RERF update RERF

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

Volume 7, Issue 2 Hiroshima & Nagasaki Summer 1995

Summer 1995 Marked by Commemorations

This summer brought two milestones: the 50th anniversary of the atomic bombings of Hiroshima and Nagasaki and the 20th anniversary of the establishment of the binational Radiation Effects Research Foundation (RERF).

Annual solemn observations held in atomic-bombed cities

An estimated combined total of 90,000 persons made the annual pilgrimages to the municipal parks located near the hypocenters of Hiroshima and Nagasaki on 6 and 9 August, respectively. In each city, the mayors spoke in remembrance of those who perished after the bombings and called for the abolition of nuclear weapons. Japanese Prime Minister **Tomiichi Murayama** attended both ceremonies.

Representing RERF at the Hiroshima event were Chairman **Itsuzo Shigematsu** and Permanent Director **Donald Harkness**. In Nagasaki, Permanent Directors **Yutaka Hasegawa** and Harkness and Nagasaki Laboratory Chief of Administration **Tadashi Nakaoka** attended.

RERF begins third decade

In late June, when the RERF Board of Directors convened, present and past employees of RERF's laboratories gathered in each city to celebrate 2 decades as the sole Japan–US research institute. The preceding US-funded entity, the Atomic Bomb Casualty Commission, had conducted research from 1947 through March 1975, in cooperation with the Japanese National Institute of Health.

Representatives of RERF's two funding agencies, the Japanese Ministry of Health and Welfare (MHW) and the US Department of Energy (DOE), spoke at the convocations.

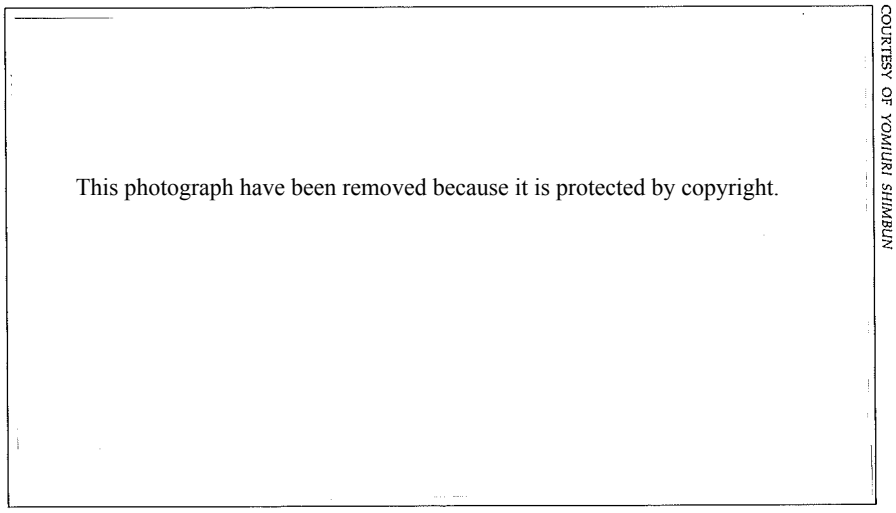
"The DOE is pledged to its original commitment to follow the bomb survivors," said **Paul J Seligman**, DOE deputy assistant secretary for health studies, in his address. (See page 3 for the full text of the opening remarks from the DOE and MHW.)

Akihito Matsumura, director-general, MHW Health Service Bureau, remarked: "We are proud that the information accumulated at RERF receives high evaluation worldwide. I would like to express my heartfelt appreciation for the efforts made so far."

Alluding to the funding difficulties faced by RERF as a result of the high value of the yen in relation to the US dollar and the Congressional budget cutting taking place in Washington, DC, a spokesman for **Manso Hamamoto**, then the Japanese Minister of Labor, said: "The situation surrounding RERF is harsh, but I believe that its 'legalization' [see the Matsumura speech on page 3] will make the basis for its existence more stable and sound. I am therefore confident that the crisis will most certainly be overcome in the near future by the efforts of the Japanese and American authorities concerned."

Also attending the ceremony were **John Zimbrick, Catherine Berkley,** and **David Williams,** who represented the US National Academy of Sciences.

Special lectures by RERF visiting directors were as follows: **Warren K Sinclair**—"The international role of RERF," and **Toshiyuki Kumatori**—"A retrospective look at the 50 years after the atomic bombings." ❑



COURTESY OF *YOMIURI SHIMBUN*

Above, in Hiroshima on the evening of 6 August in conjunction with commemorative activities, lighted paper lanterns are floated on the Motoyasu River, in keeping with the Buddhist custom of guiding the ancestral spirits safely back to the land of the dead during the summer festival known as* Bon.** ***The preserved ruins of the former Prefectural Commercial Exhibition Hall can be seen in the background.

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Perspectives

Airing a Few Thoughts about the Recent Past

by Donald Harkness,* RERF Update *Editor in Chief

The events of the past 10 months related to the efforts of the Department of Energy (DOE) to replace the National Academy of Sciences (NAS) as contractee for RERF have, at best, been enervating and, at worst, destructive to the research productivity at RERF. An enormous expenditure of time, energy, and emotion was invested by the senior research staff to thwart the intent of DOE. Happily, the plan to transfer the contract to a university has been abandoned, at least for the next 2 1/2 years, while awaiting the constitution, deliberation, and report of a multinational "blue ribbon" committee charged with reviewing RERF's research accomplishments and formulating recommendations and priorities for future research.

To be sure, much can happen in 2 1/2 years. The Presidential administration may change and with it, many faces at DOE. Or the responsible persons at DOE might abandon the plan to replace NAS, considering the broadly-based, strong objections from the international scientific community. The US responsibility for funding RERF might be transferred to another agency if DOE were to be abolished or for other reasons. My prediction is that as long as US dollars flow to RERF through an intermediary, NAS will bear that responsibility.

Issues often are not entirely what they seem or are made to seem. DOE never satisfactorily nor convincingly explained its reasons for replacing NAS though several were advanced. Almost certainly, contributing factors were the intense budgetary pressures created by the strong yen, as well as long-standing animosities between persons responsible for the RERF program at DOE and NAS. Senior officials of both organizations were remiss in not recognizing and correcting the latter situation long before that was finally accomplished. For that matter, the confrontational mode that has prevailed in the relationships between DOE and NAS and between DOE and RERF have been counterproductive and stand in marked contrast to those on the Japanese side between RERF and the Ministry of Health and Welfare.

When threatened by a change in the US administrator, the RERF department chiefs and other senior scientists took the "high road," claiming that DOE was attempting to manage or otherwise influence their research—the mere suggestion of that happening supposedly capable of destroying the credibility of all RERF research. That is rather hard to imagine since the data on which our major epidemiologic findings are based are made available to any who request them. However, the issues were complex for the department chiefs since they also must have been concerned that any change from the status quo might lead to loss of some of their autonomy.

Also it was stated repeatedly to the press that the survivors would stop cooperating with RERF if NAS no longer served as buffer between DOE and RERF. This argument is patently bogus. I daresay that the vast majority of our study participants are totally unaware of the existence of NAS, let alone its participation at RERF. In fact, that argument is ironical. NAS was much more involved here in the days of the Atomic Bomb Casualty Commission (ABCC) than it is today. For the last 6 months, as the 50th anniversary of the bombings approached, we were subjected to almost daily reminders in local news reports of the troubled and complex relationship ABCC had with the public. So it could be argued, though somewhat facetiously, that the knowledge that NAS is still the buffer might have the opposite effect and drive participants away. The whole issue is somewhat spurious since I am not convinced that, after 48 years, a buffer is needed any longer at all.

Many were overjoyed that the US Senate Committee on Appropriations wrote into the DOE appropriations bill for the Environmental, Safety and Health Program, which funds RERF, wording that directs the DOE Secretary to keep the relationship between NAS and RERF intact. Although seemingly to our advantage in this instance, I suspect that such micromanagement by Congress would be disadvantageous most of the time. Even this time, it might prove to be the latter for this directive resulted from effective lobbying efforts and likely will not be taken kindly at DOE.

One question that needs further airing is whether RERF is a suitable site for predoctoral and postdoctoral training. RERF is, for the most part, limited to conducting research that relates directly to long-term biological effects of radiation from the atomic bombings. Consequently, a student or trainee would have little opportunity to develop an independent project, and much of the work, of necessity, concerns data collected over many years. Furthermore, our scientific staff is limited in number, and those few with experience supervising the work of trainees already are overburdened. To be a successful training location, the addition to the staff of one or two experienced academic scientists would have to be strongly considered.

At first blush it may appear that not much was accomplished by the recent controversy. However, the groundwork may have been laid for finally solving the two major problems facing RERF: the absence of a long-range plan and an insufficient budget. The recommendations of the blue ribbon committee will very likely start the process of planning and, at the same time, offer the opportunities for the two governments to renegotiate the 50:50 cost sharing. Furthermore, in the future DOE will almost certainly be more circumspect about unilaterally dictating changes to this binational foundation. NAS has received a wake-up call and is establishing a committee to consider how better it can fulfill its role. Finally, everyone at RERF is now fully aware that the status quo will not be maintained indefinitely. I cannot help but believe that by removal of the current uncertainties about our future, RERF will become a stronger, more productive, and healthier organization. Even so, the other limitations mentioned above exist.

With this said, I pass the baton as chief of research and editor of *RERF Update* back to the able hands of Seymour Abrahamson, who only 12 event-filled months ago had handed it to me. I wish him and all at RERF great success in the coming months. *Gambatte*! ❑

RERF's 20th Anniversary Commemoration

Opening Remarks on Behalf of the US Department of Energy

by Paul J Seligman, Deputy Assistant Secretary for Health Studies

My colleagues and I are honored to be here in the beautiful cities of Hiroshima and Nagasaki to mark the 20th anniversary of the Radiation Effects Research Foundation (RERF).

On behalf of the United States Government and Secretary of Energy Hazel O'Leary, I would like to thank the atomic-bomb survivors, their children, and other participants for the unselfish cooperation they have extended over the past 20 years to the RERF and during the years before to its predecessor, the Atomic Bomb Casualty Commission (ABCC).

The US has provided continuous, steady support for this enterprise since its inception: first for 28 years as the ABCC and since 1975 as the RERF. Since 1975, the RERF has been truly a binational organization shared equally in terms of scientific direction, management, and financial support.

The last 20 years have seen a maturation of the RERF into the premier institute in the world for epidemiologic studies and science related to radiation health effects. Scientific results from RERF research have engendered worldwide interest and respect, contributed uniquely to the science of the effects of ionizing radiation, and form the basis of radiation protection standards worldwide.

On behalf of the many American directors, scientific councilors, and staff scientists who have served at the RERF and the ABCC, under the capable and steady hand of the National Academy of Sciences, as well as the scientists and administrators in the US who have contributed to the work, I would like to thank the Japanese scientists for the opportunity of working with you over the past 5 decades. It is a sustained working relationship built on mutual trust and admiration, sharing and genuine caring that is unique in the annals of science and mankind.

The US Department of Energy (DOE) remains deeply committed to continuation of RERF. We believe that the RERF still has significant contributions to make to science. Recent studies of late-term effects confirm the continued importance of this research.

The DOE is pledged to its original commitment to follow the bomb survivors. The RERF studies will be valuable for many years to come. The majority of the A-bomb survivors are still alive, and further data will provide reliable estimates of lifetime risk. The RERF data also provides a basis for the development of studies on other populations, such as those in the former Soviet Union. The collection and storage of blood and tissue samples from the A-bomb survivors provides research material that can be used by succeeding generations as new techniques are developed for the assessment of radiation damage. The melding of sophisticated techniques of molecular biology with the epidemiologic data is already in progress.

On behalf of the DOE, I would also like to extend our gratitude to the Ministry of Health and Welfare (MHW) for their continuing partnership as stewards of the RERF. I would personally like to thank Dr Akihito Matsumura for his willingness to work with the DOE to ensure continued sustenance for the RERF. We look forward to continuing our relationship with MHW.

While others are in a unique position to enumerate the specific accomplishments of the RERF, I would like to offer a heartfelt acknowledgment of the contributions of one man, Dr Itsuzo Shigematsu. If simple praise is in fact the highest praise, then simply, "Thank you, Dr Shigematsu," on behalf of the US Government and the countless numbers of radiation workers, patients, and survivors who have benefited from your personal commitment to the research at the RERF.

As Dr Shigematsu wisely observed at the occasion of the 10th anniversary of the RERF, the 20th anniversary also should provide a good opportunity to reflect upon the past and to make plans for greater contributions in the future. This anniversary marks an important day in the history of radiation science. Thank you for the privilege to be here with you, and congratulations to everyone who has made the RERF an international treasure. ❑

On behalf of the Ministry of Health and Welfare

by Akihito Matsumura, Director-General, Health Service Bureau

I would like to say a few congratulatory words on the 20th anniversary of the establishment of the Radiation Effects Research Foundation (RERF).

For 20 years since RERF's establishment as a US–Japan joint research organization in April 1975, the foundation's achievements have been remarkable due to the efforts of the staff in Hiroshima and Nagasaki and those concerned at the US Department of Energy and the National Academy of Sciences.

We are proud that the information accumulated at RERF receives high evaluation worldwide. I would like to express my heartfelt appreciation for the efforts made so far.

For the atomic-bomb (A-bomb) survivors, the government provides medical treatment and allowances based on two A-bomb–related laws. In December 1994, the previous two A-bomb–related laws were integrated into one to improve and make more comprehensive the measures for their health, medical treatment, and welfare. Thus, a law concerning the relief of A-bomb survivors was established, and it will be effective as of 1 July 1995.

Under this law, the government must promote research on the physical effects of A-bomb radiation and the treatment of diseases. It is essential that research studies on the effects of A-bomb radiation on man be steadily promoted to improve the comprehensive relief measures for A-bomb survivors.

As this year marks the 50th year after the atomic bombings and the 20th anniversary of the establishment of RERF, I hope the entire staff of RERF will engage itself in these important projects with renewed resolution. Also, I strongly hope that the US and Japanese directors, scientists, and other staff will cooperate with each other and realize further research achievements through mutual good faith and trust. ❑

Growth and Epilation of Human Hair in the Severe Combined Immunodeficient Mouse

Using an in vivo experimental model for human radiation exposure offers opportunities to understand the processes of radiation-induced pathogenesis.

by Seishi Kyoizumi, Department of Radiobiology, RERF

In 1988, J M McCune and his colleagues at Stanford University succeeded in implanting functional human fetal hematolymphoid organs, including thymus and lymph node tissues, into the severe combined immunodeficient (SCID) mouse (McCune et al, *Science* 241:1632–9, 1988). When I read that article, an idea came to me: SCID mice implanted with human tissues (referred to as SCID-hu mice) could be irradiated with any sources and doses of radiation and thus serve as a suitable in vivo experimental model for human radiation exposure.

Although acute and late radiation effects have been documented in the atomic-bomb (A-bomb) survivors and persons exposed in radiation accidents, such information is limited by imprecise dose estimates and difficulty in obtaining biological samples for directly analyzing the process of radiation-induced pathogenesis. As a result, it has been difficult to achieve meaningful risk estimates.

In 1989, with these issues in mind, I spent a 2-year sabbatical leave at SyStemix Inc in Palo Alto, Calif, where Dr McCune was working. There I devised a SCID-hu mouse model for the radiobiological study of human hematopoiesis (Kyoizumi et al, *Blood* 79:1704–11, 1992; *Blood* 81:1479–88, 1993; *Radiat Res* 137:76–83, 1994). After returning to RERF in 1992, my colleagues and I have continued to explore the application of SCID-hu mice to human radiation-risk analyses from various points of view. Here, I will introduce briefly a SCID-hu skin model for the study of radiation-induced human epilation.

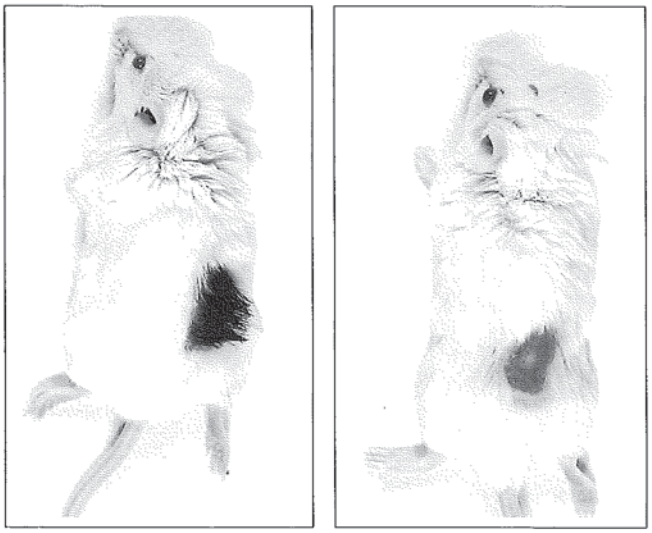

Figure 1. Left panel: a severe combined immunodeficient mouse implanted with human scalp tissue. Right panel: the human hair epilated 3 weeks after exposure to 6 Gy of X rays.

The SCID-hu mouse model for human epilation

Although epilation has long been recognized as one of the acute symptoms of ionizing radiation exposure, little is known about its dose response and mechanisms. By engrafting human skin tissue into SCID mice, we have developed an experimental model for radiation-induced epilation in humans. Skin tissue obtained from the head of a fetus who had died of malformation was engrafted onto the backs of SCID mice. The hair fell off several months after engraftment, but grew again and continued to grow for more than 1 year. About 5 months after engraftment, the skin grafts were locally irradiated with various doses of X rays. In the second week after irradiation, epilation was observed in the heavily irradiated group (exposed to ≥ 3 Gy). In the third week, no epilation was observed up to doses of 1 Gy, and the epilation rate (the proportion of fallen hairs per unit area) was found to steeply increase at 2–3 Gy. More than half of the hair fell off after irradiation with X rays at ≥ 3 Gy, and only less than 10% of the hair survived at 6 Gy (Figure 1). This is similar to the dose response for severe epilation reported in a previous study based on interviews with A-bomb survivors (DO Stram and S Mizuno, *Radiat Res* 117:93–113, 1989), supporting the

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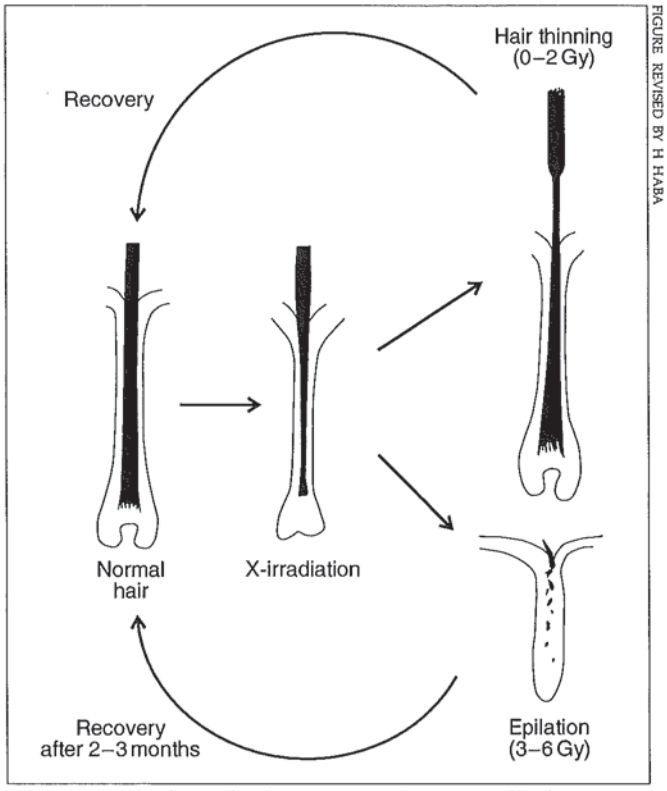

Figure 2. The hypothetical mechanism of radiation-induced human epilation.

News Briefs

✓ DOE Plan to Replace NAS Deferred for 2 Years

On 28 June, US Department of Energy Deputy Assistant Secretary for Health Studies **Paul J Seligman** announced in Hiroshima that the DOE would defer for 2 years its plans to transfer management of RERF from the US National Academy of Sciences to an American university. In the meantime, the DOE and its Japanese counterpart, the Ministry of Health and Welfare, will organize a "blue ribbon" committee of distinguished scientists to evaluate research findings and recommend priorities for future research.

✓ Scientific Council Convened in April

The 22nd meeting of the RERF Scientific Council was held 19–22 April at the Hiroshima Laboratory.

Attending members were **Tomio Hirohata**, Kyushu University; **Eisei Ishikawa**, Jikeikai University; **Hiromichi Matsudaira,** National Institute of Radiological Sciences; **Ei Matsunaga**, National Institute of Genetics; **Shigefumi Okada**, Tokyo University; **Curtis C Harris**, National Cancer Institute; **Clark W Heath Jr**, American Cancer Society; **Leonard A Herzenberg**, Stanford University; **John B Little**, Harvard University; and **Arno G Motulsky**, University of Washington. Ishikawa, Matsudaira, Matsunaga, Herzenberg, and Motulsky were reappointed as councilors.

See the centerfold supplement in this issue of *RERF Update* for the recommendations of the 1995 Scientific Council.

✓ Board of Directors Met in June

The 29th meeting of the RERF Board of Directors was held 26–28 June at the Hiroshima Laboratory.

In addition to the four permanent directors, attending Board members were **Kazuaki Arichi**, Japan Institute of International Affairs; **Toshiyuki Kumatori**, Radiation Effects Association; **Seymour Jablon**, US National Cancer Institute; **Warren K Sinclair**, US National Council on Radiation Protection and Measurements; and **Joseph E Rall**, US National Institutes of Health. Elected to replace Rall was **Patricia A Buffler**, who is dean of the School of Public Health, University of California, Berkeley. Elected to replace **Teruhiko Saburi**, Japan Health Enterprise Foundation (who was absent from the meeting), was **Masumi Oike**, who is permanent director, National Social Insurance Societies Association. Arichi, Kumatori, Jablon, and Sinclair were elected to another term as visiting directors.

✓ Departmental Restructuring Announced

In July, the RERF Hiroshima Laboratory's Department of Epidemiologic Pathology merged with the Department of Epidemiology. At the Nagasaki Laboratory, the Department of Epidemiologic Pathology merged with the Department of Epidemiology and Biostatistics. The newly restructured departments of Epidemiology each now include a Tumor and Tissue Registry Office and a Laboratory of Pathology.

✓ Hiroshima Laboratory Opened to the Public

The Hiroshima Laboratory was open to the public on Saturday, 5 August, for the first time. More than 800 persons of all ages wandered freely through the facilities, visiting scientific labs and support-service offices.

✓ Research Staff News

Seymour Abrahamson, professor of zoology at the University of Wisconsin, returned to RERF on 23 August to serve as permanent director and vice chairman for 6 months.

Akio Awa, associate chief of research, retired on 30 June. He will serve as a consultant to RERF until 31 December.

Hiroshima

Department of Radiobiology: **Mitoshi Akiyama**, chief, will begin a sabbatical leave at the Fred Hutchinson Cancer Research Center in Seattle, Washington, in mid-September.

Department of Clinical Studies: **Shizuyo Kusumi**, assistant chief, resigned on 1 August to become vice director, Radiological Epidemiology Investigation Center, Radiation Effects Association, Tokyo.

Nagasaki

Department of Clinical Studies: On 2 June, **Tomoko Nishikawa** was appointed acting chief, Division of Clinical Laboratories, and concurrently industrial health physician and research scientist, Division of Medicine. ❑

Epilation in the SCID Mouse

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validity of this SCID-hu mouse model.

The human hairs picked from the SCID-hu mice in the third and fourth week after irradiation were observed under a microscope. The hairs that fell off in the third week after high-dose irradiation (≥3 Gy) became thinner towards the roots and looked like the tips of needles. The histology of these damaged hair follicles showed that the bulb-like structure of normal hair had disappeared almost completely, and only the epithelial-like structure had survived. In the fourth week, the hairs surviving various doses of X-irradiation were clearly thin in the middle part and recovered gradually towards the root. The minimum diameter at the thinnest point of the hairs decreased dose-dependently with X-irradiation up to 3 Gy, and the mean diameter of the surviving hairs at 3 Gy was about 20 μm. These results suggest that the diameter of the hair decreases with radiation exposure, and epilation occurs as the hair breaks when its diameter decreases to approximately 20 μm or less. On the other hand, some radioresistant hairs survived even a 6-Gy irradiation. The diameter of these resistant hairs was about 25 μm and almost constant from the root to the tip. Histological analyses demonstrated that these resistant hairs were derived from hair follicles in the resting stage. Two to three months after epilation, hairs could regenerate even after a 6-Gy irradiation. However, the diameter of regenerated hairs was significantly thinner than that of nonirradiated hairs.

Implications for the mechanism of epilation

Figure 2 (see p 4) illustrates the hypothetical mechanism of radiation-induced human epilation. After irradiation, many proliferating cells in a hair matrix should be killed and decrease the activity of hair formation. In the high-dose range (≥3 Gy), the hair matrix is severely damaged or disappears, and the hair becomes thinner and finally breaks. In the low-dose range (≤2 Gy), the hair also becomes thinner, but recovers its original thickness without hair breakage as the hair matrix recovers. Even in the case of high-dose irradiation, some follicle stem cells would survive in epithelial tissue derived from damaged follicles. The presence of follicle stem cells in the follicle epithelium has been proposed recently by a French research group (A Rochat et al, *Cell* 76:1063–73, 1994). After their proliferation and differentiation, these stem cells would be able to regenerate follicle structure and reproduce a hair.

Our SCID-hu mouse system makes it possible to study radiation effects on human tissue in vivo, which can contribute significantly to our understanding of the pathogenesis of radiation-induced effects. ❑

Arteriosclerosis in the Atomic-bomb Survivors

Pulse-wave velocity measurements suggest a relationship between radiation exposure and the prevalence of arteriosclerosis.

by Hironori Ueda, Department of Clinical Studies, RERF

Longitudinal cardiovascular research has been underway in the RERF Department of Clinical Studies since 1965. Results suggest a positive association between the incidence of myocardial infarction and stroke, and atomic-bomb (A-bomb) exposure in Hiroshima (K Kodama et al, *RERF Technical Report 22-84*). The relative risk of mortality from cardiovascular disease (Y Shimizu et al, *Radiat Res* 130:249–66, 1992) and the prevalence of vascular disease (H Sawada et al, *RERF Technical Report 3-86*) was higher in the high-dose group of survivors as compared with the other groups. These findings brought to our attention the necessity of systematically evaluating vascular diseases in A-bomb survivors. To that end, we decided to examine pulse-wave velocity (PWV) in A-bomb survivors to evaluate the degree of arteriosclerosis of the aorta.

Bramwell reported that the severity of human arteriosclerosis could be noninvasively estimated by PWV (JC Bramwell et al, *Heart* 10:233, 1923). In 1970 Hasegawa et al invented a new device to measure PWV by which the compliance of the aorta could be measured (M Hasegawa, *J Jikei Univ* 85:742–60, 1970 [in Japanese]). The results of this new procedure were highly correlated with the pathological findings of arteriosclerosis of the aorta, such as intimal non-fibrous, fibrous thickening; atheromatous plaque; calcification; medial collagen; and elastin (F Ostuka, *J Jikei Univ* 88:322–37, 1973 [in Japanese]). A variety of clinical studies supported the usefulness of the new procedure (H Hara et al, *J Jpn Diab Soc* 29:737–48, 1986 [in Japanese]). Thus, to analyze the possible relationship between radiation and arteriosclerosis, we adopted PWV measurement for use in our study.

Table. Logistic regression analysis on prevalence of pulse-wave velocity abnormality

	Odds ratio	*p* value
Sex (male/female)	0.8407	0.1800
Age (10 y)	3.3191	<0.0001
Dose (1 Gy)	1.2794	0.0554
Systolic blood pressure (10 mmHg)	1.1483	0.0161
Body mass index (1 kg m^{-2})	1.0713	0.0499
Total cholesterol (10 mg dL^{-1})	1.0163	0.5925
HDL-C (10 mg dL^{-1})	0.9855	0.0646
HbA1C (1%)	1.0129	0.1428
Smoking (≥10 cigarettes per day)	0.8619	0.3117

Note: HDL-C = high-density lipoprotein cholesterol; HbA1C = hemoglobin A1C.

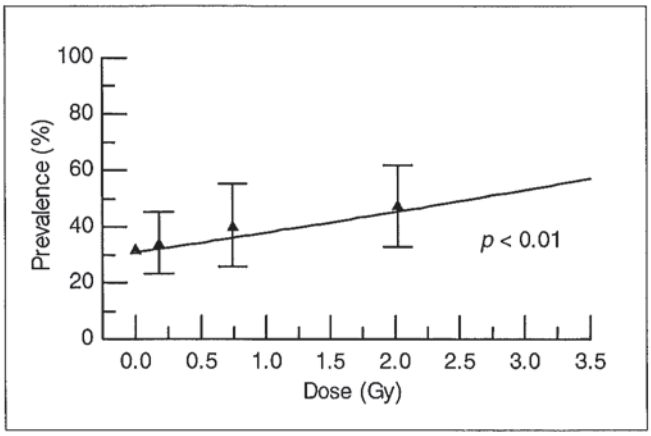

Figure. Dose response for prevalence of pulse-wave velocity abnormality among Adult Health Study participants exposed to atomic-bomb radiation in Hiroshima, adjusted for age, systolic blood pressure, and body mass index. Bars indicate 95% confidence intervals of the prevalence rate.

Subjects

In Hiroshima, Adult Health Study* (AHS) participants having Dosimetry System 1986 radiation dose estimates were studied from April 1992 to November 1993.

Materials and methods

The principle of PWV measurement rests on the fact that the lower the compliance of the vascular wall due to arteriosclerosis, the faster the transmission of pulse waves in the vascular system. The machine we used was the PWV-200 (Fukuda Corporation, Tokyo). Velocity is calculated by the distance and duration of the pulse-wave conduction, and therefore ideally we should measure the distance and conduction time of the pulse between the aortic valve and the measuring point over the femoral artery. PWV was calculated based on the data thus obtained. PWV, which is influenced by diastolic pressure, was then adjusted to a diastolic pressure of 80 mmHg.

Results

The total number of subjects in the original eligible sample was 655. After subtracting those who refused to participate in the study and a few whose PWV measurements were unusable, 536 were available for the study (males: 192, age 58 ± 9.6 years; females: 344; age 58 ± 10 years).

To evaluate the presence of bias, we analyzed differences in sex, age, and radiation dose among AHS participants who did and did not undergo PWV measurements.

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**The RERF Adult Health Study consists of about 20,000 atomic-bomb survivors and controls from Hiroshima and Nagasaki matched by age and sex. Since 1958, participants have voluntarily returned to RERF clinics for biennial examinations. In 1993, 54% of the AHS cohort was still alive. The participation rate is about 80%.*

In Memoriam: George B Darling, ABCC Director, 1957–1972

On 30 March, former Atomic Bomb Casualty Commission (ABCC) director George B Darling, 89, died at his home in the US. He served from 1957 to 1972.

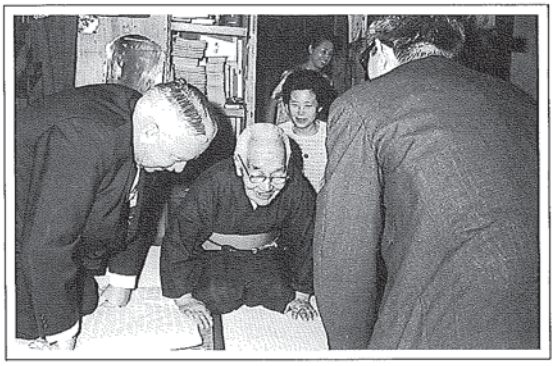
A professor of human ecology at Yale University at the time of his recruitment by the National Academy of Sciences (NAS), Darling arrived in Japan in 1957. "He came for 2 years and stayed for 15," recalled National Cancer Institute Scientist Emeritus Robert W Miller, who worked in ABCC's Department of Genetics from 1958 to 1960.

"When he became director, the clinics in Hiroshima and Nagasaki were in turmoil both scientifically and administratively," Miller wrote recently.

ABCC faced possible closing because its ". . . productivity had been so low that some contended it had done all it could do and should be phased out," wrote RERF Visiting Director Seymour Jablon in 1991 in a recollection of the Darling years at ABCC (*RERF Update* 3[1]:5–7, 1991). Jablon, a member of the 3-person Francis Committee that was dispatched in 1955 by NAS to critically review the ABCC program, recalled the import of the committee's recommendations to establish fixed, well-defined groups of exposed and non-exposed persons to be tracked over time.

"Darling took the Francis recommendations seriously," pointed out Jablon, "and he was adamant that the program not be changed to suit the ideas of each new chief of medicine or pathology."

RERF ARCHIVES



Above: George and Ann Darling in 1970 in Nagasaki, 2 years before their departure from Japan. At right: In accordance with Japanese custom, Darling bows when greeting an elderly ABCC study participant at her home in 1971. Interpreting for Darling was Kenji Joji of ABCC.

ABCC Associate Director Hiroshi Maki, who also served from 1948–1975 as director of the Japanese National Institute of Health's ABCC counterpart, the Hiroshima Branch Laboratory, wrote (*RERF Update* 3[3]:7, 1991): "I believe that Dr Darling had a deep understanding of the customs and feelings of the Japanese. This could be seen from the interest he had in upholding the solemnity of the autopsy room. He held memorial services to show his respect, and he visited the homes of the aged study participants to celebrate their longevity.

"There is no doubt that Darling's long tenure provided continuity and improved US–Japan relations," said Maki.

A Boston native, Darling graduated from the Massachusetts Institute of Technology and earned a doctorate in public health at the University of Michigan.

Darling's wife of more than 60 years, Ann, died about 3 years ago. ❑

Arterioschlerosis in the Survivors

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The two groups differed by sex and age ($p < 0.05$), but did not differ according to dose. Other risk factors of cardiovascular diseases, such as systolic blood pressure (SBP), body mass index (BMI), total cholesterol, and tobacco smoking, also did not differ in the two groups. Study participants in each category were equally distributed according to age and DS86 dose.

We defined a PWV greater than 9.0 m s^{-1} as abnormal, because previous studies indicated that those whose PWV was higher than that had more sclerotic changes in the media and intima of the aorta (Otsuka 1973). Accordingly, 201 subjects were classified into an "abnormal" PWV group and 335 into a "normal" group. The two groups differed by age and by radiation dose ($p < 0.05$). Further adjustments were made for other atherogenic risk factors. Age, SBP, and BMI correlated significantly with PWV abnormality, but dose correlated only moderately (see the Table on p 6). When comparing the ≥1-Gy group with those from the 0-dose group, the prevalence of PWV abnormality tended to be greater in the high-dose group of A-bomb survivors except in the oldest group (in which age ranged from 70 to 82 years). This might simply be attributed to error caused by the smaller number of subjects in this age group. Using age, SBP, and BMI as the relevant factors for analysis, dose response for the prevalence of PWV abnormality was significant ($p < 0.01$) (see the Figure on p 6).

Summary

PWV abnormality tended to be correlated with A-bomb radiation dose, suggesting that development of aortic arteriosclerosis may be associated with A-bomb exposure. However, we could not clearly account for the direct effect of A-bomb radiation in the development of aortic arteriosclerosis among A-bomb survivors. Further examinations will be necessary to clarify this. ❑

Recent Scientific Publications

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Approved Research Protocols

Effects of menopause on risk factors for ischemic heart disease—a longitudinal study of the Nagasaki Adult Health Study sample. M Akahoshi, M Soda, M Tsuruta, TP Rose, E Nakashima, M Saimei, S Seto, K Yano. **RERF RP 1-95. J**

The incidence of ischemic heart disease increases after menopause and the elevation of serum cholesterol that accompanies menopause is closely associated with this increase. It seems likely that elevated serum cholesterol is related to the postmenopausal decrease in estrogen, but no longitudinal study of both serum cholesterol and serum estrogen levels during the perimenopausal period has been conducted. For this reason, we propose to measure semiannually serum cholesterol and its fractions and serum estradiol in a group of premenopausal women until 1 year after the occurrence of menopause to see if the changes in serum cholesterol and its subfractions accompanying menopause are associated with changes in estradiol.

Pilot study: characterization of monoclonal gammopathy by studying the role of the BSAP gene in CD19 antigen expression. M Nobuyoshi, K Neriishi, S Kusumi, T Seyama, M Kawano, E Nakashima, K Kodama, M Akiyama, A Kuramoto. **RERF RP 2-95. J**

This is a pilot study designed to characterize benign monoclonal gammopathy (BMG) in A-bomb survivors using sensitive cellular and molecular methods. We will establish assay methods to measure using flow cytometry B-cell–specific surface antigen CD19 expression on the plasma cells from these persons and to detect B-cell lineage-specific activator protein (BSAP) mRNA using reverse transcription–polymerase chain reaction (RT–PCR) to determine how CD19 correlates with BSAP. CD19 has been identified as a marker for the transformation of normal plasma cells to the malignant cells of multiple myeloma (MM), passing through an intermediate stage as BMG plasma cells (benign plasma cells are $CD19^+$ and MM plasma cells are $CD19^-$). Recent studies suggest that the B-cell–specific transcription factor BSAP regulates CD19 gene expression. After standardizing the assay methods, this pilot study will investigate the value of measuring the B-cell–specific surface antigen CD19 and the B-cell–specific transcription factor BSAP in the plasma cells of monoclonal gammopathy patients for the early detection and/or the prediction of transformation to a definable malignancy. Only patients who give informed consent will be studied.

Publications in the Open Literature

Cancer incidence in Hiroshima and Nagasaki, Japan, 1958–1987. MT Goodman, K Mabuchi, M Morita, M Soda, S Ochikubo, T Fukuhara, T Ikeda, M Terasaki. *Eur J Cancer* 30A:801–7, 1994. **J**

The Hiroshima and Nagasaki tumour registries, which have been in operation since 1958, are among the few population-based cancer registries in Japan. This analysis evaluated cancer incidence in Hiroshima and Nagasaki between 1958 and 1987. The overall age-adjusted (World Population Standard) cancer incidence has increased from 217 to 301 per 100 000 among males, and from 176 to 197 per 100 000 among females during the first 30 years of cancer registration. The most recent rates are intermediate to rates in other countries. Despite a gradual decrease, gastric cancer remained the most common malignancy among males and females throughout the surveillance period, accounting for 24% of all cancers by the late 1980s. The rate of liver cancer has increased dramatically among males during the past 20 years, with a 2-fold increase in incidence in the past 10 years alone. The populations of Hiroshima and Nagasaki now have among the highest rates of liver cancer in the world. Breast cancer incidence in Hiroshima and Nagasaki, in contrast, is among the lowest in the world, although incidence rates have doubled since the 1960s. Other common malignancies include cancers of the lung, colon and rectum among males and cancers of the colon, cervix and lung among females.

Genetic variation detected by quantitative analysis of end-labeled genomic DNA fragments. J Asakawa, R Kuick, JV Neel, M Kodaira, C Satoh, SM Hanash. *Proc Natl Acad Sci USA* 91:9052–66, 1994.

The continuing efforts to evaluate specific human populations for altered germinal mutation rates would profit from more efficient and more specific approaches than those of the past. To this end, we have explored the potential usefulness of two-dimensional electrophoresis of DNA fragments obtained from restriction-enzyme-digested genomic DNA. This permits the analysis, on a single preparation, of approximately equal to 2000 DNA fragments varying in size from 1.0 to 5.0 kb in the first dimension and from 0.3 to 2.0 kb in the second dimension. To enter into a genetic analysis, these fragments must exhibit positional and quantitative stability. With respect to the latter, if spots that are the product of two homologous DNA fragments are to be distinguished with the requisite accuracy from spots that are the product of only one fragment, the coefficient of variation of spot intensity should be approximately less than or equal to 0.12. At present, 482 of the spots in our preparations meet these standards. In an examination of preparations based on three Japanese mother/father/child trios, 43 of these 482 spots were found to exhibit variation that segregated within families according to Mendelian principles. We have established the feasibility of cloning a variant fragment from such gels and establishing its nucleotide sequence. This technology should be highly efficient in monitoring for mutations resulting in loss/gain/rearrangement events in DNA fragments distributed throughout the genome.

Smooth piecewise linear regression splines with hyperbolic covariates. JB Cologne, R Sposto. *J Applied Stat* 21:221–33, 1994.

We propose the use of hyperbolas as covariates in piecewise linear regression splines to fit data exhibiting a multi-phase linear response with smooth transitions between phases. The hyperbolic regression spline model, fitted by non-linear regression provides an intuitive and easy way to extend to multiple phases the two-phase hyperbolic response model previously proposed by others. The small additional effort required to fit non-linear, as opposed to linear, regression models is particularly worthwhile when investigators are unwilling to assume that the slope of the response changes abruptly at the join points. Furthermore, undue influence on the join point and slope estimates, resulting from points in the transition region may be avoided by using the hyperbolic regression spline. Two examples illustrate the use of this method.

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Prediagnostic serum selenium and zinc levels and subsequent risk of lung and stomach cancer in Japan. M Kabuto, H Imai, C Yonezawa, K Neriishi, S Akiba, H Kato, T Suzuki, CE Land, WJ Blot. *Cancer Epidemiol Biomarkers Prev* 3:465–9, 1994.

Serum samples were collected in Hiroshima and Nagasaki, Japan, from 1970 to 1972 for 208 persons who in 1973–1983 developed stomach cancer; for 77 who in 1973–1983 developed lung cancer; and for controls matched for age, sex, city, and season of blood collection. Average serum levels of selenium and zinc were slightly (<5%) but not significantly lower among the cancer cases than among controls. Smoking-adjusted risks of lung cancer were elevated only among those in the lowest quartiles of serum selenium [odds ratio (OR) = 1.8] and zinc (OR = 1.3); the trends in risk of this cancer with decreasing serum levels were neither linear nor significant. Little or no excess risk of stomach cancer was observed among those with lowest levels of selenium (OR = 1.0) or zinc (OR = 1.2). These exploratory findings add to limited data available from other reports showing slightly increased risks of lung cancer associated with low blood levels of selenium, but suggest little association with either lung or stomach cancer across normal selenium or zinc ranges in this Japanese population.

Two methods for the analysis of chromosome aberration data from the atomic-bomb survivors: quasi-likelihood moment method and beta-binomial method. E Nakashima, K Ohtaki. *J Jpn Stat Soc* 24:209–19, 1994.

Two estimation methods, the maximum likelihood method under the beta-binomial model and the quasi-likelihood moment method based on the mean and variance relation, were applied to G-banding chromosome aberration data from Hiroshima atomic-bomb survivors. The chromosome aberration rate was empirically thought to be overdispersed by the intraindividual correlation or the radiation dose estimation error. Using the results of Pierce, Stram, Vaeth, and Schafer, the mean and variance relationship was formulated under the two variations to apply the quasi-likelihood method and the beta-binomial model. The quasi-likelihood moment method allows only single extra-binomial parameter but is robust, whereas the beta-binomial model allows for both dose error and intraindividual variations. Dose response parameter estimates obtained using the two methods were similar. However, the quasi-likelihood moment method is computationally less intensive than the beta-binomial maximum likelihood method. When observations are perturbed by the dose-error, the quasi-likelihood method is recommended.

The usefulness of severe combined immunodeficiency (SCID) mice to study human carcinogenesis. T Ito, T Seyama, S Kyoizumi, S Teraoka, KS Iwamoto, T Mizuno, N Tsuyama, T Asahara, K Dohi, M Akiyama. *Cancer Letters* 88:113–7, 1995.

In the present study, we engrafted normal colonic epithelia and histologically diagnosed colonic adenomas from a familial adenomatous polyposis (FAP) patient into severe combined immunodeficient (SCID) mice and subsequently examined them histologically and molecular biologically. Successful engraftment and metastasis was observed. The facts that human normal colonic epithelium and adenomatous polyps can take in SCID mice indicates the possibility that this human SCID mouse system will be useful for investigating the dynamics of human carcinogenesis in various tissues.

Spectrum of *in vivo hprt* mutations in T lymphocytes from atomic bomb survivors. I. Sequence alterations in cDNA. H Shimahara, T Kato, Y Hirai, M Akiyama. *Carcinogenesis* 16:583–91, 1995.

Recently, we found an elevated frequency of 6-thioguanine-resistant (TG^r) mutations at the hypoxanthine-guanine phosphoribosyltransferase (*hprt*) gene in T cells of peripheral blood from atomic bomb survivors and a slight, but significant, positive correlation between the frequency of mutation and radiation dose. Southern blot analysis of DNA from TG^r mutant T cells of atomic bomb survivors, however, failed to show a significant difference between the control and survivor groups. We here report mutational events at the *hprt* locus of TG^r mutant T cell clones from atomic bomb survivors as found by (i) the multiplex polymerase chain reaction (PCR) and (ii) the reverse transcription (RT)–PCR of cDNA and sequencing. The numbers of independent TG^r mutant T cell clones examined were 41 from a control group of 18 individuals who had received less than 0.005 Gy and 50 from an exposed group of 24 individuals who had received more than 1.5 Gy (mean dose 2.45 ± 0.85 Gy). Gross structural alterations, which were detected by multiplex PCR as a loss of or shift in *hprt* exon-containing fragments of genomic DNA, were found in 10–15% of the clones from both groups, thus indicating that there was no significant difference between them. The altered sequences in the HPRT cDNAs recovered from both groups were of various types. Similar proportions of base substitutions (~45%), deletions or insertions (~25%) and exon skipping (~20%) were found in both groups, indicating that neither the gross structural alterations in the genomic DNA nor sequence alterations in the *hprt* cDNA of both groups differ significantly. These results confirm our previous observation that A-bomb-induced $HPRT^-$ mutant T cells have mostly been eliminated from the peripheral blood over the decades that have elapsed since exposure. Some unique features of the mutational sequence alterations found are also described.

Optimal case-control matching in practice. JB Cologne, Y Shibata. *Epidemiol* 6:271–5, 1995.

We illustrate modern matching techniques and discuss practical issues in defining the closeness of matching for retrospective case-control designs (in which the pool of subjects already exists when the study commences). We empirically compare matching on a balancing score, analogous to the propensity score for treated/control matching, with matching on a weighted distance measure. Although both methods in principle produce balance between cases and controls in the marginal distributions of the matching covariates, the weighted distance measure provides better balance in practice because the balancing score can be poorly estimated. We emphasize the use of optimal matching based on efficient network algorithms. An illustration is based on the design of a case-control study of hepatitis B virus infection as a possible confounder and/or effect modifier of radiation-related primary liver cancer in atomic bomb survivors.

Prospective cohort study of risk factors for primary liver cancer in Hiroshima and Nagasaki, Japan. MT Goodman, H Moriwaki, M Vaeth, S Akiba, H Hayabuchi, K Mabuchi. *Epidemiol* 6:36–41, 1995. **J**

We investigated risk factors for primary liver cancer among a cohort of 36,133 residents in Hiroshima and Nagasaki, Japan, originally established to examine the association between exposure to atomic bomb radiation and disease. A mail survey to study the late effects of atomic bomb radiation was conducted among the cohort between 1978 and 1981. During the subsequent follow-up period (average 8.61 years), 242 cases of primary liver cancer were identified through population-based tumor registries in the two cities. The relative risk (RR) of liver cancer was 2.23 [95% confidence interval (CI) = 1.53–3.23] for tobacco smokers compared with those who had never smoked. Alcohol use was slightly positively associated with the risk of liver cancer, and men who had quit

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drinking had an RR of 2.33 (95% CI = 1.34–4.07) compared with those who never drank. Among alcohol drinkers, an inverse relation between years of abstinence and the rate of liver cancer was found, possibly attributable to a confounding effect of preclinical disease. The use of female hormone preparations was modestly associated with the risk of liver cancer (RR = 1.29; 95% CI = 0.59–2.84). Other risk factors included a self-reported history of radiation therapy (RR = 1.79; 95% CI = 1.34–2.40) and a history of diabetes mellitus (RR = 1.79; 95% CI = 1.31–2.43).

Somatic-cell mutations as a possible predictor of cancer risk. M Akiyama, S Umeki, Y Kusunoki, S Kyoizumi, N Nakamura, T Mori, Y Ishikawa, M Yamakido, K Ohama, T Kodama, K Endo, JB Cologne. *Health Phys* 68:643–9, 1995.

The somatic-mutation theory of carcinogenesis has received strong scientific support from results of recent studies on tumor-suppressor genes. We anticipated that people among the high risk for cancer group, either through exposure to various ionizing radiations or by virtue of unique genotypes, would also manifest increased frequencies of somatic mutation. This report presents the results of two somatic-mutation assays—at the erythrocyte glycophorin A (GPA) and lymphocyte T-cell receptor (TCR) genes—in various groups at high risk for cancer development, including atomic-bomb survivors, patients with various cancers, patients administered Thorotrast, and patients with genetic disorders that make them cancer prone. Although neither the GPA-mutation nor the TCR-mutation assay detects gene mutations directly related to carcinogenesis, increased mutation frequencies were detected by both assays in many individuals among the high-risk groups and among cancer patients. We have continued to follow up those individuals who show values of about three times higher than those of the control group. Thus, these assays may prove useful for identifying high-risk cancer groups and for estimating the effects of mutagens. Such information would constitute a valuable data base for epidemiological studies.

Relation between cold pressor test and development of hypertension based on 28-year follow-up. F Kasagi, M Akahoshi, K Shimaoka. *Hypertension* 25:71–6, 1995.

The present study examined the relation between blood pressure reactivity to cold stimulus and the subsequent development of hypertension based on a follow-up study from 1960 through 1988 of 824 normotensive participants (mean age, 35.8 ± 10.8 years) in the Adult Health Study in Nagasaki, Japan. Hypertension developed in 343 individuals during the 28 years of follow-up, with a mean incidence rate of 24.6 per 10^3 person-years. Confounding variables, including attained age, resting systolic and diastolic blood pressures, and body mass index at baseline, were adjusted using a Poisson regression model. Systolic response was found to be an independent and significant predictor. The relative risk of hypertension for systolic hyperreactors was 1.37, with a 95% confidence interval of 1.10 to 1.71. Diastolic response was significant only when resting diastolic blood pressure was also considered. The cold pressor test appears to be useful if performed on middle-aged subjects older than 40 years at the time of examination, when hypertension is more prevalent. The current results support the hypothesis that hyperreactivity is a predictor of the development of hypertension.

Further observations on abnormal brain development caused by prenatal A-bomb exposure to ionizing radiation. H Yoshimaru, M Otake, WJ Schull, S Funamoto. *Int J Radiat Biol* 67:359–71, 1995.

The pervasiveness of abnormal brain development caused by prenatal exposure to ionizing radiation is still largely unknown. The relationship between A-bomb radiation dose and two measures of neuromuscular performance, one of grip strength and the other of the fine motor coordination required in repetitive action, is described. A multivariate analysis of covariance was used to evaluate the effect of several covariates, such as prenatal radiation exposure and some physical measurements or IQ, adding city and sex as categorical factors. When mentally retarded cases were included, a statistically significant effect of radiation exposure on the grip strength and repetitive-action test scores was seen in the 8–15-week postovulation period, and a statistically suggestive effect at 16–25 weeks postovulation. No effect of radiation exposure on the two test scores was noted for prenatal exposure in either of the aforementioned periods when mentally retarded cases were excluded, but a statistically significant diminution of IQ was noted for exposures ≥ 16 weeks postovulation. We discuss, from the biological perspective, the projected standard scores for exposures ≥ 16 weeks postovulation, and the possibility of lower IQ, small head and mild mental retardation related to radiation exposures ≤ 15 weeks postovulation with mentally retarded cases excluded.

Anti-human T-lymphotropic virus type-I antibodies in atomic-bomb survivors. T Matsuo, E Nakashima, RL Carter, K Neriishi, K Mabuchi, M Akiyama, K Shimaoka, K Kinoshita, M Tomonaga, M Ichimaru. *J Radiat Res* (Tokyo) 36:8–16, 1995.

Adult T-cell leukemia (ATL), induced by human T-lymphotropic virus type-I (HTLV-I), is endemic in Nagasaki, Japan. To investigate the effects of atomic-bomb radiation on development of this specific type of leukemia, 6182 individuals in the Radiation Effects Research Foundation (RERF) Adult Health Study sample in Hiroshima and Nagasaki were examined for positive rate of HTLV-I antibody. Several lymphocyte parameters were also studied for 70 antibody-positive subjects in Nagasaki. The HTLV-I antibody-positive rate was higher in Nagasaki (6.36%) than in Hiroshima (0.79%) and significantly increased with increasing age, but no association was observed with radiation dose. Whether relationship existed between antibody titer levels and radiation dose among antibody-positive subjects was not clear. The frequency of abnormal lymphocytes tended to be higher in antibody-positive subjects than in antibody-negative subjects, and higher in females than in males regardless of radiation dose. The lymphocyte count was lower in antibody-positive subjects than in antibody-negative subjects and lower in female than in male subjects. No evidence was found to suggest that atomic-bomb radiation plays an important role in HTLV-I infection.

Effect of radiation and cigarette smoking on expression of FUdR-inducible common fragile sites in human peripheral lymphocytes. S Ban, JB Cologne, K Neriishi. *Mutat Res* 334:197–203, 1995.

In vitro X-irradiation of human peripheral blood lymphocytes increased the frequencies of fluorodeoxyuridine-induced fragile sites in a dose-related manner. However, the cells from 30 atomic bomb survivors exposed to either high or low radiation doses 47 years earlier showed no demonstrable difference in fragile site expression, indicating that fragile site induction was ephemeral in nature. When fragile sites were analyzed on the basis of tobacco smoking habits, an elevated number was observed in the smokers. The results confirm that fragile sites can be affected by recent exposure to exogenous agents, but the effect is probably of limited duration, based on the atomic bomb survivor experience.

Thyroid cancer after exposure to external radiation: a pooled analysis of seven studies. E Ron, JH Lubin, RE Shore, K Mabuchi, B Modan, LM Pottern, AB Schneider,

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MA Tucker, JD Boice. *Radiat Res* 141:259–77, 1995.

The thyroid gland of children is especially vulnerable to the carcinogenic action of ionizing radiation. To provide insights into various modifying influences on risk, seven major studies with organ doses to individual subjects were evaluated. Five cohort studies (atomic bomb survivors, children treated for tinea capitis, two studies of children irradiated for enlarged tonsils, and infants irradiated for an enlarged thymus gland) and two case-control studies (patients with cervical cancer and childhood cancer) were studied. The combined studies include almost 120,000 people (approximately 58,000 exposed to a wide range of doses and 61,000 nonexposed subjects), nearly 700 thyroid cancers and 3,000,000 person years of follow-up. For persons exposed to radiation before age 15 years, linearity best described the dose response, even down to 0.10 Gy. At the highest doses (>10 Gy), associated with cancer therapy, there appeared to be a decrease or leveling of risk. For childhood exposures, the pooled excess relative risk per Gy (ERR/Gy) was 7.7 (95% CI = 2.1, 28.7) and the excess absolute risk per 10^4 PY Gy (EAR/10^4 PY Gy) was 4.4 (95% CI = 1.9, 10.1). The attributable risk percent (AR%) at 1 Gy was 88%. However, these summary estimates were affected strongly by age at exposure even within this limited age range. The ERR was greater ($P = 0.07$) for females than males, but the findings from the individual studies were not consistent. The EAR was higher among women, reflecting their higher rate of naturally occurring thyroid cancer. The distribution of ERR over time followed neither a simple multiplicative nor an additive pattern in relation to background occurrence. Only two cases were seen within 5 years of exposure. The ERR began to decline about 30 years after exposure but was still elevated at 40 years. Risk also decreased significantly with increasing age at exposure, with little risk apparent after age 20 years. Based on limited data, there was a suggestion that spreading dose over time (from a few days to >1 year) may lower risk, possibly due to the opportunity for cellular repair mechanisms to operate. The thyroid gland in children has one of the highest risk coefficients of any organ and is the only tissue with convincing evidence for risk at about 0.10 Gy.

Prevalence rate of thyroid diseases among autopsy cases of the atomic bomb survivors in Hiroshima, 1951–1985. Y Yoshimoto, H Ezaki, R Etoh, T Hiraoka, S Akiba. *Radiat Res* 141:278–86, 1995. **J**

To examine the radiogenic risk of latent thyroid cancer, thyroid adenoma, colloid/adenomatous goiter and chronic thyroiditis, the data for 3821 subjects collected in the course of autopsies of atomic bomb survivors in Hiroshima from 1951 to 1985 by the Radiation Effects Research Foundation (RERF) were analyzed using a logistic model. About 80% of the autopsies were performed at RERF and the remainder at local hospitals. The frequencies of the above diseases were not associated with whether the underlying cause of death was cancer. However, note that our results may be influenced by potentially biasing factors associated with autopsy selection. The relative frequency of latent thyroid cancer (greatest dimension ≤1.5 cm but detectable on a routine microscopic slide of the thyroid gland) increased as the radiation dose increased and was about 1.4-fold greater at 1 Gy than in the 0-Gy dose group. The relative occurrence of thyroid adenoma also increased as radiation dose increased, and was about 1.5-fold greater at 1 Gy than in the 0-Gy dose group. Sex, age at the time of the bombing or period of observation did not significantly modify the radiogenic risks for thyroid adenoma or latent thyroid cancer. No statistically significant association was found between radiation exposure and the rates of colloid/adenomatous goiter and chronic thyroiditis. The possible late effect of atomic bomb radiation on the frequency of benign thyroid diseases is discussed on the basis of these data.

Quantitative and qualitative genetic variation in two-dimensional DNA gels of human lymphocytoid cell lines. J Asakawa, R Kuick, JV Neel, M Kodaira, C Satoh, SM Hanash. *Electrophoresis* 16:241–52, 1995.

There is a continuing need for more efficient methods to examine human (and other) populations for altered germinal and somatic cell mutation rates. To this end, we have explored the potential usefulness of two-dimensional (2-D) electrophoresis of human DNA fragments obtained from restriction-enzyme-digested genomic DNA, using samples from father/mother/child trios. On a single 2-D DNA preparation, approximately 2000 DNA fragments varying in size from 1.0 to 5.0 kbp in the first dimension and 0.3 to 2.0 kbp in the second dimension are visualized. To enter into a genetic analysis of quantitative variation, these fragments must exhibit positional and quantitative stability. With respect to the latter, if spots that are the product of two homologous DNA fragments are to be distinguished with the requisite accuracy from spots that are the product of only one fragment, the coefficient of variation of spot intensity should be approximately ≤ 0.12. At present, 482 of the spots in our preparations meet these standards. In an examination of preparations based on three Japanese mother/father/child trios, 43 of these 482 spots were found to exhibit variations that segregated within families according to Mendelian principles. Additionally, of the 2000 spots, 1114 (of which the aforementioned 482 are a subset) were deemed appropriate for the study of qualitative variation. A total of 142 variable spots were identified; the heterozygosity index for these DNA fragments was 4.4%. The genetic nature of the additional variants was again established by their segregation according to Mendelian principles. We have established the feasibility of cloning fragments from such gels and determining their nucleotide sequence. This technology should be highly efficient in monitoring for mutation resulting in loss/gain/rearrangement events in DNA fragments distributed throughout the genome.

p53 mutations in lung cancers from Japanese mustard gas workers. Y Takeshima, K Inai, WP Bennett, RA Metcalf, JA Welsh, S Yonehara, Y Hayashi, M Fujihara, M Yamakido, M Akiyama, S Tokuoka, CE Land, CC Harris. *Carcinogenesis* 15:2075–9, 1994.

Mustard gas (MG) is a mutagenic and carcinogenic alkylating agent, and is a known risk factor for occupational lung cancer. Our hypothesis is that lung cancers from MG workers contain mutations (G:C to A:T transitions) as the result of MG-produced DNA promutagenic adducts in the *p53* tumor suppressor gene. We analyzed 12 primary lung cancers from Japanese MG factory workers and 12 lung cancers from non-exposed individuals. Genomic DNA was isolated from archival paraffin-embedded tissues. Exons 5–8 were amplified by polymerase chain reaction using *p53*-specific primers, and sequenced by dideoxy termination methods. Six out of 12 lung cancers from MG workers contained a total of eight somatic point mutations: two cases had double G:C to A:T transitions; one had a G:C to T:A transversion; one case had an A:T to G:C transition; and two cases had single base deletions. Four of the six mutated purines occurred on the non-transcribed, DNA-coding strand. Out of 12 unexposed cases, there were six single base mutations in six cancers, and no double mutations. The *p53* mutational frequency in the MG-exposed cases is similar to the non-exposed controls and the usual smoking-related lung cancers reported previously. However, the distinctive double mutations (G:C to A:T transition) observed in two cases are unusual and may be related to MG exposure.

Height reduction among prenatally exposed atomic-bomb

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survivors: a longitudinal study of growth. E Nakashima, RL Carter, K Neriishi, S Tanaka, S Funamoto. *Health Phys* 68(6):766–72, 1995.

Using a random coefficient regression model, sex-specific longitudinal analyses of height were made on 801 (392 male and 409 female) atomic-bomb survivors exposed *in utero* to detect dose effects on standing height. The data set resulted from repeated measurements of standing height of adolescents (age 10–18 y). The dose effect, if any, was assumed to be linear. Gestational ages at the time of radiation exposure were divided into trimesters. Since an earlier longitudinal data analysis has demonstrated radiation effects on height, the emphasis in this paper is on the interaction between dose and gestational age at exposure and radiation effects on the age of occurrence of the adolescent growth spurt. For males, a cubic polynomial growth-curve model applied to the data was affected significantly by radiation. The dose by trimester interaction effect was not significant. The onset of adolescent growth spurt was estimated at about 13 y at 0 Gy. There was no effect of radiation on the adolescent growth spurt. For females, a quadratic polynomial growth-curve model was fitted to the data. The dose effect was significant, while the dose by trimester interaction was again not significant.

Commentary. The Radiation Effects Research Foundation of Hiroshima and Nagasaki: past, present, and future. I Shigematsu, ML Mendelsohn. *JAMA* 274(5):425–6, 1995.

SCID mice model for the in vivo study of human oncotherapy: studies on the growth and metastasis of human lung cancer. S Teraoka, S Kyoizumi, T Seyama, M Yamakido, M Akiyama. *Int J Oncol* 5:501–8, 1994.

Prognostic value of the cold pressor test for hypertension based on 28-year follow-up. F Kasagi. *Hiroshima J Med Sci* 43:93–103, 1994.

A proposed system for scoring structural aberrations detected by chromosome painting. JD Tucker, WF Morgan, AA Awa, M Bauchinger, D Blakey, MN Cornforth, LG Littlefield, AT Natarajan, C Shasserre. *Cytogenet Cell Genet* 68:211–21, 1995.

High yield of restriction fragment length polymorphisms in two-dimensional separations of human genomic DNA. R Kuick, J Asakawa, JV Neel, C Satoh, SM Hanash. *Genomics* 25:345–53, 1995.

Radon concentrations in residential housing in Hiroshima and Nagasaki. H Yonehara, T Aoyama, EP Radford, H Kato, M Sakanoue. *Health Phys* 68(5):683–8, 1995.

The current applicability of large scale biomarker programs to monitor cleanup workers. ML Mendelsohn. In: *Biomarkers and Occupational Health: Progress and Perspectives.* Edited by ML Mendelsohn, JP Peeters, MJ Normandy. Washington, DC, Joseph Henry Press, 1995. pp 9–19.

Studies of children in utero during atomic bomb detonations. Y Yoshimoto, M Soda, WJ Schull, K Mabuchi. In: *Radiation and Public Perception: Benefits and Risks* (ACS Advances in Chemistry Series No. 243). Edited by JP Young, RS Yalow. Washington, DC, American Chemical Society, 1995. pp 133–45.

p53 and Rb tumor suppressor gene alterations in retinoblastoma. M Ito, HK Mishima, K Inai, T Ito, M Akiyama. *Int J Oncology* 4: 1329–32, 1994.

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Publications of Interest Using RERF Data

A comparison of the risks of leukaemia in the offspring of the Sellafield workforce born in Seascale and those born elsewhere in West Cumbria with the risks in the offspring of the Ontario and Scottish workforces and the Japanese bomb survivors. MP Little, R Wakeford, MW Charles. *J Radiol Prot* 14(3): 187–201, 1994.

An analysis of leukaemia, lymphoma and other malignancies together with certain categories of non-cancer mortality in the first generation offspring (F_1) of the Japanese bomb survivors. MP Little, R Wakeford, MW Charles. *J Radiol Prot* 14(3): 203–18, 1994.

A review of the risks of leukemia in relation to parental pre-conception exposure to radiation. MP Little, MW Charles, R Wakeford. *Health Phys* 68(3):299–310, 1995. ❑

RERF **update** RERF

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

Editorial Policy

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

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Report of the 1995 RERF Scientific Council

Editor's note: The 1995 RERF Scientific Council met at the Hiroshima Laboratory, 19–21 April 1995. The Scientific Council Report published here is the full set of recommendations approved by the RERF scientific councilors in May. In mid-April, the general recommendations were delivered to Bruce Alberts, president of the US National Academy of Sciences, before the Academy's annual meeting.

General Recommendations

This year's meeting of the Science Council came at a period of great turmoil at the Radiation Effects Research Foundation (RERF). The US Department of Energy (DOE) decided to discontinue its contract with the US National Academy of Sciences (NAS) which has administered RERF for many years. The DOE will now be requesting American universities to compete for management of the US portion of the project's administration. The reasons for such a change appear to be complex. We perceive them to be related to a combination of circumstances, such as 1) DOE's wish to reassess the activities of RERF after many decades of work, 2) DOE's desire to strengthen its involvement in training of radiation biology specialists, and 3) DOE's responding with novel administrative arrangements at RERF in the face of Congressional desires to cut costs at all levels, particularly at DOE itself. The various developments together with the failure of DOE to communicate the full reasons for its decision led to strong reactions among RERF scientists and many other observers. We as scientific councilors are charged to ensure that the scientific activities of RERF are carried out properly, smoothly, and using the highest scientific standards. Radical changes in administrative managements are likely to affect the conduct of science and should be avoided unless carefully thought out and crafted.

The 50th anniversary of the atomic bombings occurs this year. We consider it appropriate and desirable that the scientific activities of RERF are assessed carefully and in depth by an outside expert group that has not been previously involved in RERF activities. We, therefore, recommend that a high-level international committee of distinguished scientists be appointed to carry out an assessment of RERF's current and future scientific activities. This committee should be impaneled under the sponsorship of an international body concerned with radiation biology, radiation effects on populations, and radiation protection. The panel should have representatives from Japan and the US, as well as from other countries. Even though only Japan and the US are directly concerned with RERF, we believe that RERF's mission is truly international and affects all of humankind. The newly established committee should pay particular attention to the nature and the extent of the studies to be carried out at RERF in the next 2 decades. Organizations such as the United Nations Scientific Committee on the Effects of Atomic Radiation, the International Commission on Radiological Protection, or the World Health Organization are possible sponsors, but other bodies may also be appropriate. A committee consisting of representatives of RERF, the US and Japanese sponsoring organizations (ie, the DOE and the Ministry of Health and Welfare), as well as selected radiation experts should be involved in setting up the membership of the distinguished ("blue ribbon") committee.

We welcome the idea of strengthening both training and scientific exchange activities of RERF. We therefore recommend that international postdoctoral fellowships and exchange programs be instituted to allow interested young researchers and more established scientists to work at RERF for various periods of time. We feel that the involvement of young scientists as well as of exchange scientists will lend strength to the scientific caliber of RERF's work. RERF should continue to be in the mainstream of radiation science and related fields. Enhancement of the training function and more exchange of scientists will help towards this goal.

Budgetary constraints are real and may get worse. It will therefore be increasingly difficult to fund all worthwhile research at RERF. We therefore strongly encourage RERF scientists to become more active in applying for research grants from various national and international organizations including those of Japan. In making these recommendations, we realize the existing constraint in funding with grants personnel positions in Japan.

We are concerned that the present turmoil about management may have deleterious effects on the research mission of RERF, particularly since negative newspaper reports about DOE's intentions—whether correct or not—may convince some atomic-bomb survivors to stop participating in ongoing and periodic studies.

We realize DOE's difficulties in funding a binational organization far away from the US and at the same time remain responsive to the current mood of the US Congress. Precipitous administrative moves, however, may seriously perturb difficult international relationships developed over many years. We are particularly concerned that RERF's binational character not be forgotten. This important aspect of RERF must always be considered in any future administrative moves.

We therefore recommend that DOE defer its current plan of discontinuing NAS sponsorship until the internationally distinguished committee has assessed RERF's total activities and has made its full report. We feel that such a step will defuse the current unrest among RERF's personnel, which is further accentuated by current fiscal uncertainties. This decision will have a favorable effect on the continuation of high-quality research at RERF. In this regard, we are particularly impressed by the excellent and improving scientific quality of RERF's work as presented during this meeting. RERF has a superb and unique cadre of fine scientists whose scientific activities must be maintained and fostered.

Detailed Recommendations

Epidemiology and Statistics

Work in epidemiology and statistics continues to make excellent contributions to RERF research, both in

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design and analysis of cohort studies and in collaborative efforts through a wide range of research investigations with other departments. The main components of this work involve 1) maintaining mortality and incidence data of several A-bomb survivor cohorts (LSS, in utero, F_1), as well as data from the Hiroshima and Nagasaki tumor registries; 2) analyzing updated information from those sources on a regular basis; and 3) designing and conducting specific studies related to radiation risk at particular cancer sites and in relation to nonradiation risk factors that may influence observed associations between radiation and disease. Despite present uncertainties regarding RERF resources and staffing, ***the Council strongly feels that these various tasks deserve highest priority and should not be allowed to falter.***

Low-dose studies. A substantial proportion of A-bomb survivors received relatively low doses of radiation. These segments of the follow-up cohorts deserve particular attention in light of sustained worldwide interest in low-dose radiation health effects. A-bomb survivor analyses can be of particular value when viewed in relation to effects seen in higher dose categories. At the same time, findings of increased risk caused by low-dose irradiation must be interpreted with special caution because of particular susceptibility to distortion by even minor degrees of disease misclassification and the operation of competing risk factors. The presence of slight increases in excess relative risks (ERR) for solid-tumor mortality but their absence in incidence data may represent one aspect of this problem.

Noncancer mortality. In conducting analyses for *Life Span Study Report 12*, reanalysis of noncancer mortality in relation to Dosimetry System 1986 (DS86) dose have been conducted. An additional 5 years of mortality information have been added (now 1950–1990), and patterns of increasing risk with increasing dose continue to be seen for mortality since 1965: ERR values in the neighborhood of 1.0 at higher dose levels (4 Gy or more) with statistically significant dose trends for circulatory diseases, stroke, and digestive diseases. These data deserve continued close attention, since their public health importance (attributable risk) may be substantial, given the common nature of the disease categories involved. At present, however, any meaningful biologic interpretation is difficult, in view of the particular susceptibility of such low risk levels to influences of diagnostic misclassification and risk confounding. Although an assessment of such modifying factors appears to suggest only a minor impact on risk estimates, proof of the biologic reality of these low risks requires further independent observations at RERF (see below) and elsewhere, as well as laboratory data regarding the possible role of radiation in the etiology of arteriosclerotic and other diseases.

Brain damage in utero. Earlier RERF data regarding small head size in relation to in utero dose have been updated and supplemented with interesting analyses regarding subsequent patterns of mental retardation. Although sample sizes are small, the analyses are of great interest, especially in view of findings that suggest a dose threshold of about 0.20 Gy for severe retardation but not for other effects.

In utero cohorts. Considerable progress has been made in merging the two in-utero cohorts and in clarifying the dosimetry status of the combined cohort. It is proposed to increase the sample further by adding those survivors exposed in early childhood. While such an addition will increase statistical power, it should not be viewed as a permanent analytic arrangement, given the differences in exposure conditions for pre- and post-natal states. ***The Council strongly endorses the close follow-up of survivors who were young at the time of the bombings and are now entering the age in which cancer risks increase.***

Thyroid diseases. An interesting study has been conducted regarding thyroid diseases among persons exposed to fallout radiation in Nishiyama (near Nagasaki). Although the overall frequency of such diseases was not increased, certain categories of thyroid nodules were increased about threefold. The analyses appear to be complete, and future investigations are not necessary. It will be useful to compare these data with data from similar fallout surveys elsewhere in the world regarding the relationships between thyroid pathology and particular patterns of fallout radioactivity.

1965 LSS mail survey. Important data were reviewed from the 1965 Life Span Study (LSS) mail survey, which collected information (male only, ages 40–69 y) regarding various environmental and lifestyle risk factors that might effect estimates of LSS radiation risk. These data are particularly important in the context of interpreting the low levels of increased risk observed for certain solid cancers and for the wide range of noncancer mortality. All such sources of LSS and Adult Health Study (AHS) data deserve close examination, given the vulnerability of low excess relative risk values to distortion by such competing risk influences.

Clinical Studies

The important role of the AHS continues, both in terms of the regular clinical examination of cohort members and in relation to special investigations arising from AHS data collected over time. ***The Council would once again stress the central importance of AHS follow-up and study for the RERF mission and commends the staff for their continued excellent work.***

AHS pilot mail survey. In view of the aging nature of the AHS cohort, it has previously been urged that intensified efforts be employed to maintain close follow-up of cohort members, in the face of indications that follow-up tends to become more difficult as subjects age. The survey results strongly indicate that mailed questionnaires with follow-up contact, especially with nonresponders, are remarkably effective. ***Such methods deserve to be fully implemented as soon as possible.*** The overall success of AHS cohort work very much depends on a high degree of completeness in follow-up efforts and accurate recording of all health events as the population ages.

Uterine myomata. Earlier investigations regarding the possible relation of radiation dose to uterine myomata have been extended using more sensitive ultrasonic detection approaches for diagnosing tumor. The results continue to support a relationship between dose and tumor occurrence. The results are of considerable interest since only limited information exists regarding radiation as a cause of benign tumors. Perhaps information about menstrual histories may be relevant for future studies in this area.

Pulse-wave velocity. An interesting study was described whereby measurements of pulse-wave velocity were used as a surrogate for aortic atherosclerosis. The data are of interest since they represent an independent approach to the question of noncancer radiation effects. Whereas the observed association of velocity measurements to DS86 dose tends to support the LSS mortality observation, further studies using alternate techniques such as ultrasound measurements of carotid artery arteriosclerosis may be needed to explore this area of clinical research more fully.

Psychological studies. In response to Council comments in 1991 regarding evaluation of psychological effects on A-bomb survivors, work was undertaken to explore possible approaches for future studies and to reexamine results from such a survey conducted in the 1960s. The results presented support the concept of increased effects on survivors as a function of dose. It is unclear, however, to what extent such effects may arise from increased frequency of physical disorder in those higher dose categories. In view of present resource constraints, however, further investigations of this sort would be difficult and do not deserve a high priority.

Genetic subgroups. Extensive analyses have been conducted of LSS data concerning female breast-cancer incidence according to age at the time of the bombings (ATB), age of cancer diagnosis, and DS86 dose. The results strongly indicate greatly heightened radiation risk for women exposed and diagnosed at young ages; similar, but less extensive, data were also described for colon cancer. The findings correspond well with the concept that genetic high-risk groups exist for which early onset cancer may serve as a marker. Heightened radiation sensitivity among such persons, when exposed young, is of great potential importance. ***Future investigations of these subgroups to identify genetic subgroups with higher genetic susceptibility have a high priority.*** Although such studies should make use of molecular epidemiologic approaches, clinical genetic-epidemiologic work might well be undertaken at the same time to reconstruct family histories of cancer, which alone could be of great importance in further linking these LSS findings to underlying genetic mechanisms.

Pedigree construction. Continued progress was reported regarding identification of familial relationships among LSS cohort members. The task appears to be more complicated than originally envisioned since disparities in data available from different sources appear to be frequent. Computer programs have been devised to compare and merge family data from different files (master sample questionnaires and AHS records), and consideration is being given to use of *koseki* data for further clarification of pedigrees. For the research purposes envisioned, however, it may not be necessary to conduct such complete merger and refinement of data but instead to focus efforts on confirming pedigree relationships in a sufficient number of subjects to support subsequent molecular genetic studies (see below). These efforts might focus particularly on sib-sib or parent-child pairs, using both *koseki* records, if accessible, as well as direct family interviews to confirm specific family relationships.

Research Information Center

In the face of increasing resource constraints, exceptional performance has been displayed in converting mainframe computers to personal-computer–based computing technology well ahead of schedule. Maintenance of equipment, continuous upgrading of computer programs, and ongoing staff training are essential if the new system is to realize its potential for supporting the various research efforts. ***Support for this essential aspect of RERF work has a high priority.***

Biochemical and Molecular Genetics

An example of the high quality and productive research in molecular genetics as applied to the mission of RERF is the work carried out in Chiyoko Satoh's laboratory by Jun-ichi Asakawa and Mieko Kodaira. They have made the two-dimensional electrophoretic separation of restriction fragments of genomic DNA into an excellent method of detecting genetic variants, allowing differentially amplified regions of DNA, loss of heterozygosity, and other somatic or germ-line changes in DNA to be studied directly. They are also perfecting the reproducibility of gel patterns so that high-speed automated detection of quantitative as well as qualitative changes in fragment spots are possible.

This existing technique is beginning to be applied to DNA samples from mother/father/child trios for A-bomb survivors and other irradiated individuals. The methodology is also being explored to compare cancers with normal tissues and has much promise.

An important extension of the analytical power of detecting genetic or tissue-specific differences is molecular cloning of variants so that these can be sequenced, mapped, and otherwise characterized. This is an example of sophisticated research that provides, through collaboration with at least one university, dissemination of new knowledge and at the same time helps in training other scientists in these new techniques.

These kinds of activities are strongly encouraged by the Science Council. Additional funding for this kind of "cutting edge" research should be sought from outside grants and contracts. We believe funding agencies such as those dealing with cancer prevention and treatment would find this work of great interest for their mission.

Biodosimetry

Major progress has been made by the cytogenetics group headed by Nori Nakamura during the last year. Cytogenetic examinations of Hiroshima survivors using the fluorescence in-situ hybridization (FISH) method started in April 1994 on a routine basis. This is a most efficient technique of biodosimetry.

An unexpected finding among exposed subjects with chromosomal deletions was a cluster of interstitial deletion on the long arm of chromosome 5, and the correlation of terminal deletions with chromosome length.

The Council was interested in the result of electron spin resonance (ESR) measurement using tooth enamel which Dr. Nakamura had done in collaboration with an outside scientist, who made equipment for ESR measurement available. The results of ESR analysis for known chromosome aberrations with known DS86 doses suggest that this technique could be used as a new means of biologic dosimetry, although availability of tooth samples may be limited. However, Dr. Nakamura has collected over 300 teeth samples from A-bomb survivors,

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and an ESR machine has recently been installed in his laboratory. The Council encourages the establishment of these ESR measurements in the near future.

Molecular Epidemiology Studies

The molecular pathogenesis of diseases associated with ionizing radiation is an exciting and expanding area of biomedical research. In recent years, the RERF staff has acquired skills in molecular biology and developed effective strategies for conducting investigations in the molecular epidemiology of cancer. Pilot studies have already produced interesting results. An increased frequency of RET protooncogene mutations in thyroid cancers from A-bomb survivors, as well as among children living in areas contaminated by the Chernobyl accident, and an altered mutation spectrum of the p53 tumor suppressor gene in basal-cell carcinoma in both sun-exposed and non-exposed skin of A-bomb survivors are interesting examples. The molecular analysis of unusual cancer subpopulations can also yield far reaching results. One example is the analysis of germline mutations in the BRCA1 and other cancer susceptibility genes occurring in young women with early onset breast cancer who were exposed to ionizing radiations before or during puberty. A comparison between the molecular "fingerprints" of cancer-related genes associated with ionizing radiation and those produced by other carcinogens is an important area for future investigation.

RERF should focus its limited molecular epidemiology resources on studies to test hypotheses tightly linked to its ongoing clinical and epidemiological studies of A-bomb survivors. Collaborations with colleagues in local, national, and international institutions are encouraged to leverage resources. The results from these high-priority molecular epidemiology studies of A-bomb survivors should lead to new insights in radiation carcinogenesis and generate hypotheses for future mechanistic studies.

Radiobiology of Somatic Mutations and Molecular Oncology

Mitoshi Akiyama provided an overview of the major projects in the radiobiology program, focusing in particular on the somatic mutation and molecular oncological studies in A-bomb survivors. Among the former, he described substantial progress in studies of mutation in the glycophorin-A (GPA) and T-cell receptor (TCR) loci of blood cells. A promising new approach is the molecular analysis of GPA mutants in reticulocytes. Molecular studies of FACS-sorted mutants permitted identification of the precise molecular changes and radiation dose dependence of these changes in A-bomb survivors and irradiated patients. Similar cellular and molecular level assays of radiation dose dependency were done with T-cell receptor and HPRT loci using separation by flow cytometry and polymerase chain reaction (PCR) methods. These projects appear to be progressing well and should provide valuable information concerning the ability to predict carcinogenic effects of radiation in humans by use of mutation assays in their somatic cells.

There appear to be minor correlations between age and smoking and glycophorin mutations, as well as with city (Hiroshima > Nagasaki). There are also significant, yet unexplained, sex differences (male > female), that are greater than the effect of smoking. These trends seem to correlate with those for background solid cancers. The interactive effects between ionizing radiation and other causes of cancer are important in human cancer risk assessment. Therefore, the possible interactive effects between radiation exposure and tobacco smoking on GPA mutation frequency in the cancer group as compared with the noncancer group should be examined. In addition, the strikingly lower GPA mutation frequency in females compared to males generates several hypotheses including the possible effects of sex hormones, on either hemopoietic stem cell proliferation rates or survival of GPA mutant cells.

Overall, GPA mutations appear to be a good somatic-cell indicator of radiation damage that correlates with the risk of developing solid tumors; the doubling dose for GPA mutations was 1.2 Sv as compared with 1.59 Sv for solid tumors. Whereas GPA mutant frequency reflects the life-time accumulation of mutations, the half-life of T-cell receptor (TCR) mutations is only 2–3 years. Therefore, the TCR assay is of value as a biological dosimeter of recent radiation exposure. The doubling doses appear to be much lower than for GPA mutants. Increased TCR mutations in a few A-bomb survivors appear to represent clonal expansion. These studies of TCR mutations as a somatic-cell assay for recent radiation exposure should be continued.

Stem-cell studies showed that mutations at the hematopoietic stem-cell stage, were generally stable over many years thus serving as biological dosimeters for A-bomb survivors and other types of irradiation.

The SCID-hu mouse model for human epilation is of considerable mechanistic interest since few such experimental studies have been carried out. These results contribute significantly to understanding of this radiobiological phenomenon. Additional more-basic studies of epilation including the mechanism of radioresistance of follicular stem cells would be appropriate for independent grant support. This SCID model may have important application in areas such as studies of basal cell carcinoma.

Overall, the work of the radiobiology group and collaborators is an excellent example of scientific excellence of direct relevance to the RERF mission. The extensive use of stored material and cell lines established from A-bomb survivors and only available at RERF was noted and emphasizes this unique resource.

We encourage Dr. Akiyama's group to continue with the general thrust of this work.

Genes Responsible for SCID Mutation(s)

This work aimed at identifying the responsible mouse genes for radiosensitivity and complementing these with human genes conferring resistance, was unusual in being carried out independently of other similar studies. Masumi Abe localized the responsible region to human chromosome 8. Others have moved faster in actually identifying the human and mouse genes. With the pending departure of Dr. Abe, termination of this program at RERF seems appropriate. ❑