP 4-91.**

A mail survey will be conducted using 45,000 members of the Life Span Study extended (LSS-E85) cohort to obtain and update information on epidemiologic factors, including socioeconomic backgrounds, personal habits, medical history, and obstetric and gynecologic history. To be excluded from the survey are the unexposed (not-in-city) subjects and the participants in the recent Adult Health Study program, in which interviews for collecting epidemiologic information are (and will be) routinely conducted. A relatively simple questionnaire will be sent to the respondents of the last mail survey (conducted in 1979 for males and in 1980 for females) to update information on various epidemiologic factors obtained at that time. A detailed questionnaire will be sent to the nonrespondents of the last mail survey as well as to the Nagasaki distal subjects who were added to the LSS in 1985. Data collected by the proposed study will be combined with those obtained from the previous surveys so that they can serve as a common source of information for future epidemiologic studies of the LSS cohort. Information on the most recent address obtained by the proposed survey will also be used for the address database currently being constructed.

Radiation therapy among Life Span Study subjects [addendum to RP 7-81]. K Kato, S Antoku, S Sawada, K Kodama, S Kawamura, K Mabuchi. **RERF RP 5-91.**

In a preceding study (RP 7-81), it was observed that 49 members of the Life Span Study had developed malignant neoplasms that may have been due to their previous radiation therapy.

The doses incurred to the organs and sites in which the malignant neoplasms had subsequently developed must be ascertained in order to determine whether there was a causal relationship between the malignant neoplasms and the earlier corresponding radiation therapy exposures. These doses will be estimated using a phantom human and thermoluminescent dosimetry.

Approved Commentary and Review

Piecewise linear regression splines with hyperbolic covariates. JB Cologne, R Sposto. **RERF CR 1-91.**

Consider the problem of fitting a curve to data that exhibit a multiphase linear response with smooth transitions between phases. We propose substituting hyperbolas as covariates in piecewise linear regression splines to obtain curves that are smoothly joined. The method provides an intuitive and easy way to extend the two-phase linear hyperbolic response models of Griffiths and Miller and of Watts and Bacon to accommodate more than two linear segments. The resulting regression spline with hyperbolic covariates may be fit by nonlinear regression methods to estimate the degree of curvature between adjoining linear segments. The added complexity of fitting nonlinear, as opposed to linear, regression models is not great. The extra effort is particularly worthwhile when investigators are unwilling to assume that the slope of the response changes abruptly at the join points. We can also estimate the join points (the values of the abscissas where the linear segments would intersect if extrapolated) if their number and approximate locations may be presumed known. An example using data on changing age at menarche in a cohort of Japanese women illustrates use of the method for exploratory data analysis.

Publications in the Open Literature

Gamma-ray- and fission neutron-induced micronuclei in PHA stimulated and unstimulated human lymphocytes. S Ban, MP Donovan, JB Cologne, S Sawada. *J Radiat Res* (Tokyo) 32:13–22, 1991. (RERF TR 9-90)

Development of the assay systems for detection of somatic mutation in radiation exposed people by means of flow cytometry. M Akiyama, S Kyoizumi, J Kushiro, Y Kusunoki, Y Hirai, N Nakamura. In: *Flow Cytometry and Image Analysis for Clinical Applications.* Edited by I Nishiya, LS Cram, JW Gray. Amsterdam, The Netherlands, Elsevier Science Publishers, 1991. pp 65–70

The length polymorphism in the 5′ flanking region of the human β-globin gene with denaturing gradient gel electrophoresis in a Japanese population. N Takahashi, K Hiyama, M Kodaira, C Satoh. *Hum Genet* 87:219–20, 1991. (RERF TR 7-91)

Isolation and characterization of human peripheral blood $CD4^+$ T cell clones expressing γδ T cell receptors. S Kyoizumi, M Akiyama, Y Hirai, Y Kusunoki. *Immunol Letters* 29:197–204, 1991. (RERF TR 5-90)

Update on the genetic effects of ionizing radiation [commentary]. JV Neel. *JAMA* 266(5):698–701, 1991.

Publications of Interest Using RERF Data

Absence of risk associated with exposure to radiation before conception in Japan [letter to the editor]. MP Little, MW Charles. *Br Me J* 302:1404, 1991.

Time variations in the risk of cancer following irradiation in childhood. MP Little, MM Hawkins, RE Shore, MW Charles, NG Hildreth. *Radiat Res* 126:304–16, 1991. ❑

RERF update RERF

This quarterly newsletter is published by the Radiation Effects Research Foundation (formerly the Atomic Bomb Casualty Commission), established in April 1975 as a private, nonprofit Japanese foundation. It is supported equally by the Government of Japan through the Ministry of Health and Welfare, and the Government of the United States through the National Academy of Sciences under contract with the Department of Energy.

RERF conducts research and studies—for peaceful purposes—on the medical effects of radiation on humans with a view toward contributing to the maintenance of the health and welfare of atomic bomb survivors and to the enhancement of the health of all mankind.

Editorial Policy:

Contributions to *Update* receive editorial review only and are not subjected to scientific peer review. Consequently, the opinions expressed herein are those of the authors only and do not necessarily reflect RERF policies or positions.

Dose and radiation units are given as available in the source material.

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Trinity Legacy

continued from page S-1

and a headline calculated to unnerve the most stouthearted. But as further reading in the same article revealed, in only 38 of these 2,000 safety-related incidents was there concern about a potential threat to the health and safety of the public. Most of these so-called incidents involved violations of federal safety regulations; the most common being the failure to use a grounded electrical outlet. This fact was not made known to a wary and apprehensive public.

Now, when an accident does occur, the press immediately greets us with polarized views. One group seeks to deny or instantly minimize the danger, and the other to discredit information yet to be collected, lest it reveal the accident was not a matter of great public health concern. Even the recent, careful study of the International Atomic Energy Agency regarding Chernobyl was promptly characterized as "scientifically incompetent." It did not support the scare tactics of those with special agendas. Whether this sensationalizing reflects the fact that few newspapers have bona fide science writers, who could be expected to understand and interpret the facts correctly, or an overriding compulsion to pander to that which sells, is arguable. More grievous to society than these ill-considered statements, however, has been the climate of distrust of our institutions, our technology, and one another that has been set into motion. Some years ago, for example, a major dam in China broke, and 250,000 people lost their lives, but little of this appeared in American newspapers. Are we to construe this as not newsworthy, or is this merely another instance of selective reporting?

The Public

Almost two centuries ago, Thomas Jefferson wrote: "I know of no safe depository of the ultimate powers of society but the people themselves; and if we think them not enlightened enough to exercise their control with a wholesome discretion, the remedy is not to take it from them, but to inform their discretion." This laudable sentiment is not, however, an easy nor a simple matter to implement, particularly in an era when the public seems less able or inclined to read, and seeks its information through television in 30-second bits. It is not now a question of taking their discretion from them; they are surrendering it willingly to sources only marginally better informed.

Until the accident at Three Mile Island in 1980, and the subsequent one at Chernobyl in 1986, most individuals either ignored the risk associated with nuclear energy or presumed it was small. However, these two events dramatically changed perceptions of the safety of the nuclear power industry. What was previously accepted, almost blithely by most, is now seen as a hazard beyond entertaining, or even discussing. This makes reasoned debate about the role of nuclear power in global energy production virtually impossible. Nevertheless, as concern mounts about global warming and the use of fossil fuels, the role, if any, nuclear power can play—reconciling national needs with the inherent risks—must be examined. To do so requires an informed public, one acquainted with the factual bases on which an informed judgment must rest.

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It is not clear how this state of understanding is to be achieved when the public perception of the risks of nuclear power are so muddled and confused. For example, some years ago members of the Oregon League of Women Voters were asked to rank their perceptions of the risk associated with 30 activities and technologies (P Slovic, in: *Proc 15th Annual Meeting of the National Council on Radiation Protection and Measurements*, Bethesda, Md, NCRP, 1979, pp 34–56). Nuclear power was perceived to carry a risk even greater than that from the use of motor vehicles, yet the latter causes the death of more than 45,000 Americans each year, whereas fatalities attributable to nuclear power are so few as to be counted on one hand. Ironically, electric power was rated the most beneficial of these 30 activities and technologies, substantially higher than the availability of motor vehicles.

Similar surveys conducted in other countries have yielded similar results. For example, in France, respondents to a national survey in 1988 thought the danger associated with a nuclear power plant was greater than that in uranium mining, yet mining, whether for uranium or other ores, causes more deaths each year than occur in all nuclear power facilities without regard to country (MH Barny et al, *Nucléaire et opinion publique en France: donnés sur les déchets radioactifs. Evolutions depuis 1977.* Paris: Institut de Protection et de Sûreté Nucléaire, DPS/SEGP, Note LSEES 90/10, 1990). Moreover, the risk associated with nuclear power plants is invariably seen as greater than that stemming from exposure to diagnostic or therapeutic X rays, but again, in fact, the risk of a second malignancy following X-ray therapy for a primary cancer is substantially higher than the risk of radiation-related cancer among workers in nuclear facilities.

The elements that define one's perception of risk associated with a particular activity are still poorly known. However, it is clear that individual notions hinge on many factors, including whether the risk is seen as voluntary or involuntary, chronic or catastrophic, controllable or not controllable, old or new, immediate or delayed, fatal or not fatal, and so on. It is clear too that this perception is colored by one's knowledge of the actual hazard. Surveys have shown that nuclear engineers are far less reluctant to live near a nuclear power facility than are environmentalists, and surely the former must have a better knowledge of the likelihood of an accident than the latter. Obviously in some manner the gap between the perception of risk and actuality must be closed.

It seems doubtful that education alone will be successful until we better understand how our perceptions are formed. While some opposition to an expansion of nuclear power has occurred in all countries in the last decade or so, it has been less organized and certainly less aggressive in France, which generates more nuclear energy relatively than any other country, and in Japan, where the opposition to nuclear weapons has been exceptionally vocal. What have these nations done, consciously or unconsciously, to bring this about? Their peoples are certainly not better informed. Does it, then, reflect a more autocratic bureaucracy? Or, in the case of Japan, is it attributable to the consensus seeking that characterizes so much of decision-making in this country?

Scientists and science

Scientists too have been remiss—most importantly, in failing to communicate the benefits and the hazards associated with nuclear energy in comprehensible language. This failure has created a fertile ground for rumors, misconceptions, and outright fabrications in spite of the knowledge that is available. Studies of the late occurring health effects of exposure to the atomic bombings of Hiroshima and Nagasaki began in 1948, have continued uninterrupted, and have provided a wealth of information.

The findings of these studies can be summarized simply: Mortality from a variety of cancers—leukemia and cancers of the breast, colon, esophagus, lung, ovary, thyroid, salivary glands, stomach, urinary bladder, and multiple my-

eloma—increase in frequency with increasing dose. An increase in mortality from the cancerous tumor of the lymph nodes, known as lymphoma, remains uncertain, and if the time from exposure to the development of this malignancy is long, as is true of multiple myeloma, the uncertainty may persist for some time.

Present evidence fails to suggest an increase in malignant brain tumors, and is equivocal with regard to tumors of the central nervous system other than the brain. Whether an increase in cancer of the liver occurs is unclear, as judged by the mortality findings. When the data are restricted to only those cancers known as primary, liver cancers do not increase significantly with dose; however, if the cancers termed "unspecified" are included, there is a dose-related increase. The liver is a common site of metastasis for cancers arising elsewhere, in the breast or lung, for example, and the unspecified tumors may be metastatic ones that should be assigned to other organs where an effect of radiation is known to occur.

No increase has been seen in deaths from cancers of the bone, gallbladder, nose and larynx, pancreas, pharynx, prostate, rectum, skin except melanoma, and the uterus.

Mortality from cancers other than leukemia increases significantly, generally when individuals reach the usual age of onset for a given cancer and the distribution of time from exposure to death does not differ by radiation dose, but it does depend upon the age of the individuals at the time of the bombings (ATB). The risk of cancer other than leukemia is higher among those individuals who were 0–9, or 10–19 years old ATB. Their risk has been declining, however, and significantly so among those aged 0–9 ATB. No increase has been seen in childhood cancers among the prenatally exposed, but cancers of later years are increased in frequency within this special group of survivors. The data are still limited, since only now are the prenatally exposed survivors reaching those ages in life when the natural rate of cancer increases dramatically. It will be a number of years therefore before the full impact of exposure on their risk can be assessed with the accuracy and reliability warranted.

These statements may have little meaning to the nonspecialist, but more substance can be given them by considering the additional cancers that have occurred among these groups as a consequence of their exposure. In the years from 1950–85, 202 individuals among some 76,000 under surveillance died of leukemia. About 59% of these deaths, or 119, were attributable to radiation. These same years saw 5,734 deaths from cancers other than leukemia. Approximately 8%, or 459, of these deaths were presumably due to radiation. The comparable figures for all 284,000 survivors identified in the 1950 census are 386 leukemia deaths—191 ascribable to radiation, and 10,421 deaths from malignancies other than leukemia of which 833 stemmed from exposure. These are estimates, of course, since it is presently impossible to distinguish a radiation-related cancer from one due to some other cause. However, most survivors who will die of cancer will do so as a result of the lives they lead—through smoking, drinking, and exposure to other as yet unidentified factors—and not from their exposure to atomic radiation.

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Cancer is not the only risk. The most poignant is the increase in severe mental retardation among the prenatally exposed survivors, particularly those exposed between the 8th and the 15th weeks following fertilization. Almost three-fourths of the individuals exposed to 1 Gy or more are severely retarded mentally.

When these studies began, public concern over the possible genetic effects of exposure to atomic radiation was at least as great as that over cancer, and possibly greater. To most prospective parents the thought of producing a seriously malformed infant was troubling, but it was even more intimidating when coupled with the belief that the abnormality might have arisen through an avoidable exposure to ionizing radiation. As a result, no other human population has been scrutinized more closely, continuously, or thoroughly than the children of the survivors of the bombings of these two cities.

Various strategies to detect newly arisen mutations have been employed; these include a search for alterations in the frequency of occurrence of life-threatening or socially handicapping congenital defect and premature death, or of changes of a chromosomal nature, or in the biochemical structure or activity of a variety of cellular enzymes and proteins normally present in the serum. These strategies, though different, share common aims—to estimate the probability of mutation following exposure to ionizing radiation, and to determine the public health implications of an increase in the mutations measured. These various studies, however painstaking and thorough, serve these ends unequally well, for some measure the direct product of genes and others—albeit of substantial public health importance—examine characteristics considerably removed from the molecular or cellular level at which genes act. These facts notwithstanding, the data that have accumulated provide the clearest picture we have of transmitted genetic damage following exposure of human beings to ionizing radiation. But there emerges no unequivocal evidence of radiation-related genetic damage.

The absence of a significant effect should not be construed as evidence that mutations were not induced by parental exposure to atomic radiation. At least two reasons argue otherwise. First, mutations have been seen in every animal and plant species studied under suitable experimental conditions, and it would be contrary to reason to presume that human genes are not mutable when exposed to ionizing radiation. Second, the magnitude of a difference between two or more groups that can be detected statistically depends upon the number of observations available, the "natural" frequency of the event under scrutiny, and the difference between the groups that obtains. One can, therefore, ask how adequate has this study been, or to pose the question differently, how large a difference would have had to exist to be demonstrable with a study of 76,000 infants only half of whom had one or more exposed parents?

Suffice it to state that a clinical study of the kind described would detect a doubling of the rate of major congenital malformations, and an alteration in the stillbirth or neonatal death rates of approximately 1.8 times. Since major congenital defects of the kind to which we refer, those recognizable at or shortly after birth under the conditions of these examinations, normally occur in about one out of every 100 pregnancies that persist for at least 7 months of gestation, this says that if the risk had been changed to 1 in 50 as a result of parental exposure to ionizing radiation that fact would have been recognized. It is important to bear in mind, however, that the frequency of congenital defects one finds depends upon the clinical tools at one's disposal, and the length of time the children are studied. Examinations conducted within days after the birth of an infant would not detect most cases of mental and motor retardation, nor would they be likely to identify many of those congenital defects of the heart that do not involve cyanosis and are

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commonly not detected until the infant becomes older.

As has been stated, at the outset of the studies in Hiroshima and Nagasaki, public concern about the possible genetic effects of exposure to atomic radiation was as great as that about cancer, and possibly greater. Over time, however, this emphasis has slowly shifted to more interest in cancer. This undoubtedly reflects the failure to find evidence of genetic damage, on the one hand, and the more dramatic findings on cancer, on the other. Understandably, but unfortunately, this has led to some failure to recognize that negative findings are no less noteworthy. But negative findings are more difficult to document. A single such study, particularly if it is based upon a relatively small sample, should be viewed askance. In the present instance, however, there is not merely one but numerous negative findings, and they are all based upon samples of considerable size. Nonetheless, ultimately their acceptance rests on the comprehensiveness of the study design, and the care and thoroughness with which that design has been implemented. This observation notwithstanding, negative findings should be seen as reassuring to the public, and in the specific case of the genetic studies, the findings argue forcefully against the fears of a devastating genetic effect on future generations.

These are the facts as we now know them. There is obviously much that is not known that is necessary to a rigorous estimation of the risks. We do not know the lifetime consequences of exposure — more than half of the survivors of the atomic bombings are still alive. We must project their risks from what we have seen to date. This requires not merely knowing that a particular cancer is increased as dose increases, but by how much at each dose. This rate of increase we know imperfectly. Moreover, projections can be made in a variety of ways, each yielding a somewhat different answer. It is not known which is the most appropriate and will not be known until the bulk of the survivors have died.

But the shortcomings of immediate concern lie not with the facts, but with the failure to communicate them adequately. No less importantly, however, there has been a change in the perception of the role of science in society that does not augur well. The success of the Manhattan Project has led to an increasing effort to manage scientific research as if it were a business whose survival depends upon a product rather than the advancement of knowledge. This has been especially noticeable in the national laboratories, but it is not unknown in academic institutions. There has been a proliferation of regulations without evaluation of their need or their impact on the intellectual atmosphere in which creative research occurs.

Our elected representatives

When the Manhattan Project began, its purpose, although unknown to most members of the US Congress, was clear—to construct, if possible, an atomic weapon. Once this was achieved and wartime hostilities had ceased, the nation was in need of a civil administrative structure to supervise the design and creation of nuclear weapons, to oversee the existing weapons facilities, and to encourage the development of nuclear power. To these ends in 1947 Congress approved the creation of an Atomic Energy Commission (AEC), and vested its oversight in a Joint Committee on Atomic Energy. Briefly, while the US appeared to be the sole possessor of nuclear weapons, matters went well, but with the blockade of Berlin in 1948, the first detonation of a Russian weapon in 1949, and the spread of the Cold War, matters worsened rapidly. National defense was dominated by the notion of nuclear deterrence, and this demanded more and larger weapons. Weapons design, fabrication, and testing were accelerated, and in the rush safety was compromised, although few knew the extent at the time. In retrospect, possibly as many as a million Americans, residents around nuclear weapons plants or test sites, may have been needlessly exposed to ionizing radiation because of the nuclear arms race. While it is presumed that these exposures were small and not injurious, some children living downwind of the Hanford facility in Washington, for example, may have ingested enough radioactive iodine to have a measurably increased risk of thyroid cancer.

Arguably the first manifestation of public dissatisfaction arose in the years of atmospheric testing when it was realized that the AEC was responsible not only for the measurement of levels of radioactivity at the Nevada Test Site itself, but off-site as well. A credulous public wondered whether the polluter could be trusted to accurately represent the extent of the contamination. To remedy this, Congress transferred responsibility for off-site monitoring to a newly created Bureau of Radiation Health within the Public Health Service. But the damage to credibility had already occurred. Soon there would be other changes. Our increasing dependence on foreign oil led to the creation of the Energy Research and Development Agency in 1975 and the incorporation of the activities of the AEC into this new agency. The latter was short-lived. In 1977, it was replaced by the Department of Energy.

With these changes came a greater intrusion of bureaucracy and politics, and a dissemination of regulatory and oversight responsibilities. Regulation of the commercial nuclear power establishment rests with the Nuclear Regulatory Commission; however, off the sites of these facilities regulations are formulated by the Environmental Protection Agency. Similarly, the Department of Energy is responsible for the safety of the facilities it manages, but off-site regulations are the province of the Environmental Protection Agency. This constant tinkering with the structure of the oversight agencies is not only prejudicial to their morale, but encourages a dilatory approach to difficult decisions. Although there are now more players, we still struggle with what to do about the contamination of the past and the disposal of radioactive wastes. The all too familiar syndrome "not in my backyard" stifles debate and action.

As energy consumption grows globally, and fears mount about the effects of continued use of fossil fuels on earth-warming, we can no longer temporize. A consensus must be reached on the role, if any, nuclear energy is to play in our future. To do so will require each of us to be more critical of what we read and hear, to examine the facts, and to think for ourselves rather than to be passive vessels into which the thoughts and prejudices of others are poured. Neither the proclamations of nuclear power advocates, on the one hand, nor those of the Friends of the Earth, on the other, are unprejudiced. These groups have their own agendas, and can advocate these equally shrilly, trading on the concern of the uninformed or poorly informed. In short, we must ourselves actively seek the information on which an informed judgment can be made. This is not an impossible task. There are highly readable accounts of how nuclear energy is produced, the functions of the various agencies that are involved in regulatory activities, the kind and nature of the accidents that can occur, and the like. Similar primers exist to enlighten the public on the issues that attend the disposal of nuclear wastes. But are we, as members of the public, prepared to invest the time and energy required to inform our discretions?

Our recent history suggests this is problematic. Yet ultimately the only avenue to a sound and widely acceptable nuclear policy is through an informed and committed public, willing to exercise its collective rights and responsibilities. ❑