RERF update RERF

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

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RERF Scientists Visit Chelyabinsk

In late October, a delegation from RERF visited the Ural Research Center for Radiation Medicine (URCRM) to follow up on the collaborative research agreement signed by the two parties on 12 May 1992 (see *RERF Update* 4(2):1, 1992). According to this agreement, RERF and URCRM would work closely to evaluate similarities and differences between their two data sets and to develop protocols for specific research projects. Discussions centered on potential projects in epidemiology and risk evaluation, biological dosimetry, medical follow-up, and dose reconstruction.

URCRM has been involved for many years in conducting medical follow-up studies of radiation-exposed populations, estimating internal doses, and evaluating environmental exposures, as well as doing clinical, immunologic, and cytogenetic laboratory testing.

Possible populations for collaborative study are those affected by the Techa River release or the Kyshtym accident. (For short descriptions of these incidents, see *RERF Update* 3(1):1, 1991.)

Representing RERF were **Dale Preston** (Department of Statistics), **Akio A Awa** (Department of Genetics), and **Hideo Sasaki** (Department of Clinical Studies). Key scientists in Chelyabinsk were **Alexander Akleyev**, **Mira Kossenko**, and **Marina Degteva**. The RERF delegation also met with **Nina Koshurnikova** and her colleagues from the Mayak nuclear-weapons production complex in Chelyabinsk-65. Koshurnikova described the current status of studies of workers who received elevated exposures in the early years of the Soviet nuclear-weapons program.

To analyze comparatively atomic-bomb populations and those from Chelyabinsk, standardization will be necessary, eg, with respect to registering exposed individuals, defining study cohorts, verifying cause of death, and establishing diagnostic criteria and laboratory procedures. These topics will be discussed further when a Russian delegation visits RERF. Soon thereafter, another meeting will be held to define future projects for research collaboration.

Many people affected by the Techa River release may have been exposed to doses exceeding 0.5 Gy, with some as high as a few gray. Among members of the highest exposure categories, Russian scientists have noted a "chronic radiation syndrome" (CRS), a new disease entity occurring in people exposed to substantially elevated radiation levels for an extended time.

A few pilot studies and additional analyses will be undertaken to determine the feasibility of proposed studies in such fields as cytogenetics. About 20 blood donors will be surveyed. Half of the subjects are considered to have been heavily exposed (ie, exposed to 1 Gy or more), whereas the other half will be age- and sex-matched controls. Half of the heavily exposed people have suffered from CRS, the other half—though estimated to have been exposed to the same levels of radiation—did not experience CRS.

"The URCRM scientists clarified their definition of mortality and morbidity cohorts resulting from the Techa River and Kyshtym incidents, and they helped RERF scientists better understand the nature of the comparison populations and follow-up procedures," remarked Preston.

URCRM and RERF researchers hope to develop a project to compare risk estimates derived from the RERF Life Span Study with those from the Russian cohorts.

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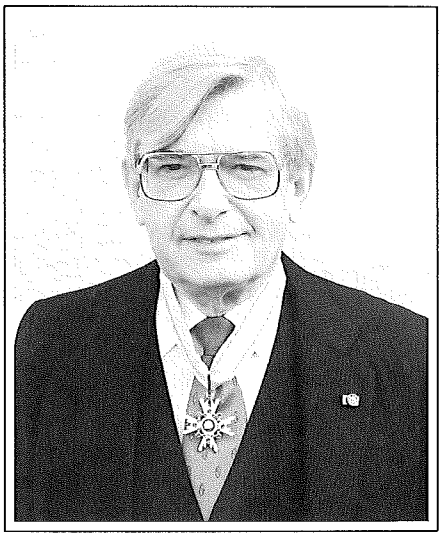
Schull Receives Imperial Award

On 3 November, longtime RERF research associate **William J. Schull** was awarded an imperial award, known as the Third Order of the Sacred Treasure—the highest imperial award bestowed upon those who are not citizens of Japan. Schull was one of this year's nine recipients of the third-class order.

In This Issue

For more than 4 decades since he assumed the post of ABCC Genetics Department chief in 1949, Schull has participated in the operation and management of ABCC–RERF, while also continuing his research activities in human genetics, first at the University of Michigan and later at the University of Texas.

In remarks made to more than 140 friends and colleagues who gathered to honor him at the Hiroshima Laboratory, Schull said, "This award has not been presented to me, but to the many people who have contributed to the ABCC–RERF research effort for so many years." ❑

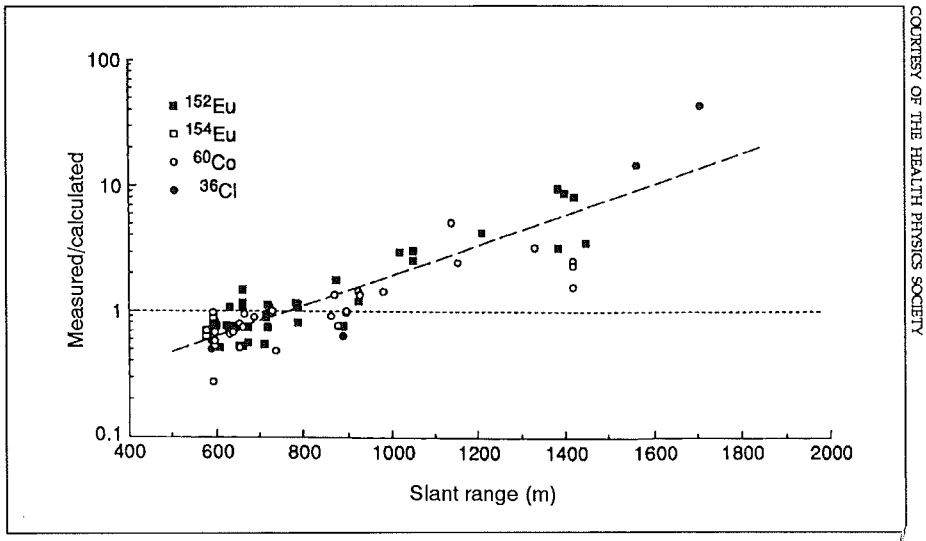


Y. OGASAWARA

Schull wearing his award

Neutrons in Hiroshima—the Problem that Won't Go Away

by J. W. Thiessen, RERF Vice Chairman & Update *Editor in Chief*



COURTESY OF THE HEALTH PHYSICS SOCIETY

Measured-to-calculated neutron-activation ratios in Hiroshima at various distances from the epicenter.

Uncertainties in the Dosimetry System 1986 (DS86) have been the subject, directly or indirectly, of many articles in *RERF Update*, so many that I won't bore the readers with a listing of them. One of the more consequential uncertainties involves the apparent discrepancy between measured thermal-neutron activation and calculated values derived from DS86. In the October 1992 issue of *Health Physics*, **Tore Straume et al** published an article (*Health Phys* 63:421–6, 1992) that summarizes and quantitates the discrepancies, and from which we reproduce (with the kind permission of the Health Physics Society) Figure 1. Although the problem has been known for some time, Straume added to the old data base by studying chlorine activation (which results in long-lived Cl-36) and Japanese investigators by measuring europium activation (to Eu-152 and Eu-154). **George Kerr** has even been able to add another Co-60 data point by investigating a large sample of steel obtained from a Hiroshima bridge that was recently razed. This additional information, found in the Figure, clearly strengthens the conclusion that there is indeed a systematic error in the DS86 prediction of thermal-neutron fluences in Hiroshima.

In this issue of *Update*, Straume discusses the possible implications of this discrepancy with respect to the estimation of radiation-risk values in humans. Although speculative in nature, Straume's argument is that "if Hiroshima neutron doses are underestimated in DS86 by the amounts observed for thermal-neutron activation, then most of the radiation-induced risk in Hiroshima would actually be due to neutrons, not gamma rays. . . ." **Dale Preston et al**, in a commentary following Straume's article, are not impressed by Straume's arguments, and they offer their own estimate of the impact. Whichever point of view turns out to be true—and I am sure that all assumptions and approaches will need to be validated by additional analyses and calculations—neutrons are likely to be back again in Hiroshima, so to say, after first having been forcefully removed. Does this mean that we are back at the tentative 1965 dosimetry (T65D)? Does it also imply that the recent increase of gamma risk factors by the Advisory Committee on the Biological Effects of Ionizing Radiation, the International Commission on Radiological Protection, and the United Nations Scientific Committee on the Effects of Atomic Radiation—to the extent that they are based on atomic-bomb survivor data—would become invalid, ie, would need to be corrected appreciably downwards? As indicated by the results of the analysis by Preston et al in this issue of *Update*, a relatively minor revision seems more likely.

Firstly, I think it is wise not to get carried away by premature generalizations of a biological nature, not based on, as yet, completely reliable physical data and assumptions. As Straume indicates in his *Health Physics* paper, there is an urgent need for additional information, such as whether Nagasaki demonstrates the same discrepancy as Hiroshima. Secondly, there are many differences between T65D and DS86 unrelated to the air-transport calculations that affect the risk factors in different directions. (See, for an overview, JW Thiessen and DC Kaul, *J Radiat Res* [Tokyo] 32(Suppl):1–10, 1991.) It is too simple to assume that the discrepancy under discussion, when corrected for, will get us back to the "old" risk factors. One would do well to remember that the increases in recent estimates of risk factors, eg, in *ICRP Publication 60*, are only partially based on dosimetric changes. More important were changes in the risk projection models used (eg, the change from absolute to relative risk models) and the inclusion of other detriments in the definition of risk. For these reasons alone, a change of more than 10% or 20% downwards (depending on the particular cancer concerned) might be a more likely correction than the one by 50% or 60% that would be necessary to bring us back to the T65D-based risk factors. But I hasten to drop this issue quickly, because this also is speculative. For the moment, a wait-and-see approach appears to be the most appropriate one. The matter has the full attention of the American and Japanese dosimetry committees, and I hope that they will be able to recommend changes to DS86 that—I nearly said "once and for all"—will resolve the issue.

One thing is certain: if neutrons are indeed "back in Hiroshima," the relative biological effectiveness (RBE) of neutrons in man will become a subject of renewed interest. A more-reliable estimate of neutron contributions to dose will, therefore, be more than welcome, whatever one may believe about the RBE of neutrons in general and particularly with respect to human exposures, for which Hiroshima may be the only well-documented case.

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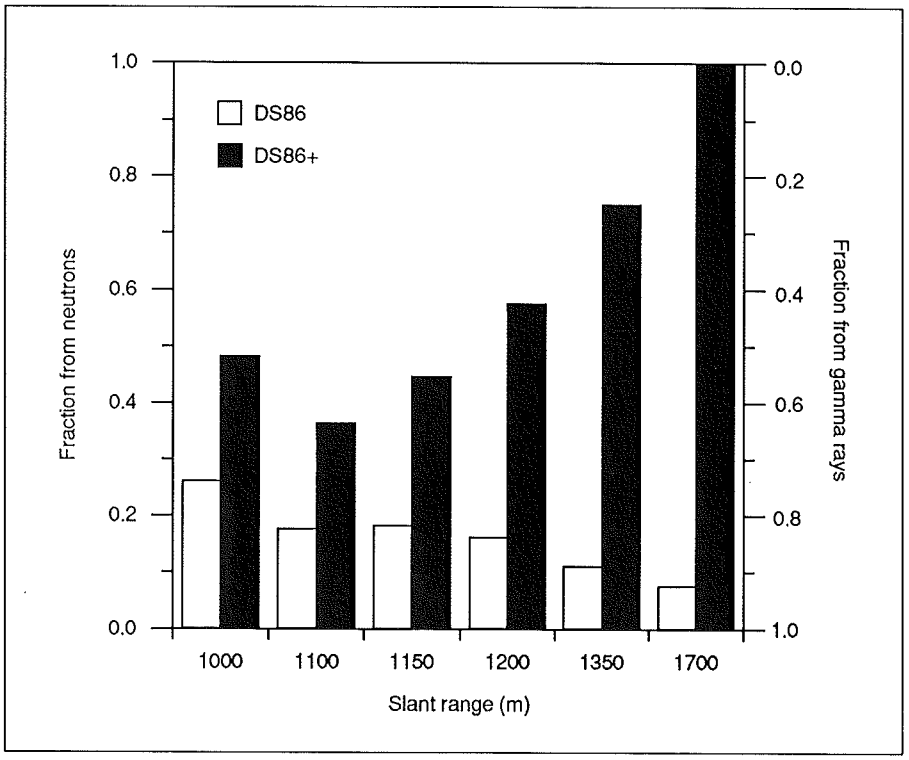
Neutron Discrepancies in the Dosimetry System 1986 Have Implications for Radiation Risk Estimates

Evidence for higher-than-predicted neutron exposures in Hiroshima raises some vexing questions.

by Tore Straume, Lawrence Livermore National Laboratory, University of California, Livermore, California

The Dosimetry System 1986 (DS86) has recently been used in influential reports by the United Nations (UNSCEAR 1988), the US National Academy of Sciences (BEIR V), and the International Commission on Radiological Protection (*ICRP Publication 60*) to estimate radiation-induced cancer risk and to make recommendations concerning appropriate radiation safety standards for workers and the public. However, a detailed comparison of neutron activation measured in mineral and steel samples from Hiroshima, with the activation levels calculated for these samples using the DS86 neutron fluence and spectrum, revealed a large discrepancy between measurements and calculations (T Straume et al, *Health Phys* 63:421–6, 1992). The discrepancy indicated that there were actually some 2 to 10 times more neutrons at relevant distances in Hiroshima than estimated by DS86. This finding has important implications for the estimation of radiation-induced cancer risk in humans.



The fraction of risk induced by neutrons in Hiroshima if the Dosimetry System 1986 is correct (DS86, white bars) or if DS86 neutron doses are increased according to the thermal-neutron activation measurements (DS86+, black bars). The fractional risk estimates are based on chromosome aberration data for Hiroshima survivors (Preston et al, RERF TR 7-88) and the effectiveness of Hiroshima-like neutrons measured in vitro (Dobson et al, Radiat Res ***128:143–9, 1991). The fraction of risk by gamma rays is indicated on the right axis and is simply 1 minus the risk from neutrons.***

Neutron activation measurements

The activation measurements available at the most relevant distances of 1–2 km in Hiroshima are presently limited to nuclides produced by thermal neutrons, which do not themselves contribute much to neutron dose. However, the measured thermal-neutron fluences in the samples are expected to be proportional to the free-in-air fast-neutron fluence at these distances and thus be proportional to neutron dose. This is because nearly all of the thermal neutrons that activated the samples actually originated from fast neutrons that were slowed down in the local environment of the sample (ie, in the ground and in buildings).

The possible effect of this discrepancy on the dosimetry for atomic bomb survivors could be that DS86 neutron doses in Hiroshima would have to be increased by as much as a factor of 2 at 1 km and a factor of 10 at 1.5 km (the so-called DS86+ dose).

Risk implications

If the neutron dose is underestimated in DS86 in proportion to the measured-to-calculated ratios for thermal-neutron activation (Straume et al, loc cit), the Hiroshima neutron dose at 1.5 km would be a factor of ~10 higher than now believed. This would result in neutrons contributing a larger fraction (and gamma rays contributing a smaller fraction) of the radiation-induced risk in Hiroshima than is predicted from DS86. Although neutrons in the DS86 system contributed less than a few percent of the dose in Hiroshima (WC Roesch, ed, *US–Japan Joint Reassessment of Atomic Bomb Radiation Dosimetry in Hiroshima and Nagasaki. DS86: Final Report*, Vol 1, 1987), they have a disproportionately large impact on radiation risk estimates because of their high relative biological effectiveness, which increases with decreasing dose (RL Dobson et al, *Radiat Res* 128:143–9, 1991).

To illustrate the potential impact of this neutron discrepancy on risk estimates inferred from the Hiroshima data, the fraction of radiation-induced risk from neutrons is estimated using chromosome aberrations measured in blood lymphocytes of Hiroshima survivors (D Preston et al, RERF Technical Report 7-88, Table 4b). This is a particularly appropriate surrogate end-

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Neutron Discrepancies

continued from page 3

point for such an evaluation because of the availability of a chromosome aberration dose-response curve (Dobson et al, loc cit) for Hiroshima-like neutrons. (Experimentally derived dose-response curves for Hiroshima-like neutrons are not available for other biological endpoints.)

The following relation was used to calculate the fraction (F_n) of aberrations produced by neutrons in Hiroshima: $F_n = Y_n/Y_t = a_n D_n/Y_t$. The aberration frequency for Hiroshima neutrons was estimated as the product of the slope (a_n) of the dose-response curve for Hiroshima-like neutrons (from Dobson et al, 1991) and the neutron dose (D_n) to bone marrow in Hiroshima survivors. (D_n values were provided by **Akio A Awa** of the Radiation Effects Research Foundation.) The total aberration frequency (Y_t) for Hiroshima survivors was obtained from D. Preston et al (loc cit) as a function of total (gamma + neutron) DS86 marrow dose (D_t). The Hiroshima aberration data (Y_t) are reported in the form "% cells with aberrations." In contrast, the a_n value by Dobson et al was reported in the form "aberrations per cell per Gy." To provide the numerator in the above equation with the same units as the denominator, Y_n was converted from "aberrations per cell" to "% cells with aberrations." This transformation was made possible by the determination that the aberrations in Dobson et al were Poisson distributed among cells.

Essentially all aberrations in blood lymphocytes of Hiroshima survivors several decades after exposure are reciprocal translocations and pericentric inversions (Preston et al, loc cit). Although the a_n coefficient employed here for Hiroshima-like neutrons was obtained in vitro for dicentrics and rings, it has been shown that reciprocal translocations and pericentric inversions are induced with the same frequency as dicentrics and rings (JN Lucas et al, *Int J Radiat Biol* 61:830–5, 1992; LG Littlefield et al, in *Medical Management of Radiation Accidents*, CRC Press Inc, Boca Raton, Fla, USA, pp 109–26, 1990). Also, considerable data now show that the reciprocal translocation frequency in blood lymphocytes of whole-body-exposed individuals is fully stable with time postexposure (T Straume et al, *Health Phys* 62:122–30, 1992; J Lucas et al, *Cytogenet Cell Genet* 60:259–60, 1992; KE Buckton et al, in *Mutagen-induced Chromosome Damage in Man*, University Press, London, pp 142–50, 1978). Therefore, the cytogenetic effectiveness of Hiroshima-like neutrons measured in vitro at first cell division postexposure can be used to estimate the aberration frequency induced by neutrons in Hiroshima survivors.

Chromosome aberration data and other parameter values for Hiroshima.[a]

Slant range (m)	D_n (Gy)	D_g (Gy)	Y_t (% cells)	Y_n (% cells)	R	D_{n+} (Gy)	Y_{n+} (% cells)
1000	0.056	2.34	18.4	4.81	1.9	0.106	8.87
1100	0.031	1.70	15.3	2.70	2.1	0.065	5.56
1150	0.019	1.22	9.2	1.67	2.5	0.048	4.10
1200	0.009	0.74	4.9	0.79	3.6	0.032	2.82
1350	0.002	0.305	1.6	0.177	6.8	0.014	1.20
1700	0.00023	0.055	0.26	0.020	15.0	0.0035	0.305[b]

[a] Effective slant-range values were estimated from the DS86 free-in-air kerma values that correspond to the bone marrow doses listed above and the dose-vs-range relationships for Hiroshima (WC Roesch, ed, *US–Japan Joint Reassessment*, Vol 1, 1987). Values for Y_t are observed percentage of cells with aberrrations minus background (ie, the group that received 0–0.005 Gy) from D. Preston et al (RERF TR 7-88, Table 4b). Y_n and Y_{n+} are percentage of cells with aberrations for DS86 and DS86+ neutron doses, estimated as described in the text. Neutron doses (D_n) to marrow were provided by Akio Awa (RERF) and gamma-ray doses (D_g) to marrow were obtained by subtracting the neutron doses from the total doses in Table 4b of RERF TR 7-88. The values for R are the measured-to-calculated ratios for thermal-neutron activation (Straume et al, *Health Phys* 63:421–6, 1992) at the indicated distances.

[b] This predicted value of 0.305% is not significantly larger than the observed value of 0.26% ± 1.68%.

The risk implication of the neutron discrepancy is illustrated in the Figure. White bars are based on the assumption that DS86 neutron doses in Hiroshima are indeed correct and do not require upward revision. In contrast, the black bars are based on the assumption that DS86 neutron doses are too low in Hiroshima and must be increased with neutrons of all energies in proportion to the measured-to-calculated thermal-neutron ratios (Straume et al, loc cit). The Figure shows that if the DS86 neutron dosimetry is correct, then neutrons contributed only a small fraction of the total radiation-induced health risk in Hiroshima. However, if Hiroshima neutron doses are underestimated in DS86 by the amounts observed for thermal-neutron activation (Straume et al, loc cit), then most of the radiation-induced risk in Hiroshima would actually be due to neutrons, not gamma rays, as currently believed. Since the DS86 gamma-ray doses for Hiroshima are approximately correct (there was relatively good agreement between gamma ray doses measured in Hiroshima and those calculated using DS86), it can be inferred from the Figure that gamma rays would contribute about 50% of the risk at 1000 m and essentially none of the risk at 1700 m. Also, the sharply increasing contribution to risk from neutrons with increasing distance (or with decreasing dose) could impact the shapes of dose-response curves obtained from the Hiroshima data; ie, the increasing neutron dose component with distance would tend to make the curves more linear at low doses than expected from DS86. ❑

Acknowledgment—This work was performed under the auspices of the US Department of Energy by the Lawrence Livermore National Laboratory under contract number W-7405-Eng-48 with support from the Defense Nuclear Agency, Project Number 92-281.

Neutrons and Radiation Risk: A Commentary

by Dale L. Preston, Donald Pierce, and Michael Væth, Department of Statistics, RERF

We do not find **Tore Straume**'s approach to risk evaluation appropriate nor his conclusions convincing (p 3 of this issue). Our primary objection concerns the unquestioned application of the in-vitro results obtained by **R. L. Dobson et al** (*Radiat Res* 128:143–9, 1991) to the RERF chromosome aberration study. There are, of course, many pitfalls in extrapolating from experimental in-vitro results to those expected in human populations. Moreover, there is a great deal of pertinent experimental evidence that has been ignored in his argument.

Conclusions about cancer risks depend mainly on what is learned from the high-dose part of the data from RERF and elsewhere, combined with the most thoughtful use of external radiobiological knowledge about the relative biological effectiveness (RBE) of neutrons, dose rate effects, and the shape of the dose-response curve. The latter category of knowledge will not be affected by possible revisions of the RERF doses. There is little direct information about RBE in the RERF cohort data. To the small extent that there may be such information, the data would support smaller RBE values if the neutron doses were increased.

We also think that it is easy to misinterpret the implications of the Figure that accompanies Straume's *Update* article (p 3). As discussed below, the modified Hiroshima neutron doses would be about 5% of the gamma doses. His results for the 1000- to 1200-m range, ie, a roughly equal contribution to risk from gamma and neutron, would then indicate only that the RBE is about 20 for doses at that range. His suggestion of a much higher RBE for the low-dose range is not novel, and, although this it an important issue, it has little bearing on risk estimates computed from the RERF cohort data, under either DS86 or the modified dosimetry.

It is more useful to see what effect the neutron changes he suggests would have on the RERF cancer risk estimates, as they are usually computed. The Table on this page shows the percentage decrease in cancer risk estimates if the Hiroshima neutron doses were to be increased as suggested by Straume et al (*Health Phys* 63:421–6, 1992). The first row results from an analysis in terms of total dose, whereas the results in the other rows were computed using dose equivalents. It is important to realize that linear cancer risk estimates from the RERF data depend on an assumed RBE largely through its value at high doses, around 1–1.5 Gy kerma. A large assumed low-dose RBE has little effect on linear dose-response analysis, both because of the unexposed group and because a large low-dose RBE results in little *absolute* change in total dose equivalent at low doses. This is the reason for use of the simple tentative dose equivalents in these calculations.

Straume et al (loc cit) originally presented tentative increases in Hiroshima neutrons as a function of slant distance. We were able to apply this relation directly rather than by using surrogate dose categories as in the Table of Straume's *Update* article. The resulting increases are slightly larger than the factors (R) given for the dose categories of his Table. Our results pertain to risks for all cancers except leukemia. They are based on a standard model in which the excess relative risk is allowed to vary with sex and age at exposure, but is assumed to be constant in time.

It is surprising to many that the risk estimates in terms of total dose would only decrease by 3%. The reason for this can be understood by considering the nature of dose-response analysis along with information in Straume's Table. As noted above, the primary effect on the dose-response slope arises from changes in total dose in the higher dose range, ie, at a distance of around 1000–1200 m. At that range, the current Hiroshima neutron estimates are about 1.5% of the gamma doses, and the tentative increase in neutrons is a factor of roughly 2.5–3. Thus, at that distance, the neutron component would increase from about 1.5% to about 4% of the gamma dose, resulting in an increase of about 2.5% (1.04/1.015) in the total dose.

Although it is important to remove as many systematic errors as possible in computing the cancer risk estimates, it should be realized that there are many uncertainties and factors that influence the risk estimates to about this extent. For example, RERF has recently found that adjustment for effects of random errors in the dose estimates, which has not previously been done in the major reports, should result in an increase in the risk estimates in the range of 10%–15%. Thus, changes of the magnitude indicated in the Table above should not, when taken in perspective, lead to substantial revision in assessments of the cancer risks of radiation. ❑

Percentage decrease in cancer risk estimates if the Hiroshima neutron doses were increased, as suggested by T. Straume et al (Health Phys ***63:421–6, 1992).***

Dose equivalent	Decrease in excess relative risk per unit dose
$D_g + D_n$	3%
$D_g + 10\ D_n$	13%
$D_g + 20\ D_n$	22%

Chelyabinsk

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US interagency group develops plans for Chelyabinsk studies

RERF has been invited to provide input into the activities of a US interagency group that is developing a strategic plan for studies of populations exposed to ionizing radiation in the southern Ural Mountains. This group, under leadership of US Department of Energy (DOE) officials, was established to follow up proposals discussed at an international workshop at George Mason University held in June 1992 (see *RERF Update* 4 (2):1, 1992).

In early December, DOE Deputy Assistant Secretary **Harry Pettengill** met with RERF Statistics Department Chief Dale Preston and was briefed about the RERF delegation's discussions in Chelyabinsk.

One of the group's first projects to be realized is the creation of a computerized data base in Chelyabinsk for preserving the information obtained to date. ❑

Biotechnology Contributes to Biological Dosimetry

Using fluorescence in-situ hybridization to detect chromosome translocations, radiation- and chemical-induced chromosome changes can be identified decades after exposure.

by Yoshiaki Kodama, Mimako Nakano, Kazuo Ohtaki, and Akio A Awa, Department of Genetics, RERF

Determining the frequency of dicentric chromosomes in the peripheral-blood lymphocytes of persons exposed to ionizing radiation has been used since the early 1960s as a biological indicator of radiation exposure. However, dicentric frequency is less effective if the analysis is performed many years after irradiation, because the frequency of cells carrying unstable aberrations such as dicentrics decreases with time; ie, the dicentrics are unstable aberrations. Earlier cytogenetic studies conducted at the Radiation Effects Research Foundation (RERF) confirmed that, in sharp contrast to the decrease in dicentric frequencies, other, stable, chromosome aberrations (mainly translocations) persist for decades in the peripheral lymphocytes of atomic-bomb (A-bomb) survivors (AA Awa et al, *J Radiat Res* 19:126–40, 1978). Thus, determining the frequency of translocations seems preferable for individuals exposed years earlier, such as the A-bomb survivors.

Although estimating translocation frequencies using both conventional and banding analyses consumes too much time to be routinely practical, recent advances in the technique of fluorescence in-situ hybridization (FISH), or "chromosome painting," allow more-rapid detection of translocation-type chromosome aberrations using whole-chromosome probes to stain chromosomes differentially (D Pinkel et al, *Proc Natl Acad Sci* [USA] 85:9138–42, 1988).

'Painting' specific chromosomes

This assay is based on applying FISH to collections of unique chromosome-specific DNA sequences to stain target chromosomes. The chromosome-specific sequences, called "whole-chromosome probe DNA," were established at Lawrence Livermore National Laboratory (LLNL), Livermore, Calif. In this approach, the DNA to be analyzed is thermally denatured so that it becomes single-stranded. This DNA is then incubated with biotinylated probe DNA under conditions that allow binding of probe DNA to target DNA sequences to which it is homologous. The bound probe can be made visible by treatment with a specific stain; nontarget DNA sequences are counterstained. Under the fluorescence microscope, the target chromosomes appear yellow, whereas nontarget chromosomes appear red (Figure 1, left panel). A translocation between a target chromosome and a nontarget chromosome can be identified, or scored, easily, because of the translocation's bicolor pattern (Figure 1, right panel).

Estimating the translocation frequency

The FISH method detects only a fraction of the total aberrations, so the total genomic translocation frequency (F_G) is calculated from the frequency of translocations (F_p) detected, as follows.

$$F_G = F_p/2.05f_p(1 - f_p)\,,$$

where f_p is the fraction of the genome painted. This calculation is based on the assumption that chromosomes are

Y. KODAMA

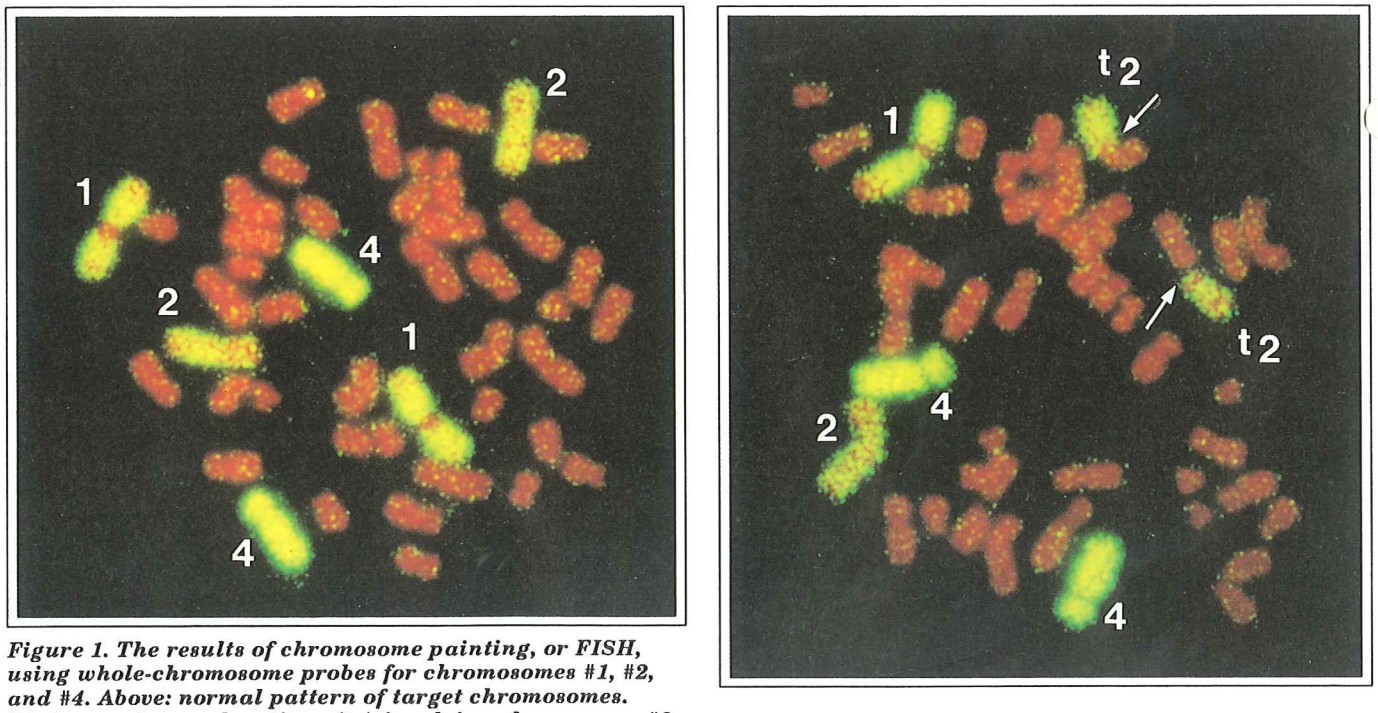


Figure 1. The results of chromosome painting, or FISH, using whole-chromosome probes for chromosomes #1, #2, and #4. Above: normal pattern of target chromosomes. Right panel: translocations (t_2) involving chromosome #2 can be seen, as well as other nontarget chromosomes.

translocated in proportion to their DNA content.

To test this assumption, we compared the chromosomal DNA content and the distribution of about 3100 translocation break sites in many thousands of cells obtained from 52 Hiroshima A-bomb survivors (JN Lucas et al, *Int J Radiat Biol* 62:53–63, 1992). There was good correlation between the distribution frequency of breaks and the DNA content of individual chromosomes (the larger the chromosome, the more the breaks; the correlation coefficient for the regression was 0.83 [$p < .001$]).

Use of translocation frequency for in-vivo biological dosimetry requires that the relationship between dose and translocation frequency be known with some accuracy. One possibility is to use in-vitro calibration curves for this purpose. This presumes that the translocation frequency measured for peripheral lymphocytes immediately after irradiation is the same as that measured in the peripheral blood years after exposure. The agreement between the translocation frequency dose-response curve measured in vitro and the translocation frequency dose-response data for the Hiroshima A-bomb survivors supports the assumption that the number of cells carrying translocation aberrations does not change over time, suggesting that the translocations did not adversely affect mitosis during the intervening years since exposure. This is supported by previous chromosome aberration data obtained in repeated examinations of A-bomb survivors conducted during the past 20 years.

Collaborative study underway between LLNL and RERF

Scientists from LLNL and RERF now are collaborating to determine the utility and sensitivity of the FISH technique for rapidly analyzing translocation frequencies using whole-chromosome probes derived from chromosomes #1, #2, and #4 and to compare the FISH measurements with those obtained using other conventional staining methods such as G-banding.

Collaborating scientists

- **J. N. Lucas** and **T. Straume**, Lawrence Livermore National Laboratory
- **D. Pinkel** and **J. W. Gray**, University of California–San Francisco

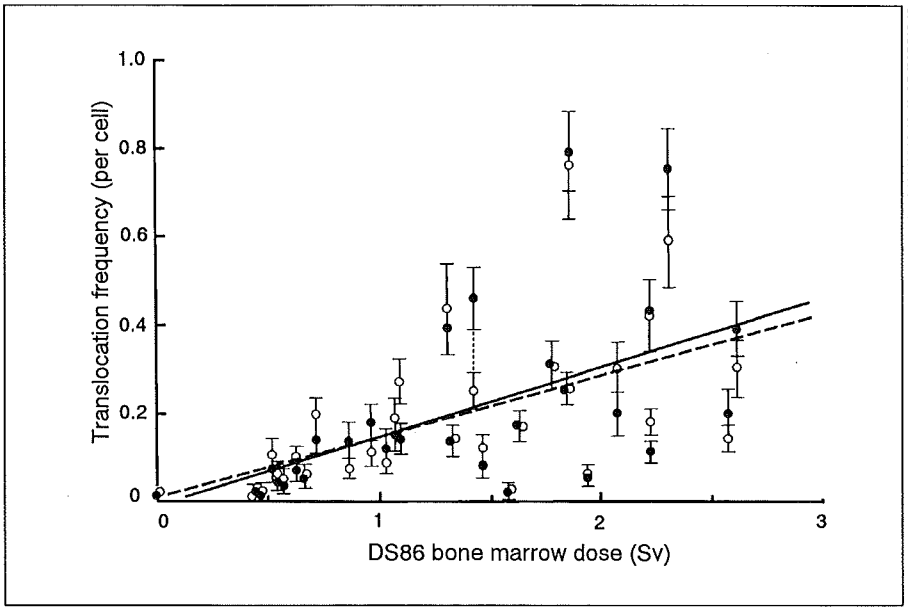


Figure 2. Translocation frequencies of 36 Hiroshima A-bomb survivors measured using either the fluorescence in-situ hybridization (FISH, open circles) method or the G-band (closed circles) method plotted against Dosimetry System 1986 bone marrow dose. Linear regressions are indicated by the dashed line for FISH and the solid line for G-banding, respectively.

Blood samples were obtained from 36 A-bomb survivors assigned physical dose estimates of 0–3 Gy. At LLNL 100–4000 cells were examined using FISH, and at RERF 100 cells were examined using the G-band method. Of the types of stable chromosome aberrations detectable by G-band analysis, only translocations were scored for comparison with FISH data. The average scoring rate for FISH analysis ranged from 200–300 metaphases per day per person, about 10 times faster than the G-band scoring rate of 20–25 metaphases per day per person. Chromosome aberration analyses were performed independently at the LLNL and RERF laboratories without knowledge of exposure status of the survivors.

Figure 2 shows for individual survivors the translocation frequencies measured using both the FISH (open circles) and G-band (closed circles) methods plotted against bone marrow physical dose. The dose-response pattern was remarkably similar for the two scoring methods, and for each person translocation frequencies obtained using the two scoring methods agreed well. As shown in Figure 3, the slope of a linear regression between the G-band and FISH measurement was 0.82 ($r = .941, p < .001$). Discrepancies in aberration frequency were seen only in a few cases. ❑

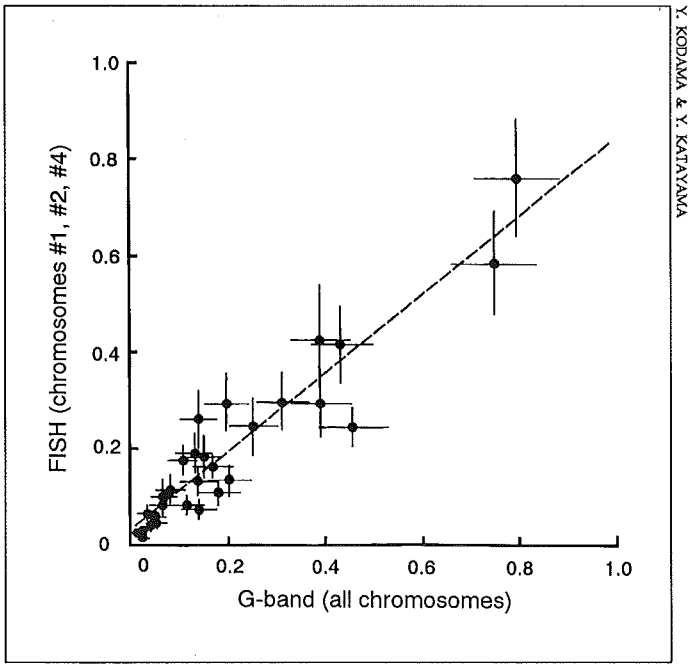


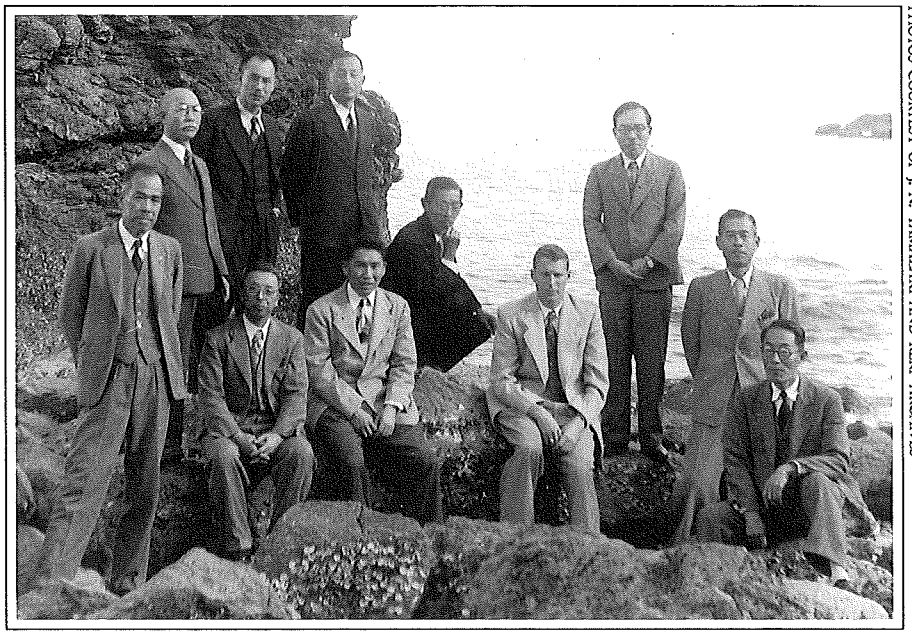
Figure 3. Measurements of translocation frequency using fluorescence in-situ hybridization (FISH) and G-band analyses (r = .941, p < .001).

More About the Early Days of the Nagasaki Lab

Setting up daily operations involved carrying out numerous administrative tasks and nurturing a mutually beneficial relationship between ABCC and the people of Nagasaki.

by James N. Yamazaki,
Physician-in-charge, ABCC
Nagasaki Laboratory, 1949–51

Editor's note: The first part of James Yamazaki's recollections were published in the previous issue of RERF Update.



PHOTOS COURTESY OF J. N. YAMAZAKI AND RERF ARCHIVES

Members of the Nagasaki City Medical Association gathered at Mogi in May 1951 for the author's farewell party: seated, from left, Harakichi Imamura, the author, Shigekuni Aritomi, Stanley Wright, and Etsu Osuga; standing, from left, Masao Ide, Kihachi Shinagawa, Yoshiro Shibata, Uraji Hayashida, Shunsuke Hayashida, and Yuzo Tomonaga.

First attempts to develop community relations

Through the grapevine, we learned of misgivings about the Atomic Bomb Casualty Commission among the citizenry of Nagasaki, so I felt it was imperative to explain ABCC's medical mission to the medical community and to governmental officials. Furthermore, because I had not been briefed about the consequences of the atomic bombing, it was incumbent upon me to learn about the experiences of the people of Nagasaki. **Kazuo Hamasaki**, an ABCC interpreter/translator, assisted me in arranging initial contacts and accompanied me because my proficiency in spoken Japanese was minimal.

Nagasaki Police Department supervisor describes the aftermath of the bombing

Katsuji Deguchi, a supervisor in the Police Department, had been the assistant chief of the anti-air raid unit for Nagasaki when the atomic bomb exploded. His story provided my first insights into the events of 9 August 1945.

He described in considerable detail the exodus of survivors that had passed by his office in the Katsuyama Primary School, which was about 3000 m from the hypocenter. Those who were able to walk crossed the mountains at Kompira and found their way through to the Nishiyama valley because all other exits were ablaze. No part of the city had been spared. Despair and demoralization was pervasive. The injured were so numerous that rescue efforts did not reach some for nearly 2 weeks, and cremation and burial efforts lasted for a similar period. People from nearby villages and towns helped to feed the survivors for more than a month, and a large segment of the population fled from the city.

Governor of Nagasaki Prefecture

Sojiro Sugiyama, prefectural governor, was very cordial from the onset, and he introduced me to other officials at dinners where exchanges of opinions developed more easily. He introduced us to life in Nagasaki by inviting us to many social functions. When word leaked that my wife, Aki, was becoming disenchanted with my evening absences because of these meetings, Gov Sugiyama sent his charming wife to visit. During one such visit, Mrs Sugiyama brought Aki a very beautiful kimono.

The Nagasaki Medical School

A very cordial relationship developed between the Nagasaki Medical School and ABCC (*RERF Update* 2[1]:9, 1990). I first met with the dean of the medical school Dr **Naomi Kageura** and Surgery Professor **Raisuke Shirabe** in Urakami just as the reconstruction of the medical school was beginning. The first unit to be rebuilt, the office of the department, was offered to ABCC for a cataract survey to be conducted by Dr **Sam Kimura** (ABCC Department of Medicine, 1949–50). The university's professor of ophthalmology, **Kinnosuke Hirose**, was already involved in such a study.

The ABCC autopsy efforts complied with the university's ongoing pathology and anatomy program, and because ABCC physicians were not licensed practitioners in Japan, Dean Kageura agreed to sign each autopsy permit. ABCC autopsies were performed in Urakami by the university's autopsy surgeon.

The dean requested that the young physicians employed by ABCC—most recent graduates of the medical school—be coached in American medical practices. In response, regularly scheduled lectures were given to the physicians by myself and visiting ABCC staff members from Hiroshima. University officials arranged that fulltime ABCC Department of Pediatrics physicians **Masahiko Setoguchi** (1949–51) and **Atsuyoshi Takao** (1948–52) also could retain their faculty appointments.

Later Dr Shirabe suggested that I explain ABCC's program at a meeting of the university's department chiefs. Although I had brought our interpreter, Mr. Hamasaki, Dr Shirabe suggested

In the fall of 1950, the Nagasaki Midwives Association met at ABCC. Standing behind the midwives, from left, are Stanley Wright, Masuo Kodani, the author, and interpreter Kazuo Hamasaki.

that it would be more appropriate and better appreciated if I were to deliver my talk in Japanese. Thus, I gave my first presentation in Japanese. I don't think they had ever encountered Japanese the way I spoke it, and I thought their serious demeanor eased as I spoke.

At my request, a roundtable discussion by survivors from the medical school was held on 7 June 1950, and Dr Kimura, **William J. Schull**, and **Koji Takeshima** from Hiroshima attended. During conversations with me, Dr Shirabe later related additional personal experiences. His report, *The Medical Survey of the Atomic Bomb Casualties*, was presented to ABCC and was later translated into English for publication (*Milit Surg* 113:251–63, 1953). It was, in fact, the first summary report of the medical effects of the atomic bombing. The report of the Joint Commission was not issued until the following year, April 1951 (in six volumes, the last was declassified on 30 November 1954). Before publication of the Joint Commission report, ABCC physicians with whom I had talked had not been briefed on its content.

Nagasaki Medical Society

At the society's general meetings, at dinner parties, and at sectional meetings of pediatricians and obstetricians, the ABCC program was explained. Considerable interest was expressed about medical practice in the US.

Nagasaki Branch of the Japan Midwives and Nurses Association

Mrs **Tei Murakami**, president, represented 106 midwives who reported to ABCC on 90%–95% of all the babies delivered in Nagasaki (*RERF Update* 2[3]:6–9, 1990). She understood the objectives of the genetics program and gave constructive criticism. Meetings of the midwives were held regularly. Dr Schull attended some of these meetings.

Nishiyama fallout survey

In March 1950, Tracer Labs surveyed the residual radiation in the Nishiyama valley upstream from the reservoir. Radioactive samples were obtained from the thatched roofs and from the silt in the reservoir. During their short stay, I accompanied the investigators and thereby learned about the fallout from the bomb. Their findings were not reported to us and did not appear in any ABCC report during that period.

The Korean War

In late June 1950, the conflict in Korea started. Only 10 minutes from Nagasaki by airplane, the conflict prompted considerable conjecture as to whether the program in Nagasaki would close. Soldiers in the Nagasaki–Sasebo area were the first to go, and not one soldier in our area returned. One day I was asked to go to the wharf to treat a merchant marine injured when a vessel had been strafed at sea.

During a lull in the fighting in early 1951, a flotilla from the Pacific Amphibious Landing Force docked in the harbor. We were asked to brief the commanding admiral and his staff about the consequences of the atomic bombing.

Other general recollections

In September 1950, at the height of a typhoon, **Stanley** and **Phyllis Wright** (Department of Pediatrics, 1950–52) were welcomed to Nagasaki. This swelled the ranks of the American professional staff to three! The timing was fortuitous because the remodeling of the "Kaikan" was nearly completed, and training of laboratory personnel was almost finished.

Soon after, Dr **Masuo Kodani**, cytogeneticist (Department of Genetics, 1947–55), arrived because of the closure of the Kure genetics program. He would oversee the genetics program in Nagasaki and continue his cytogenetics studies.

Stanley Wright assumed responsibilities for employee health care, which required close attention because there was a 10% employee turnover rate due to tuberculosis.

In October 1950, we began examining patients at the ABCC clinic in Sakurababa-machi. Within months, the patient load was comparable to that of Hiroshima, stimulated by efforts to reexamine 20% of the infants at 9 months of age. Phyllis Wright assumed responsibility for the growth and development program of school children that had been started in 1948 by Dr **W. W. Greulich**.

The PE57 study of the outcome of pregnancy among Nagasaki women was reviewed for implementation (JN Yamazaki et al, *J Cell. Comp Physiol* 43[suppl 1]:319–29, 1954). Letters from Dr **George Plummer** of the Department of Pediatrics (1950–52) indicated that PE57 was to be conducted in Hiroshima, too.

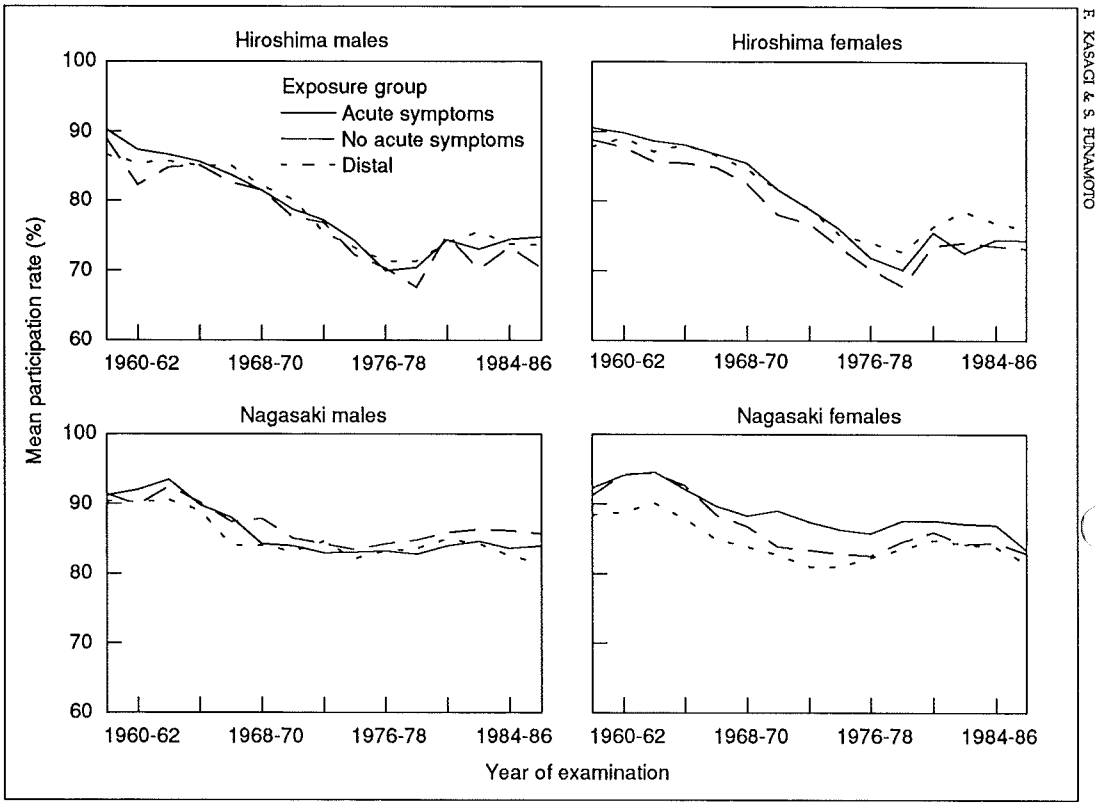
The ophthalmological study of radiation-induced cataracts conducted by Kimura and Hirose surveyed about 600 survivors who had been within 1000 m of the hypocenter. Dr **Paul Fillmore** (Department of Medicine, 1949–51) would later follow up this group of survivors (PG Fillmore, *Science* 116:322–3, 1952). The examination of 175 children for OP46, as the study was called, was completed in March 1951, although I am not aware that its results were ever published.

In early 1951, **John Bugher**, deputy director of the US Atomic Energy Commission's Division of Biology and Medicine, and **John Lawrence**, chairman of the University of California–Los Angeles Department of Medicine, spent 1 week in Nagasaki evaluating the program.

In June, I left Nagasaki a few months earlier than planned due to the illness of my wife. ❑

Facts & Figures

The Adult Health Study: Participation Rate by Exposure Group



F. KASAGI & S. FUNAMOTO

The RERF Adult Health Study (AHS) population has been followed since 1958 to observe the late effects of atomic-bomb exposure on the development of diseases or on physiological and biochemical changes. Follow-up has been based on the standardized biennial clinical examination of study participants. For such research purposes, a high and unbiased participation rate is indispensable. Issues related to maintaining a high participation rate and the effects of sex and birth cohort on participation were discussed in the last issue (*RERF Update* 4[3]: 10, 1992). Here we will address bias in the participation rate.

Since the primary purpose of the AHS is the study of radiation effects on health, it is especially important to determine whether the participation rate depends on exposure status. The Figure above compares the temporal trend in the mean participation rates for the three exposure groups, stratified by sex and city. In these plots, rates have been averaged across birth cohorts. Those alive and resident in a contact area were used as the basis for the participation rate. Regardless of sex, Hiroshima participation rates for proximal survivors who did not have acute symptoms of radiation exposure appear to be lower than those for proximal survivors who had experienced acute symptoms or for distal survivors. In Nagasaki, the distal survivors appear to have lower participation rates. Generally, participation rates by sex and city are higher in Nagasaki than in Hiroshima and higher among females than among males. ❑

Perspectives

continued from page 2

Four years of Update*—a postscript*

This issue concludes Volume 4 of *RERF Update*. Four years ago, RERF's chairman and I wrote: "It is time for a change"; I believe it is time for another: a change of the editor in chief. **Seymour Abrahamson**, RERF's present chief of research, has agreed to take over, and with his talent for communicating with others, I am convinced he will do a great job. Like myself, he can count on the professional assistance of **Beth Magura**, the managing editor, without whom there might never have been an *Update*! By a fortunate coincidence, she and I arrived at RERF at roughly the same time, and we soon discussed ways to improve RERF's communications with the outside world. Instead of trying to improve the then-existing English-language newsletter, we decided to transform it into a publication for a wider public, one that would include progress reports of ongoing research written in a style that we hoped would invite reading and inform readers in a more timely and less specialized fashion than was possible via the "normal" route, ie, through RERF technical reports and publications in the scientific literature. We also established a policy that contributions would not represent "official" RERF positions or opinions—or even a scientific consensus. If anything, this has contributed to an openness that has invited reactions and discussions and to the readability that we had in mind from the start.

The response to *Update* has been most gratifying. Beth and I have received many letters and personal remarks of interest and encouragement. We are extremely grateful for this, but we do believe that most of the credit must go the the many scientists—RERF staff members and those from outside of RERF—who have contributed throughout these first 4 years. They, more than the editors of *Update*, are responsible for its evident success. As for myself, I thank the readers who have made an effort to respond to my editorial outpourings, despite their opinionated nature or perhaps because of this.

So, good luck, Seymour! If you hadn't done it already, I would say, "Break a leg!" ❑

Recent Scientific Publications

Editor's note: The reports listed have been approved and will be distributed as soon as they are printed. Wording of the titles and summaries may be slightly altered before final printing.

Approved Technical Reports

Study on the titers of anti-Epstein-Barr virus antibodies in the sera of atomic-bomb survivors. M Akiyama, Y Kusunoki, S Kyoizumi, K Ozaki, S Mizuno, JB Cologne. **RERF TR 14-92.**

Antibody titers to Epstein-Barr (EB) virus antigens were determined on the sera of 372 atomic-bomb (A-bomb) survivors to evaluate the effect of the previous radiation exposure on immune competence against latent infection of the virus. The proportion of persons with high titers (≥1:40) of anti-early antigen (EA) immunoglobulin (Ig) G antibody was significantly elevated in the exposed survivors. Furthermore, the distribution of titers of the anti-viral capsid antigen (VCA) IgM antibody was significantly affected by radiation dose with an increased occurrence of titers of 1:5 and 1:10 in the exposed persons, although the dose effect was only marginally suggestive when persons with rheumatoid factor were eliminated from the analysis. These results suggest that reactivation of EB virus in the latent stage occurs more frequently in the survivors. However, there was neither an increased trend in the prevalence of high titers (≥1:640) of anti-VCA IgG antibody among the exposed people nor a correlation between the radiation exposure and distributions of titers of anti-VCA IgA or anti-EB virus-associated nuclear antigen (EBNA) antibodies.

Colorectal cancer incidence and radiation dose among atomic-bomb survivors, 1950–80. H Nakatsuka, Y Shimizu, T Yamamoto, I Sekine, H Ezaki, E Tahara, M Takahashi, T Shimoyama, N Mochinaga, M Tomita, R Tsuchiya, CE Land. **RERF TR 15-92.**

Colorectal cancer incidence in the Life Span Study sample during 1950–80 was investigated. A total of 730 incidence cases of colorectal cancer were confirmed from a variety of sources. Sixty-two percent of the cancers were microscopically verified, and 12% were ascertained through death certificate only.

The risk of colon cancer increased significantly with intestinal dose, but no definite increase of risk was observed for rectal cancer. Relative risk at 1 Sv and excess risk per 10^4 person-year-sievert for colon cancer were 1.80 (90% confidence interval 1.37–2.36) and 0.36 (90% confidence interval 0.06–0.77), respectively. City and sex did not significantly modify the dose response of colon cancer, but the risk decreased with age at the time of bombings. The relative risk of colon cancer does not vary substantially over time following exposure. A nonlinear dose response did not significantly improve the fit. Further, the anatomic location of the tumors indicate that the cecum and ascending, transverse and descending, and sigmoid colon seem equally sensitive to radiation. No difference in the distribution of tumor histological types was observed by radiation dose.

Rapid translocation-frequency analysis in humans decades after exposure to ionizing radiation. Y Kodama, JN Lucas, M Nakano, K Ohtaki, M Poggensee, T Straume, U Weier, D Pinkel, JW Gray, LG Littlefield, AA Awa. **RERF TR 16-92.**

This paper presents an analysis of the utility of fluorescence in-situ hybridization (FISH) with whole-chromosome probes for measurement of the genomic frequency of translocations found in the peripheral blood of individuals exposed to ionizing radiation. First, we derive the equation

$$F_p = 2.05 f_p(1 - f_p)F_G ,$$

relating the translocation frequency, F_p, measured using FISH to the genomic translocation frequency, F_G, where f_p is the fraction of the genome covered by the composite probe. We demonstrate the validity of this equation by showing that (a) the translocation detection efficiency predicted by the equation is consistent with experimental data as f_p is changed, (b) the translocation-frequency dose-response curves measured in vitro using FISH agree well with dicentric-frequency dose-response curves measured in vitro using conventional cytogenetic procedures, and (c) the genomic translocation frequencies estimated from FISH measurements for 20 Hiroshima atomic-bomb (A-bomb) survivors and 4 workers exposed to ionizing radiation during the Y-12 criticality accident are approximately the same as the translocation frequencies measured using G-banding or conventional staining. We also show that translocation-frequency dose-response curves estimated using FISH are similar for Hiroshima A-bomb survivors and for first-division lymphocytes irradiated in vitro. We conclude that translocation-frequency analysis is potentially useful for assessment of the level of acute radiation exposure independent of the time between analysis and exposure.

A novel blocker-PCR method for detection of rare mutant alleles in the presence of excess normal DNA. T Seyama, T Ito, T Hayashi, T Mizuno, N Nakamura, M Akiyama. **RERF TR 17-92.**

A novel polymerase-chain-reaction method was developed to preferentially amplify a segment of DNA containing a base-substitution mutation. This technique uses a pair of dideoxynucleotide-labeled oligonucleotides (18 mers) of normal sequences as blockers located between the two primers. By virtue of a subtle difference in the melting temperature between the blocker-normal DNA and blocker-mutant DNA hybrids, the method allows preferential amplification of the mutant DNA. We used the human N-*ras* gene as a model. Two types of N-*ras* mutations could be effectively amplified when they were present with an excess amount of normal DNA at a ratio of $1{:}10^3$. Furthermore, the sensitivity was increased 10-fold by using single-strand conformation polymorphism analysis for the amplified products, and mutant DNA was detected in the presence of a 10^4 times excess normal DNA.

Serum parathyroid hormone and calcitonin levels among atomic-bomb survivors. S Fujiwara, R Sposto, M Shiraki, N Yokoyama, H Sasaki, K Kodama, K Shimaoka. **RERF TR 18-92.**

Serum levels of calcium (Ca), parathyroid hormone (PTH), and calcitonin (CT) were examined in relation to estimated atomic-bomb radiation exposure among 1459 subjects in Hiroshima and Nagasaki.

A significant radiation effect was found on serum Ca, PTH, and CT levels, even after excluding hyperparathyroidism patients. The serum-Ca level increased with radiation dose. This increase in Ca level can be explained partly by the increase in PTH level with radiation dose. However, the dose effect on Ca still remained even after adjusting for PTH, CT, and confounding factors such as renal function, serum albumin level, and medication. PTH increased initially by 6.8% per gray, but dose response leveled off above approximately 1 Gy. CT level increased with radiation dose, probably in part due to feedback mechanisms stimulated by the increase in Ca level. However, after adjusting for Ca level, an increase in CT level with dose was still found.

Although the etiological mechanisms of the radiation effect on Ca, PTH, and CT levels are unclear, this study suggested that atomic-bomb radiation exposure may affect secretion of PTH and CT, and Ca regulation.

Approved Research Protocols

Molecular analysis of the p53 tumor suppressor gene in breast cancers of atomic-bomb survivors. T Itoh, T Seyama, T Mizuno, N Nakamura, M Akiyama, M Tokunaga, S Tokuoka, S Akiba, CE Land, K Mabuchi. **RERF RP 7-92.**

continued on next page

Recent Scientific Publications

Ionizing radiation induces mutations predominantly associated with deletions. Therefore, if the increased risk of cancer among the atomic-bomb (A-bomb) survivors were the direct consequence of genetic changes due to radiation exposure, the tumors in high-dose-exposed people would be expected to carry deletions of tumor-suppressor genes more frequently than would tumors of the non-exposed control group. In this study, we propose to examine deletions of the tumor-suppressor gene p53 in breast cancers, a disease for which the A-bomb survivors are at high risk.

Fragile-site expression assay in peripheral-blood lymphocytes: a pilot study of reproducibility and radiosensitivity in atomic-bomb survivors. S Ban, JB Cologne, K Nerishi, S Akiba. **RERF RP 8-92.**

Heritable fragile sites are rare and obey strict Mendelian genetic rules. Common fragile sites frequently occur and may be caused by exposure to environmental factors such as chemical agents, radiation, and/or viruses. Most heritable fragile sites and many common fragile sites have been demonstrated to correspond to, or occur in close proximity to, nonrandom cancer-specific breakpoints. Individuals with such fragile sites might be suspected to be at high risk for malignancies.

Although several studies have been done using the fragile-site assay, there are as yet no studies on a possible relationship between radiation sensitivity and fragile-site expression. Furthermore, some important technical aspects of the fragile-site assay (such as reproducibility and sensitivity to in-vitro radiation) are relatively unexplored. In this pilot study, we propose first to investigate the reproducibility (over time and following long-term sample storage in liquid nitrogen) and sensitivity of the assay in volunteers (preliminary phase). If intra-individual variation is relatively small, we will proceed to examine fragile sites in 150 atomic-bomb (A-bomb) survivors with differing radiosensitivities (actual testing phase). The results obtained with volunteer samples will be reviewed by the RERF chief of research and qualified outside reviewer(s) chosen by the chief of research before the actual testing phase is begun. The results of this review will be presented to the Research Protocol Committee for approval of the actual testing phase. Both rare and common fragile-site expressions will be analyzed in peripheral-blood lymphocytes using the proposed method.

Pending results of this study, we hope in the future to evaluate the fragile-site assay as a measure of susceptibility to radiation-induced cancer in a large sample of A-bomb survivors. Future studies would involve prospective follow-up of A-bomb survivors to identify incident cancers and analyze fragile-site expressions in relation to cancer-specific chromosomal breakpoints and oncogene loci. Such analyses should provide information useful for cellular/chromosomal epidemiological studies of human carcinogenesis. The present study will contribute information concerning the feasibility of such long-term studies.

Approved Commentary and Review

'Rogue' lymphocytes among Ukrainians not exposed to radioactive fallout from the Chernobyl accident: the possible role of this phenomenon in oncogenesis, teratogenesis, and mutagenesis. JV Neel, AA Awa, Y Kodama, M Nakano, K Mabuchi. **RERF CR 3-92.**

Cultured lymphocytes exhibiting extreme cytogenetic damage ("rogue cells") were observed in 8 of 24 individuals sampled in Krasilovka, a Ukrainian village that received almost no radiation contamination following the Chernobyl disaster, but such damage was not observed in lymphocytes from an additional 24 persons from two Russian towns in the more heavily contaminated area. This observation suggestes the global occurrence of these rogue cells. The present data plus a review of the literature establish the appearance of rogue cells in brief bursts simultaneously in certain members of discrete populations, suggesting that the pattern is consistent with the action of a viral trigger that acts directly or indirectly, in the latter case possibly by activating latent chromosomal retroposons. If this phenomenon occurs in other tissues, it may have important implications for oncogenesis, teratogenesis, mutagenesis, and evolution.

Publications in the Open Literature

X-ray induction of micronuclei in human lymphocyte subpopulations differentiated by immunoperoxidase staining. S Ban, JB Cologne. *Radiat Res* 131:60–5, 1992. (RERF TR 11-91)

Evaluation of four somatic mutation assays as biological dosimeter in humans. M Akiyama, Y Kusunoki, S Umeki, Y Hirai, N Nakamura, S Kyoizumi. *Radiation Research: A Twentieth-Century Perspective. Vol II. Congress Proceedings.* Academic Press, San Diego, Calif., pp 177–82, 1992

Somatic mutation at the TCR loci as a biological dosimeter of radiation-exposed people. S Umeki, Y Kusunoki, K Endoh, K Ohama, T Kodama, M Yamakido, M Akiyama. In *International Conference on Radiation Effects and Protection.* Tokyo, Japan, Atomic Energy Research Institute, 1992. pp 151–4.

BCR-ABL fusion genes are inducible by X-irradiation in vitro. T Ito, T Seyama, T Mizuno, T Hayashi, K Dohi, N Nakamura, M Akiyama. In: *International Conference on Radiation Effects and Protection.* Tokyo, Japan, Atomic Energy Research Institute, 1992. pp 146–50.

Accuracy of cause-of-death certification in Hiroshima and Nagasaki, Japan. S Jablon, DE Thompson, ME McConney, K Mabuchi. *Ann NY Acad Sci* 609:100–9, 1990.

The effect of diagnostic misclassification on non-cancer and cancer mortality dose response in A-bomb survivors. R Sposto, DL Preston, Y Shimizu, K Mabuchi. *Biometrics* 48:605–17, 1992. (RERF TR 4-91) ❑

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.

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

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