RERF update RERF

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

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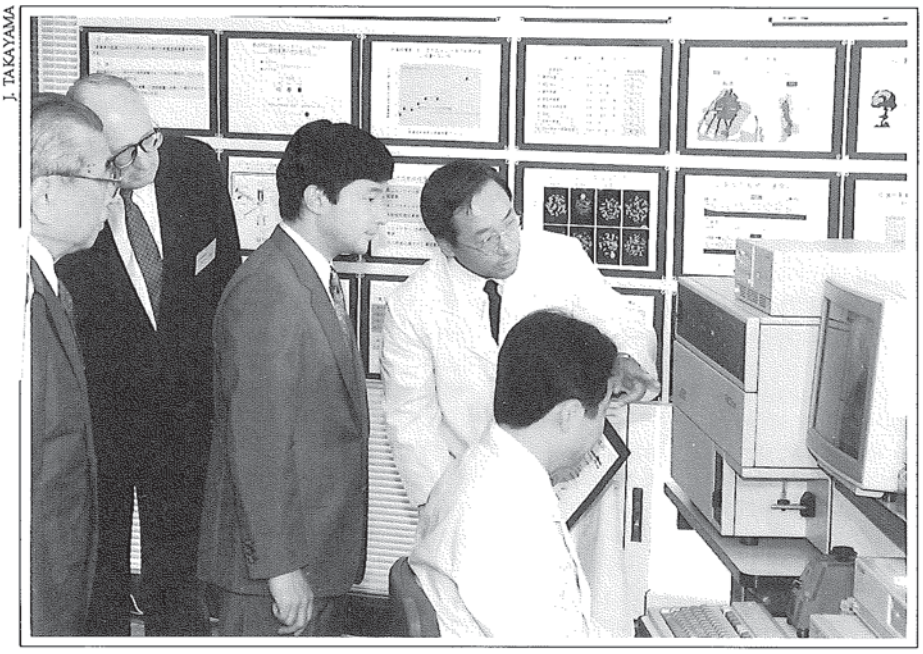
Hiroshima Laboratory Honored by Visit of Crown Prince

J. TAKAYAMA



During a visit to Hiroshima on 15 July to attend a national meeting for the promotion of blood donation activities, Crown Prince Naruhito toured the RERF Hiroshima Laboratory. At left, he is shown at a demonstration of a flow cytometer operated by research scientist Seishi Kyoizumi (seated) and explained by Radiobiology Department Chief Mitoshi Akiyama. The machine measures fluorescence from individual cells (either red blood cells or lymphocytes) at a rate of several thousand per second so that rare mutant cells can be quantitatively measured, which serves as a biological evaluation of radiation exposure. Also observing the demonstration are, from left, RERF Chairman Itsuzo Shigematsu and RERF Vice Chairman J. W. Thiessen.

Second Meeting on Radiation Hormesis Held in Kyoto

Under the auspices of the Health Research Foundation (chairman: **T. Sugahara**), together with the Institut de Pasteur de Kyoto and the Central Research Institute of the [Japan] Electric Power Industry, the International Conference on Low Dose Irradiation and Biological Defense Mechanisms was held in Kyoto, 12–16 July 1992. Although not immediately apparent from its title, the gathering's purpose was the discussion of radiation hormesis—the second meeting of this kind, the first having been held in Oakland, Calif, in 1985. Whereas the first meeting was a small gathering of mostly American scientists, the Kyoto meeting attracted some 250 speakers and participants from all over the world (about half of the participants were from Japan), with an unexpectedly strong interest shown by scientists from eastern Europe and the former Soviet Union.

Among the many subjects discussed were the following:

- The effects of reduced background radiation on viability and survival of various cell systems
- Immune stimulation by low-level radiation exposure
- The effect of low "priming doses" on the responses to subsequent higher doses
- Induction of "stress proteins" after low-dose exposure
- Low-dose responses in epidemiological studies

In the last category, the most astounding presentation was that by **Bernard L. Cohen** of the University of Pittsburgh. On the basis of a very large data base of household radon exposures and lung-cancer rates in the affected areas, he demonstrated that risk factors based on uranium-miner data grossly overpredicted lung cancer and mortality from residential radon exposure, even after correction for compounding factors.

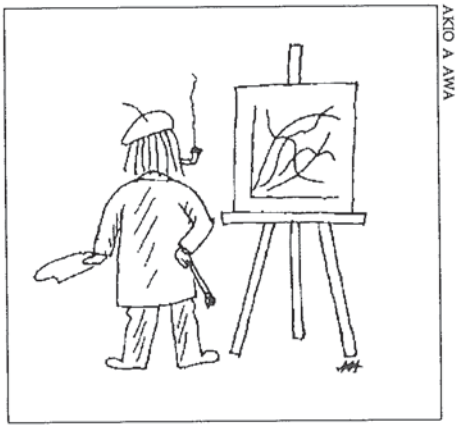
RERF collaborating research scientist **William J. Schull**, University of Texas–Houston, delivered the keynote address, "Radiation epidemiology: where do we stand and where are we going?" which will be published in a future of *RERF Update*.

Other RERF research scientists contributed the following posters: anti-Epstein–Barr antibodies in atomic bomb (A-bomb) survivors (by **Y. Kusunoki** et al), low-dose responses in A-bomb survivors (by **Y. Shimizu** et al), and the shape of cancer-incidence dose-response curves in A-bomb survivors (by **M. Væth** et al). Edited versions of the presentations by Shimizu and Væth are included in this issue. More-extensive coverage will be found in the forthcoming proceedings of the meeting, which will be reviewed in an upcoming issue of *RERF Update*. ❑

In This Issue

Paradigms: Caricatures of Reality

by J. W. Thiessen, RERF Vice Chairman & Update Editor in Chief



AKIO A AWA

Which line do you like best?

Proponents of the notion that low levels of radiation are good for you (I will refer to them as "hormesiologists") talk a lot about the "radiation paradigm," specifically, about the distortion of reality that they perceive to be hidden in the set of assumptions that results in statements such as: "Any dose of radiation, no matter how low, carries with it a certain amount of risk." The recent International Conference on Low Dose Irradiation and Biological Defense Mechanisms in Kyoto, 12–16 July 1992, set out to present data demonstrating that either adaptive mechanisms exist at low doses of radiation in various test systems or that such doses protect against higher doses received later.

Alone, these findings are not too surprising. It has been known for some time that stimulatory and protective effects at low levels of radiation exposure are not uncommon, especially for certain physiological endpoints. The question is to what extent these findings can be generalized to result in statements that such exposure is "beneficial," or, in other words, whether the validity of a hormesis paradigm is any greater than that of the radiation paradigm. Some of the more extreme hormesiologists, such as **T. D. Luckey**, go so far as to state that people should receive more radiation, rather than less, and that the current system of radiation protection should be replaced (it is not entirely clear by what). It seems to me that we are not yet ready for such a drastic step.

Not that there are no problems with the radiation paradigm (I limit the further discussion to cancer). Its underlying models assume a no-threshold linear-quadratic dose-effect relationship. This is really only indicated for the leukemia data, although for certain types of leukemia a threshold cannot be excluded (*RERF Update* 3[4]:5; 4[1]:9). RERF's newest data on cancer incidence (D Thompson et al, RERF TR 5-92, in press) show that for most cancers and for all cancers taken together, a linear relationship up to a few gray provides the best (but not necessarily the only) representation of the data. This, however, would appear to be contrary to another feature of the radiation paradigm; ie, that low-rate exposures are less effective than high-rate ones. Strict linearity, based on one-hit kinetics, would preclude such a phenomenon. Furthermore, although the model "anchors" the curve at zero dose, for some individual cancer types it looks as if a threshold followed by strict proportionality at higher doses represents the data as well as a linear no-threshold relationship (*RERF Update* 4[1]:2, 1992). In other words, the rather simple—and old—assumptions that underlie the radiation paradigm appear to me to be less and less convincing, even though they may still be acceptable when used in a cautionary, eg, public health, approach.

All this doesn't mean that we should be prepared to throw out the current paradigm, lock, stock and barrel. Talking about mathematical models, **Marc Kac** once said (in *Science* 166:695, 1969): "Models are, for the most part, caricatures of reality, but if they are good, then, like good caricatures, they portray, though perhaps in a distorted manner, some of the features of the real world. The main role of models is not so much to explain and to predict—though ultimately these are the main functions of science—as to polarize thinking and to pose sharp questions." This applies as well to paradigms, which, for all practical purposes, are also models or patterns, "ways to look at the world." Even after attending the Kyoto meeting, I feel that the radiation paradigm, warts and all, is a better caricature than the hormesis caricature, which has (still?) too many distortions to provide a recognizable portrait of the real world, and, above all, does not seem to invite the sharp questions that Kac considers to be the main role of models.

Nevertheless, it may be time to begin to reconsider our system of assumptions and models and to replace the simple two-event carcinogenesis theory that has provided the basis for both the linear-quadratic dose-effect relationship and the no-threshold assumption. The RERF cancer-incidence studies that I referred to earlier have laid the foundation for strict proportionality and even, in some cases, for the existence or appearance of a threshold. Both of these are incompatible with the earlier assumptions, which, I believe, were based on cellular (especially: transformation) studies, rather than derived from human data. In the face of new data and rapidly developing insights into the mechanisms of carcinogenesis, the present radiation paradigm may well be in the process of being superseded. Whether it will be replaced by a hormesis paradigm, however, is another question. I personally doubt it. ❑

Note: In my last editorial (*RERF Update* 4[2]:2,1992), I raised the possibility (suggested in my dream, if you remember) that radiation might well protect against cancer as it would appear to turn off more oncogenes than repressor genes. **Richard Setlow** (Brookhaven National Laboratory) was so gracious as to comment on that point. He writes: "I think that the crux of one of the problems in the effects of radiation on oncogenes and on suppressor genes is that for each cell the probability of turning on an oncogene is much much smaller than turning off a suppressor gene." He continues by mentioning experiments with an animal model in which cells contain only one suppressor gene, with a resultant extraordinarily high induction of cancer. I thank Dr Setlow for his remarks and should be wiser than to attempt to convince him otherwise. My dream persona, however, stubborn as ever, notes that Setlow talks about the probability of turning *on* oncogenes, whereas my dream raised the possibility of removal, ie, turning *off* oncogenes, from that point on, I presume, unable to be turned on by some other mechanism. Setlow's point, however, is well taken: in radiation carcinogenesis, suppressor genes play a much larger role than oncogenes. (I apologize for any overly simplistic restatement of his opinion.) ❑

Dose-response Analysis of Atomic Bomb Survivors Exposed to Low-level Radiation

A comparison of dose-effect relationships among various dose levels in the less-than-0.5-Sv region fails to indicate the presence of hormesis.

by Yukiko Shimizu,[1] Hiroo Kato,[2] William J. Schull,[3] and Kiyohiko Mabuchi[1]

Low-dose radiation effects on human beings are not well understood. From the standpoint of radiation protection, risk estimates for low-LET radiation in the low-dose range have been based on the assumption that dose response is linear no-threshold. In recent years, however, considerable literature on experimental radiation biology has been published, indicating the occurrence of certain low-dose radiation effects that may be beneficial, although such evidence is not conclusive.

Since 1950, the Atomic Bomb Casualty Commission (ABCC) and its successor, the Radiation Effects Research Foundation (RERF), have been following the Life Span Study (LSS) cohort of survivors of the atomic bombings of Hiroshima and Nagasaki. The atomic bomb (A-bomb) survivors were exposed to a broad range of whole-body radiation, and many received low doses. Indeed, among 86,520 survivors assigned DS86 dose estimates, 90% received <0.5 Sv. A previous analysis of the dose response for cancer mortality and other indices of radiation damage within the low-dose range (<0.5 Gy using the T65DR system of dosimetry) among A-bomb survivors failed to suggest the existence of a beneficial, or "hormetic," effect of radiation (H Kato et al, *Health Phys* 5:645–52, 1987).

The availability of updated cancer and noncancer mortality data for 1950–85 (Y Shimizu et al, RERF TRs 12-87, 5-88, 2-91) and cancer incidence data for 1958–87 (D Thompson et al, RERF TR 5-92, in press) and of the revised dosimetry system (DS86) prompted an extensive analysis of dose response within the low-dose

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[1]*Department of Epidemiology, RERF;* [2]*scientific consultant, RERF, and National Institute for Minamata Disease; and* [3]*Genetics Centers, University of Texas Health Science Center, Houston.*

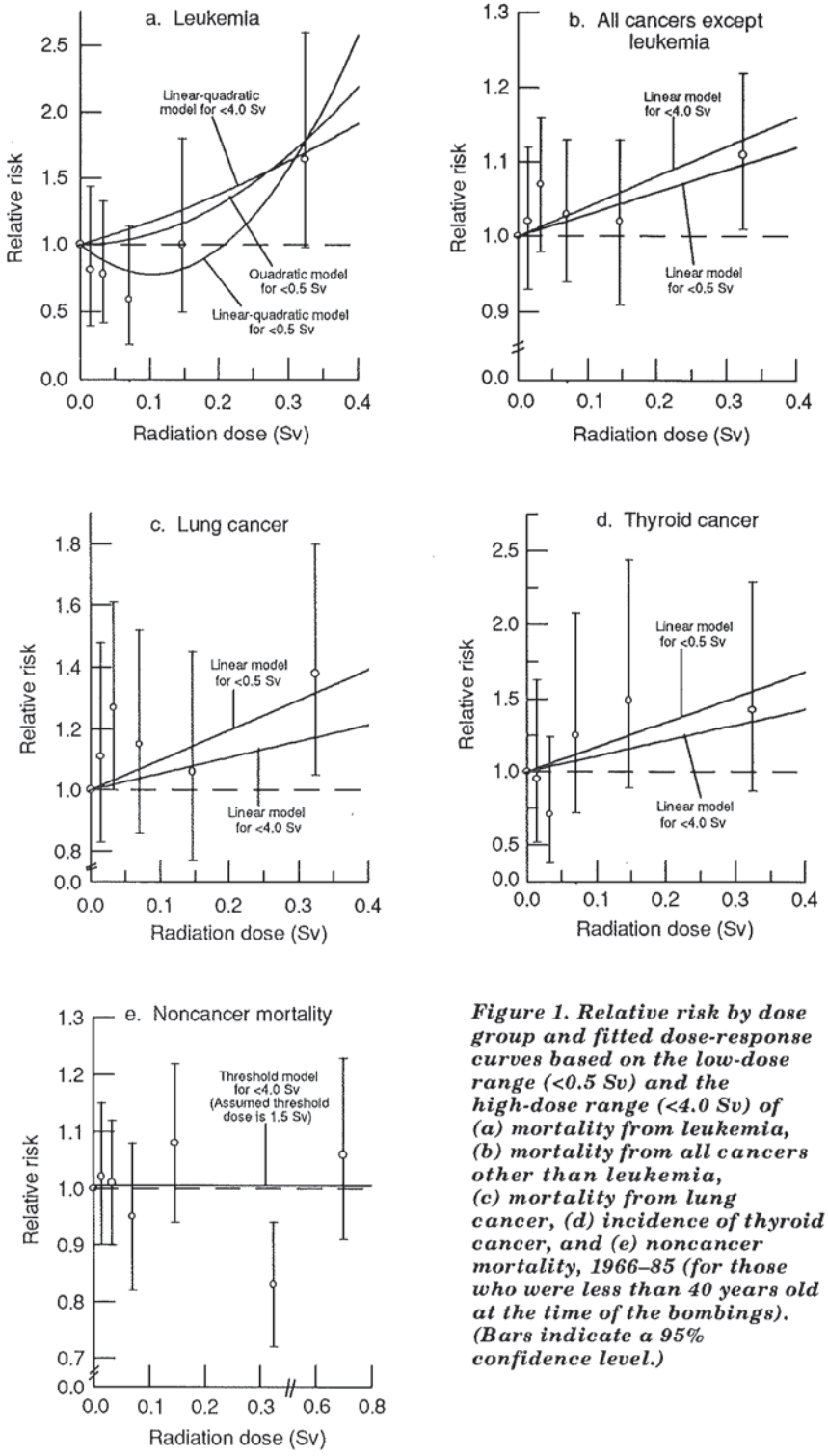

Figure 1. Relative risk by dose group and fitted dose-response curves based on the low-dose range (<0.5 Sv) and the high-dose range (<4.0 Sv) of (a) mortality from leukemia, (b) mortality from all cancers other than leukemia, (c) mortality from lung cancer, (d) incidence of thyroid cancer, and (e) noncancer mortality, 1966–85 (for those who were less than 40 years old at the time of the bombings). (Bars indicate a 95% confidence level.)

Dose-response Analysis

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range among A-bomb survivors in the ABCC–RERF Life Span Study cohort.

In the present study, the dose responses within the low-dose range (defined here as <0.5 Sv) for cancer and noncancer mortality, 1950–85, and incidence of breast and thyroid cancer, 1958–87, were analyzed, using the latest version of DS86 doses and detailed dose groups within the range we termed "low dose" in an attempt to detect the phenomenon of radiation hormesis. The analyses employed the DS86 dose equivalent with an assumed constant neutron relative biological effectiveness (RBE) of 20. The International Commission on Radiological Protection recommends a limit, on the effective dose, of 20 mSv per year, averaged over 5 years (100 mSv in 5 years), with the further provision that the effective dose should not exceed 50 mSv in any single year. Thus, the cutoff points for organ dose equivalent categories included 20 mSv and 50 mSv. The dose categories are 0 (<0.010), 0.010–0.019, 0.020–0.049, 0.050–0.099, 0.100–0.199, and 0.200–0.499 Sv.

Leukemia mortality

The relative risk (RR) (vs 0 Sv) of mortality from leukemia and the 95% confidence limits for each of the five dose groups are shown in Figure 1a. Although the RR differed among the five dose groups, it did not differ statistically from unity ($p > 0.10$). The RR for the 0.010–0.019, 0.020–0.049, and 0.050–0.099 Sv groups was less than 1. However, it is still within the range of random variation and thus should not be regarded as evidence supporting the presence of the hormetic effect. For the dose range less than 0.5 Sv, the linear regression coefficient is positive ($p = 0.06$). The linear-quadratic model fits marginally better than a linear model ($p = 0.07$), but not better than a quadratic model ($p = 0.20$). That is, the linear coefficient with minus sign in the linear-quadratic model is not statistically significant. It cannot, therefore, be said that nominal downward dose response exists in this dose range.

For a dose response including a higher dose range (<4.0 Sv), a linear-quadratic model fit significantly better than either linear or quadratic models. Both linear and quadratic coefficients in a linear-quadratic model were significantly positive. The estimated RR based on a fitted quadratic dose-response curve in the dose range <0.5 Sv tended to be lower than estimates obtained using a linear-quadratic model in the data including a higher dose range, but not statistically significantly so.

Solid-cancer mortality

For all cancers other than leukemia (Figure 1b), the RR at various dose levels in the 0.01–0.49 Sv region was elevated, although not in a statistically significant manner. A linear regression coefficient for the dose range <0.5 Sv was positive and statistically significant ($p = 0.04$). Nonlinear dose-response models did not fit any better than a linear model. The dose response for the dose range including high dose also showed that the linear model fit well. Furthermore, fitted linear dose-response curves for <0.5 Sv and <4.0 Sv were similar, although the dose response for <0.5 Sv tended to be a little lower than that for <4.0 Sv. For stomach cancer, the RR did not differ in a statistically significant way. Fitted linear dose-response curves for <0.5 Sv and <4.0 Sv were almost identical. For lung cancer (Figure 1c), regardless which dose level was used, the RR was not less than unity.

Breast and thyroid cancer incidence

Using data from the Hiroshima and Nagasaki tumor registries for 1958–87, we analyzed the incidence of breast and thyroid cancers, which are relatively nonfatal and difficult to detect by means of mortality surveys. A pattern similar to that observed for mortality from all cancers except leukemia can be seen in Figure 1b. That is, the RR differed among dose levels but did not differ statistically from unity. Fitted linear dose-response curves for <0.5 Sv and <4.0 Sv were almost identical (Figure 1d).

Noncancer mortality

For mortality from all diseases other than cancer, a significantly elevated risk was recently observed at the high-dose range (estimated threshold dose: 1.4 Gy) for younger A-bomb survivors (<40 years old at the time of the bombings) (Y Shimizu et al, RERF TR 2-91). The RRs for the subgroups within the low-dose group (<0.5 Sv) when compared with the 0-Sv group did not differ and were close to unity (Figure 1e).

Summary

Using DS86 doses, dose response was analyzed within the low-dose range (defined here as <0.5 Sv) among A-bomb survivors in the ABCC–RERF cohort in an attempt to detect the phenomenon of radiation hormesis. The present study included as endpoints cancer mortality, cancer incidence, and noncancer mortality. In general, the dose response for these indices of radiation damage differed among the five low-dose groups but failed to suggest the existence of radiation hormesis. These findings were consistent with the previous findings based on T65DR doses. ❑

47th Anniversary of Atomic Bombings Commemorated in Hiroshima and Nagasaki

NAGASAKI SHIMBUN

Children in Nagasaki bear strands of folded paper cranes and sing tribute to those who perished in the bombing.

More than 75,000 people gathered in Hiroshima and Nagasaki, 6 and 9 August, respectively, to honor those who perished as a result of the atomic bombings.

In Hiroshima, Mayor **Takashi Hiraoka** once again called for abolition of nuclear arms and refuted claims that such weapons serve as a deterrent to war. Nagasaki Mayor **Hitoshi Motoshima** appealed for the abolition of nuclear weapons by the end of the century. "We also must remember that the atomic bombings took the lives of an enormous number of people and that many survivors are suffering from solitude, old age, illness, and discrimination," he commented.

In Nagasaki, Japanese Prime Minister **Kiichi Miyazawa** also participated in the ceremony. ❑

Extrapolating Life Span Study Cancer Risk Estimates to Low-dose Radiation Exposures

The shape of the cancer incidence dose-response curve for the atomic bomb survivors provides important information for extrapolation of risk estimates from high-dose studies to low doses of exposure.

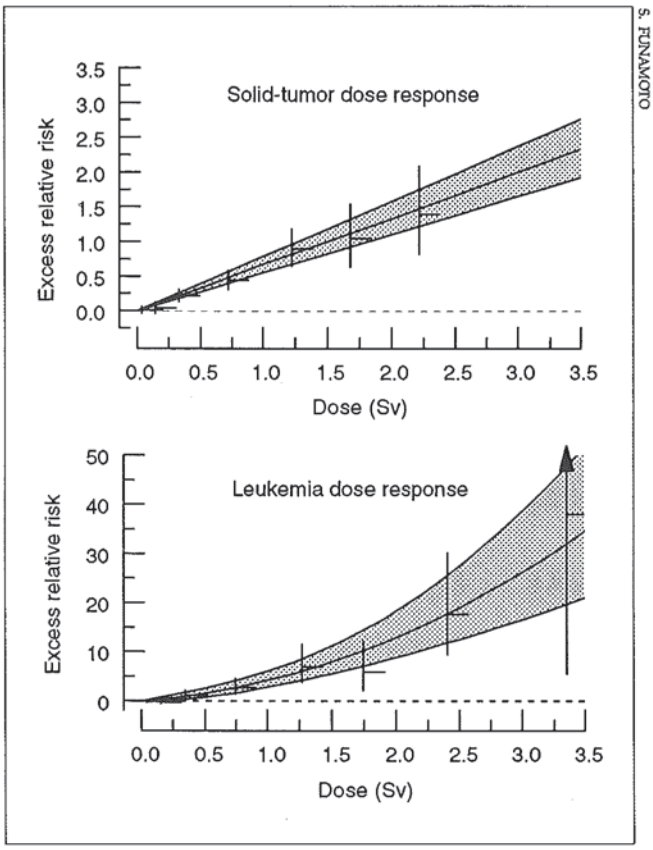
by Michael Væth,[1] Dale L. Preston,[1] and Kiyohiko Mabuchi[2]

Few large-scale epidemiological studies are available for directly evaluating the excess risk of cancer after exposure to low doses of radiation. Extrapolation from high-dose studies is therefore an important alternative method when assessing the low-dose risks. Results of this approach are, however, highly dependent on the shape of the dose-response curve predicted by the extrapolation model.

A detailed study of the shape of the cancer mortality dose-response curve using the RERF Life Span Study (LSS) mortality data recently has been published (DA Pierce and M Væth, *Radiat Res* 126:36–42, 1991). Within the context of linear-quadratic dose-response models, the maximum curvature consistent with the LSS mortality data was assessed. The extent of curvature was expressed by a low-dose extrapolation factor (LDEF). This factor gives the value by which linear risk estimates should be divided to arrive at appropriate estimates of risk at low doses and high-dose rates. The analysis indicated that LDEF values greater than 2.0–2.5 are moderately inconsistent with the LSS cancer mortality data.

In studies of the cancer risks associated with ionizing radiation, cancer incidence data are in general preferred to cancer mortality data. Within the last 10 years, much has been done to establish uniform diagnostic criteria and complete case ascertainment within the LSS cohort. As a result, a comprehensive analysis of the cancer incidence for a large number of organs has just been completed (D Thompson et al, RERF TR 5-92, in press). At the recent conference on low-dose irradiation and biological defense mechanisms held in Kyoto, 12–16 July 1992, we presented some preliminary results on the curvature of the cancer incidence dose-response function. Here we shall briefly summarize these results. The methodological approach used for these analyses is essentially identical to the one used in the previous analysis of the cancer mortality data. Therefore it is easy to compare the two sets of results.

[1]*Department of Statistics and* [2]*Department of Epidemiology, RERF*



S. FUNAMOTO

Figure 1. Excess relative risk estimates for solid tumor incidence (upper panel) and leukemia incidence (lower panel) with 95% confidence intervals

Incidence of solid tumors and leukemia

The cancer incidence dose-response function was studied for two groups of cancers: solid tumors combined and leukemia. For both, the analysis was restricted to survivors with DS86 kerma estimates ranging between 0 Gy and 4 Gy. For solid tumors, the analysis included 79,972 survivors followed during the period 1958–87. A total of 8613 solid tumors had been registered in this period. For leukemia, the follow-up started in 1950, and 231 cases were observed among the 86,325 survivors included in this analysis. For each group of cancers, the incidence data were analyzed in cross-tabulated form using the Poisson regression method that has become the standard approach for analyses of mortality and incidence in the LSS cohort. Because the shape of the dose-response curve is sensitive to random errors in the dose estimates, the complete analysis was carried out both using dose estimates as given by the DS86 dosimetry and using estimates adjusted for the effect of random errors in the dosimetry according to the approach recently developed at RERF (DA Pierce et al, *Radiat Res* 123:275–284, 1990).

The risk estimates as a function of dose depend in a complicated manner on the sex, age at exposure, and attained age of the survivor. However, the distribution of survivors according to age at exposure and sex does not differ much between dose categories, so the excess relative risk as a function of dose derived from the crude rates will, to a first approximation, describe the excess risk for a survivor at the average age of the cancer occurrence. Figure 1 shows such plots for the two groups of can-

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cers. The best-fitting linear-quadratic model and the 95% confidence intervals are also indicated on the plots. The dose response appears linear for the solid tumors, whereas substantial curvature is seen in the dose-response curve based on leukemia incidence.

Low-dose extrapolation factors based on incidence data

In the further analysis, the incidence rate was modeled as $\gamma[1 + \beta(d + \theta d^2)]$, where d denotes the relevant organ dose. The background rate γ was described as sex-specific quadratic functions of log(age) further modified by a birth-cohort effect. The parameter β, the low-dose slope, was modeled as a power function of age, with sex and age-at-exposure effects. The model was fit for a range of assumed θ values, and in each case a measure of the goodness of fit, the deviance, was computed. A plot of the deviance as a function of θ will then show how the data support various extents of curvature. To facilitate interpretation, these plots have been transformed into plots of confidence level as a function of LDEF. Figure 2 shows such plots for both data sets based on analyses with and without adjustment for random errors in the dosimetry. Confidence intervals for the LDEF readily can be obtained from this figure. The results summarized in Figure 2 clearly indicate that only LDEF values near 1 are consistent with the shape of the dose-response curve for solid-tumor incidence. This suggests that a linear model provides a good description of these data and that no low-dose correction is needed.

A quite different picture is seen for leukemia incidence. The LDEF is significantly greater than 1, the best fitting values being 2.5, and values as high as 10–15 are not ruled out by the data. Moreover, and unlike the findings for the mortality data, the LDEF for solid tumors and the LDEF for leukemia differ significantly. Further comparisons of the results based on cancer incidence with those based on cancer mortality are provided in Figure 3. For leukemia, the results are quite similar. Also, the best-fitting LDEF value for solid-tumor incidence is not that different from the LDEF computed for nonleukemia mortality, but here the confidence interval based on incidence data is much narrower. The evidence for differences in solid-tumor LDEF and leukemia LDEF is therefore much stronger in the incidence data, and a combined analysis does not seem appropriate. This suggests that the use of a common LDEF for different endpoints may not be justifiable.

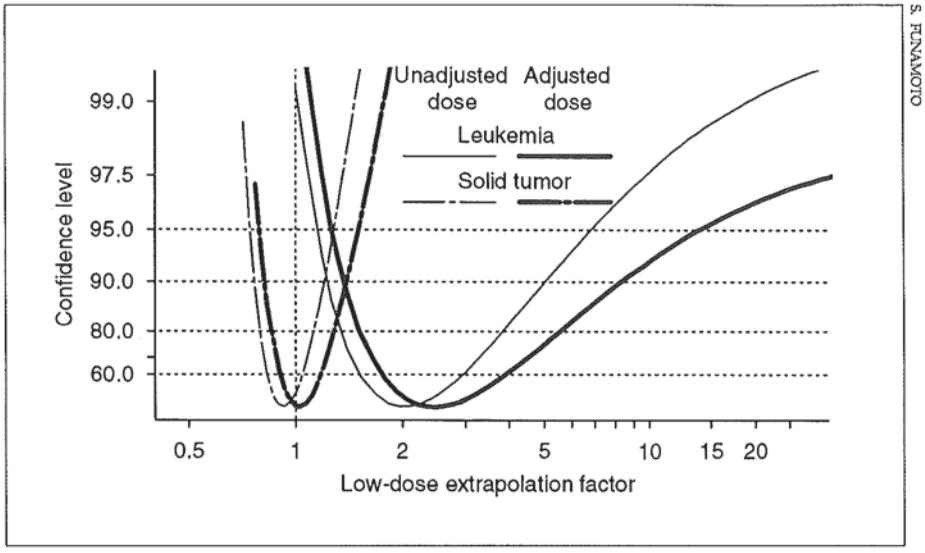


Figure 2. Estimate of low-dose extrapolation factors (LDEF) for solid-tumor and leukemia incidence in the Life Span Study based on both unadjusted and adjusted doses. Confidence levels corresponding to two-sided confidence intervals are plotted against LDEF.

Some complicating issues

Some cautionary remarks may be appropriate here. Analysis of the LSS incidence data is complicated by the fact that the survivors may move from the catchment area of the LSS tumor registry. As recommended by **R. Sposto** and **D. Preston** (RERF CR 1-92, in press), the migration effects on the risk estimates have been minimized by use of adjusted person-years in the calculations. This method aims at removing biases caused by migration and employs estimates of the residency probability as a function of dose, city, sex, age, and time, derived from a subsample of the LSS cohort. Uncertainty in the estimates of residency probability is not considered in these analyses. The likely effect of this additional uncertainty is to enlarge the confidence intervals slightly. This issue will be addressed in the future.

The shape of the cancer incidence dose response has been studied within the context of linear-quadratic models. Therefore the relevance of the range of LDEF values depends on the appropriateness of this class of models. It also should be acknowledged that the LDEF values relate to extrapolation of linear risk estimates based on high-dose/high-dose-rate exposures to low-dose/high-dose-rate exposures. The applicability of the results to situations in which the dose rates are low or exposures are highly fractionated is less clear and requires additional assumptions, which cannot be evaluated with the present data.❑

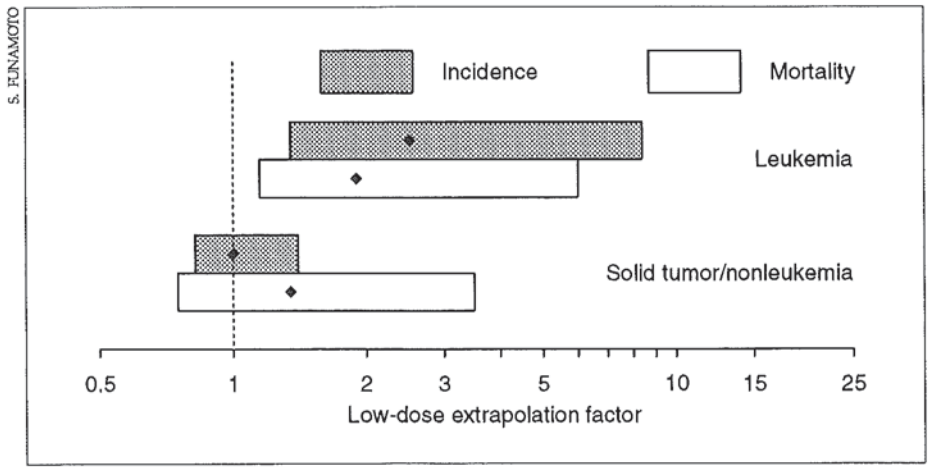


Figure 3. Comparison of 90% confidence intervals for low-dose extrapolation factors based on cancer mortality and cancer incidence. Analysis is based on adjusted doses (LSS cohort, 0–4 Gy). ◆ = maximum likelihood estimate.

Feedback

More Discussion about Radiation Carcinogenesis

Harald H. Rossi of Upper Nyack, NY, writes:

Reading **James Trosko**'s excellent article (*RERF Update* 4[1]:3–5, 1992), I was interested to note that on the basis of somewhat different considerations, he is in agreement with the conclusion, reached by microdosimetric arguments, that radiation carcinogenesis is much more likely to be due to lack of suppression rather than to mutation (HH Rossi, *Radiat Res* 128[1]:115, 1991).

Dr Trosko summarizes the complex processes intervening between initial DNA damage and the appearance of overt malignancy. It should be kept in mind that these processes (or at least one of them) must also depend on the radiation dose when the shape of the dose-effect relationship for cancer induction is different from that for the initial injury. Otherwise modifying factors would change only the amplitude rather than the shape of the primary dose-effect curve. The latter is likely to be linear quadratic, which has become an argument for fitting epidemiological data to such a function. However, this is dubious in view of the fact that experiments in animal radiation carcinogenesis frequently result in a different dose-effect relation and in some cases even reduction of the control incidence. It was also shown some time ago that with neutrons, the "target" for induction of mammary tumors in a rat strain is larger than a cell (HH Rossi and AM Kellerer, *Science* 175:200, 1972). The gap-junctional intercellular communcation (GJIC) mentioned by Dr Trosko might be involved even though the neutron energy (440 keV) was so low that the range of secondary protons was insufficient for traversal of the nuclei of adjacent cells. This may, however, not be required for interruption of cellular communication.

James Trosko replies:

I wish to acknowledge the information and insights provided by Dr Rossi.

Although I was aware of his article (*Radiat Res* 128[1]:115, 1991), the constraints of both my background and the length of my article prevented me from integrating his ideas into the article. However, three of his points deserve further critical examination, because each raises important issues related to the amount or kinds of damage done to DNA.

The first point involves "targets" for (a) "point," deletion/duplication, and "clastogenic" mutations; (b) the kinds of error-free/error-prone DNA repair; (c) cytotoxic events, either caused by DNA lesions or non-DNA lesions; and (d) epigenetic events (eg, either those related indirectly to cell death or those related directly to ionizing radiation-induced altered gene expression).

The second point is how might "modifying" factors influence the ways in which ionizing radiation might affect any of the stages of carcinogenesis (initiation/promotion/progression) and what these modifying factors might do to the shape of the dose-effect relationship for cancer induction.

Lastly, the idea that the "target" for induction of mammary tumors in a rat strain is larger than a cell could be related to the fact that, biologically, most undividing cells of the body are in a syncytium coupled by gap junctions. The "target" in these cases could be these "coupled" cells. How ionizing radiation, at low or high doses or dose rates, affects GJIC with or without cell killing is not known at present. How uncoupling at the cell level by radiation, if it exists, might influence the radiation effects at the molecular/biochemical level is unknown and should be investigated. ❑

News Briefs

J. TAKAYAMA

✓ US Ambassador Tours RERF Hiroshima Laboratory

On 8 September Michael Armacost, US ambassador to Japan, visited the Hiroshima facilities. Above from left, RERF Chief of Research Seymour Abrahamson, American Consul General (Osaka–Kobe) David A. Pabst, Armacost, RERF Chairman Itsuzo Shigematsu, and RERF Vice Chairman J. W. Thiessen view historical photographs.

✓ Abrahamson Returns as RERF Chief of Research

Abrahamson

In early August, **Seymour Abrahamson** assumed the responsibilities of RERF chief of research and permanent director. A professor of zoology at the University of Wisconson, Abrahamson returns to RERF for his second 2-year stay. He replaces **James E. Trosko**, professor of pediatrics and human development at Michigan State University, who completed his 2-year term and has returned to teaching and research.

✓ Three RERF Scientists to Visit Chelyabinsk

As the first step in a collaborative research program with the Ural Research Center for Radiation Medicine (URCRM) in Chelyabinsk, Russia, RERF Genetics Department Chief **Akio Awa**, Statistics Department Chief **Dale Preston**, and **Hideo Sasaki**, assistant chief of the Department of Clinical Studies, will visit Chelyabinsk for 1 week starting October 19.

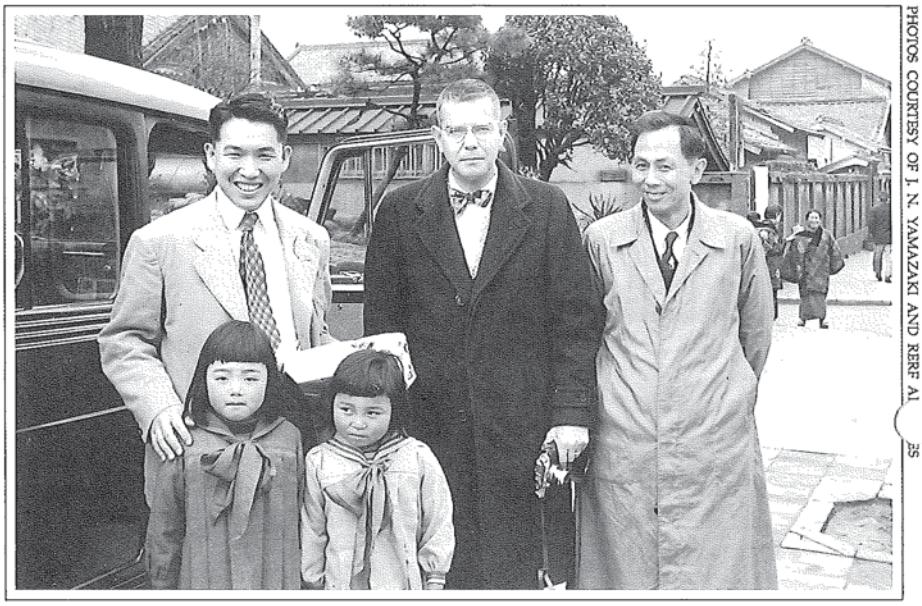
URCRM is following up about 28,000 individuals exposed as a

continued on page 10

The Early History of the Nagasaki Laboratory

How a young pediatrician spent 2 years during the late 1940s helping to develop the ABCC–RERF research program that continues today.

by James N. Yamazaki,
Physician-in-charge, ABCC
Nagasaki Laboratory, 1949–51



PHOTOS COURTESY OF J. N. YAMAZAKI AND RERF AL 25

From left, the author, Warner Wells (Department of Medicine, 1950–52), and Michinori Hamada (Department of Pediatrics, 1950–53), the only Japanese who responded to ABCC's advertisement for a doctor

In January 1948, I first learned that a medical investigation of the children of Hiroshima and Nagasaki was being considered. Upon his return from a National Research Council (NRC) meeting in Washington, DC, Dr **Ashley A. Weech**, director of Children's Hospital, Cincinnati, asked me to consider participating in the work being planned, promising me an opportunity to be in on the "ground floor" of atomic medicine.

In March, Dr Herman Wigodsky of the NRC's Committee on Atomic Casualties (CAC) wrote that "... the careful study and evaluation of children will be a major part of the project. In addition, it should be apparent that there will be ample opportunity for the study of any special problems in which you may be interested.

"... The length of appointment is for a minimum of 18 months," the letter continued. "It is the belief of the committee that the project will remain in Japan for a minimum of 10 years and we hope for at least 50 years. Consequently, the long-range possibilities of employment with this group are limitless. ... Employment is contingent upon satisfactory clearance by the FBI and the Atomic Energy Commission."

By September 1948, I had decided to join ABCC, and CAC Executive Director **Phillip Owen** approved my preparatory tutelage with Dr **Joseph Warkany**, Children's Hospital of Cincinnati. During the preceding decade, Warkany had demonstrated in systematic studies that environmental factors such as dietary restrictions could produce malformations in the mammalian embryo and fetus, and 1 year earlier he had reported malformations in rats following irradiation during gestation. (Since the early 1930s, therapeutic pelvic irradiation of pregnant women had been discontinued due to central nervous system abnormalities and eye malformations in their offspring.)

In April 1949, Owen indicated that my specific assignment in Japan would be the study of congenital malformation in the children of Hiroshima and Nagasaki. In the interim, I had met Dr **James V. Neel**, who had convincingly explained his unfolding genetics program (*RERF Update* 1[4]:7–9, 1989; 2[3]:6–9, 1990) and the involvement of pediatricians.

When en route to Japan, I was instructed by CAC to visit Dr **Stafford Warren**, dean of the newly established medical school at the University of California–Los Angeles. Within weeks of the atomic bombings, Warren had traveled to Hiroshima and Nagasaki.* He related his experiences to me, including his cordial association with Dr **Masao Tsuzuki**, Tokyo University professor of surgery, who later was a member of the first ABCC mission (*RERF Update* 1[4]:7,8; 3[4]:12–3, 1991).

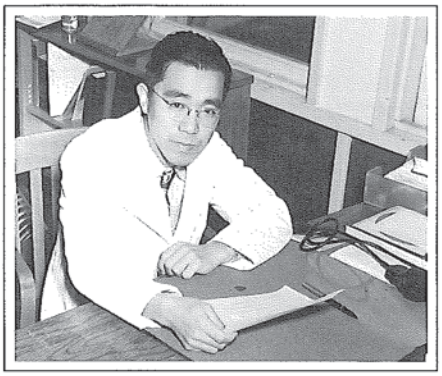
Getting started on the wrong foot

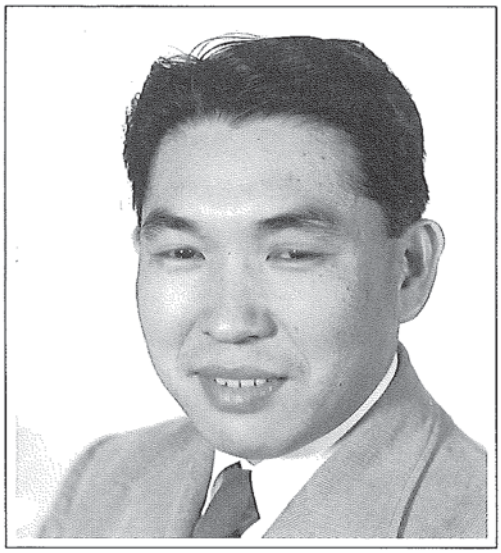
Accompanied to Japan by my wife and 5-month-old son, I arrived in Yokohama in September 1949 to learn that no suitable housing was available in Hiroshima despite written assurances to the contrary. My family remained in Tokyo until several weeks later, when housing was found in the town of Aga. In the meantime, I continued on to Hiroshima, where I met an exceptionally congenial group: Dr **William Schull**, a geneticist, and three pediatricians—a husband-and-wife team, Drs **Wayne** and **Jane Borges**, and Dr **Wataru Sutow**.

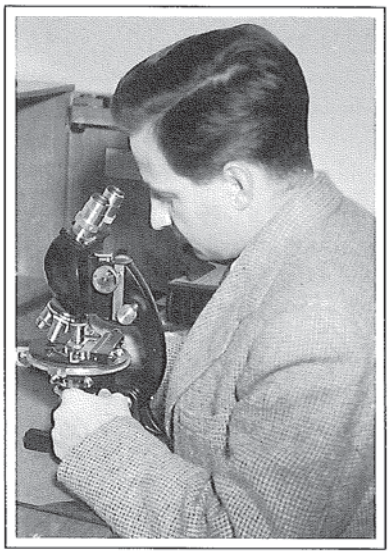
Sutow also had met with disappointment upon his arrival. His daughter was unable to attend school during his 2-year tenure with ABCC because the region's governing British Commonwealth Occupation Forces (BCOF) did not permit the children of Japanese-Americans to attend their schools.**

** At the time, Yamazaki was not aware that Warren had been the medical director of the Manhattan Engineer District and had been one of two physicians to witness the* TRINITY *detonation near Alamagordo, New Mexico, on 16 July 1945. Warren also had been the radiation safety officer for the* OPERATION CROSSROADS *nuclear tests in 1946.*

*** An official BCOF memo dated 5 March 1949 defined conditions under which American personnel were granted access to BCOF recreational, shopping, and associated facilities. Persons of Japanese extraction, except when wearing US military uniforms, were not permitted to enter most BCOF facilities.*







As a combat veteran and former prisoner of war in Germany, I was appalled and angered that members of an NRC-sponsored mission encountered such racial affronts, an opinion I expressed to the first directors of ABCC, Col **Carl Tessmer** (1948–51) and Dr **Grant Taylor** (1951–53).

The assignment in Nagasaki

A few weeks later, I was told by Tessmer and Taylor that I would be sent to Nagasaki as the physician-in-charge, an assignment never alluded to during discussions in Washington, DC. I demurred, stating my lack of inclination and administrative experience and pointing out that I was in Japan solely to undertake a pediatric inquiry. At the time, I could not have realized that this change of venue fortuitously changed my life by initiating a lifelong concern for the children of Hiroshima and Nagasaki.

In November, Taylor introduced me to Nagasaki, where we visited the recently acquired Kaikan building in Sakurababa-machi and verified that remodeling plans conformed to the clinical and laboratory needs of the projected programs. The existing ABCC activities had been scattered.

From top left, Wataru Sutow (Department of Pediatrics, 1948–50), the author in 1950, Wayne Borges (Department of Pediatrics, 1949–51), and a scene from a waiting room at the Nagasaki Laboratory

Dr **Robert Kurata** directed the genetics program from temporary quarters; ABCC doctors and nurses were given space at the Shinkozen "hospital," one of the temporary clinical units of the Nagasaki Medical School (an elementary school before the bombing); and ABCC records were maintained in offices at the fish market (*RERF Update* 1[4]:7–8, 1989; 2[3]:6–9, 1990). Even before its renovation, the Kaikan permitted consolidation of these efforts.

The lone American physician in Nagasaki

At the time of my arrival in Nagasaki I inherited myriad administrative duties, including lecturer to the recent medical school graduates hired by ABCC as well as house doctor to ABCC personnel and the US Army detachment and dependents billeted in the area. (I was occasionally called upon to make house calls in the evening.) The radiation effects study I had so eagerly anticipated was to be delayed for longer than a year (*RERF Update* 1[4]:7–8, 1989).

At the time, our main objective was to parallel in Nagasaki the ongoing ABCC operations in Hiroshima, which had a full complement of internists and pediatricians, a hematologist, a laboratory director, a pathologist, a gynecologist, a radiologist, a surgeon, statisticians, administrators, engineers, nurses, and laboratory technicians. Permanent quarters atop Hijiyama were being built. ❑

Attending a Christmas party at the Yamazaki home in Atogomachi were many of the genetics-program doctors and some ABCC staff members, including Paul Takao, Kazuo Hamasaki, Phyllis Wright, Shiro Tsuiki, and Michinori Hamada. In the front row, fourth from left, is Aki Yamazaki, the author's wife.

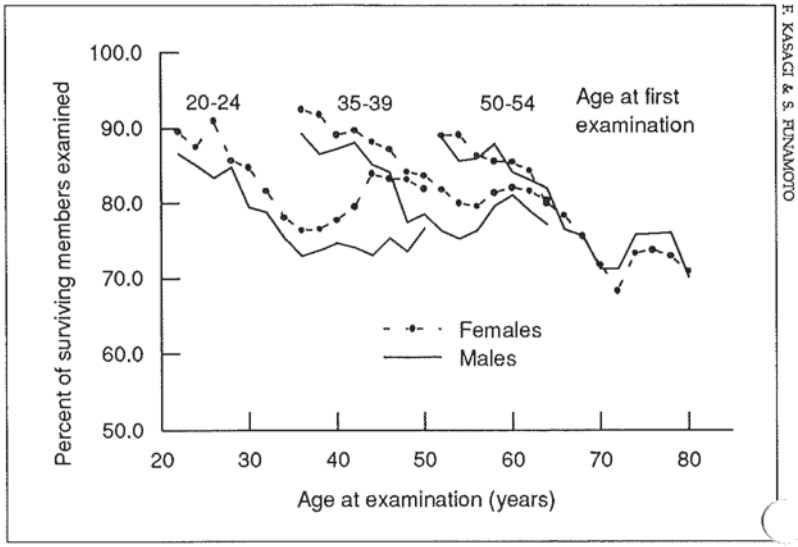
Editor's note: James N. Yamazaki's recollections will be concluded in the next issue of RERF Update.

Participation Rates in Cycles 1–15 of the Adult Health Study

The Adult Health Study (AHS) sample was established in 1958 to observe the late effects of radiation exposure among atomic bomb survivors. The cohort members are invited to receive biennial medical examinations at the ABCC/RERF clinic. These examinations are important sources of information for evaluating the risks of radiation exposure and for monitoring the health of the exposed. To maintain a high participation rate, Contacting Section personnel of the Department of Clinical Studies foster interaction with the participants, providing free transportation to the RERF laboratories, holding night clinics for those who are busy during the daytime, and scheduling in-home examinations for those who cannot come to RERF's clinics.

Figure 1 shows by sex and birth cohort the AHS participation rate during the first 15 2-year examination cycles, providing some interesting observations. First, the participation rate of females is generally higher than that of males. Second, participation rates have declined from almost 90% in the first few cycles to 75% after about 20 years (cycle 10). During this period, a similar temporal pattern is seen in each birth cohort. However, during the last 10 years, the participation rates for younger survivors have been increasing. This upward trend may be due to the positive perception of the AHS exam among cohort members as well as to an increased concern about health among younger survivors as they reach the ages of increased disease risk.

Figure 2 shows the types of examinations given to the AHS population during the 15th AHS cycle (1986–88). The high frequency of night clinic visits by those in their forties and fifties and of in-home exams for those in their seventies and eighties indicates the importance of these examination methods in maintaining a high participation rate. ❑



F. KASAGI & S. FUNAMOTO

Figure 1. Secular changes in participation rate by sex and birth cohort

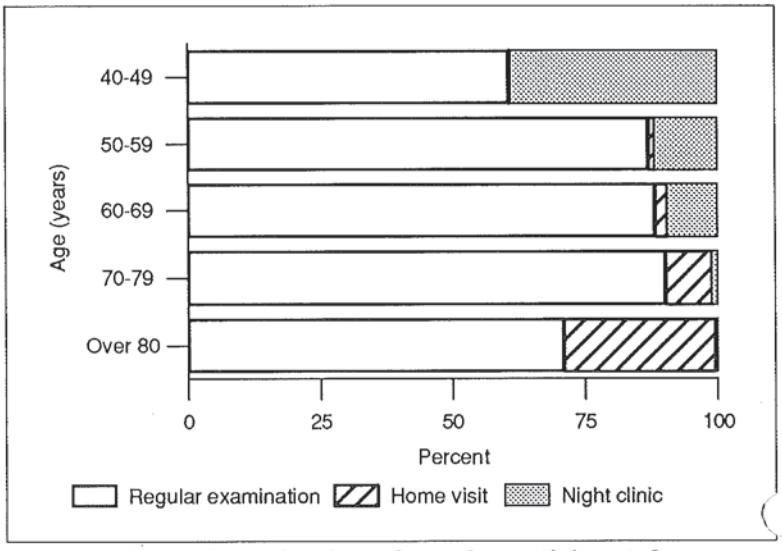


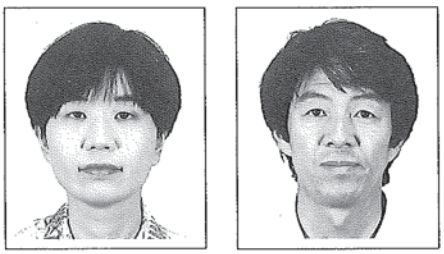
Figure 2. Types of examinations chosen by participants by age (Adult Health Study population, 15th cycle, 1986–88)

News Briefs

continued from page 7

result of the accidental release of radioactive wastes into the Techa River around 1950. By agreement between the two institutions, possible joint research in such areas as epidemiology/statistics, dosimetry, and medical follow-up may be undertaken. During this first visit, areas of common interest will be identified and training programs will be considered.

"These collaborative efforts have great scientific potential, considering the combined size of the A-bomb survivor and Techa River populations and the contrasting types of radiation exposures," said RERF Epidemiology Department Chief **Kiyohiko Mabuchi.**



From left, Fujiwara and Asakawa

✓ Research Staff News

Hiroshima

Department of Clinical Studies: **Saeko Fujiwara** of the Division of Medicine has been promoted to senior scientist.

Department of Genetics: **Junichi Asakawa** of the Laboratory of Biochemical Genetics has been promoted to senior scientist.

Department of Radiobiology: Research scientist **Yuko Hirai** of the Laboratory of Immunology has been promoted to associate senior scientist.

Department of Statistics: Research scientist **Donald A. Pierce** has returned to RERF for the third time. A professor of statistics at Oregon State University, he served as chief of the RERF Department of Statistics, 1986–88. He will analyze Life Span Study cancer data.

Department of Epidemiology: Research scientist **Marc T. Goodman** has joined RERF for 1 year. He will study the effects of diet on cancer among members of the Life Span Study cohort. ❑

Recent Scientific Publications

Editor's note: The reports listed have been approved and will be distributed as soon as they are printed. Wording of the titles and summaries may be slightly altered before final printing.

Approved Technical Reports

Restricted expression of recombination activating gene (RAG-1) in mouse lymphoid tissues. A Yamamoto, H Fujinaga, M Atsuta, K Hamatani. **RERF TR 7-92.**

In an attempt to determine the distribution of recombinase activity in the mouse thymus, spleen, and lymph nodes, we used the in situ hybridization method to examine the expression of the recombination activating genes RAG-1 and RAG-2. Expression of RAG-1 was found in most cortical thymocytes but not in the majority of medullary thymocytes. Although hybridization signals of RAG-2 were not as intense as those of RAG-1, the localization of RAG-2 transcripts was similar to that of RAG-1. In the spleen, expression of RAG-1 was found only in limited cells near the sinus, and the majority of the cells within the follicle were negative for RAG-1 transcript. In nude mice, RAG-1–expressing cells were detected in the same regions, which suggests that in situ hybridization signals of RAG-1 in the spleen are due to the cells of B-cell origin. In the lymph nodes, expression of RAG-1 was found only in the medullar region. Expression of RAG-2 transcript in the spleen and the lymph nodes, if any, was too faint to allow determination of the specific localization. These results suggest that most of the cortical thymocytes and some cells in the spleen are capable of rearranging T-cell receptor genes and immunoglobulin genes, respectively, but the possible involvement of the RAG-1 transcript in RAG-1–positive cells of the spleen and the lymph nodes in functions other than the rearrangement of genes could not be ruled out.

In vitro survival response of irradiated G_0 lymphocytes from atomic bomb survivors: lack of evidence for a population bias in the high-dose cohort. N Nakamura, R Sposto, M Akiyama. **RERF TR 8-92.**

An in vitro colony assay was employed for X-ray dose-survival studies of peripheral blood lymphocytes from 117 Adult Health Study participants with Dosimetry System 1986 doses less than 0.005 Gy and from 84 participants with doses greater than or equal to 1.5 Gy. The mean (coefficient of variation) D_{10} values (the X-ray dose required to kill 90% of cells) for these two groups were 3.40 Gy (7.5%) and 3.34 Gy (7.8%), respectively. No statistically significant differences in their distributions were detected. In addition, neither sex nor age affected the in vitro radiosensitivity of lymphocytes for either group or for all subjects combined. Therefore it was concluded that, as far as the G_0-lymphocyte colony assay is concerned, there is no evidence for preferential loss of individuals with higher cellular radiosensitivity among the high-dose atomic bomb survivors. However, it should be noted that the interindividual variations in cellular radiosensitivity were not large compared with the experimental variations. Consequently, the abovementioned results should be considered to be due to the small heterogeneity of lymphocyte radiosensitivity among the survivors.

Breast disease in atomic bomb survivors: results of a histopathology review. M Tokunaga, CE Land, Y Aoki, T Yamamoto, M Asano, E Sato, S Tokuoka, G Sakamoto, DL Page. **RERF TR 9-92.**

The risk of female breast cancer in association with radiation dose is well established, based upon follow-up studies of the atomic bomb survivors and other exposed populations. This association is especially strong for women exposed before age 20 years and appears to be much weaker among women exposed after age 40. In this study, breast tissue samples from high-dose and low-dose autopsy cases of the RERF Life Span Study sample were examined in detail to determine whether either nonproliferative or proliferative breast lesions are associated with radiation dose.

The results suggest that proliferative disease in general and atypical hyperplasia in particular are associated with radiation dose and that the risk is strongest for subjects who were ages 40–49 years at the time of the bombings. It is hypothesized that this finding may be related to the age dependence of radiation-induced breast cancer, in the sense that potential cancers reflecting early-stage changes induced at these ages by radiation may receive too little hormonal promotion to progress to frank cancers.

Radiosensitivity of atomic bomb survivors as determined with a micronucleus assay. S Ban, JB Cologne, S Fujita, AA Awa. **RERF TR 10-92.**

If atomic bomb (A-bomb) survivors include a disproportionately large number of either radioresistant or radiosensitive persons, the surviving population would provide a biased estimate of the true risk of radiogenic cancer. To test this hypothesis, the in vitro X-ray sensitivities of peripheral blood lymphocytes obtained from 937 A-bomb survivors were measured with a cytokinesis-blocking micronucleus assay. Background frequencies (no irradiation in vitro) of micronuclei show a wide distribution. Frequencies in both males and females tend to increase with increasing donor age. Frequencies in females are significantly higher than in males. Donor age decreases the sensitivity of lymphocytes to in vitro X-ray exposure at a rate of about 0.001 micronuclei per cell-year-gray. There is no effect of donor sex on in vitro radiation sensitivity. A-bomb radiation and cigarette smoking had no significant effect on background and X-ray–induced micronuclei frequencies. Thus, there is no difference in radiosensitivity of peripheral blood lymphocytes between proximally and distally exposed survivors.

Radiation cataracts among Hiroshima atomic bomb survivors, 1949–64. WJ Schull, M Otake, S Funamoto. **RERF TR 11-92.**

This report reexamines the quantitative relationship of exposure to ionizing radiation to the occurrence of cataracts (posterior lenticular opacities) seen in the years 1949–64 among 2249 Hiroshima atomic bomb (A-bomb) survivors whose Dosimetry System 1986 (DS86) doses are known. Among several different dose-response relationships with or without two thresholds, the best fit based on binomial odds regression models is achieved with a linear-linear dose-response relationship that assumes different thresholds for the two types of radiation. The neutron and gamma regression coefficients, 1.99 Gy^{-1} (95% CI: 0.28–4.73 Gy^{-1}) and 5.14 Gy (95% CI: 1.38–14.77 Gy), based on this model, are suggestively higher for the neutron dose and significantly higher for the gamma dose than previously reported. The estimates of the two thresholds are also significantly different from zero. They are 0.06 Gy with 95% lower and upper bounds of 0.03 Gy and 0.10 Gy for the neutron dose and 1.08 Gy with 95% bounds of 0.51 Gy and 1.45 Gy for the gamma dose, respectively. The safety zone for radiation-induced cataracts is estimated to be a 1.75-Sv threshold with 95% lower and upper bounds of 1.31 and 2.21 Sv using DS86 eye organ dose equivalents, assuming a neutron RBE of 18. The latter value is derived from the ratio of the two thresholds, that is, 1.08 Gy for gamma rays and 0.06 Gy for the neutron dose.

Thyroid diseases among atomic bomb survivors in Nagasaki. S Inoue, Y Shibata, H Hirayu, N Yokoyama, A Kurata, M Izumi, S Nagataki, K Shimaoka. **RERF TR 12-92.**

The effects of external radiation exposure on thyroid disease, both malignant and benign, are discussed on the basis of a prevalence study of 1001 males and 1586 females in the Nagasaki Adult Health Study cohort who were examined from October 1984 through April 1987. A high-resolution ultrasonic scanning technique was used to determine the thyroid volume and to detect structural abnormalities. Serum hormones including thyrotropin and thyroglobulin were assessed as well. The prevalence of

continued on next page

Recent Scientific Publications

each thyroid disease was analyzed on the basis of a linear logistic model with modifying factors such as sex and age at the time of the bombing as well as the risk factor of dose to the thyroid.

A significant change with dose to the thyroid was not observed in any of the levels of serum hormones assessed. Thyroid disease was, on the whole, observed more frequently in females than in males. Solid nodules were found in 15 males and 75 females, including thyroid cancer in 3 males and 18 females. The prevalence of solid nodules was significantly higher in females than in males. Furthermore, a significant increase with dose to the thyroid was demonstrated in females, whereas in males none of the factors showed an association with prevalence. A diagnosis of hypothyroidism was given to 12 males and 44 females, and a concave dose-response relationship was demonstrated for antibody-positive spontaneous hypothyroidism. The results of the present study suggest that radiation tumorigenesis is still present even more than 4 decades after atomic bomb exposure.

Stable chromosome aberrations among atomic bomb survivors. DO Stram, R Sposto, D Preston, S Abrahamson, T Honda, AA Awa. **RERF TR 13-92.**

A statistical analysis of data on stable chromosome aberrations collected between 1968 and 1985 by the Radiation Effects Research Foundation (RERF) on 1703 individuals exposed to atomic bomb (A-bomb) radiation in Hiroshima and Nagasaki, Japan, reveals different dose-response relationships in the two cities, as well as significant effects of both time of assay and age at exposure. In Hiroshima, the proportion of cells with aberrations increased by 0.080 per sievert at low doses for the last time period, assuming a constant neutron radiation relative biological effectiveness (RBE) of 10 relative to gamma radiation. In Nagasaki, the low-dose increase was 0.0126 per sievert. In unexposed individuals there was no difference in the proportion of cells with aberrations with respect to any variable except time of assay. The estimated proportion of cells with aberrations increased rapidly with time during the first years of the programs, presumably as a result of technical improvements in the assay methods. The data suggest a complex, nonlinear interaction between radiation and age at exposure on the stable aberrations measured many years later. There was evidence that radiation exposure was more effective for producing these stable aberrations at some lower ages at exposure, although the interpretation of this interaction is difficult. Modeling neutron and gamma components of dose separately, in a way that allows the neutron RBE to vary with dose, yielded an estimated limiting dose RBE of 707 (95% confidence bound [200, ∞]), with a low-dose response of approximately 0.008 aberrations per sievert. This RBE is much higher than the published RBE for induction of aberrations in vitro. Even after allowing the RBE to vary with dose level, there is significant evidence of difference in the dose response of aberrations in the two cities. Both the high estimated RBE and the difference in dose response by city suggest systematic dose estimation errors in which neutrons were underestimated in Hiroshima and/or gamma rays were overestimated in Nagasaki. Random dosimetry errors affect the shape of the estimated dose response but have little effect on the estimated low-dose response.

Approved Research Protocol

Establishment and operation of storage system of leukemia cells. S Kusumi, K Kodama, K Mabuchi, M Akiyama, H Dohi, N Kamada, A Kuramoto, JE Trosko. **RERF RP 6-92.**

A system will be established to store leukemia cells derived from bone marrow and peripheral blood from leukemia cases occurring among Life Span Study (LSS) participants.

Publications in the Open Literature

Evidence for in vivo clonal proliferation of unique population of blood CD4$^-$/CD8$^-$ T cells bearing T-cell receptor α and β chains in two normal men. Y Kusunoki, Y Hirai, S Kyoizumi, M Akiyama. *Blood* 79:2965–72, 1992. (RERF TR 6-91)

Restricted expression of recombination activating gene (RAG-1) in mouse lymphoid tissues. A Yamamoto, M Atsuta, K Hamatani. *Cell Biochem Funct* 10:71–7, 1992. (RERF TR 7-92)

Risk of cancer among atomic bomb survivors. Y Shimizu, H Kato, WJ Schull. *J Radiat Res* (Tokyo) 32S2:54–63, 1991.

Development of a flow-cytometric HLA-A locus mutation assay for human peripheral blood lymphocytes. J Kushiro, Y Hirai, Y Kusunoki, S Kyoizumi, Y Kodama, A Wakisaka, AJ Jeffreys, JB Cologne, K Dohi, N Nakamura, M Akiyama. *Mutat Res* 272:17–29, 1992. (RERF TR 3-91)

A novel blocker-PCR method for detection of rare mutant alleles in the presence of an excess amount of normal DNA. T Seyama, T Ito, T Hayashi, T Mizuno, N Nakamura, M Akiyama. *Nucleic Acids Res* 20:2493–6, 1992. (RERF TR 17-92)

'Rogue' lymphocytes among Ukrainians not exposed to radioactive fallout from the Chernobyl accident: the possible role of this phenomenon in oncogenesis, teratogenesis, and mutagenesis. JV Neel, AA Awa, Y Kodama, M Nakano, K Mabuchi. *Proc Natl Acad Sci USA* 89:6973–7, 1992.

Studies of the mortality of A-bomb survivors. 9. Mortality, 1950–1985: Part 3. Noncancer mortality based on the revised doses (DS86). Y Shimizu, H Kato, WJ Schull, DG Hoel. *Radiat Res* 130:249–66, 1992. (RERF TR 2-91)

Hyperparathyroidism among atomic bomb survivors in Hiroshima. S Fujiwara, R Sposto, H Ezaki, S Akiba, K Neriishi, K Kodama, Y Hosoda, K Shimaoka. *Radiat Res* 130:372–8, 1992. (RERF TR 8-90) ❑

RERF **update** RERF

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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.

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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.

Units of radiation and radioactivity are given as found in the source material.

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