

RERF update RERF

News & Views from the US-Japan Radiation Effects Research Foundation
Volume 1, Issue 3 Hiroshima & Nagasaki Autumn 1989

Memory of 1945 Events Renewed Annually

Early August marks the yearly commemoration of two solemnly observed days: 6 and 9 August 1945, when the world's first atomic bombs were detonated about 500 meters above Hiroshima and Nagasaki.

Annually, thousands of people—Japanese and foreigners alike—converge upon both cities to bear witness to the destructive power of nuclear weapons, which in these first crude and relatively low-power forms caused the deaths of an estimated 175,000 persons. Of the 330,000 persons living in Hiroshima City in August 1945, between 90,000 and 120,000 died before the end of the year. In Nagasaki, too, about a third of the population perished.

Gathered in the Peace Parks of both cities, Japanese public officials and citizens from all walks of life offered prayers for the repose of the souls of atomic-bomb (A-bomb) victims, and they meditated upon the goal of world peace.

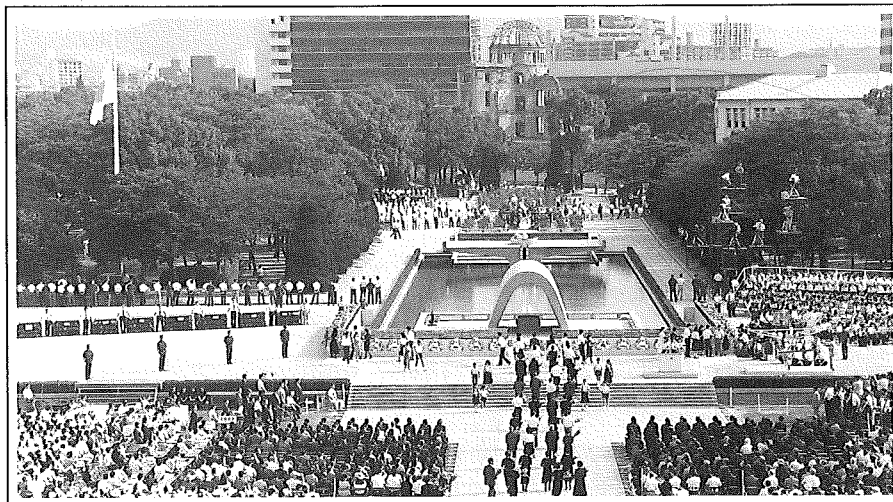
In Hiroshima, the ceremony focuses upon the granite Cenotaph, the repository for 49 volumes that list the names of more than 152,000 known A-bomb victims as well as A-bomb survivors who have since passed away. About 4,000 names were added during the past year. The Flame of Peace, located behind the Cenotaph, blazes more fiercely at the moment of the Hiroshima bombing to symbolize the conflagration that enveloped the city after the bomb blast.

Similarly, in Nagasaki 2,272 names were added to that city's list of deceased during the late morning ceremony attended by thousands of people.

In both cities, national and local officials addressed the large crowds, which this year included participants of the Second Mayors' Conference for World Peace who represented 98 cities from 33 countries.

Then Japanese Prime Minister **Sousuke Uno**, who afterward visited Hiroshima's Peace Museum which houses relics related to the bombing, said: "Our country, as the sole nation to have suffered an atomic attack, is determined that the tragedies of Hiroshima and Nagasaki should never be repeated."

Himself an A-bomb survivor, Mayor **Takeshi Araki** read Hiroshima's Peace



An oasis of green in the midst of bustling Hiroshima, Peace Park is the focus of annual commemoration ceremonies to honor the atomic-bomb victims and to promote the causes of world peace and nuclear disarmament.

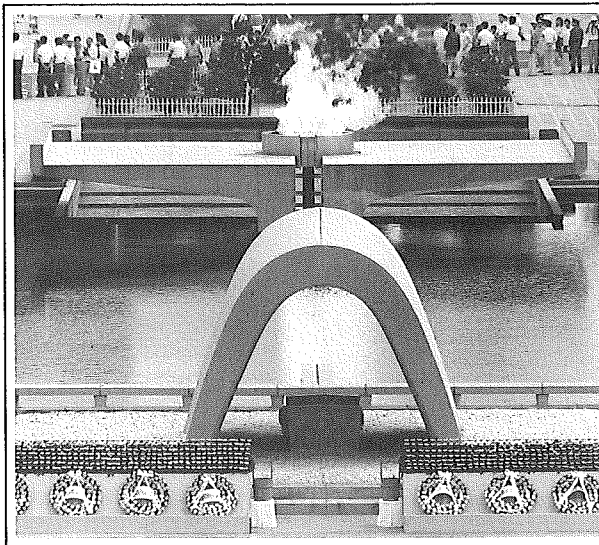
Declaration for 1989: "Building upon the Intermediate Nuclear Forces treaty, the United States and the Soviet Union are now negotiating for reductions in their strategic nuclear forces. The cold-war framework of East-West relations... is beginning to crumble after having defined postwar politics for so long, and the world is groping its way toward a new order of international peace. It is imperative that we seize the

moment to build a brighter future for all humankind."

In the Nagasaki Peace Declaration, Mayor **Hitoshi Motoshima**, an outspoken critic of Japan's role in World War II, stated: "Let us think deeply about the events from the attack on Pearl Harbor to the destruction of Nagasaki by an atomic bomb. The Pacific War began at Pearl Harbor and ended at Nagasaki, claiming in the process more than 20 million lives.

Let us reflect with sincerity on the war and pray for the repose of the souls of the many people from both Japan and other countries who were the victims of this dark chapter in history."

Each year the RERF permanent directors attend these commemorative ceremonies. In addition, many RERF employees make personal pilgrimages to these sites—some with their children, as yet another generation learns about the catastrophes that befell Hiroshima and Nagasaki 44 years ago. □



At the moment of detonation, the eternal Flame of Peace flares up fiercely behind the memorial Cenotaph, which is modeled after a haniwa or house for the dead found in prehistoric tombs in Japan.

What is a "Survivor"?

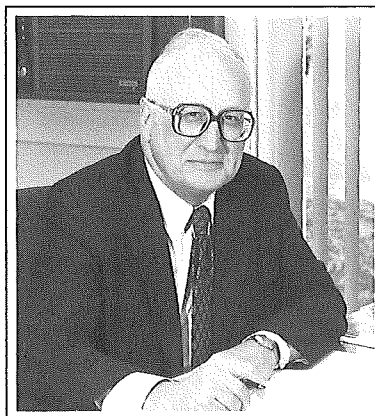
by J.W. Thiessen

RERF Vice Chairman & Update Editor-in-Chief

As is appropriate at this time of year, this issue of *Update* gives particular attention to the human aspects of the events of 1945, in addition to the scientific aspects that are well represented also. Many of our readers may not be aware of the existence of A-bomb survivors in the United States, about whom we have a short article in this issue. The front page, reporting on the memorial ceremonies in Hiroshima and Nagasaki, mentions the registries of deceased survivors, maintained in the Peace Parks of both cities. This made me wonder whether the annual addition of names to these registries does not actually imply that all those listed have, in fact, died as a consequence of the bombings, a conclusion that is—at least scientifically—untenable.

By extension, thinking about the term "survivor," I was struck by the fact that this word is often used in a very loose sense, especially when discussing the plight of survivors. Let me make it clear that I have no intention to diminish, in any way, the real suffering that many survivors have been subjected to or that is still ongoing. I do believe, however, that the classification "survivor" may create a fear of suffering that may well be worse than the actual pain, and, in many cases, as I hope to show, is not justified.

In our own research, although we may speak about survivors in a generic sense also, we routinely define the classes of survivors and the findings in those classes very precisely. Without such definition, it would be hard to state anything of scientific significance. Therefore, a generalization of the kind: "Survivors have a greater chance of developing cancer than those who have not been subjected to the effects of the bomb"—scientific in nature—is not necessarily true for each survivor, although it implies that it is. Only a subgroup of them was exposed to "notable" levels of radiation. So as not to get entrapped in trying to define what is "notable," I will for the sake of argument use a dose of at least 0.1 Gy, at which point the chance of a radiogenic cancer begins to exceed roughly one in a hundred, averaged over all ages and both sexes, according to the latest risk estimations by the BEIR Committee, based on RERF data (more about this in the next issue of *Update*). This dose (or rather: free-in-air kerma) was



Thiessen

extant at approximately 2,000 meters from the hypocenter (a little less in Hiroshima, a little more in Nagasaki). Given the presence of approximately 35,000 survivors within the 2-km range (data from the 1950 census), we might conclude that these people are, given the basic assumptions, at an increased risk of cancer.

In the late 1950s, the Japanese government started to make arrangements for the

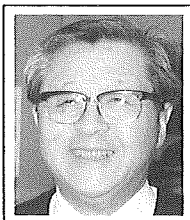
medical and financial support of the survivors (in Japanese: *hibakusha*, pronounced "he-bahk-shah," both singular and plural), which resulted in the distribution of "A-bomb handbooks" to all eligible survivors. Initially, only the occupants of the city districts within a 2-km radius were considered eligible, but consideration of fallout and "black rain," and humanitarian and political pressures led to a broadening of the eligibility limits, to the point that now about 165,000 people in Hiroshima Prefecture, and nearly 100,000 in Nagasaki Prefecture (a total of roughly 350,000 in all of Japan) are handbook holders. In other words, they are certified as survivors. I don't think it is inappropriate to say that the majority of this group is highly unlikely to have a significantly increased risk of cancer compared to those not meeting the eligibility requirements, yet many of these people might feel, by the simple fact of being a handbook holder, that they do.

This is, of course, a highly simplified discussion of a complex subject. Without a full understanding of the social, psychological—and yes—political issues involved, one should not pretend to know what, in all these senses, is a "survivor." In this issue, I only wanted to bring up the fact that different people mean different things when they speak about "A-bomb survivors," and that it is important to keep these differences in mind when discussing issues related to survivors. □

News Briefs

✓ RERF Researchers Retire After 30 Years of Service

The RERF laboratories bid a fond but sad farewell to two 30-year veterans: former Epidemiology Chief **Hiroo Kato** and radiologist **Walter Russell**.



Kato

Kato joined the ABCC in 1958 after a short period with the Ministry of Health and Welfare. Noted for his extensive contribution to the Life Span Study of mortality among A-bomb survivors, Kato is the co-author of 150 publications in the open literature and 78 ABCC-RERF technical reports.

Involved in diagnostic radiology and the monitoring of medical X-ray exposures of A-

bomb survivors, Russell was instrumental in sending 30 candidates to the US and UK to become board certified as radiologists at a time when the radiology specialty was new to Japan.

Also a prolific author of scientific articles and technical reports, Russell proudly noted that of the radiologists trained abroad, six are now department chiefs—five in Japan and one in the US.

✓ Soviet Scientist Observing Research Activities in Japan

Representing the medical institute responsible for follow-up studies related to the Chernobyl nuclear power plant accident, **Olga Tsvetkova** is spending four months observing clinical and laboratory activities at RERF's Hiroshima and Nagasaki facilities as well as at other institutes and hospitals throughout Japan. She is chief of the International Scientific Cooperation Department

at the USSR Scientific Center of Radiation Medicine in Kiev.

✓ Pathology Specimens Received

The Armed Forces Institute of Pathology recently returned to RERF a large collection of slides and paraffin blocks including autopsy and surgical pathology specimens that had been acquired by the AFIP in the 1940s and '50s. The interesting history of this US-Japan exchange will appear in a future issue of *Update*.

✓ 'Second Generation' A-bomb Survivors Convene

The children of A-bomb survivors from Japan and Korea met in Nagasaki for the first time early in August to discuss government relief measures on their behalf, health concerns, and problems related to social discrimination.

continued on page 5

Variation in human radiosensitivity?

Studying possible differences in radiation susceptibility among A-bomb survivors may provide a biological basis for defining uncertainties associated with A-bomb dosimetry

by **Nori Nakamura and Mitoshi Akiyama**
RERF Department of Radiobiology, Hiroshima

Uncertainties associated with the physical dosimetry of the A-bomb survivors continue to be scrutinized by creators of the DS86 dosimetry system. (See D.C. Kaul, *RERF Update* 1(2):4, 1989.)

Concurrently, biological evidence of radiation exposure, e.g., the occurrence of severe epilation among A-bomb survivors, is being used to analyze for the possible errors in dose received by survivors. (See D. Stram, *RERF Update* 1(2):5, 1989.)

Complicating these efforts is the possibility that human sensitivity to acute effects of radiation exposure varies from person to person. By means of in-vitro dose-survival studies using fibroblast colony assays, some researchers have claimed the existence of interindividual variations possibly due to genetic factors. Therefore, estimation of dose errors based on the occurrence of severe epilation will require two sets of data—the normal distribution of individuals with various radiosensitivities and the deviation from normality at each dose level among ABCC-RERF's long-term study cohort.

To collect such biological information, the development of the lymphocyte colony assay was a prerequisite because of ethical constraints related to obtaining skin biopsies from many healthy individuals. Using recombinant interleukin-2 along with appropriate feeder cells recently made possible the formation of lymphocyte colonies in vitro with high cloning efficiency (Nakamura et al, *RERF TR* 15-89). This lymphocyte assay has proved to be an efficient alternative to the fibroblast assay for assessing heterogeneity in human radiosensitivity derived from genetic variation. In addition, evidence does support the fact that the lymphocyte assay measures mitotic death commonly observed for many cultured cells and, importantly, that epilation may also be caused by the mitotic death of hair follicle cells.

Contrary to published results for fibroblasts, our results using the lymphocyte assay suggest very little interindividual variations in radiosensitivity. This conclusion is derived mainly from two observations during a lymphocyte dose-survival study: 1) repeated tests of one donor and 2) a single test for many different individuals. The mean \pm SD of D_{10} (a parameter used for statistical analysis which denotes the dose required to kill 90% of the lymphocytes) is 3.66 ± 0.21 Gy (the coefficient of variation [CV] = 5.7%) after repeated testing of a single donor ($n = 28$), and it was 3.58 ± 0.19 Gy (CV = 5.3%) after a single test of 31 different individuals (ages 20–72) (Nakamura et al, loc. cit.). The analysis of variance showed that interexperimental variation was not significantly greater than interindividual tests. The 95% upper confidence limit for the CV of the different individuals' D_{10} is 3.6%. Hence, it would be very unlikely for the true CV among individuals to be greater than 3.6%.

In the studies using skin fibroblasts, the CV for the mean of D_0 (the mean lethal dose or the dose required to reduce the surviving fraction to $e^{-1} = 0.37$ at the linear portion of the dose-survival curve) is reportedly 10%–20% for repeated testing of some cell strains and for a number of different strains (*Int J Radiat Biol* 38:575, 1980; *ibid.* 54:899, 1988; *ibid.*, 911; *Cancer Res* 40:920, 1989; *ibid.*, 926). Thus, it is thought that the discrepancy in the variability of dose-survival curves between our lymphocyte data and the published fibroblast data may be derived from two sources: 1) biased sampling of lymphocyte donors in our study or 2) an inherent artifact in the fibroblast study which increases the apparent variability.

To clarify this point, matched samples of lymphocytes and skin fibroblasts from 22 Japanese patients were tested. The results showed that the CV for the mean of the D_{10} value was 6% for the lymphocytes, and 11% for the fibroblasts (J. Kushiro et al, *RERF* technical report, submitted). By comparing dispersions of the observed data along the fitted curve, one can see that the actual data of fibroblasts are better distributed along the fitted curve than those of lymphocytes, demonstrating that greater variability of our present fibroblast survival curves is not derived from greater dispersion. Thus, current results suggest that interindividual variation is inherent to the fibroblast assay and is quite small as far as lymphocytes irradiated at G_0 are concerned. In addition, lymphocytes from more than 100 Adult Health Study participants have been recently tested in our laboratory and the CV for the mean D_{10} value was about 7%, very close to the

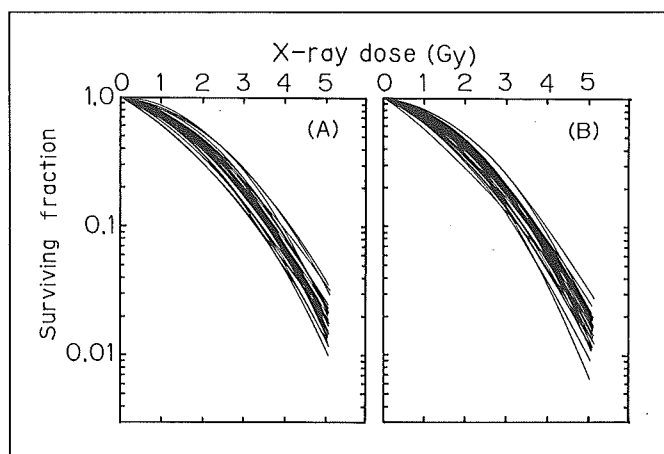


Figure 1. Dose survival curves from 28 repeat tests of a single donor (A) and for a single test of 31 individuals (B).

value for repeated testing of a single donor (Nakamura et al, unpublished data). This study originally was designed to test the hypothesis that a greater fraction of genetically radiosensitive individuals might have been lost from members of the ABCC-RERF study cohort who received high radiation doses. But this is not indicated by the data, simply because interindividual variation of lymphocyte radiosensitivity is considerably less than expected from the published fibroblast data.

One unresolved issue relates to fibroblast data that are mainly obtained from cells irradiated at a logarithmic growth stage, whereas in a lymphocyte assay cells are at the resting G_0 stage during irradiation. Testing matched samples of G_0 and growing lymphocytes from the same donors will provide an answer to whether cell stage differences at the time of in-vitro X irradiation affect the variability of individual radiosensitivity. Such a study is now being planned in our laboratory.

In the previous issue of *RERF Update*, Daniel Stram discussed recent findings on the greater effects of radiation exposure among those who experienced severe epilation, such as induction of chromosome aberrations and leukemia mortality (Stram, loc. cit.). Laboratory tests are needed to clarify whether such greater effects are a result of genetic heterogeneity in human radiosensitivity or are a reflection of errors associated with dosimetry—the latter being suggested by our current results even though a single biological endpoint, cell killing, was used for these tests. □

Radiation-induced Aberrant Chromosomes in Cultured Skin Cells of A-bomb Survivors

by Takeo Honda
RERF Department of
Radiobiology, Nagasaki

One of the most intriguing but difficult questions regarding late A-bomb radiation effects on survivors is whether radiation-induced chromosome aberrations persisting in somatic cells of the exposed persons are involved in the development of somatic diseases such as neoplasms. This question has remained unsolved since cytogenetic studies were initiated at ABCC more than 20 years ago. This was mainly due to the limitations of the blood culture method, i.e., the low yield of chromosomally aberrant cells and the short life of PHA-stimulated lymphocytes under culture conditions, as well as the difficulties in obtaining skin tissues and other specimens that can be cultured for long periods of time and provide suitable materials for this kind of cytogenetic investigation.

Recently, however, in collaboration with three other medical institutions we began studies of the chromosomes of cultured skin cells obtained from A-bomb survivors in Nagasaki. For the first time, we demonstrated not only various kinds of radiation-induced chromosome aberrations in skin cells of the survivors, but also marked clonal proliferation of certain chromosomally abnormal cells. These cytogenetic results obtained from survivors encouraged us to analyze the marked proliferation of clone cells containing chromosome aberrations and the possible relationships of specific oncogenes

to the breakpoint sites, using the G-banding technique.

We have so far managed to analyze only two clones derived from two A-bomb survivors among 11 for whom skin

of clonal origin.

With regard to the rate of clone cells versus the total cells examined in these two specimens, 42 of 220 cells in Case 1 showed abnormal chromosomes, and 20

Table 1. Type and frequency of clone cells observed in two A-bomb survivors

Case	Type	Number of clone cells*	Number of aberrant cells	Total number of cells observed
1. N.S.	t(1p-;Fq+)	20 (9.1)*		
	t(Bq-;18q+)	6	42	220
	t(Cq+;Cq-)	2		
2. M.H.	t(2q-;Dq+)	32 (36.4)	34	88
Total		60 (19.9)	76 (25.2)	308

* Percentage is shown in parentheses.

cell chromosomes were observed, but the results of G-banding analysis as described in the following paragraphs suggest a strong relationship between specific oncogenes and breakpoint sites.

The two skin specimens were obtained from two survivors: a woman (N.S., Case 1) and a man (M.H., Case 2) aged 63 and 69 at the time of examination, respectively. They were exposed to A-bomb radiation at 1,240 and 1,718 meters from the hypocenter and developed acute symptoms, such as epilation, hematemesis, fever and diarrhea. Their DS86 doses are unavailable, but according to the T65D system, the doses were 181 rad (1.8 Gy) for the woman and 44 rad (0.44 Gy) for the man.

Our skin culture method was simple. The skin tissues from the two subjects

were minced and cultured in a CO₂ incubator on MEM medium containing 15% bovine serum for 3–5 weeks and then were harvested for chromosome preparation. G-banding was performed in addition to the ordinary Giemsa staining for chromosome analysis.

Among a total of 308 cells examined, as shown in Table 1, 76 cells or 25.2% had abnormal chromosomes and 79% of these were

of these or 9.1% of the total cells examined had translocation t(1p-;Fq+). In this specimen, t(Bq-;18p+) and t(Cq+;Cq-) were also observed in six and two cells, respectively.

In Case 2, 34 of 88 cells (39%) examined showed chromosome abnormalities, and 32 of these or 94% of the aberrant translocations containing cells were of a singular origin with t(2q-;Dq+). Chromosome abnormalities in the remaining two cells were entirely different from the clone cells.

Next we examined if a relationship exists between the radiation-induced breakpoints of abnormal chromosomes in these clone cells and the loci of proto-oncogenes.

The G-banding partial karyotype of the clone cells observed in Case 1 is shown in Figure 1 in comparison to the standard pattern based on international criteria. It is suggested that the breakpoint on the abnormal chromosome is located near the band 1p11 to 1p22 of the short arm of chromosome 1 and on 20q13 in chromosome 20.

It has been reported that the locus of oncogene *N-ras* is located on the band 1p11-12 or 1p22, and *src* on 20q13.

In Case 2, the translocation breakpoints were suggested by G-banding analysis to be at or near t(2;13)(q14;33). The loci of the two oncogenes, though different from those in Case 1, are located at or close to the breakpoints: oncogene *lca* at 2q14 (M.C. Yoshida, Hokkaido University, personal communication) and *cbl* at 13q33.

The fact that the breakpoints of abnormal chromosomes in two kinds of clone cells are located at or near the loci

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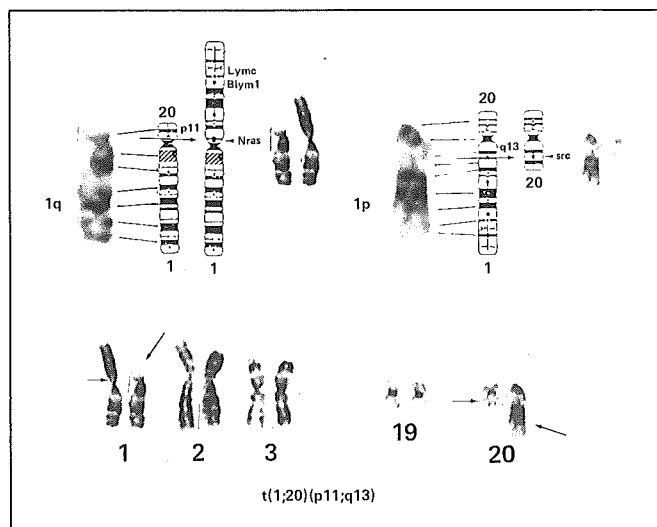


Figure 1. On each chromosomal map, this G-band partial karyotype shows t(1;20)(p11;q13) and two loci of the proto-oncogenes *N-ras* and *src* (Case 1).

North American A-bomb Survivors Meet Japanese Doctors

For decades, A-bomb survivors residing in the US and Canada received few of the official relief benefits offered to their counterparts back in the homeland. More than half of these survivors are known as *kibei nisei*, who in accordance with the Japanese-American traditions of that day, had returned to Japan to acquire Japanese education and remained there after the outbreak of the Pacific War. Exposed to A-bomb radiation, many later returned to America—the country of their birth—after official restoration of their citizenship.

Back in America, the A-bomb survivors faced not only social and cultural problems, but ineligibility for medical insurance due to their A-bomb exposure. Finally, in 1977 the Hiroshima Prefectural Medical Association sponsored the first consultations with A-bomb survivors.

Last year four survivors from the US received special medical treatment ranging from one to six months in duration at the Hiroshima Red Cross A-Bomb Hospital, Hiroshima University, and other local facilities. Beginning in 1989, the association will provide ¥5 million (about US\$36,000) annually for medical treatment in Japan, and the Hiroshima prefectural and city governments will annually subsidize this with ¥500,000 (about US\$3,500) each.

This year, the seventh biennial medical team traveled to Los Angeles, Honolulu, Seattle and San Francisco, where they were assisted by American volunteers and hosted by local medical associations. RERF physicians **Kazunori Kodama** and **Hideo Sasaki**, and Research Assistant **Tadaaki Watanabe** of the departments of Clinical Studies and Epidemiology were part of the seven-person team from Hiroshima.

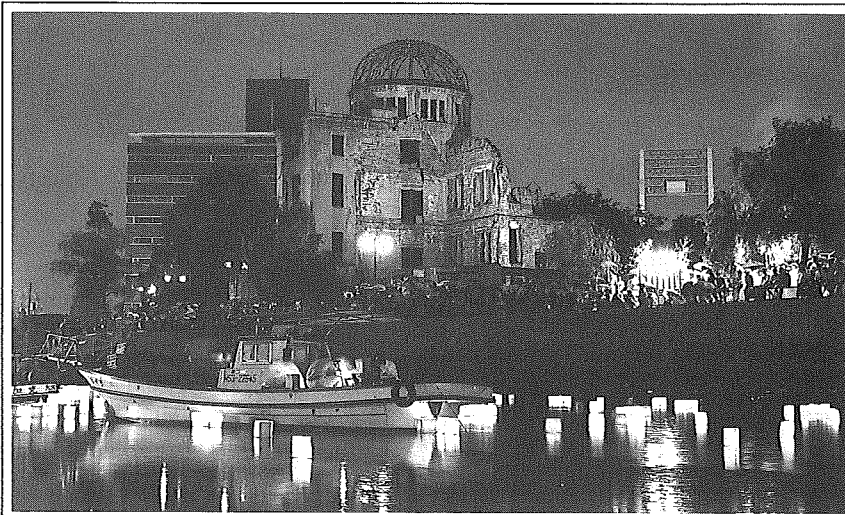
In advance, the Committee of A-Bomb Survivors in the US, which is based in San Francisco, distributed questionnaires prepared in Japan to its 751 members. As a result, a total of 406 persons were seen this year: 101 men and 305 women whose average age is in the late 50s. The city-by-city count was: Los Angeles—132, San Francisco—115, Honolulu and Wailuku—113, and Seattle—46 (including Canadians). Results

of the 1989 consultations are not yet available.

According to the 1987 survey, about 26% of North American survivors were proximally exposed to A-bomb radiation, including six out of 14 in-utero survivors. Most were between 15 and 19 years old at the time of the bombing.

The 1987 results also revealed that

68.1% of survivors required medical treatment or follow-up. Hypertension was noted in 25%, followed by obesity, hyperlipidemia, heart disease, thyroid disease, osteoarthritis and diabetes mellitus. Subjective symptoms reported most frequently were complete exhaustion or fatigue, heat intolerance, numbness of the body, and loss of vigor. □



The A-Bomb Dome provides a solemn backdrop as varicolored paper and wood lanterns are set adrift each 6 August to honor the souls of those who perished in the atomic bombing of Hiroshima.

A-Bomb Dome to be Repaired

Untouched for 22 years, the world's best known symbol of nuclear disaster is literally falling apart. The forces of nature and the effects of nearby traffic have destabilized the A-Bomb Dome to such a degree that structural repair is urgently needed to ensure its preservation.

As of early September, more than ¥200 million (US\$1.5 million) had been collected via 5,800 contributions from within Japan and from abroad. An RERF employee bazaar that raised more than ¥62,000 (about US\$500) for the repair work is characteristic of grass-roots support for this endeavor.

Why save the decrepit structure? As the director of the Hiroshima International Cultural Foundation, **Akira Yamamoto**, phrased it: "... the importance of the A-Bomb Dome lies not merely in its value as testimony to the events of 1945; it also calls out a warning to all of us who live in this nuclear age not to repeat the mistakes of the past."

The Hiroshima City Government, which is itself supplying ¥100 million, will continue to accept contributions through 25 December 1989. Repairs are scheduled to begin in October. □

News Briefs

continued from page 2

Local media reports cited RERF research which indicates that to date "... there is no significant difference in the incidence of disease between the second generation survivors and people of the same age whose parents were not exposed to the atomic bombing."

✓ Survivors' Teeth May Reveal Real Radiation Doses

Researchers at RERF and from the Research Institute for Nuclear Medicine and Biology of Hiroshima University are collecting teeth from A-bomb survivors for future use in ESR analysis. In two years, 130 teeth

have been collected from persons who had been within 2 km of hypocenter at the time of the bomb blasts. After several more years, if the technical problems related to ESR have been partially resolved, the absorbed dose of these teeth will be measured at RINMB. Biological endpoints, such as chromosome aberrations and somatic cell mutations, will be determined concurrently at RERF.

✓ Death of Cytogenetics Expert Mourned

Sajiro Makino, professor emeritus at Hokkaido University, passed away on 6 August at the age of 83. Makino served as an ABCC consultant from 1966–1975, and actively contributed to the development of RERF's cytogenetics program.

✓ 'Black Rain' Estimates for Nagasaki Revised

The National Institute of Radiological Sciences recently revealed new estimates of the range of radioactive fallout generated by the Nagasaki atomic bomb.

Based on a photograph taken 40 minutes after the detonation, researchers at the Meteorological Research Institute used a supercomputer to determine that the cloud reached a height of about 11,000 meters. They were then able to estimate how far radioactive particles were carried by the 1.5 meter-per-second westerly wind blowing in Nagasaki on the day of the bombing.

It is now thought that black rain, which

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Central Archives To Be Created at RERF

Faced with the possible loss of valuable research documents, the board of directors unanimously approved the creation of a research documentation repository at RERF.

During the last 40 years, the Foundation's informal research documentation, such as protocols, manuals, memoranda, correspondence and consultant's reports, has gradually

accumulated to form an irreplaceable resource. Although the long-established research protocol and technical report series chronicles RERF's formalized research efforts, access to and storage of informal documents have never been systematized.

Already the safekeeping of such material is threatened by the imminent retirement of many long-term employees, whose careers have spanned the entire duration of the ABCC-RERF research program. In addition, the routine turnover of foreign staff members is yet another source of lost documents.

To prepare for safe, systematic storage that will efficiently provide access to these materials, a few staff members were concurrently assigned as of 1 September to begin preliminary planning for these archives. **Kokichi Omae** is acting chief of the new office.

Readers of *Update* who possess any documents of relevance that may possibly be missing from RERF are encouraged to contact Permanent Director **Yutaka Hasegawa** (FAX No. 082-263-7279). □

International Oral Presentations

The 5th International Conference on Environmental Mutagens, Cleveland, Ohio, 10-15 July 1989.

♦ *Comparison of cytogenetic, HPRT and glycophorin A studies in A-bomb survivors.* M Akiyama, S Kyoizumi, Y Hirai, M Hakoda, N Nakamura, AA Awa.

♦ *Approaches to DNA methods for the detection of heritable mutations in humans.* C Sato, K Hiyama, N Takahashi, M Kodaira.

The 7th International Congress of Immunology, West Berlin, 30 July-5 August 1989.

♦ *Cloning and analysis of human peripheral CD4+ lymphocytes lacking membrane expression of the TcR-CD3 complex.* M Akiyama, S Kyoizumi, Y Hirai, Y Kusunoki.

The 12th Congress of the International Society on Thrombosis and Haemostasis, Tokyo, 19-25 August 1989.

♦ *Possible role of lupus anticoagulant-dependent endothelial cell injury on recurrent fetal loss.* S Kusumi, T Shimomura, K Oda, A Kimura, K Fujimura, A Kuramoto, M Yamamoto, Y Satoh.

The 2nd Meeting of the International Society for Trace Element Research in Humans, Tokyo, 28 August-1 September 1989.

♦ *Serum selenium and zinc and the risk of lung and stomach cancer in Japanese.* M Kabuto, H Imai, C Yonezawa, WJ Blot, K Neriishi, S Akiba, T Suzuki, CE Land.

Aberrant Chromosomes

continued from page 4

of four different oncogenes suggests a mechanism for the potentially active proliferation of clone cells, which is noteworthy. We believe that the in-vitro cell culture conditions provided a selective growth advantage for these cells whose chromosomes were broken at or near oncogene sites. We suggest that in the in-vivo condition the same growth advantage will be available to such cells given appropriate changes in the tissue environment.

We are conducting detailed analyses in an attempt to elucidate the relationship between radiation-induced breakpoints of chromosomes and the loci of oncogenes while increasing the number of clone cases. In addition to the cytogenetic analyses, the expression of proto-oncogenes that are expected to be present on the breakpoints is being examined by immunochemical techniques. □

News Briefs

continued from page 5

fell between 20 and 60 minutes after the explosion, fell most heavily in the Nishiyama district 3 kilometers east of the hypocenter, but extended as far as 15 kilometers east of the hypocenter to Makishima Island.

✓ Chairman Speaks at Mayors' Peace Conference

Itsuzo Shigematsu, RERF chairman, discussed the medical effects of nuclear weapons at the Second Mayors' Conference for World Peace, held in Hiroshima and Nagasaki 5-9 August. Scheduled to coincide with the annual atomic-bomb commemoration ceremonies in both cities, the conference was attended by representatives from about 100 cities. Thirty-eight Japanese and 14 American cities sent delegates in support of appeals for world peace and the abolition of nuclear weapons.

✓ Chinese Scientist at Hiroshima Laboratory

Visiting Research Fellow **Sun Quanfu** will focus on review of epidemiological methods employed in RERF's Life Span Study and study of methods of analysis during his one-year stay in the Department of Epidemiology. He is from the Laboratory of Industrial Hygiene in Beijing.



From left: Mabuchi, Preston, and Kodama.

✓ Research Staff Appointments Announced

Department of Epidemiology: Department of Epidemiologic Pathology Chief **Kiyohiko Mabuchi** is concurrently serving as chief of the Department of Epidemiology, following the retirement of **Hiroo Kato**. **Midori Soda** is concurrently serving as section chief of the Tumor and Tissue Registry Office and as assistant department chief of the Department of Epidemiologic Pathology at the Nagasaki Laboratory.

Department of Statistics: **Dale L. Preston** was named chief of the department upon returning to Hiroshima after two years at the US National Cancer Institute, Bethesda, Md. He had previously served as chief of RERF's Research Information Center. Research Associate **Shoichiro Fujita** has been promoted to associate senior scientist. University of Florida associate professor **Randolph L. Carter** has joined the department as a research associate.

Department of Clinical Studies: **Kazunori Kodama** is now acting chief of the department, having replaced former chief **Yutaka Hosoda**, who has been appointed departmental scientific advisor following his recent retirement. Research Associates **Saeko Fujiwara** and **Shizuyo Kusumi** have been promoted to associate senior scientists.

✓ BEIR V Committee Member Visits Foundation

Jacob L. Fabrikant of the Donner Laboratory, University of California-Berkeley, spent several days at the Hiroshima and Nagasaki laboratories, where he lectured on risk assessment and met with staff members.

In the next issue of *Update*, look for Fabrikant's article on risk estimates and the role RERF's data played in the forthcoming conclusions of the BEIR V Committee. □

Recent Scientific Publications

Approved Technical Reports

Reliability of soluble IL-2 receptor measurements obtained with enzyme-linked immunosorbent assay. M Akiyama, M Takaishi, Y Murakami, R Ueda, M Yamakido, T Tsubokura. **RERF TR 9-89.**

Using an enzyme-linked immunosorbent assay (ELISA), human soluble interleukin-2 receptors (IL-2Rs) were measured in the serum of patients with various autoimmune system diseases. To study the sensitivity and specificity of the assay, the soluble IL-2Rs were measured in the culture supernatants and in the cell extracts of peripheral blood mononuclear cells activated with phytohemagglutinin (PHA), purified protein derivative of tuberculin, and allogeneic lymphocytes, as well as in the serum of patients with various collagen diseases. The results correlated well with reports from other laboratories. For example, when stimulated by PHA, the greatest amount of soluble IL-2Rs was produced very rapidly. In addition, soluble IL-2R levels in the serum of collagen disease patients were significantly higher than those in healthy persons, who themselves had low levels of detectable soluble IL-2Rs.

It is hoped that reliable ELISA measurements of soluble IL-2Rs in the serum of A-bomb survivors will assist in the interpretation of data collected during the work described in RP 2-87, a study of autoimmunity and autoimmune diseases in the Adult Health Study.

Abdominal ultrasonographic screening of Adult Health Study participants. WJ Russell, Y Higashi, T Fukuya, Y Hosoda, J Murakami, A Mizushima, A Kawashima, S Murayama, T Ohuchida, F Mihara, M Takagi, S Fujita. **RERF TR 10-89.**

To assess ultrasonography's capabilities in the detection of cancer and other diseases, abdominal ultrasonographic screening was performed for 3,707 Hiroshima and 2,294 Nagasaki A-bomb survivors and comparison subjects who participated in the Adult Health Study from 1 November 1981 to 31 October 1985 in Hiroshima and from 1 August 1984 to 31 July 1986 in Nagasaki. A total of 20 cancers were detected, consisting of 7 hepatomas, 3 gastric cancers, 3 renal cancers, 2 cancers of the urinary bladder, and 1 cancer each of the ovary, pancreas, colon, ureter and liver (metastatic). The cancer detection rate was 0.33%. The diagnoses of 7 cancer subjects in each city were subsequently confirmed at autopsy or surgery; diagnoses of 4 cancer subjects in Hiroshima and 2 in Nagasaki were obtained from death certificates. Among the 20 cancer patients, 13 were asymptomatic. After the ultrasonographic detection and diagnosis of these 20 cancers, the medical records of each of the 20 cancer patients were reviewed for any evidence of cancer detection by other examining techniques, and the records of only 3 patients revealed such recent detection. The tumor and tissue registries were similarly checked, but no evidence of earlier diagnosis of their disease was found. Ten of

the cancer patients had received radiation doses from the A-bombs ranging up to 3,421 mGy (DS86), but no correlation was established between cancer prevalence and the A-bomb doses. A variety of tumors, 259 in number and most probably benign, were also detected with ultrasonography. In addition, numerous other abnormalities were diagnosed, with prevalences of 7.7% for cholelithiasis, 5.7% for renal cysts, and 3.8% for liver cysts. No statistical analysis was performed concerning the prevalence of the diseases detected.

Calibration of $Mg_2SiO_4(Tb)$ thermoluminescent dosimeters for use in determining diagnostic X-ray doses to Adult Health Study participants. K Kato, S Antoku, S Sawada, WJ Russell. **RERF TR 11-89.**

Characteristics of $Mg_2SiO_4(Tb)$ thermoluminescent dosimeters (TLDs) were ascertained preparatory to measuring dose from diagnostic X-ray examinations received by Adult Health Study (AHS) participants. These detectors are small, relatively sensitive to low-dose X rays, and are appropriate for precise dosimetry. Extensive calibration is necessary for precisely determining doses according to their thermoluminescent intensities. Their sensitivities were investigated by dose according to X-ray tube voltage and by exposure direction to obtain directional dependence. Dosimeter sensitivity lessened due to the fading effect and diminution of the planchet. However, these adverse effects can be avoided by storing the dosimeters at least 1.5 hours and by using fresh silver-plated planchets. Thus, the TLDs, for which sensitivities were determined in this study, will be useful in subsequent diagnostic X-ray dosimetry.

Incidence of thoracic vertebral fractures among Adult Health Study participants, Hiroshima and Nagasaki, 1958-86. S Fujiwara, S Mizuno, Y Ochi, H Sasaki, WJ Russell, Y Hosoda. **RERF TR 12-89.**

The incidence of thoracic vertebral fractures (TVF) in a fixed Hiroshima and Nagasaki population of 16,027 was determined by sex, age, and atomic bomb ionizing radiation exposure. Diagnosis was based on lateral chest radiographs made from 1 July 1958 to 28 February 1986. Born between 1880 and 1940, the subjects were categorized by sex into 10-year birth cohorts. When examined by birth cohort and age at onset, the age dependency of TVF incidence showed a good fit to a log-linear regression model. In females, TVF incidence tended to be lower in the younger birth cohorts and tended to increase with age in all birth cohorts. With each 10-year increase in age, the incidence among females increased by a factor of 1.7. In males, the incidence was significantly lower in the younger birth cohorts, but did not increase with age. The incidence decreased by a factor of 0.5 in males and 0.6 in females as the birth cohort age became younger. TVF incidence was greater in males until the age of 50, was equal by sex in the sixth decade, and was greater among females, who were 60 years of age or older.

TVF incidence did not differ by city, and

no correlation with A-bomb radiation exposure was demonstrated.

Approved Research Protocols

Screening of stem cell mutation in lymphoid lineage among A-bomb survivors and its characterization. Y Hirai, Y Kusunoki, S Kyoizumi, M Hakoda, N Nakamura, AA Awa, R Sposto, M Akiyama. **RERF RP 7-89.**

A study of A-bomb survivors is proposed to identify individuals in whom the mutant frequency of peripheral T lymphocytes is more than 10 times higher than the average in a control group. In such individuals, it is assumed that mutations may have occurred in the stem cells of the lymphoid lineage as a result of exposure to A-bomb radiation. Therefore, an analysis of chromosomes and HPRT genes will be undertaken for each mutant colony to determine its clonality. In addition, rearrangement of T-cell receptor genes and B-cell mutation frequency will also be examined to estimate the stage of differentiation at which the mutation may have occurred.

Senile changes of the brain in Hiroshima and Nagasaki A-bomb survivors. M Kishikawa, M Otake, T Kobuke, M Iseki, H Kondo, M Tokunaga, H Fujii, I Nishimori. **RERF RP 8-89.**

This investigation will consider the late effects of radiation exposure on aging of the central nervous system by attempting to determine if observable changes of the brain may have resulted from A-bomb exposure.

For 4,611 members of the extended Life Span Study (3,677 from Hiroshima and 934 from Nagasaki), brain tissues obtained during autopsies performed from 1951-86, as well as DS86 organ dose estimates for the brain, are available. A study group of 107 subjects, including 91 in Hiroshima (38 males and 53 females) and 16 in Nagasaki (6 males and 10 females), was chosen from among those who had been 30-39 years old at the time of exposure, 50 years old or more at the time of death, and whose organ dose to the brain was 0.10 Gy or more. A total of 109 subjects, 93 from Hiroshima (52 males and 41 females), and 42 from Nagasaki (25 males and 17 females), was chosen from among those exposed to less than 0.01 Gy for use as controls. A total of 190 subjects, 95 each from the study and control groups (158 in Hiroshima and 32 in Nagasaki), will be selected for the current study with as close matching as possible for sex and age (for both age at exposure and age at death).

Using special stains, serial sections will be prepared for the three brain sites (the hippocampus and parahippocampal gyrus, the tip of the frontal cortex, and the tip of the occipital cortex). These sections will be examined for senile plaques, neurofibrillary tangles, granulovacuolar degeneration, and such vascular lesions as amyloid angiopathy by the pathologists without previous knowledge of the exposure status, age, sex or underlying disease of each subject. The

continued on page 8

Recent Scientific Publications

continued from page 7

results will be examined for relationships to radiation dose and aging effects.

Detecting erythrocyte mutations at the glycophorin A locus in Nagasaki A-bomb survivors and in Hiroshima area poison gas workers (addendum to RP 7-88). S Umeki, S Kyoizumi, S Matsusaki, T Honda, M Yamakido, N Nakamura, M Akiyama. *RERF RP 9-89*.

Using the methods described in RP 7-88, it is proposed to measure erythrocyte mutant frequencies in 210 Nagasaki A-bomb survivors and in 135 poison gas workers.

Approved Commentaries and Reviews

An overview of the cancer mortality data on the A-bomb survivors. DA Pierce. *RERF CR 1-89*.

A brief description is given of the cancer mortality data at RERF, with the aim of providing some general perspective on the extent of the excess cancer mortality for those who may not be inclined to glean this information from the more comprehensive reports on the Life Span Study. In addition, a summary is given of the changes in dosimetry given by the recently installed DS86 system. Even a cursory view of these changes requires consideration of several factors: changes in air doses, in environmental and organ shielding factors, in the extent of the neutron component, and in effects of truncation of exposures at 6 Gy. Finally, a brief discussion is given of the evolution of radiogenic cancer risk estimates during the past 10–15 years.

Cancer risk estimation from the A-bomb survivors: extrapolation to low doses, use of relative risk models, and other uncertainties. DA Pierce, M Vaeth. *RERF CR 2-89*.

Generalizations regarding radiogenic cancer risks from the A-bomb survivor data of RERF involve a large number of well-identified uncertainties and approximations. These include extrapolation to low doses and dose rates, projections in time, sampling variation, the quality of the data, extrapolation to other populations, and the use of simplifying conventions. This paper discusses some of these issues, with emphasis on the first three. Results are given regarding the maximum "linear-quadratic" curvature consistent with these data, taking into account uncertainties in individual exposure estimates. Discussion is given regarding use of relative risk models and projection of lifetime risks, emphasizing results for those who were old enough at exposure to have been followed up for a major part of their lives, and stressing the speculative aspects of conclusions about those exposed as children. By combining these results and by briefly discussing other uncertainties itemized above, comment is made on the evolution of risk estimates over the past 15 years.

Calculating excess lifetime risk in relative risk models. M Vaeth, DA Pierce. *RERF CR 3-89*.

When assessing the impact of radiation

exposure, it is common practice to present the final conclusions in terms of excess lifetime cancer risk in a population exposed to a given dose. The present investigation was mainly a methodological study focusing on some of the major issues and uncertainties involved in the calculation of such excess lifetime risks and related risk projection methods. The age-constant relative risk model used in recent analyses of the cancer mortality observed in the follow-up of the cohort of A-bomb survivors in Hiroshima and Nagasaki was used to describe the effect of radiation exposure on cancer mortality. In this type of model, the excess relative risk is constant in age-at-risk, but depends on the age-at-exposure.

Calculation of excess lifetime risks usually requires rather complicated life-table computations. Here a simple approximation to the excess lifetime risk has been proposed and the validity of the approximation for low levels of exposure has been justified empirically as well as theoretically. This approximation has provided important guidance in understanding the influence of the various factors involved in risk projections. Among the further topics considered were the influence of a latent period, the additional problems involved in calculations of site-specific excess lifetime cancer risks, the consequences of a leveling off or a plateau in the excess relative risk and the uncertainties involved in transferring results from one population to another.

The main part of this study relates to a situation characterized by a single, instantaneous exposure, but a brief discussion of the problem as it relates to a continuous exposure at a low dose rate is also given.

Publications in the Open Literature

Changes in the radioactive environment due to the Chernobyl nuclear plant accident. I Shigematsu, S Fujita. *Gazo Shindan-J Med Imaging 9:314–22*, 1989 (in Japanese).

Detection of somatic mutations at the glycophorin A locus in erythrocytes of atomic bomb survivors using a single beam flow sorter. S Kyoizumi, N Nakamura, M Hakoda, AA Awa, MA Bean, RH Jensen, M Akiyama. *Cancer Res 49:581–8*, 1989.

Effects of blood pressure changes on development and regression of electrocardiographic left ventricular hypertrophy: A 26 year longitudinal study. N Ashizawa, S Seto, K Kitano, K Toyama, H Sasaki, K Kodama, Y Hosoda, K Shimaoka, Y Shibata, K Hashiba. *J Am Coll Cardiol 13:165–72*, 1989.

Cloning of phenotypically different human lymphocytes originating from a single stem cell. M Hakoda, Y Hirai, H Shimba, Y Kusunoki, S Kyoizumi, Y Kodama, M

Akiyama. *J Exp Med 169:1265–76*, 1989.

Dental radiography exposure of the Hiroshima and Nagasaki populations. S Antoku, M Hoshi, WJ Russell, T Kihara, S Sawada, K Takeshita, M Otake, H Yoshinaga, DR Beach. *Oral Surg 67:354–60*, 1989.

Tracheobronchial calcification in members of a fixed population sample. T Fukuya, F Mihara, S Kudo, WJ Russell, RR Delongchamp, M Vaeth, Y Hosoda. *Acta Radiol 30:277–80*, 1989.

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Detection of circulating tumor associated antigen with a murine monoclonal antibody, LISA 101, selected by reversed indirect enzyme-linked immunosorbent assay. N Kohno, S Kyoizumi, M Tanabe, T Oyama, MR Vossler, M Yamakido, M Akiyama. *Cancer Res 49:3412–9*, 1989. □

RERF update RERF

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