RERF update RERF

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

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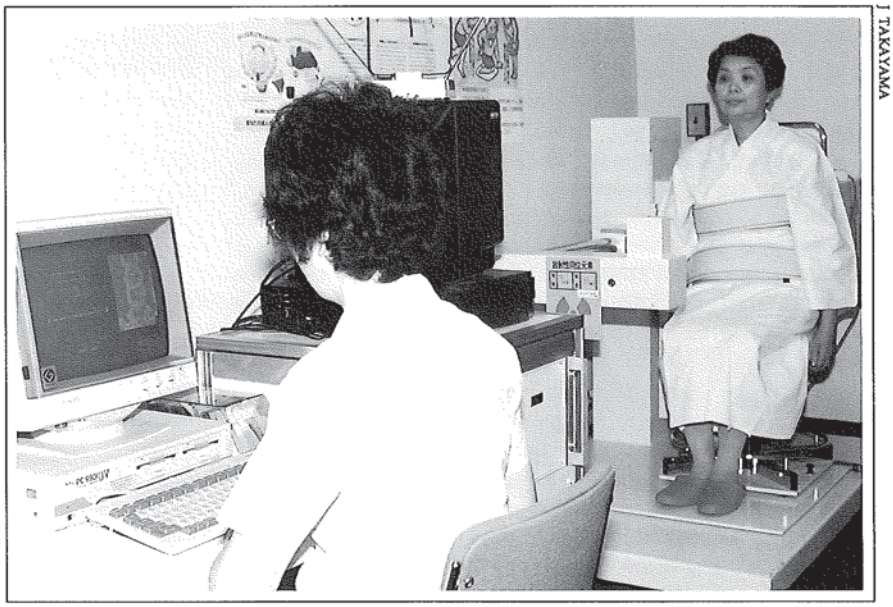
Health Monitoring Workshop Held at RERF

Scientists from Japan, the United States, and New Zealand gathered at RERF's Hiroshima Laboratory, 25–27 January, to review RERF's biennial atomic-bomb-survivor health examinations, which were started in 1958 in Hiroshima and Nagasaki.

Known as the Adult Health Study (AHS), the examination system's primary purpose has been to determine physiologically or biochemically the types of diseases and abnormalities occurring among the AHS participants and to collate this information with other life experiences and death.

"To ensure the continued usefulness of the AHS examinations, more-efficient procedures and newer technologies must be introduced to obtain the kind of clinical information needed to offset the steady attrition of the study population," commented Clinical Studies Department Chief **Kazunori Kodama**. "Because 40% of the AHS population has already died and the participation rate among the elderly has been steadily decreasing, our present methods of collecting data may be insufficient."



J TAKAYAMA

Bone density is one physiological measurement that has been performed since May 1989 via the RERF Adult Health Study's biennial medical examinations.

Workshop participants advocated the following to optimize the examination program:

♦ Determine which diseases and conditions are of greatest interest, eg, by focusing on the common causes of morbidity or mortality among the Japanese.

♦ Upgrade feedback to AHS members via telephone or mail contacts to increase dwindling participation rate, and formally evaluate such efforts.

♦ Shorten the 2-year interval between examinations because information on noncancer deaths for 80% of cases is now ascertained from death certificates alone. Customize approaches to data collection.

♦ Change the content of the present health examinations after evaluating each item, specimen, or measurment for time requirements; scientific rationale; standardization, validation, and comparability over time within the AHS and other studies; and potential for adverse psychological effect.

♦ Improve collection of morbidity and mortality data through cooperative endeavors and joint research with local medical associations and major hospitals. Consider contacting family, doctors, or police after sudden, unattended deaths. ❑

Health Monitoring Workshop Participants

Hiroshi Yanagawa (co-chair), Jichi Medical School, Tochigi
J David Curb (co-chair), University of Hawaii at Manoa, Honolulu
Robert B Wallace, University of Iowa College of Medicine, Iowa City
Gary D Friedman, The Permanente Medical Group, Inc, Oakland, Calif
Hirotsugu Ueshima, Shiga University of Medical Science, Ohtsu City
Shigeru Hisamichi, Tohoku University School of Medicine, Sendai
Tsutomu Hashimoto, Wakayama Medical College, Wakayama

Invited speakers
Robert Beaglehole, University of Auckland School of Medicine, Auckland, New Zealand
Shunroku Baba, National Cardiovascular Center, Osaka

In This Issue

Perspectives

A Change in the Editorship

by Seymour Abrahamson, RERF Chief of Research & Update Editor in Chief

Abrahamson

I wish to take this opportunity on behalf of all of us to thank **J W Thiessen** for conceiving of *RERF Update* and developing it into a world-class research newsletter that continues to generate accolades from the international scientific community. I hope that I can live up to the role model established by Dr Thiessen.

A part of the job is made easier for me because of the major conscientious effort provided by **Beth Magura**, who I know has devoted many of her weekends and evenings to ensuring the quality of the *Update* product. A second part of this publication process that is made easier for me results from the remarkable cooperation I know I will receive from our scientific staff in preparing the scientific articles about work in progress, which of course is the major reason for the existence of this newsletter. During the last week in March, we completed the 20th annual Scientific Council meeting, held in Nagasaki, and some 20 presentations were made by our staff. On the basis of what was presented, it is abundantly clear that our program is still a relatively untapped vein of critical information regarding the health effects of radiation. With the majority of the surviving population initially exposed at early ages, our epidemiology on cancer risk is subject to many changes, as are our concepts of risk. We will continue to have more-powerful statistical tools to analyze our results and more-sophisticated molecular approaches to determine the nature of radiation-induced somatic and hereditary alterations. The ABCC-RERF Adult Health Study, now in its 36th year, can be expected to provide deeper insights into the direct as well as the indirect effects of radiation on health issues and the aging process in an extraordinarily long-lived population. We are just beginning to unravel the role of family relationships among the survivors themselves and have much to learn about the influence of such first-degree relationships and responses to radiation insult. The rapid advances in biodosimetry should lead to a clearer understanding of dose-related responses by discriminating between dose error and biological heterogeneity. These issues and many more will be considered in the forthcoming issues of *RERF Update*.

As a binationally supported foundation, we face a difficult economic future requiring carefully reasoned choices both by our sponsors and by ourselves. We can only hope the rush of events does not limit our ability to respond. This then is the negative side. ❑

News Briefs

✓ RERF Scientific Council Gathers in Nagasaki

The 20th meeting of RERF's scientific advisory council was held 29–31 March 1993 at the Koseinenkin Kaikan in Nagasaki to review the ongoing research direction of the Foundation.

RERF's scientific councillors are: **Kunio Aoki**, Aichi Cancer Center, Nagoya; **Curtis C Harris**, US National Cancer Institute; **Clark W Heath Jr**, American Cancer Society; **Leonard A Herzenberg**, Stanford University School of Medicine; **Eisei Ishikawa**, Jikeikai University School of Medicine; **Toshiyuki Kumatori**, Radiation Effects Association, Tokyo; **John B Little**, Harvard University School of Public Health; **Ei Matsunaga**, National Institute of Genetics, Mishima; **Shigefumi Okada**, University of Tokyo; and **Arno G Motulsky**, University of Washington.

Observers at the meeting included **Kazuaki Arichi**, Japan Institute of International Affairs; **Harry J Pettengill**, **Milton Eaton**, and **Robert Goldsmith**, US Department of Energy; **Charles W Edington** and **Alvin G Lazen**, US National Research Council; **Edward M Malloy**, US Embassy; **Ruey S Lin**, National Taiwan University; **Teruhiko Saburi**, Japan Foundation for Aging and Health; **Yukio Sato**, Ministry of Foreign Affairs; **Tsutomu Sugawara**, Kyoto University; **Shuichi Tani**, Ministry of Health and Welfare.

Sasaki

Akiba

✓ Sasaki Appointed Chief of Medicine at Atomic-bomb Survivor Health Facility

On 1 April, RERF Clinical Studies Assistant Department Chief **Hideo Sasaki** assumed the position of chief of medicine at the Hiroshima Atomic-bomb Survivors' Welfare Center. Sasaki, who had worked at RERF for 11 years, hopes to continue collaborating with his former RERF colleagues.

✓ Akiba Named to Kagoshima University Faculty

On 30 November 1992, former Epidemiology Assistant Department Chief **Suminori Akiba** assumed the position of professor, Public Health Chair, Kagoshima University Medical School.

✓ Research Staff News

Hiroshima

Department of Statistics: **Robert Delongchamp**, research scientist, joined RERF in March. Previously a statistician with Dow Corning, he will apply statistical methods to assessments of health risk.

Department of Epidemiology:

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Breast Cancer in the RERF Life Span Study

Dose-related excess risk may be profoundly influenced by genetic factors and reproductive history.

by Charles E Land, Radiation Epidemiology Branch, National Cancer Institute, Bethesda, Maryland, and M Tokunaga, Department of Epidemiologic Pathology, RERF

Increased breast-cancer risk in women is a relatively well quantified late effect of atomic-bomb radiation exposure. It has also been studied extensively among patients receiving multiple X-ray exposures for diagnostic or therapeutic purposes related to tuberculosis, scoliosis, benign breast disease, or enlarged thymus. Data from medically irradiated populations and the RERF Life Span Study (LSS) sample became available at about the same time and have developed more or less in parallel; the first study by **C Wanebo** et al (*New Engl J Med* 279:667–71, 1968) of breast-cancer incidence in the ABCC-RERF clinical subsample was prompted by **I MacKenzie**'s finding of increased risk among former patients of a Nova Scotian tuberculosis sanitorium (*Br J Cancer* 19:1–8, 1965).

The particular scientific value of the series of LSS sample studies is enhanced by two important facts: First, radiation-related risk among women exposed during childhood or adolescence is higher than risk following exposure during adult life, and the LSS sample, whose age distribution in 1945 was typical of urban Japan, has a large fraction of survivors exposed when young. Second, parallel analyses by **J Boice** et al (*Radiology* 131:589–97, 1979), **C Land** et al (*JNCI* 65:353–76, 1980) and, most recently and convincingly, **D Preston** et al (in preparation), have made it clear that the risk of radiation-related breast cancer is about the same for comparable groups of exposed Japanese and Caucasian women, even though normal breast-cancer rates are far lower in Japan. Thus, at any given radiation dose, the ratio of excess risk to baseline risk is much greater in the LSS sample than in any other population now being studied, which means that the LSS data tend to be more informative about details of risk and about the nature of radiation-induced cancer.

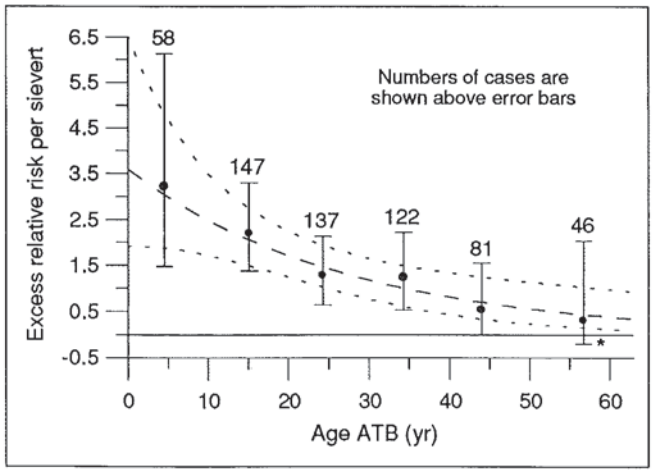
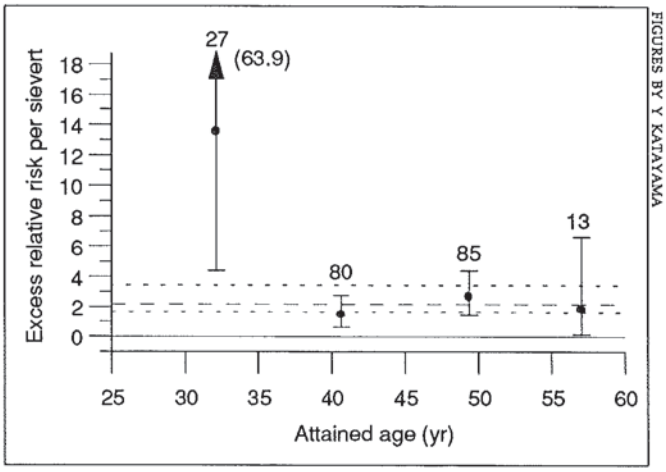


Figure 1. Fitted linear-model estimates of excess relative risk per sievert with 90% confidence limits by age at the time of the bombings (ATB) for discrete intervals and as a smooth function of age. *Minimum feasible value for lower limit.



FIGURES BY Y KATAYAMA

Figure 2. Fitted linear-model estimates of excess relative risk per sievert with 90% confidence limits for women under 20 yr old at the time of the bombings by interval of attained age and for all attained ages combined. Numbers of cases are shown above error bars.

The most recent site-specific study of breast cancer in the LSS sample (M Tokunaga et al, RERF draft technical report) is based on 807 cases diagnosed from 1950–85, including 68 survivors who were under 10 yr old at the time of the bombings (ATB) and 230 who were between 10 and 19 yr old ATB. As might be expected, findings with respect to dose response and its modification by age ATB, attained age, and time following exposure were similar to those reported by **D Thompson** et al (RERF Technical Report 5-92; *Radiat Res*, in press) on the basis of tumor-registry diagnoses from 1958–87 for that part of the LSS sample still living in Hiroshima and Nagasaki. In particular, the dose response is marked and strongly linear, excess relative risk (ERR) decreases with increasing age ATB (Figure 1) or increasing attained age, and, controlling for age, ERR varies little by time following exposure. Risk was relatively low for women 40 yr old or older ATB, but there is now a statistically significant excess in that group.

A surprising finding from the more detailed analysis in the site-specific study is that the ERR was markedly higher for early-onset breast cancer (ie, cases diagnosed before age 35) than for cancer diagnosed at later ages. The contrast is extreme: among women under 20 yr old ATB, the ERR at 1 Sv was 13.5, with 90% confidence limits (4.4, 68.9) for early-onset breast cancer vs an ERR of 2.0 (1.3, 3.0) at ages 35 or older ATB; moreover, age-specific estimates were essentially uniform for attained ages 35–44, 45–54, and 55 yr or older (Figure 2). One possible explanation is that it may reflect the existence of a genetic subgroup with high sensitivity to radiation-induced breast cancer. This interpretation is supported by recent findings regarding the genetic basis for breast-cancer risk, especially at early ages: less than 1% of the general population is thought to account

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Breast Cancer in the Life Span Study

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for one-third of the population risk before age 29, due to an inherited, autosomal dominant mutation (E Clauss et al, *Am J Hum Genet* 48:232–42,1991; B Newman et al, *Proc Natl Acad Sci USA* 85:3044–8, 1988). Because all the somatic cells of women with this inherited syndrome would already have one mutated allele, they might be unusually sensitive to radiation. It seems likely that a tumor-suppressor gene is involved, a possibility currently being investigated at RERF.

It is remarkable that, with the exception of a few early-onset cases, radiation-related breast-cancer risk closely tracks underlying age-specific population rates in the sense that, for fixed age ATB, ERR shows no trend with either attained age or time following exposure. This suggests that all breast cancers, whether or not radiation-related, are influenced similarly by other factors that vary with age. In all general populations studied, reproductive history is strongly related to risk. In particular, women with a first full-term pregnancy before age 20 have about one-third the risk of women who did not have such a pregnancy before age 30, and other factors related to that variable, such as number of children and lactation history, are also correlated with risk.

A case-control interview study, based on cancers diagnosed before 1980 and matched to controls on the basis of age ATB, city, and radiation dose, was carried out to determine (1) if the usual risk factors were operating in the LSS sample, (2) whether these factors interacted with radiation dose to influence breast-cancer risk, and (3) whether differences in radiation-related ERR by age ATB could be explained in terms of reproductive history ATB. As expected, age at first full-term pregnancy was strongly, and positively, related to risk (Figure 3), as were several correlated variables (C Land et al, 1993a, submitted). Number of births and total cumulative lactation period each were strongly, and negatively, related to risk even after adjustment for age at first full-term pregnancy.

Interaction of the above factors with radiation dose was investigated using estimates of dose-related ERR (see Figure 1) obtained from incidence data (C Land et al, 1993b, submitted). For all three of the factors, an additive relationship with dose could be ruled out at a high level of confidence, whereas a multiplicative (ie, synergistic) relationship was consistent with the observations (Figure 4). Thus, for example, early age at first full-term pregnancy appeared to be protective against

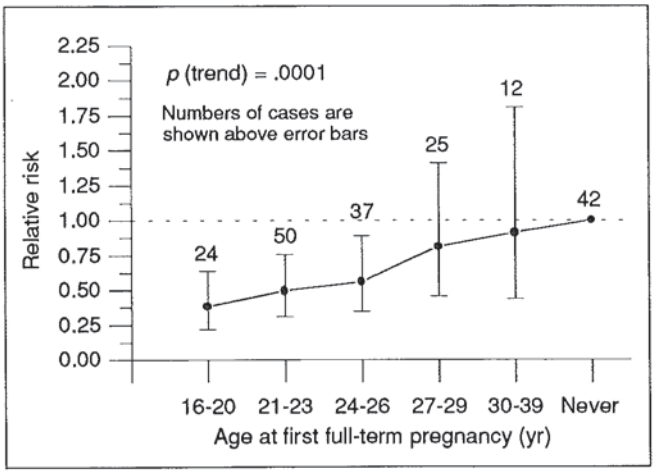


Figure 3. Estimated relative risk of breast cancer by age at first full-term pregnancy (90% confidence intervals).

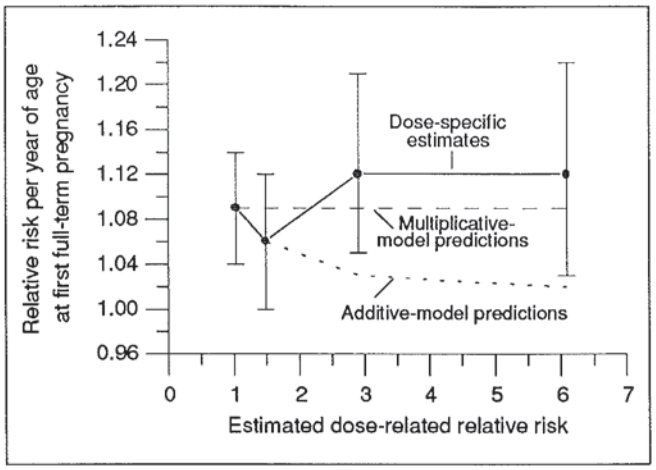


Figure 4. Estimated relative-risk multiplier per year of age at first full-term pregnancy: dose-specific values vs corresponding predictions, according to the multiplicative and additive models for interaction with radiation dose.

both baseline and radiation-related breast-cancer risk in approximately the same ratio (ie, a threefold reduction of baseline cancer risk is accompanied by about the same reduction in dose-related risk at any dose level). The evidence for synergy was essentially limited to the first of the three factors, in the sense that the evidence against additivity for the other two appeared to be explainable in terms of their correlations with age at first full-term pregnancy.

Analyses still in progress concern the role of reproductive history ATB as a modifier of radiation dose response. The relationship appears to be complex. One interesting preliminary result is that the apparently protective effect against *radiation-induced* breast cancer of early age at first full-term pregnancy seems clear among women who did not experience such a pregnancy before radiation exposure or among women exposed during childhood or adolescence (which is almost the same thing). For women exposed after their first full-term pregnancy or as adults, however, evidence for synergy is weaker, probably because the level of dose-related excess risk is lower.

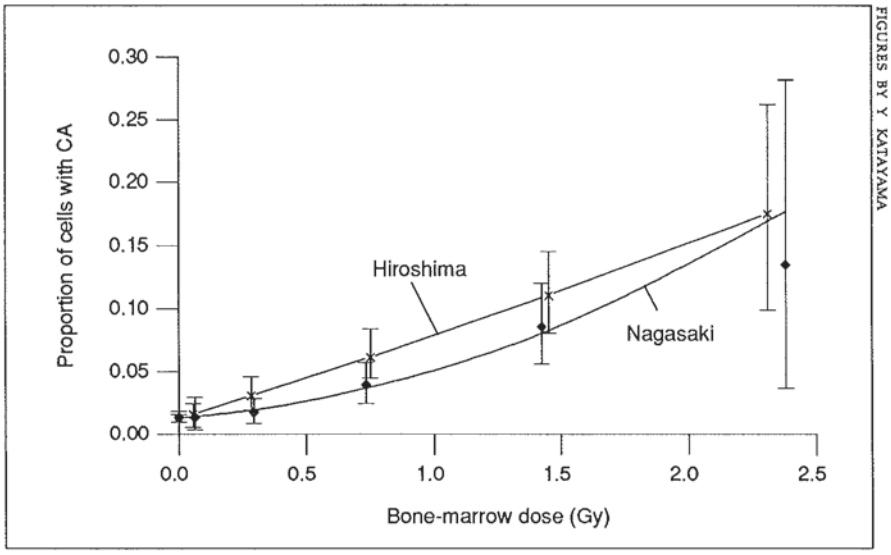
To our surprise, earlier breast-cancer data from the LSS sample revealed that there is (1) a high radiation-related risk in this population, which has one of the world's lowest breast-cancer rates and (2) an excess risk from exposure before breast development. Recently, we also have been surprised by evidence suggesting a strong genetic component to the risk of radiation-related, early-onset breast cancer and by the contrast between the additive interactive relationship of radiation dose with baseline risk (Japan vs the US) and the apparently synergistic relationship of dose with reproductive history. It seems likely that radiation competes with other risk factors related to certain differences in breast-cancer rates worldwide, but that the influence of reproductive history is expressed by promoting factors that act similarly upon potential cancers related to radiation exposure or other cancer initiators.

If present risk patterns continue, we can expect about 480 more breast cancers during the remaining lifetimes of the LSS members, of which about 155 may be related to radiation dose. More than 70% of the new cases and 90% of the radiation-related cases are expected to occur among women who were under 20 yr old ATB. Thus, we may expect more information from continued follow-up of this population. ❑

Stable Chromosome Aberrations among Atomic-bomb Survivors: an Update

RERF chromosome-aberration data suggest underestimation of neutrons in Hiroshima and/or overestimation of gamma rays in Nagasaki. The authors also discuss an indication that dose response may be related to age at exposure.

by Daniel O Stram, Department of Preventive Medicine, University of Southern California, Los Angeles, and Richard Sposto, EMMES Corporation, Potomac, Maryland



FIGURES BY Y KATAYAMA

Figure 1. Bone-marrow dose response of chromosome aberrations (CA) for Hiroshima and Nagasaki. A constant RBE of 10 was used so that rates of chromosome aberrations were plotted against $D_g + 10\ D_n$ ***at each dose level.***

RERF's efforts to develop biologically based methods of estimating dose encompass attempts to validate the existing physical dosimetry system and to establish a basis for using a biological outcome as a surrogate for physical dosimetry when such dosimetry is not available. Here we will report on a detailed statistical analysis (D Stram et al, RERF TR 13-92) of a large chromosome-aberration data set compiled for a subset of members of the Adult Health Study* (AHS) by the RERF genetics research program, beginning in the late 1960s.

As of December 1989, these studies had yielded estimates of chromosome-aberration rates using one or more blood samples for 1703 individuals in the AHS cohort assigned dose estimates less than 4 Gy shielded kerma.

Regression model

A regression model was fitted to investigate the effects of time, age, city, and radiation dose on the proportion of cells, P_i, with aberrations observed for the ith individual. Our basic model was

$$\mu_i = E(P_i) = \alpha(1 + \beta_1 D_i + \beta_2 D_i^2)\ . \qquad (1)$$

The parameter α in Equation (1) is the background proportion of aberrations, and the parameters β_1 and β_2 define a linear-quadratic dose response in RBE-weighted dose D_i. By allowing parameters β_1 and β_2 to depend on city, different dose-response relationships can be fit in each city. Similarly, α was allowed to depend upon time of assay to allow for changes in overall yield of chromosome aberrations related to improvements in laboratory procedures used to detect aberrations during the years of the RERF program.

To estimate the effect of age at exposure on stable-chromosome-aberration rates, a second model,

$$\mu_1 = \alpha[1 + \gamma(\beta_1 D_i + \beta_2 D_i^2)]\ , \qquad (2)$$

introduces a multiplicative dose-response modifier γ, which is allowed to depend on age. This allows the modeling of possible age-dependent sensitivity to radiation exposure in the production of stable chromosome aberrations. In Equations (1) and (2), the dose estimates used were constant RBE-weighted bone-marrow dose. A final model allowed for estimating relative biological effectiveness (RBE) using a varying RBE model. Here, the neutron and gamma components of dose were modeled separately so that

$$\mu_i = \alpha(1 + \zeta_1 D_{g,i} + \zeta_2 D_{g,i}^2 + \zeta_3 D_{n,i})\ , \qquad (3)$$

where D_g and D_n are gamma and neutron components, respectively. The $\kappa_n = \zeta_3/\zeta_1$ is the limiting (low-dose) RBE of neutron radiation, so that κ_n can be interpreted as the ratio of the linear slopes for gamma and neutrons at a dose so small that there is no contribution from the term for gamma squared.

Results

Figure 1 shows the results when a simple quadratic model as in Equation (1) is fit separately within the two cities and also the average proportion of chromosome aberrations within six dose categories. The two regression lines differ significantly ($p < .001$), with the dose response in Hiroshima being almost linear and that in

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** The AHS originally consisted of 20,000 atomic-bomb survivors and controls from Hiroshima and Nagasaki matched by age and sex. Since 1958, these participants have voluntarily returned to the RERF clinics for biennial medical examinations.*

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Nagasaki exhibiting significant upward curvature.

Effect of time of assay, sex, and age at exposure

A large effect of time of assay was found in the data and strongly affected the estimates of α in Equation (1) when these were allowed to vary with year of assay. In particular, chromosome-aberration rates measured after 1971 were much higher than rates from 1968–1971. This increase was most likely due to improvements in laboratory procedures that led to better detection of aberrations. The sex of a survivor was found to have no measurable influence on either the background rate or dose response. Small increases in background rates with age at assay were detected, but these were significant only when data from samples collected before 1972 were removed from the analysis. The dose response appeared to differ significantly with age at exposure, but in a complicated way. The model in Equation (2) was used to examine this effect.

Figure 2 shows the estimates of the relative slope of the dose response for each of 11 age-at-exposure categories. No simple, smooth function of age at exposure could be found that adequately describes the effect. The strongest single effect was in the 5- to 9-yr category (p = .003), followed by the 15- to 19-yr category (p = .006), then followed by the 45- to 49-yr category (p = .07), which when combined account for most of the overall differences.

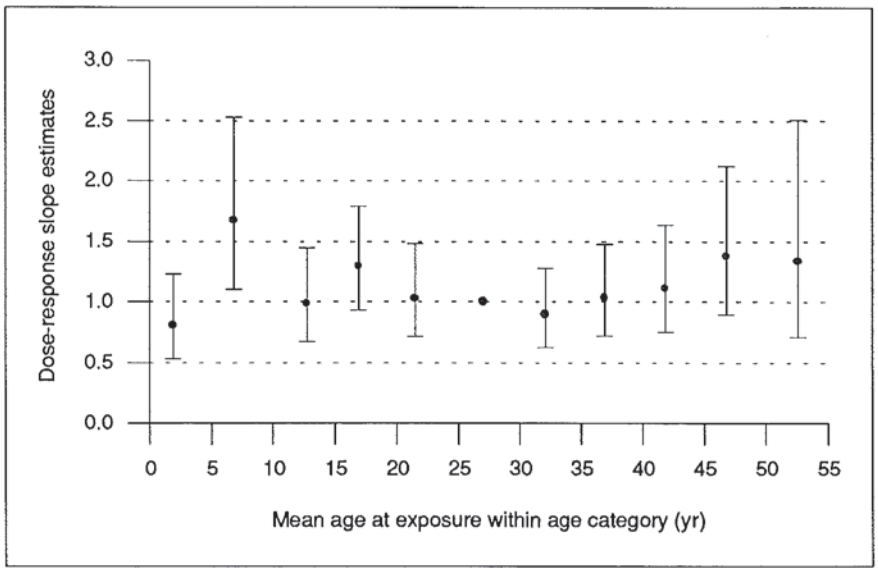

Figure 2. Effect of age at exposure on estimated chromosome-aberration dose response. Dose-response slope estimates relative to the dose response estimated for ages 25–29 are plotted against mean age at exposure.

The RBE of neutrons

It is well known that the relative effectiveness of gamma rays and neutrons in inducing biological effects differs depending on the level of exposure (see S Abrahamson, *RERF Update* 1[1]:3, 1989). This arises primarily because the gamma radiation produces a linear-quadratic dose response and neutron radiation produces a linear response with a much steeper slope than the initial linear slope of the gamma dose response. Although the shape of the RBE function will depend somewhat on the scale in which the effect is measured (eg, total number of stable aberrations in a given number of cells vs proportion of cells with stable aberrations), this limiting low-dose RBE, which is the ratio of the initial linear slopes of the neutron and gamma dose-response curves, should be invariant to scale of measurement. The most direct way to estimate the limiting RBE of neutrons is to model the dose response using the neutron and gamma components of dose separately, as in Equation (3). Using this equation, the estimate of limiting RBE, κ_n, is equal to 707 with a 95% confidence interval (200, ∞). Given the very wide confidence interval for this parameter, the point estimate is practically meaningless. However, the lower confidence bound implies a limiting RBE for the data that is much greater than that suggested by in-vitro experiments.

Discussion

The use of variable RBE models to explain the city differences produces estimates of the limiting RBE of neutrons that appear to be much higher than expected based upon in-vitro studies of cell sensitivities. This is suggestive of either underestimates of the neutron component in Hiroshima and/or the overestimates of gamma rays in Nagasaki. The marked difference, by city, in the dose-response slope at low doses may also be suggestive of the same problem. For example, if the neutron component estimated in Hiroshima were increased, this would reduce the apparent slope at low doses in this city and would bring it somewhat more in line with Nagasaki, as well as reduce the apparent RBE of neutron dose. Similar effects would occur if the gamma component in Nagasaki were reduced.

Age at exposure does appear to modify the dose-response relationship given here; however, the age pattern exhibited an unexpected "sawtoothed" shape over the ages 0–20 yr. Effects other than age-dependent radiosensitivity, such as dose-estimate errors occurring differentially by age category or biological differences in the stability, may play a role in this apparent age effect in the data.

The use of biologically based dose estimates in the absence of physical dosimetry involves issues beyond describing the observed dose-response functions among subjects such as the atomic-bomb survivors. One of these is determining the degree of individual variation in dose response, since the accuracy of dose estimates based on an endpoint such as chromosome aberrations will clearly depend upon individual variation in radiosensitivity. At present, it is unknown how much of the large apparent variation in individual chromosome aberrations, shown in Figure 1, is due to radiosensitivity variations or how much is due to random errors in the Dosimetry System 1986 estimates. This and related issues are the subject of continued exploration in the atomic-bomb-survivor studies. ❑

The Saga of the Rogue Lymphocytes

A story of scientific serendipity—of an entirely unexpected discovery that assumed a life of its own, leading the investigators on an unexpected path neither had trod before.

by James V Neel, University of Michigan Medical School, Ann Arbor, and Akio A Awa, Department of Genetics, RERF

During the period 1962–1976, one of us (JVN) was devoting a major share of his time to multidisciplinary genetic, medical, and anthropological studies of some of the least acculturated Indian tribes of Central and South America. Part of this exercise was intended to develop biological baselines for populations far from the pollutants of civilization. Each of the approximately dozen expeditions that occurred during that period had its own specific set of objectives. For the expedition of 1969, one of those objectives was cytogenetic studies of members of a very unacculturated tribe of American Indians, the Yanomama, living in southern Venezuela and northern Brazil.

The choice of that objective was strongly influenced by the presence at the Department of Human Genetics in Ann Arbor of **Arthur Bloom**, well known to some of the old-timers at the Radiation Effects Research Foundation (RERF). Arthur had played a seminal role in initiating the cytogenetic program at the then Atomic Bomb Casualty Commission (ABCC), and it was from ABCC that JVN had recruited Arthur to come to Ann Arbor as a member of the Department of Human Genetics. He brought with him high qualifications for examining cultured lymphocytes for damage. What JVN and Arthur clearly expected was that the cultured lymphocytes of these American Indians would show significantly less damage than was encountered in cells cultured from members of highly industrialized countries, such as Japan or the United States.

On that particular expedition, it was necessary to establish a temporary cytogenetics laboratory in Venezuela. At that time, **Shozo Iida**, long a mainstay in the ABCC–RERF Cytogenetics Laboratory, was spending a year with Bloom in Ann Arbor, and Iida assumed the responsibility for setting up this laboratory. It was not an easy task. However, all went well, and we cultured cells from some 49 Amerindians. To our great surprise, about 1 in every 200 of the 3175 cells examined showed a strikingly abnormal karotype, as illustrated in Figure 1, bottom panel. (The top panel shows a normal cell.) No investigator had previously recorded anything of this nature. We took a deep breath and published the data, knowing full well that we would have to confirm our finding on subsequent expeditions. The next year—1970—we repeated the same studies in another Yanomama village. This time, there were only 2 of these cells out of 5652 scored. This was certainly not the kind of confirmation we had been looking for, so, the following year, we went back to the villages in which we had made the original observation. This time the laboratory scored 9716 cells, finding only 1 abnormal cell of this type. We had not really confirmed our original observation, and most of our friends in cytogenetics felt that we must really have done something pretty terrible to that first set of cultures to obtain such abnormal cells.

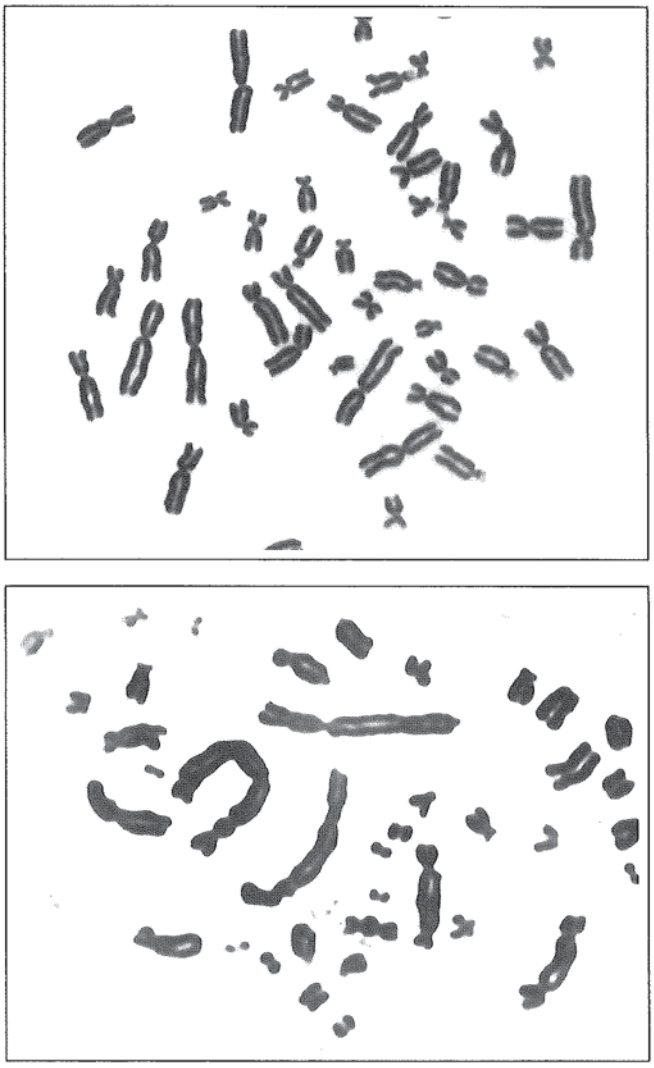

Figure 1. Top panel: Normal cell from a Japanese male. Bottom panel: Amerindian rogue cell.

There the matter rested until 1984, when **D P Fox** and his associates, in the course of chromosomal studies on oil-rig workers and deep-sea divers, for the most part employed in the North Sea oil fields, found that 6 individuals out of the 280 studied exhibited cells of the same type we had observed earlier. All of the persons exhibiting these cells were divers, and it was surmised that the cells were due to the conditions associated with diving. The next year, **Janet Tawn** and her associates published a study scoring 500 cultured lymphocytes from each of 12 presumably normal young subjects from the United Kingdom who underwent the studies as part of the preemployment examinations required by the British Nuclear Fuels Co. Two of these persons exhibited the same type of abnormal cells. She was in a better position to

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Rogue Lymphocytes

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follow up her subjects than we had been: when these individuals were studied 50 days later, the cells had disappeared. Here was justification for our inability to find the cells when we went back to the same American Indian village.

Meanwhile, there had been interesting developments at ABCC–RERF. One of us (AAA) had first noted in 1967 one of these cells in a control subject. By 1984, Awa had observed a total of 24 of these cells among some 102,170 cells scored from control individuals in the cytogenetics program. This frequency of 1 in 4257 cells examined was far below the frequency observed in the first study of the Amerindians, but there was no doubt they were the same kind of abnormal cells (Figure 2, top panel).

The circumstances of the ABCC–RERF studies permitted some epidemiological observations not feasible in the studies on American Indians: in Japan there was no age or sex difference in the frequency with which the cells were encountered nor was there any seasonal effect, and the frequency with which they were observed appeared more or less constant from year to year. It was at this time that we coined the term "rogue" to describe these cells. (*Webster's Dictionary* defines a rogue as an individual exhibiting a chance biological variation or deviating from the type of a variety or breed.)

The next chapter in this story occurred in 1990, when the RERF Cytogenetics Laboratory received for cytogenetic analysis a series of blood samples obtained by teams sponsored by the International Atomic Energy Agency (IAEA) during the medical studies on the inhabitants of the Chernobyl area. To our surprise and pleasure, in 24 samples collected from the small *control* village of Krasilovka, among 4789 cells scored, there were 9 rogues (Figure 2, bottom panel). Again, there was no age or sex effect, but one additional interesting clue did emerge: The IAEA studies had included complete blood counts, and the inhabitants of this village showed a relative lymphocytopenia, the hallmark of a recent virus infection. By now, a pattern in the appearance of these cells was beginning to emerge. These cells occur in a variety of ethnic groups, where they appear in specific localities and in specific individuals in temporary bursts. At the height of such a burst, perhaps 1 in 200 lymphocytes will be of this type. In the intervals between bursts, the population frequency is more like 1 in 4000 to 5000 cells.

Thus far, these cells have been observed only among cultured lymphocytes. We see no reason to believe that the phenomenon is restricted to lymphocytes, but the necessary studies to demonstrate their presence in other types of cells will be difficult, since it is not easy to observe the first postculture cell division in these other cell types. Let us assume that they are widespread throughout the body. What is their cause, and what are their implications?

With respect to cause, at the moment our favorite hypothesis is that they result from the activation of latent retroviruses (transposons) in the genetic material. The lymphocytopenia we observed in the inhabitants of Krasilovka, characteristic of a recent viral infection, suggests that the activation of these transposons could result from a viral infection of unspecified nature. In this connection, we note that there are said to be approximately 1 million transposon (retroviral) footprints in DNA, the significance of which is under great debate. Some of these transposons are so vestigial that they could not be functional, but others appear to have a character consistent with their periodic activation. An alternative hypothesis invokes a direct effect of an infection with a papovavirus. One member of this virus family, SV40, is known to break chromosomes in cells infected in cell cultures, and, although SV40 does not appear to infect humans, there are other papovaviruses that do.

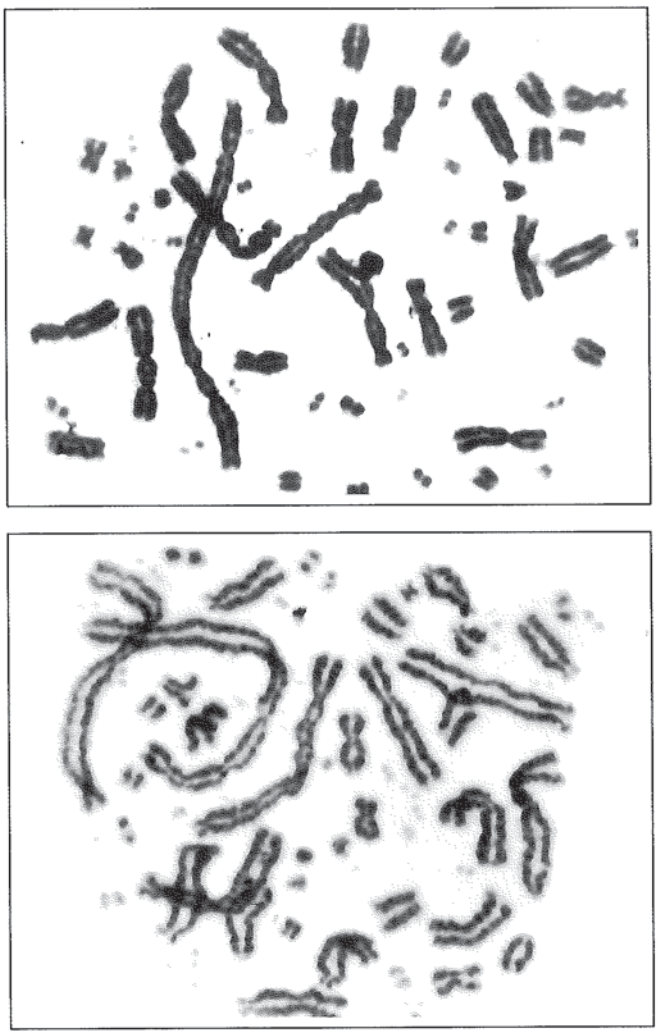

Figure 2. Top panel: Rogue cell from a Japanese female. Bottom panel: Ukrainian rogue cell.

With respect to the implication of the cells, we have in a recent publication allowed ourselves to be quite speculative (*Proc Nat Acad Sci USA* 89:6973–7, 1992). Most of these cells could not possibly pass through a cell division successfully. The damage is far too great. Perhaps none of them can pass through a mitotic cell division, in which case these are "dead-end" cells, of no biological significance. However, there is quite a range in the damage observed, and we suggest that perhaps 1 in 1000 of these cells (the least damaged) is capable of reproduction. Although this is a rare event, even if only 1 in 5000 cells is of this type, there should be circulating in the body at any one time 2.5×10^6 of these cells, of which 2.5×10^3 might be capable of cell division. Comparable figures might apply to other susceptible tissues. We have suggested that in somatic tissue, the survivors among these cells might contain the chromosomal rearrangements that are sometimes a point of departure for a neoplasm. In the germline, the survivors among these

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Rogue Lymphocytes

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cells might ultimately be responsible for some of the chromosomal abnormalities encountered in aborted fetuses and newborn infants.

Finally, we come to the ultimate speculation. Increasingly, it appears that there are two types of genetic events in the evolution of DNA. One type consists of "point mutations" involving one or a few nucleotides. The other type consists of rearrangements, which either result in gene duplications or in the juxtaposition of DNA "domains," a juxtaposition from which evolve genes with new functions. In a recently published paper, we in Ann Arbor argued that the nucleotide-type mutations are primarily due to errors in DNA replication at the time of cell division (*Proc Nat Acad Sci USA* 89:7036–40, 1992). Now we are beginning to wonder whether the driving factor for the domain or duplication types of mutation might not be transposon activation. In this case, our observations, quite serendipitous, have lifted the corner of the veil that has until now concealed evidence of this type of activity in humans. There has been abundant evidence in such organisms as corn and *Drosophila* for the role of transposons in creating mutations, but, thus far, only a few hints for humans.

All kinds of future studies come to mind. What is very much needed is a way of locating individuals who are having bursts of such cells, so that enough cells can be harvested for the kinds of studies that are the next steps in investigating this phenomenon. For instance, we would like to do fluorescent in-situ hybridization (FISH) staining to reveal the pattern of rearrangements. Are there preferred chromosomal break points? We have attempted FISH staining with some of the old slides but have been unsuccessful. The technique requires newly identified rogue cells. There is also a need for serological studies of individuals exhibiting a burst of cells, looking for antibody tracers from the postulated trigger virus. Finally, will there be findings of increased transposase activity in persons with these cells? ❑

News Briefs

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Yasuyuki Fujita, Epidemiologic Pathology assistant department chief and acting chief of the Tumor and Tissue Registry Office, is concurrently assigned to the Epidemiology Department.

Senior scientist **Yukiko Shimizu** has been promoted to assistant department chief.

Department of Radiobiology: Laboratory of Immunology research scientist **Tomonori Hayashi** has resigned to spend 2 years at Michigan State University working with former RERF Chief of Research **James Trosko**. Hayashi will study the effects of radiation on the intercellular transmission system of human blood cells.

Visiting scientist **Takako Yamakido** will spend 2 years studying somatic mutation. She is from Hiroshima University School of Dentistry.

Department of Clinical Studies: **Masaharu Nobuyoshi** is now a research scientist in the Division of Medicine.

On April 1, **Hironori Ueda** joined RERF as a research scientist in the Division of Medicine.

Research Information Center: **Scott Pohlman** is now assistant chief of the Information Systems Laboratory.

Nagasaki

Department of Clinical Studies: **Masazumi Akahoshi**, who is concurrently serving as acting assistant department chief and acting chief of the Division of Medicine, was also appointed acting chief of the Division of Radiology on 1 April.

✓ Highlights of the RERF Lecture Program

On 14 October 1992, **Richard Okinaka**, Los Alamos National Laboratory, discussed a DGGE approach for detecting mutational hotspots induced in human cell cultures by X rays.

Darwin R Labarthe, University of Texas Health Science Center–Houston, lectured on 29 October 1992 about cardiovascular risk factors in children.

Norio Niikawa, Nagasaki University School of Medicine, on 4 November discussed chromosome microdissection-microcloning and its application to chromosome painting.

On 25 November, **Lonnie Kapp**, University of California at San Francisco, spoke about cloning and characterization of a candidate gene for AT complementation group D.

Robert J Molinari of AT Biochem on 11 December lectured about improved methods and materials for mutation detection.

On 14 December, **Raymond R Tice** of Integrated Laboratory Systems, Research Triangle Park, NC, spoke about the single-cell gel assay, an electrophoretic technique for detecting DNA damage in individual cells.

Eugene P Cronkite, Brookhaven National Laboratory, Associated Universities, Upton, NY, on 23 April talked about the effects of radiation, benzene, and AZT on hemopoietic stem cells and leukemogenesis.

✓ Nagasaki Laboratory Employee Honored by Prefecture

In late November, Nagasaki Laboratory interpreter-translator **Brian Burke-Gaffney** was presented with a meritorious service award from the prefectural governor, **Isamu Takada**. Burke-Gaffney is the first foreigner to receive this award. A freelance writer and part-time language specialist with Nagasaki City, he recently portrayed a Christian priest in a historical television drama broadcast nationwide on one of Japan's publicly funded networks.

✓ In Memoriam: Arthur J McDowell

On 19 January, **Arthur J McDowell** died in Washington, DC. In 1957–58, McDowell helped plan, organize, and implement the Adult Health Study. ❑

RERF Reports and Reprints Available Upon Request

Technical reports, as well as reports in the Commentary and Review Series, are usually listed on the last pages of each issue of *RERF Update*. Reports that are "approved" should be considered as "in-press" publications that may not yet be available for distribution.

Journal reprints are kept on file and may be requested directly from the authors or from the RERF Publication and Documentation Center (PDC).

Requests received for reports or reprints that are unavailable will be retained and filled as soon as possible.

Forward requests to Chief, RERF, PDC, 5-2 Hijiyama Park, Minami-ku, Hiroshima, 732 Japan. Fax: 81-82-263-7279. E-mail: c/o B Magura at 101126.3573@compuserve.com. ❑

The *Lucky Dragon* Incident and ABCC: Part I

On 1 March 1954, a multi-megaton nuclear device was exploded on the island of Bikini, resulting in the contamination of several of the Marshall Islands and, as it turned out later, of the tuna-fishing boat the Lucky Dragon *with 23 fishermen aboard.*

by Merril Eisenbud, Chapel Hill, North Carolina

Editor's note: Following is a condensed account of the Lucky Dragon *incident and the Atomic Bomb Casualty Commission's (ABCC) involvement, taken from Merril Eisenbud's book* An Environmental Odyssey *(reviewed in* RERF Update *3(2):9, 1991) with permission of the University of Washington Press. Eisenbud served with the US Atomic Energy Commission for many years and at one time was the contract administrator for the ABCC. The second part of this excerpt will appear in an upcoming issue of* RERF Update.

PHOTO COURTESY OF MERRIL EISENBUD

The Atomic Bomb Injuries Investigation and Research Committee met in Tokyo in March 1954 to discuss the radioactive contamination of the fishing vessel, the* Fukuryu Maru. *On the right side of the table are, from left, ABCC Director John Morton (1953–54), US Embassy First Secretary William Leonhart, and the author. Across the table, starting second from left are: Isamu Nagai, who from 1957–1975 was ABCC associate director (in his capacity as director of the Japanese National Institute of Health's Nagasaki Branch Laboratory), and Masanori Nakaidzumi, who also later served as an ABCC associate director (1956–64). Third from the end is Kenjiro Kimura, a noted radiochemist.

Unknown to anyone until the fishing vessel returned to its home port of Yaizu in Japan on March 14, the inhabitants of the Marshall Islands and the twenty-eight servicemen on Rongerik were not the only ones affected by the BRAVO* fallout. At the time of the explosion, the *Fukuryu Maru* (*Lucky Dragon*) *No. 5*, a 100-ton tuna fishing boat with a crew of twenty-three, was about eighty miles east of Bikini when the crew saw a bright flash and realized that they had witnessed a nuclear explosion. They immediately sailed away from Bikini, but after four hours encountered a fallout of white particles so large as to be individually visible. The fishermen later reported that by the time the fallout stopped, the ship appeared to have been coated by a thin layer of snow.

The US had declared the area around Bikini a restricted zone, which was known to the fishermen. The evidence indicates that they were just outside the specified boundary at the time of the explosion and were nervous about being apprehended by the US authorities because the same crew had been found poaching in Indonesian waters one year earlier and had spent some time in jail as a result. It was apparently for this reason that the crew made no mention by radio of the fact that they became sick, starting a few days after the fallout. By the time they reached their home port 14 days later, all the crew were seriously ill.

I learned about the *Fukuryu Maru* the same way most people did, from Japanese news reports that a fishing boat had returned to its home port of Yaizu (south of Tokyo) with twenty-three crew members suffering from radiation sickness. The story did not seem credible to me at first because I was familiar with the extensive precautionary sweeps made over the area in advance of a test. I had in fact flown on one such search and was impressed with what I thought was the thoroughness of the procedure. Nevertheless, **Bugher** [John Bugher, deputy director of the Division of Biology and Medicine of the Atomic Energy Commission] contacted **John Morton**, newly appointed director of the Atomic Bomb Casualty Commission in Hiroshima, and asked him to obtain whatever information was available. . . .

It took very little time for Morton to confirm from his Japanese colleagues that the men were suffering from radiation sickness, and that the boat was highly radioactive, as was its cargo of tuna fish, which had been disposed of by burial. On the morning of March 19, Bugher and I participated in a conference call from Morton who said a consultant was badly needed to advise the US embassy as well as the Japanese on the radiological aspects of the matter, and that it would be desirable that I proceed to Tokyo immediately. . . .

. . . The call from Morton came at 11:30 A.M., at the conclusion of which it was decided that I should proceed to Washington for a conference at AEC headquarters before leaving for Japan. It took me a few hours to collect the instruments and reference material I knew I would be needing, and I left on the four P.M. plane from La

*Code name for the detonation.

Guardia where Irma [the author's wife], my mother, and our three boys where waiting for me with the bags she had packed. When I arrived in Bugher's office, he had my passport, my authorization for travel to Japan, my tickets, and an ample travel advance. We discussed the important implications of what had happened in the Pacific, and he told me that about one million pounds of tuna were suspected of being contaminated. This added a new dimension to an already complicated situation.

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We reached Honolulu at 5:30 A.M. and only then did I find that the *Lucky Dragon* affair had blossomed into a full blown international incident. I was met at the airport by Commander **Deller**, who was on the CINCPAC [Commander in Chief, Pacific Theater] staff and was my liaison with JTF-7 [Joint Task Force 7]. He briefed me on the latest developments in the Marshalls. Rumors about the evacuation of Marshallese had reached the international press, abetted of course by the sensational stories from Japan. The problem was exacerbated, so far as I was concerned, by the announcement of a small pharmaceutical company that they were sending a drug to Japan that would help the fishermen. The medicine was no more than a common over-the-counter skin burn lotion, but Bugher, who of course knew nothing about the shipment, had cabled prominent members of the Japanese medical profession that I was on my way to Japan to assist them, and when they learned of the announcement of the publicity-seeking pharmaceutical company, it was assumed that I had some miracle drug with me. As I left Honolulu, I was surprised to read about this in the *Honolulu Times*, and it disturbed me more than a little.

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PHOTO COURTESY OF *ASAHI SHIMBUN*

The author, left, upon arrival in Tokyo in March 1954.

Because I had been sitting on the opposite side of the plane, I was not aware of the large number of reporters and photographers waiting for the plane, and, had I seen them, I would have assumed they were waiting for another passenger. There were about thirty of them, behind a barricade at the edge of the apron. They were close enough to take pictures, which appeared in the newspapers the next morning, but, except for the few seconds it took for me to descend from the plane, they saw no more of me that evening. . .

En route, **Leonhart** [William Leonhart, First Secretary of the US Embassy] briefed me efficiently about the state of things. The Japanese people were angry about the fallout on the *Lucky Dragon*. They were the only people ever to have been hurt by atomic bombs, first during the war, and now again. The Japanese scientists were making sensational statements to the media. The formal peace treaty between the US and Japan had only recently been signed, and this was the first postwar crisis in the relations between the two countries. The bottom had dropped out of the tuna market. No one in Japan fully understood the technical implications of the event, and I should expect to spend considerable time providing information to both the Japanese and the Americans.

"This was the first serious interruption in the otherwise smooth relationship that had existed between the two countries since the end of World War II."

After a restless night I had a breakfast conference with John Morton, who was also staying at my hotel. He was in a very difficult position. His entire career had been spent as a surgeon on the staff of the University of Rochester Medical School, from which he had recently retired as chairman of the Department of Surgery. He knew nothing about radiation medicine but was invited to come to Japan because he had developed a good reputation as a scientific administrator. He was in no position to answer the kinds of questions that were being asked. How should the doses to the fishermen be calculated? What radioactive substances were in the fallout? What was the allowable level of contamination in tuna fish? How is radiation illness treated?

After breakfast we began a round of conferences and visitations that continued for three weeks. I spent the first hour reading the cables that had been going back and forth between Tokyo and Washington, from which I could sense the deterioration in the relationship between the two countries during the few days in which Japanese scientists, newspaper writers, and some officials had vented their fears and hatred against the US and its military forces in Japan. . . . This was the first serious interruption in the otherwise smooth relationship that had existed between the two countries since the end of World War II. It was suggested by some Americans that the fishermen were spying on the US bomb tests. Could this have been so? In the end there was no evidence to support the allegation. Were the fishermen as sick as claimed by some of the Japanese physicians? They were indeed sick and getting sicker by the day. Could the US

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The *Lucky Dragon* Incident

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provide medical assistance? Very little. After all, the Japanese had been through the atomic bombings of two cities only nine years before, and many of the physicians involved in treatment of the survivors were now treating the fishermen. . . .

Immediately after my arrival, the Japanese scientists expressed a desire to meet with me. Unfortunately, there was a considerable amount of rivalry between different groups of scientists. The staff at Tokyo University was at odds with the group at the National Institute of Health, and the local physicians in Yaizu were unhappy because some of the fishermen had been transferred to a hospital in Tokyo. The Japanese government had appointed an official committee to investigate the incident and recommend the steps that should be taken. The ambassador was advised that all communications of a scientific nature between the US and Japanese should be through that committee, which was chaired by **Rokuzo Kobayashi**, director of the Japanese National Institute of Health. I met with his committee on March 24, accompanied by Morton, and representatives of the Far East Command and the embassy. It was a difficult conference because very few Japanese scientists spoke English and the interpreters from the diplomatic offices were not familiar with many of the scientific terms being used.

RERF ARCHIVES

Tsuzuki

It was at that meeting that I had my first example of the misunderstandings that can arise from subtle errors in translation. **Masao Tsuzuki**, a physician who had been barred from his position as professor of surgery by General **[Douglas] MacArthur** because he had held the rank of rear admiral in the Imperial Navy (ie, he had been "purged" in the vernacular of the times), was in Yaizu on the day of our meeting, but left word with one of the committee members that he would return to his home by eleven o'clock that evening and that it was urgent that I call on him. That seemed a strange time for a visit, but since the message was transmitted by a member of the Japanese Foreign Office, arrangements were made for an embassy car to pick me up at the Sanno Hotel in time for our meeting in his home. When we arrived the house was dark, but our knock on the door wakened Tsuzuki, who received us in his kimono. It turned out that he did want to speak to me, and had left a message that I should *call* him at the designated time, not *call on* him. Fortunately he spoke enough English to understand the humor of the situation and we sat for more than one hour getting acquainted. That private conversation early in my visit was very fortunate because Tsuzuki became very relaxed as we sipped warm sake. I developed an understanding of him that was to prove useful in the difficult days ahead and would lead to a close friendship that lasted until his death in 1961.

Tsuzuki had been one of the most controversial of the Japanese scientists and had not shown a willingness to accept the assistance of the ABCC staff, represented by the director, John Morton. Tsuzuki was surprisingly frank in telling me of his resentment because the US occupation forces had confiscated a report he had written following his survey of the effects of the bombings in Hiroshima and Nagasaki. He had led the team of Japanese physicians that entered the two cities to provide medical assistance but he was never allowed to publish his report. [For descriptions of later expeditions in which Tsuzuki participated, see *RERF Update* 1(4):7–8, 1989; 3(4):12–3, 1991; 4(2):12–3, 1992.] I was familiar with that report, which actually had been translated into English and published, under his authorship, as an appendix to a report issued, but not widely circulated, by the US National Research Council. [Also see typescript dated 25 February 1946, attributed to the Special Committee for the Investigation of the Effects of the Atomic Bomb, National Research Council in Japan, 1946. RERF Library, Hiroshima.] It was true that Tsuzuki's report, which was a classic, did not receive the recognition that it deserved.

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Following the long day of conferences, first with the committee and then with Tsuzuki, it was clear to me that there were a number of separate but interrelated problems to be adessed:

1. The clinical management of the twenty-three fishermen: In my opinion there was little help to be offered. The US had no methods of treating acute radiation sickness that were not already known to the Japanese physicians.

2. The dose received by the fishermen: This included that delivered by external radiation because they lived for fourteen days on a ship covered with radioactive dust, and by internal radiation because the fallout particles were inhaled or ingested.

3. The concerns of the Japanese that the Pacific tuna would be contaminated.

By the time of my arrival, the Japanese physicists had already estimated the external radiation dose using crude instruments that were nevertheless quite reliable in their expert hands. However, they did not know how to estimate the dose delivered by radionuclides deposited in the bodies of the fishermen. In 1954, even the radioactive species present in bomb fallout were secret, but by the time I arrived, Japanese radiochemists had made progress in analyzing particles of fallout collected from the *Lucky Dragon*. However, their results were purely qualitative, and they were unable to separate nuclides that had similar chemical properties. They were fortunate to have the assistance of Professor **Kenjiro Kimura**, an internationally respected radiochemist who had attracted attention after the bombings by concluding, correctly, that the Nagasaki bomb utilized plutonium because he had found traces of that element in samples of soil collected from an area in which rainout had occurred. He had also discovered previously that he could produce U-237 in the laboratory by bombardment of U-238 with fast neutrons. In my first meeting with him he told me he had found U-237 in the "Bikini ashes," from which he concluded that the March-1 explosion involved the fission of U-238, which was still a secret known by only a few scientists back home.

In response to my cable to him, **Harley** [John Harley, chief of the radiochemical section at the Health and Safety Laboratory, HASL] advised that the isotopic content of the bomb debris would be similar to the tables of fission products that had been published in the open literature, from which the Japanese scientists concluded that Sr-90 was the isotope that would be of greatest danger to the fishermen.

I had requested samples of urine from the fishermen with the understanding that I would send them to Harley for analyses at HASL. The amounts of the various nuclides in the urine would give us a clue as to the quantities that were deposited in their bodies. On the basis of the results received from the laboratory I advised the committee that the amount of radioactivity deposited in the bodies of the fishermen was insignificant in relation to the dose received externally. This came as a big surprise to me because the men had lived for fourteen days in an environment contaminated with radioactivity to an unprecedented extent. In fact, the analytical results were so unexpected that I initially wondered about their validity, but any doubts were dispelled a few months later when one of the fishermen died of serum hepatitis and his tissues were analyzed for the major radionuclides by Professor Kimura. He confirmed our findings: only insignificant amounts of radioactivity were found in the body of the deceased fisherman.

Shortly after my arrival in Japan, General **Hull**, who had replaced Douglas McArthur as Supreme Commander of the Allied Forces in the Pacific, asked to meet me and some of his staff at their headquarters in the Dai Ichi building. By the time of our conference, the true importance of the BRAVO fallout seemed obvious to me: Thermonuclear weapons had the ability to contaminate tens of thousands of square miles with lethal amounts of radioactivity. This was what we at HASL had suspected but now we had the proof.

In my briefing of Hull I made it clear that I was in no position to discuss the full military and political implications of the Bikini fallout, but it was quite obvious that thermonuclear weapons were far more destructive than had been anticipated by the military planners with whom I had been discussing this possibility for the past two years. Hull didn't pursue this point, which was understandable, considering my position.

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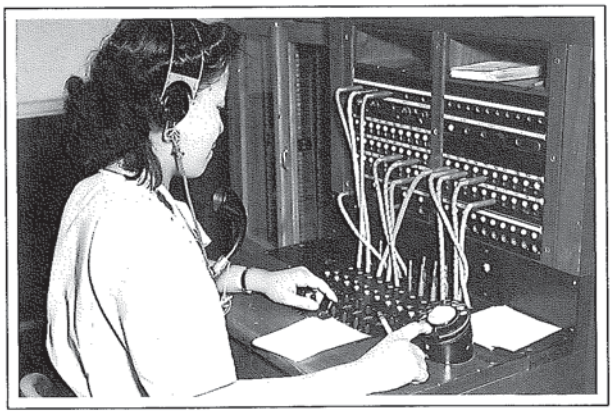
During the first week of my visit, much of the time of the embassy staff, as well as Morton and myself, was spent negotiating with the committee to get permission for American physicians to examine the fishermen. The Japanese scientists were reporting daily on their medical status. The condition of the men was said to be deteriorating: they had lost their hair, had developed skin ulcers from burns caused by the beta particles emitted from the fallout that deposited on their skin and, more ominously, their white blood counts were continuing to decline. The interest of the ABCC in having contact with the cases was understandable. ABCC was responsible for one of the largest medical follow-up studies in history, which was concerned with the delayed effects of exposure to radiation. The twenty-three Japanese fishermen were the largest group of persons suffering from the immediate effects of radiation since the bombings of World War II. In the United States, physicians who were interested in developing methods of treating acute radiation injury wanted to collaborate with the Japanese physicians. But the Japanese were adamant that they wanted no help in dealing with the patients, although they did welcome any assistance I could provide that would help them to understand the physical and radiochemical problems they were facing. ❑



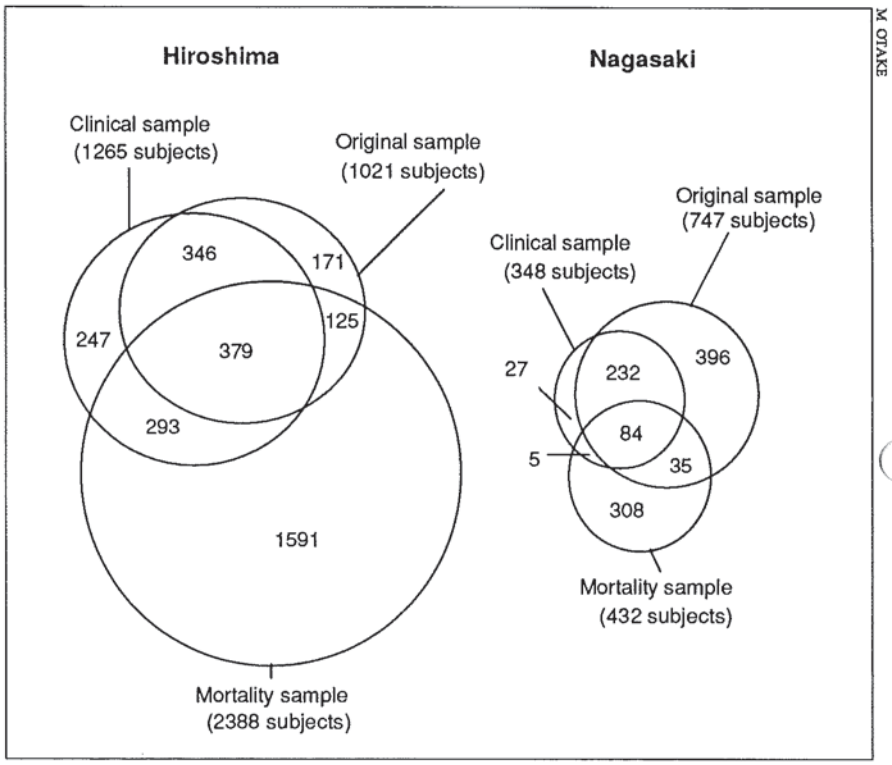
Morita-san at the ABCC switchboard in 1950

Connections to the Past

If you would like to contribute to *RERF Update*'s growing collection of historical articles, we would be glad to hear from you. Contact the editors of *RERF Update* by mail, fax (81-82-263-7279), or E-mail: 101126.3573@compuserve.com.

Facts & Figures

In-utero Sample Composition



M OTAKE

Documentation of the harmful effects of ionizing-radiation exposure on the development of the human brain consists largely, but not exclusively, of the many Atomic Bomb Casualty Commission–Radiation Effects Research Foundation (ABCC–RERF) studies of survivors exposed prenatally to the atomic bombings of Hiroshima and Nagasaki. Over the years, several different but overlapping samples of individuals prenatally exposed to the atomic bombings have been established (GW Beebe and M Usagawa, RERF TR 12-68). Differences among the three main overlapping samples reflect the different purposes for which they were initially chosen, such as the bases for clinical examinations or mortality surveillance. The original sample, used to assess changes in IQ, was established in Hiroshima in 1953 and in Nagasaki in 1955 from a variety of sources including the records of births occurring in these cities from 6 August (Hiroshima) and 9 August (Nagasaki) 1945 to 31 May 1946 and the reproductive histories of families enrolled in the genetics study undertaken at ABCC from 1948 to 1954. The original sample is composed of 1768 individuals (M Otake and WJ Schull, RERF TR 7-86). The clinical sample, established in 1959 and used to assess the risk of brain damage in a study of severe mental retardation, is composed of 1613 individuals exposed prenatally (JW Wood et al, ABCC TR 11-66). The last of the three main samples—the mortality sample—is composed of 2820 individuals and was used to investigate mortality among those exposed in utero via a large-scale, well-designed epidemiological study and to differentiate, if possible, between true exposure effects and systematic effects passed through the mother (H Kato and RJ Keehn, ABCC TR 13-66). The present mortality sample is composed of 2802 individuals, excluding 18 ineligible cases (Y Yoshimoto et al, RERF TR 4-88). ❑

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

A longitudinal study of growth and development among prenatally exposed atomic-bomb survivors. M Otake, Y Fujikoshi, WJ Schull, S Izumi. **RERF TR 19-92.**

Growth retardation due to exposure to the atomic bombings was evaluated for 455 individuals with nine repeated measurements of stature from age 10–18 yr using growth-curve analysis and either two covariates, Dosimetry System 1986 (DS86) uterine absorbed dose and postovulatory age (weeks), or three covariates, DS86 uterine dose, DS86 uterine dose squared, and postovulatory age. Of the several comparisons made by city, sex, DS86 dose, and postovulatory age, the largest significant difference was noted between males and females. However, no significant difference was found between Hiroshima and Nagasaki males or females except for all trimesters combined and for the first trimester in males only based on a linear-quadratic (L-Q) dose response. A highly significant growth retardation due to DS86 uterine absorbed dose (in gray) was observed in all trimesters combined and in the first and second trimesters of pregnancy. In the first trimester, all parameter estimates based on a linear (L) or L-Q dose-response relationship were negative in relation to DS86 uterine absorbed dose. The parameter estimates in the second trimester were negative for a constant term and positive for a L or L-Q term, but growth and development, ie, stature, showed an apparent declined trend dependent on DS86 uterine dose. The positive estimate tended slightly to be close to a control level of growth as dose increased. A significant difference was determined by a multivariate test statistic to determine whether a set of two or three parameter estimates including a constant term related to a L or L-Q dose-response relationship is signifi-

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Recent Scientific Publications

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cantly different from zero. Radiation-related growth retardation was demonstrable as a longitudinal result of the repeated measurements of stature for individuals 10–18 yr old. The dose effect in the third trimester was not significant using either the L or the L-Q model.

The first outward sign of the beginning of the secondary development of boys (the adolescent growth spurt) appears at age 14 yr on the average. Accordingly, growth, based on a linear dose-response relationship, was analyzed for 704 and 838 children with four repeated measurements of stature from ages 10–13 yr and 15–18 yr, respectively. An attempt by prematurity and maturity has been made by increasing the number of individuals, which in turn increases the statistical power. The retardation effect was conspicuous at ages 10–13 yr and through ages 15–18 yr. Growth retardation in the former group (10–13 yr) was highly significant for all trimesters combined but only suggestive for the first trimester. However, the latter group (15–18 yr) revealed a highly significant growth retardation for both the first and second trimesters. The relationship between birth weights and repeated measurements of stature in adolescence is discussed on the basis of results of growth-curve analyses.

Radiation-associated lung cancer: a comparison of the histologies of lung cancers in uranium miners and in atomic-bomb survivors. CE Land, Y Shimosato, G Saccomanno, S Tokuoka, O Auerbach, R Tateishi, SD Greenberg, S Nambu, D Carter, S Akiba, R Keehn, P Madigan, TJ Mason, M Tokunaga. **RERF TR 20-92.**

A panel of Japanese and American pulmonary pathologists reviewed tissue slides of lung cancers diagnosed among Japanese atomic-bomb survivors and American uranium miners and classified the cases according to histological subtype. Blind reviews were completed on 92 uranium miners and 108 atomic-bomb survivors, without knowledge of population, sex, age, smoking history, or level of radiation exposure. Consensus diagnoses were obtained with respect to principal subtype, including squamous-cell cancer, small-cell cancer, adenocarcinoma, and less-frequent subtypes. The results were analyzed in terms of population, radiation dose, and smoking history. As expected, the proportion of squamous-cell cancer was positively related to smoking history in both populations. The relative frequencies of small-cell cancer and adenocarcinoma differed significantly in the two populations, but this difference was adequately explained by differences in radiation dose or, more specifically, dose-based relative-risk estimates based on published data. Radiation-induced cancers appeared more likely to be of the small-cell subtype and less likely to be adenocarcinomas in both populations. The data appeared to require no additional explanation in terms of radiation quality (alpha particles vs gamma rays), uniform or local irradiation, inhaled vs external radiation source, or other population differences.

Approved Research Protocols

Relationship between radiation dose and infection by B and C hepatitis virus in the Adult Health Study. S Kusumi, K Kodama, K Nerishi, H Nonaka, M Akahoshi, M Akiyama, S Akiba, K Mabuchi, JB Cologne, K Shimaoka. **RERF RP 9-92.**

The relationship between liver disease and radiation exposure found in previous Atomic Bomb Casualty Commission/Radiation Effects Research Foundation (ABCC/RERF) studies can, at least partially, be explained by the increased prevalence of hepatitis B virus (HBV) carriers among the highly exposed survivors, although this increased prevalence is not clearly understood. Following the availability of the serum assay for the hepatitis C virus (HCV), the role of HCV in the development of hepatitis and other liver disorders has recently become the focus of attention. It is suspected that the HCV infection may play a major role in the development of liver diseases in Japanese. In the proposed study, AHS participants in Hiroshima and Nagasaki will be tested for HCV and HBV (i) to determine the HCV infection rate as a function of radiation dose and (ii) to identify HBV carriers and determine their HBe antigen levels. Also proposed is the follow-up of HCV antibody-positive subjects and HBV carriers to better understand the course of HCV- and HBV-related liver disorders among atomic-bomb (A-bomb) survivors. The HBV data to be obtained will help clarify the association of radiation dose with HBe antigen level, which is considered to be related to hepatitis B activity, and will help determine the seroconversion rate among the HBV carriers identified in this study and in past RERF HBV studies. Data obtained from this study will also enable us to analyze the risk of liver disorders associated with HCV and HBV infection among the A-bomb survivors.

Approved Commentary and Review

Estimating the temporal distribution of exposure-related cancers. RL Carter, R Sposto, DL Preston. **RERF CR 4-92.**

The temporal distribution of exposure-related cancers is relevant to the study of carcinogenesis. Statistical methods for extracting useful information from data on tumor latency periods, however, are not well developed. Distinguishing between incidence and latency and the contamination of background cases are two problems that must be addressed. In this paper, we present methods for estimating both the conditional distribution given exposure-related cancers observed during the study period and the unconditional distribution. The methods adjust for confounding influences of background cases and the relationship between latency period and incidence. Two alternative methods are proposed. The first is based on a structured, theoretically derived model and produces direct inferences concerning the distribution of interest but often requires more-specialized software. The second relies on conventional modeling of incidence and is implemented through readily available and easily used computer software. Inferences concerning the effects of dose and other covariates, however, are not always obtainable directly. We present three examples of the use of these methods and suggest criteria for choosing among them. The first approach was used, with a log-logistic specification of the distribution of interest, to analyze times of onset to bone sarcoma among a group of German patients who were injected with radium-224. Similarly, a log-logistic specification was used in the analysis of time of onset to chronic myelogenous leukemias among male atomic-bomb survivors. We used the alternative approach, involving conventional modeling, to estimate the conditional distribution of exposure-related acute myelogenous leukemias among male atomic-bomb survivors between 1 October 1950 and 31 December 1985. All analyses were performed using Poisson regression methods for analyzing grouped survival data.

Publications in the Open Literature

Accurate and rapid detection of heterozygous carriers of a deletion by combined polymerase chain reaction and high-performance liquid chromatography. J Asakawa, C Satoh, Y Yamasaki, S Chen. *Proc Natl Acad Sci USA* 89:9126–30, 1992. (RERF TR 22-92)

Radiation-related ophthalmological changes and aging among Hiroshima and Nagasaki

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Recent Scientific Publications

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A-bomb survivors: A reanalysis. M Otake, SC Finch, K Choshi, I Takaku, H Mishima, T Takase. *Radiat Res* 131:315–24, 1992. (RERF TR 18-91)

A simple and rapid method for HLA-DQA1 genotyping by polymerase chain reaction-single strand conformation polymorphism and restriction enzyme cleavage analysis. T Hayashi, T Seyama, T Ito, Y Kusunoki, Y Hirai, N Nakamura, M Akiyama. *Electrophoresis* 13:877–9, 1992.

Radiation-related small head sizes among prenatally exposed A-bomb survivors. M Otake M, WJ Schull. *Int J Radiat Biol* 63:255–70, 1993. (RERF TR 6-92)

Molecular cytogenetic approaches to biological dosimetry and to characterization of specific genetic changes in human tumors. JW Gray, AA Awa, A Kallioniemi, O Kallioniemi, JN Lucas, K Matsumura, D Pinkel, M Sakamoto, T Straume, M Vooijs, F Waldman, W Kuo. In: *Radiation Research: A Twentieth-Century Perspective. Vol II. Congress Proceedings.* San Diego, Calif, Academic Press, 1992. pp 166–71.

Colorectal cancer incidence among atomic bomb survivors, 1950–80. H Nakatsuka, Y Shimizu, T Yamamoto, I Sekine, H Ezaki, E Tahara, M Takahashi, T Shimoyama, N Mochinaga, M Tomita, R Tsuchiya, CE Land. *J Radiat Res* (Tokyo) 33:342–61, 1992. (RERF TR 15-92)

Childhood thyroid cancer in Belarus. I Shigematsu, JW Thiessen. *Nature* 359:681, 1992. (Letter)

Studies on immune responses to Epstein-Barr virus among A-bomb survivors. Y Kusunoki, S Kyoizumi, K Ozaki, JB Cologne, M Akiyama. In: *Low Dose Irradiation and Biological Defense Mechanisms.* Amsterdam, The Netherlands, Elsevier Science Publishers BV, 1992. pp 63–6

Dose-response analysis among atomic-bomb survivors exposed to low-level radiation. Y Shimizu, H Kato, WJ Schull, K Mabuchi. In: *Low Dose Irradiation and Biological Defense Mechanisms.* Amsterdam, The Netherlands, Elsevier Science Publishers BV, 1992. pp 71–4

The shape of the cancer incidence dose-response curve for the A-bomb survivors. M Væth, DL Preston, K Mabuchi. In: *Low Dose Irradiation and Biological Defense Mechanisms.* Amsterdam, The Netherlands, Elsevier Science Publishers BV, 1992. pp 75–8

Somatic cell mutations on erythrocyte GPA and lymphocyte TCR loci in Thorotrast patients. M Akiyama, S Umeki, S Kyoizumi, Y Kusunoki, Y Hirai, N Nakamura, JB Cologne. In: *Low Dose Irradiation and Biological Defense Mechanisms.* Amsterdam, The Netherlands, Elsevier Science Publishers BV, 1992. pp 335–8

Publications of Interest Using RERF Data

Criteria for the use of Sartwell's incubation period model to study chronic diseases with uncertain etiology. RD Horner, Samsa G. *J Clin Epidemiol* 45:1071–80, 1992

The risks of leukaemia and non-cancer mortality in the offspring of the Japanese bomb survivors and a comparison of leukaemia risks with those in the offspring of the Sellafield workforce. MP Little. *J Radiol Prot* 12(4):203–18, 1992

Fitting the Armitage-Doll model to radiation-exposed cohorts and implications for population cancer risks. MP Little, MM Hawkins, MW Charles, NG Hileth. *Radiat Res* 132:207–21, 1992

Using the Armitage-Doll model to evaluate radiation-induced cancer risk. MP Little, MM Hawkins, MW Charles, NG Hileth. Nuclear Electric Technology Division Report TD/ETB/ REP/7008, 1992. (Published in *Radiat Res,* see above listing.)

Current status of studies of the Japanese atomic bomb survivors. CR Muirhead. *Radiological Protection Bulletin* No. 138, 1993. pp 4–6

A comparison of the risks of childhood leukaemia from parental pre-conception exposure to radiation in the Sellafield and Dounreay workforces and the Japanese bomb survivors. MP Little. *J Radiol Prot* 11(4):231–40, 1991.

Preconception exposure risks in the Sellafield and Dounreay workforces and the Japanese bomb survivors. MP Little. Nuclear Electric Technology Division Report TD/RPB/REP/0077, 1991. (Published in *J Radiol Prot,* see above listing.)

Risks of radiation-induced cancer at high doses and dose rates. MP Little. *J Radiol Prot* 13(1):3–25, 1993 ❑

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