RERF update RERF

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

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Mutagenesis Experts Brainstorm at RERF

Determining the possible genetic effects of A-bomb irradiation on the offspring of survivors has long been a major goal of ABCC–RERF research. During a recent germline mutagenesis workshop held at the Hiroshima Laboratory, 12–14 November, international experts and staff scientists reaffirmed that this cohort of survivors' children, which may be the most important source of information related to human mutation studies, provides unique scientific opportunities.

"Having evolved steadily through its 40-year history, the program now finds itself on the threshold of the 21st century when emerging molecular techniques for detecting mutations at the DNA level are especially promising," remarked RERF Chief of Research **James Trosko**. Trosko and Biochemical Genetics Laboratory Chief **Chiyoko Satoh** invited to RERF specialists representing a wide range of expertise in molecular technologies, human mutation analysis, and automated DNA analyzing systems.

University of Michigan Professor Emeritus of Human Genetics and long-time ABCC–RERF associate **James V Neel** reviewed the accumulated knowledge of the multiple indicators of potential radiation-induced genetic damage. These include: congenital malformation; stillbirths; death among live-born children (up to an average age of 26.2 years); the physical development of children at birth, at 9 months of age, and at school age; sex ratio; sex aneuploidy and reciprocal translocations; biochemical changes in the blood and serum proteins; and prevalence of cancer up to an average age of 20 years.

"In summary, studies have not shown a statistically significant effect of parental exposure on any individual indicator, although the overall difference between the indicators in the children of the exposed and controls does tend toward the direction of a radiation effect," stated Neel, who has been involved in the program since 1946 when he helped to found it.

Satoh described current efforts at RERF to store primary and permanent cell lines of peripheral B-lymphocytes for long-term availability. Such cell lines—composed of cells from both parents (either distally or proximally exposed) and at least one child—have already been established for about 700 families.

Satoh also discussed three techniques being developed and applied at RERF:

♦ Denaturing gradient gel electrophoresis (DGGE), which uses DNA fragments amplified by the polymerase chain reaction (PCR) to detect small variations;

♦ A modification of Southern blotting of conventional agarose gel electropherograms that facilitates the detection of large insertions, deletions, or rearrangements of DNA which might be induced by radiation exposure; and

♦ The application of high-performance liquid chromatography of the PCR products, whereby selected segments of DNA can be screened for deletions.

Lively discussion centered on issues related to limitations in the search for mutational change in DNA; integration of new DNA studies with the results of past studies; the choice of indicator genes which ought to be analyzed at the DNA level (eg, DNA sequences of uncertain or no function as opposed to genes encoding functional products related to human health); technical advances that may contribute to greater efficiencies; cooperation with national and international efforts to study the human genome; and extending the study to

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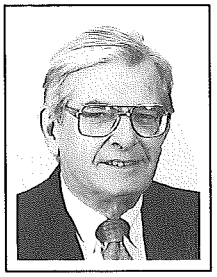
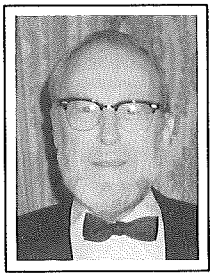
Neel and Schull Receive 1991 Conte Award



Schull



Neel

Cited for their joint efforts which "have contributed much of what is now known about the genetic effects of radiation in humans," RERF Permanent Director **William J Schull** and ABCC–RERF associate **James V Neel** were presented with the 1991 Silvio O Conte Award in Boston on 1 November. The Conte Award honors individuals for basic or applied environmental research or for related contributions to the public health.

Chosen for their "critically important studies on the genetic effects of ionizing radiation, particularly in the Hiroshima and Nagasaki atomic bomb survivors, ...both Professors Neel and Schull have educated a generation of researchers in human population genetics, and their own extensive research collaborations have led to this sharing of the Conte Award, sponsored by the General Electric Co," reads the award citation.

Neel is emeritus professor of human genetics and internal medicine at the University of Michigan. He is a member of the National Academy of Sciences, and a recipient of the National Medal of Science.

Presently one of RERF's 6 permanent directors, Schull is also professor of human genetics at the University of Texas Graduate School of Biomedical Science at Houston. He is an honorary member of the Japanese, Peruvian, and Chilean societies of human genetics. ❑

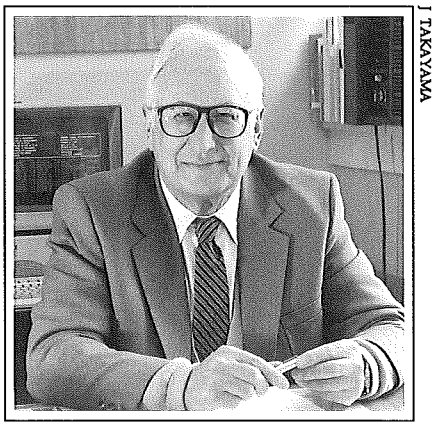
Risk: Relative or Absolute?

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

This issue of *RERF Update* provides a good opportunity to reflect on risk and risk assessment. In "Facts & Figures" (p 14) readers will find some preliminary information on dose-response functions and temporal patterns, based on tumor registry data from 1950 (leukemia) and 1958 (solid cancer) through 1987. These data are contained in an upcoming RERF publication now under review. I would like to use these figures as the point of departure for some thoughts on risk, and on how it might be best expressed.

One of RERF's most important findings, solidified by the recent registry data, is that a relative risk model fits cancer rate data far more accurately than an absolute risk model. This provides a solid basis for the idea that radiation ties into a mechanism of carcinogenesis that is more generally valid, rather than that it produces cancer via a specific mechanism that is different from, and independent of, the general mechanism of carcinogenesis. RERF Chief of Research **James Trosko** will address the role of radiation in carcinogenesis in the next issue of *Update*, and I will defer to him for a further discussion on this point.

If it is true that the relative risk model provides the most accurate description of radiation dose response, why is there still so much interest in absolute risk? A look at "Facts & Figures" will demonstrate that there are very basic differences in "risk behavior" between the two: As for relative risk, leukemia is, by far, the most serious radiation risk, and the risk of solid cancer of any type, compared to leukemia, is very much lower. The (derived) absolute risk figures show exactly the reverse, because of the folding-in of background cancer rates, which are much higher for solid cancers than for the leukemias. The question is: "Which is, biologically speaking, the most significant risk, relative or absolute?"



J TAKAYAMA

Thiessen

The answer depends very much on the purpose for which risk numbers are to be used, and on the way in which they have been used historically. For example, in earlier days, with very little solid information on dose response, but with an urgent need for a basis on which radiation protection concepts could rest, absolute risk was simply the most practical quantity. It was assumed that, after an appropriately chosen latent period, radiation would produce excess cancer over a given period of time, relatively short for leukemia, but maybe 30 years for solid cancers, and all available data were applied to this risk model. This kind of algorithm resulted in the earliest risk numbers, expressed as excess cancer deaths per 10^x person-years per unit of dose. These numbers could then be compared with, eg, accidental death rates in "safe industries," and, voilà, a basis for determining acceptable radiation levels was born. As risks from chemical carcinogens are often also expressed in this way, a general scheme for comparing carcinogens is thus available.

For purposes of radiation protection, absolute risk may still be the most practical, and even the most appropriate. Precision is not required, and scientific considerations,

continued on page 9

Mutagenesis Workshop

continued from page 1

the genetic effects of environmental mutagens or accidental radiation exposures.

"Impressed by the program's progress, the panelists agreed that it would now be appropriate to begin a pilot study employing a limited number of different types of genetic loci from a sample of survivors' children and controls," noted Trosko. "But the panel recognized that as the situation is now understood, demonstrating a statistically significant difference in mutation rates between the children of the exposed and the controls represents an enormous task ('a second genome project'), and success would probably depend on technical developments yet to come.

"The participants recommended that RERF collaborate with other research programs," he continued. "Because of the complex issues related to the use of these human cell lines outside of RERF for other purposes, any collaborative efforts would require careful monitoring to protect the rights of the A-bomb survivors who have voluntarily participated in this research." ❑

Germline Mutagenesis Workshop Participants

Panelists

Michael Dean, US National Cancer Institute, Frederick, Md
Tasuku Honjo, Kyoto University Faculty of Medicine
Harvey W Mohrenweiser, Lawrence Livermore National Laboratory
Richard M Myers, University of California–San Francisco
James V Neel, University of Michigan, Ann Arbor
Ohtsura Niwa, Hiroshima University
Michio Oishi, Tokyo University
Yoshiyuki Sakaki, Tokyo University
Masao Sasaki, Kyoto University
Takao Sekiya, Japanese National Cancer Center Research Institute
Eiichi Soeda, Institute of Physical and Chemical Research
Edward M Southern, Oxford University
Waclaw Szybalski, University of Wisconsin
R Bruce Wallace, Beckman Research Institute, Duarte, Calif
Stephen T Warren, Emory University School of Medicine, Atlanta, Ga

Observers

Ernest H Y Chu, Hong Kong University of Science and Technology
Charles W Edington, US National Research Council
Toshiyuki Kumatori, Radiation Effects Association, Tokyo
Mortimer L Mendelsohn, Lawrence Livermore National Laboratory
Brian C Myhr, Hazelton Washington Inc, Kensington, Md
Shigefumi Okada, Tokyo University
Istvan Szentesi, Human Genome Research Ltd, Szeged, Hungary

Radiation-induced Mental Retardation: An Update

The authors discuss the abnormalities in brain architecture that may follow prenatal exposure to ionizing radiation.

by William J Schull, RERF
Permanent Director, and
Masanori Otake, RERF
Department of Statistics

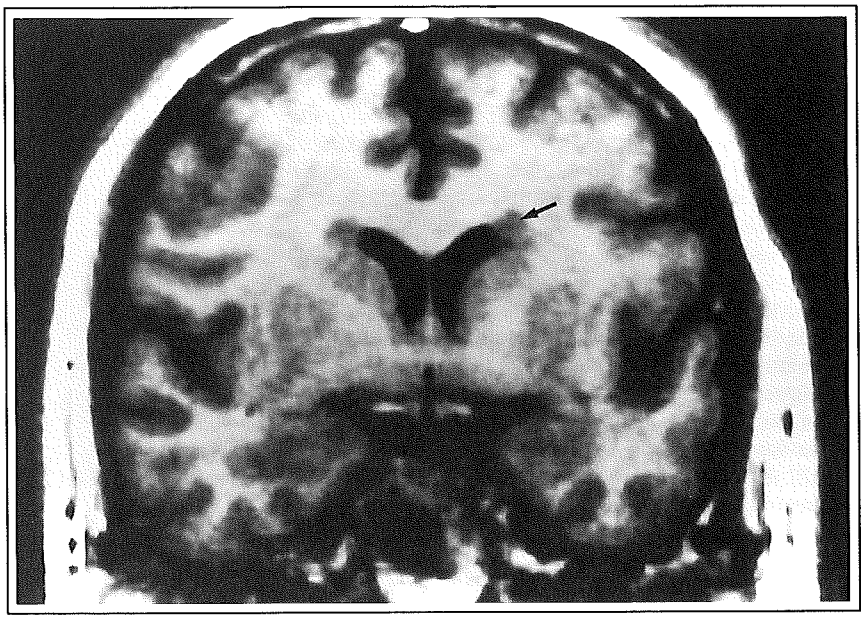


Figure 1. A coronal section through the brain of a survivor exposed prenatally in the 8th to 9th week following ovulation. Note the ectopias at the lateral margins of the ventricles above the caudate nucleus (arrow).

Forty years have elapsed since it became apparent that prenatal exposure to the atomic bombings of Hiroshima and Nagasaki increased the frequency of mental retardation and the occurrence of an "atypically" small head. Much has since been learned about the stages in embryonic and fetal development at which these events are most likely to occur, and other subtle impairments of brain development have been identified, but the biologic picture remains incomplete. We are still uncertain about the "true" dose-response relationship, and whether a threshold does or does not exist. Neither of these uncertainties, despite their importance to regulatory agencies, seems likely to yield to epidemiological studies alone. If answers are to be found, they must lie in a better understanding of the cellular and molecular events involved in the development of the cortex. This will, in turn, require a closer integration of epidemiologic and experimental studies, particularly those of a molecular biological nature, than has yet been achieved.

A priori, the damage that has been seen could be attributable to a variety of biologic events working singly or in concert, and ranging from neuronal cell killing to impaired cellular reproduction, to mismanaged neuronal migration, to failures in normal synaptogenesis. But the relative importance of these different possible contributors remains unknown. Thus far, the most informative insights have come either from a small number of autopsy examinations or from the use of magnetic resonance imaging, a recently introduced noninvasive means of visualizing the living brain. Even here the information is quite limited, and can be summarized simply.

Autopsy findings

Four deceased survivors, who were prenatally exposed, have been autopsied. Two were mentally retarded; two were not. Only one received a high dose of more than 1 Gy. The others received doses less than 0.01 Gy. In the two with normal intelligence, the brains were of normal weight and the architecture appeared normal on visual inspection and microscopically. Both of the mentally retarded individuals, however, had brains that weighed substantially below normal. One had a brain weighing 840 g and the other 1,000 g (normal weight is about 1,450 g). Multiple slices through the larger brain, that of a female exposed in the 31st postovulatory week, revealed the usual pattern of gray and white matter and no evidence of swelling from the accumulation of fluid in the spaces between the brain cells which could have increased brain weight. She died at age 20 of heart failure.

The other mentally retarded individual, a male with the smaller brain, died at age 16, of acute meningitis of probable viral origin. If he had been carried to the normal termination of a pregnancy, he would have been exposed in the 12th postovulatory week, but given his birth weight (1,950 g), he was undoubtedly premature. His weight suggests that he was actually exposed at about the 8th or 9th week following fertilization since a full-term Japanese infant would now weigh about 3,200 g (but possibly somewhat less at the time of his birth in 1946). The estimated dose to his mother's uterus was approximately 1.2 Gy.

Sections across the cerebrum revealed massive amounts of gray matter around the lateral ventricles, especially in the vicinity of the caudate nucleus, but also around the hippocampus. Microscopic examination of these misplaced gray areas revealed an abortive laminar arrangement of nerve cells, imitating the usual arrangement of the cortical neurons. The cerebellum and the curved ridges on the floor of the inferior horn of the lateral ventricle, the hippocampi, were normal visually and on microscopic study. However, the two protuberances on the under surface of the brain beneath the corpus callosum, called the mamillary bodies, were absent. These structures are presumed to play a role in memory since mamillary lesions are frequently associated with amnesia.

Misplaced gray matter was not observed in any of the other 3 autopsied cases, including the second mentally retarded individual. However, similar migratory errors have been seen in experimental rodents exposed to ioniz-

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Editor's note: The subject discussed in this article is more fully addressed in RERF TR 13-91 (see page 14 for summary).

Mental Retardation

continued from page 3

ing radiation at the equivalent time in development, and have been reported in other human fetuses exposed to massive amounts of ionizing radiation equally early in development.

Magnetic resonance imaging

Although the number of individuals that have been studied using magnetic resonance imaging is also small, several different anomalies of development have been seen. These correlate well with what is known of the embryological events transpiring at the time of their exposure. The findings on the neuroimaging of the 2 survivors exposed in the 8th or 9th week following fertilization do not differ qualitatively and are similar to those seen at autopsy in the case described above. When brain size is taken into account in both instances, there appears to be some increase in the size of the ventricles, but more importantly, there has been a failure of a significant number of neurons to migrate from the proliferative zone to their proper functional sites. One of these 2 individuals also exhibits an underdeveloped area in the left temporal region (see Figure 1). However, in these 2 cases, unlike the boy who was autopsied, the mamillary bodies are present and appear of normal size.

Ectopic gray matter has been seen in other instances of mental retardation not related to exposure to ionizing radiation, but its prevalence among mentally retarded individuals is not reliably known. The limited data that are available suggest that the nature of the migratory error could be different in the 2 instances. In the cases we describe, the failure occurs on both sides of the developing brain; whereas in nonradiation-related mental retardation it commonly involves only 1 side—although bilateral cases are known— and the ectopic area is often just beneath the cortex rather than around the ventricles. Ectopic gray matter is not invariably associated with mental retardation. Neuroimaging of individuals with the inherited Fragile X syndrome, among whom varying degrees of mental retardation commonly occur, has not revealed this defect. Among some 27 individuals who have been studied, just 8 were found to be abnormal. Seven of these individuals exhibited only a mild enlargement of the ventricles, but in 1 case a moderate, generalized dilation was seen. Autopsy studies have, however, disclosed abnormalities in dendritic spine morphology—very thin, long tortuous spines with prominent heads and irregular dilatations were noted. This suggests a developmental error occurring after migration was completed. Neuroimaging of 2 individuals exposed in the 12th to 13th postovulatory week reveals no conspicuous areas of misplaced neurons, but does show a faulty brain architecture. Again the abnormalities seen are surprisingly similar in the 2 cases. The prominently rounded elevations of the brain, the gyri, are enlarged, and the sulci, the furrows or trenches separating the gyri, are shallower than normal. One of the cases studied at this time exhibited a corpus callosum (the network of nerves which provides communication between the 2 halves of the brain) that was markedly smaller than normal (see Figure 2), and a poorly developed cingulate gyrus (the prominence lying immediately above the corpus callosum), suggesting an aberration in the development of the band of association fibers that passes over the corpus callosum. In both of these instances, the cistern involved in the recirculation of cerebrospinal fluid lying immediately behind and between the 2 lobes of the cerebellum, known as the cisterna magna, was markedly enlarged.

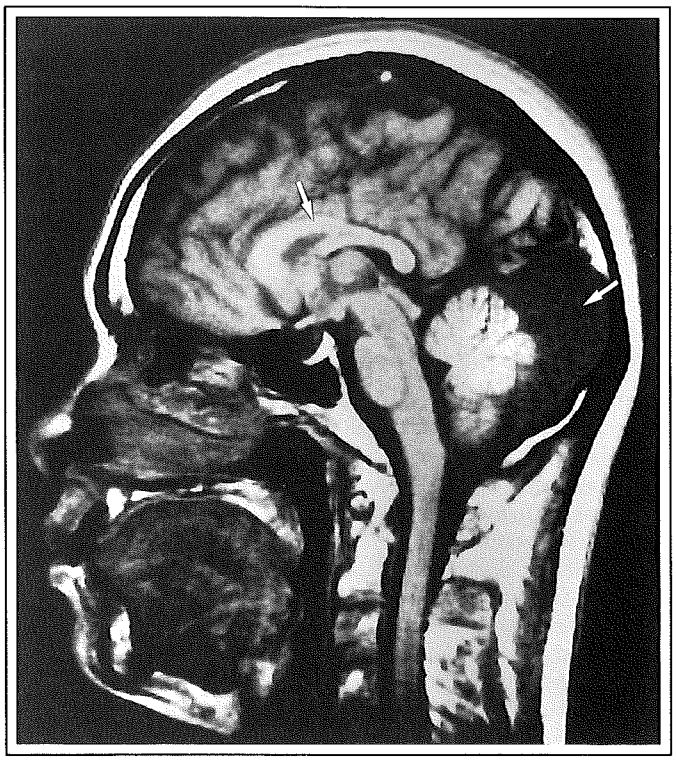

Figure 2. A sagittal section through the brain of a survivor exposed prenatally in the 12th to 13th week following ovulation. Note the enlarged cisterna magna (right arrow) and the deformed corpus callosum (left arrow).

Still later in development, at the 15th week, neither ectopic gray areas nor conspicuous changes in brain architecture were seen. Presumably the functional impairment that exists must be related to the connections that occur between neurons, possibly similar to the abnormality in the Fragile X syndrome described above. Experimental evidence shows that exposure at this time in the development of the brain in other primates leads to a diminished number of connections between neuronal cells. If all these connections have functional significance, then the diminution must compromise performance in some manner.

Although the observations just described are more informative than the simple determination of the frequency of mental retardation as a function of dose, they do not tell us what cellular or molecular events are impaired. However, when coupled with recent experimental findings, they are provocative. It is now clear that each cortical neuron has not only a designated date of birth, but a definite functional address. Since neuronal cells arise largely in specific proliferative, circumventricular zones, proper function implies migration. The process by which immature neuronal cells move from their sites of birth to those of their normal function is an active, timed phenomenon dependent on an interaction between their shapes, their surface membranes, and their guidance cells. Any damage to these membranes, however transitory, could conceivably impair migration. While there is presently no direct evidence of the effects of low doses of irradiation on the membranal properties of either neurons or the radial glial cells which guide them, experiments are underway which should provide some of the missing information. Finally, in interpreting the neuroimages that do not show evidence of ectopic gray matter, it warrants bearing in mind that the establishment of connections is essential to the survival of a neuron; those that do not form such connections die. The process of formation is competitive and neuronal cells that arrive late are obviously at a disadvantage. ❑

A-bomb Irradiation and Leukemia Types: An Update

A recent reclassification of leukemia cases among atomic bomb survivors demonstrates that the effects of radiation exposure differ depending on leukemia type.

by Masao Tomonaga,[1] Tatsuki Matsuo,[1] and Randolph L Carter[2]

Recent advances in hematology and molecular biology have consistently established that spontaneously occurring (de novo) leukemias consist of 4 major types: acute myeloid leukemia (AML), acute lymphoid leukemia (ALL), chronic myeloid leukemia (CML), and chronic lymphocytic leukemia (CLL). It is now apparent that they occur through distinct genetic abnormalities including oncogenes in the differentiation process of hematopoietic stem cells.

During the last 4 decades, extensive studies carried out at ABCC–RERF and other institutions have established that A-bomb irradiation did induce excess cases of leukemia—in particular, acute leukemia and CML. In the early postbombing period, the leukemogenic effects of A-bomb irradiation were apparently greater in individuals exposed at younger ages, and they declined more rapidly in subsequent years. Among those who were older at the time of bombings (ATB), the effects appeared later and persisted longer.

Most of the earlier studies concentrated on acute leukemia and CML, based on case ascertainment using the diagnostic methods of the early 1960s and the T65D dose estimates. The number of leukemia cases in the 120,000-member Life Span Study (LSS) cohort was insufficient to analyze the effects of radiation exposure on finely categorized leukemia types. Neither did the older diagnostic methods distinguish between AML and ALL from the present immunological point of view, thus rendering extensive study of each subtype very difficult. More recently, however, the widespread adoption of the French-American-British classification system does provide the morphological and cytochemical criteria for distinguishing between AML and ALL, and these have proved highly efficient in subsequent immunological marker analyses.

Since the early studies were conducted, new leukemia entities have been identified such as adult T-cell leukemia (ATL). Induced by the HTLV-1 virus, ATL is endemic to the island of Kyushu where Nagasaki City is located.

Reclassification of leukemia cases among the A-bomb survivors

Leukemia cases can now be classified into 21 categories. Since the size of the LSS cohort does not allow such fine distinctions, we supplemented the LSS data with additional cases

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Ratios of relative risks[a] for comparing radiation exposure effects on acute lymphoid, chronic myeloid, and other leukemia types to corresponding effects on acute myeloid leukemia.

Leukemia type[b]	Shielded kerma (mGy)	Time period						
		1945–1950	1951–1955	1956–1960	1961–1965	1966–1970	1971–1975	1976–1980
ALL	0	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	1–49	10.92**	7.49**	5.14**	3.53**	2.42	1.66	1.14
	50–499	9.99**	5.82**	3.39**	1.97	1.15	0.67	0.39
	500–1499	3.32	3.00*	2.70*	2.44	2.20	1.98	1.78
	≥1500	20.70**	12.25**	7.25**	4.29**	2.54	1.50	0.89
CML	0	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	1–49	12.10**	7.21**	4.30**	2.56*	1.53	0.91	0.54
	50–499	6.91**	5.82**	4.90**	4.12**	3.47**	2.92*	2.46
	500–1499	9.88**	6.97**	4.92**	3.47**	2.45	1.73	1.22
	≥1500	11.68**	5.47**	2.56**	1.20	0.56	0.26	0.12*
OTHER	0	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	1–49	0.14	0.20	0.30	0.45	0.67	1.00	1.49
	50–499	0.14	0.24	0.42	0.74	1.29	2.26	3.96
	500–1499	2.44	1.52	0.95	0.59	0.37	0.23	0.14
	≥1500	2.03	1.43	1.01	0.71	0.50	0.35	0.25

[a]Risk of leukemia types at given kerma levels, relative to the risk in the nonexposed, divided by the corresponding relative risk of acute myeloid leukemia. Relative risk ratios greater than 1.0 suggest a greater radiogenic effect on the given leukemia than on AML; ratios less than 1.0 suggest a greater effect of the given level of radiation on AML risk.

[b]Acute lymphoid leukemia (ALL); chronic myeloid leukemia (CML); and other leukemia types, including adult T-cell leukemia, as well as other specifically diagnosed leukemias (OTHER).

*Relative risk ratios significantly different from 1.0 at the 0.10 level of significance.

**Relative risk ratios significantly different from 1.0 at the 0.05 level of significance.

Leukemia Types

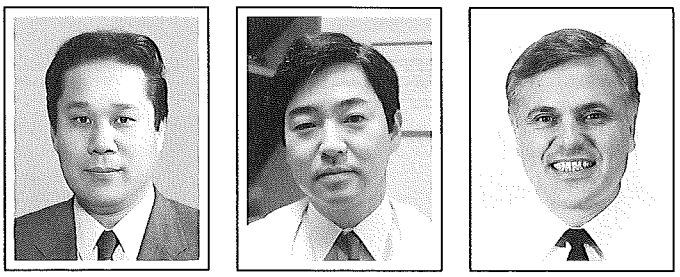
continued from page 5

from the entire cohort of A-bomb survivors, referred to here as the "open city" sample. Through 1980, 766 cases were registered at ABCC–RERF among survivors who were within 9 km of the hypocenter ATB. Of these, 493 (177 LSS cases) were reclassified based on adequate hematological and pathological preparations, and 413 (157 LSS cases) of these had been assigned DS86 estimates. After carefully checking for possible selection biases, we used these 413 cases to estimate the proportions of ALL, AML, CML, and other types of leukemia (here referred to as "OTHER") as functions of DS86 estimate, age ATB, city, and time since exposure. Then the estimated proportions were used to calculate the ratios of relative risks (RRR) in order to compare the effects of kerma, age ATB, city, and time since exposure on the incidence of ALL, CML, and OTHER relative to those effects on AML incidence. The AML category was chosen as the reference type because it is the most prevalent of all leukemias. Such RRRs provided a method for statistical analysis of differential effects of irradiation on major leukemia types, thus allowing use of supplemental cases from the open city population of survivors. (The full technical report by M Tomonaga et al, RERF TR 9-91, is now in press.)

New information

Incidence rates of all 4 leukemia types increased with kerma. The effects of radiation exposure on incidence were significantly greater for ALL and CML than for AML and OTHER (see table on p 5). Kerma values less than 50 mGy and probably as low as 16 mGy apparently produced excess cases of ALL and CML (see table), whereas kerma values greater than 50 mGy and probably at least 229 mGy were required to produce excesses in AML. These differential effects disappeared in time as ALL and CML incidence rates returned to background levels.

In the 2 lowest kerma categories (1–49 and 50–499 mGy), the estimated incidence either remained constant or increased slightly as the population of survivors aged. However, in the 2 highest categories (500–1499 mGy, and ≥1500 mGy), the estimated incidence rates of all types among those who were less than 16 years old ATB declined with elapsed time since exposure. ALL and CML incidence declined similarly among those exposed as adults, whereas the incidence of AML either remained constant or increased with time. An excess of AML and ALL, but not CML and OTHER, remained through the final study period (1976–80) in the ≥1500-mGy category (see table).



The authors, from left: Tomonaga, Matsuo, and Carter.

Time to onset of ALL, AML, and CML decreased as kerma increased. The rate of decline, however, was greater for ALL and CML than for AML. The resulting differences at high values of kerma reflect shorter incubation times for A-bomb-induced ALL and CML than for AML. When controlling for leukemia type, the time to onset of leukemia was not significantly affected by age ATB.

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

Thus, the analysis of recently reclassified leukemia cases from the LSS and additionally from the open city population revealed several important findings:

♦ A-bomb radiation exposure affected the induction of the major leukemia types in different ways. ALL and CML were induced earlier and at lower doses compared with AML, suggesting greater effects of A-bomb irradiation on ALL and CML incidence.

♦ An excess of both AML and ALL remained through 1980.

♦ The generally higher incidence of non-ATL leukemias observed among exposed individuals in Hiroshima compared with Nagasaki may simply be an extension of proportionately different background rates of leukemia.

♦ The previous results concerning the relationship between age ATB and time to onset of leukemia could not be confirmed in this study. Independent of leukemia type, age ATB was not significantly related to the time to onset of leukemia.

♦ The reclassification task revealed that the morphological picture for A-bomb-induced leukemias is indistinguishable from that of de novo human leukemias.

These findings provide us with some insights for understanding radiation-induced leukemogenesis as well as de novo leukemogenesis. Age distributions are known to be distinct between different types of de novo leukemia. These distinctions were also observed in A-bomb-related leukemias. A-bomb irradiation may have induced leukemia by accelerating de novo leukemogenesis in a subpopulation of survivors prone to develop leukemias. ❑

RERF Reports Available Upon Request

RERF Update lists technical reports, as well as reports in the Commentary and Review Series, usually on the last 2 pages of each issue. We often receive inquiries from readers who are wondering why they haven't yet received copies of listed reports. Reports that are "approved" should be considered as "in press" publications that may not yet be available for distribution. As soon as they are printed, they will be distributed to those on the appropriate mailing lists.

Readers interested in receiving reports should select one or more of the following subject categories: radiation effects on humans; reanalyses using the DS86 dose estimates; Life Span Study—cancer and noncancer mortality; Adult Health Study—disease incidence and aging; genetic studies—chromosome abnormalities, biochemical genetics; in utero radiation exposure (mental retardation); cancer epidemiology—tumor registries, histopathology; radiobiology; A-bomb dosimetry; and statistical methodologies.

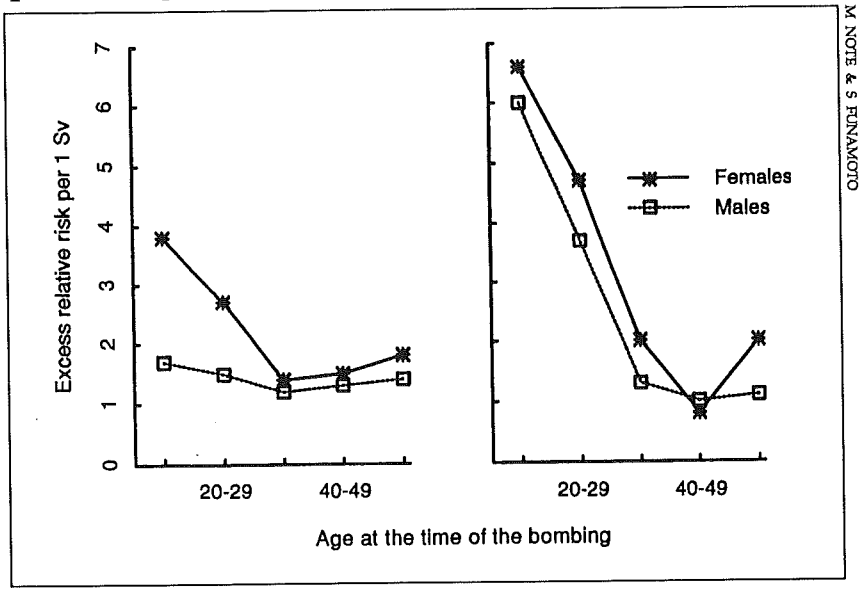
Please send your name, address, and subject area(s) to Chief, RERF Publication and Documentation Center, 5-2 Hijiyama Park, Minami-ku, Hiroshima, 732 Japan. Fax: 81-82-263-7279. ❑

Radiation, Smoking, and Lung Cancer

A binational study provides new insights into the effects of smoking and radiation exposure on different histological types of lung cancer.

by Kiyohiko Mabuchi,[1] Charles E Land,[2] and Suminori Akiba[1]

Lung cancer is one of the leading forms of cancer in many countries. Cigarette smoking is considered to be the most important cause of lung cancer, whereas occupational exposures represent a less frequent but significant cause. Epidemiologic evidence also suggests that nutritional factors and certain host characteristics may modify an individual's risk of developing lung cancer. Ionizing radiation has long been known to be capable of causing lung cancer, and it is an important cause in some populations, including the A-bomb survivors. In addition to the multiplicity of etiologic factors involved, lung cancer is characterized by different cell types in which it is manifested. These features complicate risk assessment because due consideration must be given to possible confounding and modifying effects of nonradiation factors. At the same time, they present an ideal prototype for studying multifactorial aspects of cancer induction involving radiation and more common cancer-causing agents, such as cigarette smoking.



M. NOTE & S. FUNAMOTO

The excess relative risk of lung cancer per 1 Sv not adjusted for the additive effect of smoking (left) and adjusted assuming additive effect of smoking (right). (Redrawn from K Kopecky et al, RERF TR 13-86.)

How does smoking affect risk estimation?

The analysis of the most recent incidence data for 1950–1987 based on the tumor registries shows that lung cancer has one of the higher relative risks associated with radiation exposure. It is estimated that almost one-fifth of the observed exposed lung cancer cases are attributed to exposure to the A-bombings. The estimated excess relative risk (ERR) at 1 Sv is 0.95 and a significant dose-response relationship is demonstrated. A striking finding is that, among the usual risk modifiers such as age at exposure, attained age, sex, and time since exposure, sex has the strongest effect: Women have an estimated ERR of 1.93, about 4 times as high as that of men (0.48). This sex differential is largely explained by the difference in background cancer incidence between the sexes. The background male incidence is almost 3 times as high as the female incidence, most likely reflecting the higher prevalence of smoking in men than in women. Previously, K Kopecky et al (RERF TR 13-86) demonstrated that the sex difference in the relative risk of lung cancer in the A-bomb survivors diminished after adjustment had been made assuming additivity of the effect of smoking and radiation exposure (Figure 1).

How does smoking interact with radiation exposure?

It is clear that smoking and radiation have a combined effect on lung cancer. What is less clear is the precise manner in which these 2 factors interact with each other. Although an additive effect was suggested by Kopecky et al, the BEIR IV Committee noted that neither an additive nor a multiplicative model of interaction could be rejected on statistical grounds based on data from a case-control study of the A-bomb survivors (*Health effects of exposure to low levels of ionizing radiation* [BEIR V Report], Washington, DC, National Academy Press, 1990). Findings from studies of US uranium miners have been interpreted as supporting a multiplicative model for the interaction between cigarette smoking and exposure to radon progeny. According to the BEIR IV Committee's analysis, a submultiplicative model may provide a more accurate description of the underlying relationship.

An accurate description of the statistical relationship is important not only for those concerned with risk assessment but also for those interested in mechanisms of radiation-induced cancer. For example, the presence of a multiplicative effect implies a synergism and suggests the presence of a biological interaction between the 2 factors. A better understanding of the association between smoking and lung cancer is also essential. For example, in Japan the relative risk of lung cancer associated with cigarette smoking has been much lower than that reported for the United States. This may be rather surprising in view of the widespread smoking habits prevailing in Japan. The explanation has been offered that the lack of cigarettes during World War II resulted in a 20- to 30-year lag in the nationwide adoption of smoking habits (EL Wynder et al, *Cancer* 67:746–63, 1991). However, the relative risk has begun to increase in more recent birth cohorts, ie, those who were still young when the war ended (S Akiba and T Hirayama,

[1]*RERF Department of Epidemiology;* [2]*RERF consultant, and health statistician, US National Cancer Institute, Radiation Epidemiology Branch, Bethesda, Md.*

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Smoking and Lung Cancer

continued from page 7

Environ Health Perspect 87:19–26, 1990). It will be interesting to observe the effect of this change on future radiation–smoking interaction analyses of the A-bomb survivor data.

What do different histological types mean?

Lung cancer can be categorized into 3 major cell types: squamous cell carcinoma, small cell carcinoma, and adenocarcinoma. It has been shown that cigarette smoking is related to all 3 types of cancer, although the relationship is stronger for the squamous cell and small cell types than adenocarcinoma. In the A-bomb survivors, radiation exposure was found to increase the risk for all 3 major types of lung cancer also, but the risk for small cell carcinoma appeared to be greater than that for the other 2 types. Preliminary results from a recently completed binational study of lung cancer in US uranium miners and Japanese A-bomb survivors provide new insights into the interrelationship among smoking, radiation dose, and radiation quality as they relate to histologic presentations of cancer. The objectives of this study were, first, to determine whether there are differences in histologic types of lung cancer between the 2 populations, and, second, to assess how differences in radiation exposure and other factors can explain any observed difference in histologic presentation of lung cancer. Previous studies by Gino Saccomanno and his colleagues (V Archer et al, *Cancer* 34:2056, 1974; G Saccomanno et al, *Cancer* 62:1402–8, 1988) had suggested that the frequency of small cell carcinoma might be unusually high among the heavily exposed uranium miners.

Comparison of the 2 populations is of special interest because they have distinctly different radiation-exposure characteristics: The uranium miners were exposed to nonpenetrating alpha radiation from inhaled radon progeny over a prolonged period of time, whereas the A-bomb survivors were almost instantaneously exposed to mostly penetrating gamma rays from an external source. The radon progeny attach to dust particles which tend to be deposited in the large and medium bronchi, whereas the smaller bronchi—having a larger aggregate surface area—received most of the bronchial radiation from A-bomb exposure. Since squamous cell and small cell carcinomas originate mainly in the large and medium bronchi (adenocarcinoma is more likely to occur in the small bronchi), differences in histologic types between the 2 populations might be expected on radiobiological grounds.

To conduct a comparison in a controlled and standardized manner, a binational panel of pathologists, 4 Americans headed by **Gino Saccomano** (St Mary's Hospital, Grand Junction, Colo) and 4 Japanese led by **Yukio Shimosato** (Japanese National Cancer Center, Tokyo), reviewed pathology specimens available for 108 lung cancer patients from the Life Span Study cohort of A-bomb survivors and 92 uranium miners with lung cancer studied in Colorado. To the extent practicable, the cases were selected from each population to be evenly divided between high and low doses. Histologic diagnoses were classified using the WHO classification for pulmonary neoplasms. As expected from the earlier studies, the relative frequencies of lung cancer classified into the 3 main types were indeed different in the 2 populations. Most of the uranium miner cases, but only one-eighth of the A-bomb survivor cases, had small cell carcinoma. Nearly half of the A-bomb cases, but only less than one-tenth of the miner cases, had adenocarcinoma; squamous cell carcinoma made up about one-third of both series.

The exposures of the cases selected from the 2 populations were such that far more of the uranium miner cases than A-bomb survivor cases were likely to have been caused by radiation exposure, based on published dose-response estimates (*Health risks of radon and other internally deposited alpha particle emitters* [BEIR IV Report], Washington, DC, National Academy Press, 1988; BEIR V Report, 1990; Y Shimizu et al, *Radiat Res* 121:120–41, 1990). The only female cases were among the A-bomb survivors, and there were also differences with respect to age and year of diagnosis. Male A-bomb survivors smoked about as much, on the average, as uranium miners, but the proportion of female smokers, and the amount smoked per smoker, was substantially less among the female survivors. The analytical problem for the investigators was to determine how much of the observed population difference with respect to histological type could be explained in terms of the variables just mentioned and how much could not be explained and therefore might plausibly be attributed to population differences, including radiation quality and internal vs external sources of exposure.

As expected, squamous cell carcinomas occurred disproportionately among smokers, and their relative frequency increased by cumulative number of cigarette pack years, with or without adjustment for age, calendar year, sex, population, or radiation exposure. The relative frequencies of small cell carcinoma and adenocarcinoma were markedly different in the 2 populations, as discussed above, and remained so even after adjustment for age and year of diagnosis, sex, and smoking history. Somewhat surprisingly, however, the difference was drastically reduced by adjustment for radiation dose, leaving essentially no apparent population difference to be explained by factors not included in the analysis. Thus it appeared that the difference in histological type distribution between populations can be attributed to the fact that far more of the miner cases were radiation-related, and it was not necessary to suppose that different types of radiation or different modes of exposure result in different types of lung cancer.

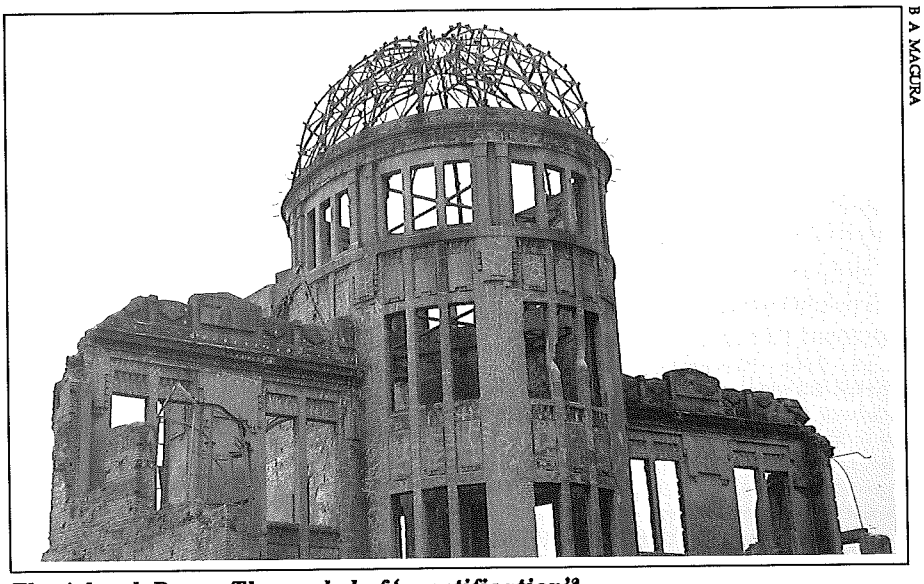
The adjustment for "radiation dose" mentioned in the previous paragraph was actually in terms of estimated radiation-related risk, ie, the estimated probability that a given A-bomb survivor or uranium miner case was caused by the exposure received. When the individual exposure experiences in the 2 populations were evaluated on this common scale, the distribution of histological types appeared to conform to a single pattern in which, regardless of population, radiation-induced cancers tended disproportionately to be of the small cell type, and nonradiation-related lung cancers were correspondingly more likely to be adenocarcinoma.

Many questions still remain to be resolved in this interesting area of research. Will the nature of interactive effect between cigarette smoking and radiation exposure change in the A-bomb survivors as younger birth cohorts with more intense smoking exposure enter ages of high cancer rate? How does the cessation of smoking modify the interactive effect? Does the sequence of exposure events make any difference? These are some of the important epidemiologic questions. However, understanding the underlying biological mechanisms will require more than just answering these questions. For example, RERF is currently involved in another collaborative study, also focusing on lung cancer and also contrasting the A-bomb survivors with another population, that seeks to identify, in certain tumor suppressor genes, "molecular fingerprints" that may be unique to ionizing radiation or to other carcinogens such as alkylating agents. ❑

Feedback

The 'Sanctification of Hiroshima': Part 2

*Editor's note: This letter to the editor comments on a "Perspectives" editorial published in autumn (**RERF Update** 3[3]:2, 1991).*



B.A. MAGURA

The A-bomb Dome: The symbol of 'sanctification'?

Dr Thiessen is probably correct in arguing that the "sanctification of Hiroshima"—with its implied creation of powerful religious taboos against the use of nuclear weapons—would have little effect on renegade dictators such as Saddam Hussein. I have but 2 points that might complement Dr Thiessen's thoughtful observations.

First, I prefaced my conception of the sanctification of Hiroshima with a question: "How can mankind survive for millennia, given that the knowledge of how to make nuclear bombs can never be forgotten?" My answer was to establish powerful and long-lasting taboos against the use of nuclear weapons. Taboos of such power and longevity to deter would-be transgressors must be religious in character. Only those moral strictures that pass into religious beliefs have a chance of possessing such force and of lasting, as moral sanctions, essentially forever.

Second, since I proposed the sanctification of Hiroshima, I have become the honorary chairman of the local Oak Ridge Committee in charge of erecting a "Friendship Bell" to commemorate the 50th anniversary of the founding of Oak Ridge. The Friendship Bell is to be a replica of the traditional Japanese bell which I rang when I visited Hiroshima's Peace Park.

The Friendship Bell would be another step in the sanctification of Hiroshima. But I realize that in the near term—before the taboo signified by the sanctification of Hiroshima has been deeply established in our collective human consciousness—additional, practical steps must be taken to prevent the use of nuclear bombs and other agents of mass destruction such as poison gas and biological weapons.

The most pressing need is to create a fundamentally peaceful world,

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Risk

continued from page 2

though important, are not necessarily the commanding ones. The matter is different, I believe, when applied to practical ("real") risk and risk assessment in more direct terms, eg, from an individual point of view. As cancer is a prevalent risk among the many that determine our mortality, radiation can be looked upon as a modifier of a quantity that itself is being affected by other factors, operating differently under different conditions. Those factors may vary from person to person (as they do), the concept of relative risk—if we, for the moment, assume that it can be considered to apply as a general principle—would allow us to define the excess risk independent of the underlying "base-risk." For example, the radiogenic lung cancer risk, in absolute terms, might well be different in smokers and non-smokers. From a relative-risk point of view, however, the risk could be the same. This matter has not entirely been decided yet (see the article by **K Mabuchi** et al on p 7), but it appears to me that the case for radiogenic cancer as being etiologically independent of the "base cancer" is becoming less and less convincing.

Another use of absolute risk in preference over relative risk is for the estimation of radiation consequences in large population groups (entire countries, continents, the world). Nuclear weapons' testing and nuclear energy have always been popular targets for such calculations. Chernobyl is another. A recent example is found in a publication of the International Physicians for the Prevention of Nuclear War: "Radioactive heaven and earth" (New York, 1991). There, it is calculated that "the radioactive material [from nuclear weapons' testing] that will be delivered to the world population until the year 2000 will eventually cause about 430,000 cancer fatalities" (p 42). The report indicates that this represents a life-time risk of dying from fallout-induced cancer to the average person of approximately 0.02%, compared to an overall cancer fatality rate of about 20%, ie, 3 orders of magnitude lower. What provides a better impression of the "real risk": the number 430,000 as an absolute risk, or 0.001 as the (average) relative risk? I hold that the latter is the most appropriate quantity, not the first, assuming that the relative risk extends to the ultra-low exposure region, which is a different question altogether, of course.

One may object to the use of relative risk, because it, by itself, may not be a constant either, but dependent on age at exposure, sex, and time since exposure, to name a few. Although the book is still not closed on the impact of these factors, I for one feel that this still does not argue for the use of absolute risk: the product of 2 quantities, each with its own uncertainties, wouldn't produce fewer, but more uncertainties. Heaven knows that there are enough of those already, especially when talking about low-dose effects. About the latter problem, see the next issue of *Update*, with some interesting articles to look forward to! ❑

News Briefs

✓ RERF Radiobiology Chief Nationally Recognized

In mid-September, Radiobiology Department Chief **Mitoshi Akiyama** was named a councilor of the Japanese Cancer Association at its 50th annual meeting by **Takashi Sugimura**, president of the Japanese National Cancer Center, Tokyo. Of 200 councilors nationwide, Akiyama is the first RERF research scientist to be so named and is one of only two councilors from the Hiroshima area.

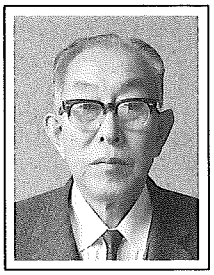
✓ Yorichika Honored by US National Research Council

In late November, **Edward K Yorichika** was honored at a special awards luncheon for his more than 40 years of service to the National Research Council as an interpreter and translator. Yorichika was appointed chief of the Publication and Documentation Center in May.

"Over the years, he has gained the complete trust of everyone for whom he has interpreted, because of his ability to accurately communicate the essence of important discussions in meetings," remarked **Charles W Edington**, director of the NRC Board on Radiation Effects Research.

✓ In Memoriam: Kiyoshi Shimizu and Austin Brues

Kiyoshi Shimizu: Formerly chief of the ABCC Department of Medical Sociology, Shimizu had been engaged in health administration on the national and local levels for many years. He became a professor in the Research Institute for Nuclear Medicine and Biology, Hiroshima University, in 1961, and after his retirement in 1970, he was invited to join ABCC. He was noted for his efforts on behalf of the A-bomb Survivors Special Measures Law. He passed away on 24 July at the age of 84.



Shimizu

Austin Brues: A pioneer in the study of the biological effects of radiation exposure, Brues was one of the original members of the Atomic Bomb Casualty Commission (see p 12 for a related story) who traveled to Hiroshima and Nagasaki in 1946. He was the director of 2 divisions at Argonne National Laboratory—the biology division from 1946–50 and the medical research division from 1950–62. Since 1979, he served as emeritus professor of medicine at the University of Chicago. He passed away on 27 February at the age of 85.

✓ Highlights of the RERF Lecture Program

On 4 October, **J David Curb** of the Kuakini Medical Center, Honolulu, spoke about epidemiological studies of aging in the Honolulu Heart Program.

On 8 November, **Dan Geraghty**, Fred Hutchinson Cancer Research Center, Seattle, discussed the human leukocyte antigen class I multigene family, specifically complete characterization of its members and cloning of the 2 megabase class I region in yeast artificial chromosomes.

Takashi Sugimura, president of the Japanese National Cancer Center, Tokyo, talked about multiple steps of carcinogenesis and how they affect cancer prevention on 16 December. ❑

✓ Darling Sends Greetings

Now living in New Haven, Conn, 85-year-old George B Darling is shown at left with Toyoko Sperry, wife of RERF Business Administrator Richard Sperry. The couple report that Darling, who was ABCC director for 16 years, is "well, alert, and despite the loss of his dear wife, Ann, is the same charming host as ever. He's full of stories and sends his greetings to his former colleagues in Japan." In the photo, Darling holds a cane given to him by the Nagasaki Laboratory staff in 1972 at the time of his departure from Japan. (Photo: R Sperry)

Sanctification: Part 2

continued from page 9

one in which countries no longer believe it necessary to threaten their neighbors with massive retaliation. To have suggested such a world before the stunning events in eastern Europe would have been impossibly unrealistic. But the world is different now. President Bush's "New World Order," which evoked wry smiles when he pronounced it, must now be taken seriously: for example, Israel and the Palestinians are negotiating even as I write.

The development of defensive technology might help stabilize this New World Order. Though some say that the Patriot missiles actually were less effective than was claimed at the time, none can deny that the Patriots greatly influenced the political course of the Gulf War. More than this, the Patriots, though technologically unsophisticated, have obliged military planners to take defensive postures seriously. And as defensive technologies improve, can we not look forward to a world in which mutually assured destruction is replaced by mutually assured survival?

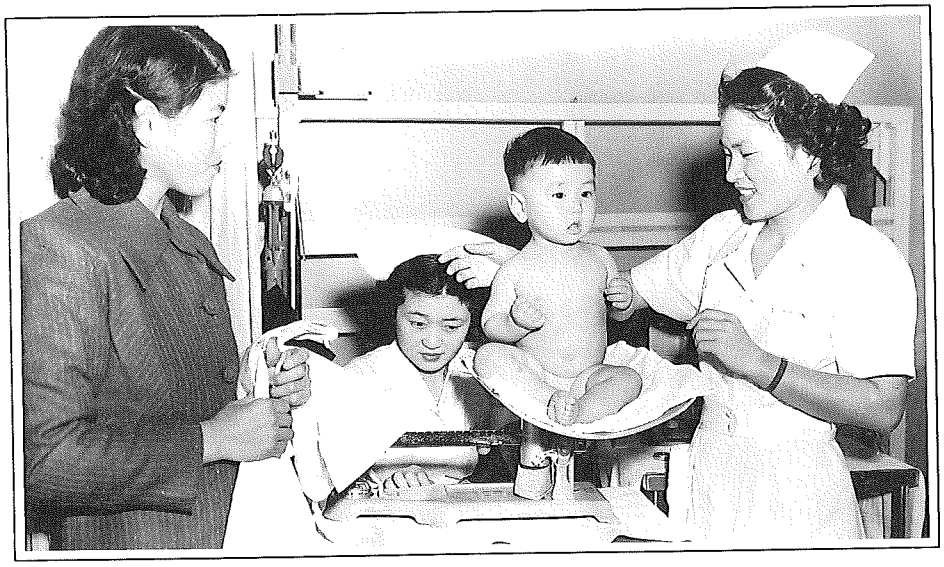
But in such a fundamentally peaceful world, we shall still have to deal with renegades like Saddam Hussein. For such adventurers, only the strangest of sanctions will be effective. This means that certain behavior involving weapons of mass destruction must be recognized as "crimes against humanity," punishable, after due legal process, by death.

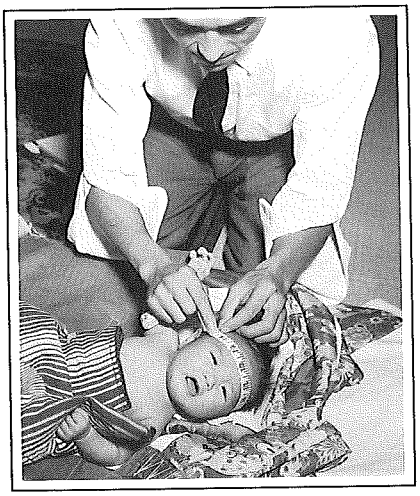
The Security Council of the United Nations, guided by agencies such as the International Atomic Energy Agency, will have to be given the authority to impose this ultimate sanction—death—on individual transgressors.

To empower the Security Council to impose such severe punishment on individual transgressors is an action that could be contemplated only if the transgression were universally recognized as being extraordinarily heinous—if, indeed, it were recognized as being a crime against humanity. And here is where the sanctification of Hiroshima plays a role: the sanctification provides a moral sanction for designating such behavior as heinous and for empowering the institutions of the world polity to punish the transgressor. It is for this reason that I believe the sanctification of Hiroshima ought to be encouraged, especially by those of us who have participated in the development and have studied the effects of nuclear weapons.

—Alvin M Weinberg

Book Review





Data collection began in the home and continued at the ABCC clinic.

The Children of Atomic Bomb Survivors—A Genetic Study, edited by James V Neel and William J Schull, National Academy Press, Washington, DC, 1991, 518 pp, US$49.95 (hard cover), US$29.95 (paperback).

This voluminous book constitutes a compilation of 13 landmark publications containing the results of the various genetic studies carried out in Hiroshima and Nagasaki, the earliest one reprinted from a *Science* paper dated 10 October 1947—reporting on the Genetics Conference of the Committee of Atomic Casualties, National Research Council—and the latest one the Neel and Lewis paper "The comparative radiation genetics of humans and mice," reproduced from the *Annual Review of Genetics*, 1990. In between, there is a wealth of information on subjects such as pregnancy outcomes (both the original 1956 analysis and the 1990 reanalysis); sex ratio among the children of exposed parents; the mortality, cytogenetics, and cancer incidence of these children; and, maybe most importantly, the value of the doubling dose for genetic mutations, taking into account all data collected so far.

For someone like myself, who has been involved in RERF research for only 10 years, it is astounding to realize that the book covers work carried out over some 40 years—all under the patronage of Neel and Schull, and in one institute. Work that has been instrumental in arriving at our present concepts of radiation genetics in human beings and at the quantitative evaluation of genetic risk. No less astounding is the paucity of genetic effects found in a study of this size and intensity, contrary to the earliest expectations—contrary too, I fear, to the still widespread public misunderstandings on the fate of the "children of Hiroshima." I hope that this publication may, once and for all, lay to rest anxieties of genetic doom among the children of A-bomb survivors. RERF is now preparing an overview of the genetic study results in Japanese—in layman's terms—to be distributed widely, based on Neel and Schull's chef d'oeuvre.

The series of reprints is bracketed by two original contributions by Neel and Schull. The first one is an "Orientation," which describes the historical beginnings and phases of the genetics research program and discusses the significance of the data on the genetic doubling dose, now estimated at 2 Sv for acute radiation exposure and at 4 Sv for chronic exposures, substantially higher than previous estimates still in use by UNSCEAR and ICRP, which are based on mouse data. The last section, called "The future of these studies," discusses whether there is a need for further studies of the F_1. The authors argue for continuation of the ongoing studies on cancer incidence and mortality and for extending studies to the DNA level using the immortalized B-lymphocyte cell lines from approximately 700 "trios" of father, mother, and child (or children) now being collected. These studies would allow a more definitive approach to the question of recessive damage, and should render unnecessary studies on any further generations. Given all of this, however, it appears that the signal "mission completed" is still a few decades away, ie, at around the time that the A-bomb survivor population itself has been reduced to a very small number.

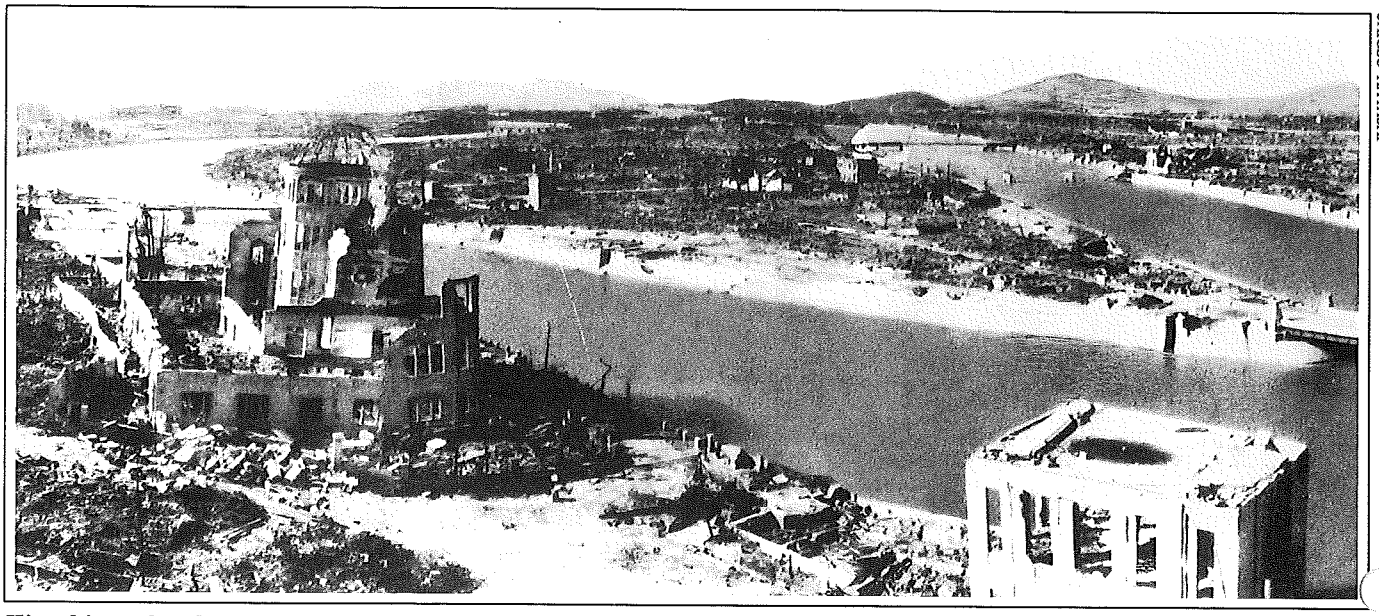
—J W Thiessen

LSS Noncancer Mortality Data Available on Disk

An updated version of the Life Span Study (LSS) Report 11 data will soon be available on high-density disk for users outside the Foundation. The original disk, which contains the data on cancer mortality for 19 organ sites or systems used in Report 11, parts 1 and 2, was described in the spring 1990 issue (*RERF Update* 2(1):9, 1990). The new data set includes additional information on 8 categories of noncancer mortality considered in Report 11, part 3 (Y Shimizu et al, RERF TR 2-91, in press). These categories are: all diseases except neoplasms and diseases of the blood and blood-forming organs; infectious diseases; circulatory diseases; stroke; heart disease (equivalent to circulatory disease except stroke); respiratory diseases; digestive diseases; and other diseases.

To obtain copies of this data set on DOS-formatted floppy disk, contact the RERF Publication and Documentation Center, Adminstration and Support Section, 5-2 Hijiyama Park, Minami-ku, Hiroshima, 732 Japan. Facsimile: 81-82-263-7279.

There is a charge of US$50 per disk. Please specify the type of disk required—3.5- or 5.5-inch. ❑



SHIGEO HAYASHI

Hiroshima, October 1945. At left, the ruins of the Industrial Promotion Hall—today's A-bomb Dome—and to its right, the present site of Peace Park. Fourteen months after this photo was taken, Paul Henshaw and his colleagues visited Hiroshima and Nagasaki, where the necessities of daily life were still hard to come by.

The ABCs of the Early Days

With 4 other Americans and a noted Japanese surgeon, the author journeyed through Japan in 1946 on behalf of the National Research Council to assess the feasibility of undertaking scientific studies in the war-ravaged nation. More than 4 decades later, he shares some recollections including the naming of the Atomic Bomb Casualty Commission.

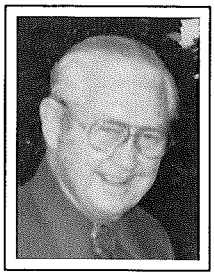
by Paul Henshaw

Editor's note: In an earlier issue (RERF Update *1(4):7–8, 1989), **James V Neel** told how he had been assigned in 1946 by the US Army Medical Corps to accompany to Japan 2 civilian consultants selected by the National Research Council, **Austin Brues** and **Paul Henshaw**, noted radiation biologists. Two other medical officers, **Melvin Block** and **Frederick Ullrich**, rounded out the American contingent that would report on the prospects for setting up a research program in Hiroshima and Nagasaki.*

Tokyo

In Tokyo, we immediately contacted Col **Crawford Sams**, head of the Public Health and Welfare Section of General Headquarters, Supreme Commander of the Allied Powers. He, together with a Col **Johnson** offered the use of a special train which was maintained in Japan to deal with emergencies such as those caused by earthquakes and typhoons. It had a laboratory car, a passenger car, a sleeping car, and a service car with an electric generator and a jeep. This was special, and it raised the status of our group, both in our own eyes and in the eyes of those who came in contact with us.

Several people joined our group in Tokyo, including **Masao Tsuzuki**, professor of surgery at the University of Tokyo—a prestigious position. Automatically a likeable person, he was not only a scientist and physician, but an effective diplomat as well. To maintain his standing among doctors outside Tokyo, he explained that he always had a bit of advice for these physicians when he met them. For them it was special to be advised by the eminent professor because it improved their standing with their patients. Dr Tsuzuki explained the objective of our working group to the people we met in Hiroshima and Nagasaki, and without him our work would have been more difficult.



Henshaw, 1990

Hiroshima

In 3 jeeps, we loaded out from Kure, site of Japan's largest naval base. It was December and cold. We traveled along the ocean highway and up a small hill to the edge of the city. As we drove over the hilltop, we had almost a full view of Hiroshima. Shivers raced up and down my spine. There it was—the aftermath of the catastrophe I had read so much about. It seemed that little had been done during the 16 months since the bombing except to clear the streets a bit.

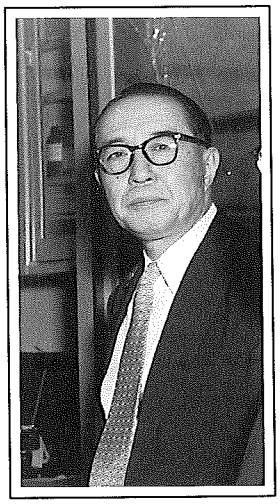
I thought of the 70,000 people who had lost their lives in a fraction of a second, of the families that had been broken or destroyed. I also thought of Pearl Harbor, London, Hamburg, and Munich.

Arrangements had been made for us to meet the mayor of Hiroshima at 9 AM on the steps of city hall, a reinforced concrete building that showed the effects of a great force from above which crunched it, causing dangerous cracks in many places. Dr Tsuzuki introduced us and we were taken to a second-floor room. There was no glass in the windows and it was very cold. Several charcoal braziers were taken from workers in other rooms and brought in for our benefit. Even with

continued on next page

our heavy coats, it was still uncomfortable. Dr Tsuzuki attempted to explain about our mission to the mayor and a few other officials, but because of the cold we did not get much of a conversation going.

Soon the mayor suggested that we have tea. In the room where we were taken, there was a long table covered with a very dingy tablecloth. The mayor took a position at one side of the table, and I in my heavy coat, was seated directly opposite him. Soon he stood and addressed the group, starting as follows: "I apologize for these humble circumstances, but I hope you will understand." The remark set off a barrage of thoughts in my head—some with elements of humility and guilt, some renewing my determination to get on with our task, and some contributing to my growing revulsion for war.



Tsuzuki, in the early 1950s

From my present vantage point, the mayor's remark brings to mind another profound and very moving Japanese statement. In Hiroshima's Peace Park, there is a memorial plaque that reads in translation: "Rest in peace. These errors shall not be repeated."

Observations

Arrangements were made for us to meet and talk with people who were atomic bomb victims—also to make and collect pictures.

One day when fetal injury was being discussed, Dr Tsuzuki asked if we would like to talk with a midwives' group. Being offered an unexpected opportunity, we promptly expressed our delight.

In the living room of a cottage in the outskirts of Hiroshima, we met a group of sedate Japanese ladies in black kimonos, sitting in straight chairs with their hands folded neatly in their laps. Not a word was being spoken. As I looked around, I was horrified. I thought if somehow we could break the ice here, I would never fear facing any other kind of group. Dr Tsuzuki was equal to the occasion. Quickly he explained that the American doctors were interested in their work and asked whether any had seen birth abnormalities since the atomic bombing. This released a free expression and we were on our way. Yes, they had seen abnormalities, but they were not different from abnormalities seen before the bombing. This told us that bomb radiations did not produce any unique form of grotesqueness. After a nice visit, the ladies stood in line outside the cottage waving as we drove away in our jeeps.

Nagasaki

In Nagasaki, it was easy to see why the casualty numbers had been lower. Whereas Hiroshima is located on flat delta land, the portion of Nagasaki that had been bombed is located in a fairly small valley between 2 low mountain ranges, creating a comparatively narrow exposed area. In Nagasaki, there were 2 targets: Mitsubishi Steel and Iron Works on the bay and Mitsubishi Torpedo Works 2 miles upriver between the mountains. The Nagasaki Hospital and School of Medicine was about halfway between and therefore was almost exactly at ground zero. Both targets were destroyed.

Both in Hiroshima and Nagasaki, we saw the difficulties of performing a long-range study—of locating survivors, of getting even a reasonable estimate of the radiation exposure each had received, and then of following each one through time.

How the Atomic Bomb Casualty Commission got its name

On the train between Osaka and Tokyo, in the laboratory car—I think it was—our group was discussing the report we would make to the National Research Council in Washington. Filled with profound impressions about Japan and its people—and also the awesomeness of atomic weapons—we felt good about the work we had done. We had a feeling of importance about the study we were to propose, and, at the same time, strong impressions of the difficulties involved in even approximating the radiation exposures associated with the different radiation-induced injuries.

At the outset, there was the question of to whom we were reporting. I remember so clearly some of the thoughts that ran through my head. First of all, I said to myself, we were functioning as a commission, and clearly it was a commission to deal with atomic casualties. "Atomic Bomb Casualty Commission," I said to myself. Then when I thought of the initials, ABCC, I was not only fascinated with the name but with the fact that it identified precisely what we were and what might be a name for the facility that might emerge. I mentioned the possible name to the others, and slowly we began to use it. A name thus had been adopted.

In retrospect, it is clear that the ABCC has been much more than a scientific study. It has been the means for melding hearts and minds and of creating friendships and mutual respect. ❑

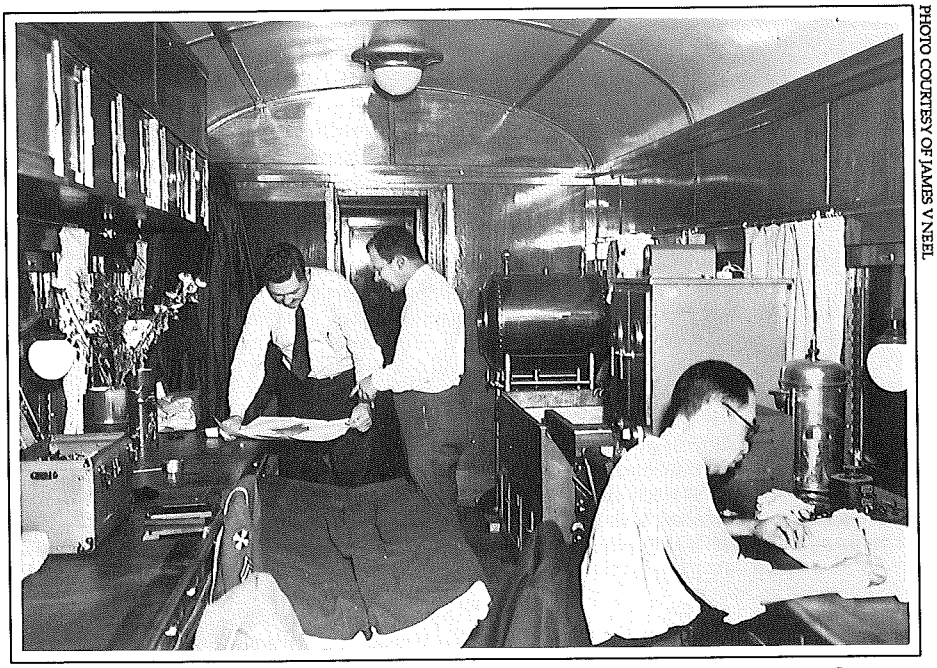


PHOTO COURTESY OF JAMES V NEEL

Aboard the "disaster train" that doubled as their mobile laboratory and accommodations, three members of the six-member Atomic Bomb Casualty Commission are shown at work in early 1947. From left, the author, Austin Brues, and Masao Tsuzuki, the eminent Tokyo University professor of surgery whose presence greatly facilitated early interactions with community leaders in Hiroshima and Nagasaki.

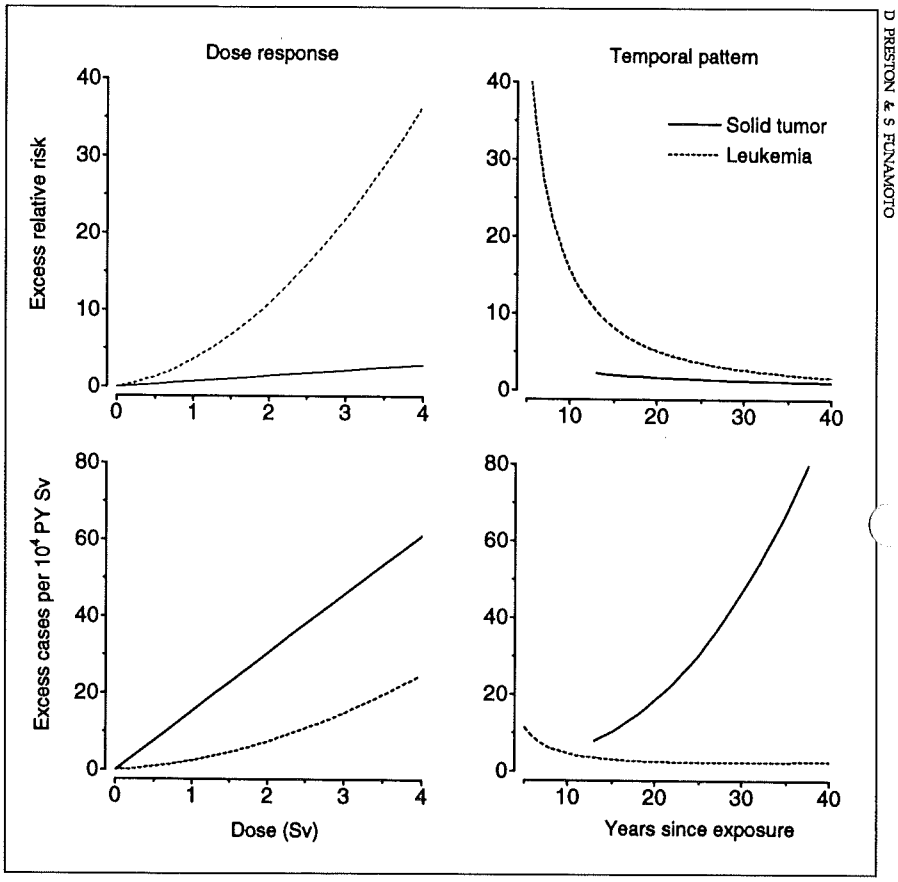
Facts & Figures

Solid Tumor and Leukemia Relative Risk

These figures compare the dose response and temporal patterns for the excess risk of solid tumor and leukemia incidence (all types combined) in the RERF Life Span Study. Risks are plotted for a 25-year-old Hiroshima male. The lefthand column shows the fitted dose response 20 years after exposure. The righthand column shows the temporal pattern following an exposure to 1 Sv.

The plotted curves are based on parametric excess relative risk (ERR) models fit to the incidence data. The solid tumor data cover the 1958–87 period. The ERR model is linear in dose and includes sex, age at exposure, and time since exposure effects. The leukemia data cover the period from 1950–87. The ERR is modeled as a time-dependent quadratic function of dose with sex and age at exposure effects. A constant RBE of 10 was assumed in both models.

Although these plots do not provide a complete picture of the nature of the excess cancer risk in the LSS, they do indicate the marked contrast in the patterns of leukemia and solid tumor risks, and they highlight the importance of considering both relative and absolute risks in discussions of radiation effects. ❑



D PRESTON & S FUNAMOTO

Recent Scientific Publications

Editor's note: The reports listed have been approved, and will be distributed as soon as they are printed.

Approved Technical Reports

X-ray induction of micronuclei in human lymphocyte subpopulations differentiated by immunoperoxidase staining. S Ban, M Nakano, JB Cologne. **RERF TR 11-91.**

In this report, we sought to confirm the radiosensitivity of human peripheral blood lymphocytes using a micronucleus assay. Mononucleated cells isolated from peripheral blood were irradiated with X rays. After being cultured for 3 days, the cells were fixed and stained using the immunoperoxidase staining technique. Lymphocyte subpopulations were characterized by means of the monoclonal antibodies Leu4 (CD3), Leu2a (CD8), and Leu19 (CD56).

Dose-response curves were obtained by scoring the number of micronuclei in binucleated cells that reacted with specific antibody and were then stained. The dose response of CD^+ (suppressor/cytotoxic) cells was quite similar to that of $CD3^+$ (pan T) cells. In comparison, $CD56^+$ (natural killer) cells were significantly less sensitive, although scorable binucleated $CD56^+$ cells made up less than 4% of the total number of binucleated cells.

A simple, quick method for HLA-DQA genotyping by PCR-SSCP analysis. T Hayashi, T Seyama, T Ito, Y Kusunoki, Y Hirai, N Nakamura, M Akiyama. **RERF TR 12-91.**

A simple, quick method for characterizing polymorphisms at the HLA-DQA locus has been developed. The procedure involves the selective amplification of the polymorphic second exon of the DQA locus by the polymerase chain reaction (PCR), followed by analysis of the amplified DNA with nondenaturing polyacrylamide gel electrophoresis after heat-denaturation of the amplified DNA (PCR-SSCP analysis). HLA-DQA alleles were classified into four major groups: DQA1, DQA2, DQA3, and DQA4 using this PCR-SSCP analysis. It would be feasible to use this PCR-SSCP analysis for detecting point mutations at various positions in a fragment as well as new HLA-DQA genotypes.

Brain abnormalities among the mentally retarded prenatally exposed atomic bomb survivors. WJ Schull, H Nishitani, K Hasuo, T Kobayashi, I Goto, M Otake. **RERF TR 13-91.**

An increased occurrence of severe mental retardation, with or without accompanying small head size, at specific gestational ages has been the most conspicuous effect on brain development of prenatal exposure to the bombings of Hiroshima and Nagasaki. A variety of biological mechanisms could be responsible for this finding, including cell killing and mismanaged neuronal migration. We describe here the findings on magnetic resonance imaging of the brains of five of these mentally retarded individuals, all of whom were exposed in the 8th through the 15th weeks following fertilization, the gestational period shown to be the most vulnerable to radiation-related damage. In the two cases exposed at the 8th or 9th week following fertilization, large areas of ectopic gray matter are seen, strong evidence of a failure of the neurons to migrate to their proper functional sites. The two individuals exposed in the 12th or 13th week show

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no readily recognized ectopic gray areas, but do show mild macrogyria, which implies some impairment in the development of the cortical zone. Moreover, both have mega cisterna magna. Finally, the one individual seen who was exposed still later in development, in the 15th week, shows none of the changes seen in the other four individuals. This person's brain, though small, appears to have normal architecture.

These findings are discussed in terms of the embryological events transpiring at the time of the prenatal exposure of these individuals to ionizing radiation.

A longitudinal study of the association between ABO blood phenotype and total serum cholesterol level in the Adult Health Study, 1958–86. FL Wong, K Kodama, H Sasaki, M Yamada, HB Hamilton. **RERF TR 14-91.**

This study examines the relationship between ABO blood phenotype and total serum cholesterol level in a Japanese population to determine whether an elevated cholesterol level is associated with phenotype A, as has been demonstrated consistently in many West European studies. Studies of this nature in non-white populations are scarce; available findings have generally failed to demonstrate the relationship, suggesting racial heterogeneity. Cross-sectional data of various racial groups with age categories ranging from neonates to adults exhibited varying results, including nonsignificant ABO–cholesterol associations. This raised the question of an age effect as a possible explanation for the discrepancies. It has also been suggested that the ABO–cholesterol association may not be apparent in populations with low fat intake or low mean cholesterol levels. We addressed these hypotheses by examining long-term data on total serum cholesterol levels collected serially from survivors of the atomic bombings of Hiroshima and Nagasaki who were participants of the Adult Health Study program at the Atomic Bomb Casualty Commission–Radiation Effects Research Foundation between 1958 and 1986. A longitudinal statistical method of growth curve analysis for serially measured response is used to model age-dependent changes in cholesterol levels within individuals. The effects of the ABO polymorphism in modifying the resultant growth curve are also examined. We demonstrate that total serum cholesterol levels were elevated on average by about 4 mg/dL in phenotype A compared to non-A phenotypes in the Japanese (p = .027), and that this relationship is maintained from early to late adulthood. Thus, phenotype A individuals may be predisposed to cardiovascular disease through one of its major risk factors. This is the first study of the ABO–cholesterol association in the Japanese, and the first that is based on a cohort with longitudinally collected total serum cholesterol data.

Combining diagnostic categories to achieve improved agreement between death certificate and autopsy classifications of cause of death of atomic bomb survivors, 1950–87. RL Carter, E Ron, K Mabuchi. **RERF TR 15-91.**

Several investigators have observed less than desirable agreement between death certificate and autopsy diagnoses for most specific causes of death, and even for some causes grouped by major disease category. Our results from data on 5,130 members of the Life Span Study (LSS) cohort of atomic bomb survivors in Hiroshima and Nagasaki who were autopsied at the Atomic Bomb Casualty Commission–Radiation Effects Research Foundation prior to September 1987 were equally discouraging. Among diseases with more than 10 cases observed, confirmation rates ranged from 13% to 97% and detection rates from 6% to 90%. Both were greater than 70% for only 6 of 60 disease categories studied and for only 1 of 16 categories defined by major ICD classifications (neoplasms). This deficiency suggests cautious interpretation of results from studies based on DC diagnoses.

To determine whether any groupings of diagnoses might meet acceptable accuracy requirements, we applied a hierarchical clustering method to data from these 5,130 cohort members. The resulting classification system had 10 categories: breast cancer; other female cancers; cancers of the digestive organs; larynx cancer; leukemia; nasal, ear, or sinus cancer; tongue cancer; external causes; vascular disease; and all other causes. Confirmation and detection rates for each of these categories were at least 66%. Although the categories are broad, particularly for nonneoplastic diseases, further divisions led to unacceptable accuracy rates for some of the resulting diagnostic groups.

Using the derived classification system, there was 72% agreement overall between death certificate and autopsy diagnoses compared to 53% agreement for a second system obtained by grouping strictly by major disease category. Eighty-seven percent agreement was observed for a similar classification system with vascular disease grouped with all other nonneoplastic diseases. Further agglomeration achieved very little additional improvement. Accuracy rates for some of the categories of the 10 category diagnostic system defined above varied with various covariates. For example, accuracy decreased with increasing age at death for most of these categories. Thus, subpopulations exist for which accuracy rates can be expected to be either better or worse than for the whole population. While these results do not necessarily dictate which diseases and/or populations should be studied in future cause-specific mortality investigations, they do provide investigators with useful information pertinent to the planning of their study, analysis of data, and interpretation of results.

Evidence for increased in vivo somatic mutations in T-cell receptor genes in lymphocytes but not in the glycophorin A gene in erythrocytes of Thorotrast patients. S Umeki, S Kyoizumi, Y Kusunoki, N Nakamura, M Sasaki, T Mori, Y Ishikawa, JB Cologne, M Akiyama. **RERF TR 16-91.**

Recent discoveries of cancer suppressor genes have strengthened the somatic mutation theory of carcinogenesis. Since exposure to ionizing radiation is a well-recognized risk factor for cancer among other human health defects, and since ionizing radiation can induce mutations, an accurate way of measuring somatic mutation frequencies could be a useful tool for evaluating cancer risks. In the present study, we have examined in vivo somatic mutation frequencies at the erythrocyte glycophorin A (GPA) and T-cell receptor (TCR) loci in 18 Thorotrast patients. These patients have been continuously irradiated with alpha particles emitted from the internal deposition of thorium dioxide and thus have increased risks of certain malignant tumors. When compared with controls, the results showed a significantly higher frequency of mutants at the lymphocyte TCR loci but not at the erythrocyte GPA loci in the Thorotrast patients. The discrepancy between the results of the two assays is discussed.

Approved Commentaries and Reviews

The influence of death certificate errors on cancer mortality trends. E Ron, DG Hoel, R Carter, K Mabuchi. **RERF CR 2-91.**

Over the past few years, several papers have suggested a recent increase in cancer mortality based on death certificate diagnoses. To explore the effect of death certificate errors on temporal trends in cancer mortality, we analyzed the data from the Radiation Effects Research Foundation's autopsy program in Hiroshima and Nagasaki. This series includes 5,886 autopsies conducted between 1961 and 1987. Our analyses were focused on lymphoma, breast cancer, brain neoplasms, multiple myeloma, and melanoma, because of concern over reports of their increased mortality. These 172 autopsy cases were referred to as "sites of interest." A significant difference in detection rates over time was observed for sites of interest primarily due to a large rise between 1976 and 1987. For the remaining cancers, excluding stomach and lung ("other"), the pattern was similar to that seen for sites of interest, but the fluctuation over time was not statistically significant. Confirmation rates generally increased with time except for sites of interest.

As a measure of bias in mortality rates due to death certification errors and as a method to quantify under- or overestimation of death certificate-based mortality rates, an adjustment factor (confirmation rate + detection rate) was calculated. The higher the adjustment factor, the greater the need to compensate for underreporting. For sites of interest the adjustment factor decreased

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Recent Scientific Publications

dramatically over time, but it did not change significantly for other cancers. When the adjustment factors for sites of interest and other cancers were compared, a statistically significant difference was found. For sites of interest, a significant interaction between type of cancer and period was seen. Our findings indicate that considerable care must be shown when interpreting temporal trends in cancer vital statistics.

Use of the tumor registries in Hiroshima and Nagasaki for incidence studies in the atomic bomb survivors. K Mabuchi, M Soda, E Ron, M Tokunaga, S Ochikubo, S Sugimoto, T Ikeda, M Terasaki, DL Preston, D Thompson. **RERF CR 3-91.**

More than 30 years ago, population-based tumor registries were established in Hiroshima and Nagasaki for the collection and management of cancer incidence data for the communities and for the assessment of cancer risk associated with atomic bomb (A-bomb) radiation exposure. This report, one of a series of papers on cancer incidence, describes methodologic aspects of the tumor registries and discusses issues of data quality in the context of the Life Span Study (LSS) cohort, the major A-bomb survivor population. The tumor registries in Hiroshima and Nagasaki are characterized by active case ascertainment based on search and abstraction of medical records at area hospitals. This is augmented by tissue registries operational in the area and a number of clinical and pathological programs undertaken over the years among the A-bomb survivors. Using conventional measures of reliability, the Hiroshima and Nagasaki tumor registries have a death certificate-only (DCO) rate of less than 9%, a mortality/incidence (M/I) ratio of about 50%, and a microscopic verification (MV) rate in excess of 70%, which place these registries among the best in Japan and comparable to many established registries worldwide.

All tumor registry data pertaining to the LSS population were assembled, reviewed, and processed with special attention given to the quality and uniformity of data based on standardized procedures. Special studies and monitoring programs were also introduced to evaluate the quality of LSS tumor incidence data. Analyses were performed to examine the quality of incidence data overall and across various substrata used for risk assessment, such as age, time, and radiation dose groups. No significant associations were found between radiation dose and data quality as measured by various indices. These findings support the use of the present tumor registry-based data for cancer incidence studies in the A-bomb survivors.

Publications in the Open Literature

Organ doses received by atomic bomb survivors during radiological examinations at the Radiation Effects Research Foundation. K Kato, S Antoku, S Sawada, WJ Russell. *Br J Radiol* 64:720–27, 1991. (RERF TR 19-89)

Organ doses to atomic bomb survivors during photofluoroscopy, fluoroscopy and computed tomography. K Kato, S Antoku, S Sawada, T Wada, WJ Russell. *Br J Radiol* 64:728–33, 1991. (RERF TR 2-90)

The incidence of thoracic vertebral fractures in a Japanese population, Hiroshima and Nagasaki, 1958–86. S Fujiwara, S Mizuno, Y Ochi, H Sasaki, K Kodama, WJ Russell, Y Hosoda. *J Clin Epidemiol* 44:1007–14, 1991. (RERF TR 12-89)

Editor's note: Following is a partial listing of the papers included in the Volume 32 supplement of the Journal of Radiation Research (March 1991). The remainder of the articles will be listed in the next issue.

The dosimetry system 1986 (DS86) and the tentative dosimetry system 1965 (T65D): How do they compare, what is left to do? JW Thiessen, DC Kaul. *J Radiat Res* (Tokyo) 32S:1–10, 1991.

Allowing for dose-estimation errors for the A-bomb survivor data. DA Pierce, DL Preston, DO Stram, M Vaeth. *J Radiat Res* (Tokyo) 32S:108–21, 1991. (RERF TR 2-89)

Recent uses of biological data for the evaluation of A-bomb radiation dosimetry. DO Stram, R Sposto. *J Radiat Res* (Tokyo) 32S:122–35, 1991.

Medical X-ray doses's contributions to the ionizing radiation exposures of atomic-bomb survivors. K Kato, S Sawada. *J Radiat Res* (Tokyo) 32S:136–53, 1991.

The LD_{50} associated with exposure to the atomic bombing of Hiroshima and Nagasaki. S Fujita, H Kato, WJ Schull. *J Radiat Res* (Tokyo) 32S:154–61, 1991. (RERF TR 17-87)

Multiple myeloma among atomic bomb survivors. M Ichimaru, K Mabuchi. *J Radiat Res* (Tokyo) 32S:168–71, 1991.

Parathyroid tumors in atomic bomb survivors in Hiroshima: A review. N Takeichi, H Dohi, H Ito, H Yamamoto, K Mabuchi, T Yamamoto, K Shimaoka, K Yokoro. *J Radiat Res* (Tokyo) 32S:189–92, 1991.

Thyroid cancer: Epidemiological study of thyroid cancer in A-bomb survivors from extended Life Span Study cohort in Hiroshima. H Ezaki, N Takeichi, Y Yoshimoto. *J Radiat Res* (Tokyo) 32S:193–200, 1991.

Follow-up studies of breast cancer incidence among atomic bomb survivors. M Tokunaga, CE Land, S Tokuoka. *J Radiat Res* (Tokyo) 32S:201–11, 1991.

Mortality among atomic bomb survivors. Y Shimizu, H Kato, WJ Schull. *J Radiat Res* (Tokyo) 32S:212–30, 1991. (RERF TR 5-88)

Cancer risk among in utero-exposed survivors. Y Yoshimoto, H Kato, WJ Schull. *J Radiat Res* (Tokyo) 32S:231–38, 1991.

Tumor registries and cancer incidence studies. K Mabuchi, M Soda. *J Radiat Res* (Tokyo) 32S:239–44, 1991.

Hyperparathyroidism. S Fujiwara. *J Radiat Res* (Tokyo) 32S:245–48, 1991. (RERF TR 8-90)

Brain damage among the prenatally exposed. M Otake, WJ Schull, H Yoshimaru. *J Radiat Res* (Tokyo) 32S:249–64, 1991. (RERF TR 16-87)

Persistent chromosome aberrations in the somatic cells of A-bomb survivors, Hiroshima and Nagasaki. AA Awa. *J Radiat Res* (Tokyo) 32S:265–74, 1991. ❑

RERF update RERF

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

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

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

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