RERF **update** RERF

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

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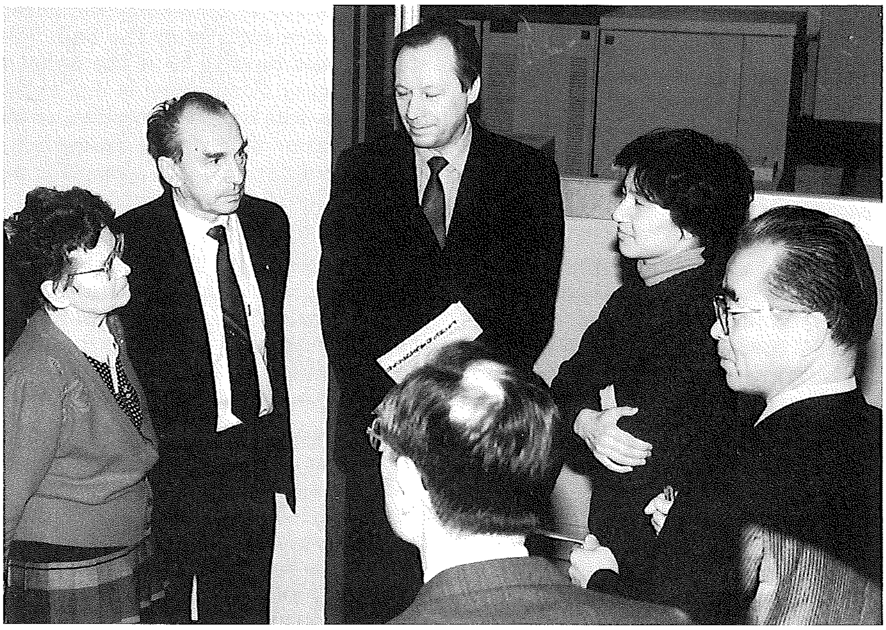
Soviets Discuss Follow-up of Populations Affected by Contamination in the Ural Mountains

In recent years, the Soviet Union has acknowledged incidents involving environmental contamination from military nuclear facilities in the southern Ural Mountains. One such incident that occurred four decades ago—the outflow of radioactive waste fluids from a plutonium reprocessing facility into a river—was first revealed to foreign scientists only in June 1990 at a Japan–USSR conference held in Tokyo. In late January, six Soviet scientists visited Japanese radiation research facilities, including RERF's Hiroshima Lab, to discuss the follow-up of this and other contamination incidents.

"The exposure data obtained from these Ural Mountain studies will probably be more relevant to some situations encountered as a result of the Chernobyl accident than data from Hiroshima and Nagasaki, where people were instantaneously exposed to high doses of atomic-bomb radiation," commented RERF Chairman **Itsuzo Shigematsu**.



J. TAKAYAMA

During their visit to the Hiroshima Laboratory, Soviet scientists tour RERF's Research Information Center. From left: N. Koshurnikova, L.A. Buldakov, E. Belyaev, RIC Acting Chief Jill Ohara, and Interpreter Kenji Ota. In foreground, RERF Permanent Director Yutaka Hasegawa.

The Techa River incident

From 1949 to 1952, partially processed waste fluids from a plutonium reprocessing facility were allowed to flow into the Techa River in the Russian Republic. Strontium-89, Sr-90 and Cs-137 in the wastes were released to the tune of 3 million Ci (110 PBq), resulting in what one Soviet technical report termed "massive radioactive environmental contamination."

Approximately 28,000 people living in 38 villages along the river "received substantial internal and external beta and gamma irradiation," with absorbed doses to bone marrow ranging up to 3 Gy, according to a report by **M.M. Kosenko, M.O. Degteva,** and **N.A. Petrushova**, Institute of Biophysics, Chelyabinsk Branch Office. Average doses are estimated at 0.46 Gy.

Since the river was the main source of drinking water for portions of the region, about 7,500 people from the upper reaches of the Techa were resettled. The water supply of other residents was converted to underground sources.

Followed up since 1951, the affected population has experienced a statistically significant increase in both acute and chronic granulocytic leukemia. Thirty-seven leukemia cases have been observed, most having occurred between the fifth and 20th year after exposure. Based on morbidity and mortality data, leukemia risk has been calculated as 0.48–1.10 per 10^4 person-year-Gy (using the absolute risk model and a linear dose-response function). The corresponding figure from A-bomb survivors in Hiroshima and Nagasaki is 2.43–3.49 per 10^4 person-year-Gy.

The Kyshtym accident

In 1957, a high-level radioactive waste storage tank exploded at a nuclear plant in Kyshtym, releasing a cloud containing Ce-144, Zr-95, and Nb-95, with an estimated radioactivity of 20 million Ci (740 PBq) and affecting 34,000 people. Individual doses ranged up to 0.9 Gy (average dose, 0.02 Gy). Dose assessments, based on environmental food-chain models, were not confirmed by direct measurements.

Leukemia morbidity has been studied among 1,054 individuals evacuated from the most contaminated areas (Sr-90 > 400 Ci/km^2), as well as from regions of lesser contamination (1–4 Ci/km^2 and 0.1–1 Ci/km^2). No leukemia risk estimates were made available. ❑

Soviet Visitors to RERF

L.A. Buldakov, deputy director, Institute of Biophysics, USSR Ministry of Public Health, Moscow
Evgeni N. Belyaev, deputy minister of health, Ministry of Health of the RSFSR, Moscow
Alexander V. Akleev
M.M. Kosenko
N. Koshurnikova
Marina O. Degteva
Institute of Biophysics, Chelyabinsk Branch Office, Chelyabinsk

Perspectives

The Future of Human Radiation Research

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

Under the title given above, a workshop was held from 4–8 March at Schloss Elmau, a quiet, beautiful place located in the Bavarian Alps area a few kilometers from the Austrian border. Cosponsored by the Commission of the European Communities, the US Department of Energy, the International Agency for Research on Cancer, and RERF, the meeting was an exciting opportunity for discussions between epidemiologists, statisticians, and experimentalists—particularly with respect to the mechanisms of carcinogenesis, and the role and interactions of these disciplines in elucidating those mechanisms.

The workshop was organized as a series of discussion sessions, with introductory remarks by session chairpersons and panel members invited for their specific expertise in the field under discussion. Six sessions were devoted to cancer—one each to leukemia, lung, breast, and thyroid cancer, one to cancer in general, and one to cancer from combined exposures. The two remaining sessions were devoted to a discussion of basic research approaches, and of analytical methodologies.

It was somewhat of a surprise to me that especially among Europeans so much attention was devoted to "outlying" studies such as those on the Sellafield/Seascale situation, and the more recently published alleged leukemia induction by naturally occurring radon presumably dissolved in fat cells in the bone marrow. One participant referred to this interest as one relating effects to "homeopathic doses," a rather interesting expression in this context! Another participant noted that risk factors for leukemia induction from paternal exposure such as in the Sellafield study would have to be of the order of 20% per gray if induction is due to the six-month dose before conception, or 2% if the lifetime dose is the determining factor (compared to the generally accepted value of 0.5% per gray).

As for the Sellafield study, it was reported that a study in the Dounreay area did not confirm the Sellafield/Seascale data, nor was any increased leukemia incidence found in the only other comparable area—that near the La Hague reactor in France.

There were many discussions involving agreements or discrepancies with RERF data. A very interesting analysis, comparing lung cancer data among uranium miners and among A-bomb survivors, was presented by **Wolfgang Jacobi** (Neuherberg, FRG), who stressed essential differences in dose response and cancer cell types between the two groups of studies. Another interesting discussion was that on the various studies concerning the relationship between radiation exposure and leukemia, in addition to the two mentioned earlier. It was pointed out that there are still large unresolved uncertainties, e.g., in the value of the dose-rate reduction factor.

Some of the workshop's most interesting discussions took place during the sessions on basic science and statistics. It is clear that we are seeing a growing rapprochement between basic scientists and those with a more statistical or epidemiological bent. There were a number of instances in which one group suggested a hypothesis based on its own insights that would be testable by the other. The growing emphasis on mechanistic rather than purely descriptive models, e.g., to characterize dose-response relationships or risk projections, may well benefit from the kind of multidisciplinary approaches mentioned in many of the workshop sessions. Approaches such as the rapid development of new ideas on carcinogenesis (e.g., the one on radiation interactions with cellular growth control factors I referred to in my last editorial) may make it possible to arrive at a more solid basis for the prediction of low-level radiation effects than the largely descriptive models used so far. ❑

News Briefs

✓ Meeting of the Minds

In mid-January, three former RERF chiefs of research happened to meet at the University of Wisconsin's McArdle Laboratories where current RERF Chief of Research James Trosko presented a lecture honoring one of their colleagues. From left, Roswell K. Boutwell (1984–86), Seymour Abrahamson (1988–90), Kelly H. Clifton (1980–82), and Trosko.

✓ Annual Scientific Council Meeting Convenes in Hiroshima

The long tradition of consultative gatherings to review the progress of RERF's research program continued with the convening of the 18th meeting of the Scientific Council, 25–27 March.

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

Observers at the council meeting included: **Hiroyuki Doi**, Japanese Ministry of Health and Welfare; Assistant Secretary of Energy for Environment, Safety and Health **Paul L. Ziemer** and **Milton Eaton**, US Department of Energy; **John E. Burris** and **Charles W. Edington**, National Research Council; **Seymour Abrahamson**, University of Wisconsin; and **Lon R. White**, US Department of Health and Human Services.

✓ Japanese Government To Establish Memorial Facilities

The Japanese government will request that RERF and other radiation research and medical institutes in Hiroshima and Nagasaki cooperate in the creation of memorial facilities for the victims of the atomic bombings. Scheduled to open in 1995—the 50th anniversary of the bombings—the multi-purpose centers are an expression of condolence from the Japanese government, the first of this type to receive government sponsorship. The facilities will be centers for research in radiation medicine and also will collect, store, and disseminate information related to the bombings, and will assist in efforts to care for radiation-exposed people.

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Issues

Neutron RBE for A-bomb Survivors

RBE values near the maximum observed in radiobiological experiments might be the cause for intercity differences in dose-effect curves.

by H.H. Rossi, Professor Emeritus, and M. Zaider, Department of Radiation Oncology, Columbia University, New York, N.Y.

The DS86 attributes to neutrons a much smaller fraction of the absorbed doses at Hiroshima and Nagasaki. Nevertheless, the neutron component must have augmented the biological effects. We have shown that this contribution should be minor—assuming a maximum neutron RBE of about 50 (H.H. Rossi and M. Zaider, *Health Phys* 58:645–7, 1990). In that analysis, we employed an approximate treatment involving stated simplifications. In view of the importance of the subject, it is appropriate to provide a more complete analysis. Although this does not materially change the conclusions of our previous report, it shows that RBE values near the maximum observed in radiobiological experiments can be a cause of intercity differences.

Some attempts to account for the biological effectiveness of neutrons in the Japanese cities have assumed various dose-independent values of neutron RBE. As pointed out by **Seymour Abrahamson**, this conflicts with the well-established fact that neutron RBE depends on absorbed dose, i.e., the degree of effect (*RERF Update* 1(1):3, 1989a; *RERF Update* 1(2):8, 1989b). Abrahamson also suggested that a suitable source of appropriate values may be the results of studies involving chromosome aberrations in human lymphocytes (D.C. Lloyd et al., *Int J Radiat Biol* 28:75–90, 1975; D.C. Lloyd et al., *Int J Radiat Biol* 29:169–82, 1976). These are the only human data that seem sufficiently accurate for numerical analysis, and they have also been considered to be typical of RBE relations founded in radiobiology. For these reasons, they have been recommended as the basis of the selection of the quality factor, Q, in radiation protection (*The quality factor in radiation protection*, Bethesda, Md., ICRU, 1986).

The chromosome data were analyzed according to the frequently employed formula:

$$\varepsilon(D) = \alpha D + \beta D^2 \ , \qquad (1)$$

which has often been termed the linear-quadratic (L-Q) relation. $\varepsilon(D)$ is the yield of aberrations at the absorbed dose, D, and α and β are constants. In general, both constants depend on radiation quality.

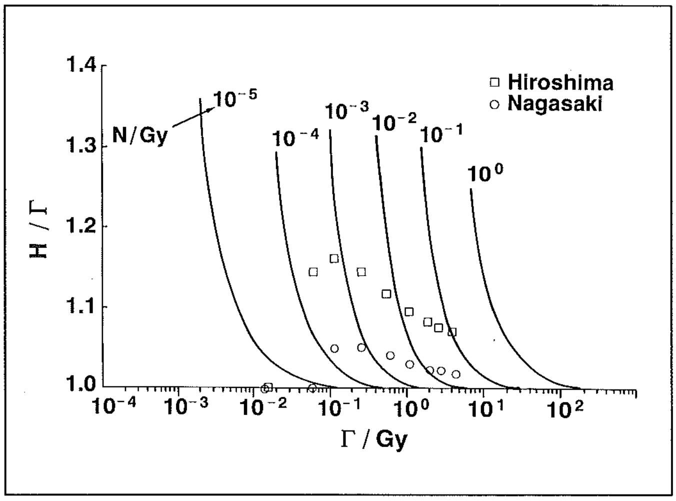
In our previous publication (Rossi and Zaider, 1990), we adopted the usual simplification of ignoring the quadratic term for neutrons with the consequence that at a very high absorbed dose the RBE of the mixed radiation field was calculated to be less than 1. Here the quadratic component will be included.

It is uncertain whether the coefficient, β, for the quadratic component has different values for neutron and gamma radiation. There are reports that β is greater for high-LET radiations (A.M. Kellerer et al., *Radiat Res* 65:172–86, 1976; E.J. Hall et al., *Radiat Res* 52:88–98, 1972). On the other hand, an analysis of the chromosome data indicated that β may be less for neutrons, although there seemed to be no statistically significant indication against equal values of β for both 0.7-MeV neutrons and gamma radiation (M. Zaider and D.J. Brenner, *Radiat Res* 103:302–16, 1985). Here the common value of 0.056 Gy^{-2} will be employed. Adopting different values would not affect the calculations appreciably.

Another factor ignored in our previous publication (Rossi and Zaider, 1990) is the synergism between neutrons and gamma radiation (Zaider and Rossi, *Radiat Res* 83:732–9, 1980). Despite its minor importance, it will be included here.

Finally, there is the phenomenon of saturation which is difficult to deal with (Rossi and Zaider, in: *Quantitative mathematical models in radiation biology*, Berlin–Heidelberg, Springer Verlag, 1988, pp. 111–8). It is generally unimportant at absorbed doses of less than several gray and has not been included in this analysis.

It should again be stressed that adopting the L-Q formulation does not necessarily imply that such quantities as cancer mortality depend on radiation dose according to



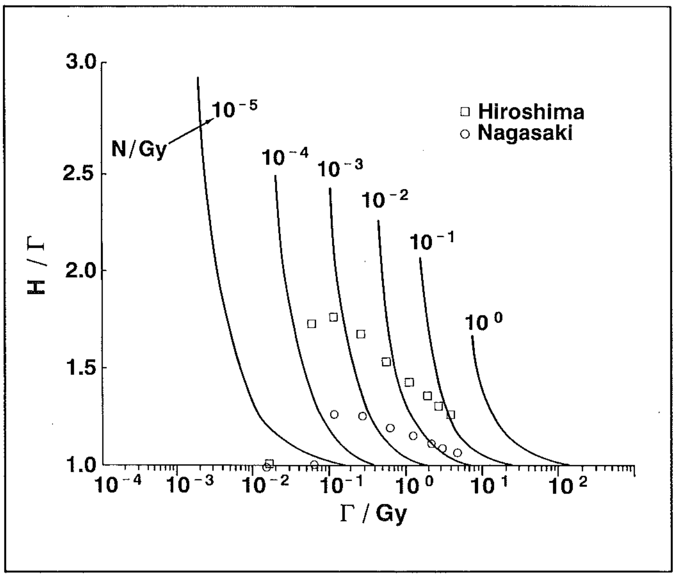


***Figure 1 (top). The ratio of* H, *the equivalent gamma-ray dose, and,* Γ, *the actual gamma-ray dose that is augmented by a neutron dose,* N. *The abscissa is* Γ. RBE_M = 74. *The squares and circles correspond to the correlated gamma and neutron doses to the bone marrow in Hiroshima and Nagasaki, respectively. In Figure 2 (bottom), the* RBE_M = 200.**

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Neutron RBE

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the L-Q relation. The equations given here should be considered to apply to cellular lesions following which there may be complicated interactions leading to manifest biological effects. If, following production of lesions, these interactions are independent of the type of radiation applied, their RBE is the same as that for the lesions, although the dose-effect curves may have various shapes (H. Rossi, in: *Proc 8th Symp on Microdosimetry*, Luxembourg, CEC, pp. 539–49, 1982).

Numerical relations

It is convenient to make a slight change in the notation employed in our previous publication (Rossi and Zaider, 1990). The basic relations are

$$\varepsilon(\Gamma) = g\Gamma + c\Gamma^2, \tag{2a}$$

and

$$\varepsilon(N) = nN + cN^2, \tag{2b}$$

where Γ and N are the absorbed doses of gamma and neutron radiations, g and n the coefficients of the linear terms, and c the common coefficient for the quadratic term. The values given in the statistical analysis (Zaider and Brenner, 1985) of the observational data are

$$g = 1 \cdot 10^{-2}\ \mathrm{Gy}^{-1},$$
$$c = 5.6 \cdot 10^{-2}\ \mathrm{Gy}^{-2},$$

and

$$n = 0.74\ \mathrm{Gy}^{-1}.$$

The gamma radiation is from Co-60 and the neutrons are fission neutrons with $\bar{E} = 0.7$ MeV. These may be considered to be the energies most nearly representative of the spectra in the Japanese cities.

The ratio n/g indicates that RBE_M (the maximum RBE at very low doses) is 74. In our previous analysis (Rossi and Zaider, 1990), we employed the figures provided by Lloyd et al. (1975, 1976) that make RBE_M equal to about 52.

The principal quantity to be calculated is H, the gamma radiation dose that has the same biological effect as mixtures of gamma radiation and neutrons:

$$\varepsilon(H) = gH + cH^2 = g\Gamma + nN + c(\Gamma + N)^2. \tag{3}$$

The interaction between the two radiations causes c to be multiplied by the square of the sum of the doses rather than by the sum of the squares (Zaider and Rossi, 1980).

The solution of equation 3 is

$$H = \left(\frac{1}{2c}\right)\left\{\sqrt{g^2 + 4c\,[\,g\Gamma + uN + c(\Gamma + N)^2\,]} - g\right\}. \tag{4}$$

Figure 1 presents H/Γ vs Γ for various values of N. It thus shows the ratio of the effective gamma-ray doses and the actual gamma-ray doses when the latter are augmented by various neutron doses. In this form, the data can be used for a range of combinations of the two radiations.

As an example, data for bone marrow doses at Hiroshima and Nagasaki are shown in Figure 1 in the same representation. The mean neutron and gamma doses, as well as attenuation factors, have been taken from Y. Shimizu et al. (*Radiat Res* 121:120–41, 1990).

Discussion

It appears that significant differences in the dose-effect curves in the two cities cannot be attributed to neutrons on the basis of DS86 and an RBE_M (the maximum RBE equal to n/g) of about 74.

As given here, the importance of neutrons is somewhat greater than in Rossi and Zaider (1990). This is primarily due to the somewhat different values of the coefficients g, n, and c given in Zaider and Brenner (1985) and in Lloyd et al. (1975, 1976).

The neutron contribution to the biological effect is small even though the neutron RBE reaches high values at low doses. However, these were received at great distances where the *relative* neutron dose was very low. Near ground zero, the neutron doses were a greater fraction of the total, but they were so high that the RBE is low.

It seemed desirable to determine whether a substantial increase in RBE_M could cause an appreciable contribution of neutrons to the observed effects. The maximum RBE values observed in experimental radiation carcinogenesis are near 200 (ICRU, 1986). An equivalent change increases n from 0.74 Gy^{-1} to about 2.0 Gy^{-1}. As shown in Figure 2, this does indeed lead to significantly larger ratios of H/Γ.

If it can be shown that such large RBE values lessen any discrepancies between the Hiroshima and Nagasaki data, an important implication is that the Q values recommended for radiation protection by the ICRU (1986) are too low and that in protection against high-LET radiations, and especially neutrons, Q should be substantially increased.

Author's note: In commenting on an earlier manuscript, **W.K. Sinclair** (personal communication, NCRP, Bethesda, Md., 1990) has pointed out that large RBE values are implied in a paper by **D.L. Preston** and **D.A. Pierce** (*Radiat Res* 114: 437–66, 1988) in their Table XIV. A simple extrapolation of the city effects suggest that RBE values of about 40 and 90 for leukemia and nonleukemia, respectively, would be required to eliminate the city differences. This table is based on the assumption of a dose-independent RBE and even larger values should result from the kind of analysis presented here.

Although Sinclair and we are aware of uncertainties in this deduction, it appears quite probable that the subject of RBE requires further attention and that its dependence on absorbed dose should be a central feature of further investigations. ❑

Editor's note: Preston and Pierce have discussed direct estimates of the RBE based on models for the joint effect of gamma and neutron radiation. Results show that the maximum likelihood estimates for the nonleukemia RBE is about 12, and for leukemia, the RBE is about 30 (Preston and Pierce, RERF TR 9-87, Figure 5). The estimates have very large standard errors.

News Briefs

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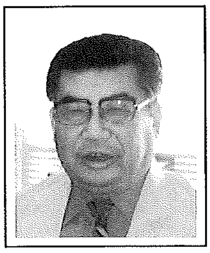
✓ In Memoriam: Hisao Sawada

On 7 February, **Hisao Sawada** passed away at the age of 66. He joined ABCC's Department of Medicine in 1950 and became the first deputy chief of that department in 1975 when ABCC was reorganized into RERF. In 1984 and 1985, he served concurrently as chief of the departments of Research Support and Medicine. When he retired in 1986, he was Research Support Department chief.



Sawada

✓ Mission to Moscow Discussed Chernobyl Assistance

Itsuzo Shigematsu, RERF chairman, and **Atsushi Kuramoto**, director of Hiroshima University's Research Institute for Nuclear Medicine and Biology, took part in a meeting of Japanese and Soviet experts in Moscow in early March. The mission, organized by the Japanese Ministry of Foreign Affairs, discussed medical cooperation and relief measures for the people affected by the Chernobyl nuclear power plant accident. The Japanese government has already contributed about US $20 million to the program through the World Health Organization. The visit included a trip to Obninsk, the site chosen for WHO's planned International Center for Radiation Health Issues.

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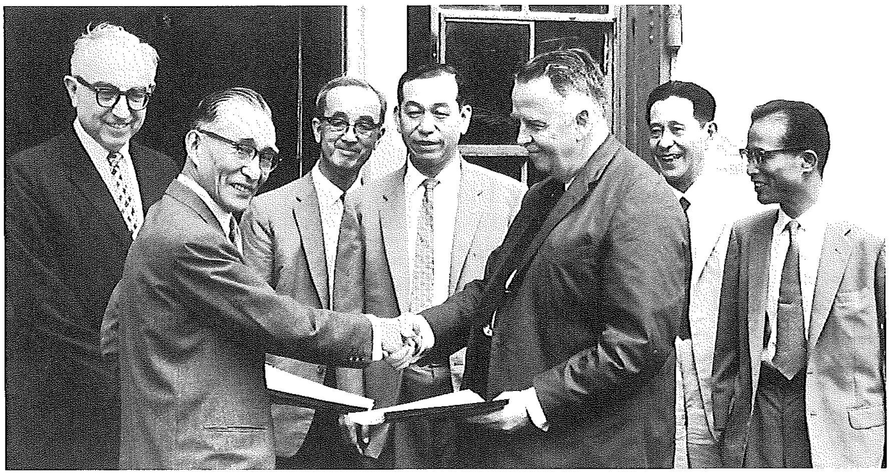
Looking Back

Darling Directorship Spanned 15 Years of Change

In 1957, George B. Darling succeeded Robert Holmes as Atomic Bomb Casualty Commission director, a position he served in until his retirement in 1972. During the longest tenure of any director, Darling presided over a fundamental change in ABCC and a redirection of its program.

by Seymour Jablon, Expert, US National Cancer Institute



In August 1958, the first written agreement between the US and Japan to formalize cooperative research endeavors was exchanged to mark the beginning of the Life Span Study. Above, beginning second from left: JNIH Director Keizo Nakamura, ABCC Associate Director Masanori Nakaidzumi (1956–64), Japanese Public Sanitation Bureau Chief Takehisa Omura, George Darling, ABCC Associate Director Hiroshi Maki (1948–75), and Japanese Public Sanitation Bureau Planning Section Chief Taisuke Kawasumi. At left, Darling, ABCC's fifth director. He served from June 1957 until December 1972, the longest tenure of any ABCC director.

Before 1957, ABCC studies of the atomic bomb survivors had resulted in only a handful of significant publications.

Jim Neel and **Jack Schull**'s classic work (1956) on the effect of exposure to the atomic bombs on pregnancy terminations in Hiroshima and Nagasaki had demonstrated that, although radiation exposure may well have caused mutations, the number was not large enough to be detectable even from the examination of tens of thousands of births in the two cities. By 1952, it had become clear that radiation exposure was a cause of leukemia (**Jarrett Folley** and colleagues), and in the same year **George Plummer** published the first report concerning mental retardation accompanied by small head size in children whose mothers had been exposed to atomic bomb radiation during pregnancy. As early as 1949, **David Cogan** had reported the occurrence of radiation-induced cataracts in some A-bomb survivors. Malignant diseases other than leukemia, however, had not yet been reported and, as we know now, had barely started to occur in the year George Darling arrived in Japan and would not be recognized until several years later.

In 1972, when Darling left Japan, the ABCC had become established as the major source of information concerning radiation carcinogenesis, effects on the fetus, and chromosomal aberrations; the estimates of cancer risk following radiation exposure contained in the National Academy of Sciences report on the biological effects of ionizing radiation—BEIR 1972—were based, in large part, on the data published and analyzed by ABCC. Similarly, the 1972 publication of UNSCEAR's *Ionizing radiation: levels and effects* began almost every one of the subsections on different forms of cancer with the data on A-bomb survivors.

The evolution of ABCC

How did this happen? Why did ABCC—an organization whose productivity had been so low that some contended it had done all it could do and should be phased out—become the preeminent source of information on the biological effects of ionizing radiation? It was not the doing of a single person; the contributions to planning, organization, and staffing by **R. Keith Cannan**, chairman of the National Research Council's Division of Medical Sciences, and by **Thomas Francis Jr.**, the head of the University of Michigan's Department of Epidemiology, were of strategic importance. But planning and organization alone bear no fruit; the organization must be focused on the task, and the plans must be realized. Darling saw clearly what needed to be done; he was prepared to devote to the task the many years that he knew would be needed, and he brought the ABCC from its former condition to its present place as the foremost source of information about the effects of radiation on humans.

George Darling was a graduate of the Massachusetts Institute of Technology, and received a Doctorate of Public Health from the University of Michigan. After some years with the Michigan Department of Public Health, he joined the Kellogg Foundation. Following the end of World War II, he became vice president for medical affairs at Yale University and later, when in a reorganization that position was abolished, Professor of Human Ecology. He held that position until 1957, when he was persuaded by Cannan that there was an opportunity to make important contributions to science, to humanity, and to

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Editor's note: The author's long association with ABCC–RERF began in 1955 when he journeyed to Japan as a member of the Francis Committee, which reviewed ABCC's research program. Jablon also was RERF's Statistics Department chief, 1960–63 and 1968–71. He later served as the National Research Council's associate director for international affairs from 1978–87.

15 Years of Change

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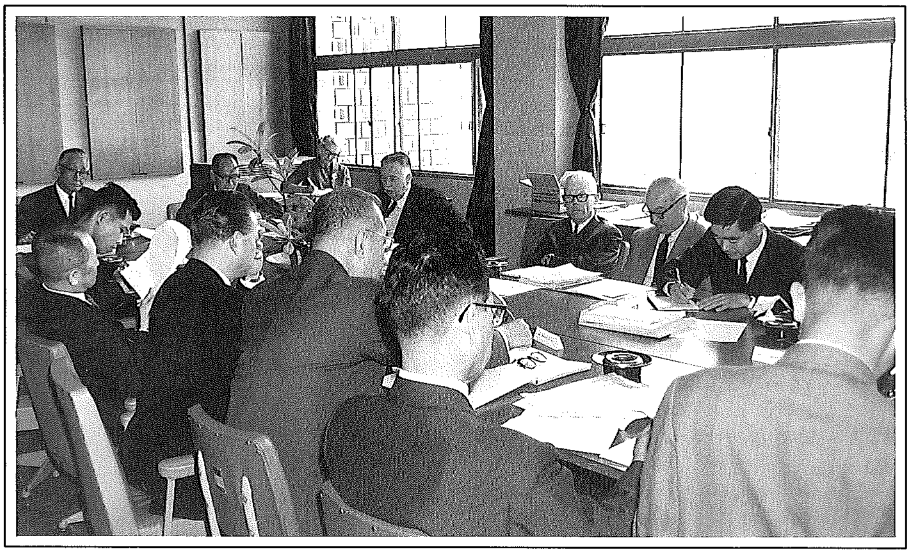
international understanding, at ABCC.

What, specifically, did he do? What were his accomplishments? Several were of critical importance.

He ensured the continuity of the program

In the earliest days of ABCC, although the work of **H.J. Muller** and others had shown the importance of genetic studies and it was clear that one of the mutagenic effects of radiation might be an increase in congenital malformations, little was known about possible somatic effects. There had been reports of shortened life span following radiation exposures, and this led to the hypothesis, since discarded, of "accelerated aging." Clinical studies at ABCC were begun without clear objectives. In consequence, various researchers developed their own agendas. With a few exceptions, physicians from the US came for two-year "tours," each with his or her own idea about what might be useful to do. Plans for observations changed, and the idea of establishing a specific cohort had not taken root.

The Francis Committee's report (1955) had emphasized the critical importance of continuity. An important element of such a plan was the establishment of fixed, well-defined groups of exposed and non-exposed persons that would permit determination of disease rates and tracking of changes over time. Darling took the Francis recommendations seriously and was adamant that the program not be changed to suit the ideas of each new chief of medicine or pathology.



Pathology kyogikai *(joint consultative meeting), April 1967. Seated on the far side of the table, from left: JNIH Director Keizo Nakamura, unidentified man, Darling, Albert Hilberg (US Public Health Service), R. Keith Cannan (US NRC), and ABCC Interpreter Kenji Yorichika. At left, reading a manuscript, Takemune Soda, director of the Japanese Institute of Public Health.*

He coordinated the research programs

In the early years of the program, there was no effort to achieve coordination although it is evident that pathology studies could provide support to the clinical examination program, and vice versa, only if the two programs were focused on the same persons.

Based upon the Francis Committee's recommendations for a Unified Study Program, the subjects for the clinical examination program were chosen to be a subset of the cohort upon which the life span mortality study was based. The autopsy, tumor registry and leukemia registry programs were also based on that cohort. Even the biochemical genetics program was able to supplement the cohort of children derived from the original genetics studies with additional children, offspring of members of the life span cohort, since they could be ascertained from the official mandatory family records, known as *koseki.*

Above, gathered for a Scientific Advisory Committee meeting in 1963 were: from left, Thomas Francis Jr., ABCC Interpreter Kenji Joji, Darling, and ABCC Associate Director Masanori Nakaidzumi. Seated opposite Darling: JNIH Director Keizo Nakamura. JNIH Nagasaki Branch Laboratory Director Isamu Nagai is seated at the end of the table.

He emphasized the importance of collaboration with Japanese scientists

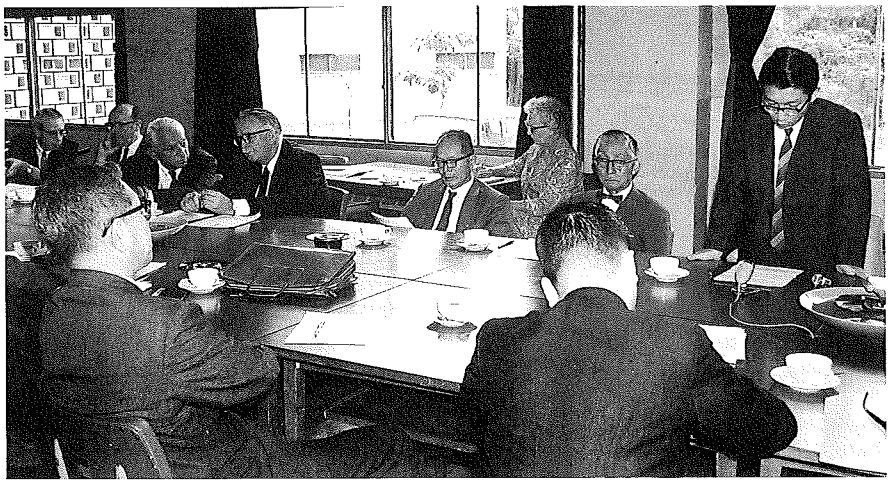
When the ABCC was first established in the late 1940s, the Allied Occupation of Japan was still in place, and the Japanese people were busy trying to rebuild their country and grow enough food to survive. The ABCC drew its support from the Occupation forces and shared in its prestige and commanding position. In short, ABCC did whatever it wanted to do.

As the years passed, Japan's recovery and the end of the Occupation combined to make anomalous the position of ABCC as a foreign institution studying Japanese in Japan. Although it would be many years before the anomaly was resolved by the abolition of ABCC and the establishment of RERF in 1975, it was evident to Darling that foreigners could not, in the long run, maintain the studies without the collaboration of Japanese scientists, government agencies, and universities.

In the earliest years, ABCC had the help of Japanese associate directors (**Hiroshi Maki** and **Isamu Nagai**), but Darling brought in other scientists—many who were retiring professors—as department heads and consultants. The dean of Japanese radiologists, **Masanori Nakaidzumi**, for example, was able to smooth relations between ABCC and the Japanese radiological community; **Keizo Nobechi**, an eminent epidemiologist, organized a department of epidemiology and brought in several young epidemiologists (including **Hiroo Kato**, who recently retired after 30 years of service to ABCC–RERF).

It was impossible for ABCC to maintain itself indefinitely with a staff of foreigners who came and went at two-year intervals. On the other hand, it was futile to expect young Japanese researchers in any discipline to be willing to come to ABCC for long periods or short, except at the behest of their professors. Darling recognized the problem and effected a solution.

As a result, ABCC acquired a group of young and energetic Japanese biochemists, geneticists, pathologists, epidemiologists and biostatisticians, without whom the program would have perished.



Above, Katsuhiko Yano of ABCC's Department of Medicine (far right) reports to the Adult Health Study* kyogikai *in 1967. Facing the camera, from left, Gilbert Beebe, Kenneth Johnson, ABCC Department of Medicine Chief Benedict Harris, Darling, unidentified man, and JNIH Director Keizo Nakamura. In the photo at left, Department of Medical Sociology Chief Scott Matsumoto, left, receives a certificate for 10 years of service to ABCC (1957–67) from Darling.

He integrated the program with Japanese institutions

When the ABCC was established in 1948, it had been decided that the Japanese National Institute of Health (JNIH), an organization of the Ministry of Health and Welfare, would be the corresponding agency to ABCC. Branch laboratories of JNIH were established in both Hiroshima and Nagasaki. These laboratories functioned in close harmony with the ABCC research departments.

Darling, however, in consultation with the JNIH director, decided to strengthen and formalize the relationship. Formal, bilingual research protocols were prepared and reviewed not only by ABCC but also by JNIH for the major studies: the Life Span Study, the Adult Health Study, the pathology program, studies of the survivors' offspring, and others. Joint consultative committees, or *kyogikai* were established for each of the major programs. A senior Japanese advisory committee was formed, which was chaired by the JNIH director and included in its membership, among others, the presidents of the universities in the two cities, medical school deans, and officials of the national government and of local medical associations.

He inaugurated bilingual publications

The earliest publications from the ABCC, mostly written by the foreign staff, were in English and usually appeared in American journals. This emphasized the foreignness of ABCC and provided fuel for the activists who opposed the organization on the grounds that the Americans were treating the Japanese sufferers like "guinea pigs," were not interested in treating the survivors, were hiding the results of the studies and were using the research as part of the American government's preparation for a new imperialist war.

As one of his first acts, George Darling ruled that *all* publications would appear first in bilingual format, as ABCC technical reports. The authors were free to publish in either Japanese or English (or any other language) only *after* the report had been accepted as a bilingual technical report. An enormous burden on the translators, this was part of the reason that publication of technical reports was often delayed. But the action was critically important in demonstrating the institute's dedication to open publication and to making the results of the studies available to Japanese as well as the rest of the world.

It is interesting to note that, after 1975, when the ABCC was succeeded by RERF, with a Japanese chairman and a binational board of directors and equal representation of Japanese and American citizens, bilingual publication of technical reports seemed less essential. Many reports are now printed only in English with a translated summary.

He recovered the Joint Commission materials

The US Joint Commission for the Investigation of the Atomic Bomb in Japan, which had been active in 1946 and had been directed by the military, had, as a matter of course, deposited pathology specimens, reports, and lists of data at the Armed Forces Institute of Pathology (AFIP) in Washington. Perhaps at that time there was no real alternative—the Japanese people and universities were devoting their energies to rebuilding and reestablishing their institutions and could spare little attention for storing and safeguarding the medical data and specimens. There were, however, repeated accusations that the Americans had removed the materials from Japan for nefarious purposes, and the situation became a continuing source of friction with some elements of Japanese society. Darling was determined to remove this irritant and finally succeeded. The pathology slides and other materials were returned in 1969 to the universities in Nagasaki and Hiroshima.

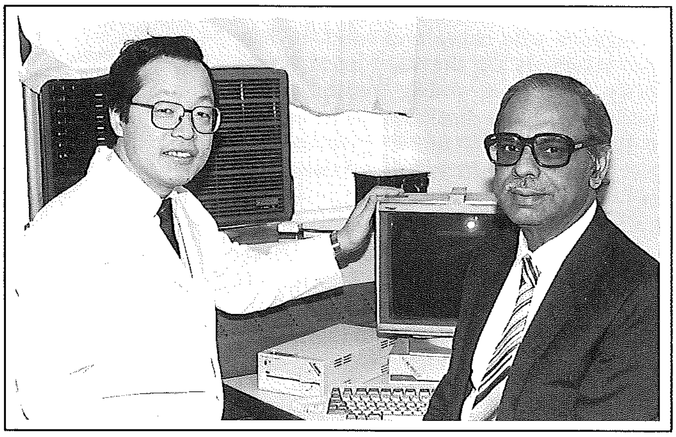
The ABCC was a unique research organization, and no one person deserves exclusive credit for its success. Many persons made critically important contributions and those of **Shields Warren** and, particularly, **R. Keith Cannan**, were essential. But, while foresight, plans and preparation were important, the task of execution remained. Without the skillful, thoughtful, patient, and dedicated efforts of George Darling, it is doubtful that ABCC could have achieved the success that it had or could have survived as long as it did. ❑

See the next issue of RERF Update *for recollections of George Darling written by former ABCC Associate Director* ***Hiroshi Maki*** *and former ABCC–RERF Translation Section Chief* ***Kenji Joji.***

Visiting Investigator Discusses High-background Radiation Study in Southern India

Along a narrow, 160-km-long strip of coastline in southwestern India, a sizable population lives among scattered, naturally occurring deposits of monazite, ilmenite, rutile and other rare earth elements. The area having the highest concentration of these sands supports about half a million inhabitants who receive an average estimated yearly exposure of 300–400 mR.

This population and the newly initiated Natural Background Radiation Cancer Registry (NBRCR) were the focus of **P. Gangadharan**'s two-week stay at RERF's Hiroshima Lab. An investigator at the registry, which is part of the Regional Cancer Centre in Trivandrum, the capital of Kerala State, Gangadharan consulted with RERF staff and outlined the registry's research efforts, noting that "the area provides unusual opportunities to study the effects of low-level background radiation on human populations."



J. TAKAYAMA

RERF Clinical Studies Chief Kazunori Kodama and visiting researcher P. Gangadharan discuss the low background radiation study in the Indian state of Kerala.

RERF Permanent Director **William J. Schull** agrees. "The size of the population under scrutiny and the annual doses involved make the Kerala study potentially the most informative of the various high background studies that have been initiated."

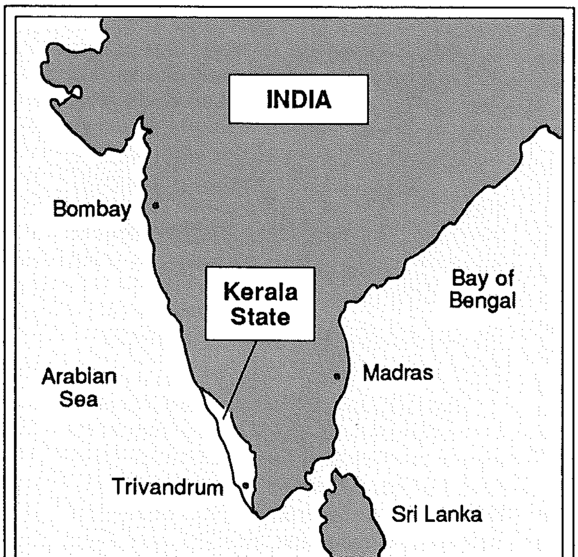
Alpha, beta and gamma exposures result from the sands' naturally occurring thorium and uranium, and internal deposition takes place via ingestion and inhalation. Although Gangadharan says that most of the population receives either no exposure or "normal" exposures of 100 mR annually, approximately 25% receive >500 mR per year. Of these, about 9% receive >1,000 mR per year and about 1% receive >2,000 mR annually.

Initiated in late 1990, the NBRCR program is concentrating on an administrative subdivision located about 105 km north of Trivandrum, where the coastal area has the highest concentration of monazite sands.

"In the state of Kerala, there is a strip of land almost 50 km long and not more than 5 km wide between the sea on the west and the backwaters on the eastern side," explained Gangadharan. "This narrow strip of land has the maximum concentration of radioactive sands."

The monazite deposits—together with other rare earths—occur in patches along the coast that have been mined for decades, yielding thorium for gas lantern mantles and titanium oxide used in producing pigment. However, the area's half a million people are primarily engaged in fishing, agriculture, and related activities.

The study's objectives are: 1) to measure cancer incidence in the area, 2) to assess whether the incidence differs from that of other population groups, 3) to determine the incidence pattern in the area, 4) to compare the incidence pattern with that of other areas, and 5) to establish whether incidence and incidence pattern are related to the background radiation, and, if so, whether there is a dose effect.



Kerala State in southern India

Investigators have faced some problems in the early stages of their study. "The available medical services and facilities are far below the required level needed to run a cancer registry using standard registry system methodology," Gangadharan admitted. "An active registration system has to be developed in order to record cancers occurring among the population.

"For meaningful data analysis, we need matching information on a base population," he continued. "The usual national census data does not provide the data required for such purposes, thus a population characteristics census was devised and is being implemented to supply information unavailable from national census data." For example, the registry questionnaire includes life style issues, including habits such as tobacco smoking and the chewing of *pan*, a mixture of betel leaf, betel nut, and lime.

An area distinguished by low birth and death rates and a literacy rate of 80%–90% (compared with the national average of about 50%), the average life expectancy for Kerala State is about 70 years—10 to 15 years longer than the national average.

Aiming to identify prevalent cancer cases before recording incident cases in the study's first phase, a field staff—consisting of a sociologist, a statistician, three supervisors, 14 enumerators and a supporting staff—will enumerate the population, medically examine a selected group, and then will begin surveillance. Monthly visits by Regional Cancer Centre medical officers will gradually evolve into weekly clinics. The second phase of the study will focus on identification of new cancer cases by regional health care workers.

Radiation measurements of the region and its inhabitants will be undertaken with the technical advice of the Bhabha Atomic Research Centre in Bombay, said Gangadharan.

With 30-year doses seven to eight times higher than the 6-R 30-year doses in the high-background area of Yangjiang, Guangdong Province, People's Republic of China, RERF's Schull remarked that "this study could contribute much to our understanding of low dose and low-dose-rate exposures."

Supervised by radiation oncologist **M. Krishnan Nair**, director of the Regional Cancer Centre in Trivandrum, the NBRCR study is funded by the Atomic Energy Department, Government of India. ❑

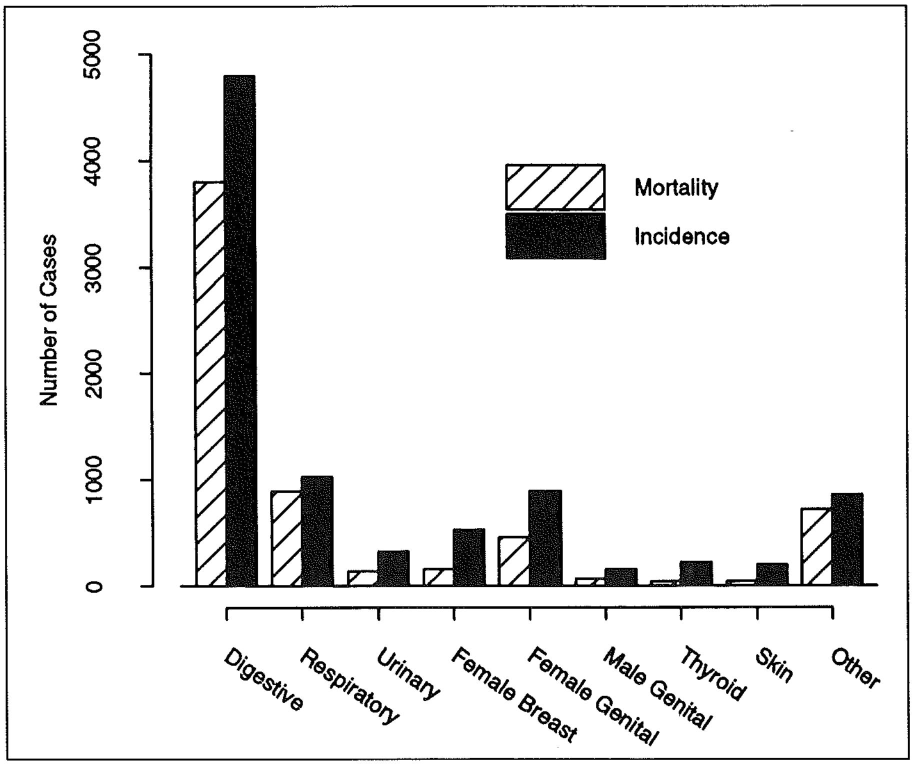
Facts & Figures

Cancer Incidence and Mortality in the LSS, 1958–87

To date, most reports on the late effects of radiation on cancer in the Life Span Study cohort have focused on mortality. In recent years, a major effort has been made to include the quality of the population-based Hiroshima and Nagasaki tumor registries in RERF studies by producing a registry of cancer incidence in the LSS. Important for several reasons—including better diagnostic quality and a greater quantity of cases—LSS cancer incidence will be reported soon in a series of comprehensive reports. Having a greater number of cases is particularly important for relatively nonlethal cancers, such as cancers of the breast, thyroid, and skin, for which analyses of mortality are of little, if any, use.

Not established in Nagasaki until 1957 and in Hiroshima until 1958, the tumor registries are mainly limited by incomplete coverage of the LSS cohort, which includes people who have migrated from the registry catchment areas.

The accompanying figure compares the number of solid tumor cases available for mortality and incidence analyses of the LSS from 1958 through 1987 (the period covered in the tumor registry reports). During this time, 22,187 deaths occurred among LSS members, of which 6,336 were coded as cancer deaths on death certificates, whereas the registries contain data on 9,010 first primary tumors.



Solid tumor cases available for mortality and incidence analysis of the Life Span Study, 1958–1987.

Even for categories comprising generally fatal tumors, such as digestive and respiratory tumors, the tumor registries contain about 20% more cases than are reported in the mortality series. This results from including living cases in the registry data and from inaccuracies in the cause of death as reported on death certificates. For less fatal cancers, the differences are even more striking; for breast cancer, the registry series includes 3.3 times as many cases as the mortality series, whereas for thyroid and skin cancer, respectively, the numbers of cases in the registry are 4.4 and 4.8 times the number of cases in the mortality data. ❑

News Briefs

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✓ Nagasaki Prefecture Plans Project To Treat Overseas A-bomb Survivors

Nagasaki Prefecture is planning to begin an international exchange project to support the medical treatment of overseas A-bomb survivors as well as other radiation-exposed people. The plan, announced by Prefectural Governor **Isamu Takada** on 25 February, calls for a coordinating body composed of representatives of RERF, the Red Cross Nagasaki A-bomb Hospital, Nagasaki University School of Medicine, and other institutions in the prefecture to organize cooperative efforts to prepare for dispatching medical personnel abroad and accepting overseas medical teams for training. A system to centralize storage and dissemination of information related to the treatment of radiation-exposed people has been proposed.

A similar plan in Hiroshima Prefecture has been allocated approximately ¥53 million (US $400,000) for its first year.

✓ Highlights of the RERF Lecture Program

On 18 January, **Kiyohiko Sakamoto**, Tohoku University School of Medicine, Sendai, lectured on fundamental and clinical studies of low-dose total body irradiation on tumor control.

James E. Cleaver, University of California–San Francisco, spoke on 25 January about the size and DNA sequence dependence of deletion mutations induced in human cells by radon alpha particles.

Dorothy Deeg, Ministry of Health, Welfare and Cultural Affairs, Rijswijk, the Netherlands, on 28 January spoke about aspects of aging.

On 13 February, **P. Gangadharan**, Regional Cancer Centre, Trivandrum, India, outlined problems in the study of radiation-induced cancers in India (see page 8).

Donald A. Pierce, Oregon State University, Corvallis, described a new approach to analyses of the A-bomb survivor cancer data and comparative inferences regarding types of cancer on 18 February.

On 20 February, RERF Research Associate **Elaine Ron** spoke on the delayed effects of scalp irradiation during childhood.

On 27 March, **Oliver Smithies**, University of North Carolina at Chapel Hill, delivered a lecture on altering genes in animals and humans by targeting.

✓ Research Staff News

Hiroshima

Research Information Center: Research Associates **Scott Pohlman** and **Mensah Solomons** have joined the Information Systems Laboratory. They will provide hardware and software support for personal computing and networking applications.

Pohlman was previously employed by Contel Corp., in St. Louis, Mo. Solomons comes to RERF from the Dallas Area Rapid

continued on next page

Recent Scientific Publications

Approved Technical Report

Mortality among the offspring (F_1) of atomic bomb survivors, 1946–85. Y Yoshimoto, WJ Schull, H Kato, JV Neel. **RERF TR 1-91.**

We compare deaths occurring in the years 1946–85 in a cohort of 31,159 children born to parents, one or both of whom were exposed to the atomic bombing of Hiroshima or Nagasaki, and who received a combined (i.e., joint) gonadal dose of 0.01 Sv or more, with deaths in a comparable control group, totaling 41,069 children. The average combined gonadal dose equivalent for the exposed parents was 0.435 Sv. Gonadal doses were calculated using the recently established DS86 system, supplemented by an ad hoc system for those children for whom a DS86 dose could not be computed for one or both parents. At the end of 1985, those members of the study groups born in 1946 had reached 39 years of age, whereas those born in the years 1966 through 1984 had not yet reached their 20th birthday. The mean age of living members of the cohorts was 28.8 years.

When a linear relative risk model is fitted to the data, no statistically significant increase in the risk of mortality attributable to diseases other than neoplasms is noted following parental exposure, the excess relative risk being 0.030 (±0.046) per sievert based on the subset of individuals with DS86 doses, assuming the RBE of neutrons to be 20. For fatal cancer, in confirmation of an earlier report on cancer incidence below the age of 20 in this same group, again no statistically significant effect as parental radiation dose increased was observed. Finally, although the present method of analysis using Poisson regression and person-years at risk of death seems more appropriate now, particularly as the cohort ages, since earlier analyses of mortality in the F_1 cohort have been based on a simple linear regression of the frequency of death on parental dose, this model was also fitted to the data used in the relative risk estimate to provide some continuity with the past. The results give an intercept of 0.0420 (±0.0015) and a linear regression coefficient of 0.00169 (±0.00157) per sievert. This leads to the calculation of a (statistically nonsignificant) excess relative risk of 0.040, in good agreement with the excess obtained by fitting the relative risk model. An analysis based on the full sample, using not only the DS86 dose group but also the ad hoc dose group, yields essentially the same result as the analysis restricted to the DS86 dose group.

Approved Research Protocols

Studies of salivary gland tumors among the RERF Extended Life Span Study cohort, Hiroshima and Nagasaki, 1950–87. T Saku, Y Hayashi, O Takahara, M Tokunaga, S Tokuoka, K Mabuchi, M Soda, E Ron, DL Preston, CE Land. **RERF RP 1-91.**

The incidence of major and minor salivary gland tumors (benign and malignant) diagnosed between 1950 and 1987 will be studied within the RERF Extended Life Span Study sample. Tumors will be ascertained from the tumor and tissue registries in Hiroshima and Nagasaki as well as autopsy files, surgical files, and death certificates maintained by RERF and other major medical institutions. Analyses regarding the shape of the dose-response curve, age at exposure, sex, temporal patterns, and histological type will be conducted.

Studies on skin cancer incidence among the RERF Extended Life Span Study cohort, Hiroshima and Nagasaki, 1950–87. M Kishikawa, T Kobuke, M Iseki, N Sadamori, S Yamamoto, M Soda, M Tokunaga, S Tokuoka, K Mabuchi, E Ron, DL Preston, CE Land. **RERF RP 2-91.**

The skin appears to be more sensitive to the carcinogenic effects of ionizing radiation than has previously been thought. The proposed study will be the first to evaluate skin cancer incidence within the RERF Extended Life Span Study sample in Hiroshima and Nagasaki. Tumors will be ascertained from the tumor and tissue registries in Hiroshima and Nagasaki as well as from autopsy, surgical record files, and death certificates maintained by RERF and other major medical institutions. Special efforts will be made to ascertain cases diagnosed at private dermatology clinics. Analyses regarding the shape of the dose-response curve, age-at-exposure, sex, temporal patterns, and histological type will be conducted.

Publications in the Open Literature

Phagocytic and bactericidal activities of leukocytes in whole blood from atomic bomb survivors. S Sasagawa, Y Yoshimoto, E Toyota, S Neriishi, M Yamakido, M Matsuo, Y Hosoda, SC Finch. *Radiat Res* 124:103–6, 1990. (RERF TR 1-89)

Determination of specific activity of cobalt (Co-60/Co) in steel samples exposed to the atomic bomb in Hiroshima. T Kimura, N Takano, T Iba, S Fujita, T Watanabe, T Maruyama, T Hamada. *J Radiat Res* (Tokyo) 31:207–13, 1990. ❑

News Briefs
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Transit Authority, Dallas, Tex. A native of Ghana, he studied at Soviet universities for six years and is fluent in Russian.

✓ RERF Experts Will Take Part in Chinese Low Background Radiation Study

A joint Japanese–Chinese research effort to begin in April will team experts from RERF, the Health Research Foundation in Kyoto, and investigators from other universities and institutions in Japan with researchers from the Laboratory of Industrial Hygiene in Beijing in a long-term study of the effects of low-level background radiation on the people of Yangjiang, Guangdong Province, an agricultural district in southern China. Chinese studies of this area since 1972 have shown a two- to fourfold increase in the incidence of Down's syndrome in the population versus a control group, yet little difference in the rate of leukemia or other cancers in the area.

✓ Reprint Requests Received from 37 Countries

During fiscal year 1989–90, RERF received 426 reprint requests from 37 nations. American researchers requested 30% of the total. Investigators from the Federal Republic of Germany followed with 7%. As a group, the USSR and seven eastern European countries accounted for 31% of the total. Japan ranked 10th, requesting only 4% of the reprints provided by RERF.

RERF reprints are available on request by contacting the RERF Publication and Documentation Center. ❑

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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