RERF update RERF

News & Views from the US–Japan Radiation Effects Research Foundation
Volume 1, Issue 1 Hiroshima & Nagasaki Spring 1989

Chernobyl-related Scientific Exchanges Increase between RERF and Soviet Union

Three years have passed since the accident at Reactor No. 4 of the Chernobyl nuclear power plant focused worldwide attention on the environmental and health consequences of a major radiological mishap involving the peacetime use of atomic energy.

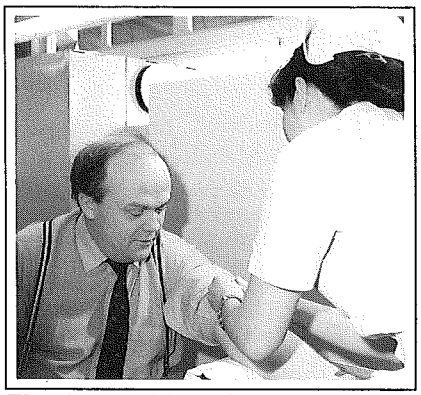
Aware that certain aspects of the Chernobyl accident's aftermath parallel those following the atomic bombings of Hiroshima and Nagasaki, RERF has fostered contacts with Soviet scientists in the hope of sharing experience relevant to radiation research.

"Knowledge gained from the Chernobyl accident may prove to be useful to research at RERF," explained RERF Chairman **Itsuzo Shigematsu.** "The effects of radiation per se are the dominant characteristics of the Chernobyl accident, whereas in the case of the atomic bombings the effects of blast and thermal rays overlap with those of radiation effects. Hence, data from Chernobyl could significantly advance mankind's knowledge of radiation effects."

Early in 1987, four Soviet scientists spent three days in Hiroshima visiting RERF and local facilities including Hiroshima's A-bomb Hospital and A-bomb Survivors Welfare Center.

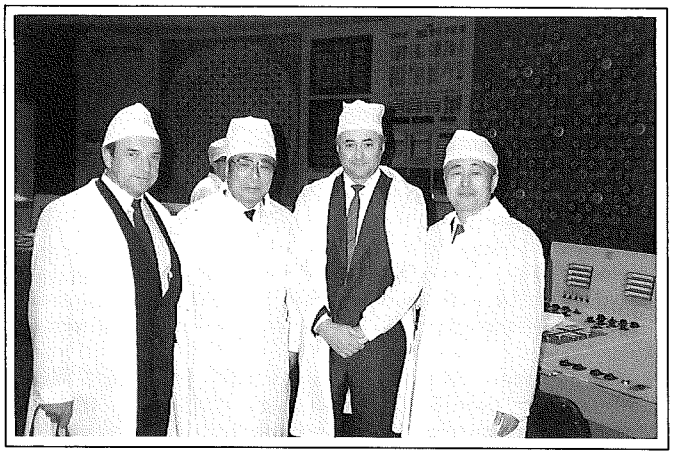
As delegation leader, **Andrei Ivanovich Vorobjov** of the Central Institute for the Advanced Training of Physicians in Moscow described the postaccident emergency actions, which included evacuation of about 135,000 residents from the disaster area. Within a few days, patients in serious condition were transferred 800 km away to Moscow where bone marrow transplants were attempted.

At a daylong meeting, the Soviet delegation listened to staff reports of RERF's long-term follow-up studies of A-bomb survivors, which emphasized the methods and techniques used in establishing a fixed radiation-exposed population, in estimating radiation doses and in starting life-span, morbidity, and genetic studies.



The vice president of the USSR Academy of Sciences gives blood to be analyzed by RERF researchers for biological indicators of radiation exposure at Chernobyl.

"The Soviet medical group is now establishing a medical follow-up system for leukemia and thyroid diseases based on the data obtained during its visit to Hiroshima," commented Shigematsu. "Knowledge of these diseases is directly attributable to the physical contributions of the A-bomb survivors and we hope that RERF's database can now be used to help those involved in the Chernobyl accident."



RERF Chairman Itsuzo Shigematsu (second from left) and Hiroshima University's Atsushi Kuramoto (far right) visit the control room at the Chernobyl nuclear power plant during their 10-day trip to the Soviet Union in the fall of 1988.

In October 1988, Shigematsu and **Atsushi Kuramoto,** director of Hiroshima University's Research Institute for Nuclear Medicine and Biology, journeyed to Leningrad, Moscow and Kiev—including the Chernobyl power plant site—to exchange opinions based on experience acquired in Hiroshima and Nagasaki.

"This visit was mutally very worthwhile," said Shigematsu. "Cooperative agreements for investigating the aftereffects on the health of accident survivors are now being developed between Japan, the United States and the Soviet Union."

In December 1988, the vice president of the USSR Academy of Sciences, **Yevgeni Velikhov** visited the Hiroshima Laboratory and was briefed on the Foundation's follow-up program. On-site within days of the reactor explosion, Velikov discussed aspects of the postaccident emergency operation which he supervised.

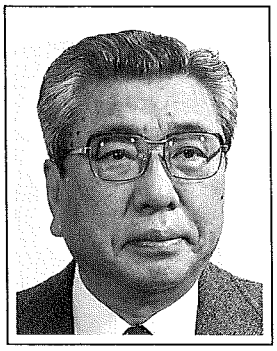
According to RERF Vice-Chairman **J.W. Thiessen,** it was agreed that institutional contacts between Soviet scientific laboratories and RERF would be useful. He viewed RERF's present system of visiting scientists as a productive way to establish collaborative efforts.

RERF's most recent Soviet visitors were **Oles Pyatak,** deputy director of the USSR Scientific Center of Radiation Medicine in Kiev, and **Olga Tsvetkova,** director of the center's International Cooperation Department. They attended the Foundation's Radiation Carcinogenesis Workshop, 16–18 March.

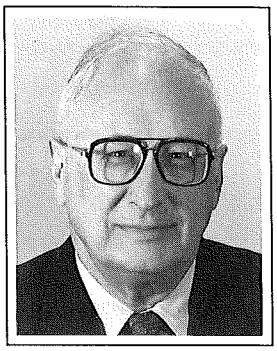
In the near future, it is hoped that a Soviet scientist will spend several months in Japan in association with various radiation research institutes. ❑

Time for a Change

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



Shigematsu



Thiessen

After nearly 170 issues of our Japanese and English newsletters, and more than 40 years of US–Japanese collaboration in the study of late radiation effects in A-bomb survivors, it is time for a change. The newsletter, as many of you know it, has faithfully recorded the happenings at the Radiation Effects Research Foundation, both socially and scientifically. This double role, efficient as it may have been, gave the newsletter an inherently unbalanced character: on the one hand, it aimed at being a house organ, with all the bits of news that are important to the members of the RERF family; on the other hand, it tried to be informative with respect to scientific developments. It could never fully meet both purposes, so we have decided to separate the two functions—the internal and the external—and create two different newsletters.

The Japanese version will aim at truly reflecting RERF as a living organization, with news items of a social nature and with information of a scientific character of interest to all of RERF. Since more than 95% of the Foundation's staff is Japanese, only a few English-speaking people will have to do without this information—a strong stimulus to step up their efforts to speak and read Japanese!

The English newsletter, which will appear quarterly rather than monthly as before, aims specifically at providing information on the scientific life at RERF and is intended to be read by that section of the worldwide scientific community that is interested in the results of studies of radiation effects in humans and their application in the estimation of risk and the protection of health against ionizing radiation. The name of this new publication reflects the purpose: it will provide a periodic update on the status of RERF research, including the involvement of our scientists in international collaboration and discussion, and that of foreign visiting scientists performing research at RERF.

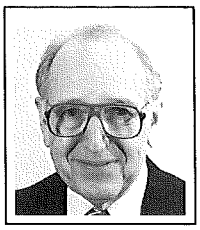
Because all estimates of radiation-related harm in man find their basic foundation in the work done in Hiroshima and Nagasaki, *RERF Update* will serve as the central point for the dissemination and discussion of new data, concepts and ideas generated at RERF. It will not replace our basic publications (such as those in the Technical Report Series and the Commentary and Review Series), but will highlight and, when appropriate, discuss them.

We want *RERF Update* to be read. Consequently, we will give particular attention to being readable, interesting, and worth your time. Although we do not pretend to be a scientific journal, we will accept letters to the editor, and we intend to be responsive to the discussion of viewpoints other than our own.

RERF is a binational organization, but it actually belongs to the world. We are proud of our tradition and accomplishments, even though they are based on tragic events of nearly 43 years ago. We all believe that the kind of studies that we perform not only enrich the fund of scientific data on the consequences of the use of nuclear weapons, but also contribute to the well-being of the survivors themselves, and ultimately, to the furthering of knowledge that will benefit mankind as a whole. We hope that our newest effort now before you may play a small part in reaching those objectives. ❑

News Briefs

✓ American Permanent Director Assumes Post at RERF



Marks

In mid-January, **Sidney Marks** assumed the post of permanent director as successor to **Stuart C. Finch,** who returned to the US in December.

Marks obtained a medical degree from the University of Illinois in 1942, an M.S. in physics at the University of Idaho in 1961, and a Ph.D. in biostatistics at the University of California at Los Angeles in 1970. After serving as associate professor of surgery and internal medicine at the University of Maryland School of Medicine in the early '70s he served in various posts including epidemiologist-pathologist for the US Atomic Energy Commission and coordinator in human studies and biostatistics for the US Energy Research and Development Administration. From 1976 to 1986, Marks was associate manager of the Environment, Health and Safety Research Program Office at Battelle Pacific Northwest Laboratories.

✓ US–Japan Dose Reassessment Workshop Held in Hawaii

Scientists from Japan and the US gathered in Honolulu, 8–10 March, to discuss the biases and other uncertainties that may underlie the revised dosimetry system for the A-bomb survivors—now known as DS86. As originally planned, this meeting enabled researchers to consider completed relevant models and calculations. Other findings were discussed, such as new data from neutron activation in cobalt, europium and chlorine, plus some additional TLD measurements carried out after publication of the final DS86 report. *RERF Update* will report further on this meeting in an upcoming issue.

Representing RERF were Chairman **Itsuzo Shigematsu,** Vice-Chairman **J.W. Thiessen,** statisticians **Dale L. Preston, Michael Vaeth, Daniel O. Stram, Shoichiro Fujita,** and interpreter **Kenji Yorichika.**

✓ Permanent Director Attends NCRP Meeting

Seymour Abrahamson, RERF chief of research, will attend the annual meeting of the NCRP in Washington, D.C., 5–7 April. A member of the NCRP board of directors, Abrahamson will speak on "The genetic effects of irradiation: of mice and men."

✓ RERF Scientific Council Convened in March

The Scientific Council, RERF's major research advisory committee, gathered at the Hiroshima Laboratory from 13–15 March for its annual meeting. The agenda included discussions of the different tumor registries operated by RERF; reports on cancer incidence studies and future plans; studies of thyroid disease, autoimmune disorders, and hypercalcemia; dosimetry issues (including DS86 and "biological dosimetry"); neutron RBEs; biochemical and cytogenetics; low-dose risk estimates; immunologic studies; and radiosensitivity issues.

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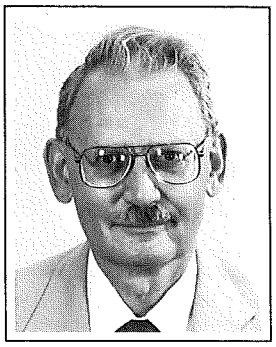
A Radiobiological Rationale for Applying RBE to Neutron Exposures in A-bomb Data

by Seymour Abrahamson
RERF Chief of Research



Abrahamson

The question of assigning RBEs to neutrons may now only be an academic issue. The exposed populations of Hiroshima and Nagasaki received neutron doses, and these doses are now estimated to be considerably lower than estimated by T65DR procedures. In recent reevaluations of the health effects employing DS86 dose values for somatic and genetic endpoints, the various published reports use a constant RBE to adjust for the neutron contribution; RBEs of 1, 5, 10, and 20 have been chosen arbitrarily.

In most experimental systems in which low-LET radiations are studied versus high-LET radiations, the general rule is that RBE increases with decreasing dose when an extensive dose range is studied. This results from the fact that most neutron energies studied produce their effects in a linear proportion to dose, i.e., with constant slope. At high neutron doses, because of cell killing, the slope may diminish. On the other hand, acutely delivered X-ray and γ-ray radiations (the low-LET radiations) produce responses which plot as curvilinear, both having a linear slope over a low dose range (0.01–0.3 Gy or thereabouts), in other words, a linear-quadratic relationship. Thus, a constant and maximum RBE is seen when the linear slopes of the two radiation types are compared. At higher doses of acutely delivered low-LET radiation, the RBE progressively decreases. The use of a high constant RBE runs the risk of inflating the high dose estimates and therefore simultaneously reduces the risk per unit dose.

We have attempted to develop a sliding RBE scale which is derived from biological experiments. We chose the human cell cytogenetic studies of Lloyd et al (*Int J Radiat Biol* 29(2):169-82, 1976), in which 0.7 MeV neutrons were shown to have a constant slope, αn:

$$Y_n = 83 \times 10^{-2}/D,$$

in which Y_n is the aberration yield for neutron radiation.

The same test system, when studied with acute gamma radiation over a wide dose range, generated an aberration yield that was fitted by the equation:

$$Y_\gamma = 1.6 \times 10^{-2} D + 5.0 \times 10^{-2} D^2 .$$

For any A-bomb dose mix received by individuals or population groups, the estimated γ and neutron yield was predicted from the previous equations. The RBE was then computed by the following relationship. This equation, developed by Michael Vaeth of the RERF Statistics Department, simplified an earlier version:

$$RBE = \frac{Y_n}{Y_\gamma} \times \frac{D_\gamma}{D_n} .$$

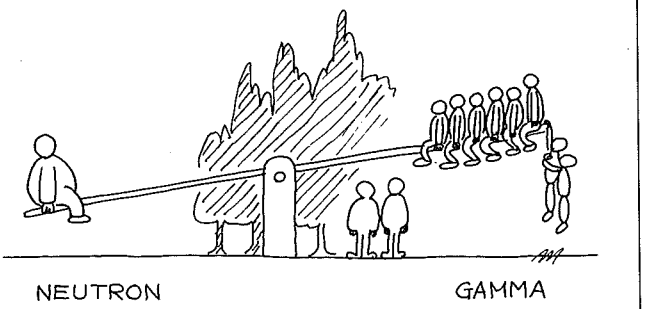
The assigned neutron dose was then adjusted by the computed RBE for that specific dose mix.

In the table below, using an RERF data set, one observes how the RBE varies with dose.

D_γ	D_n	RBE
0.31	0.001	26.0
0.70	0.01	15.5
1.85	0.035	8.7
2.5	0.08	5.9

The analysis indicates that an RBE of 15 is about the average value for doses between 0.3–1.0 Gy and one of about 7 is the average for doses from 1.0–2.5 Gy.

While some might object to the use of the cytogenetic endpoint, in practice the procedure can be adapted for any biological endpoint in which adequate experimentation has permitted the development of satisfactory dose-response curves for both types of energy. I would be interested in responses to this approach from others. ❑



News Briefs

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RERF Scientific Council members are: **Eisei Ishikawa,** Jikei University School of Medicine; **Masanori Kuratsune,** Nakamura Gakuen University and College; **Toshiyuki Kumatori,** Radiation Effects Association; **Ei Matsunaga,** National Institute of Genetics; **Shigefumi Okada,** Radiation Biology Center, Kyoto University; **Mortimer L. Mendelsohn,** Lawrence Livermore National Laboratory; **Robert W. Miller,** National Cancer Institute; **Arno G. Motulsky,** University of Washington; and **Donovan J. Thompson,** University of Washington.

✓ Chinese Research Fellows at Hiroshima Laboratory

By agreement with the Chinese Ministry of Public Health, two research fellows are now working on projects at the Hiroshima Laboratory.

Huang Hua is spending 16 months in the Immunology Laboratory using limiting dilution analysis to study EB virus-specific cytotoxic T cell precursor frequency to determine if 40 years after A-bomb radiation exposure the immunofunctions of survivors show damage. He will also help establish immortalized B cell lines from the aging A-bomb survivors to ensure the preservation of these cells for future research.

During his six-month stay in the Research Information Center, **Zhu Hanmin** will assemble historical data for use in an ongoing RERF library-retrieval and manuscript-management database project.

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Random Errors in Radiation Exposure Estimates

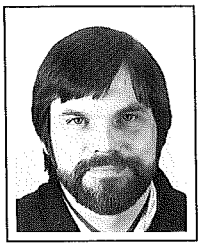
by Michael Vaeth and Daniel O. Stram
RERF Department of Statistics

Much of the research at RERF involves the study of radiation dose response for biological endpoints such as cancer mortality among A-bomb survivors. Over the years this work has been greatly facilitated by the development of radiation dosimetry systems which assign estimated doses to individuals in the study population of Hiroshima–Nagasaki survivors. However, it has long been recognized by researchers that the existence of random errors in radiation dose estimates has an impact on the ability to generalize the Hiroshima–Nagasaki data to the outside world. One basic problem is that dosimetry estimates subject to random errors will tend to cause attenuation in observed dose response. For example, when cancer risk estimates based on Hiroshima and Nagasaki are used to set radiation exposure limits for regulatory purposes, these risks may be underestimated, as a function of dose, due to the presence of random errors in the estimates provided by the radiation dosimetry.

Of course, both random errors and systematic errors in radiation dose estimates distort dose-response relationships. With the new DS86 dose estimates, some systematic errors were corrected. A large fraction of the uncertainty in dose estimates is now due to uncertainty in input data maintained by RERF—primarily survivor location and shielding history. Errors in these data can reasonably be thought of as independent from survivor to survivor.

The two most important considerations involved in assessing the likely effect of random dosimetry errors on dose-response estimation using the Hiroshima–Nagasaki data are the size and the homogeneity of these random errors, relative to true radiation dose for a subject. Based on early work by statisticians at RERF (Jablon, ABCC TR 23-71, 1971), it was generally believed that the earlier T65D dose estimates had a standard deviation of approximately 30% of true dose. Now many parties are interested in questions about random errors in the context of DS86. A detailed uncertainty analysis is being developed by the creators of the DS86 system. This attempts to separate uncertainty in DS86 doses into a number of different sources, in order to determine how errors in these sources propagate to become errors in individual dose estimates. A preliminary version of this analysis overall tends to be more optimistic than Jablon, i.e., these uncertainty estimates are usually less than 30%. However, not all aspects of the uncertainty in the input parameters are accounted for. Nevertheless, they generally support the idea that random errors, due to uncertainty in position and shielding, indeed constitute a considerable portion of the inherent variability in dose estimates, and perhaps account for more variability than do errors in systematic inputs such as weapons yield, burst position, etc.

Another potential source of information about the size and homogeneity of random errors in dose estimates is from biological outcome data themselves. For example, Gilbert (*Radiat Res* 98:591–605, 1984) attempted to use reports of radiation sickness, collected for the majority of survivors in Hiroshima and Nagasaki, to assess whether errors in dose estimates were homogeneous by city and shielding category (in the open, in a Japanese house, etc.). While this work has certain limitations, other biological outcomes—in particular information on chromosome aberration data collected for more than 1,000 survivors to date—also have potential as biological indicators of the extent of random uncertainty in dose estimates.



Vaeth

Stram

The development of statistical methods that properly account for random errors in dose estimates is not a trivial task, even when the magnitude of these errors is assumed to be known. A technical report written by statisticians at RERF describing some basic approaches has recently been approved (Pierce et al, RERF TR 2-89, 1989). This report discusses the calculation of random-error-adjusted radiation dose estimates, once a model for dose measurement errors has been established. These adjusted doses can then be used in the analysis of linear dose-response models, in order to adjust for attenuation in dose response. Calculations based on a lognormal 35% error model, which the authors tentatively recommend, lead to the following adjustments:

DS86 kerma (Gy)		0.50	1.00	2.00	3.00	4.00	5.00	6.00
Adjusted values	H*	0.50	0.95	1.79	2.56	3.28	3.98	4.64
	N**	0.50	0.98	1.86	2.68	3.46	4.20	4.92

*Hiroshima **Nagasaki

Some might find this adjustment procedure to be unjustifiable, given the care with which the DS86 system has been developed to give the best possible individual dose estimates. It must be stressed that these estimates are designed to adjust for biases in linear dose-response analyses and should not be thought of as improved dose estimates themselves. The logical process by which these adjusted values are determined takes as its first premise the assumption that the DS86 system works perfectly—i.e., if correct input data for location and shielding are supplied, then a correct dose is produced. The result of the calculations gives an average true dose for all those with estimated DS86 dose estimates at the values given in the table, where the averaging is necessary due to an assumed level of error in actual input data.

Based on the lognormal 35% errors model, it is found that an adjusted estimate of excess relative risk for all cancers except leukemia is about 13% greater than an estimate making no allowance for random errors in the exposure estimates. This increase is reduced to 9% if, as is sometimes done, survivors with dose estimates above 4 Gy are eliminated from the analysis. Similar studies for other radiogenic endpoints are currently being undertaken.

The work presented in RERF Technical Report 2-89 may be most useful in determining the robustness of certain findings, such as cancer risk estimates, to assumed levels of imprecision in the dosimetry system. Adaptations of the framework established in the report to other error models larger or smaller than the 35% criterion are easily accomplished. Another area to which the approach taken by Pierce et al is of potential help is in evaluating the meaning of observed associations between radiogenic outcomes such as early effects (radiation sickness) and late effects (cancer mortality). More on this subject will be presented in later issues of *RERF Update*. ❑

Workshop Considers Foundation's Future Research in Immunology

Numerous experts gathered at the Hiroshima Laboratory on 28 and 29 November 1988 to discuss immunology studies that could contribute to RERF's research on the late effects of A-bomb radiation in humans. This was the second of four workshops on different subjects intended to help determine the future course of the Foundation's research programs.

Invited workshop participants indicated in their written appraisal that RERF research during the past 10 years has been thorough in documenting radiation effects on the immune system and in uncovering unusual immunological abnormalities that provide important information on normal lymphoid cell development. Continuation of these approaches was encouraged. They also deemed it important to complete ongoing survey projects. Pursuit of creative ideas from within the immunology group at RERF itself was also encouraged.

When reviewing past research, evidence was presented that indicated a small but significant decline in both the number of certain peripheral T cells and their responsiveness to PHA. This effect is dependent on age and A-bomb radiation dose, suggesting possible immunologic effects of irradiation in the survivor population.

With this in mind, workshop participants focused on two major areas of interest to RERF: 1) the question of whether a selection bias exists in members of the surviving population—in this case, one that favored those with stronger immune responses; and 2) whether immunologic approaches and methodologies could be helpful in studying mutation rates and effects on tumor susceptibility of lymphoid and hematopoietic tissues.

Following are briefly stated recommendations for future or ongoing research at RERF:

Lymphocyte physiology

◆ Ongoing studies to characterize differences in T cell subsets in the survivor population were considered important to expand the general understanding of lymphoid development from precursors in humans and the possible effects of radiation on that process.

◆ To examine differences in T lymphocyte responsiveness, the use of limiting dilution analysis or precursor frequency analysis of alloreactive and autoreactive T cells, responding in mixed lymphocyte culture, was recommended.

◆ Since the markers and tools are unavailable at this time, the effects of irradiation on the hematopoietic stem cell population and early precursor populations cannot be readily determined now. Preservation of peripheral blood was suggested, while awaiting improved methodology.

◆ At the present time, it is possible to measure the proportion of cells in the cell cycle using the FACS with certain cell cycle markers and antibodies. A pilot study of a small number of survivors could be useful to determine if a significant difference exists between the exposed and unexposed, though dramatic results were not predicted.

◆ Since autoantibodies and autoimmune diseases may reflect some impact of radiation on normal immune function, ongoing RERF studies on autoantibody surveillance for autoimmune diseases were deemed useful.

◆ Significant information on HLA bias, i.e., the loss of certain HLA types from increased susceptibility to infection, radiation or disease, could be critically examined among the 1,000 high-dose survivors in the Adult Health Study, by means of existing or soon to be developed RFLP techniques. Precise typing of HLA antigens from these survivors now or later in preserved cells or cell lines derived from them was recommended.

Detecting somatic mutations using immunological parameters

◆ One possible effect of in utero irradiation could be the generation of new HLA alleles, as has been observed in pregnant female mice. To determine if similar events occurred among in utero-exposed A-bomb survivors, family studies of this cohort by classical HLA typing (or the more sophisticated RFLP typing) of parents and siblings could reveal new alleles. Data could also be obtained on the frequency of recombinational events within the HLA region which could be compared to the normal recombination frequency of 1%. The use of polymerase chain reaction was also suggested to look for insertions and deletions in MHC Class II genes.

◆ A related set of experiments was recommended to detect potential chromosomal rearrangements and potentially increased mutation rates due to irradiation using hypervariable mini-satellite probes, especially ones that may map to the HLA region.

Possible deviations in use of immunoglobulin V_H genes or T cell receptor $V\beta$ genes

◆ Since significant differences in repertoire are observed in certain disease states, in which there appear to be major distortions in the use of certain V genes, examining the use of V regions of immunoglobulin and T cell receptor genes was considered to be justified. Only now is it possible to undertake detailed analysis of the V region of immunoglobulin and TCR use. However, the methods are complex, not fully developed and inappropriate for immediate application to RERF studies.

The immediate recommendation was to obtain peripheral blood cells for freezing in preparation for later analysis.

Relationship of radiation exposure to HTLV-1 carriers

◆ Since 20% of Nagasaki's A-bomb survivor population is HTLV-1 serologically positive, it should be possible to compare the frequencies of HTLV-1 antibodies in exposed and nonexposed controls.

◆ A careful study of the HTLV-1-related disorders in the A-bomb survivor population and the control carriers could provide information on possible relationships between radiation exposure and susceptibility to HTLV-1-related disorders.

◆ Stored leukemia tissue specimens could be examined using HTLV probes to see whether the A-bomb survivor population had any excess of HTLV-1-related diseases.

Relationships to cancer and lymphoid-expressed oncogenes

◆ By studying the increased occurrence of myelomas in the A-bomb survivor population, mechanisms of oncogene activation associated with primary tumorigenesis or progression and/or defined new human oncogenes could be further clarified.

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Professional Staff Regulations Will Take Effect Soon

The long-pending regulations for the RERF professional staff will become effective in the near future, reported Permanent Director **Yutaka Hasegawa** who supervised the drafting of these guidelines.

Although existing regulations such as the Rules of Employment refer to RERF professional staff, details about their qualifications, conditions of employment, and duties were not previously stated in detail. As a result, the RERF Executive Committee recently finalized new professional staff regulations, the major points of which are as follows:

General overview of regulations

These regulations are primarily intended to help secure qualified scientists and to appropriately reward those who have accomplished excellent research work. Duties, responsibilities and qualifications are clearly delineated, detailing the procedures established for employment which include probational employment for all cases.

Posts of senior and associate scientists, which had nominally existed for some time, are substantiated by more concrete definitions of their status. In addition, position allowances are defined for senior scientists.

Equal opportunities for research work and accessibility to RERF materials are guaranteed to all professional staff members. Conditions for approval of entrusted studies and participation in outside research are also outlined.

A work performance evaluation, which formally applied only to RERF's general staff, has now been introduced for the professional staff. Decisions on promotion, demotion or special salary increases will be based on these work performance evaluations.

Sabbatical leave overview

These regulations are intended to improve the quality of research conducted by RERF's professional staff members, as well as to broaden their research spectra by providing opportunities for study or collaboration at institutions other than RERF—including those outside Japan.

Sabbatical leave will be granted to a professional staff member who has demonstrated excellent research achievements and has worked at RERF for a continuous period of at least seven years or, in case of intermittent service, for a total period of nine years or more.

As a rule, the period of sabbatical leave will be one year, with a maximum of four sabbaticals permitted during each professional staff member's employment at RERF.

Those granted sabbatical leave are expected to devote themselves solely to their proposed research. Such professional staff members will be exempted from all RERF duties and will receive salary, allowances, travel expenses, and other expenses necessary for research work during the sabbatical leave, unless the host institution provides such benefits.

When sabbatical leave is completed, professional staff members must return to RERF without undue delay, and a research report must be submitted on the work accomplished during the sabbatical leave. ❑

Program Reviews

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Preserving peripheral blood, tumor and tissue samples

◆ Workshop recommendations stressed the urgency of storing and preserving peripheral blood from high-dose survivors as well as peripheral blood lymphocytes from the in utero and F_1 populations along with relevant family members in order to permit family studies to be carried out. It was recommended that at a minimum the peripheral blood lymphocytes be frozen. If additional blood material is available, it would be optimal to use interleukin-2 in order to expand the T cell subpopulation and to use EB virus to obtain immortalized B cell populations. It would be important to ascertain whether freezing impairs the ability of EBV to transform cells. Similarly, it was advised that serum from as many individuals as possible be obtained and frozen.

◆ In as many autopsies as is feasible not only pathologic tissue and tumor tissue should be frozen, but samples from a variety of organs and tissues including bone marrow should be frozen. As new molecular probes and tools are developed, the frozen tissues will be available for analysis in the future.

A complete report on this workshop will be published in the Commentary and Review Series of RERF publications. ❑

Immunology Workshop Participants

Tomio Tada (workshop cochairman), Department of Immunology, Faculty of Medicine, University of Tokyo

Takehiko Sasazuki, Medical Institute of Bioregulation, Kyushu University, Fukuoka

Sonoko Habu, Immunology Laboratory, School of Medicine, Tokai University, Isehara

Morinobu Takahashi, Department of Immunobiology, Cancer Research Institute, Kanazawa University, Kanazawa

Junji Yodoi, Institute for Immunology Research, Faculty of Medicine, Kyoto University, Kyoto

Max D. Cooper (workshop cochairman), Howard Hughes Medical Institute, University of Alabama, Birmingham, Ala.

Frederick W. Alt, College of Physicians and Surgeons of Columbia University, New York, N.Y.

Dennis Y. Loh, Howard Hughes Medical Institute, Washington University, St. Louis, Mo.

Jack L. Strominger, Department of Biochemistry and Molecular Biology, Harvard University, Boston, Mass.

Masaru Nonaka, Department of Immunobiology, Cancer Research Institute, Kanazawa University, Kanazawa

Irving L. Weissman, Laboratory of Experimental Oncology, Department of Pathology, School of Medicine, Stanford University, Stanford, Calif.

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Recent Scientific Publications

Publications in the Open Literature

In vivo mutant T cell frequency in atomic bomb survivors carrying outlying values of chromosome aberration frequencies. M Hakoda, M Akiyama, Y Hirai, S Kyoizumi, AA Awa. *Mutat Res* 202:203–8, 1988.

Soft X-ray dosimetry and RBE for survival of Chinese hamster V79 cells. M Hoshi, S Antoku, N Nakamura, WJ Russell, RC Miller, S Sawada, S Mizuno, S Nishio. *Int J Radiat Biol* 54:577–91, 1988.

Preparation of anti-*ras* M_r 21,000 protein monoclonal antibodies and immunohistochemical analyses on expression of *ras* genes in human stomach and thyroid cancers. K Yoshida, K Hamatani, H Koide, H Ikeda, N Nakamura, M Akiyama, H Tsuchiyama, E Nakayama, H Shiku. *Cancer Res* 48:5503–9, 1988.

Immunological responses of aging Japanese A-bomb survivors. ET Bloom, M Akiyama, EL Korn, Y Kusunoki, T Makinodan. *Radiat Res* 116:343–55, 1988.

Neutron RBEs at Hiroshima. In *Radiological Research Laboratory 1988 Annual Report.* DJ Brenner (in collaboration with DL Preston, J Marcum, SD Egbert, W Woolson). New York, Columbia University College of Physicians and Surgeons, 1988. pp 65–8

Somatic mutation in peripheral lymphocytes of former workers at the Okunojima poison gas factory. J Yanagida, S Hozawa, S Ishioka, H Maeda, K Takahashi, T Oyama, M Takaishi, M Hakoda, M Akiyama, M Yamakido. *Jpn J Cancer Res* 79:1276–83, 1988.

Age and dose related alteration of *in vitro* mixed lymphocyte culture response of blood lymphocytes from A-bomb survivors. M Akiyama, OL Zhou, Y Kusunoki, S Kyoizumi. *Radiat Res* 117:26–34, 1989.

Cloning of in vivo-derived thioguanine-resistant human B cells. M Hakoda, Y Hirai, Y Kusunoki, M Akiyama. *Mutat Res* 210:29–34, 1989.

Biological dosimetry. AA Awa. *Isotope News* 2:6–8, 1989 (in Japanese).

Approved Technical Reports

Imbalance of blood group A subtypes and the existence of a superactive *B gene in Hiroshima and Nagasaki.** HB Hamilton, A Yoshida, V Dave. **RERF TR 22-88.**

Blood type A can be classified into subgroups A_1, A_2, and A_1-A_2 intermediate (A_{int}) on the basis of serological criteria. An excess of A_2B over A_2, noted in some black populations and among the Japanese, though not in Caucasoids, is inconsistent with the classical Mendelian mode of inheritance of the allelic A^1 and A^2 genes. Characterization of the enzymatic properties of blood group A and B enzymes in the serum has shown that serological type A_2B blood of some blacks contains A_1 enzyme and a superactive B* enzyme. An excess of A_2B found in a study of more than 15,000 residents of Hiroshima and Nagasaki prompted investigation of the characteristics of the A and B enzymes in 60 blood samples, 37 from individuals in 13 unrelated families and 23 from other unrelated individuals in the two cities. Among 29 samples unequivocally typed serologically as A_2B, 15 were confirmed as A_2B enzymatically; 9 contained A_1 and B* enzymes, not A_2 or B enzymes, thus being A_1B^*; 2 contained A_{int} and B* enzymes, thus being $A_{int}B$; results from the remaining 3 were ambiguous. Hiroshima differs from Nagasaki in the frequency of the A_2B serological type and also in the occurrence of the B* enzyme, Nagasaki having a higher proportion of both. Judging from those cases where a family study was possible, the transmission of the B* enzyme appears to be compatible with the Mendelian mode of inheritance. The excess of serological A_2B in the Japanese appears to be ascribable, at least in part, to the relatively high frequency of a *B** gene.

Summary of the studies at ABCC-RERF concerning the late hematologic effects of A-bomb exposure in Hiroshima and Nagasaki. SC Finch, CA Finch. **RERF TR 23-88.**

The most significant late hematologic effect of A-bomb radiation exposure in the populations of Hiroshima and Nagasaki has been the increased occurrence of leukemia. The radiation effect for leukemia has disappeared in Nagasaki but slightly elevated rates still exist in Hiroshima. Multiple myeloma also is radiation-related, but there is only a suggestive relationship for malignant lymphoma. No evidence exists of a late radiation effect for primary disturbances of hematopoiesis in the absence of malignant disease. Somatic hematopoietic markers of previous radiation exposure include lymphocyte chromosomal aberrations and an increased frequency of mutant T lymphocytes deficient in hypoxanthine phosphoribosyltransferase. A radiation effect also has been observed for the frequency of mutant erythrocytes lacking expression of glycophorin-A protein on the membrane. There is no evidence for radiation-induced disturbance of granulocyte function, but age-related accelerated decline in the immunological functions of T lymphocytes and age-related alteration in the number of certain subsets of circulating T and B lymphocytes appear to be radiation-related. A number of radiation-related hematology research proposals which might be considered for the future are included in this report.

Whole-blood phagocytic and bactericidal activities of A-bomb survivors, Hiroshima and Nagasaki. S Sasagawa, Y Yoshimoto, E Toyota, S Neriishi, M Yamakido, M Matsuo, Y Hosoda, SC Finch. **RERF TR 1-89.**

This in vitro study evaluated the phagocytic and bactericidal activities of leukocytes in aliquots of whole blood from Hiroshima and Nagasaki A-bomb survivors for *Staphylococcus aureus*. The data were analyzed by multiple linear regression using the equation

$$Y = b_0 + \sum_{i=1}^{7} b_i X_i + \sum_{i=1}^{3} c_i (X_i X_4) + e \ ,$$

where X_1, X_2, and X_3 are dummy variables of age categories, X_4, X_5, X_6, and X_7 are indicator variables for sex, exposure to A-bomb radiation, city, and neutrophils, respectively, and X_iX_4 is interaction between the dummy variables for age categories and sex. Any significant effects of exposure to A-bomb radiation could not be detected for both phagocytic and bactericidal activities of whole blood from A-bomb survivors. In addition, there were no significant effects of age categories, sex or city, except in neutrophil counts.

Approved Research Protocols

Guidelines for the conduct of site-specific cancer incidence studies among A-bomb survivors, Hiroshima and Nagasaki. M Tokunaga, K Mabuchi, H Kato, K Shimaoka, CE Land. **RERF RP 9-88.**

This research protocol defines guidelines for conducting a series of pathoepidemiological studies of the incidence of specific cancers as late effects of A-bomb radiation exposure among the RERF Extended Life Span Study population. These guidelines are intended to simplify the preparation of subsequent research plans for site-specific cancer incidence studies and to provide uniformity in the basic design and conduct of studies. The combination of improved tumor and tissue registries and previous experience with other cancer incidence studies at RERF should facilitate the compilation of accurate information about radiation risk and the induction of specific tumors. Modifying factors such as age at the time of the bombing and sex as well as other carcinogenic factors such as smoking and hormone levels, when feasible, will also be considered.

The proposed studies will involve the members of several departments at RERF and pathologists from the university and community hospitals of both Hiroshima and Nagasaki. Other pathologists and clinical investigators with expertise in certain specific cancers also may participate in some of the studies. The proposed studies will be undertaken with the cooperation of the tumor registries of the Hiroshima and Nagasaki City Medical Associations and the tissue registries of the Hiroshima Prefectural Medical Association and the Nagasaki City Medical Association.

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Recent Scientific Publications

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For each cancer site, a specific research protocol will be submitted, describing the background and significance of the proposed study and identifying responsible investigators. Benign tumors may also be included for some sites.

Prevalence of radiation-related skin lesions in Adult Health Study population, Hiroshima and Nagasaki. M Yamada, K Migita, S Yamamoto, H Yoshida, K Kodama, Y Hosoda, K Shimaoka, DE Thompson, SC Finch. **RERF RP 1-89.**

At the time of the regularly scheduled examination, all participants of the Adult Health Study in both Hiroshima and Nagasaki will have a standardized dermatologic examination for the detection of skin cancer, precancerous lesions, and some related disorders. Suspicious lesions will be photographed and/or biopsied. Data will be analyzed upon completion of one cycle (2 years) of AHS examinations.

Hypercalcemia in A-bomb survivors, Hiroshima and Nagasaki (addendum to RERF RP 11-86). S Fujiwara, S Akiba, R Sposto, H Ezaki, K Neriishi, M Yamada, Y Hosoda, S Inoue, K Shimaoka, M Shiraki. **RERF RP 2-89.**

This study is intended to determine whether subclinical hyperparathyroidism (HPT) or reduced secretion of calcitonin (CT) from the thyroid gland is involved as a possible cause of hypercalcemia, which was found among A-bomb survivors in a previous study of the prevalence of HPT in A-bomb survivors.

In this proposed addendum to RP 11-86, Hiroshima and Nagasaki Adult Health Study participants who are scheduled for physical examination during January 1989–December 1990 will be classified into groups by age, sex, and radiation dose. A random sample from each group will be selected for the purpose of measurements of serum calcium, high-sensitivity parathyroid hormone (HS-PTH), intact PTH, and CT levels to determine the effect of radiation exposure on the secretion of PTH and CT. Cases of subclinical HPT which are found in this proposed study will be followed up to determine whether clinical manifestation of symptoms subsequently develops.

Osteoporosis in Hiroshima A-bomb survivors. S Fujiwara, Y Makidono, H Sasaki, K Neriishi, K Kodama, Y Hosoda, S Mizuno, H Orimo. **RERF RP 3-89.**

This two-year study of all Adult Health Study participants in Hiroshima will consider the relationship between radiation exposure and the development of osteoporosis as an index of aging. All persons who elect to participate will be evaluated for bone mineral content (BMC) by means of a dual photon bone densitometer, for vertebral compression fractures by diagnostic chest X-ray studies, for nutritional considerations, and for a number of other possible confounding factors. A selected group of 50 persons having doses of more than 1 Gy and an equal number of age- and sex-matched controls will be evaluated for certain serum and calcium metabolic factors which may influence BMC.

ABO phenotype association with risk factors of cardiovascular disease in the Adult Health Study and its relation to radiation exposure, Hiroshima and Nagasaki. FL Wong, K Kodama, K Neriishi, H Sasaki, M Akahoshi, Y Shimizu, HB Hamilton. **RERF RP 4-89.**

The proposed study will examine whether the association between ABO and cardiovascular disease (CVD), and ABO and some risk factors of CVD such as total serum cholesterol and blood pressures, also exist in the Japanese population. This is of special interest since findings among blacks and non-Japanese Asians have so far been equivocal or negative, suggesting racial heterogeneity. Moreover, no known studies of this type have been conducted to date on the Japanese which makes the study of unique importance. The Adult Health Study (AHS) data from Hiroshima and Nagasaki will also enable the study of the effects of radiation on such relationships, which might shed some light upon the recently reported dose response in individuals with myocardial infarction. The risk factors measured at each examination cycle of the AHS will be examined for their relationships with ABO phenotypes after correcting for the effects of covariates, including radiation dose. Multivariate statistical methods will be employed to study the simultaneous effects of various blood markers, including ABO, on lipid levels. The ABO CVD association will be examined by using confirmed CVD cases up to 1978.

Pathology studies in Hiroshima and Nagasaki. Revised research plan. SC Finch, M Tokunaga, K Mabuchi. **RERF RP 5-89**

A revised platform protocol for the conduct of pathology studies at RERF is described. Involvement of community hospital and university-based pathologists in site-specific cancer incidence studies at RERF and Life Span Study community cooperative autopsy programs in each city are proposed as alternatives for the RERF autopsy and surgical programs which have been terminated. Emphasis is placed on the continuing importance of pathology in tumor verification and incidence studies and in the definition of all histopathologic changes which may represent late radiation effects. ❑

News Briefs

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✓ Nagasaki Laboratory Sets Up Radioisotope Facility

The new Nagasaki RERF Radioisotope Laboratory will support the clinical studies, cytogenetics, and cell biology programs, and will allow the introduction of modern molecular techniques in the laboratory itself, rather than in space borrowed from Nagasaki University.

✓ RERF Director Permanently Stationed in Nagasaki

For the first time in the history of RERF, one of the Foundation's six permanent directors will reside in Nagasaki beginning in mid-April. This and other administrative changes are expected to improve communications between the two RERF laboratories and to enhance the effectiveness and scientific output of the entire organization.

J.W. Thiessen, RERF vice-chairman, will relocate and become director of the Nagasaki Laboratory. Former Chief of the Nagasaki Laboratory **Katsutaro Shimaoka** has been appointed RERF associate chief of research. Permanent Director **Yutaka Hasegawa** will assist Thiessen as consulting director to the Nagasaki Laboratory.

✓ RERF Vice-Chairman Appointed to CEC Advisory Panel

RERF Vice-Chairman **J.W. Thiessen** served as a member and rapporteur of an international panel of independent experts, which will advise the Commission of the European Communities on the feasibility of studying the health effects in Europe that may result from the Chernobyl nuclear reactor accident. The panel met inBrussels, 27–28 February.

✓ Genetics Chief Journeys to US National Laboratory

Department of Genetics Chief **Akio Awa** and Research Associate **Kazuo Ohtaki** recently visited Lawrence Livermore National Laboratory to learn more about a pioneering chromosome-specific staining method. As recommended by the 1988 Scientifife Council, efforts are now underway to determine how this way of fluorescently marking chromosomal structural abnormalities can best be used to appraise the effects of A-bomb radiation. ❑

RERF update RERF

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