

## Radiobiology Program Evaluated as RERF Initiates Multinational Departmental Review

by Seymour Abrahamson  
Associate Chief of Research

As recommended by the Blue Ribbon Panel (1996), the first multinational peer review of an RERF department was undertaken on 13-15 January 1998 at the Hiroshima laboratory with the evaluation of the Department of Radiobiology's program. The eight-member external panel was charged with reviewing Radiobiology's program as a whole and addressing areas in which RERF and the department might better conduct the program. The panel was chaired by Dr. Roger Cox, head of the Radiation Effects Department of the UK's National Radiological Protection Board.

Included in the panel's charge were the scientific review and evaluation of ongoing and future work; evaluation of staff and their research activities; and analysis of program operation, including staff interactions, collaborations, and scientific management. In addition, recommendations were sought with regard to general and specific staffing levels and program needs as well as suitability of physical facilities and research equipment to the Radiobiology program.

The process began with an overview of the department by Dr. Toshio Seyama, acting Radiobiology chief, followed by researchers' presentations of their activities in molecular oncology, molecular epidemiology, and im-

*See Peer Review on page 7*

# 放影研 RERF update

Radiation Effects Research Foundation News and Views  
Hiroshima and Nagasaki, Japan

## ABCC/RERF: Commemorating the First 50 Years and Looking Ahead

On 13 and 14 June, 1997, the National Academy of Sciences (NAS; the Academy) hosted a special symposium to commemorate the 50 years of scientific investigation conducted by the Atomic Bomb Casualty Commission (ABCC; 1947-75) and its successor, the Radiation Effects Research Foundation (RERF; 1975 to present). President Truman's original directive to NAS to initiate a long-term investigation of the health effects from the atomic bombings was displayed in the Academy auditorium. Approximately 300 attended the event, and a large contingent of retired ABCC employees trav-



**Directors Toast ABCC/RERF's 50th Anniversary**

From left to right: Sheldon Wolff, Donald Harkness, J. W. Thiessen, James Trosko, Itsuzo Shigematsu, Charles Edington, Seymour Abrahamson, William J. Schull, Stuart Finch, Anthony Pisciotto, and Gilbert Beebe. (Courtesy of Dr. Abrahamson)

eled from Japan for this special occasion and presented Dr. Alberts, president of the Academy, with a commemorative vase before the symposium began.

*See Anniversary on page 6*

## Dr. Itsuzo Shigematsu Retires Shigenobu Nagataki Becomes RERF's Fourth Chairman

At the end of the working day 30 June, Dr. Itsuzo Shigematsu presented Dr. Shigenobu Nagataki with his chairman's notebook and, with it, the leadership of RERF. After 16 years and four terms as the Foundation's third chairman, Dr. Shigematsu retired to assume the role of RERF consultant emeritus. During his tenure, Dr. Shigematsu represented RERF to the international and local communities in various capacities. Among his activities,

Dr. Shigematsu served as a member of the Main Commission of the International Commission on Radiological Protection (ICRP), chairman of the advisory committee for the Chernobyl Project of the International Atomic Energy Agency (IAEA), and president of the Hiroshima International Council for Health Care of the Radiation-Exposed (HICARE). For his work in radiation epidemiology and protection,

*See New Chairman on page 18*

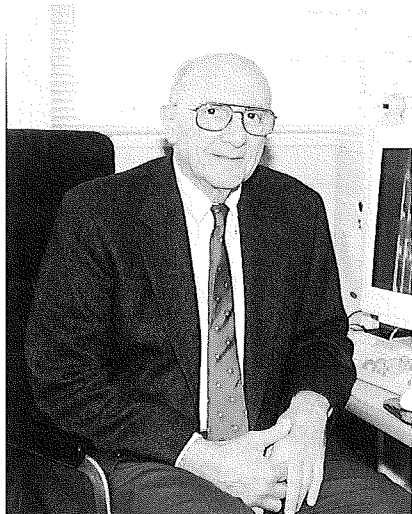


## 放影研 RERF update

Volume 9, Issue 1, Spring 1998

### In this Issue

Physical versus Biological Dosimetry .....	3
Acute Effects and DS86 Dose Estimates for Distal Survivors .....	4
DS86 Gamma and Neutron Colon Dose Estimates .....	8
Board of Directors Meeting .....	9
24th Scientific Council Meeting ..	10
Workshops/Training Course .....	11
RERF News .....	14
Research Staff News .....	17
RERF On-line: www.rerf.or.jp .....	19
Protocols and Publications .....	20



This past year has seen many changes at RERF. After 16 years, our much-honored chairman, Dr. Shigematsu, who had led the Foundation through a remarkable period of achievement, and also through some very trying budgetary crises, retired. This same year saw Dr.

### ***New Leaders Face Busy Schedule in First Quarter***

*by Sheldon Wolff, Vice Chairman, Chief of Research, and Update Editor-in-Chief*

Hasegawa, Dr. Schull, as well as Mr. Hirano leave. Thus we began to face the future with an entirely new team of Directors as well as a new head of the Secretariat.

Those of us on this team were new-comers to RERF, but have all worked very hard to learn and to become efficient. For a while our job was even more difficult because of the unexpected health problem suffered by Dr. Nagataki, our new chairman. I am happy to say, however, that he has made remarkable progress, for which we are all grateful.

This coming year at RERF was, and will be, a very busy one for all of us. In January in accord with the recommendations of the Blue Ribbon Panel, we began the first of our multinational departmental reviews, in which the work of the Department of

Radiobiology was reviewed and then reported to our Science Council at their March 18-20 meeting. During the three months of January to March we also had two workshops under our program of International Collaboration.

All of this activity will culminate in June's board of directors meeting. While all of this goes on we are also carrying out our main task, our extensive research program, are vigorously proceeding with the program of openness to the public, and are moving forward to establish even stronger relations with the universities in Nagasaki and Hiroshima. None of this could happen without the staff giving its usual exceptional assistance and cooperation in supporting the activities of the foundation. □

### ***New Year Marks New Era for RERF***

*by Shigenobu Nagataki, Chairman*

Last year, RERF celebrated the 50th anniversary of the establishment of ABCC/RERF. At the same time, after 16 years as RERF's leader, Dr. Shigematsu presented me with the chairman's notebook, RERF welcomed Dr. Wolff as its new vice chairman and chief of research, and Dr. Taira took over as director for Nagasaki. It was a year of great change and much anticipation. In the coming year, ABCC/RERF's 50th anniversary will be commemorated in Nagasaki as it was in 1997 in Hiroshima. With the new year, then, the Foundation steps into a new era.

At the 24th meeting of the Scientific Council last fall in San Francisco, the question of the multinational peer review of RERF research activities recommended by the Blue Ribbon Panel was discussed. In January, an eight-member panel of specialists in the field of radiobiology representing Japan, the US, and the UK came to Hiroshima to carry out the first review of the Department of Radiobiology. Their findings were on the agenda of March's 25th Scientific Council meeting. Additional proposals regarding RERF's research procedures were on both meetings' agendas as well, and

these are expected to expand RERF's current research base.

In November, Nagasaki's Local Liaison Council convened after more than ten years. Representatives of A-bomb survivors' organizations, medical associations, hospitals, universities, local assemblies, and administrative agencies gathered for an active discussion on the relationship between RERF and the local community. A similar meeting is planned this year in Hiroshima.

RERF opened its doors to both the Hiroshima and Nagasaki facilities in the summer and fall. Guests learned about our daily activities by viewing panel displays, looking into microscopes, and speaking with the staff members who do the research.

RERF is a leading research institute in the world. I am proud of our staff and their important contributions, and one of my responsibilities will be to continue to make RERF attractive to a new generation of young scientists. Moreover, we must never forget that the basis of our research is the unsparing cooperation received from Hiroshima's and Nagasaki's atomic-bomb survivors.

It is also extremely important for



RERF's development that local people understand our research activities through such means as the liaison council discussions and our annual open houses.

Financially, RERF is expected to follow a policy of retrenchment due to the stringent budget situations in both the US and Japan. Though this will no doubt be difficult for the staff, it is my hope that directors and staff will unite and draw upon their resources to overcome the situation.

We know that we have many more scientific contributions to make for the benefit of society, and we look forward to our second half century. □

# Physical versus Biological Dosimetry

## Comparison of Electron Spin Resonance (ESR) Estimation of Tooth Enamel

### Dose and Cytogenetic Data of Hiroshima Survivors

by Nori Nakamura

Chief, Department of Genetics

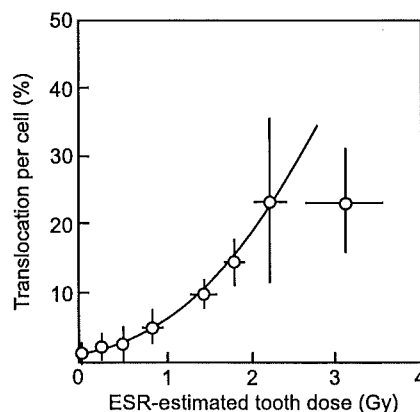
Using electron spin resonance (ESR) of tooth enamel to estimate atomic-bomb (A-bomb) gamma-ray dose received, we have recently examined 100 teeth donated from Hiroshima A-bomb survivors (Nakamura *et al.* in press). To evaluate possible contamination from dental x-ray exposures, which affect mostly buccal surfaces, each tooth was divided into its buccal and lingual parts for subsequent independent enamel isolation and ESR measurement. Nearly 20 teeth showed considerably larger ESR-estimated doses in their buccal parts than in their lingual parts, which first seemed to indicate a considerably large contribution from dental x-ray exposure. However, it was found that most of these discrepant cases were incisors and canines. Because it is difficult to imagine that dental x-ray exposures affected mainly front teeth only and ultraviolet light exposure is reported to induce an ESR signal, the results are most likely attributable to solar light exposures (Romanyukha *et al.* 1996).

Next, cytogenetic examination was conducted for 61 of 69 tooth donors, and the results were compared with ESR estimates. Translocation frequency in lymphocytes and ESR-estimated dose for buccal and lingual parts of molars and lingual parts of front teeth, i.e., incisors and canines, showed a dose response for translocations as we would expect from in vitro gamma-ray irradiation experiments (Figure 1). However, the buccal parts of front teeth yielded definitely fewer translocations, and this is attributable to tooth-dose overestimation from solar light exposure contamination (Figure 2).

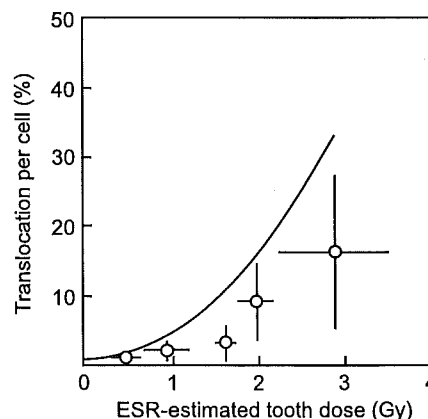
When the average doses in buccal parts were compared with those of lingual parts of the same teeth, the difference was largest for first incisors and declined following tooth position deeper in the mouth, i.e., 0.5 Gy for first incisors, 0.3 Gy for second incisors, 0.2 Gy for canines and small molars, and 0.04 Gy for large molars, including wisdom teeth. Because lingual parts of front teeth can also be affected by solar light exposures, although to a lesser extent than their buccal parts, these excess doses in buccal parts are probably minimal estimates attributable to solar light exposures.

We conclude that both tooth enamel ESR and cytogenetic tests of blood lymphocytes are useful measures for retrospective dose estimation of individuals. To be

prudent, we should either avoid measuring front teeth or make an additional effort to eliminate solar light-induced ESR signals in using front teeth.



**Figure 1.** Translocation frequency versus ESR dose of lingual parts of molars, which are least likely affected by factors other than A-bomb gamma rays. Each point represents an average of five individuals, and bars represent standard deviations of the means. The line represents expected dose response, which is 70% of translocation yield measured by FISH (Lucas *et al.* 1995) because conventional Giemsa staining used in the present study is known to overlook 30% of translocations (Ohtaki *et al.* 1982).



**Figure 2.** Translocation frequency versus ESR dose of buccal parts of front teeth, which are most likely affected by solar light exposures.

#### References

- Lucas JN, Hill F, Burk C, Fester T, Straume T. Dose-response curve for chromosome translocation measured in human lymphocytes exposed to  $^{60}\text{Co}$  gamma rays. *Health Physics* 1995; 68:761-5.
- Nakamura N, Miyazawa C, Sawada S, Akiyama M, Awa AA. A close correlation between electron spin resonance (ESR) dosimetry from tooth enamel and cytogenetic dosimetry from lymphocytes of Hiroshima atomic-bomb survivors. Submitted to the *International Journal of Radiation Biology*, in press.
- Ohtaki K, Shimba H, Awa AA, Sofuni T. Comparison of type and frequency of chromosome aberrations by conventional and G-banding methods in Hiroshima atomic bomb survivors. *Journal of Radiation Research* 1982; 23:441-9.
- Romanyukha AA, Wieser A, Regulla D. EPR dosimetry with different biological and synthetic carbonated materials. *Radiation Protection Dosimetry* 1996; 65:389-92. □

## Acute Effects and DS86 Dose Estimates for Distal Survivors

by Dale Preston, Chief, Department of Statistics

At a North Asia Region meeting of the International Physicians for the Prevention of Nuclear War (IPPNW) held in Nagasaki in November 1997, Professor M. Tomonaga of the Nagasaki University School of Medicine described the findings of an early US report on the occurrence of acute effects among slightly more than 600 respondents in a sample of about 900 hospitalized atomic-bomb survivors in Hiroshima and Nagasaki. Professor Tomonaga noted that this report, which was carried out for the Manhattan District in September 1945 and declassified by the US government in 1979, indicates a relatively high incidence of epilation and bleeding in survivors who were 2.25 to 4.25 km from the hypocenters at the time of the bombings. Since the IPPNW meeting, a number of newspaper articles and other reports on the findings of the "Manhattan Investigation Team" have appeared. Several of these articles have suggested that the findings presented in the Manhattan District report (MDR) cast doubts on the adequacy of the DS86 estimates of survivor doses. In view of the interest in the MDR, it is worthwhile to examine the major sources of data on acute effects in bomb victims with regard to their relationship to DS86 dose estimates and to consider what these data can or cannot tell us about problems with the dosimetry. As discussed below, acute effects data from these sources, which include the MDR, reports on other early large-scale studies, and RERF records, it becomes clear that the MDR is an unreliable guide to the prevalence of acute effects as a function of distance from the hypocenter. While there are important questions about aspects of DS86 doses, the nature of these uncertainties is such that the rather crude biological dosimetry provided by information on the prevalence of acute effects such as epilation and bleeding does not provide much useful information for addressing these concerns.

### Data sources

Surveys of acute health effects experienced by bomb victims began within a few weeks of the bombings. Beginning in September 1945, several groups associated with the US Armed Forces carried out surveys. In addition to the MDR study, studies were organized by the US Armed Forces Pacific Theater General Headquarters (Oughterson Investigation Team); the US Navy (Warren Investigation Team); and the US Air Force (Strategic Bombing Investigation Team). At about the same time, Japanese research groups, including teams from Tokyo Imperial University, Kyoto Imperial University, and the Kumamoto University Medical School carried out studies in Hiroshima and Nagasaki. The Tokyo University study, which included more than 4,400 people, was the largest of these initial studies.

As these early studies were being carried out, the US Armed Forces General Headquarters (GHQ) established the Joint Commission on the Effects of the A-bombs to develop a comprehensive large-scale assessment of radiation effects. The Joint Commission assessment involved investigators from the US Armed Forces Pacific

Theater General Headquarters, the Manhattan District, the US Navy, and the Japanese Imperial Government (Tokyo Imperial University). In November 1945, this group reported on the prevalence of acute effects based on their survey of more than 13,000 survivors.

In each of these surveys, for survivors who were within 2.5 km of the hypocenter, the prevalence of acute effects decreased rapidly with distance. The reports also all note that some survivors beyond 2.5 km from the hypocenter suffered from acute effects. In particular, the Tokyo University and Joint Commission groups found 1 to 2% prevalence for epilation or bleeding among distal survivors whereas, in contrast, 10 to 20% of the distal respondents in the MDR indicated they had suffered from epilation or bleeding. Prevalence rates for distal survivors decreased slowly with distance in all of the reports. This general pattern of a rapid decrease for proximal survivors to low, and largely distance-independent, rates for more distal respondents suggests that presence of epilation or other symptoms among survivors who were more than about 3 km from the hypocenter may reflect factors other than radiation.

From 1947 through the late 1950s, ABCC researchers collected data on acute effects for several hundred thousand survivors, including virtually all of the 86,000 survivors in the Life Span Study (LSS) with DS86 dose estimates. The rates for epilation and bleeding in the LSS as a function of distance are similar to those noted in the Tokyo University and Joint Commission reports. The LSS rates for survivors within 2 km are also similar to those seen in the MDR. However, like the rates described by the Tokyo University and Joint Commission researchers, the prevalence of acute effects for LSS survivors beyond 2 km are considerably lower than those described in the MDR. Table 1 summarizes the characteristics of the major surveys.

### Summary of major findings

The panels in Figure 1 show how the prevalence of epilation varies with distance based on the Tokyo University, Joint Commission, ABCC, and MDR data. The MDR results are included in each panel to facilitate comparison of the findings. Although not shown here, plots for the occurrence of bleeding show a similar pattern to that seen here, with the relatively large estimates for distal survivors in the MDR.

The figure highlights the fact that the prevalence of epilation for distal survivors found by the MDR researchers is considerably higher than that for the other studies. In order to understand this difference, it is useful to consider how the MDR study differs from the other acute effects studies. The MDR is the smallest of the four studies considered here and includes the smallest number and proportion of distal survivors as shown in Table 2.

Although the MDR considers only a small number of distal survivors, sample size alone is probably not the primary explanation for the difference in rates. A more likely cause of bias is the fact that, unlike the other studies,

Table 1. Major survey characteristics

Study	Data collection	People	Nature of sample
Manhattan District	September 1945	644 (both cities)	Hospital inpatients
Tokyo University	October 1945	4,406 (both cities)	Inpatients, Outpatients, General population
Joint Commission	November 1945	6,663 (Hiroshima) 6,427 (Nagasaki)	Inpatients, Outpatients, General population
Life Span Study	1947 – 1957	58,500 (Hiroshima) 28,132 (Nagasaki)	General population

Table 2. Comparison of number and proportion of distal survivors

Study	Distal group	Number of distal survivors (%)	Epilation prevalence
Manhattan District	2.25 – 4.25 km	56 (9%)	14%
Tokyo University	2.6 – 3 km	503 (11%)	1.7%
Joint Commission	2.6 – 5 km	3,565 (27%)	1.6%
Life Span Study	2.6 – 4 km > 4km	24,224 (28%) 15,278 (18%)	1.5% 0.5%

the MDR rates are based solely on reports of hospitalized patients. While it is likely that a high fraction of proximal survivors were hospitalized, it is unlikely that the small proportion of distal survivors who were hospitalized would be representative of all distal survivors. Moreover, in view of the small and largely distance-independent proportion of distal survivors who reported epilation or bleeding, hospitalized distal survivors might be expected to have a higher rate of radiation-like acute effects than the full population of distal survivors. This type of bias would be less pronounced for proximal survivors.

The LSS is the only study that provides data on the severity of epilation (classified as none, slight (less than 25% hair loss), moderate (25 – 75% hair loss), or severe. It is noteworthy that virtually all of the epilation reported by distal LSS survivors is categorized as slight and there are no reports of severe epilation among these survivors.

On the other hand, a large fraction of the epilation cases among survivors within 2 km were described as severe.

### Conclusions

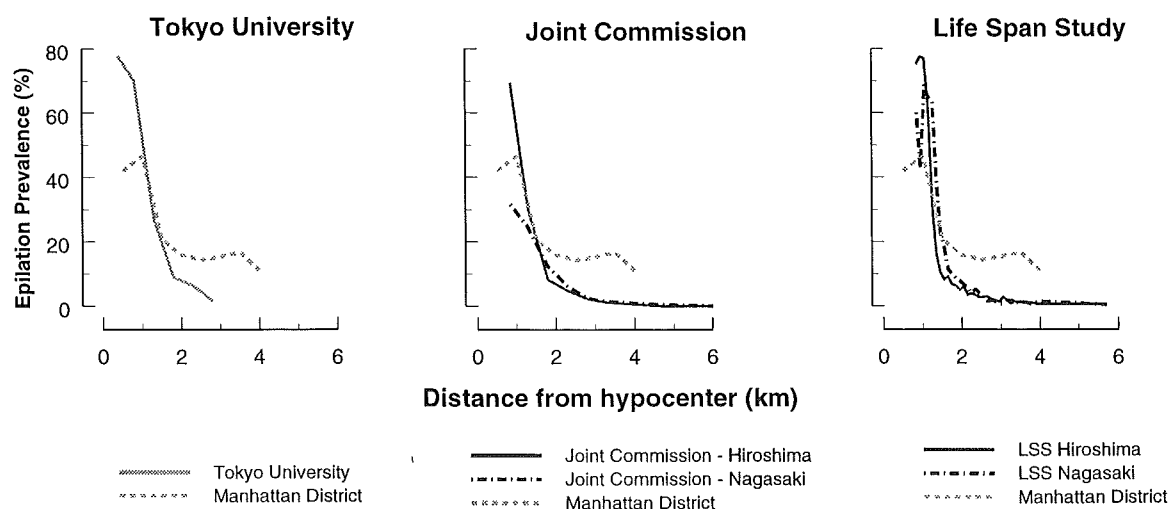
We have reviewed the major sources of information on the prevalence of acute effects, including ABCC/RERF data and data obtained independently by various groups who investigated these issues in the months immediately after the bombings. Except for the high prevalence rates for distal survivors reported in the MDR, we find that there is good agreement in estimates of the distance-dependent prevalence of epilation or bleeding. The MDR notes a considerably higher prevalence of acute effects for distal survivors than the other reports that is probably due to bias caused by restriction

of the MDR sample to hospitalized survivors. All of the studies note some reports of radiation-like acute effects among distal survivors, but it seems likely that these effects are due to factors other than radiation. Taken as a whole, available data on the prevalence of acute effects do not suggest that distal survivors received large doses of radiation.

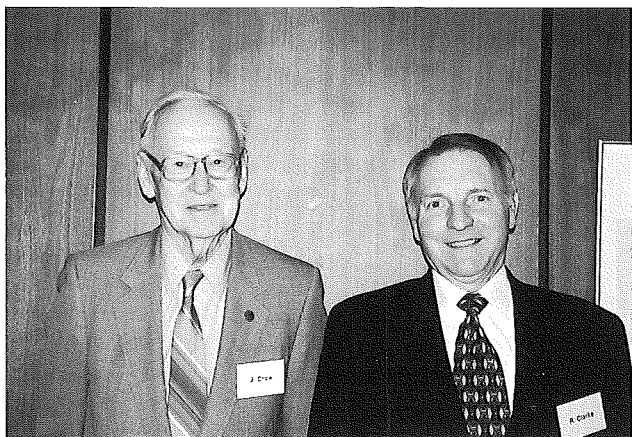
The occurrence of acute effects, such as epilation or bleeding, following radiation exposure is not a precise dosimeter. Thus, the fact that there is nothing in the acute effects to suggest that there are gross errors in DS86 doses does not mean that there are not problems with DS86 estimates. In the decade since the introduction of DS86, US and Japanese researchers have worked to understand distance-dependent discrepancies between measurements of thermal (low energy) neutron exposures in various

*Continued under Acute Effects on page 7*

### Epilation by Distance







#### **Chairs of 1975 and 1995 RERF Review Committees**

James F. Crow, PhD, (left) headed the Crow Committee, which published its review report of ABCC in February 1975, and Roger Clarke, PhD, who headed the Blue Ribbon Panel, which presented its RERF review report to Dr. Shigematsu in July 1996.



#### **ABCC Panelists**

from left to right, Drs. Beebe and Miller, Mr. Rappaport, and Drs. Maki and Neel.



#### **RERF Panelists**

from left to right, Drs. Edington and Schull, Mr. Jablon, and Drs. Sugahara and Finch. Standing is Dr. Charles Land, who introduced the two panels. (Anniversary photos courtesy of Dr. Abrahamson)

#### **Anniversary continued from page 1**

The symposium opened with greetings and words of appreciation from Dr. Alberts; Dr. Itsuzo Shigematsu, chairman of RERF; Dr. Tara O'Toole, assistant secretary of the US Department of Energy; and Mr. Shotaro Oshima, minister from Japan's US Embassy.

Dr. Charles Land, of the U.S. National Cancer Insti-

tute, then introduced two panels, one comprising representatives who had served at ABCC and the other former RERF directors. The ABCC panel was moderated by former director, Gilbert Beebe, and included Drs. Hiroshi Maki, former associate director, Robert Miller, and James Neel, the first acting director, as well as Mr. Michael Rappaport. Dr. Stuart Finch moderated the second panel and was joined by Drs. Charles Edington, William J. Schull, and Tsutomu Sugahara and Mr. Seymour Jablon. (Each of the panels is pictured at the left.) Panelists recalled some of the highlights of their research, including major challenges and accomplishments.

Six topic areas were selected for the two scientific sessions based on recommendations of the Blue Ribbon Panel (BRP) Report: risk estimation, noncancer endpoints, the molecular and genetic basis of cancer, RERF dosimetry, studies of the  $F_1$  population, and training collaborations. Each topic was introduced by two panel co-chairs from RERF who were followed by several invited panelists, one of whom was invited to present a keynote talk. All panelists were asked to focus on future directions and how the more promising results recently obtained at RERF might be investigated in more detail. After the initial presentations, the audience was encouraged to participate and ask questions.

The first scientific session, moderated by RERF Chair Itsuzo Shigematsu and Paul Gilman, executive director, Commission on Life Sciences, NAS, focused on the current status of RERF projects and future research directions and covered the first three topics. The risk estimation panel was co-chaired by Dale Preston, chief, Department of Statistics, and Kiyohiko Mabuchi, chief, Hiroshima Department of Epidemiology, RERF, and invited panelists were Albrecht Kellerer, University of Munich, Germany; Geoffrey Howe, Columbia University; Susan Preston-Martin, University of Southern California; and Ethel Gilbert, US National Cancer Institute. Kazunori Kodama, chief, Hiroshima Department of Clinical Studies, and Masazumi Akahoshi, acting chief, Nagasaki Department of Clinical Studies, RERF, co-chaired the panel on noncancer endpoints. Participants in that discussion were Steven Lipshultz, Rochester University; and Eric Boerwinkle, University of Texas Health Science Center at Houston. The molecular and genetic basis of cancer group was co-chaired by Toshio Seyama, acting chief, Department of Radiobiology, and Kiyohiko Mabuchi. Those panelists included Curtis Harris, US National Cancer Institute, and Maurice Fox and Tyler Jacks, both of the Massachusetts Institute of Technology.

In the second scientific session, moderated by Evan Douple, director, Board of Radiation Effects Research, NAS, and RERF Vice Chairman and Chief of Research Sheldon Wolff, symposium participants focused on the remaining topics. RERF Statistics Chair Dale Preston and Nori Nakamura, then assistant chief, Department of Genetics, co-chaired the panel on RERF dosimetry, whose members included Tore Straume, University of Utah; Warren Sinclair, National Council on Radiation Protection and Measurement; Masaharu Hoshi, Hiroshima University; and John Zimbrick, Purdue University. Chiyoko Satoh, Genetics Department Chief, and Kiyohiko Mabuchi co-chaired the panel concerned with  $F_1$  population stud-

See *Anniversary* at top of next page

*Anniversary continued from bottom of previous page*

ies, and panelists included James Neel, University of Michigan; Seymour Abrahamson, University of Wisconsin; and William J. Schull, University of Texas Health Science Center at Houston. The final panel, dealing with training collaborations, was co-chaired by Akio Awa, RERF assistant chief of research, and Joseph Weiss, US Department of Energy. Panelists were Elaine Ron, US National Cancer Institute; Joel Breman, US National Institutes of Health; and Jaak Sinnaeve, the European Commission. In the latter session, panelists described plans for involving young investigators in the research ongoing at RERF.

The symposium program was summarized by Dr. Roger Clarke, Director of the National Radiological Protection Board in the United Kingdom. Dr. Clarke was BRP chair, and he expressed his appreciation that the Panel's major recommendations were being addressed at RERF.

Symposium participants also enjoyed two important Washington social events, a reception hosted by the Japanese government at their embassy, which was attended

by about 250, and a reception hosted by the Department of Energy and NAS at the Decatur House at Lafayette Square, also attended by 250 symposium participants. At the second event, Dr. Shigematsu, on the occasion of his retirement, was presented with several awards in recognition of his 16 years of outstanding service as RERF chair.

The symposium was considered a success in that it commemorated the world's most extensive and important studies of the health effects of radiation; it renewed many long-time acquaintances of people who had served ABCC/RERF over the years; it documented the highlights of the many scientific accomplishments that have resulted from the important research; it fostered the exchange of important ideas for RERF's future research directions; and it recognized the many contributions of retiring RERF Chairman Dr. Shigematsu and introduced new chairman, Dr. Shigenobu Nagataki. Symposium proceedings are expected to be published in 1998 and will feature on the cover the painting *Experimental Laboratory-Small Life* by RERF's assistant chief of the Secretariat, Mr. Torao Sasaki. □

*Peer Review continued from page 1*

munology. Each presentation was followed by reviewer questions. After then inspecting research facilities and engaging in individual discussions with researchers, the peer-review team prepared their recommendations. After submission of those recommendations to Chief of Research Sheldon Wolff, they were forwarded to Scientific Council members for attention at their March meeting.

Radiobiology researchers and their presentations were: Dr. Sadayuki Ban: *Genetic alterations responsible for primary breast cancer of A-bomb survivors*; Dr. Kiyohiro Hamatani: *Activation of RET oncogene in thyroid cancer among survivors*; Dr. Keisuke S. Iwamoto: *The search for the molecular events responsible for A-bomb-radiation-induced liver carcinogenesis*; Dr. Terumi Mizuno: *Possible molecular radiation fingerprints in A-bomb-survivor skin cancer*; Dr. Seishi Kyoizumi: *Molecular epidemiology/immunology overview*; Dr. Yoichiro Kusunoki: *Long-term impairment of the hematolymphoid system and its relation to disease in A-bomb survivors*; Dr. Yuko Hirai: *Detection of AT heterozygotes by ATM protein expression*; Dr. Tomonori Hayashi: *Immunologic background in A-bomb survivors: Possible population bias and susceptibility to diseases*; Dr. Seishi Kyoizumi: *Blood cell bank for molecular epidemiology*; and Dr. Yuko Hirai: *Collection of tumor-tissue samples: Current status and future plans*.

*Acute Effects continued from page 5*

materials and DS86 estimates of these exposures. At the same time, improvements in the underlying models have led to changes that will affect dose estimates.

Although there is still no consensus on the nature of future DS86 changes, it seems likely that they will have a relatively small impact on doses. In particular, there are three general areas in which changes in dose are likely. First, it seems that gamma dose estimates, especially in Hiroshima, may have to be increased by 10 to 15%. Second, it is also likely that there will be an increase in Hiroshima neutron dose estimates, but the magnitude of this change is not at all certain. In the most extreme scenarios, beyond about 1,600 meters, Hiroshima neutron doses might change by a factor of 10, though it is probable that the final changes will not be this large. However, even if the neutron doses change by a factor of 10 for Hiroshima survivors beyond 1,600 meters from the hypocenter, the impact on the total dose is small. This is because for Hiroshima survivors at these distances, neutrons account for less than 0.3% of the

All specialists in some aspect of radiobiological research, review panel members included: Dr. Joe W. Gray, professor, Laboratory Medicine and Radiation Oncology, Cancer Center, University of California, San Francisco School of Medicine, USA; Dr. Masao Sasaki, professor, Radiation Biology Center, Kyoto University, Japan; Dr. J. Martin Brown, professor and director, Division of Radiation Biology, Department of Radiation Oncology, Stanford University School of Medicine, USA; Dr. Yusuke Nakamura, director, Human Genome Center, Laboratory of Molecular Medicine, Institute of Medical Science, The University of Tokyo, Japan; Dr. Karl T. Kelsey, associate professor, Occupational Medicine and Radiobiology, Harvard University School of Public Health, USA; Dr. Ohtsura Niwa, professor, Radiation Biology Center, Kyoto University, Japan; and Dr. Kiyoshi Takatsu, professor and chair, Immunology Department, The Institute of Medical Science, The University of Tokyo, Japan. Drs. Gray and Sasaki are RERF scientific councilors. Dr. Nakamura was absent from the proceedings.

Panel recommendations will provide an in-depth analysis of existing research projects with an aim to guiding future research efforts given personnel and biological resource limitations. Reviews will be conducted annually on a rotating basis so that each year, a different program will be evaluated. Each year, then, a new panel of international experts in the given specialty will be convened. □

total DS86 dose, so a ten-fold increase in neutrons would increase total dose estimates for these survivors by no more than 3%. The third area in which changes are likely involves dose estimates for Nagasaki factory workers. Biodosimetric data suggest that doses for this relatively small, but important, group of survivors are overestimated by DS86 (as they were in the previous dosimetry). Overall, it appears that as a result of the eventual changes to DS86, individual dose estimates may be increased by 10 to 15% for most survivors, and neutrons may account for a somewhat larger fraction of the total dose for Hiroshima survivors than at present. Such changes will have only a minimal impact on number of survivors whose estimated dose is greater than (say) 5 mGy or on the distances at which people could receive such doses. □

*Note: Additional material on this topic in both Japanese and English, including a different version of the figure and the text of one the original newspaper reports are available from the RERF home page (<http://www.rerf.or.jp>). □*

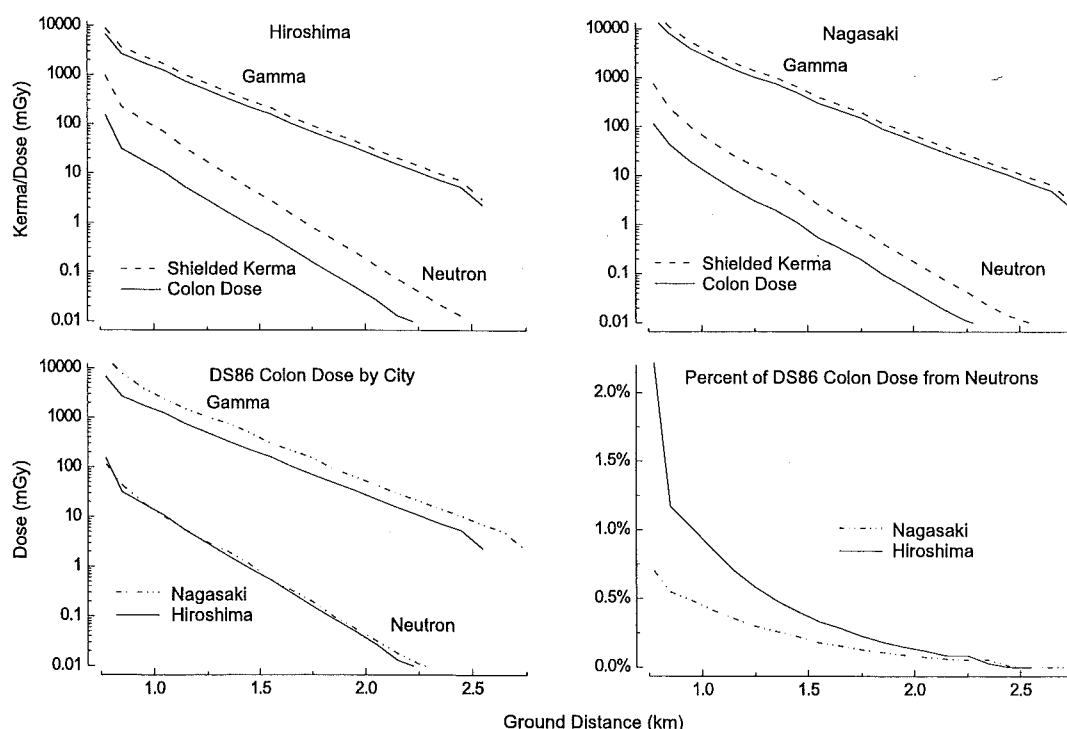
## DS86 Gamma and Neutron Colon Dose Estimates for LSS Survivors by Distance

Most analyses at RERF are made in terms of DS86 dose estimates without explicit consideration of distance. However, the relationship between dose and distance is important in consideration of various issues. Distance from the hypocenter is the primary determinant of dose, with external and self-shielding having important but secondary roles. This note and the figures presented below describe the relationship between DS86 dose estimates and the distance for survivors in the LSS cohort.

The final report (Roesch 1987) completed at the time of the introduction of the DS86 system included tables (p. 131) and figures (p. 133) comparing DS86 and T65D free-in-air gamma and neutron kerma estimates by city. Part 1 of LSS Report 11 (Shimizu *et al.* 1990) included plots of shielded gamma and neutron kerma versus distance estimates for survivors in the two cities. These plots, especially those in Report 11, provide useful summaries of aspects of the DS86 doses, but they have some limitations. In particular, there have been no published tables presenting the data used for the shielded kerma plots and no plots or tabulated data describing the organ-dose versus distance comparisons. In addition, since publication of early reports, the DS86 system has been extended to include additionally proximally exposed survivors, primarily Nagasaki factory workers.

The figures below display the average gamma and neutron components of shielded kerma and colon dose for LSS survivors within 2,600 meters of the hypocenter in Hiroshima and 2,800 meters in Nagasaki. (Total kerma estimates for survivors at greater distances are estimated to be less than 0.001 mGy.) The data plotted are averages for survivors in 100-meter (ground) distance categories. The top two panels compare kerma and colon-dose estimates for the two cities. As these plots indicate, neutron doses are reduced to a greater extent than gamma doses by passage through the body. The lower left panel presents a direct comparison of gamma and neutron colon-dose estimates versus distance in the two cities. It can be seen that at a given distance, gamma doses in Nagasaki are greater than those in Hiroshima while neutron doses are quite similar. The lower right panel shows the percentage of total colon dose that arises from neutrons as a function of distance for the two cities. It is noteworthy that for Hiroshima at distances beyond 1.5 kilometers, at which there are uncertainties about DS86 neutron-dose estimates, neutrons account for less than 0.4% of the total dose.

A table with the data from which these plots were made is available on RERF's home page: [www.rerf.or.jp](http://www.rerf.or.jp).



### References

Roesch WC. US-Japan Joint Reassessment of Atomic Bomb Radiation Dosimetry in Hiroshima and Nagasaki Final Report. Radiation Effects Research Foundation, Hiroshima, 1987.

Shimizu Y, Kato H, Schull WJ, Preston DL, Fujita S, Pierce DA. Studies of the mortality of A-bomb survivors. 9. Mortality, 1950-85: Part 1. Comparison of risk coefficients for site-specific cancer mortality based on the DS86 and T65DR shielded kerma and organ doses. Radiation Research 1989; 118(3):502-24. □



## Board of Directors Holds 31st Meeting in Washington

by Richard D. Sperry, Administrative Advisor, Secretariat

The 31st meeting of RERF's board of directors was held on 11 and 12 June 1997 in the board room of the National Academy of Sciences in Washington, DC. The meeting was held in conjunction with the symposium hosted by NAS commemorating ABCC/RERF's golden anniversary. Major items of business were discussion of the Blue Ribbon Panel's (BRP) July 1996 recommendations, RERF's responses to those recommendations, and the recommendations from the November 1996 23rd Scientific Council meeting in Irvine, California, review of the FY1996 research activities report, and consideration of various other matters, including FY1997 and 1998 budgets.

One of the BRP recommendations concerned the terms of office of Scientific Council members. The Board decided that the terms should be extended from four to five years with reappointment to be approved under exceptional circumstances for no more than one term. In addition, a new system whereby two councilors change annually was introduced. In accordance with the BRP recommendations and agreement of the Scientific Council, all ten councilors resigned as of 30 June, and ten new members were elected. To stagger their terms, appointments were approved for one, two, three, four, and five years each for one US and one Japanese councilor for the first term only. These changes required a revision of the Act of Endowment.

Relocation of the Foundation was discussed, but it was clear that unless needed funds are allocated, there will be no resolution of this issue.

International collaborative activities, including those of directors, staff members, and the substantial number of overseas visitors who receive training and briefings at RERF, were presented. It was noted, in particular, that many visitors from the former USSR engage in RERF training sessions lasting from a few days to one or two months.

Dr. Clark Heath, a scientific councilor, presented the Council's concerns regarding the issue of F<sub>1</sub> survivor (first generation offspring) studies. Study of the F<sub>1</sub> survivors was recommended by the Blue Ribbon Panel, but the Sci-

entific Council was not in full agreement with its recommendations. After much discussion, the Council agreed that a tightly focused two-part study should be undertaken. The study is to include the clinical exami-

nation of those F<sub>1</sub> adults previously examined in the Biochemical Genetics Study, particularly those whose parents were exposed to a high level of radiation, and a mail questionnaire.

See **Board Meeting** on page 32



**Pictured from left to right, front to back:** *Row one:* Visiting Directors Dr. Jonathan M. Samet, chairman, Department of Epidemiology, The Johns Hopkins University School of Hygiene and Public Health, and Dr. Masumi Oike, permanent director, National Social Insurance Societies Association; *RERF Permanent Directors* Dr. Itsuzo Shigematsu, chairman, and Dr. Sheldon Wolff, vice chairman and chief of research; *Visiting Director* Dr. Warren K. Sinclair, president emeritus, National Council on Radiation Protection and Measurements; and *Permanent Director* Dr. Shigenobu Nagataki; and *RERF Interpreter* Ms. Miyuki Hosoya; *Row two:* *RERF Operating Committee Member* Mr. Yasukiyo Hirano, chief, Secretariat; *RERF Observer* Dr. Akio Awa, RERF consultant and associate chief of research; *RERF Permanent Director* William J. Schull; *Department of Energy (DOE) Observer* Dr. Frank Hawkins, director, Office of International Studies; *MHW Observers* Dr. Hiroshi Maruyama, assistant director, and Mr. Hiromasa Kuroki, Planning Division, Health Service Bureau; *RERF Interpreter* Ms. Naomi Umehara; *RERF Observer* Mr. Shizuo Inoue, administrative advisor; *Row three:* *NAS Observer* Dr. Paul Gilman, executive director, Commission on Life Sciences (CLS); *RERF Observer* Mr. Torao Sasaki, assistant chief, Secretariat; *DOE Observer* Mr. Joseph Weiss, Japan Project Team, Office of International Studies; *NAS Observers* Dr. Evan Douple, director, Board on Radiation Effects Research, CLS, and Ms. Catherine S. Berkley, administrative associate, CLS, National Research Council; *RERF Interpreter* Ms. Eiko Ishizaki; *RERF Operating Committee Member* Mr. Richard D. Sperry, administrative advisor, Secretariat; *RERF Observer* Mr. Hiroyuki Tominaga, assistant chief, Secretariat; and Mr. Michael E. Rappaport, former RERF business administrator (not a meeting participant). **Not pictured:** *Supervisor* Mr. David Williams, senior financial advisor, NAS, and *Science Councilor* Dr. Clark W. Heath, Jr., vice president for epidemiology and statistics, American Cancer Society. Those absent included: *Visiting Directors* Dr. Toshiyuki Kumatori, chairman, Radiation Effects Association; Mr. Kazuaki Arichi, permanent director, Japan Institute of International Affairs; and Dr. Patricia A. Buffler, dean and professor of epidemiology, School of Public Health, University of California, Berkeley; and *Supervisor* Dr. Shudo Yamazaki. □

Photo by Cable Ristdon Photographers, Alexandria, Virginia

## 24th Scientific Council Deliberates on Multinational Peer Review

by Akio Awa

Consultant and Associate Chief of Research

The 24th meeting of RERF's Scientific Council was held on 23 October 1997 at the ANA Hotel in San Francisco, California, with eight of the ten councilors in attendance. Due to his sudden illness, Chairman Shigenobu Nagataki was unable to attend. On the meeting's agenda were new operating rules for the Council, establishing the multinational peer review recommended by the Blue Ribbon Panel, and RERF's departmental structure reorganization.

After Drs. John B. Little and Hiromichi Matsudaira were elected as the Council's respective American and Japanese cochairmen for the year, new Council operating rules were discussed as were selection of the first department to undergo multinational peer review and nomination of members for the review panel.

Changes in operating procedures included the request that future research projects included in meeting materials be as specific as possible. It was also agreed that future meetings be three days and equally divided between, first, deliberations on research results and future research plans and, second, the summary of multinational peer-review results and compilation of Scientific Council recommendations.

With regard to the multinational peer review, RERF requested that the Department of Radiobiology be reviewed first, the Council approved the request, and panel membership was considered. Drs. Joe W. Gray and Masao Sasaki were selected to represent the Scientific Council. The Council concluded that a scientific councilor did not need to chair the panel, though that had been recommended by both the Blue Ribbon Panel and earlier scientific councilors. Nearly 20 candidates were nominated for panel membership, and final selection was left to RERF based on availability of each candidate. Dr. Roger Cox of UK's National Radiological Protection Board was nominated as a candidate to chair the panel, again with his availability a factor. Scheduling of the peer review was to be made no later than mid-February, and Dr. Wolff was charged with coordinating the schedule and

selecting panel members.

Reorganization of RERF's research departments had been recommended at an earlier Scientific Council meeting, and RERF had prepared and delivered its responses at the June meeting of RERF's board of directors. RERF's plan envisages the integration of the present five research departments into three groups, a clinical studies group encompassing the present clinical studies department, an epidemiology and statistics group including the current epidemiology and statistics departments, and a basic research group comprising the current genetics and radiobiology departments. Each

of these groups would have its own associate chief of research and pursue theme-specific projects and promote research exchange. The Scientific Council highly appraised the plan and indicated that it would be given more specific review at its next meeting. The Council proposed that the groups be called clinical sciences, population sciences, and biological sciences. RERF will further develop this plan for consideration by both the next Scientific Council and Board of Directors meetings.

The 25th Scientific Council meeting was held 18-20 March in Hiroshima, and a meeting report will appear in the next *Update*. □



**Pictured from left to right, front to back:** *Row one:* Science Councilors Maurice S. Fox, Lester Wolfe Professor of Molecular Biology, Massachusetts Institute of Technology; Hiromichi Matsudaira, consultant, Japan Science and Technology Corporation; and Theodore L. Phillips, professor and chair, Radiation Oncology; and RERF Vice Chairman and Chief of Research Sheldon Wolff. *Row two:* Science Councilors Joe W. Gray, professor, Laboratory Medicine, University of California, San Francisco; Shinichiro Ushigome, professor, Department of Pathology, Jikei University School of Medicine; Masao Sasaki, professor, Radiation Biology Center, Kyoto University; Shigefumi Okada, professor emeritus, The University of

Tokyo; and John B. Little, James Stevens Simmons Professor of Radiobiology, Harvard School of Public Health. *Row three:* Observer Masayuki Kimura, director, Planning Division, Health Service Bureau, Japanese Ministry of Health and Welfare (MHW); from RERF: Naomi Umehara, interpreter, Translation Office, Administration and Support Section; and Senjun Taira, permanent director; and Observer Toshinobu Satoh, assistant director, Planning Division, Health Service Bureau, MHW. *Row four:* Akio Awa, RERF Consultant and Associate Chief of Research; Observer Joseph Weiss, program manager, US Department of Energy Postdoctoral Fellowship Program, and Japan Project Team Administrator; from RERF: Kazumasa Kunitoshi, chief, Secretariat; and Akiko Enami, chief, Director's Office, General Affairs Section. *Row five:* Observer Catherine Berkley, administrative associate, Board of Radiation Effects Research, Commission on Life Sciences, National Research Council, US National Academy of Sciences (NAS); and RERF Interpreter Eiko Ishizaki, Translation Office, Administrative and Support Section; and Supervisor David Williams, senior financial advisor, NAS. *Back row:* RERF Administrative Advisor Richard D. Sperry; and Observer Evan Douple, director, Board of Radiation Effects Research, Commission on Life Sciences, National Research Council, NAS. □

**Thyroid Cancer Pathology Subject of March Workshop**

by Kiyohiko Mabuchi

Chief, Department of Epidemiology, Hiroshima

On 1-4 March 1998, RERF hosted a thyroid cancer pathology workshop at its Hiroshima laboratory in an effort to ascertain ways in which RERF's future molecular biological studies may provide further insights into the nature of radiation-induced thyroid cancer in atomic-bomb survivors and other populations. Following an intensive two-day histological examination of nearly 200 thyroid cancers by a panel of pathologists, a one-and-a-half day open discussion of new approaches in molecular biology took place. Panelists included Yuzo Hayashi, Department of Pathology, Hiroshima Asa Citizens Hospital; Nobuo Tsuda, Department of Clinical Laboratories, Nagasaki University School of Medicine; Atsuhiko Sakamoto, Department of Pathology, The University of Tokyo Faculty of Medicine; and Sir Dillwyn Williams, Strangeways Research Laboratory, Cambridge University, England.

Presentations included those by our staff of RERF's ongoing epidemiological and molecular studies and those by visiting workshop participants: James A. Fagin, director, Division of Endocrinology and Metabolism, University of Cincinnati College of Medicine, Ohio, USA: *Molecular pathology of thyroid tumors*; Sir Dillwyn Williams: *Childhood thyroid cancer after Chernobyl*; Arthur B. Schneider, professor of medicine and section chief, Endocrinology and Metabolism, University of Illinois College of Medicine, Chicago, Illinois, USA: *The Chicago study of thyroid tumors after external irradiation*; Atsuhiko Sakamoto: *Pathology of thyroid cancer in Japan*; Kiyohiko Mabuchi, chief, and Shoji Tokuoka, consultant, RERF Department of Epidemiology, Hiroshima: *Epidemiology, risk patterns, and pathology*; Dale Preston, chief, RERF Department of Statistics: *Results of the pathology panel review*; Toshio Seyama, acting chief, and Kiyohiro Hamatani, research scientist, RERF Department of Radiobiology: *RERF molecular oncological research program on thyroid cancer*; and Marco A. Pierotti, Division of Experimental Oncology A,

Instituto Nazionale Tumori, Milan, Italy: *Oncogenic activation in sporadic and in radiation-associated papillary thyroid carcinomas*.

Other participants were: Suminori Akiba, professor, Department of Public Health, Faculty of Medicine, Kagoshima University School of Medicine, Kagoshima; Satoshi Fujii, Pathology II, Hiroshima University School of Medicine (HUSM); Takeshi Hara, Department of Nature Medicine (DNM), Atomic Bomb Disease Institute (ADI), Nagasaki University School of Medicine (NUSM); Kouki Inai, professor, Second Department of Pathology, HUSM; Akihiro Ito, Department of Cancer Research, Division of Environmental Biology (DEB), Research Institute for Radiation Biology and Medicine (RIRBM), Hiroshima University (HU);

Masahiro Ito, Department of Molecular Pathology, ADI, NUSM; Kenji Kamiya, Department of Development Biology and Oncology, Division of Molecular Biology, RIRBM, HU; Masahiro Matsuura, Pathology II, HUSM; Hiroyuki Namba, DNM, ADI, NUSM; Elaine Ron, chief, Radiation Epidemiology Branch, National Cancer Institute, National Institutes of Health, USA; Shuneki Shoji, Department of Environmental Mutation (DEM), DEB, RIRBM, HU; Yukio Takeshima, Pathology II, HU; Hiromitsu Watanabe, DEM, DEB, RIRBM, HU; Shuji Yonehara, senior chief, Laboratory, Division of Pathologic Research, Onomichi General Hospital; and Kazuya Zeki, First Department of Internal Medicine, University of Occupational and Environmental Health, Fukuoka. □

**Workshop Explores F-Value as Fingerprint for Radiation Exposure**

By Nori Nakamura

Chief, Department of Genetics

Specialists in radiation cytogenetics from the USA, Japan, England, and Germany assembled in Hiroshima on 24 February for an F-Value Workshop. F-value, the term given to the ratio of interchromosomal aberrations, such as dicentrics, to intrachromosomal chromosome aberrations, such as ring chromosomes, has been suggested as a fingerprint indicating exposure to radiation of different ionizing density or linear energy transfer (LET).

The workshop was organized by Dr. Nakamura, chief, Department of Genetics, and included the following presentations: A. A. Awa, consultant and associate chief of research, RERF: *F-value for inter- and intra-chromosomal aberrations in lymphocytes of A-bomb survivors—Hiroshima and Nagasaki*; David J. Brenner, Center for Radiological Research, Columbia University, New York, USA: *Interarm or intra-arm intrachromosomal exchanges versus interchromosomal exchanges: Which could provide the larger high-LET fingerprint?*; Manfred Bauchinger,

Forschungszentrum für Umwelt und Gesundheit, Neuherberg/Oberschleissheim, Germany: *LET dependence of yield ratios of radiation-induced chromosomal aberrations*; Gale L. Littlefield, Cytogenetics Laboratory, Oak Ridge Associated Universities, Inc., Tennessee, USA: *F-ratios for dicentrics and rings in human lymphocytes exposed to low- or high-LET radiation in vitro or in vivo*; David C. Lloyd, Radiation Effects Department, National Radiological Protection Board (NRPB), Chilton, Didcot, UK: *Data from the NRPB laboratory relevant to the question of F-values*; James D. Tucker, Biology and Biotechnology Research Program, Lawrence Livermore National Laboratory, California, USA: *F-ratios in exposed and unexposed human populations and in cultured cells exposed to gamma radiation*; Julian R. Preston, Chemical Industry Institute of Toxicology, Research Triangle Park, North Carolina, USA: *Interpreting the F-value*; Masao S. Sasaki, Radiation Biology Center, See **F-Value** at top of next page

*F-Value continued from previous page*  
 Kyoto University, Japan: *Experimental evidence for the F-value as a chromosomal fingerprint of the quality of radiation.* Sheldon Wolff, RERF vice chairman and chief of research, led a general discussion following the formal presentations.

It was agreed that the theoretic-

cal idea of the F-value is attractive. However, actual data reported by these researchers showed that F-value data of X or gamma rays varied considerably among laboratories. Within individual laboratories, the difference in F-values, when a difference existed, was not as large between high and low LET radiations as originally sug-

gested by Brenner. Consequently, F-value does not seem to be a practical biological indicator of radiation fingerprint to discern exposure to radiations of different quality. A possibility was raised that other parameters may be more relevant. A summary of the workshop is expected to be published in *Radiation Research*. □

## American and Japanese Scientists Consider Atomic-Bomb Dosimetry Re-evaluation at October Workshop

by Shoichiro Fujita

Assistant Chief, Department of Statistics

American and Japanese scientists met at RERF in Hiroshima on 20 to 21 October 1997 for the Fourth Workshop for the Evaluation of Atomic-Bomb Radiation Doses in Hiroshima and Nagasaki. Partially supported by RERF, this was one of a series of informal workshops by the A-bomb Dosimetry Research Group (ADRG) to promote discussion of questions about DS86, including the issue of neutron measurement. Unlike previous meetings in this series, in which most of the participants were Japanese, there were a large number of U.S. participants. This workshop was the first since the May 1996 meeting of the US and Japan Dosimetry Committees at which most of the principal U.S. and Japanese scientists directly involved in DS86-related measurements and computations met for general discussions on these issues. The participants agreed that it is important for questions about DS86 to be resolved as quickly as possible.

The program included the following presentations: Kiyoshi Shizuma, Hiroshima University: *Residual activity of <sup>152</sup>Eu and <sup>60</sup>Co in Hiroshima and Nagasaki*; Dean Kaul and Stephen Egbert, Science Application International Corporation (SAIC, San Diego, California): *Possible sources of error: Fluence, dose, and shielding at Hiroshima and Nagasaki*; Masaharu Hoshi, Hiroshima University, secretary, ADRG: *What should be done to solve the DS86 problems?—Possible explanation and subjects to verify*; Yutaka Ito, National Laboratory for High-Energy Physics, Tsukuba, Japan: *Present status of the low-background, low-energy beta-ray detector development to estimate the fast neutron fluence for the Hiroshima atomic bomb*; Wayne Lowder, NAS Committee on RERF Dosimetry, USA, and

Takashi Maruyama, Radiation Effects Association, Tokyo: *Plans for the review of DS86-related measurement data*; Dale Preston and Shoichiro Fujita, Department of Statistics, RERF: *Currently available A-bomb-dosimetry-related materials*; and Nori Nakamura, Department of Genetics, RERF: *Biodosimetry of A-bomb survivors: Cytogenetics and electron spin resonance (ESR)*.

Others participating in the workshop discussions were: Hiromi Hasai, Hiroshima Denki Institute of Technology, head, ADRG; Evan Douple, U.S.

National Academy of Sciences; Satoru Endo, Hiroshima University; Tetsuji Imanaka, Kyoto University; Kazuo Iwatani, Hiroshima University; Tsuneto Nagatomo, Nara University of Education; Takamitsu Oka, Kure University; Tokushi Shibata, National Laboratory for High-Energy Physics, Japan; Shoji Sawada, professor emeritus, Nagoya University; Toshihiro Takatsuji, Nagasaki University; Sheldon Wolff, RERF; and Robert Young, independent radiation health effects consultant, Washington, DC. □

## Workshop Examines Mathematical Models of Cancer Process

by Claire Sherman

Research Scientist, Department of Statistics

In an effort to promote biologically based modeling techniques in analyzing cancer incidence in the Japanese atomic-bomb survivor cohort, a half-day "Mechanistic Models for Radiation Carcinogenesis Workshop" was conducted in RERF's Hiroshima auditorium 30 October 1997. Three outside researchers joined two RERF statisticians in presenting their views of the cancer process in terms of the features of various mathematical models. Approximately 35 people participated in the workshop, including science and mathematics faculty from Fukuoka, Hiroshima, and Nagasaki Universities and the University of Tokyo in addition to epidemiology, genetics, radiobiology, and statistics staff from RERF.

Michiaki Kai of the University of Tokyo presented a two-stage carcinogenesis model to analyze solid cancer incidence in atomic-bomb survivors, work he described in the October 1997 issue of *Radiation Research*. E. Georg

Luebeck of the Fred Hutchinson Cancer Research Center, Seattle, Washington USA, then discussed the characteristics of the incidence function of the two-stage model and its flexibility in fitting a large variety of cancer incidence data.

Megu Ohtaki of Hiroshima University and Don Pierce of RERF then took up the Armitage-Doll mathematical model of carcinogenesis to demonstrate the modified model's suitability to current carcinogenesis theories. Dr. Ohtaki's model showed that mutation and cellular death are the primary components of the cancer process, while Dr. Pierce's model was consistent with the results from descriptive regression models of excess absolute risk.

Claire Sherman of RERF concluded the workshop by suggesting that cancer incidence alone is not sufficient to deduce mechanism and that molecular, biochemical, and cellular data should be implemented for this task. □

**Workshop Elucidates Genetic Susceptibility to Radiation-Induced Cancers**

by Keisuke S. Iwamoto, Research Scientist, Department of Radiobiology

RERF hosted a workshop on genetic susceptibility to radiation-induced cancer at its Hiroshima laboratory 8-10 July 1997 to discuss the path RERF should pursue in the area of molecular epidemiology and oncology relating to this topic. Speakers from Japan, the United States, Belgium, Sweden, and the United Kingdom made presentations on such topics as the priority of cancer types to study, types of assays to use, tissue procurement, possibilities of collaborations with other laboratories, and ethical issues. Thirty-seven people took part in the workshop, including presenters, RERF staff, and participants from a number of Japanese medical schools and research institutes.

Genetic susceptibility to cancer refers to the heritable aspects of this disease, in which mutations in certain genes are passed from generation to generation. Molecular epidemiological studies track down culprit genes through analysis of DNA from multiple family members who develop similar cancers. Such studies have identified numerous candidate genes responsible for breast, colon, and endocrine neoplasias among others.

RERF's interests in these familial cancer genes lie in whether the same genes can be responsible for cancers caused by environmental factors such as radiation and whether persons at high risk for contracting cancer because they have inherited a damaged cancer-related gene are even more sensitive to developing cancer after

radiation exposure.

Presentations included: **International Commission on Radiological Protection (ICRP) Report on Genetic Susceptibility:** Roger Cox, Department of Biomedical Effects, National Radiological Protection Board, UK: *An Overview*; Charles E. Land, US National Cancer Institute (NCI), National Institutes of Health: *Retinoblastoma Follow-Up*; and Ranajit Chakraborty, Human Genetics Center, University of Texas School of Public Health, USA: *Population Modeling Issues*; **Overview of RERF Studies:** Epidemiology Chief Kiyohiko Mabuchi and Statistics Chief Dale Preston: *RERF Studies: Cohorts, Resources, and Cancer Risks*; and Acting Radiobiology Chief Toshio Seyama: *Current and Future Molecular Epidemiology Studies*; **Breast Cancer:** Drs. Mabuchi and Land: *RERF-Planned Early Onset Study*; Margaret Tucker, Genetic Epistemology Program, NCI: *BRCA Genes and Breast Cancer*; Victoria Huff, Experimental Pediatrics Division of Pediatrics, M. D. Anderson Cancer Center, USA: *BRCA Genes*; and Hiroshi Aida and Kenichi Tanaka, Niigata University School of Medicine, Japan: *Mutational Analysis of BRCA1 in Japan*; **Other Promising Studies:** Drs. Preston and Elaine Ron, Radiation Epidemiology Branch, NCI: *Risk Estimates on Skin, CNS (central nervous system), and other Tumors*; Kenshi Komatsu, Research Institute for Radiation Biology and Medicine,

Hiroshima University, Japan: *Nature and Gene Localization of AT Variant*; Hideyuki Saya, Kumamoto University School of Medicine, Japan: *NF2 Gene in Brain Tumors*; and Takao Sekiya, National Cancer Center Research Institute, Japan: *Detection of Abnormalities in Uncharacterized Regions of Genomic DNA in Cancer Cells*; **Suggestions from other Groups and Possible Collaborations:** Dr. Tucker: *NCI Cancer Genetics Program*; Dr. Huff: *M. D. Anderson Program*; and Kenneth H. Chadwick, Commission of the European Community, Belgium: *European Community Program*; and **Ethical Issues and Genetic Counseling:** Hiraku Takebe, Kyoto University School of Medicine, Japan: *Ethical Issues in Japan*. Dr. Lars-Eric Holm, director of the Swedish Radiation Protection Institute of Sweden's National Institute of Public Health, also gave a special lecture entitled "Cancer Risk in Children with Hemangioma Receiving Radiotherapy," and more than half of the three-day workshop comprised informal discussions.

As Dr. Cox concluded the workshop, he emphasized the international significance of RERF's resources and the Foundation's need to "respond to the opportunities presented by recent advances in molecular carcinogenesis and cancer genetics." It was understood that there would be a great many hurdles to overcome but that RERF would meet the challenge with the support and cooperation of many inside and outside the organization. □

**Biological Dosimetry and ESR Workshop Venue for Idea Exchange**

by Nori Nakamura, Chief, Department of Genetics

On 24-26 March 1997, 13 researchers from the Russian Federation, the US, and Germany met with RERF researchers at RERF's Hiroshima laboratory to discuss improved methods of radiation dose assessment and learn of research plans concerning those exposed to radiation from nuclear processing facilities in the former USSR. The exposed include former workers at the Mayak facilities in Ozyorsk, the former secret city near Chelyabinsk, in the South Urals, as well as residents around the Techa River, which was contaminated by radioactive substances released from the Mayak facilities.

To date, epidemiological studies have demonstrated increased incidence of leukemia in both the workers and those residing near the river, and lung cancer has often been more

prevalent in the plant workers due to plutonium inhalation. An increase in other cancers has also been noted.

The significance of these studies lies in the lack of availability of information on risks associated with long-term chronic radiation exposure. This information and that from studies of atomic-bomb survivors, whose exposure was instantaneous, are instrumental in establishing permissible exposure levels for radiation workers and the general public.

Biological dosimetry is the process by which past radiation exposure dose may be evaluated via the examination of blood and other body substances. Chromosome studies have been the primary assessment methods. However, in recent years, electron spin resonance (ESR) machines have been improved and enable dose

estimation through the examination of the tooth enamel. Though Mayak workers wore film badges to measure their exposure to radiation, ESR has provided a means to verify that data. Since those living along the river had no film badges, measurement of their exposures has been less certain. In addition, internal exposure must be considered. It is expected that this issue will be resolved by the year 2000.

Workshop participants included: **Russian Federation:** A. L. Bouldakov, D. E. Klechenko, and Y. I. Gavrilin, *Institute of Biophysics*; E. Vassilenko, *Mayak Production Association*; M. Degteva, *Urals Research Center for Radiation Medicine*; V. Skovortsov and V. A. Pitkevich, *Medical Radiation Research Center*; and Y. O. Konstantinov, *Institute of Radi-*

See *Workshop* on page 32



## Biodosimetry Training Course Cohosted by IAEA and HICARE

by Nori Nakamura

Chief, Department of Genetics

To offer researchers from throughout the Asia-Pacific region practical experience in chromosome aberration testing, RERF presented its "Training Course in Biodosimetry" to 15 people representing 11 countries at its Hiroshima laboratory from 29 September to 3 October 1997. Participants were selected by the International Atomic Energy Agency (IAEA) from radiation institutes, nuclear institutes, and general hospitals in countries with IAEA affiliations. Trainees received instruction in three cytogenetic testing methods.

Biodosimetry is the assessment of radiation dose by the study of blood or other specimens from those exposed. RERF's Dr. Akio Awa has long employed a conventional Giemsa staining method to study aberration frequencies in chromosomes of cultured lymphocytes. Workshop participants were trained in this conventional staining method as well as in the preparation of chromosome samples, G-banding, and fluorescence *in situ* hybridization (FISH).

Flow cytometry and electron spin resonance (ESR) are two other recent biodosimetric techniques carried out at RERF. Flow cytometry became available about ten years ago; it employs a device called a flow cytometer to examine the frequency of mutated cells in erythrocytes or lymphocytes stained with special antibodies. The Department of Radiobiology conducts these studies. More recently, ESR has enabled radiation dose assessment through the examination of tooth enamel with an electron spin resonance machine. Dr. Nakamura carries out this research. Though no training was offered in these two methods, trainees received brief lectures on them and visited the laboratory to see how they work.

Lecturers and their presentations included: Sheldon Wolff, director, RERF: *Historical Perspectives*; Akio Awa, consultant and associate chief of research, RERF: *Detection of Aberrations by Giemsa Staining*; Yoshiaki Kodama, laboratory chief, RERF: *Basic Information about Fluorescence in Situ Hybridization (FISH)*; Isamu Hayata, department chief, National Institute of Radiological Sciences

(NIRS), Chiba, Japan: *Automated Cytogenetics*; Kimio Tanaka, assistant professor, Research Institute for Radiation Biology and Medicine (Geniken), Hiroshima University: *Multicolor FISH and Interphase FISH*; I. Turai, IAEA, Austria: *Chernobyl Accident: Review of Health Consequences*; Yujiro Kamiguchi, professor, Asahikawa Medical College: *Cytogenetics in Human Sperm*; Nori Nakamura, assistant chief, Genetics, RERF: *Electron Spin Resonance on Tooth Enamel*; Seishi Kyoizumi, laboratory chief, RERF: *Somatic Mutation Assays*; Makoto Akashi, laboratory chief, NIRS: *Clinical Indicators of Radiation Exposure*; Kiyohiko Mabuchi, chief, Epidemiology, RERF Hiroshima: *Cancer Risk among the Mayak Workers and the Techa River Residents*; and Masao Sasaki, professor, Kyoto University: *Chromosomal Methods for Dose Assessment*. RERF

speakers also made the following presentations on radiation effects in atomic-bomb survivors: Dale Preston, chief, Statistics: *Cancer and Noncancer Risks*; Kiyohiko Mabuchi, chief, Epidemiology: *In Utero Exposure*; Don Pierce, senior scientist, Epidemiology and Statistics: *Low-Dose Risk*; Chiyoko Satoh, chief, Genetics: *Monitoring the Genetic Effects*; and Kazunori Kodama, chief, Clinical Studies: *Clinical Findings*.

Trainees came to RERF from Bangladesh, China, India, Indonesia, Malaysia, Pakistan, the Philippines, South Korea, Sri Lanka, Thailand, and Vietnam. The IAEA supported travel and hotel expenses for workshop participants, and the Hiroshima International Council for Health Care of the Radiation-Exposed (HICARE) provided financial support, including travel expenses, for Japanese lecturers. □

## RERF News

### Nagasaki Local Liaison Council Convenes for First Time in a Decade

by Senjun Taira

#### RERF Permanent Director Overseeing Nagasaki Laboratory

For the first time in more than ten years, the Nagasaki Local Liaison Council met on 25 November 1997 to renew its efforts in establishing community understanding of and cooperation in RERF's research activity. The Council, established in 1975, is charged with engaging in a dialogue in which RERF may learn of community concerns and express its own concerns in the Foundation's efforts to better address the needs of atomic-bomb survivors and study participants. The 22 councilors include members of Nagasaki's prefectural and city governments, the university and its medical school, hospital, and Atomic Disease Institute, local hospitals and medical associations, and various nonprofit and survivors' foundations. Nagasaki University President Tetsuo Yokoyama was elected council chair.

Because of the prolonged interval between meetings and the change in the Council's makeup, a five-member panel from RERF introduced the

Foundation's research and activities and the Blue Ribbon Panel's recommendations and responded to questions. RERF representatives were Vice Chairman Sheldon Wolff, Permanent Director Senjun Taira, and Secretariat Chief Masakazu Kunitoshi, from RERF's Hiroshima laboratory, and Nagasaki's Epidemiology Department Chief Yoshisada Shibata and Clinical Studies Chief Masazumi Akahoshi.

In the ensuing discussion, a twelve-member secretarial committee representing various fields was developed to consider routine Council matters. Additional meetings will be called as necessary to discuss such matters as Nagasaki's open house scheduling.

Council membership and other details were addressed at two preliminary sessions under the supervision of Permanent Director Shigenobu Nagataki during his oversight of the Nagasaki laboratory prior to his assuming RERF chairmanship. □

## Nagasaki RERF Hosts First Open House

by Yoshisada Shibata

Chief, Department of Epidemiology, Nagasaki, and  
Chair, Open House Working Committee

RERF's Nagasaki laboratory held its first open house 8 August 1997, the day before the 52nd anniversary of the atomic bombing of Nagasaki. The lab's 305 visitors were invited to tour the facilities, view informational panels, study blood and tissue specimens under the microscope, access RERF's home page at computer displays, watch video presentations, speak with staff members regarding their work, and have their blood pressure and body fat measured. RERF is actively engaged in making itself more accessible for public scrutiny, and the open house attempted to educate visitors about the scope of ABCC/RERF's activity.

Fifty panels explained principles of atomic radiation, damage caused by the bombings, and late health effects

experienced by survivors, including data from the Life Span and Adult Health Studies and dosimetry research. Clinical laboratory technicians were available to explain such things as the operation of the autacentrifuge and freeze dryer for blood used in pathological studies.

Visitors were asked to complete questionnaires that included respondents' age and sex as well as their home cities, familiarity with RERF, and response to the open house, and the response to this first Nagasaki open house was very encouraging. Those who visited ranged in age from four to 82 and represented a broad cross-section of interests. Included among the visitors were several physicians from the USSR, who were studying at Nagasaki University or

undergoing training at the invitation of the Nagasaki Association for Hibakushas' Medical Care (NASHIM), Republic of Belarus Health Minister Zelenkevich and Senator Drobyshevskaya, and several others who were visiting Nagasaki for memorial activities. Generally, the panels showing the study methods and achievements of ABCC/RERF were favorably received, and visitors seemed to be quite impressed by blood and tissue samples and actual examinations.

The open house's benefits extended to the employees in that they were able to see more clearly the relationship between each area's daily operations and how those activities contribute to the whole of RERF's research, thereby better understanding their own roles in the Foundation. □

## Open House and Ceremony Mark ABCC/RERF's Anniversary

by Kiyohiko Mabuchi

Chief, Department of Epidemiology, Hiroshima, and Chair, Commemorative Events Planning Committee

*"The program of the last 50 years constitutes one of the longest and largest . . . and best, ongoing epidemiological health studies in the world. The results obtained here are not only important for us to understand possible health effects on the survivors but are used worldwide to establish the scientific risks of radiation to the health of all people. This is work in which we can all take pride and which certainly merits our celebrating 50 years of successful operations."*

Sheldon Wolff, RERF Vice Chairman and Chief of Research  
Greeting, ABCC/RERF Memorial Ceremony, 4 November 1997

To commemorate ABCC/RERF's 50 years of research activity, the Hiroshima laboratory held its third open house 3 November 1997 in conjunction with a memorial ceremony and lecture on 4 November.

The first two open houses had been conducted on 5 August, the day before Hiroshima's A-Bomb Day observance, when many visitors came into the city, so there was concern that turnout might be lower on the new date. However, 3 November was Culture Day, a Japanese holiday, and RERF welcomed 677 visitors. Some arrived prior to the scheduled opening time, and the day's activities ended 45 minutes after the scheduled closing. Photos of ABCC/RERF's history were on display in addition to panels illustrating damages caused by the A-bombing. Other panels presented current research and international collaborative projects. Researchers were available to explain the panels and their work. Microscopes were set up

for visitors to examine chromosomes and cancer cells, and computers provided the opportunity for guests to explore the Internet. The exceptional attendance, including repeat visits by some who have come to earlier open houses, and the positive responses voiced by those attending this year's event are very heartening.

The following day, A-bomb survivors, members of the local medical community, representatives of the Ministry of Health and Welfare and local governments, and RERF employees, past and present, were invited to the Hiroshima International Conference Center at the Peace Park to participate in ABCC/RERF's golden anniversary remembrance. More than 300 people attended. Representatives of the atomic-bomb survivors, Hiroshima's city and prefectural medical associations, Hiroshima University and its medical school and hospital, the Research Institute for Radiation Biology and Medicine, and ABCC/

RERF employees were presented with certificates and plaques of appreciation for their contributions to ABCC/RERF. Dr. Tsutomu Sugahara, professor emeritus at Kyoto University and chair of the Health Research Foundation of the Kyoto Emeritus Club and former RERF scientific councilor and visiting director, presented a lecture entitled "A Radiobiologist and ABCC/RERF: Retrospection and Perspective." After the formal presentations, a reception was held at RERF. □

### ERRATUM

In the Autumn 1996 Update, 8(1), in "A Quick Look at Life Span Study Report 12, Part I" by Pierce et al., page 11, lines 12-16, the two sentences should read: "For those exposed as children, the **ERR** was initially quite high but has decreased during follow-up. The large **ERR** at young ages is the result of dividing a fairly small EAR by a quite small background rate." (The two highlighted words replace the term EAR used previously.) □



Photo by Masumi Yamada

### ***In Memoriam: Katsutaro Shimaoka***

Dr. Katsutaro Shimaoka, associate chief of research at RERF's Nagasaki laboratory from 1 January 1991 until his retirement 31 March 1994, passed away peacefully in the US 25 May 1997 after a 13-year struggle with cancer. He was 65.

Dr. Shimaoka joined RERF as chief of Nagasaki's Department of Clinical Studies on 11 October 1986 and was promoted to chief of the Nagasaki laboratory 1 February 1987 prior to his appointment as associate research chief. He took the lead in the

thyroid studies of Nagasaki AHS subjects and Nishiyama residents conducted jointly with the Nagasaki University School of Medicine.

Dr. Shimaoka is survived by his wife, Tomoko, two daughters, Julia and Eva, and a son-in-law, Seth Marder. In a letter to Dr. Nagataki, Mrs. Shimaoka reported that Dr. Shimaoka's ashes were sprinkled over the Pacific Ocean in honor of his wish to be with his two mother countries.

RERF joins the family in their sorrow at his loss. □

## **Two Teams Examine 435 Atomic-Bomb Survivors in Four US Cities**

*by Kazuo Neriishi and Masaharu Nobuyoshi, Department of Clinical Studies*

*and Tadaaki Watanabe and Nobuko Shiba, General Affairs Section, Secretariat, RERF Hiroshima*

From 17 to 30 July 1997, two medical teams dispatched by the Hiroshima Prefectural Medical Association and RERF examined atomic-bomb survivors and their children now residing in the US and Canada. An estimated 1100 survivors live in the US, and 435 were examined in four cities, Los Angeles and San Francisco, California, Honolulu, Hawaii, and Seattle, Washington during this 11th biennial examination. Blood, urine, stool, and thyroid function tests, gynecological examinations, and electrocardiograms were administered. Gynecologists were included in the teams for the first time at the request of survivors examined.

Each team consisted of five physicians and three administrative staff members from RERF, Hiroshima City and Prefecture, and MHW. One physician from RERF's Department of Clinical Studies Division of Medicine and one member from the Secretariat's Division of General Affairs joined each team: Dr. Kazuo Neriishi, Division of Medicine Chief, and Ms. Nobuko Shiba, representative from General Affairs, participated in the Los Angeles/Seattle examinations; and Dr. Masaharu Nobuyoshi, a research scientist, and Mr. Tadaaki Watanabe, General Affairs Section Chief, took part in the San Francisco/Honolulu examinations. Additional assistance came from American physicians from examination sites, some of whom had trained in Hiroshima under the auspices of the Hiroshima International Council for Health Care of the Radiation-Exposed (HICARE), and other volunteers, often from US survivors' groups, who lent great support to the project.

In 1976, as it considered the need

to examine US A-bomb survivors, the Hiroshima Prefectural Medical Association began to establish affiliations with regional American medical associations to enable Japanese physicians without US physician licensing to conduct survivor examinations in the US under the supervision of licensed American doctors. These now include the Los Angeles Medical Association, the San Francisco Medical Society, the King County Medical Society (Seattle), and the Hawaii Medical Association. The program was legally sanctioned as a supplementary provision of the California State Medical Practitio-

ners' Law in 1986.\* Since the program's inception in 1977, a total of 3483 survivors living in the US and Canada have taken part in the medical examinations.

### **Reference**

\*Shibata J, Ota N, Sasaki H, Neriishi K, Hirabayashi N, Watanabe T, Okada K, Ide Y, Onizawa M, Fukuhara T. Report on the results of the tenth medical examination of atomic-bomb survivors resident in North America. *Journal of the Hiroshima Medical Association* 1996; 49:5-41 (pages 5-6). □

## **ABCC Archivist Visits Hiroshima**

In March 1997, Margaret A. Irwin, special collections librarian and coordinator of the ABCC Collection at the Houston Academy of Medicine at the Texas Medical Center Library, visited RERF in Hiroshima at the invitation of Drs. Shigematsu and Schull. Ms. Irwin was charged with the tasks of examining available materials related to the atomic bombings to ascertain how they might best be utilized and how they might be preserved for future use. She was also engaged in discussions pertaining to how RERF and the Texas archive can collaborate most effectively to make ABCC-related materials accessible to those interested in the organization's history and research activity.

In an effort to contribute to world peace, the ABCC Archive was established in Houston in 1986. The collection comprises materials donated by former ABCC and RERF administrators, researchers, and employees.

Contributions to and inquiries about the archive increase monthly. In Ms. Irwin's words, "The individual collections offer insight while the entire collection offers a comprehensive view of the attitudes, goals, and activities of the Commission from the late 1940s through its evolution into the Radiation Effects Research Foundation." In this same regard, Ms. Irwin cites the particularly revealing aspect of the pictures, which serve to complement the written materials.

In recognition of ABCC/RERF's 50 years of accomplishments, the Texas Medical Center Library hosted a commemorative exhibit of materials from the Archive in 1995 in conjunction with smaller displays at the Schull International Symposium.

For more ABCC Archive information, you may e-mail Ms. Irwin at: Margaret@library.tmc.edu. The fax numbers are 713/790-7056 and 713/790-7052. □

### **Dr. Wolff to Receive BELLE Award**

**Sheldon Wolff**, RERF vice chairman and chief of research, has been selected as the first recipient of the Leonard Sagan BELLE Award, presented in recognition of outstanding achievement in enhancing understanding of the biological effects of low-level exposures to chemicals and radiation. As a part of the award, Dr. Wolff will receive a \$2000 honorarium, a plaque, and an invitation to write an article based on his research for *Human and Experimental Toxicology*, the official journal of the British Society of Toxicology. The award is named in honor of scientist Dr. Leonard Sagan, who passed away in December. □

### **Dr. Kodama Represents RERF at WHO REMPAN Meeting**

Dr. Kazunori Kodama, chief, Department of Clinical Studies, Hiroshima, attended the meeting of the World Health Organization (WHO) Radiation Emergency Preparedness and Assistance Network (REMPAN) in Rio de Janeiro, Brazil 9 to 14 November 1997.

### **Epidemiology Assistant Chief Honored**

**Yukiko Shimizu**, assistant chief, Department of Epidemiology, Hiroshima, was one of four women receiving recognition by the Japan Women Scientists' Association at the organization's second annual awards ceremony 7 June 1997 in Tokyo. Dr. Shimizu was awarded the encouragement prize for her contribution to epidemiologic studies relating to the estimation of radiation risks and for her part in the recently published *Life Span Study Reports 11 and 12*. As she accepted her award, Dr. Shimizu spoke of the follow-up study of atomic-bomb survivors that has been conducted for 50 years at RERF. She thanked all who have been involved in those studies through the years and acknowledged them as fellow recipients of the honor. Dr. Shimizu was nominated for the award by the Japan Radiation Research Society.

The Japanese Women Scientists' Association has established this annual award to encourage promising female scientists, to promote scientific study by females, and to advance the status of women in science. This year's other recipients included Masa Ikuse, the founder of basic pollen science in Japan; Michiko Ishii, a member of the House of Councillors and

Japan's first woman science minister; and Kazue Kurihara, who was recognized for her research on interacting molecular sources. One of last year's recipients was Chiaki Mukai, Japan's first female astronaut. □

### **Administration**

**Sheldon Wolff**, professor emeritus of cytogenetics and radiology at the University of California, San Francisco, joined RERF as a permanent director 5 December 1996. On 23 January 1997, he succeeded **William J. Schull** as vice chairman and chief of research. Dr. Schull vacated the office 22 January 1997 to return to Houston, Texas, where he is director and Ashbel Smith professor at the Human Genetics Center of the School of Public Health of the University of Texas. During his eight-month appointment, Dr. Schull prepared RERF's "Five-Year Strategic Research Plan and Program Management" document.

**Akio Awa**, RERF consultant, was appointed associate chief of research effective 18 February. Dr. Awa retired from RERF 30 June 1995 after 28½ years of service, during which he worked as a research scientist before becoming chief of the Department of Genetics. Since his retirement, Dr. Awa has been a consultant.

**Yutaka Hasegawa** stepped down as permanent director 31 March after more than eight years in that role. Dr. Hasegawa left to assume a directorship of the Department of International Cooperation and professorship in the School of Health and Welfare Sciences of the International University of Health and Welfare in Tochigi Prefecture.

On 30 June, **Itsuzo Shigematsu** retired as chairman after guiding RERF for 16 years, becoming consultant emeritus at RERF. Permanent Director **Shigenobu Nagataki** then resigned as permanent director to take over leadership from Dr. Shigematsu 1 July. (See cover story.)

**Yasukiyo Hirano**, also retired 30 June as chief of the Secretariat after more than 14 years at RERF. Mr. Hirano stayed on to serve as advisor to the Secretariat from 2 July to 30 September.

**Senjun Taira**, director, Tohoku Regional Medical Affairs Office, was appointed 1 August as permanent director, filling the position vacated by Dr. Nagataki. Dr. Taira has also served as director of the medical cooperation department of the Japan International Cooperation Agency (JICA).

**Seymour Abrahamson**, emeritus professor of zoology and genetics, University of Wisconsin, returned to RERF to assume the role of associate chief of research 10 January 1998.

### **Hiroshima**

#### **Department of Clinical Studies**

**Hironori Ueda**, research scientist, Division of Medicine, resigned effective 31 March 1997.

**Masaki Shimizu** was appointed as a research scientist in the Division of Medicine 1 April 1997. Dr. Shimizu came to RERF from his position as internist and technical official with the Ministry of Health and Welfare at National Sanatorium Yanai Hospital, Yamaguchi Prefecture.

#### **Department of Epidemiology**

**Kojiro Koyama** was appointed as a research scientist 1 January 1997 and promoted to the position of chief of the Tumor and Tissue Registry Office 1 January 1998. Dr. Koyama received his M.D. in 1984 and was a practicing urologist for ten years before enrolling in the School of Public Health at the University of Alabama, Birmingham, receiving his M.P.H. in Epidemiology in the summer 1996, and coming to RERF.

**Gerald B. Sharp** was appointed research scientist 4 November 1997. Dr. Sharp came to RERF from St. Jude Children's Research Hospital in Memphis, Tennessee, where he was associate investigator and staff epidemiologist in the Department of Hematology/Oncology.

**Eric J. Grant** joined RERF as a research assistant in the Epidemiologic Analysis Laboratory 1 December 1997. Prior to his appointment at RERF, Mr. Grant served four years as a research programmer in the Division of Medicine at the University of Michigan Medical Center.

#### **Department of Genetics**

**Chiyoiko Satoh**, department chief, retired effective 31 December 1997, after 24 years of service to RERF. She was employed as a research scientist 10 February 1973 and became department chief 1 January 1994. In collaboration with Dr. Neel of the University of Michigan, Dr. Satoh spearheaded the biochemical F<sub>1</sub> genetics study, first screening for protein variants in over one million loci and subsequently initiating the collection and development of transformed cell lines from 1000 families for future DNA studies. Her pioneering efforts

*Continued at top of next page*

*Continued from previous page*

will have lasting effects on RERF's studies. Dr. Satoh will remain at RERF as a consultant in the department for the coming year.

**Nori Nakamura**, assistant department chief, took over as chief 1 January 1998.

#### *Department of Radiobiology*

**Takako Suzuki**, research scientist in the Immunology Laboratory, resigned at the expiration of her appointment on 31 August 1997 to accompany her husband to the United States, where he is studying.

**Toshio Seyama**, assistant chief, was promoted to acting department chief 1 January 1998.

#### *Department of Statistics*

**Robert R. Delongchamp**, research scientist, resigned 1 December 1996 and returned to the U.S. as a researcher for the Division of Biometry and Risk Assessment at the National Center for Toxicological Research in Jefferson, Arkansas.

**Claire D. Sherman** was appointed research scientist 1 June 1997. Dr. Sherman came to RERF from the University of California, Davis, where she was director of the Biometrics Unit of the UCD Cancer Center and adjunct assistant research professor in the Department of Epidemiology and Preventive Medicine.

#### *Information Technology Department*

**Jill L. Ohara**, department chief, resigned effective 30 December 1996 after 16 years with RERF. Ms. Ohara made strong contributions in developing statistical software, converting RERF's mainframe computing system to a distributed network system, organizing RERF's worldwide Internet presence, and initiating work to modernize the major research data bases. She returned to the United States, where she is now employed by Sunhawk Corporation in Seattle, Washington. Her leadership, exemplified by her unstinting efforts, fairness, gentle persuasiveness as a motivator, and level-headedness as a problem solver, will be sorely missed by RERF and be a boon to her new employers.

**Michael K. Morimoto** joined ITD as a research scientist 1 October 1997. Mr. Morimoto came to RERF from his position as assistant language teacher in Okayama Prefecture. His prior work included positions with Intergraph, a Fortune 500 company, where he specialized in large corporate computer networks and the Internet, as well as various other com-

panies, a genetic engineering laboratory, and a tumor registry.

#### *Publication and Documentation Center*

**Rosalyn Uhrig Vu** became chief editor 30 April 1997. She is a freelance writer and editor and served as adjunct instructor of English as a second language and English composition at two Columbus, Ohio colleges before coming to RERF. Ms. Vu was also editorial assistant for the *American Journal of Obstetrics and Gynecology* for five years.

Ms. Vu succeeded **Beth Magura**, who resigned 18 November 1996 to return to the US, where she was employed as a senior technical editor by Digital Equipment Corporation of Littleton, Massachusetts. Ms. Magura began editorial work at RERF in 1988. She served as managing editor of *Update*, the English-language newsletter she helped to develop, and made a great contribution as a member of RERF's World Wide Web editorial committee in constructing the

RERF web site. Ms. Magura's efforts to learn the latest desktop publishing and web communications technologies and share that information with her co-workers and her diligence and thoroughness in producing RERF publications will be remembered well.

PDC Department Chief **Takeo Murata** retired 30 June 1997 after 40 years of service to RERF. Mr. Murata was a field investigator, statistical technician, chief of General Affairs, and assistant chief of the Secretariat before his promotion to PDC chief. He also served as HICARE liaison manager, helping to promote relations between RERF and local organizations.

**Kimiko Ono**, assistant center chief, replaced Mr. Murata as department chief effective 1 July.

#### *Nagasaki*

#### *Department of Clinical Studies*

**Tan Tominaga** was promoted from acting chief to chief of the Division of Clinical Laboratories 1 August 1997. □

#### *New Chairman continued from page 1*

Dr. Shigematsu received numerous awards, which included in recent years a gold medal of distinguished service from the Royal Swedish Academy of Sciences, fellowship in the Royal College of Physicians of London, and the Second Class Order of the Sacred Treasure presented by Emperor Akihito.

As Dr. Shigematsu prepared to leave RERF, he emphasized the organization's great achievements as ABCC/RERF marked its 50th year, and he expressed his appreciation to all of the individuals and organizations who had offered their support to him and the Foundation through the years—RERF's administrators and staff, those concerned with the research in Hiroshima and Nagasaki, the US and Japanese governments, and all others. Offering his best wishes for RERF's continued success in its second half-century, Dr. Shigematsu retired.

Dr. Nagataki joined RERF as a permanent director in April, following his March retirement as dean of the Nagasaki University School of Medicine, where he had been on faculty since 1980. During that time, Dr. Shigematsu invited his participation in the Ministry of Health and Welfare's research team, and Dr. Nagataki was appointed as an RERF consultant. Through the collaboration of RERF and Nagasaki University, Dr. Nagataki conducted a study of the radioactive fallout in the Nishiyama

District, which included a report on the increased incidence of autoimmune thyroid diseases in atomic-bomb survivors. Dr. Nagataki has also been active in research concerning Chernobyl, particularly in the area of childhood thyroid cancer studies, and served as expert for the survey of the accident site. As director of the Nagasaki Foundation for the Promotion of Peace, Dr. Nagataki was engaged in activities advancing international peace.

In his inaugural speech, Dr. Nagataki highlighted the relationship of RERF's research "to every one of the survivors" as well as to the Hiroshima and Nagasaki communities, the Japanese and American governments, who sponsor the research, and to the global community. He also pointed out that current studies will assume new significance as science unfolds and new discoveries change perceptions of existing data. He described science as "the common language" by which researchers in 50 or 100 years will communicate their understanding of the effects of radiation on the survivors of the atomic bombings. With this in mind, Dr. Nagataki called for an effort to seek out and encourage young scientists to carry RERF's studies into the future. Dr. Nagataki spoke of the "heavy responsibility" he feels as RERF's new leader, but he said that he looks forward to the future with the continued support of all those at RERF. □



## RERF On-line: [www.rerf.or.jp](http://www.rerf.or.jp)

by John Cologne

Chair, WWW Editorial Subcommittee

RERF's mission is to contribute to the well-being of the atomic-bomb survivors and to the health of all humankind. This mission requires the communication of research findings to the scientific community and the public. The Internet, through the World Wide Web (WWW), offers a new means to accomplish this task, and RERF has established its own site on the Web: [www.rerf.or.jp](http://www.rerf.or.jp). Major credit for this is due to Ms. Kimiko Ono, chief of the Publication and Documentation Center, who serves as WWW coordinator and oversees the web site on a daily basis.

As a service to the scientific community, publicly available RERF data can now be downloaded on-line, and researchers interested in RERF can keep abreast of news, recent publications, workshops, research summaries, and other aspects of the Foundation's activities by periodically visiting the web site. To help fulfill our obligation to the public, the web site provides information on radiation effects contributed by RERF scientists edited and written in common language at a non-technical level. Reflecting our binational composition, parallel sites are maintained in English and Japanese.

The WWW offers three advantages over traditional publishing media: unlimited content, ease of updating, and two-way communication. Traditional publications, such as brochures, are limited in size, can become outdated quickly, and offer no direct opportunity for questions and feedback. On the other hand, Web site information allows inclusion of any number of images to aid understanding as well as easy updating, and readers may comment or seek further information via e-mail.

The RERF web site is not ornate. Compared to many commercial and non-profit sites, it is blatantly lacking in color and moving images. This is not due to poor technical capability or lack of creativity but to RERF's mission. That mission is both exciting and somber—exciting because of the scope of state-of-the-art research in science and risk assessment, somber because of the subject of our investigation. We think that the excitement of the research speaks for itself through colorful images of DNA and cells, lucid descriptions of biological mechanisms, and medical and epidemiologic facts and findings. The overall design of the web site is, therefore, subdued to reflect the catastrophic event that resulted in our existence.

The bottom line in deciding what level of effort should be expended in maintaining RERF's web site is the site's utility to the general public and the scientific community—not our perception of it, but in reality. The site does not exist merely because we think it is needed; it is maintained and modified in response to how it is actually used. We assess that usage partly through the amount of e-mail correspondence received, the number of RERF publications requested on-line, the number of copies of RERF data downloaded, the number of times the site is viewed, and the feedback received from people who browse the site. A few examples of how RERF's WWW site has been utilized follow.

During February 1998, the web site averaged about

5,000 outside hits per day from over 50 countries. (A "hit" means opening one page in the site; most people will browse dozens of pages on a single visit.) Approximately one-third of those were from within Japan. Since its inception in November 1996, the site has elicited more than 150 initial e-mail contacts, most questions subsequently answered by RERF scientists or collaborators, and sometimes resulting in several exchanges. Thirty-four copies of RERF data have been transferred since the data downloading system became available in the spring of 1997. Our publication center has received about ten on-line requests per month for publication reprints and research reports, technical reports, commentary and review papers, DS86 publications, and RERF bibliographies. We have also received dozens of questions from students studying the atomic-bomb disasters or writing reports on their effects. When we are unable to point them to the appropriate answer in our site, an RERF scientist has usually corresponded with them directly to help answer their questions.

Many users have expressed gratitude for responses to their personal questions about radiation received from RERF researchers. Two particularly touching examples are:

*"Thank you for your generous and prompt response to my inquiry. It is certainly comforting to know your organization exists to help in matters like this, and I am most impressed by the service you have provided. I hope that some of my tax dollars are supporting your efforts."*

*"Thank you very, very much for taking time to respond to our radiation question. My wife joins me in expressing our gratitude for your interest, care, and dedication to your profession."*

An even more significant example is that of a gentleman who found RERF's web site and asked by e-mail if his father's death by liver cancer might have been related to exposure to the A-bomb. Dr. Nori Nakamura, who was at the time chair of the committee that founded the web site, carried on a detailed discussion with the gentleman by e-mail on radiation- and non-radiation-related risk factors for liver cancer. Dr. Nakamura's frankness and compassion so moved the gentleman that he donated ¥1,000,000 to RERF.

What about the future of the WWW at RERF? Researchers looking for RERF publications on specific topics or by certain authors will soon be able to search for and locate them on-line. Announcements, preliminary programs, and abstracts of upcoming seminars and workshops will be distributed through the Internet. Individual departments have begun producing WWW pages specific to their activities. (For example, the Statistics Department disseminates information and programs useful in analyzing mortality and cancer-incidence data.) Internal (not accessible outside RERF) WWW pages are used to circulate general staff information,

*Continued at top of next page*

*Continued from previous page*

seminar announcements, and the like inside RERF; this activity will surely expand in the next few years.

As the future of publishing progresses toward the Internet, RERF must consider the WWW's role in its own activities. Internet publishing allows more timely distribution of news and information, more frequent updating as research progresses, and a greater volume of material for exactly the same effort but without the costs of printing and mailing. For example, the computer

provides many more images—in color—than the printed page. The major drawbacks seem to be the reluctance of some readers to switch from the printed page to a computer screen, the need to have hard copies for archival and official purposes, and the lack of availability of computers to many potential readers.

I would appreciate hearing your comments on the utility of RERF's web site and how you would use it vis-à-vis traditional RERF publications. My e-mail address is: [cologne@rerf.or.jp](mailto:cologne@rerf.or.jp) □

## Newly Approved Research Protocols and Recent Publications

*Following are listings of the two research protocols (RP) approved (with their summaries) and the 84 manuscripts reported published by RERF staff members since the last issue of Update, which appeared in November 1996. Note that publications are arranged in reverse order according to the research protocol numbers with which they are connected. Publications not directly related to a given research protocol are listed separately after these in alphabetical order by first author. Investigators' and authors' names are followed by their affiliations in parentheses. The following codes are used to identify RERF departments:*

<i>Clinical Studies, Hiroshima</i>	<i>C</i>
<i>Clinical Studies, Nagasaki</i>	<i>CN</i>
<i>Epidemiology, Hiroshima</i>	<i>E</i>
<i>Epidemiology, Nagasaki</i>	<i>EN</i>
<i>Genetics</i>	<i>G</i>
<i>Radiobiology</i>	<i>R</i>
<i>Statistics</i>	<i>S</i>
<i>Information Technology</i>	<i>IT</i>
<i>RERF Director</i>	<i>D</i>

*(Japanese) after an entry indicates that the original article is in Japanese; (J) after an entry listed with an RERF Report number indicates that a Japanese translation is available.*

*Abstracts are included for articles designated as RERF Reports, which are those publications that have undergone internal review prior to journal submission. Following acceptance and publication by a peer-reviewed journal, reprints are purchased from the publisher and bound with a Japanese summary in RERF Report covers. Abstracts for articles that are not RERF Reports are also included for those publications for which we have a file-copy summary.*

### Research Protocols

**RP 1-97 Pilot study of genetic background of AHS population: Identification of markers in potential candidate genes associated with hypertension** Takahashi N (G), Murakami H (C, G), Yamada M (C), Kasagi F (S), Kodama K (C), Satoh C (G) (J)

An elevation of blood pressure has been observed with increasing radiation dose in survivors exposed when younger than 20 years at the time of the bombings. A significant relationship between the prevalence of systolic hypertension and radiation dose has also been observed in those who were relatively young at the time of examination. Recent genetic analyses have produced results supporting the existence of (a) gene(s) inducing predispo-

sition to hypertension. In the proposed pilot study, the association between hypertension and either known markers or new markers of hypertension-related genes will be investigated in a small population. If markers constituting inherited predisposition to essential hypertension are identified by this study, it may help explain why hypertension is more prevalent in the high-dose exposure group.

**RP 2-97 (Addendum to RP 2-90) Lyophilization of blood samples for DNA extraction to be obtained from Adult Health Study subjects in Hiroshima and Nagasaki** Hayashi T (R), Kyoizumi S (R), Fujiwara S (C), Kodama K (C), Tominaga T (CN), Akahoshi M (CN), Seyama T (R) (J)

This RP supplements the program established under Research Pro-

tol (RP) 2-90 to store blood samples from the approximately 7,000 Adult Health Study (AHS) participants in Hiroshima and Nagasaki. The current RP provides for the separation and storage of DNA for multiple small-scale molecular analyses to avoid depletion of the RP 2-90 supply.

Under the existing protocol, we have been cryopreserving viable blood cells from AHS participants for later use in functional assays or large-scale molecular analyses. Though DNA analyses by the polymerase chain reaction (PCR) require relatively small numbers of cells, removing cells for analyses from those stored results in wastage because repeated freeze and thaw cycles cause deterioration of the biological materials.

Under this supplement, as an additional preparation step, blood intended for DNA analysis will be separated from the existing RP 2-90 samples and collected on 20 paper discs for each sample prior to cryopreservation to provide separate samples for individual studies. As a result, one disc may be removed from the stored material for future use without jeopardizing the remaining sample. By separating samples for DNA studies prior to cryopreservation of the biological samples, more studies can be conducted with less loss to the overall sample. In this way, for a given analysis, less biological material will be used, thereby protecting the limited supply of sample.

### Recent Publications

**RPs 8-93 and 1-92** Nakamura N (G), Miyazawa C (Ohi University School of Dentistry), Akiyama M (R), Sawada S (Research Institute for Radiobiology and Medicine, Hiroshima University), Awa AA (G). Biodosimetry: Chromosome aberration in lymphocytes and electron paramagnetic resonance in tooth enamel from atomic-bomb survivors. World Health Statistics Quar-

terly 1996; 49(1):67-71.

**RP 8-93** Kodama Y (G), Nakano M (G), Ohtaki K (G), Delongchamp RR (S), Awa AA (G), Nakamura N (G). Estimation of minimal size of translocated chromosome segments detectable by fluorescence *in situ* hybridization. *International Journal of Radiation Biology* 1997(January); 71(1):35-9. (*RERF Report* 5-96)

Apparent non-reciprocal translocations are commonly observed using fluorescence *in situ* hybridization. We hypothesize that these are "hidden" reciprocals due to one translocated segment being too small to detect. Assuming that the translocation breakpoints distribute randomly, the proportion of reciprocal to nonreciprocal exchanges can be used to estimate the minimal detectable size of translocated segments. To estimate segment size in this study, cytogenetic data for 120 A-bomb survivors were used. Among 2295 aberrant metaphases, 1629 exhibited reciprocal translocations and 666 nonreciprocal. Of the nonreciprocal translocations, 501 showed only a painted chromosome segment, translocated to an unpainted chromosome with centromere; and 165 showed only an unpainted chromosome segment, translocated to a painted chromosome with centromere. On the basis of the above two assumptions, we obtained the most likely estimates for minimal detectable sizes:  $11.1 \pm 0.8$  Mb for the painted and  $14.6 \pm 0.6$  Mb for the unpainted chromosomes. The implications of these findings are discussed.

**RPs 7-93, 3-93, and 3-92** Iwamoto KS (R), Mizuno T (R), Ito T (R), Akiyama M (R), Takeichi N (Hiroshima University School of Medicine), Mabuchi K (E), Seyama T (R). The feasibility of using decades-old archival tissues in molecular oncology/epidemiology. *Nagasaki Igakkai Zasshi* (Nagasaki Medical Journal) 1996; 71:224-9. (Proceedings of the 37th Late A-bomb Effects Research Meeting, 1996). (**Japanese**)

**RP 7-93** Mizuno T (R), Kyoizumi S (R), Suzuki T (R), Iwamoto KS (R), Seyama T (R). Continued expression of a tissue-specific activated oncogene in the early steps of radiation-induced human thyroid carcinogenesis. *Oncogene* 1997 (September) 18; 15(12):1455-60. (*RERF Report* 3-97)

Ionizing radiation is a well-known risk factor of cancer development, but the mechanism of radiation-induced carcinogenesis is not clear. Chromosomal rearrangements induced by radiation most likely are one of the principal genetic alterations resulting in malignant transformation. The chimeric BCR-ABL associated with chronic myelogenous leukemia (CML) and H4-RET oncogenes associated with thyroid papillary carcinoma are the result of a translocation and inversion, respectively. *In vitro* studies showed these genes were induced by high doses of X-irradiation in cell lines. Studies also show that therapeutic external X-ray doses as high as 60 Gy for treatment of various childhood cancers including Hodgkin's disease significantly increase the risk of thyroid cancer. Therefore, we examined the induction and persistence of these chimeric genes in human thyroid tissues transplanted in SCID mice after 50 Gy exposure as a function of time for 2 months to elucidate the early events of thyroid carcinogenesis. The H4-RET genes were detected on day 2 and throughout the 2-month period. On the other hand, BCR-ABL genes were detected on day 2 and were undetectable subsequently. These results suggest that ionizing radiation causes various oncogene activations, but cells with only specific gene alteration uniquely associated with thyroid carcinogenesis are selectively retained, demonstrating one of the early events in the beginnings of radiation carcinogenesis in human thyroid tissues.

**RP 4-93** Oishi K (CN), Shibata Y (EN), Nakamura T (Nagasaki University School of Medicine [NUSM]), Tsujihata M (School of Allied Medical Sciences, Nagasaki University), Akahoshi M (CN), Matsuo T (Atomic Disease Institute [ADI], NUSM), Tomonaga M (ADI, NUSM), Nagataki S (NUSM), Shimaoka K (CN). Autoantibodies and immunoglobulins in atomic-bomb survivors with human T-lymphotropic virus type I. *Internal Medicine* 1996 (August); 35(8):624-8. (*RERF Report* 15-94)

The association of human T-lymphotropic virus type I (HTLV-I) with autoimmune disorders was investigated on the basis of prevalence of antinuclear antibody (ANA), rheumatoid factor, and anti-thyroglobulin

antibody as well as immunoglobulin (Ig) serum level (IgG, IgA, and IgM). The subjects, all atomic-bomb survivors, were 59 HTLV-I-seropositive people without HTLV-I-associated myelopathy or adult T-cell leukemia and 149 HTLV-I-seronegative persons. The mean serum level of IgM was higher in HTLV-I-seropositive subjects than in HTLV-I-seronegative subjects, and a significant association with HTLV-I and sex was indicated in the IgM serum level. No association with HTLV-I was indicated in the prevalence of the autoantibodies except for ANA. These results suggest some clear humoral immunity differences between HTLV-I-infected and noninfected subjects, but whether HTLV-I infection can lead to autoimmune disorders remains uncertain.

**RP 3-93**, See also RPs 7-93 and 3-92, Iwamoto *et al.*

**RPs 1-93 and 7-89** Suzuki T (R), Kyoizumi S (R), Saito M (R), Yamaoka M (R), Hirai Y (R), Kusunoki Y (R), Kodama K (C). Analysis of hematopoietic stem cells in peripheral blood of atomic-bomb survivors. *Nagasaki Igakkai Zasshi* (Nagasaki Medical Journal) 1996 (September 25); 71 (special issue):200-4. (Proceedings of the 37th Late A-bomb Effects Research Meeting, 1996). (**Japanese**)

**RP 3-92**, See also RPs 7-93 and 3-93, Iwamoto *et al.*

**RP 9-92** Fujiwara S (C), Kusumi S (C), Cologne JB (S), Akahoshi M (CN), Kodama K (C), Yoshizawa H (Hiroshima University School of Medicine). Review of positive rate of hepatitis C virus antibody among atomic bomb survivors. FY-1996 Report of A-bomb Disease Research Teams. Tokyo: Nippon Koshueisei Kyokai (Japan Public Health Association); 1997, 34-6. (**Japanese**)

**RP 1-92**, See also RP 8-93, Nakamura *et al.*

**RP 1-92** Nakamura N (G), Miyazawa C (Ohi University School of Dentistry). Alkaline denaturation of dentin—A simple way to isolate human tooth enamel for electron spin resonance dosimetry. *Journal of Radiation Research* 1997 (June); 38(2):173-7. (*RERF Report* 9-97)

*Continued at top of next page*

*Continued from previous page*

Electron spin resonance (ESR) of tooth enamel is a recently developed method for the retrospective dose estimation of human radiation exposures. The assay requires isolation of enamel from dentin, which is difficult because the boundary between enamel and dentin is not easily discernible. Here, we describe a simple method for isolating enamel by alkaline denaturation of dentin. The method requires 4 weeks, but scratching of the denatured and, hence, softened dentin is needed only once a week. Above all, no special skill is required. We found that the alkaline treatment did not cause deterioration of the ESR signal recorded in enamel exposed to 2 Gy of  $\gamma$ -rays prior to its isolation. The assay is particularly suited for teeth containing many cracks that were generated during long-term storage after extraction of the teeth. Such teeth tend to disintegrate during enamel isolation processes, which poses difficulties to mechanical isolation of the enamel from individual small pieces.

**RP 3-91 and 3-89** Fujiwara S (C). Epidemiological study of osteoporosis. Sanfujinka Chiryō (Obstetrical and Gynecological Therapy) 1996; 72(3):279-83. (Japanese)

**RP 3-91 and 3-89** Fujiwara S (C). Epidemiological study of osteoporosis in a Japanese population. Hong Kong Journal of Gerontology 1996; 10 (Suppl):300-2. (Proceedings of the Fifth Asia/Oceania Regional Congress of Gerontology, Hong Kong, 19-23 November 1995).

**RP 3-91 and 3-89** Fujiwara S (C). Epidemiology of osteoporosis-associated fracture. Laboratory Animal Technology and Science 1996; 8:295-9. (Japanese)

**RP 3-91 and 3-89** Fujiwara S (C). Frequency and distribution of vertebral fracture. Clinical Calcium 1996; 6(7):819-21. (Japanese)

**RP 3-91 and 3-89** Fujiwara S (C). Quality of life: Risk factors of osteoporosis. Fujita T, ed. Metabolic Bone Disease and Quality of Life. Tokyo: Iyaku Journal Co.; 1996, 112-21. (Japanese)

**RP 1-91** Saku T (Nagasaki University School of Dentistry), Hayashi Y

(Hiroshima Asa Citizens' Hospital), Takahara O (Red Cross-Nagasaki A-Bomb Hospital), Matsuura H (Hiroshima Citizens' Hospital), Tokunaga M (Kagoshima City Hospital), Tokuoka S (RERF Consultant), Soda M (EN), Mabuchi K (E), Land CE (National Cancer Institute). Salivary gland tumors among atomic-bomb survivors, 1950-1987. Cancer 1997 (April 15); 79(8):1465-75. (RERF Report 16-95) (J)

**Background:** Malignant and benign tumors of the salivary glands have been associated with exposure to ionizing radiation from various sources, including the atomic bombings in Hiroshima and Nagasaki. However, questions remain unanswered regarding the nature and size of the risk and specific types of tumors involved.

**Methods:** The incidence and pathology of malignant and benign tumors of the salivary glands was studied in the Life Span Study cohort of atomic-bomb survivors followed by the Radiation Effects Research Foundation (RERF) in Hiroshima and Nagasaki, Japan. Incident cases diagnosed during the period 1950-1987 were ascertained from the tumor and tissue registries of Hiroshima and Nagasaki and supplemented by additional case findings from autopsy, biopsy, and surgical specimens maintained at RERF and other institutions. Pathology slides and medical documents were reviewed by a panel of four pathologists who classified tumors using the World Health Organization classification scheme. Analyses were performed of histologic features associated with radiation exposure.

**Results:** Of 145 tumors of the salivary glands identified (119 of the major and 26 of the minor salivary glands), 120 (83%) were histologically confirmed by the current investigators. Among 41 malignant tumors, the frequency of mucoepidermoid tumor was disproportionately high at high radiation doses ( $P = 0.04$ ); among 94 benign tumors, the frequency of Warthin's tumor increased with increasing radiation dose ( $P = 0.06$ ). The nature of the tumor was undetermined for the remaining ten cases. Mortality from malignant tumors of the salivary gland was inversely related to radiation dose, reflecting the predominance of mucoepidermoid carcinoma at high dose levels in this series. In

one case with high radiation exposure, mucoepidermoid carcinoma of the parotid gland was accompanied by a pre-existing or coexisting Warthin's tumor.

**Conclusions:** These findings, supported by population-based analyses in a companion study reported elsewhere, suggest a causal role for ionizing radiation in salivary gland tumorigenesis, particularly for mucoepidermoid carcinoma, and in the induction of one type of benign tumor (Warthin's tumor).

**RP 3-89** Fujiwara S (C), Kasagi F (S), Yamada M (C), Kodama K (C). Risk factors for hip fracture in a Japanese cohort. Journal of Bone and Mineral Research 1997 (July); 12(7):998-1004. (RERF Report 12-96)

**Risk factors for hip fracture were determined from a Japanese cohort.** A cohort of 4573 people (mean age  $58.5 \pm 12.2$ ) who participated in the Adult Health Study in 1978-1980 were subsequently followed by biennial examinations up to 1992. Fifty-five incident hip fractures not due to traffic accidents were identified by medical records during the follow-up period. Poisson regression analysis showed that baseline low body mass index (BMI), regular alcohol intake, prevalent vertebral fracture, and having five or more children significantly increased the risk of hip fracture, and low milk intake and later age at menarche were marginally associated with increased fracture risk, after multivariable adjustment. Regular alcohol intake doubled the risk of hip fracture (relative risk 1.91, 95% confidence interval 1.07-3.42). Those individuals who had a vertebral fracture had 2.6 times higher risk than those who did not. The risk was 2.5 times higher among women who had five or more children than women with one or two. Body height, health status, marital status, intake of fish, coffee, tea, and Japanese tea, smoking, exposure to atomic-bomb radiation, and age at menopause were not associated with hip fracture. Relative risk for hip fracture decreased with decreasing number of preventable risk factors (low BMI, low milk intake, and regular alcohol intake). We conclude that many factors, such as BMI, milk intake, alcohol intake, prevalent vertebral fracture, age at menarche, and number of children, are related to the

risk of hip fracture, and prevention programs need to focus on reducing preventable risk factors.

**RP 3-87** Kusunoki Y (R), Morishita Y (R), Maki M (R), Kyoizumi S (R), Hirai Y (R), Akiyama M (R), Kodama K (C). Effects of atomic-bomb radiation on human immune responses (12). Analysis of T cell function using the limiting dilution analysis. Nagasaki Igakkai Zasshi (Nagasaki Medical Journal) 1996 (September 25); 71(Special issue):218-23. (Proceedings of the 37th Late A-bomb Effects Research Meeting, 1996). (Japanese)

**RP 3-87** Ishioka N (R), Umeki S (R), Hirai Y (R), Akiyama M (R), Kodama T (Hiroshima University School of Medicine [HUSM]), Ohama K (HUSM), Kyoizumi S (R). Stimulated rapid expression in vitro for early detection of in vivo T-cell receptor mutations induced by radiation exposure. Mutation Research 1997 (May 23); 390(3):269-82. (RERF Report 2-96)

The T-cell receptor (TCR) mutation assay for in vivo somatic mutations is a sensitive indicator of exposure to ionizing radiation. However, this assay cannot be immediately applied after radiation exposure because expression of a mutant phenotype may require as long as several months. In the present study, we eliminate this time lag by stimulating lymphocytes with a mitogen that can accelerate the turnover of TCR protein expression in T-cells. When lymphocytes obtained from healthy donors were irradiated with various doses of X-rays and cultured with human interleukin-2 after phytohemagglutinin (PHA) pulse stimulation, the mutant frequency (MF) of CD4<sup>+</sup> T-cells increased dose dependently during the first 7 days, then decreased rapidly due to the growth disadvantage of mutant cells. This suggests that PHA stimulation can shorten the expression time of a mutant phenotype to within a week after radiation exposure. The relationship between radiation dose and TCR MF on the seventh day was best fitted by a linear-quadratic dose-response model. We applied this improved TCR mutation assay to gynecological cancer patients who received 5 days of localized radiotherapy, totaling about 10 Gy. The in vivo TCR MF in the patients did not change

within a week after radiotherapy, whereas the in vitro TCR MF of PHA-stimulated lymphocytes from the same patients significantly increased 7 days after initiating culture. The estimated mean radiation dose to the peripheral blood lymphocytes of the cancer patients was about 0.9 Gy, based on the in vitro linear-quadratic dose-response curve. This estimated dose was close to that described in a previous report on unstable-type chromosome aberrations from cervical cancer patients after receiving the same course of radiotherapy. On the basis of these findings, we propose that the improved TCR mutation assay is a useful biological dosimeter for recent radiation exposure.

**RP 3-87** Umeki S (R), Suzuki T (R), Kusunoki Y (R), Seyama T (R), Fujita S (S), Kyoizumi S (R). Development of a mouse model for studying in vivo T-cell receptor mutations. Mutation Research 1997 (September 18); 393(1-2):37-46. (RERF Report 2-97)

An experimental system was established to study in vivo T-cell receptor  $\alpha\beta$  (TCR) mutations in murine CD4<sup>+</sup> T-lymphocytes. The frequency of TCR-defective mutant T-cells that have the CD3-4<sup>+</sup> surface phenotype, was measured using two-color flow cytometry of splenic T-cells passed through nylon wool. The spontaneous TCR mutant frequency (MF) in BALB/c mice ( $2.3 \times 10^{-4}$ ) was significantly lower than the frequencies of C57BL/6 ( $4.0 \times 10^{-4}$ ) and C3H/He ( $4.2 \times 10^{-4}$ ) mice. The general trend of the TCR MF started to increase at 3 days after whole-body X-irradiation, reached a peak level at 2-3 weeks, and then gradually decreased with a half-life of about 2 weeks. To analyze how the dose responses for each strain of mouse differed 2 weeks after X-irradiation, the TCR MF dose responses were fitted to a linear-quadratic or a quadratic curve. The coefficients of the quadratic terms in both models for BALB/c mice were significantly higher than those for the other two strains. These findings suggest that some genetic factor(s) may control the susceptibility of somatic genes to both spontaneous and radiation-induced mutagenesis. Establishing an animal model for in vivo TCR mutations will contribute to the clarification of certain unresolved aspects of TCR mutagenesis in humans and will further

advance knowledge of screening for environmental mutagens.

**RP 6-86** Kawamura S (C), Kasagi F (S), Kodama K (C), Fujiwara S (C), Yamada M (C), Ohama K (Hiroshima University School of Medicine [HUSM]), Ito K (HUSM). Prevalence of uterine myoma detected by ultrasound examination in the atomic-bomb survivors. Radiation Research 1997 (June); 147(6):753-8. (RERF Report 3-96)

Benign tumors of several organs have been demonstrated to occur as late effects of atomic-bomb exposure, and a recent addition to the list of affected organs is the uterus. The increased incidence of uterine myoma noted in Radiation Effects Research Foundation (RERF) Adult Health Study Report 7 (Wong *et al.*, *Radiat. Res.* 135, 418-430, 1993), however, was based on self-reported information, optional gynecological examination, and patient-requested ultrasound examination. Thus, the possibility of dose-related bias in case detection was a serious concern. Therefore, the relationship between the prevalence of uterine myoma and dose to the uterus was examined after excluding as much bias as possible by asking all women who had undergone biennial examinations from December 1991 through December 1993 to undergo ultrasound examinations. Among 2506 female participants in Hiroshima, the uterus was visualized by ultrasound examination in 1190, and 238 were found to have uterine nodules. Multiple logistic analysis using Dosimetry System 1986 uterine doses revealed a significant dose response for the prevalence of uterine nodules. The odds ratio at 1 Gy was 1.61 (95% confidence interval: 1.12-2.31). It is unlikely that the observed relationship after adjusting for bladder filling, volume of the uterus, age, and menopause status was the result of dose-related bias. These results support previous findings at RERF and provide further evidence that radiation exposure is one of the factors associated with uterine myoma.

**RP 7-85** Asakawa J (G). High resolutional two-dimension electrophoresis of DNA: a refinement of RLGS method. Tanpakushitsu Kakusan Koso (Protein, Nucleic Acid  
*Continued at top of next page*



Continued from previous page  
and Enzyme) 1996 (February);  
41(2):170-7. (Japanese)

**RP 7-85** Kuick R (University of Michigan School of Medicine, USA [UMSM]), Asakawa J (G), Neel JV (UMSM), Kodaira M (G), Satoh C (G), Thoraval D (UMSM), Gonzalez IL (Hahnemann University, Pennsylvania, USA), Hanash SM (UMSM). Studies of the inheritance of human ribosomal DNA variants detected in two-dimensional separations of genomic restriction fragments. *Genetics* 1996 (September); 144(1):307-16.

We have investigated the variation in human ribosomal DNA repeat units as revealed in two-dimensional electrophoretic separations of genomic restriction fragments that were end-labeled at *NotI* cleavage sites. The transcribed portion of the ribosomal DNA results in ~20 labeled fragments visible on each gel as multicopy spots. We have mapped these spots to the sequences responsible for their appearance on the gels based on their migration positions and direct sequencing of spots, and we describe several previously unreported sources of variation. By studying mother/father/child families, we gained information on how much of the between-repeats variation is due to differences between and within repeat arrays on homologous chromosomes. Two instances in which a child exhibited more copies of a particular fragment than were present in the parents are described and hypothesized to be due to events such as multiple unequal sister-chromatid exchanges or gene conversions.

**RP 7-85** Satoh C (G), Kodaira M (G). Effects of radiation on children. (Scientific correspondence). *Nature* 1996 (September 19); 383(6597):226.

**RP 7-85** Satoh C (G), Takahashi N (G). Denaturing gradient gel electrophoresis of DNA fragments attached with a GC-clamp. *Tanpakushitsu Kakusan Koso (Protein, Nucleic Acid and Enzyme)* 1996 (April); 41(5):556-60. (Japanese)

**RP 7-85** Takahashi N (G), Satoh C (G), Asakawa J (G), Kodaira M (G). Monitoring of germline mutations in A-bomb survivors by DNA-level examination of their children. *Environmental Mutagen Research Communi-*

*cations* 1996; 17:301-6. (Proceedings of Mini Symposium, the 24th Annual Meeting of Japan Environmental Mutagen Society, Osaka, Japan, 20-22 November 1995). (Japanese)

**RP 7-85** Thoraval D (University of Michigan School of Medicine, USA [UMSM]), Asakawa J (G), Kodaira M (G), Chang CC (UMSM), Radany E (UMSM), Kuick R (UMSM), Lamb B (UMSM), Richardson B (UMSM), Neel JV (UMSM), Glover TW (UMSM), Hanash SM (UMSM). A methylated human 9-kb repetitive sequence on acrocentric chromosomes is homologous to a subtelomeric repeat in chimpanzees. *Proceedings of the National Academy of Sciences of the United States of America* 1996 (April 30); 93(9):4442-7.

We have implemented an approach for the detection of DNA alterations in cancer by means of computerized analysis of end-labeled genomic fragments separated in two dimensions. Analysis of two-dimensional patterns of neuroblastoma tumors, prepared by first digesting DNA with the methylation-sensitive restriction enzyme *Not I*, yielded a multicopy fragment that was detected in some tumor patterns but not in normal controls. Cloning and sequencing of the fragment, isolated from two-dimensional gels, yielded a sequence with a strong homology to a subtelomeric sequence in chimpanzees and previously reported to be undetectable in humans. Fluorescence *in situ* hybridization indicated the occurrence of this sequence in normal tissue, for the most part in the satellite regions of acrocentric chromosomes. A product containing this sequence was obtained by telomere-anchored PCR using as a primer an oligonucleotide sequence from the cloned fragment. Our data suggest demethylation of cytosines at the cloned *Not I* site and in neighboring DNA in some tumors, compared with normal tissue, and a greater similarity between human and chimpanzee subtelomeric sequences than was previously reported.

**RP 7-85** Thoraval D (University of Michigan School of Medicine, USA [UMSM]), Asakawa J (G), Wimmer K (UMSM), Kuick R (UMSM), Lamb B (UMSM), Richardson B (UMSM), Ambros P (Children's Cancer Re-

search Institute, Austria), Glover TW (UMSM), Hanash SM (UMSM). Demethylation of repetitive DNA sequences in neuroblastoma. *Genes, Chromosomes and Cancer* 1996 (December); 17(4):234-44.

Altered genomic methylcytosine content has been described for a number of tumor types, including neuroblastoma. However, it remains to be determined for different tumor types whether specific loci or chromosomal regions are affected by a methylation change or whether the change is random. We have implemented a computer-based approach for the analysis of two-dimensional separations of human genomic restriction fragments. Through the use of methylation-sensitive restriction enzymes, methylation differences in genomic DNA between tumor and normal tissues can be detected. We report the cloning and sequencing of two fragments detectable in two-dimensional separations of genomic DNA of neuroblastomas. These fragments were found to be a part of repetitive units that exhibited demethylation in neuroblastoma relative to other tumor types. Our finding of a distinct pattern of methylation of repetitive units in neuroblastoma suggests that altered methylation at certain loci may contribute to the biology of this tumor.

**RP 7-85** Wimmer K (University of Michigan School of Medicine, USA [UMSM]), Thoraval D (UMSM), Asakawa J (G), Kuick R (UMSM), Kodaira M (G), Lamb B (UMSM), Fawcett J (Los Alamos National Laboratory, USA), Glover TW (UMSM), Cram S (Los Alamos National Laboratory, USA), Hanash SM (UMSM). Two-dimensional separation and cloning of chromosome 1 *NotI-EcoRV*-derived genomic fragments. *Genomics* 1996 (December); 38(2):124-32.

The two-dimensional (2-D) separation of genomic digests has provided the means to analyze over 2000 unique restriction fragments simultaneously in a single gel for genetic variation as well as for genomic alterations in cancer. By utilizing different combinations of restriction enzymes or different electrophoretic conditions, the number of analyzable fragments in multiple 2-D patterns can be augmented. We have previously shown the feasibility of distinguishing between spot intensities representing

fragments from one allele and from two alleles and have implemented approaches for the cloning of fragments of interest in 2-D gels. In this study, the 2-D separation and cloning of chromosome 1 *NotI*-*EcoRV*-derived genomic fragments was performed. Three hundred forty-six *NotI* fragments in whole genomic preparations were assigned to chromosome 1. To verify the reliability of the assignment, two of the *NotI* fragments attributed to chromosome 1 were cloned and sequenced. The fragments that contained CpG islands were mapped by FISH to 1p35-p36.1 and to 1p13.3-p21, respectively. Our study indicates the feasibility of analyzing 2-D separations of whole genomic digests for the detection of alterations in specific chromosomes. The large number of restriction fragments attributed to chromosome 1 provides the means to screen 2-D patterns for chromosome 1 deletions and amplifications with a high marker density.

**RP 6-85** Neriishi K (C), Yoshimoto Y (E), Nobuyoshi M (C), Fujimura K (Research Institute for Radiation Biology and Medicine [RIRBM], Hiroshima University [HU]), Kimura A (RIRBM, HU), Momita S (Atomic Disease Institute [ADI], Nagasaki University School of Medicine [NUSM]), Tomonaga M (ADI, NUSM), Kodama K (C). Longitudinal study of monoclonal gammopathy in atomic-bomb survivors. *Nagasaki Igakkai Zasshi* (Nagasaki Medical Journal) 1996 (September 25); 71(Special issue):209-13. (Proceedings of the 37th Late A-bomb Effects Research Meeting, 1996). (Japanese)

**RP 6-85** Neriishi K (C), Yoshimoto Y (E), Nobuyoshi M (C), Kodama K (C), Fujimura K (Research Institute for Radiation Biology and Medicine [RIRBM], Hiroshima University [HU]), Kimura A (RIRBM, HU), Momita S (Atomic Disease Institute [ADI], Nagasaki University School of Medicine [NUSM]), Tomonaga M (ADI, NUSM). Longitudinal study of M-proteinemia among atomic-bomb survivors. FY-1996 Report of A-bomb Disease Research Teams. Tokyo: Nippon Koshueisei Kyokai (Japan Public Health Association); 1997, 32-3. (Japanese)

**RPs 4-85 and 2-75** Kodama K (C),

Kasagi F (S), Fujita S (S), Fujita Y (E). Epidemiological studies on physical activity and indices of aging. *Saishin Igaku* (Modern Medicine) 1996 March; 51(3):368-76. (Japanese)

**RP 18-81** Kyoizumi S(R), Suzuki T(R), Teraoka S(R), Seyama T(R). Radiation sensitivity of human hair follicles in SCID. *Radiation Research* 1998 (January); 149(1):11-18. (REF Report 13-96)

We developed an experimental model for studying the growth and epilation of the human hair follicle by implanting human scalp tissue onto immunodeficient C.B-17 *scid/scid* mice. The skin grafts showed continuous growth of black human hairs for at least one year and maintained the normal histological structure of a human hair follicle and other tissues associated with the skin. Using this *in vivo* model, we evaluated the effect of irradiation on the function of human hair follicles. Localized X irradiation (1 to 6 Gy) induced hair loss dose-dependently and synchronously in the third week after irradiation. The hairs undergoing epilation showed a gradual decrease in width toward the root. The minimum width at the thinnest portion of the surviving hair four weeks after irradiation suggested that epilation resulted from the breaking of hairs when the hair width decreased to less than 20 micrometers. After the highest-dose irradiation, the normal structure of the hair bulb was totally abrogated, and long and narrow epithelial tissues associated with regressed papillary cells remained. The surviving epithelia were morphologically similar to the outer epithelial sheath of the follicle associated with palisadic basal cell layers. In the third week some cells in the basal layers of the surviving epithelium in each follicle expressed proliferating cell nuclear antigen. By about nine weeks after irradiation, the complete structure of the follicle regenerated, with hair growth activity even in the grafts irradiated at the highest dose, although about 30% of the hairs did not regrow. These findings suggest that follicular stem cells that survive high-dose exposure in the sheath-like epithelial tissue can reproduce the complete follicle structure. This animal model can be used to assess the effects of radiation exposure on human skin

and to identify and characterize human follicular stem cells.

**RPs 16-78 and 18-59** Otake M (Faculty of Environmental Science and Technology, Okayama University), Neriishi K (C), Schull WJ (University of Texas Medical School, USA). Cataract in atomic-bomb survivors based on a threshold model and the occurrence of severe epilation. *Radiation Research* 1996 (September); 146(3):339-48. (REF Report 13-95)

This report re-examines the relationship of radiation dose to the occurrence of cataracts among 1742 atomic-bomb survivors seen in the years 1963-1964 for whom the degree of epilation and Dosimetry System 1986 (DS86) doses are known. Of these individuals, 67 had cataracts. A relative risk model with two thresholds, one for the epilation group and the other for the no-epilation group, has been fitted to the data using a binomial odds regression approach and a constant relative biological effectiveness (RBE) for neutrons of 10. Among these models, a linear-linear (L-L) dose-response relationship with two thresholds presents the best fit. Under the L-L threshold model based on DS86 eye organ dose estimates for the epilation and no-epilation groups, the slope estimate for the epilation group was 1.6-2.0 times greater than that for the no-epilation group, but no statistical difference between the two slope estimates was noted. The estimated threshold for the epilation group was 0.86 Sv and 1.54 Sv for the no-epilation group, but again the difference between the two threshold estimates is not statistically significant. When an L-L relative risk model with two thresholds was fitted to the data assuming the dose estimates to be in error by 35%, or when the data were restricted to the 1105 individuals exposed in Japanese houses at distances of less than 2500 m, where the DS86 doses are thought to be most reliable, the results were almost the same as those for the individuals for whom unadjusted DS86 eye organ dose estimates were used.

**RP 14-78** Goodman MT (E), Cologne JB (S), Moriwaki H (E), Vaeth M (S), Mabuchi K (E). Risk factors for primary breast cancer in Japan: 8-year follow-up of atomic-bomb survivors.

*Continued at top of next page*

*Continued from previous page*

Preventive Medicine 1997 (January-February); 26(1):144-53. (*RERF Report* 1-97)

**Background:** Findings from the Life Span Study (LSS) of the health effects of exposure to atomic-bomb radiation have documented a strong dose-response relation between radiation exposure and breast cancer incidence.

**Purpose:** We analyzed data from the LSS cohort to identify nonradiation risk factors for breast cancer and to determine whether these factors were independent of the effects of radiation on breast cancer occurrence.

**Methods:** Breast cancer incidence was ascertained among a cohort of 22,200 residents of Hiroshima and Nagasaki, Japan, who had completed a mail survey between 1979 and 1981 to study nonradiation risk factors for disease. During the subsequent follow-up period (average 8.31 years), 161 cases of primary breast cancer were identified through population-based tumor registries in the two cities.

**Results:** The risk of breast cancer was inversely related to age at menarche and weakly positive in relation to age at menopause and years of menstruation. A significant negative association of full-term pregnancy against breast cancer was observed, although the number of pregnancies beyond the first was not related to the rate of breast cancer in the cohort. Women having their first full-term pregnancy before age 30 were at decreased risk of breast cancer relative to older women, but there was no trend. A nonsignificant, positive trend in risk was associated with increasing weight and body mass ( $\text{kg}/\text{m}^2$ ). The risk of breast cancer among women with a history of estrogen use was 1.64 (95% confidence interval 1.02-2.64) and with diabetes 2.06 (95% confidence interval 1.27-3.34). It was not possible to distinguish among additive and multiplicative models of the joint association of radiation dose and various non-radiation-related exposures (age at menarche, full-term pregnancy, female hormone preparations) identified in this analysis.

**Conclusions:** Nonradiation risk factors for breast cancer among Japanese atomic-bomb survivors were consistent with those identified among other populations of women, although

the prevalence of common risk factors was low. Reproductive factors and hormone use appear to act independently of radiation exposure on breast cancer risk in this population.

**RP 4-75** Yoshimoto Y (E), Soda M (EN), Mabuchi K (E). Study of mortality and cancer incidence among the offspring of atomic-bomb survivors, 1946-1990. *Nagasaki Igakkai Zasshi* (Nagasaki Medical Journal) 1996; 71:299-304. (Proceedings of the 37th Late A-bomb Effects Research Meeting, 1996). (**Japanese**)

**RP 2-75**, See also **RP 4-85**, Kodama *et al.*

**RP 2-75** Akahoshi M (CN). Mild depression among atomic-bomb survivors. FY-1996 Report of A-bomb Disease Research Teams. Tokyo: Nippon Koshueisei Kyokai (Japan Public Health Association); 1997, 26-7. (**Japanese**)

**RP 2-75** Kasagi F (S), Kodama K (C), Yamada M (C), Fujiwara S (C). Study of low-level-radiation dose exposure and prevalence of diseases with consideration of confounding factors. FY-1996 Report of A-bomb Disease Research Teams. Tokyo: Nippon Koshueisei Kyokai (Japan Public Health Association); 1997, 73-4. (**Japanese**)

**RP 2-75** Kodama K (C), Fujiwara S (C), Yamada M (C), Kasagi F (S), Shimizu Y (E), Shigematsu I (D). Profiles of non-cancer diseases in atomic-bomb survivors. *World Health Statistics Quarterly* 1996; 49(1):7-16.

**RP 2-75** Kodama K (C), Kasagi F (S), Fujiwara S (C), Yamada M (C), Kawamura S (C), Masunari N (C). Study of prevalence of prostate hypertrophy among atomic-bomb survivors. FY-1996 Report of A-bomb Disease Research Teams. Tokyo: Nippon Koshueisei Kyokai (Japan Public Health Association); 1997, 37-8. (**Japanese**)

**RP 2-75** Kodama K (C), Mabuchi K (E), Shigematsu I (D). A long-term cohort study of the atomic-bomb survivors. *Journal of Epidemiology* 1996 (August); 6 (Suppl 3):S95-S105.

The Atomic Bomb Casualty Commission (ABCC), the predecessor of

the Radiation Effects Research Foundation (RERF), was established in 1947 to conduct long-term, comprehensive epidemiological and genetic studies of the atomic-bomb (A-bomb) survivors. Today, this study still depends upon the voluntary cooperation of several tens of thousands of survivors of the bombings of Hiroshima and Nagasaki. An in-depth follow-up study of mortality in the study population of 120,000 persons, including A-bomb survivors and controls, has continued since 1950. The study of tumor incidence was initiated through record linkage with a tumor registry system in Hiroshima and Nagasaki in 1958. In the same year, biennial medical examinations of 20,000 individuals began. Follow-up studies also have been conducted on in-utero-exposed persons and first-generation offspring of the survivors. On the basis of these studies spanning nearly half a century, we know that the occurrence of leukemia and cancers associated with A-bomb radiation is higher than among the non-exposed. Among the A-bomb survivors, radiation cataracts, hyperparathyroidism, delayed growth and development, and chromosomal aberrations also occur more often. However, to date, no evidence exists of genetic effects in the children of A-bomb survivors. It should be kept in mind that such study results could never be obtained without the cooperation of A-bomb survivors.

**RP 2-75** Yamada M (C), Wong FL (S), Kodama K (C), Sasaki H (C), Shimaoka K (CN), Yamakido M (Hiroshima University School of Medicine). Longitudinal trends in total serum cholesterol levels in a Japanese cohort, 1958-1986. *Journal of Clinical Epidemiology* 1997 (April); 50(4):425-34. (*RERF Report* 3-95)

The 28-year follow-up of a Japanese cohort, having collected vast amounts of data collected on total serum cholesterol (TC), provided an exceptional opportunity to examine TC temporal trends. The longitudinal statistical method of growth-curve analysis was used to elucidate the age-related changes in TC levels and to characterize these trends in relation to sex, birth cohort, time period, place of residence, and body mass index (BMI).

Japanese TC levels at initial examination were remarkably lower than those in western countries. Dur-

ing the study period from 1958 to 1986, TC levels increased dramatically with age in both sexes. The slope of the cholesterol growth curve was steeper for women than for men, with the difference growing larger after age 40 years. Drastic changes in Japanese behavior and lifestyle especially westernization of the diet, are thought to have affected the TC values as time-period effects. As a result of this temporal change, which affected different cohorts at different ages, TC values were higher in members of the younger cohort. The increase of the TC values as time-period effects were larger in the earlier period than in the later period. These time-period effects appeared to be almost similar in men and women. The TC growth curves also varied by city of residence. Subjects in urban areas had higher TC values than subjects in rural areas. Changes associated with BMI from 1958 to 1986 were only partially responsible for the increased steepness of the TC growth curve.

**RP 1-75** Pierce DA (S, E), Shimizu Y (E), Mabuchi K (E), Preston DL (S). A quick look at Life Span Study Report 12, Part 1. Hiroshima Igaku (Journal of the Hiroshima Medical Association) 1997 (January 28); 50(1):100-2. (Japanese)

**RP 1-75** Pierce DA (S, E), Shimizu Y (E), Preston DL (S), Væth M (S), Mabuchi K (E). Response to the letter of Drs. Rossi and Zaidler. Radiation Research 1996 (November); 146(5):591-3.

**RP 1-75** Pierce DA (S), Shimizu Y (E), Preston DL (S), Væth M (University of Aarhus, Denmark), Mabuchi K (E). Response to the letter of M. P. Little. Radiation Research 1997 (October); 148(4):400-1.

**RP 1-75** Shimizu Y (E), Mabuchi K (E), Preston DL (S), Shigematsu I (D). Mortality study of atomic-bomb survivors: Implications for assessment of radiation accidents. World Health Statistics Quarterly 1996; 49(1):35-9.

**RP 24-62** Otake M (Faculty of Environmental Science and Technology [FEST], Okayama University [OU]), Schull WJ (D), Lee S (FEST/OU). Threshold for radiation-related severe mental retardation in prenatally ex-

posed A-bomb survivors: A re-analysis. International Journal of Radiation Biology 1996 (December); 70(6):755-63. (RERF Report 1-96) (J)

Significant effects on the developing human brain of exposure to ionizing radiation are seen among individuals exposed in the 8th–25th week after ovulation. These effects, particularly in the highly vulnerable period of 8–15 weeks after ovulation, manifest themselves most dramatically as an increased frequency of severe mental retardation. However, the distribution of cases of severe mental retardation suggests a threshold in the low-dose region. The 95% lower bound of the threshold in those survivors exposed 8–15 weeks after ovulation was zero for the individual data based on the simple linear model and 0.15 Gy based on the exponential linear model used in our previous report (1987), but the 95% lower bound of the threshold based on all of the data including 21 additional cases with known doses appears to be 0.05 Gy using the maximum likelihood estimates derived from an exponential-linear model. The latter model was selected because it provides the best fit from the standpoint of the stability and reasonableness of the estimates among the five models applied to the data. When two probably non-radiation-related cases of Down's syndrome are excluded from the 19 mentally retarded cases exposed 8–15 weeks post ovulation, the 95% lower bound of the threshold is in the range of 0.15–0.25 Gy based on the exponential-linear model used in 1987, but is in the range of 0.06–0.31 Gy when the more reasonable and better model applied here is used. For exposure in the 16–25-week period based on the same model, the 95% lower bound of the threshold changed from 0.25 to 0.28 Gy, both with and without inclusion of the two probable non-radiation-related mentally retarded cases; one of these cases was probably familial in origin since there was a retarded sibling, and the other due to infection, since the individual had Japanese B encephalitis at age 4 years.

**RP 2-61** Delongchamp RR (S), Mabuchi K (E), Yoshimoto Y (E), Preston DL (S). Cancer mortality among atomic-bomb survivors exposed *in utero* or as young children, October 1950–May 1992. Radiation

Research 1997 (March); 147(3):385-95. (RERF Report 7-96)

Cancer mortality for the period from October 1950 through May 1992 was analyzed in atomic-bomb survivors exposed *in utero*. Risk estimates for this group were also compared to those for survivors who were less than 6 years old at the time of exposure. The cohorts studied include 807 *in utero* survivors and 5,545 persons exposed during childhood with all members of both groups having estimated doses of at least 0.01 Sv. The comparison group includes 10,453 persons with little (<0.01 Sv) or no exposure. Analyses were limited mainly to cancer deaths occurring between the ages of 17 and 46. Only 10 cancer deaths were observed among persons exposed *in utero*. However, there is a significant dose response with an estimate of excess relative risk per sievert (ERR/Sv) of 2.1 (90% confidence interval of 0.2 to 6.0). This estimate does not differ significantly from that for survivors exposed during the first 5 years of life. The cancer deaths among those exposed *in utero* involved leukemia (2), female-specific organs (3) and digestive organs (5). Nine deaths occurred in females, where the excess risk for all solid cancers has a 90% confidence interval on the ERR/Sv of 1.6 to 17. Significant risks were found for cancers of the digestive system [90% confidence interval (CI) on the ERR/Sv of 0.7 to 20] and for female-specific cancers (90% CI on the ERR/Sv of 0.7 to 42). These risks do not differ significantly from those seen in females exposed as children. There were no deaths from solid cancer in men exposed *in utero*. The ERR/Sv has an upper 95% confidence bound of 2.5, which does not differ from that for exposed children, where the upper 95% confidence bound is 1.5. The sexes differ even when female-specific cancers are excluded from the comparison. Although there were only two leukemia deaths among those exposed *in utero*, the leukemia death rate for this group is higher than that in the comparison group ( $P = 0.054$ ) with an exposure effect that is about half the magnitude and not significantly different from that seen after childhood exposure ( $P = 0.103$ ). However, there is no evidence of a dose response among those exposed *in utero*

*Continued at top of next page*

*Continued from previous page*

because no high-dose leukemia deaths were observed, a result that differs considerably from that for those exposed as children. There is a need for caution in the interpretation of these data. First, the number of cancer deaths is small; second, there is unexplained significant difference in the mortality from solid cancer between the sexes; and third, the excess of leukemia in those exposed *in utero* is not reflected in an increasing dose response.

**RP 29-60** Tomonaga M (Atomic Disease Institute, Nagasaki University School of Medicine [NUSM]), Matsuo T (NUSM), Kimura A (Research Institute for Radiation Biology and Medicine [RIRBM], Hiroshima University [HU]), Oda K (RIRBM, HU), Kamada N (RIRBM, HU), Preston DL (S), Shimizu Y (E), Mabuchi K (E). Review of dose-dependent risk of hematopoietic disorders other than leukemia (myelodysplastic syndrome, hypoplastic anemia, etc.) in the RERF LSS cohort. FY-1996 Report of A-bomb Disease Research Teams. Tokyo: Nippon Koshueisei Kyokai (Japan Public Health Association); 1997, 39-40. **(Japanese)**

**RP 18-59**, See also **RP 16-78 Otake et al.**

**RP 18-59** Hoshi M (Research Institute for Radiation Biology and Medicine [RIRBM], Hiroshima University [HU]), Takada J (RIRBM, HU), Endo S (RIRBM, HU), Shizuma K (Faculty of Engineering [FE], HU), Iwatani K (FE, HU), Oka T (Kure University), Fujita S (S), Nagatomo T (Nara University of Education), Hasai H (Hiroshima Denki Institute of Technology). Future problems in assessment of atomic-bomb radiation dosimetry. FY-1996 Report of A-bomb Disease Research Teams. Tokyo: Nippon Koshueisei Kyokai (Japan Public Health Association); 1997, 79-80. **(Japanese)**

**RP 18-59** Watanabe T (E), Fujita S (S). Collection of exposed materials in Hiroshima (FY 1990). FY 1990 Study Reports Concerning A-bomb Diseases, Report by A-bomb Radiation Evaluation and Review Committee. Tokyo: Nippon Koshueisei Kyokai (Japan Public Health Association); 1991,

54-62. **(Japanese)**

**RP 18-59** Watanabe T (E), Fujita S (S). Collection of exposed materials in Hiroshima (FY 1992). FY 1992 Study Reports Concerning A-bomb Diseases, Report by A-bomb Radiation Evaluation and Review Committee. Tokyo: Nippon Koshueisei Kyokai (Japan Public Health Association); 1993, 38-42. **(Japanese)**

**RP 18-59** Watanabe T (E), Fujita S (S). Collection of materials exposed to atomic bomb radiation in Hiroshima and Nagasaki (FY 1996). FY 1996 Report of A-bomb Disease Research Teams. Tokyo: Nippon Koshueisei Kyokai (Japan Public Health Association); 1997, 81-3. **(Japanese)**

### ***Publications Not Emanating from Specific Protocols***

Asakawa J (G). Screening of germ cell mutation using two dimensional gel electrophoresis of DNA. Hoshasen Seibutsu Kenkyu (Radiation Biology Research Communications) 1997 (December); 32(4):357-60. **(Japanese)**

Awa AA (G). Analysis of chromosome aberrations in atomic-bomb survivors for dose assessment: Studies at the Radiation Effects Research Foundation from 1968 to 1993. Stem Cells (Radiation Injury and the Chernobyl Catastrophe) 1997; 15S2:163-73.

Exposure to ionizing radiation causes damage to living cells, especially to DNA in the cell nucleus. The degree of this cellular damage depends on the amount of radiation administered. This review discusses current findings concerning radiation-induced chromosome aberrations that were produced in 1945 and that can still be observed in the somatic cells of atomic-bomb survivors in Hiroshima and Nagasaki. The scoring methods of G-banding and fluorescence *in situ* hybridization are compared. In addition, some findings concerning chromosomal aberrations in citizens of the former Soviet Union affected by the Chernobyl accident are presented.

Awa AA (G). Rogue cells. Hoshasen Seibutsu Kenkyu (Radiation Biology Research Communications) 1997 (December); 32(4):241-56. **(Japanese)**

Cologne JB (S). Counterintuitive matching. Epidemiology 1997 (May); 8(3):227-9.

Fujita S (S), Okamoto Y (EN), Mizushima N (EN), Yamashita T (EN), Watanabe T (E). Collection of exposed materials in Nagasaki. FY-1991 Study Reports Concerning A-bomb Diseases, Report by A-bomb Radiation Evaluation and Review Committee. Tokyo: Nippon Koshueisei Kyokai (Japan Public Health Association); 1992, 30-42. **(Japanese)**

Fujita Y (E), Mabuchi K (E), Ito C (Health Management and Promotion Center, Hiroshima A-Bomb Casualty Council). Study on National Death Index (NDI). FY-1996 Report of A-bomb Disease Research Teams. Tokyo: Nippon Koshueisei Kyokai (Japan Public Health Association); 1997, 8-9. **(Japanese)**

Hirai Y (R). Amount and function of ATM protein in cell lines from AT heterozygotes. Hoshasen Seibutsu Kenkyu Radiation Biology Research Communications) 1997 (December); 32(4):351-6. **(Japanese)**

Ito M (Atomic Bomb Disease Institute [ADI], Nagasaki University School of Medicine [NUSM]), Yamashita S (ADI, NUSM), Ashizawa K (NUSM), Motomura T (NUSM), Namba H (ADI, NUSM), Hoshi M (Scientific Data Center for Atomic-Bomb Disaster, Hiroshima University), Shibata Y (EN), Sekine I (ADI, NUSM), Panasyuk GD (Gomel Specialized Medical Dispensary, Gomel, Belarus), Nagataki S (NUSM). Pediatric thyroid disease around Chernobyl: Morphological aspects of the Chernobyl Sasakawa Health and Medical Cooperation Project. In: Chernobyl: A decade. Yamashita S and Shibata Y, eds. Elsevier Science; 1997, 107-22.

Ito M (Atomic Disease Institute [ADI], Nagasaki University School of Medicine [NUSM]), Yamashita S (ADI, NUSM), Ashizawa K (NUSM), Nishikawa T (NUSM), Namba H (ADI, NUSM), Sekine I (ADI, NUSM), Hoshi M (Research Institute for Radiation Biology and Medicine, Hiroshima University), Shibata Y (EN), Nagataki S (NUSM). Childhood thyroid diseases around Chernobyl viewed from aspiration cytological biopsy. Nagasaki Igakkai Zasshi



(Nagasaki Medical Journal) 1996 (September 25); 71(Special issue):230-3. (Proceedings of the 37th Late A-bomb Effects Research Meeting, 1996). **(Japanese)**

Kimura T (Japan Chemical Analysis Center [JCAC]), Fukushima H (JCAC), Iba T (JCAC), Fujita S (S), Watanabe T (E), Maruyama T (National Institute of Radiological Sciences), Fukano S (Japan Radioisotope Association [JRA]), Hamada T (JRA). Analysis of  $^{60}\text{Co}$  in iron materials in Hiroshima. FY-1991 Study Reports Concerning A-bomb Diseases, Report by A-bomb Radiation Evaluation and Review Committee. Tokyo: Nippon Koshueisei Kyokai (Japan Public Health Association); 1992, 1-7. **(Japanese)**

Kimura T (Japan Chemical Analysis Center [JCAC]), Takano N (JCAC), Iba T (JCAC), Fujita S (S), Watanabe T (E), Maruyama T (National Institute of Radiological Sciences), Hamada T (Japan Radioisotope Association). Analysis of  $^{60}\text{Co}$  in iron materials in Hiroshima. FY-1990 Study Reports Concerning A-bomb Diseases, Report by A-bomb Radiation Evaluation and Review Committee. Tokyo: Nippon Koshueisei Kyokai (Japan Public Health Association); 1991, 1-5. **(Japanese)**

Kodama Y (G), Awa AA (G), Nakamura N (G). Biological fingerprint of high LET radiation—Related to Brenner's hypothesis. Hoshasen Seibutsu Kenkyu (Radiation Biology Research Communications) 1997 (December); 32(4):257-66. **(Japanese)**

Kosako T (Research Center for Nuclear Science and Technology, The University of Tokyo), Fujita S (S), Hamada T (Japan Radioisotope Association), Tajima E (Nuclear Safety Research Association). Database for reevaluation of A-bomb dose in Hiroshima and Nagasaki. FY 1991 Study Reports Concerning A-bomb Diseases, Report by A-bomb Radiation Evaluation and Review Committee. Tokyo: Nippon Koshueisei Kyokai (Japan Public Health Association); 1992, 43-4. **(Japanese)**

Kosako T (Research Center for Nuclear Science and Technology, University of Tokyo), Fujita S (S), Hamada T (Japan Radioisotope Association),

Tajima E (Nuclear Safety Research Association). Data base for reevaluation of A-bomb dose in Hiroshima and Nagasaki. FY-1990 Study Reports Concerning A-bomb Diseases, Report by A-bomb Radiation Evaluation and Review Committee. Tokyo: Nippon Koshueisei Kyokai (Japan Public Health Association); 1991, 63-80. **(Japanese)**

Kossenko MM (Urals Research Center for Radiation Medicine, Russian Federation [URCRM]), Degteva MO (URCRM), Vyushkova OV (URCRM), Preston DL (S), Mabuchi K (E), Kozheurov VP (URCRM). Issues in the comparison of risk estimates for the population in the Techa River region and atomic bomb survivors. Radiation Research 1997 (July); 148(1):54-63.

Plutonium production in the former Soviet Union began in 1949 at the Mayak Production Association located between the cities of Chelyabinsk and Ekaterinbourg in the southern Ural mountains about 1200 km east of Moscow. During the first few years of Mayak's operation, almost 30,000 people living on the banks of the Techa River received significant internal and external exposures as a consequence of the release of large quantities of radioactive materials from Mayak. Studies of levels of radioactive contamination and health effects in this population began in the early 1950s. A systematic follow-up of a fixed cohort that includes all people who were living in Techa River villages in 1949 was begun about 30 years ago. In this paper, we describe the Techa River cohort, outline the nature of the exposures and discuss the status of follow-up for the period from 1950 through 1989. While noting the limitations of the current epidemiological follow-up data, we also compare the demographic and mortality structure of the Techa River cohort with the Life Span Study cohort of Japanese atomic-bomb survivors. It is seen that, despite a number of limitations, the current data suggest that the risks of mortality from leukemia and other cancers increase with increasing radiation dose in the Techa River cohort. This finding suggests that, with continued improvements in the quality of the follow-up and dosimetry, the Techa River cohort has the potential to provide quantita-

tive estimates of the risks of chronic low-dose-rate radiation exposures for an unselected general population that will be an important complement to the estimates based on the Life Span Study that are used as the primary basis for numerical assessments of radiation risk.

Mori T (National Institute of Radiological Sciences), Seyama T (R). Gene analysis of malignant tumors in Thorotrast-disease patients. FY-1996 Report of A-bomb Disease Research Teams. Tokyo: Nippon Koshueisei Kyokai (Japan Public Health Association); 1997, 52-5. **(Japanese)**

Nagataki S (D), Ashizawa K (Nagasaki University School of Medicine [NUSM]), Yamashita S (Atomic Bomb Disease Institute, NUSM). Cause of childhood thyroid cancer after the Chernobyl accident. Thyroid 1998 (February); 8(2), 115-117.

Nakamura N (G). Are DNA damages by exposure to low level of radiation qualitatively similar to those occurring spontaneously? Hoshasen Seibutsu Kenkyu (Radiation Biology Research Communications) 1997 (December); 32(4):361-4. **(Japanese)**

Nakamura N (G). Biological dosimetry. Nuclear System Association, ed. Nuclear Energy and Advanced Technology [I] NSA/Commentaries: No.2. Tokyo: Japan Atomic Industrial Forum, Inc.; 1994, 63-81. **(Japanese)**

Nakamura N (G). International workshop on radiation dose reconstruction using biological dosimetry and ESR. Hiroshima Igaku (Journal of the Hiroshima Medical Association) 1997 (June); 50(6):563-2. **(Japanese)**

Nakamura N (G), Kodama Y (G), Awa AA (G). Is there a genetic instability in lymphocytes of A-bomb survivors? Hoshasen Seibutsu Kenkyu (Radiation Biology Research Communications) 1997 (December); 32(4):346-50. **(Japanese)**

Nakamura N (G), Miyazawa C (Ohu University School of Dentistry), Sawada S (Research Institute for Radiobiology and Medicine, Hiroshima University), Akiyama M (R), Awa AA (G). ESR dose estimation using tooth

*Continued at top of next page*

*Continued from previous page*

enamel from Hiroshima A-bomb survivors. III. Results of 69 survivors for correlation between stable chromosome aberration frequency and ESR signal intensity. *Journal of Radiation Research* 1995 (December); 36(4):320.

Nakano M (G), Kodama Y (G), Itoh M (G), Ohtaki K (G), Nakamura N (G). Screening of clonal chromosome aberrations in A-bomb survivors by FISH. *Hoshasen Seibutsu Kenkyu (Radiation Biology Research Communications)* 1997 (December); 32(4):341-5. **(Japanese)**

Nakashima E (S). Analysis of extra-trinomial data from developmental toxicity experiments using estimating equations. *Japanese Journal of Biometrics* 1996; 17(1):1-13.

For the analysis of data from developmental toxicity experiments that exhibits overdispersion, the beta-binomial model (Williams 1975) or the Dirichlet-multinomial model, an extension of the beta-binomial model, (Chen et al. 1991), is often used. However, investigations of these models suggest that when heterogeneous intra-litter correlations are incorrectly modeled as homogeneous, the mean parameter estimates become biased (Kupper et al. 1986). Further, even if the intra-litter correlation is correctly modeled, problems of bias of the parameter estimate and coverage probability of the parameter (e.g. coverage probability of 95% confidence band) still exist (Liang and Hanfelt 1994). Liang and Hanfelt (1994) recommended the use of quasi-likelihood method for the inference instead of the beta-binomial maximum likelihood method.

In this paper, two methods of analysis of extra-trinomial data using estimating equations are proposed. One is the quasiliquelihood/pseudolikelihood estimating equation method proposed by Carroll and Ruppert (1982) and Breslow (1989), which is also seen as a generalized estimating equations method, and the other is the quasiliquelihood/method of moments proposed by Williams (1982). From the results of White (1982), the parameter estimates are consistent when the mean model is correctly specified and the robust variance estimates of the parameter estimates can be calculated. An example

of analysis using data from teratological experiments is given.

Nakashima E (S). Some methods for estimation in a negative-binomial model. *Annals of the Institute of Statistical Mathematics* 1997; 49(1):101-15. **(RERF Report 10-96)**

To clarify the advantage of using the quasiliquelihood method, lack of robustness of the maximum likelihood method was demonstrated for the negative-binomial model. Efficiency calculations of the method of moments and the pseudolikelihood method in the estimation of extra-Poisson parameters in a negative-binomial model were carried out. Especially when the overdispersion parameter is small, both methods are relatively highly efficient and the pseudolikelihood estimate is more efficient than the method of moments estimate. Two examples of the quasiliquelihood analyses of count data with overdispersion are given. The bootstrap method also is applied to the data to illustrate the advantage of the method of moments or pseudolikelihood method in the estimation of the standard errors of the mean parameter estimates under the negative-binomial model.

Okajima S (Nagasaki University), Okamoto Y (EN), Yamashita T (EN), Watanabe T (E). Collection of exposed materials in Nagasaki. FY-1990 Study Reports Concerning A-bomb Diseases, Report by A-bomb Radiation Evaluation and Review Committee. Tokyo: Nippon Koshueisei Kyokai (Japan Public Health Association); 1991, 43-53. **(Japanese)**

Pierce DA (S), Preston DL (S). On: 'No evidence for increased tumor rates below 200 mSv in the atomic bomb survivors' data'. *Radiation and Environmental Biophysics* 1997 September; 36:209-10.

Satoh C (G), Kodaira M (G), Asakawa J (G), Takahashi N (G), Kuick R (University of Michigan School of Medicine, USA [UMSM]), Hanash (UMSM), Neel JV (UMSM). Techniques for detecting the genetic effects of the atomic bombings applicable to the study of the genetic effects of natural radiation. Wei L, Sugahara T, Tao Z, eds. *High Levels of Natural Radiation 1996—Radiation Dose and*

*Health Effects*. Amsterdam: Elsevier Science Publishers BV; 1997, 385-90. (Proceedings of the Fourth International Conference on High Levels of Natural Radiation, Beijing, China, 21-25 October 1996).

Shibata J (Hiroshima Prefectural Medical Association [HPMA]), Ota N (Hiroshima Red Cross and A-Bomb Hospital), Sasaki H (Health Management and Promotion Center, Hiroshima A-Bomb Casualty Council), Neriishi K (C), Hirabayashi N (Research Institute for Radiation Biology and Medicine, Hiroshima University), Watanabe T (E), Okada K (Hiroshima Prefecture), Ide Y (Hiroshima City), Onizawa M (Ministry of Health and Welfare), Fukuhara T (HPMA). Report on the results of the tenth medical examination of atomic-bomb survivors resident in North America. *Hiroshima Igaku (Journal of the Hiroshima Medical Association)* 1996 (January); 49(1):5-41. **(J)**

Yamakido M (Hiroshima University [HU]), Dohy H (Hiroshima Prefectural Medical Association [HPMA]), Neriishi K (C), Nobuyoshi M (C), Sawamura A (Research Institute for Radiation Biology and Medicine, HU), Kataoka T (HU Hospital), Sanada M (HU Hospital), Kawamoto H (Hiroshima Municipal Hospital [HMH]), Kataoka M (Health Management and Promotion Center, Hiroshima A-bomb Casualty Council), Masui H (HMH), Watanabe T (RERF Secretariat (ISec)), Shiba N (Sec), Morino K (Hiroshima Prefecture), Hirata M (Hiroshima City), Kazama N (Ministry of Health and Welfare), Fukuhara T (HPMA). Report on the results of the eleventh medical examination of atomic-bomb survivors resident in North America. *Hiroshima Igaku (Journal of the Hiroshima Medical Association)* 1998 (January); 51(1):5-31. **(J)□**

### **RERF Publications**

Comments and recommendations (abstract) of the 23rd RERF Scientific Councilors Meeting. *Hiroshima Igaku (Journal of the Hiroshima Medical Association)* 1997 (March); 50(3):286-8. **(Japanese)**

Comments and recommendations of the 22nd RERF Scientific Councilors

Meeting. Hiroshima Igaku (Journal of the Hiroshima Medical Association) 1995 (September); 48(9):1024-9. (Japanese)

Report of the Blue Ribbon Panel. Hiroshima Igaku (Journal of the Hiroshima Medical Association) 1996 (Sept.); 49(9):1243-4. (Japanese)

RERF bibliography of publications, 1995. Hiroshima Igaku (Journal of the Hiroshima Medical Association) 1996 (July); 49(7):1000-2. (Japanese)

RERF bibliography of publications, 1996. Hiroshima Igaku (Journal of the Hiroshima Medical Association) 1997 July; 50(7):699-701. (Japanese)

RERF directors, supervisors, and scientific councilors (as of August 1997). Hiroshima Igaku (Journal of the Hiroshima Medical Association) 1997 (September); 50(9):868. (Japanese)

RERF directors, supervisors, and scientific councilors (as of September 1995). Hiroshima Igaku (Journal of the Hiroshima Medical Association) 1995 (November); 48(11):1213. (Japanese)

### Commentary and Review Series

Mendelsohn ML, A simple reductionist model for cancer risk in atom-bomb survivors. Hoshasen Seibutsu Kenkyu (Radiation Biology Research Communications) 1998 (January); 33(1):12-24. (Japanese) (Commentary and Review Series 1-96) (Note: This was originally published in English in National Institute of Radiological Sciences Symposium Series Number 26.)

### Publications Using RERF Data

Hoel DG (National Institute of Environmental Health Sciences [NIEHS], USA), Dinse GE (NIEHS). Using mortality data to estimate radiation effects on breast cancer incidence. Environmental Health Perspectives 1990 July; 87:123-9.

Huffer FW (The Florida State University [FSU], USA), McKeague IW (FSU). Survival analysis using additive risk models. Florida State University Technical Report No. M-756

and U.S. Army Research Office Technical Report No. D-96, April 1987.

Kottbauer MM (Atomic Institute, University of Austria, [AIAus]), Fleck CM (AIAus), Schollnberger H (AIAus). A recalculation of the age-dependent dose-effect relationship of the Life Span Study of Hiroshima and Nagasaki. In: 1996 International Congress on Radiation Protection, Proceedings/Volume 4. Vienna, Austria, International Radiation Protection Association 1996, pp.143-5. (Proceedings of the Ninth International Congress of the International Radiation Protection Association, Vienna, Austria, 14-19 April 1996).

Kottbauer MM (AIAus), Fleck CM, Schollnberger H (AIAus). A recalculation of the dose-effect relationship of the 'Life Span Study' of Hiroshima and Nagasaki with the 'Single-Hit Model' [with summary in English]. In: Radiobiology and Radioprotection (Modern Development and Tendency of Radiobiology). Heinemann G and Pfoh H, eds. Austria, Scientific Committee on Radiation Protection 1996, 120-4. (Proceedings of the 28th Anniversary Meeting of the Scientific Committee Members on Radioprotection Associated with the Research Field of Radiation Effects/Radiobiology within the GAST Committee, Hanover, 23-25 October, 1996). (German)

Little MP (National Radiological Protection Board, UK [NRPB]). Are two mutations sufficient to cause cancer? Some generalizations of the two-mutation model of carcinogenesis of Moolgavkar, Venzon, and Knudson, and of the multistage model of Armitage and Doll. Biometrics 1995 December; 51(4):1278-91.

Little MP (NRPB). Generalisations of the two-mutation and classical multistage models of carcinogenesis fitted to the Japanese atomic bomb survivor data. Journal of Radiological Protection 1996; 16(1):7-24.

Little MP (NRPB). The projection of cancer and overall mortality rates in extreme old age and their impact on population cancer risks. Journal of Radiological Protection 1996; 16(3):153-66.

Little MP (NRPB). Are two mutations sufficient to cause cancer? Modelling radiation-induced cancer in the Japa-

nese atomic bomb survivors using generalizations of the two-mutation model of Moolgavkar, Venzon and Knudson and of the multi-stage model of Armitage and Doll. In: Health Effects of Low Dose Radiation: Challenges of the 21st Century. London: Thomas Telford Services Ltd. 1997, 169-74. (Proceedings of the conference organized by the British Nuclear Energy Society, Stratford-upon-Avon, UK, 11-14 May 1997).

Little MP (NRPB). Comments on the article "Studies of the mortality of atomic bomb survivors. Report 12, Part I. Cancer: 1950-1990" by DA Pierce, Y Shimizu, DL Preston, M Væth and K Mabuchi (Radiation Research 1996 July; 146(1):1-27) (Letters to the editor). Radiation Research 1997 (October); 148(4):399-401.

Little MP (NRPB). Estimates of neutron relative biological effectiveness derived from the Japanese atomic-bomb survivors. International Journal of Radiation Biology 1997 (December); 72(6):715-26.

Little MP (NRPB), Charles MW (School of Physics and Space Research, University of Birmingham, UK [SPSR]). The risk of non-melanoma skin cancer incidence in the Japanese atomic-bomb survivors. International Journal of Radiation Biology 1997 (May); 71(5):589-602.

Little MP (NRPB), Charles MW (SPSR), Hopewell JW (Research Institute, University of Oxford, Churchill Hospital), Mayall A (NRPB), Lloyd DC (NRPB), Edwards AA (NRPB), Sharp C (NRPB), Cooper JR (NRPB). Assessment of skin doses. Documents of the NRPB Vol. 8, No. 3. Chilton, Didcot, Oxon, UK: National Radiological Protection Board 1997, 43 pp.

Little MP (NRPB), de Vathaire F (Gustave Roussy Institute, France), Charles MW (SPSR), Hawkins MM (Childhood Cancer Research Group, UK), Muirhead CR (NRPB). Variations with time and age in the relative risks of solid cancer incidence after radiation exposure. Journal of Radiological Protection 1997; 17:159-77.

Little MP (NRPB), Muirhead CR (NRPB). Evidence for curvilinearity  
*Continued at top of next page*

## 32 Publications, Board Meeting, Workshop

*Continued from previous page*

in the cancer incidence dose-response in the Japanese atomic-bomb survivors. *International Journal of Radiation Biology* 1996 (July); 70(1):83-94.

Little MP (National Radiological Protection Board [NRPB]), Muirhead CR (NRPB). Curvilinearity in the dose-response curve for cancer in Japanese atomic bomb survivors. *Environmental Health Perspectives* 1997 (December); 105(Suppl 6):1505-9.

Little MP (NRPB), Muirhead CR (NRPB), Boice JD (Radiation Epidemiology Branch [REB], National Cancer Institute [NCI], USA), Kleinerman RA (REB/NCI). Using multistage models to describe radiation-induced leukaemia. *Journal of Radiological Protection* 1995; 15(4):315-34.

Little MP (NRPB), Wakeford R (British Nuclear Fuels PLC, UK), Charles MW (SPSR), Anderson M (Danish Cancer Society, Denmark). A comparison of the risks of leukaemia and non-Hodgkin's lymphoma in the first generation offspring ( $F_1$ ) of the Danish Thorotrast patients with those observed in other studies of parental pre-conception irradiation. *Journal of Radiological Protection* 1996; 16(1):25-36.

McKeague IW (FSU). Regression analysis for grouped survival data using additive risk models. *International Statistical Institute Satellite Meeting, Kyoto, 3-5 September 1987.*

Mine M (Scientific Data Center for the A-bomb Disaster [SDCAD], Nagasaki University School of Medicine [NUSM]), Okumura Y (Atomic Disease Institute, NUSM), Honda S (SDCAD, NUSM), Kondo H (SDCAD, NUSM), Yokota K (SDCAD, NUSM), Tomonaga M (SDCAD, NUSM). Mortality of A-bomb survivors in RERF population. *Nagasaki Igakkai Zasshi [Nagasaki Medical Journal]* 1996 September 25; 71(Special Issue):309-12. (Proceeding of the 37th Late A-bomb Effects Research Meeting, 1996). (**Japanese**)

Thomas DC (University of Southern California, USA). A model for dose rate and duration of exposure effects in radiation carcinogenesis. *Environmental Health Perspectives* 1990 July; 87:163-71.□

**Board Meeting** *continued from page 9*

An important change in financial policy was discussed after Dr. Hiroshi Maruyama of the Japanese Ministry of Health and Welfare (MHW) reported that as a result of MHW talks with the US Department of Energy (DOE) following the BRP report, the two governments had decided that the Japanese government would bear the costs of the Adult Health Study and the ongoing  $F_1$  studies as a part of atomic-bomb survivors' relief measures. Additionally, it was reported that the US National Academy of Sciences (NAS) expenses paid by DOE are now to be included in the US-Japan equal-sharing system. The result of these two changes is that Japan's subsidy has increased while that of the US has decreased. To implement these changes, two conditions were imposed by the Japanese Ministry of Finance to which the DOE agreed, that RERF will continue to streamline its operations to reduce staff and that US directors be reduced from two to one.

Budget proposals for Japanese fiscal year 1997 and 1998 were approved. The new US-Japanese cost-sharing formula significantly improved the budget outlook for both years so that no major budgetary problems are expected. Reduction in the total number of nonprofessional staff will continue during 1997 and 1998. There is no plan to reduce the professional research staff, and if suitable candidates can be found, the research staff may increase.

The retirement after 16 years of Chairman Itsuzo Shigematsu and the appointment of Dr. Shigenobu Nagataki as his successor were approved effective 30 June 1997. Dr. Sheldon Wolff's term as director was renewed, and although Dr. William Schull had retired in January 1997, it was agreed that in accordance with the Act of Endowment, he would perform the official duties of permanent director until a successor assumes office. A candidate to succeed Dr. Nagataki in the position of permanent director was identified, and it was agreed that a mail ballot would be taken later. This position was assumed by Senjun Taira after the formal balloting was completed in July 1997.

Mr. Kazumasa Kunitoshi of the Chugoku Regional Finance Bureau was appointed Chief of the Secretariat as successor to Mr. Yasukiyo Hirano,

who retired at the end of June.

It was agreed that the next Board meeting should be held in Hiroshima on 17 to 19 June 1998.□

**Workshop** *continued from page 13*

*tation Hygiene; United States:* A. C. Bouville, *National Institutes of Health*; E. Haskell and T. Straume, *University of Utah*; and J. Zimbrick, *Purdue University*; and **Germany:** P. Jacob, *GSF (Forschungszentrum für Umwelt und Gesundheit)*.□

*This 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 its Ministry of Health and Welfare and that 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 Policy**

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

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

### **Editorial Staff**

Editor-in-Chief: *Sheldon Wolff*  
Editorial Committee: *Akio Awa, Donald Pierce, Yoshisada Shibata*  
Editorial Consultant: *Seymour Abrahamson*  
Managing Editor: *Rosalyn Vu*  
Proofreaders: *Kimiko Ono, Fumie Maruyama*  
Production Assistant: *Tomoe Sugiyama*  
Photographer: *Kiyoko Yamayoshi*  
Printer: *Sanko, Inc.*

### **Mailing Address**

*RERF Update*  
5-2 Hijiyama Park  
Minami-ku, Hiroshima-shi  
732-0815 Japan

### **Facsimile**

81-82-261-3197 or 81-82-263-7279

### **Internet Address**

*General inquiries and reprint requests:*  
pub-info@rerf.or.jp

### **RERF World Wide Web Site**

*Various portions of this newsletter may be found on the RERF World Wide Web site at: <http://www.rerf.or.jp>*