RERF update RERF

News & Views from the US–Japan Radiation Effects Research Foundation
Volume 2, Issue 1 Hiroshima & Nagasaki Spring 1990

Aging Research Reviewed at RERF

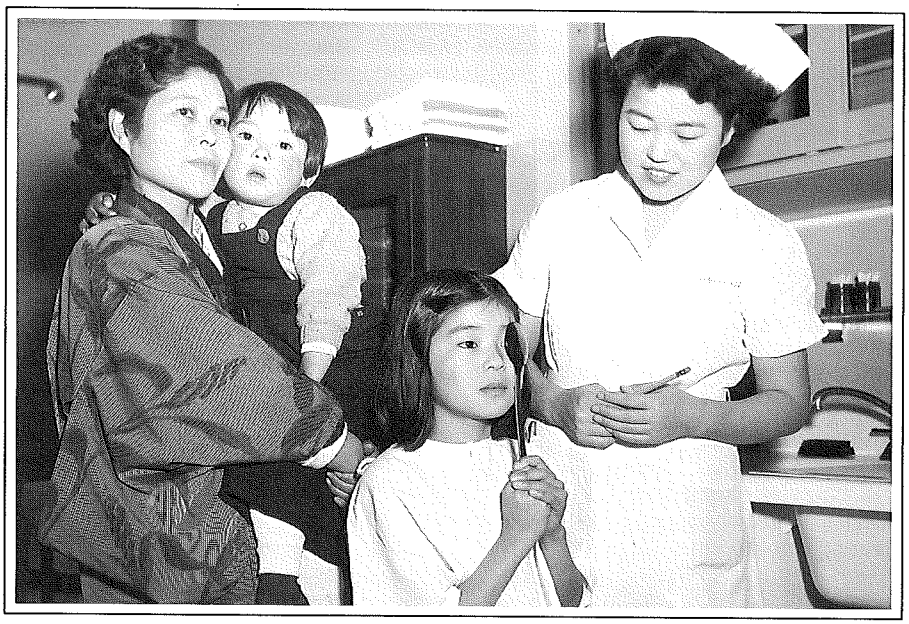
Though the wartime populations of Hiroshima and Nagasaki were in all probability typical of most Japanese cities, the detonation of the atomic bombs bestowed upon the survivors an unwanted but admittedly unique status that in the next decade may provide additional clues not only to the long-term effects of radiation exposure, but to the mechanisms of aging as well.

In all living systems, aging is a normal process that involves biological and physiological changes. How to precisely demonstrate the mechanisms underlying this process has been an elusive search until recently. Technical developments now allow us to more accurately measure molecular, cellular, tissue, and organ changes that one day may permit us to characterize and quantify such changes as indices of aging. As the underlying elements are understood more thoroughly, we may be able to moderate or even retard some of the more seriously debilitating aspects of the aging process.

In regard to the A-bomb-exposed populations, a major concern is whether their radiation exposures will lead to diminished life span by accelerating the normal aging processes. To date, the most significant radiation effect appears to be an increased possibility of cancer at higher radiation exposures.

However, other aspects of aging are also of specific concern to RERF, and the aging workshop panelists—who are pioneers in new molecular approaches—will help to determine how RERF's future studies may answer the question: "Does radiation exposure accelerate aging and increase the serious noncancer disorders associated with shortened life span?"

How RERF's ongoing research has thus far touched upon age-related topics is outlined below.



The wide range of age groups represented among RERF's Adult Health Study participants may prove to be instrumental in revealing aspects of the aging process unforeseen before the development of new cytogenetic and biomolecular techniques. The AHS has monitored about 20,000 persons for more than 30 years.

Experts from Japan and the United States met with RERF scientists at the Hiroshima Laboratory 29–30 March to ponder whether research conducted at RERF can contribute to our knowledge of the mechanisms of aging.

The Adult Health Study

At RERF, 20,000 Adult Health Study participants from Hiroshima and Nagasaki have been matched for age, sex, and radiation exposure (or lack of exposure). From these, 5,000 survivors were known to have suffered acute radiation symptoms, whereas an equal number were presumed to have received similar radiation exposure but experienced no subsequent acute effects. The other 10,000 individuals—either far from the hypocenters (>2,000 m) and/or not in the cities at the time of the bombings (ATB)—were selected to serve as appropriate controls for the exposed populations. Since 1958, these individuals have voluntarily returned to our clinics for biennial medical examinations. It is this population and some specific subsets, such as the in utero-exposed group, that are expected to provide basic information on the aging process under normal nonexposed conditions and as it relates to their radiation exposure.

It should be mentioned that animal experiments to study radiation exposure and life-shortening have for the most part concluded that induced cancer mortality alone accounts for the entire life-shortening process. However, such studies can not detect any increased morbidity associated with exposure, nor do typical animal population studies include the type of medical scrutiny of vital and other health endpoints that can be followed in a continuing medical program designed for humans.

Moreover, most animal experiments start with a selected homogeneous population of a fixed age and follow that group through life. In contrast, the AHS cohort consists of individuals from all age groups, including those who were exposed in utero. RERF has been able to follow each birth cohort through its life span, hence the potential exists for finer discrimination of aging and health effects in both unexposed and radiation-exposed individuals. For example, tentative RERF results strongly suggest that those women who were under 20

continued on page 10

Perceptions of ABCC

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

This issue will extensively cover the early years of our research efforts, as a follow-up to James Neel's first article on that subject in the winter issue of *Update*.

Though the subject matter is of his own choosing, **Koji Takeshima**, at our request, has written a particularly interesting article about the feelings that motivated him—and perhaps others—to cooperate with Americans at the fledgling Atomic Bomb Casualty Commission (ABCC). His sentiments—those of a practicing Buddhist clergyman and physician—reflect an introspective approach that was instrumental in recruiting Japanese medical personnel to work at ABCC. It is only fair to say that without such a willingness to collaborate our research program might well have found an untimely conclusion.

This does not mean that the spirit of cooperation was general and spontaneous. Especially in Hiroshima, ABCC was widely criticized for its foreign—or if you will un-Japanese—character; for providing only diagnostic, not therapeutic, functions; for—according to some—treating survivors as guinea pigs; and for isolating itself from the community atop Hijiyama, a small mountain in the southeastern part of the city.

In this issue of *Update*, these and other perceptions of ABCC's relationship with the communities (both medical and public) of Hiroshima and Nagasaki are seen from quite different perspectives.

A little book, written in 1953 by **Hiroyuki Agawa** (now one of Japan's most prominent novelists) and published in the translation of **John M. Maki** under the title *The Devil's Heritage* in 1957, gives a number of personal accounts of the aftermath of the bombing in Hiroshima, not unlike those found in **John Hershey**'s book *Hiroshima* and in **Michihiko Hachiya**'s *Hiroshima Diary*. Mr. Agawa has graciously given us permission to publish extensive quotes from his (now extremely hard to find) book, as these pertain to the perceptions of ABCC which were widely held at that time. It is interesting to note that many of the opinions described in *The Devil's Heritage* are still occasionally heard, although tempered by the passing of time, and, of course, far less commonly than in 1953. But it was probably not until ABCC had been replaced (in 1975) by the truly binational organization as we know it today, that a change in general attitudes occurred—not in the least because of extensive efforts to improve relations with the Hiroshima medical community.

In Nagasaki, the situation appears to have been different from the beginning, possibly because of the historically determined international outlook of the city and the practical absence of xenophobia in its citizens—conditions which give the city a particularly attractive character even today. The Nagasaki University Medical School, the oldest Western-style medical school in Japan, was founded a little more than 150 years ago through the educational activities of a Dutch physician, **Johannus Pompe van Meerdervoort**, and the faculty is still very much oriented towards international relations. It also is the center of the medical community in the city and prefecture, a situation different from that in Hiroshima, where the university does not play such a central role. In Nagasaki, cooperation with ABCC was a natural development, without (at least most of) the negative connotations found in Hiroshima. When the first American physician in Nagasaki, **James Yamazaki**, left the city in 1951 after a two-year stint as pediatrician and physician-in-charge, the medical school faculty and student body offered him a certificate of appreciation, in which ABCC's role in furthering medical education in Nagasaki was recognized and highly praised. We publish a translation of the text of that certificate in this issue of *Update*, with a sampling of the signatories to that document (496 in all!), reading like a "Who's Who" in the Nagasaki medical community.

Thiessen in Hiroshima

I personally cannot help but see a clear contrast between the attitudes in Hiroshima and Nagasaki, a contrast that is less pronounced but distinctly persists even today.

Sellafield report stimulates discussion

With the Gardner et al. paper in the *British Medical Journal* (*Brit Med J* 300:423–29, 429–34, 1990), the British Nuclear Fuels reprocessing plant now known as Sellafield (to many still better known as Windscale, its former designation) made news again. Given the number and character of the reactions to that paper in the short time since its publication (17 February 1990), we can expect a lively, if not emotional, discussion on the scientific merits and consequences of this study. Reactions so far have ranged from ". . . it would be premature to recommend formal changes to radiation protection limits" (from **Valerie Beral**'s editorial comment in the *BMJ*) to ". . . the moral is that occupational exposure will have to be reduced" (*Nature*'s **John Maddox**, in the 22 February issue of that journal). It amazes me (it shouldn't: I am 62 years old) that so many clearly intelligent people still assume that correlation establishes a cause–effect relationship. This may be understandable from the point of view of the litigants in the slew of cases against the British nuclear industry, who may consider this a finding that will convinc(juries or courts. But what to think of another editorial in *Nature* (344:90, 8 March 1990) that already accepts the findings of Gardner et al. by speaking of the ". . . now-plausible hypothesis that radiation exposure may occasionally be responsible for leukemia among immediate offspring"?

I have no desire to push the discussion into the realm of speculation, nor to take a strong stand pro or con. However clear the facts of the case may be in Sellafield, facts in Hiroshima and Nagasaki, obtained in an analysis of 31,150 live-born children from parents with combined radiation exposures exceeding 10 mSv, point in a different direction. A RERF technical report on this study (Yoshimoto et al., TR 4-90) was recently approved, and a summary of this technical report can be found on page 12 of this issue.

As **Seymour Abrahamson** indicates in an analysis starting on page 3, the biological plausibility for a genetic mechanism to explain the Sellafield data is rather low. But even if one were to assume a radiation-induced genetic mechanism to childhood leukemia—a disease not considered to be a genetic disease by experts in the field, childhood diseases with a recognized genetic basis should also have

continued on page 4

Childhood leukemia at Sellafield—a genetically transmitted mutational disease?

by Seymour Abrahamson
RERF Chief of Research

Editor's Note: In his capacity as an NCRP Committee 1 member, the author has recently been pondering the issue of genetic modeling and disease transmission—pertinent in light of recent reports from England linking parental radiation exposure to leukemia in offspring. Following is a portion of Abrahamson's recent report to Committee 1, which reflects his personal opinions and approaches—not the official stance of the Radiation Effects Research Foundation.

Undoubtedly much will be written about the thesis that the excess leukemia cluster observed around the nuclear reprocessing facility in Sellafield, England, resulted from preconceptually induced paternally transmitted germinal mutations—particularly because the fathers of several leukemic children were employed at the plant and had film-badge readings that were both high in the first six months before conception and in the range of 100 mSv or higher during the decade preceding conception (Gardner et al., *Brit Med J* 300:423–29, 429–34, 1990).

The issue in question is one of germinally induced mutation rates that would give rise to mutant offspring who in the Sellafield case exhibit childhood leukemia. Since such an outcome is assumed to be a male-induced mutation rate condition, we can concentrate our analysis on experimental mammalian studies in male germ cells. This will permit an estimate of risk resulting from radiation exposure and a comparison of these results with the Sellafield experience.

Two major classes of germ cell stage and radiation condition are of concern here. More radiosensitive than the spermatogonia, postgonial cells consist of mature sperm spermatids and spermatocytes (herein referred to as the sperm sample), and are usually recovered in the first 3 months after exposure. Representing the stem cell population, spermatogonia are usually of most interest because mutations induced in them will accumulate and be copied manyfold to descendant sperm cells. These gonial cells—unlike most of the sperm stages—respond differently to acute and chronic radiation exposures: chronic exposures at high doses produce fewer mutations than equivalent acute doses. Thus, it takes a higher dose of chronically delivered radiation to produce the same total mutation rate as an acute irradiation.

The doubling dose (DD), the dose required to produce a mutation rate equal to the spontaneous mutation rate, is thus greatest for chronically irradiated gonial cells, lower for acutely irradiated gonial cells and still lower for sperm stages (during which the dose rate will usually not affect the mutation rate).

Used by the BEIR and UNSCEAR genetic committees to assess genetic risk to human populations, DD estimates are derived from experimental mouse studies and independently from the lower 95% confidence limits of an earlier F_1 progeny study from Hiroshima and Nagasaki (Schull et al., RERF TR 7-81; *Science* 213:1220–27, 1981). A recent conservative, i.e., prudent, estimate of the DD for chronically exposed gonial cells is cited as 1 Sv (100 rem) (BEIR V, 1990; UNSCEAR, 1988). For acutely exposed gonia, the value is 0.7 Sv (70 rem), based on linear quadratic extrapolation (Abrahamson, NCRP, in press). Although mouse studies generally indicate that sperm cells are 2–5 times more sensitive than acutely irradiated spermatogonia, in this analysis we will assume a a sensitivity 10 times greater and thus a DD of 0.07 Sv (7 rem or 70 mSv). Using these conventional mutation approaches, the Sellafield outcome reported by Gardner et al. will be assessed.

> ***"For leukemia, virtually no human data suggest that it is an inherited disease. But for argument's sake, an unconventional model for leukemia inheritance will be presented here. . . ."***

Next, the genetic conditions necessary for transmitting a genetic disease must be considered. For leukemia, virtually no human data suggest that leukemia is an inherited disease (James V. Neel, University of Michigan, personal communication, 1990). But for argument's sake, an unconventional model for leukemia inheritance will be presented here to provide a potential genetic basis to the Sellafield hypothesis: childhood leukemia mutations will be assumed to act like "dominant" lethal mutations, i.e., children receiving such mutations will die before reaching reproductive maturity and thus will not transmit the mutations. In our model, not only will dominant mutations for leukemia act in this way, but so too will recessive mutations. This is because a child receiving a newly arisen recessive mutation is virtually assured of becoming homozygous for that gene. Conventional spontaneous mutation rates on the order of 10^{-5} per gene in a blood cell population ranging from 10^9 to 10^{11} throughout childhood guarantee that thousands of cells will be homozygous at some point.

How does germinal mutation contribute to leukemia? To assume that all childhood leukemias are derived germinally is an extreme or worst-case assumption and is also contradicted by the observation that the atomic bomb survivors who were children when exposed show a dose-dependent increase in childhood leukemia. For these children, a leukemia rate of about 10^{-3} person-year-gray was demonstrated. Thus, radiation exposure and presumably other carcinogens and spontaneous events are capable of producing the disease in *somatic cells*.

Supposing in our model that the germinal contribution to leukemia could be 100%, 50%, 25%, 10% or 5%, what dose conditions would be required to increase the relative risk of leukemia by a factor of 2, keeping in mind that greater relative risks (such as 3–8) require proportionately higher doses?

Until the age of 20, among both the A-bomb survivors' children and the children of the unexposed, leukemia incidence does not differ significantly. It is about $5 \cdot 10^{-4}$ or an annual incidence of $2.6 \cdot 10^{-5}$ person-year-gray) (Yoshimoto et al., RERF TR 4-90, see page 12 of *Update* for the TR summary).

If germinal mutations account for 100% of this leukemia mutation incidence, the spontaneous mutation rate would have to be $2.5 \cdot 10^{-4}$ per gamete, assuming an equal contribution from both sexes. If the DD to sperm is 0.07 Sv, this would double the male contribution ($2.5 \cdot 10^{-4}$ spontaneous + $2.5 \cdot 10^{-4}$ induced) but would not double the leukemia incidence. That would require an additional 0.07 Sv ($2.5 \cdot 10^{-4}$ induced) which together with the spontaneous female contribution ($2.5 \cdot 10^{-4}$ per gamete) would now give a rate of 10^{-3}.

continued on next page

Perspectives

continued from page 2

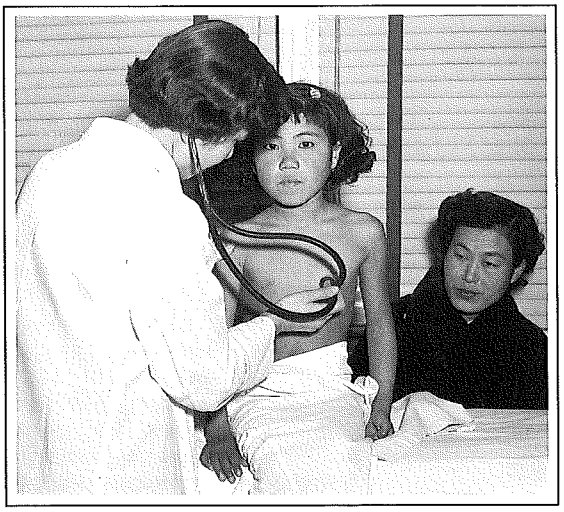
shown an increase in the Seascale population. Without such an increase, it will be hard to explain why radiation is so selective in its action on the genome.

Aging research at RERF

At this writing, the last RERF workshop in a series initiated to advise the Foundation on future developments in its research program has ended. More extensive coverage of its discussions and recommendations will be found in the next issue of *Update*.

The front-page article in this issue discusses some of the past and ongoing research that is relevant to elucidating the phenomenon of aging. As a natural outgrowth of our 30-year-long biennial examinations of the well-defined Adult Health Study population, RERF researchers will be able to evaluate the effects of radiation exposure on processes such as "accelerated aging," and "premature aging" by delving into the Foundation's treasure house of information on the physiologic aging process.

Our cohorts themselves are "aging" rapidly, of course, which provides a particular stimulus for research in the short term. The largest of our cohorts, the Life Span Study cohort, shows this dramatically. In 1950, shortly after the beginning of our studies, the average age of cohort members was 33.3 years, and the size a little over 91,000. This year, the average age has increased to 61.5 years, with a reduction in size to nearly 52,000—approximately 57% of the original number. In another 10 years, the average age will be 68.2 years, and the cohort size further reduced to 44%. Ten years later, in 2010, 30% of the original cohort will still be alive, with an average age of 75.2.



Representing all age groups, the RERF Life Span Study cohort totaled about 91,000 persons in 1950. For more than 30 years, participants have received biennial health examinations, providing a vast database relevant to long-term radiation effects, as well as to the mechanisms of aging. It is estimated that in the year 2010 30% of the original cohort will still be alive, thus enabling data collection for more than six decades.

Even more striking is the statistic that gives the average age of our living cohort members at the time of the bombings (ATB): in 1950, this number was 28.3, today it is 16.5. In the years 2000 and 2010, it is estimated that the average ages ATB will be 13.2 and 10.2, respectively. Clearly, during the coming years quite a few of those exposed very young ATB will enter the ages dominated by cancer and other diseases of old age, and some unique information will become available, provided there is a good research program to obtain it.

Rather frequently, questions arise about the future of RERF. I think that the answers to those questions need to be formulated soon, precisely and decisively. To me at least, it is evident that the future of our studies will be exciting and productive. Despite the tragic events that gave rise to our research, the knowledge derived from it may well turn out to be uniquely relevant to the early diagnosis and prevention of cancer, and may provide insights into mechanisms of aging not obtainable otherwise. ❑

Childhood Leukemia

continued from page 3

Table 1 shows the required doses to different male germ cell stages to result in a leukemia relative risk of 2, assuming different germinal contribution frequencies.

This conventional mutation analysis clearly illustrates that only the worst-case assumption (a 100% germinal contribution to leukemia induction) and mature sperm cell stages require doses in the general range (about five times greater) of those received by the Sellafield males to result in a doubling of leukemia risk. If the germinal mutation contribution to leukemia is low, 50% or less, then it should be obvious that the Sellafield leukemias could not be of paternal origin.

Of course, it can be argued that this analysis is contrived to produce the given result—that if a sperm DD of 0.01 or 0.015 Sv had been chosen, then leukemia relative risk would have doubled. This would require that the human germ line be 100 to 200 times more sensitive to leukemia induction than highly inbred mouse strains which have a high natural incidence of leukemia (T. Nomura, "Further studies on X-ray and chemically induced germ-line alterations . . . ." In: *Genetic toxicology of environmental chemicals. Part B: Genetic effects and applied mutagenesis.* New York, Alan R. Liss, Inc., 1986). Moreover, postulating such a low DD to sperm would suggest that acutely exposed spermatogonial cells would also have a lower DD. Adopting the worst-case model, a DD lower than 0.7 Sv would most assuredly have led to a significant increase in leukemia in the atomic bomb F_1 cancer study.

I have attempted to examine the implications of the Gardner et al. report in the context of radiation genetics using information consistent with animal and human studies. Although some factors may have been overlooked in these approaches, at the moment this analysis suggests that the estimated paternal doses to the Sellafield workers are too low to result in the endpoint being discussed, i.e., childhood leukemia.

Perhaps somatic cell cytogenetic and mutation analysis would be useful in determining if the accumulated film badge doses of the Sellafield workers agree with biological dosimetry data. ❑

Erratum

Reported incorrectly in the winter 1989–90 issue of *Update*, the topic of N. Taniguchi's 13 October lecture was superoxide dismutase and its implications on aging and cancer.

Table 1. Dose (in sievert) needed to increase the relative risk of leukemia by a factor of 2 at five different levels of germinal contribution

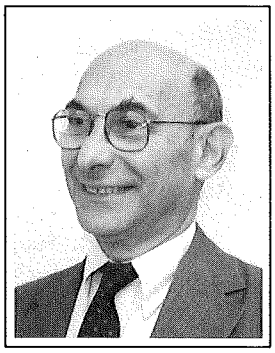
Germinal contribution to disease	Dose (Sv) required to produce a leukemia relative risk of 2 to:		
	Sperm*	Spermatogonia (acute dose*)	Spermatogonia (chronic dose*)
100%	0.14	1.4	2.0
50%	0.28	2.8	4.0
25%	0.56	5.6	8.0
10%	1.4	14.0	20.0
5%	2.8		

* Assumes a doubling dose of 0.07, 0.7 and 1.0 Sv for sperm and for acutely and chronically exposed gonia, respectively.

How RERF Data Influenced the New BEIR V Risk Estimates

A member of the Committee on the Biological Effects of Ionizing Radiation, the author expands upon lectures given at the RERF laboratories by discussing the role of RERF data in the development of the new BEIR V risk estimates recently published by the US National Academy of Sciences.

by Jacob L. Fabrikant
Donner Laboratory and Donner Pavilion
University of California–Berkeley



Fabrikant

Important new information from humans has mainly come from further follow-up of existing epidemiological studies, notably the Japanese atomic-bomb (A-bomb) survivors and the ankylosing spondylitis patients; from new epidemiological surveys, such as patients treated for cancer of the cervix; and from combined surveys, including workers exposed in underground mines. In spite of a considerable amount of research, only recently have there been efforts to apply the extensive laboratory data in animals to define the dose–incidence relationship in the low-dose region. There simply are insufficient data in the epidemiological studies of large human populations to estimate risk coefficients directly from exposure to low doses.

By far, the most important survey contributing to current radiation risk assessment is that of the Japanese A-bomb survivors, which provides the greatest amount of information—and frequently the only information—required for reassessing previous risk estimates. The average period of follow-up to 1985 approaches 29 years, with 2,185,000 person-years at risk. The data are based on the DS86 individual dosimetry for each survivor: the radiation dose was whole-body and instantaneous, the absorbed doses ranging from 10 mGy to 6 Gy, with a mean whole-body absorbed dose of 295 mGy. The new data, published in RERF Technical Report 5-88, indicate that the carcinogenic effect of atomic radiation in the Hiroshima and Nagasaki survivors—the risk per unit dose—is higher than previously estimated. There are three explanations for this.

First, the reassessment of the dosimetry, resulting in DS86, has substantially reduced the high-LET neutron component. Second, the number of cancer deaths has increased with continued follow-up, which is particularly evident in survivors who were irradiated early in life: the cumulative radiation-associated excess of cancer death has risen from 133 in 1975 to 236 in 1985. Third, there have been developments in the method to calculate the cancer rate, based on age at risk and time since exposure (Preston and Pierce, *Rad Res* 114:437–66, 1988). The overall effect has been that the carcinogenic risk per unit dose equivalent has increased some 40–70% for solid tumors, depending on the tissue at risk and its depth in the body, and more for leukemia.

Two models used to project an overall cancer risk estimate for an exposed population—the additive and multiplicative risk projection models—were examined by the BEIR V Committee. The additive risk model, which assumes that the excess cancer risk is independent of the natural cancer incidence, was rejected by the committee. A modified multiplicative model was accepted, as this model appeared to be more closely related to the excess cancer mortality experience among the A-bomb survivors. However, the reliability of either model for cancer of a specific type or site, or for those persons exposed at a younger age, remains uncertain.

The limited data available to examine the dose-response relationships at low doses have made it necessary to extrapolate from high-dose data. The Japanese leukemia data still conform to the linear-quadratic nonthreshold model, whereas for cancer deaths other than leukemia the data support a linear nonthreshold model in the dose range below 4 Gy. The BEIR V Committee found that only for leukemia, cancer of the lung, female breast, and digestive system were sufficient data available to permit the calculating of numerical risk estimates. All other cancers were modeled as a group. Except for the special circumstances of the carcinogenic effects of internally deposited alpha emitters and for certain selected studies of the thyroid gland and the breast, it has been the mortality experience of the A-bomb survivors that was selected in both the 1988 report of the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) and the BEIR V report (Health effects of exposure to *low levels of ionizing radiation: BEIR V.* Washington, D.C., NAS Press, 1990) as the most appropriate basis for projecting risk estimates of carcinogenic effects for the general population.

Table 1. Lifetime excess cancer risk estimates cancer mortality per 100,000 persons exposed* (Source: BEIR V report)

	Leukemia		Nonleukemia	
Exposure	Males	Females	Males	Females
• Continuous, 1 mSv/y, lifetime				
Best estimate	**70**	**60**	**450**	**540**
• Continuous, 10 mSv/y, ages 18–64				
Best estimate	**400**	**310**	**2480**	**2760**
• Instantaneous, 0.1 Sv: population-weighted average of ages at exposure				
Best estimate	**110**	**80**	**660**	**730**

*Values rounded to nearest 10. Same dose equivalent to all organs.

The cancer risk estimates developed by the BEIR V Committee, compared to those calculated by UNSCEAR in its 1988 report, are as follows:

Leukemia: The UNSCEAR report projected an excess cumulative lifetime mortality in relation to age at the time of exposure to be about 100 deaths per 10,000 persons at 1 Gy of low-LET radiation for both the additive and the multiplicative models, and a 40-year plateau period of risk. The BEIR V estimate of lifetime risk, based on a linear-quadratic dose-effect curve and a modified multiplicative model, is similar. Both in the A-bomb survivors and the ankylosing spondylitics, the relative risk of leukemia varies less with age than the absolute risk; the latter is substantially greater in individuals exposed during childhood or late adult life.

continued on next page

News Briefs

✓ RERF 's 15th Anniversary To Be Celebrated in April

To commemorate the establishment of RERF, the binational research institute that replaced the American-administered Atomic Bomb Casualty Commission, ceremonies will be held in Hiroshima and Nagasaki on 13 and 16 April, respectively. About 440 current and 200 former employees are expected to attend these events.

✓ 17th RERF Scientific Council Convened in Nagasaki

Ten experts and several observers met in Nagasaki 26–28 March for the annual review of RERF's research programs. Providing recommendations on the relevance and scientific quality of ongoing RERF studies were: **Kunio Aoki**, Nagoya University School of Medicine; **Eisei Ishikawa**, Jikeikai University School of Medicine; **Toshiyuki Kumatori**, Radiation Effects Association, Tokyo; **Ei Matsunaga**, National Institute of Genetics; **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 School of Medicine.

✓ Residual Radioactivity in Soil To Be Estimated

At the request of Hiroshima's "black rain" reassessment committee, residual soil radioactivity from uranium-235 and uranium-238 will be measured by Hiroshima University's Research Institute for Nuclear Medicine and Biology beginning next year. The soil samples to be used had been collected in 1986 and 1988 by the Ministry of Health and Welfare at 107 spots within 30 km of hypocenter for an earlier study of cesium-137 and strontium-90.

✓ A-bomb Radiation Research Group Plans 31st Meeting

About 250 doctors and specialists are expected to attend the 31st meeting of the Atomic Bomb Late Effects Research Group in Nagasaki on 3 June. Experimental research on radiation carcinogenesis, and recent developments related to malignancies of the hematopoietic system occurring among A-bomb survivors will be the main topics.

✓ Research Staff Appointments Announced

Hiroshima

Department of Statistics: **Fumiyoshi Kasagi** and **John B. Cologne** have joined the department as research associates. Kasagi formerly worked at the National Cardiovascular Disease Center in Osaka, where he was involved in a large-cohort study. At RERF, he will assist the Department of Clinical Studies in analyzing Adult Health Study data. A recent graduate of the University of Washington's biostatistics program, Cologne is interested in nonparametric smoothing procedures and will work on problems related to modeling cancer risks and noncancer morbidity in the Life Span Study.

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

Department of Epidemiology: Research associate **Yukiko Shimizu** has been promoted to associate senior scientist.

Department of Clinical Studies: Formerly chief of the Division of Medicine, **Hideo Sasaki** has been promoted to assistant department chief. Former Division of Clinical Laboratories Chief **Kazuo Neriishi** has been appointed chief of the Division of Medicine. **Shizuyo Kusumi** is concurrently serving as chief of the Division of Clinical Laboratories and as associate senior scientist, Division of Medicine.

Department of Radiobiology: Now a research associate in the Laboratory of Immunology, **Tomonori Hayashi** was formerly employed by Wakunaga Pharmaceutical Co. He previously performed characterizations and functional analyses of bioactive substances, such as growth factors, using biotechnology and immunochemistry.

Nagasaki

Department of Clinical Studies: Division of Medicine Chief **Tatsuki Matsuo** has been promoted to assistant chief of the department.

✓ Highlights of the RERF Lecture Program

On 12 January, **Tao Zufan**, Laboratory of Industrial Hygiene, Beijing, People's Republic of China, spoke about the epidemiological studies conducted in that country's high background radiation areas.

Fritz Melchers of the Basel Institute for Immunology, Basel, Switzerland, discussed B cell development on 31 January.

On 7 February, **R.H. Clarke**, who is director of the United Kingdom's National Radiological Protection Board, lectured about the NRPB's activities. ❑

BEIR V Risk Estimates

continued from page 5

Cancers other than leukemia: The Japanese experience indicates a dose-dependent excess mortality from solid cancers during the 1950–85 period to be representative of an excess relative risk of 1.29 at 1 Gy and an absolute risk of 7.41 cancer deaths per 10,000 person-year-gray (kerma); the corresponding values for organ-absorbed dose are 1.41 and 10.13, respectively. The UNSCEAR age-specific risk estimates indicate the cancer excess to be very much greater in those irradiated in childhood than during adult life; the BEIR V Committee narrowed the age cohorts and derived estimates consistent with these findings.

Since the risk models were derived primarily from data on acute or single high dose-rate exposures, the application of these models to continuous low dose-rate exposures requires consideration of a "dose rate effectiveness factor" (DREF). The BEIR V Committee suggests a range of DREFs that may be applicable. Such reductions are only applied to the nonleukemic risks, as the leukemia risks already contain an implicit DREF of about 2 owing to the use of the linear-quadratic model. The 1980 BEIR III Committee chose a DREF of about 2.25 from the leukemia data and applied it to the nonleukemia data as a fixed constant. The BEIR V Committee concluded that it could not justify the assumption of the same dose-response model for all sites, and used separate dose-response models, with no DREF. However, both the 1988 UNSCEAR report and the 1990 BEIR V Committee report suggest that the use of a DREF at the lower end of a 2–10 range, applied to human radiation carcinogenesis, would be reasonable.

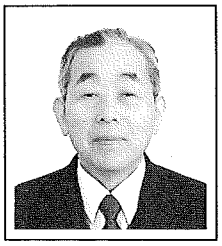
Finally, the BEIR V Committee estimated life-time risks for leukemia and all other cancers resulting from two continuous exposure situations: life-time and from 18–65 years, and a population-weighted instantaneous exposure to all persons of all ages. The results are shown in Table 1.

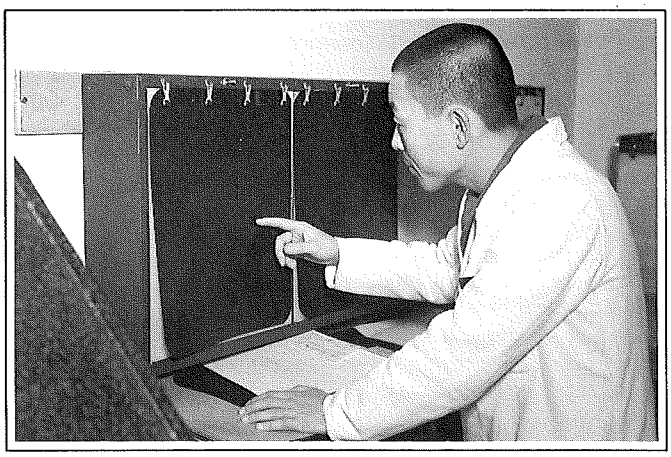
The BEIR V Committee recognized that the new information and data available since the 1977 recommendations of the ICRP resulted in risk estimates that were appreciably higher than previously recorded. Comparison of the risk projections in the BEIR V report and the 1980 BEIR III report indicates that, overall, risk estimates are consistently greater by a factor of 3 or more. The major differences between the two sets of estimates are for the additive risk model as used by BEIR III. The BEIR V Committee concluded that, in the light of the data now available, the assumption of a constant additive excess risk is no longer tenable, and that the risk estimates from the model provided in the 1980 BEIR III report were much too low, by factors of about 1.5–2. Accordingly, the committee concluded that the new data and methods required the reassessment of the previous risk estimates for the carcinogenic effects of low-dose radiation. The next step is now the consideration by ICRP of the latest UNSCEAR and BEIR reports in order to determine the extent to which an update of its 1977 recommendations is appropriate. ❑

Cooperative Spirit Engendered by Buddhist Ideals

During the lean postwar years, ABCC struggled to gain a foothold in both Hiroshima and Nagasaki. The American-born author—a surgeon who helped recruit many of ABCC's early Japanese doctors—reveals the sentiments that spurred himself and others to work side-by-side with Americans, who only a year earlier, had been their wartime adversaries.

by Koji Takeshima
Takeshima Surgical Hospital
Higashi Hiroshima





Today, Takeshima, above, owns a clinic in a suburb of Hiroshima. At right, he is shown in 1949 examining x-ray images at ABCC.

For three years during World War II, I was assigned as an army surgeon to military hospitals and the "Special Attack" Corpsmen Training Center of the Army Air Force in the Japanese homeland. Shortly after the war ended, I was discharged from military service, and I returned to Hiroshima, my hometown. There, I learned that my younger brother, who had been employed at Hiroshima City Hall, had died in the atomic bombing. My elder sister, concerned about his safety, had searched throughout Hiroshima for many days, but alas my brother never returned.

Amidst this grief, in 1946—the year after war's end, I was studying surgery at the Hiroshima Red Cross Hospital. In December, Dr. **James V. Neel**, an American, called on Dr. **Ken Takeuchi**, director of the Red Cross Hospital. Dr. Neel began a hematology study of atomic bomb survivors in two rooms of the hospital's Radiology Department. Later, a genetics study of the second generation of A-bomb survivors in Hiroshima was started, and meetings were frequently held with the officers of the Midwives Association in Hiroshima City.

The cooperation extended by the Midwives Association in the midst of the sad situation in Hiroshima was indeed great. In their hearts, the American scientists must surely have been struck with admiration at the magnanimity of the people of Hiroshima. The cooperation extended by the members of the Midwives Association and the citizens was beyond description.

Buoyed by our Buddhist upbringing, my sister and I, while grieving over our brother's death, decided to cooperate with ABCC. My sister served for many years as a member of its Statistics Department, and I worked for six years (1947–1953) as a physician in the Hematology and Genetics departments.

At this point, I would like to consider the attitude that resulted in the cooperation of the Midwives Association and the citizens at large.

First, the cause of the Pacific War, as the Japanese viewed it, was related to Japan's ambition to expand its small territory. Other countries claimed that Japan—a country with limited resources—had begun stockpiling petroleum reserves, thereby threatening the world. Thus, petroleum sales to Japan were suspended. Confronted with this, Japan began to feel menaced by the petroleum shortage and finally attacked Pearl Harbor, which led to the outbreak of the Pacific War.

Considering this chain of events, which began with Japan's mounting ambitions and terminated in the atomic bombing of Hiroshima and Nagasaki, it should be noted that the people of both countries resorted to very sinful inhumane actions. These actions are, I believe, not a question of whether the Japanese or the Americans were to be blame. The tragedy arose from our having forgotten the will of the gods and Buddha.

Here, the words of an Indian buddha impress me deeply: "I must be grateful that it has been my lot not to be compelled to commit patricide or matricide in my lifetime." And, Shinran Shonin, a Japanese saint, said: "Man may deport himself in any manner depending on the circumstance in which he is placed."

If I had been in the position of Tojo and the others who began Japan's involvement in the Pacific War, or of one who developed the atomic bomb or ordered the bomber captains to drop the first atomic bombs, I might have done the same. I should be thankful that I was not in such positions. From a moral viewpoint, I would have been equally guilty.

The teachings of Buddha expound upon the previous life, the present life, and the future life. A famous *haiku* written by the Japanese saint Gyoki Bosatsu 1,100 years ago reads: "When I hear a mountain bird cry *horo-horo*, I think it might be father, I think it might be mother." Thus, the birdsong reminded the saint that the pigeon may have been his father or his mother in a previous life, in accordance with the Buddhist belief that no living beings in this world are strangers but that all are intimately related.

Perhaps there would be no disputes if we would but feel that all life in this world—not just humankind—is our kin, our companion.

With such Buddhist precepts in our hearts, my sister and I became inclined to cooperate with ABCC. In a similar fashion, the Midwives Association and citizens of Hiroshima cooperated wholeheartedly and with hope for the future.

Most ABCC employees and most citizens of Hiroshima had relatives who fell victim to the atomic bomb. Their cooperation was most welcome and impressed me profoundly. Even now, it arouses a deep feeling of gratitude. We must not forget how much the ABCC of today owes to the cooperation of these people.

Finally, in my opinion, we human beings must build a peaceful world and universe in accord with the will of the gods and Buddha by containing as much as possible our desires and our anger, by lessening ignorance and lack of understanding, and by not taking self-centered actions.

It should be our obligation to the people who perished as a result of the atomic bombings that we never forget this pledge. ❑

Extracts from *The Devil's Heritage*

by Hiroyuki Agawa
(translation by John M. Maki)

Editor's Note:
In order to preserve the flavor of the original translation (published in 1957 by The Hokuseido Press, Tokyo), no annotations or footnotes have been made to the passages quoted. Because of the rarity of the book, reference to chapter and page have been omitted. In fairness to the author, we must state explicitly that we have abstained from trying to provide a balanced extract of his book. Many explanatory remarks and modifying statements also occur in the book, especially those made by ABCC officials. But they are not as interesting (nor enlightening) with respect to the subject covered, i.e., the largely negative attitudes of the people who play major roles in the narrative quoted below.

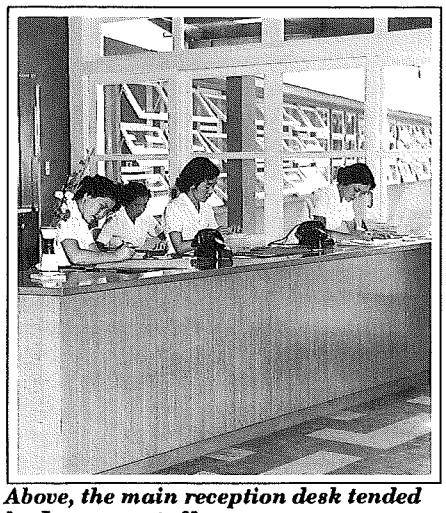
* * *

Noguchi got off the streetcar at a stop called *Hijiyama-shita* and climbed the broad slope.

Occasionally a jeep or station wagon with the letters "ABCC" on the body would pass him going the other way and quietly go down the slope or would overtake him and powerfully climb the hill. In the cars he could see women, looking like *nisei* [American-born Japanese], riding with stacks of documents on their laps or groups of young mothers riding together and carrying their children.

The road wound to the left and wound to the right and reached the newly cleared ground on the mountain top. There standing in a row were a number of colorful, American-style, quonset-type buildings. . . .

When one pushed open the door and went in through the entrance, there was an odor that seemed faintly foreign. At the information desk on the right, two or three very beautiful Japanese women (perhaps nurses?) were sitting . . . .



Above, the main reception desk tended by Japanese staff.

He had to wait for a while. He sat down on a sofa in a corner of a place like a lobby in front of the information desk and idly looked at the American magazines, the children's picture books and at one side the children's wooden horse. The floor was scrupulously clean with a high, slippery luster. The combination of colors, preferred by Westerners, on the desk, the ceiling, and the window-frames. The faintly aromatic odor he noticed when he entered. The strikingly lipsticked nurses quietly going to and fro, in their pure white uniforms. All this appeared to make this a so-called "little foreign country" entirely different from Hiroshima.

* * *

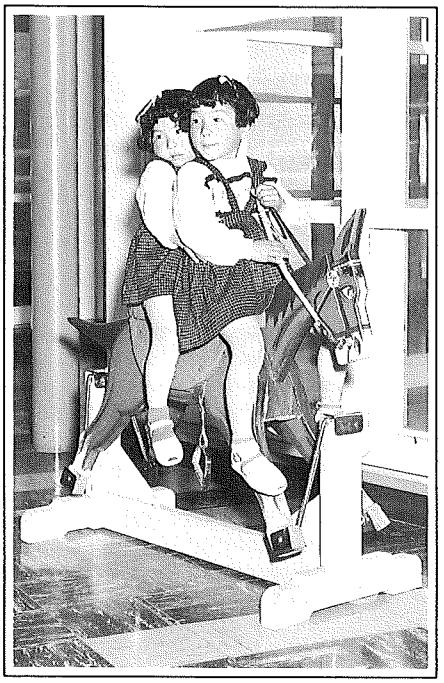
". . . Hiroshima and Nagasaki are the only two places in the world where people have actually had experience with the atomic bomb. Speaking plainly, as far as I can see, this ABCC is skillfully collecting data from the Japanese in order to establish a scientific defensive policy in the event that America undergoes an atomic bomb attack in World War III.

". . .Usually, the reason patients go to the doctor is that they want to be cured. But there's no place that knows as much about handling atomic bomb wounds as the ABCC. Already they've been carrying out research investigations for seven years, but it's very strange that their medical treatment plans call only for giving information to a few private doctors treating individuals scattered through the town. Even though they haven't found a method to determine atomic bomb symptoms 100 percent in every case, it makes you feel that they could produce some kind of an answer, doesn't it? That's one reason why they say that people here are being used as guinea pigs. . . ."

* * *

"That's so, but it's still a curious thing. There are a lot of Japanese doctors, but since racial prejudice is really strong they probably couldn't make any kind of demand or a declaration. And so they've all become used to eating and being used. The pay also is a lot better than in Japanese hospitals. But some of those fellows do nothing everyday but peer into ears, others only check blood-types, others only do urinalysis. The only ones who get their hands on any of the collected data are the top Americans and they probably don't show it around.

"What I find so disagreeable about these Japanese doctors—it's all right to cooperate with the ABCC, but—is that with all that equipment and after spending seven years at it they haven't come up with a single thing that would ease the suffering of their fellow Japanese. . . . There might not be any point to it, but I feel that at least they ought to resign."



To Japanese citizens who began participating in ABCC's programs in Hiroshima, the shiny new American-style facilities, including oddities like the wooden hobby horse shown above, created a "little foreign country" separate from the city itself.

* * *

". . .to date they haven't found anything that would indicate that children born in Hiroshima since then have been affected by the atomic bomb."

"Did you hear that it was also true of children who were being carried at the time?"

"Well, there wasn't anything very clear on that but I thought I heard something like that."

"If you did, it's a lie," Inoue said. "We might be prejudiced because of what's happened to us, but as we understand it the ABCC not only doesn't treat people but feels that for the purposes of its own research it's best to keep people just as they are because after they're healed the work can't be continued. How about that? This isn't only my own opinion. Pediatricians I know say the same thing. I think that my views are not mistaken. Those backing the ABCC don't show their real intentions." ❑

1951: Words of Appreciation for ABCC

Editor's Note: When James Yamazaki, ABCC's pediatrician and physician-in-charge, returned to America in 1951 after two years in Nagasaki, he received a certificate of appreciation from Nagasaki University, the translated text of which follows:

Nagasaki University receives great benefit from the presence of the Atomic Bomb Casualty Commission in Nagasaki City.

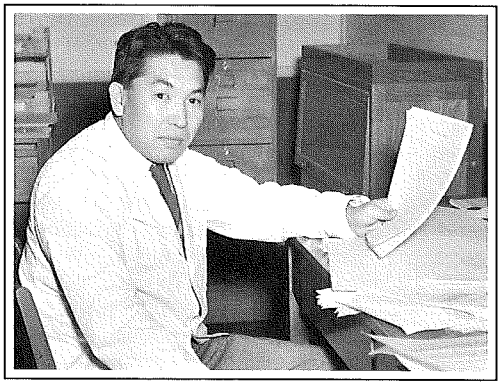
For example, the university's Department of Pathology has expeditiously studied stillborn babies and general autopsy cases to collect data on atomic bomb diseases. Other research at the university has been similarly assisted.

The university's predecessor, Nagasaki Medical College, formerly had the greatest number of books and journals among the medical colleges in Japan. But these books and journals were burnt to ashes at the time of the atomic bombing. Though scientific literature and reference materials are scarce, our current budget barely allows the purchase not only of back issues but also of new foreign journals. Under these circumstances, the benefit Nagasaki University as a whole receives from the abundant documents in the ABCC Library is immeasurable. In each department, a staff conference is held weekly and what one staff member may have read at ABCC is heard by many others. In addition, we frequently convey the content of ABCC journals to other universities in Japan upon their request.

Consequently, we wish to express our thanks to ABCC and to petition that ABCC will stay in Nagasaki for many years to come.

Since 219 faculty members and 277 students actually signed this certificate, only a few of the signatories are listed here:

Genji Matsuda, former dean, Nagasaki Medical School (NMS)
Raisuke Shirabe (deceased), NMS surgery professor and former RERF visiting director
Joji Tasaki, now vice president of Oita Medical College and known as *Joji Shirabe*, since he adopted the family name of Raisuke Shirabe, whose daughter he married
Issei Nishimori, present-day RERF consultant
Michito Ichimaru, professor, Atomic Disease Institute, Nagasaki, and RERF consultant
Katsuaki Joya, former president of the Nagasaki Prefectural Medical Association
Yasushi Miyake, former director, A-Bomb Hospital, Nagasaki
Nagatoshi Fujita, present director, A-Bomb Hospital
Yoshiatsu Naito, present dean, Nagasaki Medical School
Hideo Tsuchiyama, present president, Nagasaki University ❑



Yamazaki at work in Nagasaki on 19 February 1950.

Life Span Study Cancer Mortality Data Available on Disk

The DS86 cancer mortality and average organ transmission factor data for those RERF Life Span Study (LSS) cohort members who had been assigned revised dose estimates by December 1987 are now available on high-density 3.5- and 5.25-inch floppy disks (in DOS format) for users outside the Foundation.

The three files on the disk contain the following information: Life Span Study cancer mortality data for 1950–1985, city-specific and age-at-exposure-specific transmission factors used to compute organ dose estimates, and detailed descriptions of the data and file format, as well as disease groupings with their ICD codes.

Though identical to data used in the BEIR V Committee's analyses for the BEIR V report (NAS, 1990), these data do differ somewhat from RERF's LSS Report 11 data sets. For site-specific analyses in LSS Report 11, a separate data set was created for each tumor type. In addition, Report 11 analyses were based upon less detailed stratification on age-at-exposure than is provided on these disks—the number of records in each LSS Report 11 data set being about 1,600.

However, the population of atomic bomb survivors being considered is identical to that used for analyses discussed by Preston and Pierce (RERF TR 9-87; *Rad Res* 114:437–66, 1988) and in LSS Report 11, Parts 1 and 2 (RERF TR 12-87; *Rad Res* 118:502–24, 1989; RERF TR 5-88; *Rad Res* 121:120–41, 1990).

The main file summarizes cancer mortality from 1 October 1950 through 31 December 1985 for 75,991 members of the extended Life Span Study cohort for whom DS86 dose estimates could be computed as of December 1987. Cohort members not included in this tabulation include 26,517 people who were not in the cities at the time of the bombings, 2,384 survivors for whom dose estimates could not be computed due to inadequate shielding information, and 15,237 survivors assigned the earlier T65DR dose estimates, but for whom DS86 estimates could not be computed.

Each record in the main file contains data for a single cell in a cross-tabulation over city, sex, age-at-exposure, total DS86 kerma, and time-since-exposure. For each cell the data are:

- Integer class mark codes for city, sex, age-at-exposure, DS86 total kerma, and time-since-exposure.
- An integer index for 160 strata defined by city, sex, age-at-exposure, and time periods.
- The total number of person-years in the cell.
- The total number of deaths from any cause in the cell.
- Person-year-weighted mean values for the gamma, neutron, and total kerma in milligray.
- Person-year-weighted mean values for time-since-exposure and age-at-exposure (attained age can be computed as the sum of these two values).
- The number of cancer deaths in each of 19 nonexclusive categories.

All fields in each record are separated by at least one blank so the file can be easily read by any program capable of reading a blank delimited ASCII file. Certain FORTRAN formats can also be used.

Persons interested in obtaining a copy of this data on disk should contact the RERF Editorial Office, 5-2 Hijiyama Park, Minami-ku, Hiroshima, 732 Japan (facsimile: 082-263-7279). The cost per disk is US$50. Please specify the type of disk required. ❑

Aging Research at RERF

continued from page 1

ATB are experiencing an increased occurrence of cardiovascular disorder which might be related to high-dose exposure.

Detailed information has been and will continue to be collected and analyzed on conditions such as cardiovascular diseases, stroke, senile dementia, cataract, glaucoma, and vertebral fracture—all known to be age-related and/or in some cases related to a specific birth cohort. Individuals who were older ATB, for example, grew up under a very different dietary regimen than those who are now in their forties. Life span has been dramatically affected by improved nutrition, medical care, and infectious disease control.

Physiological aging

A potentially very interesting analysis being developed by **Shoichiro Fujita** of RERF's Statistics Department follows about 8,000 AHS members who in 1970–72 were studied for nine physiological aging factors (Belsky et al., RERF TR 11-78). With respect to survival about 15 years later, one group which had been classified as physiologically old was compared to a second group equivalent in chronological age but determined to be physiologically young. Among the physiologically old group, Fujita finds a higher mortality rate, which is not associated with either radiation or cancer. Thus, the physical factors measured by Belsky et al. may be an index of aging. More in-depth study of available health records and biological measurements is required to uncover any key mechanisms.

Chromosome aberration studies

Using peripheral blood cells, cytogenetic studies on AHS participants were initiated at RERF almost as soon as technical developments permitted. Cytogenetics research at RERF has already demonstrated significant structural chromosome aberration responses to increasing radiation dose, with recent analyses indicating a specific sensitivity within some of the younger ATB groups. Cells containing these rearranged chromosomes are not at severe selective disadvantage and thus they persist for many decades after induction. On the other hand, aneuploid cells—cells either with extra chromosomes or lacking in specific chromosomes of the normal set—would for the most part not persist even if induced by irradiation. But such aneuploid cells do seem to increase in number as the age of survivors increases. Several different lines of evidence by RERF Genetics Department Chief **Akio A Awa** and his colleagues point to this.

As mentioned earlier, although loss/gain cells are usually at a disadvantage, in fact certain combinations seem to favor cell proliferation. Some interesting models of aneuploidy, aging, and cancer may be developing from these studies.

Somatic mutation studies

An almost direct counterpart to RERF's cytogenetic studies are the studies of specific gene mutations in peripheral blood cells as conducted in RERF's Radiobiology Laboratory by **Mitoshi Akiyama** and his coworkers. With new selection techniques, millions of cells can be rapidly screened electronically to detect rare mutant events. In RERF's cytogenetic studies, every appropriate dividing cell must be examined microscopically and each chromosome must be scrutinized. Technically, this is particularly demanding, difficult, and time-consuming—thus the obvious advantage of the selective mutation systems employed in the gene mutation approach. To date, studies of three different gene loci in lymphocytes and in one red blood cell system have revealed the age dependence of mutation frequency as well as the long-term persistence of mutations—exceeding 40 years, as substantiated in the A-bomb survivors by the association of higher mutation frequencies with increased exposure ATB.

For some of the mutation systems, it will be possible to do molecular analysis of the altered genes in an effort to differentiate between those alterations in the gene DNA resulting from radiation or from spontaneous aging events.

Loss of immune response

Finally, another area of considerable activity in radiobiology and clinical studies is radiation- and age-related changes in immune responses. The immune system is an extraordinarily complex array of cells of the T, B, and NK lymphocyte classes and other members of the blood cell population interacting with the aforementioned lymphocytes. Both the aging process and radiation exposure can and do alter the frequencies of this array of cells and their subsets, thus affecting the way an individual will respond when challenged by foreign antigenic material—bacteria and viruses, for example. Reduced response opens the door to increased infections, a common cause of morbidity among the elderly.

The immune system must also discriminate between its own body's material and foreign chemical material. Loss of this ability can lead to the phenomenon of autoimmunity, in which the immune system attacks other cells of the body, such as in rheumatoid arthritis. Among AHS participants, the occurrence and characteristics of deranged immune systems will be analyzed by **Saeko Fujiwara** of the RERF Clinical Studies Department in collaboration with the radiobiology staff. ❑

Editor's Note: Specific recommendations of the Aging Workshop panelists will be published in the summer issue of Update.

Aging Workshop Participants

Earl P. Benditt, Department of Pathology, University of Washington School of Medicine, Seattle
Yoshisada Fujiwara, Department of Radiation Biophysics, Kobe University School of Medicine
Paul M. Gallop, Laboratory of Human Biochemistry, Children's Memorial Hospital, Boston, Mass.
Katsuiku Hirokawa, Department of Pathology, Tokyo Metropolitan Institute of Gerontology
Kunihiko Kato, Department of Zoology, Faculty of Science, University of Tokyo
George M. Martin, Department of Pathology, University of Washington School of Medicine, Seattle
Tetsuya Ono, Department of Radiation Research, Tohoku University School of Medicine, Sendai
James R. Smith, Department of Virology & Epidemiology, Baylor College of Medicine, Houston, Tex.
Lon R. White, US National Institute on Aging, Bethesda, Md.

Invited Discussants

Sataro Goto, Department of Biochemistry, Toho University, Funabashi
Shuichi Hatano, Department of Social Welfare, Shukutoku University, Chiba
Tohru Kita, Department of Geriatrics, Kyoto University

Invited Observers

Kunio Aoki,* Nagoya University School of Medicine
Curtis C. Harris,* US National Cancer Institute, National Institutes of Health, Bethesda, Md.
Clark W. Heath Jr.,* American Cancer Society, Atlanta, Ga.
Leonard A. Herzenberg,* Stanford University School of Medicine, Stanford, Calif.
Toshiyuki Kumatori,* Radiation Effects Association, Tokyo
Ei Matsunaga,* Japanese National Institute of Genetics, Mishima
Mortimer L. Mendelsohn,* Lawrence Livermore National Laboratory, Livermore, Calif.
Arno G. Motulsky,* University of Washington School of Medicine, Seattle
Shigefumi Okada,* Faculty of Medicine, University of Tokyo
Akira Shishido, RERF supervisor, Japanese National Institute of Health, Tokyo
Itsuro Sobue, Nagoya University School of Medicine
Tsutomu Sugahara, RERF visiting director, Kyoto University
James E. Trosko, University of Michigan (incoming RERF permanent director), Ann Arbor

**Members of the RERF Scientific Council*

Recent Scientific Publications

Approved Technical Reports

The observed relationship between the occurrence of acute radiation sickness and subsequent cancer mortality among A-bomb survivors in Hiroshima and Nagasaki. K Neriishi, DO Stram, M Vaeth, S Mizuno, S Akiba. **RERF TR 18-89.**

In an analysis of data obtained from the Life Span Study, a follow-up study of a fixed population of 73,330 atomic bomb survivors in Hiroshima and Nagasaki, the slope of a linear dose response between the estimated dose of ionizing radiation and leukemia mortality was found to be steeper ($p < 0.001$), by a factor of 2.5, among those who reported epilation within 60 days of the bombings, as compared to those who did not experience this acute radiation symptom. For non-leukemic cancer mortality, the dose-response relationship was only slightly affected ($p > 0.2$) by the presence of epilation.

The results for leukemia were not modified by age or sex and were consistent in both cities. These observations suggest that those individuals who experienced early effects of radiation were more likely to die of leukemia during the follow-up period than individuals who were exposed to the same level of A-bomb radiation but did not develop epilation. The robustness of this finding on the interaction of two difficult but important problems was investigated. These were the validity of a linear dose-response model for leukemia, and the level of assumed precision of the radiation dosimetry system used for assignment of dose estimates to individual survivors. Assuming 35% random dose errors and a dose-response function cubic in dose, the excess relative risk for leukemia was still estimated to be 1.89 times higher for the group with epilation, and the p-value for a test of association between leukemia and epilation remained significant at the 0.10 level. If 50% random dosimetry errors are assumed using the same cubic model, the dose response in the epilation group is estimated to be 1.58 times higher than the others, but is not significant ($p < 0.3$).

Organ doses to atomic bomb survivors from radiological examinations at the Radiation Effects Research Foundation. K Kato, S Antoku, S Sawada, WJ Russell. **RERF TR 19-89.**

When estimating the risks of oncogenesis and cancer mortality as a result of atomic bomb radiation exposure, medical X-ray doses received by the A-bomb survivors must also be estimated and considered. Using a phantom human, we estimated the X-ray doses received by A-bomb survivors during routine biennial medical examinations conducted at RERF as part of the long-term Adult Health Study (AHS), since these examinations may represent about 45% of the survivors' total medical irradiations. Doses to the salivary glands, thyroid gland, lung, breast, stomach, and colon were measured using thermoluminescent dosimeters. The results reported here will aid in estimating organ doses received by individual AHS participants.

Estimating spontaneous mutation rates at enzyme loci in *Drosophila melanogaster*. T Mukai, T Yamazaki, K Harada, S Kusakabe. **RERF TR 20-89.**

Spontaneous mutations were accumulated for 1,620,826 allele · generations on chromosomes that originated from six stem second chromosomes of *Drosophila melanogaster*. Only null-electromorph mutations were detected. Band-electromorph mutations were not found. The average rate of null-electromorph mutations was $2.71 \cdot 10^{-5}$ per locus per generation. The 95% confidence interval (μ_n) was $1.97 \cdot 10^{-5} < \mu_n < 3.64 \cdot 10^{-5}$ per locus per generation. The upper 95% confidence limit of the band-electromorph mutation rate was $2.28 \cdot 10^{-6}$ per locus per generation. It appeared that null mutations were induced by movable genetic elements and that the mutation rates were different from chromosome to chromosome.

Variations with time and age of the excess cancer risk among atomic bomb survivors. DA Pierce, M Vaeth, DL Preston. **RERF TR 21-89.**

This report has two aims: 1) to describe and analyze the age/time patterns of excess cancer risk in the atomic bomb survivor cohort followed up by the Radiation Effects Research Foundation (RERF), and 2) to describe statistical methods which are used in RERF's analyses of data on mortality and morbidity in the cohort. In contrast to previous analyses of the cohort cancer mortality data, substantial use is made of Japanese national cancer rates for the purpose of investigation of the age/time variations in excess risk. This analysis considers mortality from all cancers except leukemia as a group. Primary attention is given to description in terms of the age-specific excess relative risk, but the importance of appropriate descriptions of the absolute excess risk is also emphasized. When models for the excess risk allow variation with age and time, both constant relative and absolute excess risk models provide very similar fits to the data. Previous reports have indicated that for a given age-at-exposure and sex, the excess age-specific relative risk is remarkably constant throughout the current follow-up period. Statistical analysis here indicates that for those less than about 35 years of age at exposure there is no departure from this pattern, beyond ordinary sampling variation. For those over about 35 years of age at exposure, there is modest evidence of an increasing trend in the excess relative risk, which could be plausibly attributed to effects related to the minimal latent period. Some brief consideration is given to modeling the absolute excess risk as the product of an age-at-exposure and time-since-exposure effect. Interpretation of these results, particularly in regard to projections beyond the current follow-up, is discussed.

Spontaneous loss and alteration of antigen receptor expression in mature $CD4^+$ T cells. S Kyoizumi, M Akiyama, Y Hirai, Y Kusunoki, K Tanabe. **RERF TR 22-89.**

The T-cell receptor CD3 (TCR/CD3) complex plays a central role in antigen recognition and activation of mature T cells, and therefore abnormalities in the expression of the complex should induce unresponsiveness of T cells to antigen stimulus. Using flow cytometry, we detected and enumerated variant cells with loss or alteration of surface TCR/CD3 expression among human mature $CD4^+$ T cells. The presence of variant $CD4^+$ T cells was demonstrated by isolating and cloning them from peripheral blood, and their abnormalities can be accounted for by alterations in TCR expression such as defects of protein expression and partial protein deletion. The variant frequency in peripheral blood increased with aging in normal donors and was highly elevated in patients with ataxia telangiectasia, an autosomal recessive inherited disease with defective DNA repair and variable T-cell immunodeficiency. These findings suggest that such alterations in TCR expression are induced by somatic mutagenesis of TCR genes and can be important factors related to age-dependent and genetic disease-associated T-cell dysfunction.

Detecting deletions, insertions, and single nucleotide substitutions in cloned β-globin genes and new polymorphic nucleotide substitutions in β-globin genes in a Japanese population using ribonuclease cleavage at mismatches in RNA:DNA duplexes. K Hiyama, M Kodaira, C Sato. **RERF TR 1-90.**

The applicability of ribonuclease (RNase) cleavage at mismatches in RNA:DNA duplexes (the RNase cleavage method) for determining nucleotide variant rates was examined in a Japanese population. DNA segments of various length obtained from four different regions of one normal and three thalassemic cloned human β-globin genes were inserted into transcription vectors. Sense and antisense RNA probes uniformly labeled with ^{32}P were prepared. When RNA probes of 771 nucleotides (nt) or less were hybridized with cloned DNAs and the resulting duplexes were treated with a mixture of RNases A and T1, the length of products agreed with theoretical values. Twelve possible mismatches were examined. Since both sense and antisense probes were used, uncleavable mismatches such as G:T and G:G which were made from one combination of RNA and DNA strands could be converted to the cleavable C:A and C:C mismatches, respectively, by using the opposite combination. Deletions and insertions of 1 (G), 4 (TTCT), 5 (ATTTT) and 10 (ATTTTATTTT) nt were easily detected. A polymorphic substitution of T to C at position 666 of the second intervening sequence (IVS2-666) of the β-globin gene was detected using genomic DNAs from cell lines established from the peripheral B lymphocytes of 59 unrelated Japanese from Hiroshima or those amplified by polymerase chain reaction (PCR). The frequency of the gene with C at the IVS2-666 (allele *C*) was 0.48 and that of the gene with T (allele *T*) was 0.52. The associations of the two alleles were in agreement with Hardy-Weinberg proportions. No contradiction to

continued on next page

Recent Scientific Publications

continued from page 11

Mendelian inheritance was observed in the results obtained from 11 family studies. Two new polymorphic substitutions of C to A and A to T were detected at nt positions 1789 and 1945 from the capping site, respectively, using genomic DNAs amplified by PCR. We conclude that it would be feasible to use the RNase cleavage method combined with PCR for large-scale screening of variation in chromosomal DNA.

Organ doses to examinees during photofluorography, fluoroscopy and computed tomography. K Kato, S Antoku, S Sawada, T Wada, WJ Russell. **RERF TR 2-90.**

Since World War II, radiological practice in Hiroshima and Nagasaki has steadily changed, such as in the radiographic screening of the chest for pulmonary tuberculosis, mass radiological screening for gastric cancer, the greater use of fluoroscopy and radiography for detecting gastrointestinal abnormalities, and in the use of newly developed imaging techniques, notably computed tomography (CT). The increased use of these radiological procedures has resulted in increased radiation doses to examinees.

Increasing knowledge of radiation effects has focused attention on gonad doses, on active bone marrow doses, and on doses to various organs and organ systems.

In the present study, doses to the salivary glands, thyroid gland, breast, lung, stomach and colon incurred during mass radiologic gastric screening, mass radiographic chest screening, upper gastrointestinal series and CT were experimentally ascertained. We also measured gonad doses and active bone marrow doses incurred during CT. In these experiments, a phantom human was used to simulate radiological examinations in community hospitals. The doses were measured using thermoluminescent dosimeters inserted in the phantom human. Organ doses incurred during CT examination were much greater than for other examinations. For example, the active bone marrow of ribs incurred 50 mGy per examination during chest CT.

Results obtained in our study will be used to document doses received by Adult Health Study subjects during their radiological examinations, and will help determine the role of medical X-ray exposures in the development of cancer and other abnormalities among A-bomb survivors and comparison subjects.

An improved method for detecting genetic variation in DNA using denaturing gradient gel electrophoresis. N Takahashi, K Hiyama, M Kodaira, C Satoh. **RERF TR 3-90.**

We have examined the feasibility of denaturing gradient gel electrophoresis (DGGE) of RNA:DNA duplexes to detect variations in genomic and cloned DNAs. The result has demonstrated that use of RNA:DNA duplexes makes DGGE much more practical for screening a large number of samples than use of DNA:DNA heteroduplexes, because preparation of RNA probes is easier than that of DNA probes. Three different ^{32}P-labeled RNA probes were produced. Genomic or cloned DNAs were digested with restriction enzymes and hybridized to labeled RNA probes, and resulting RNA:DNA duplexes were examined by DGGE. The presence of a mismatch was detected as a difference in the mobility of bands on the gel. The experimental conditions were determined using DNA segments from cloned normal and three thalassemic human β-globin genes. The results from experiments on the cloned DNAs suggest that DGGE of RNA:DNA duplexes will detect nucleotide substitutions and deletions in DNA. In the course of these studies, a polymorphism due to a single base substitution at position 666 of IVS2 (IVS2-666) of the human β-globin gene was directly identified using genomic DNA samples. A study of 59 unrelated Japanese from Hiroshima was undertaken in which the frequency of the allele with C at IVS2-666 was 0.48 and that of the allele with T was 0.52.

This approach was found to be very effective for detecting heritable variation and should be a powerful tool for detecting fresh mutations in DNA, which occur outside the known restriction sites.

Frequency of malignant tumors during the first two decades of life in the offspring (F_1) of atomic bomb survivors. Y Yoshimoto, JV Neel, WJ Schull, H Kato, M Soda, R Eto, K Mabuchi. **RERF TR 4-90**

The incidence of cancer prior to age 20 has been determined in children born to atomic bomb survivors and to a suitable comparison group. Tumor ascertainment was through death certificates and the tumor registries maintained in Hiroshima and Nagasaki. The rationale for the study stemmed from the evidence that a significant proportion of childhood tumors such as retinoblastoma and Wilms' tumor arise on the basis of a mutant gene inherited from one parent plus a second somatic cell mutation involving the allele of this gene.

Gonadal radiation doses were calculated using the recently established DS86 system, supplemented by an ad hoc system for those children whose parents' (one or both) DS86 dose could not be computed but for whom a dose could be developed on the basis of the available information. The total data set consisted of: 1) a cohort of 31,150 liveborn children, one or both of whose parents received ≥0.01 Sv of radiation at the time of the A-bombings (an average conjoint gonad exposure of 0.435 Sv), and 2) two suitable comparison groups, totaling 41,066 children.

A total of 92 cancer cases at ages less than 20 years was confirmed; 49 and 43 cases, respectively, in the 0 Sv and ≥0.01 Sv groups. A multiple linear regression analysis revealed no increase in malignancy in the children of exposed parents. However, examination of the data suggested that only 3.0%–5.0% of the tumors of childhood observed in the comparison groups are associated with an inherited genetic predisposition that would be expected to exhibit an altered frequency if the parental mutation rate were increased. There is thus far no confirmation of the positive findings of Nomura in a mouse system.

Approved Commentary and Review Reports

A review of radiation-related brain damage and its threshold in the prenatally exposed atomic bomb survivors. M Otake, WJ Schull, H Yoshimaru. **RERF CR 4-89.**

The occurrence of severe mental retardation, IQ test scores and school performance have been reviewed in an effort to determine whether a threshold for radiation damage exists among the in utero-exposed atomic bomb survivors. Significant effects of ionizing radiation exposure on the developing brain are seen during two time periods: 8–15 weeks and 16–25 weeks after fertilization. Although a linear dose-response relationship adequately describes the observed frequency of severe mental retardation among those exposed in the 8th through the 15th gestational week, when using the DS86 dosimetry a suggestion of a threshold is seen, whereas this is not true when using the previous T65 dosimetry. In the former instance, when two cases of Down's syndrome occurring among those exposed in the 8- to 15-week time period are excluded, the 95% lower bound of the threshold appears to range from 0.12–0.23 Gy. Both T65D and DS86 dosimetries suggested a damage threshold of 0.23–0.70 Gy, occurring in the 16- to 25-week period. The IQ score and school performance data showed a greater linearity when employing the DS86 than when using the T65DR dosimetry. But at doses under 0.10 Gy, the effects were not great, and the dose-predicted values were similar to those in the control group. ❑

RERF update RERF

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

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

Editorial Staff:
Editor-in-chief: J.W. Thiessen
Managing editor: Beth Magura
Production editor: Fumie Maruyama
Photographers: Junso Takayama
Sunao Tanaka
Cartoons by: Akio A Awa

Mailing Address:
RERF Update
5-2 Hijiyama Park
Minami-ku, Hiroshima
732 Japan

Facsimile: 082-263-7279