RERF update RERF

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

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Scientific Council and Board of Directors Convened in June

This year the Foundation's annual advisory and oversight committees—the Scientific Council and the Board of Directors—met in separate but consecutive meetings, held 13–15 June and 22–24 June, respectively. This revised schedule allowed US Department of Energy and Japanese Ministry of Health and Welfare (MHW) representatives to confer with participants as fiscal constraints tighten upon the research program.

In the Scientific Council report, cochairmen **Ei Matsunaga** and **Clark Health Jr**, stated: "As solutions to these difficulties are sought, it is important that we not lose sight of the scientific mission of RERF and its vital importance. That mission remains as it was originally stated in 1946: 'A long-range continuing study of the biological and medical effects of the atomic bomb in man.' "

During the 2-day formal session, 24 papers were delivered, and each department also informally described work in progress. A few highlights are summarized here.

Life Span Study

Updated through 1990, *RERF Life Span Study* (LSS) *Report 12* is now in the final stages of preparation. This report will emphasize that radiation risks depend on sex, age at exposure, and time since exposure. Estimates will be presented to illustrate this dependence. The inadequacies of the traditional risk estimates calculated without regard to sex and age at exposure will be discussed. Although the main focus will be relative risk, the excess risk in terms of absolute-risk models will be described in more detail than in earlier LSS reports. In particular, sex and age-at-exposure effects are much less pronounced on the absolute-risk scale. Dose-specific lifetime excess risks for the LSS cohort will be presented for the first time, and site-specific risk estimates will be included. The authors warn against overinterpreting the differences in these estimates because much of the variability can be explained by sampling variation. Because 85% of the atomic-bomb survivors exposed when less than 30 years old were still alive in 1990, the importance of continued follow-up will be emphasized.

The pathologic features of various cancer types were reviewed for the councilors. Literally hundreds of specimens had been histologically analyzed, providing RERF researchers with insight into malignancy types and cancer sites that are most responsive to radiation and other risk factors. Preliminary analyses of tumors of the skin, salivary gland, liver, and central nervous system, as well as studies in progress, were also reported.

International collaborative studies

During the past months, RERF researchers have continued to assist scientists from the Ural Research Center for Radiation Medicine (URCRM), Chelyabinsk, Russia, and Branch Laboratory 1 of the Institute of Biophysics (FIB-1) in Chelyabinsk-65 with training, database development, epidemiologic analysis, and laboratory analysis of chromosome and gene changes in the somatic cells of the local population. About 28,000 persons from the Chelyabinsk area received external and internal radiation exposures averaging 0.4 Gy after the accidental release of radioactive waste resulting from plutonium reprocessing. The FIB-1 cohort includes about 20,000 workers at the Mayak plutonium reprocessing plant. Long-term, low-dose-rate population exposures, such as those being studied at URCRM and FIB-1, may contrast markedly with the experience of the atomic-bomb survivors. Despite the limited financial resources available, scientists at RERF and in Chelyabinsk are working to strengthen their collaborative efforts.

Genetics research

In biochemical genetics, a much-improved technique of simultaneously studying mutations in hundreds of genes for mother-father-child DNA analysis was explained, as well as pilot studies to measure mutations in specific target genes in 100 families.

In cytogenetics, an insightful analysis of the chromosome-aberration frequency of 2292 survivors hinted that systematic dosimetry revisions may be required—especially for those exposed in Nagasaki factories and tenement houses.

Furthermore, preliminary results of concurrent biodosimetry based on chromosome aberrations and electron-spin-resonance of tooth enamel from the same 10 survivors are revealing remarkably comparable results, in contrast to the outlier status of five of these survivors in terms of their aberration frequency versus their Dosimetry System 1986 dose attribution. (See related article on p 6.)

Radiobiology

Red-blood-cell M and N antigens are markers of somatic-cell gene mutation, making them an important tool for biodosimetry. Yet, because a mature red blood

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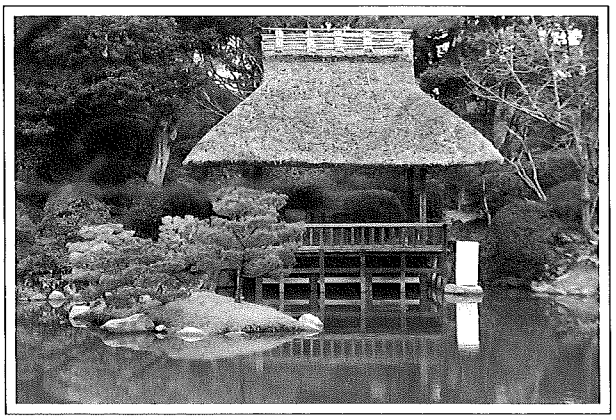
In This Issue

Perspectives

A Place of Tranquility amidst the Crisis

by Seymour Abrahamson, RERF Chief of Research* & Update *Editor in Chief



A parting shot from Editor in Chief Abrahamson, who completed his second 2-year term as RERF chief of research on 30 June. A teahouse in* Shukkeien, *a formal Japanese strolling garden that was destroyed in the atomic bombing of Hiroshima and was later rebuilt.

During the week of 13 June, the research review by the RERF Scientific Council was concluded, and the scientific staff reported their outstanding progress over the last year. During the following week, the RERF Board of Directors met at the Hiroshima Laboratory to finalize the new budget and to approve the Scientific Council report, as well as other recommendations and regulation changes required by law. Interspersed between these two meetings were discussions between representatives of the US Department of Energy (DOE), the Japanese Ministry of Health and Welfare (MHW), the National Academy of Sciences (NAS), the RERF executive committee, and members of the NAS staff working at RERF.

Since the previous issue of *Update* was published, the MHW has agreed to lend the DOE US$2 million for fiscal year 1994–95. The DOE will request extra funding to support next year's research program, and RERF will reduce staff by 25%—more than 100 positions—through a 5-year moratorium on replacements for mandatory retirees. Replacements for 6 voluntary retirements occurring this year have been approved, and this number may be increased in upcoming years after the next series of DOE–MHW talks in October 1994. Permanent directors were reduced from six to four on 30 June.

The NAS staff at RERF will total at most 12 persons by December, and it is unlikely anyone will be replaced before the DOE and NAS agree to a working budget, including appropriate contracts for staff presently working without formal agreements.

In response to these stringent measures, RERF has initiated plans to phase out the radiobiology program in Nagasaki over the next 2 years. Professional staff will be asked to move to Hiroshima Laboratory departments, and technical staff will be transferred to vacated positions in other more essential programs at the Nagasaki Laboratory. The Secretariat and the Publication and Documentation Center at the Hiroshima Laboratory will be downsized by retirements and by transfers to other programs. The Hijiyama Hall dining room was closed at the end of June, and other retrenchments are expected. Other research and clinical programs survive, but with reduced staffing.

Because the dollar's value remains at less than 100 yen, RERF faces further budgetary pressures, and little additional help can be expected unless other US government agencies involved in radiation protection see fit to rescue RERF as the US National Cancer Institute did in 1975. (See Robert W Miller's article, p 8.)

I personally believe other solutions must be sought to maintain RERF's research integrity. The drastic downsizing will create a stranglehold on RERF's ability to respond to new research developments. Soon every voluntary retirement will become a critical position for the department in which it occurs. The operations budget (ie, the nonpersonnel-related budget) is now determined by the total number of staff, not by the number of research scientists. Thus research supplies and equipment are being reduced even though the overall number of researchers is decreasing only slightly. The fiscal year 1994–95 budget for laboratory equipment and supplies is about 35% less than last year, providing little more than replacement equipment for most programs. Unless this situation is markedly improved in the upcoming year's budget at the latest, research programs will be seriously impaired. This is occurring when research quality and productivity—especially during the past decade—have been at their highest levels. Either a change in the 50–50 cost sharing should be negotiated by the two governments or, as the RERF Labor Union suggests, a department such as Clinical Studies could be supported by MHW funds exclusively and independently of RERF joint support.

I have stated elsewhere that RERF can certainly become a leaner more-thrifty organization, but I had not envisioned that "termination" syndrome would envelop us. Both funding agencies stress their continuing support for our mission, but it will take more than protestations of good faith to keep RERF's mission vital and progressive.

I profoundly hope RERF surmounts the present problems and continues to make its important contributions to world knowledge.

This is my last task as editor in chief of *Update* since taking over in the spring of 1993 from the gifted founder of this newsletter, **JW Thiessen**. **Beth Magura** also deserves extraordinary praise for maintaining this newsletter's high quality and reader interest.

I turn the helm over to my very able colleague, **Donald Harkness**, who was formerly chairman of the University of Wisconsin's Department of Medicine. I wish him great success both as RERF chief of research and as editor in chief of *RERF Update*. ❑

Science, Radiation Protection, and the NCRP

The author discusses cancer risk estimates, which are based largely on the studies of atomic-bomb survivors, and their uncertainties.

by Warren K Sinclair, President Emeritus, National Council on Radiation Protection and Measurements, Bethesda, Maryland

Editor's note: The following is an abridged version of the 17th Lauriston S Taylor lecture that was delivered in Washington on 7 April 1993 at the annual meeting of the National Council on Radiation Protection and Measurements (NCRP).

In this discussion, I will focus especially on uncertainties in current risk estimates for radiation-induced cancer. This risk is the largest component of health detriment due to radiation exposure at low doses and is estimated by the International Commission on Radiological Protection (ICRP) and NCRP to have a value, on average, of 5% per sievert for a population of all ages and 4% per sievert for an adult population of workers. These values are derived from the data in the RERF Life Span Study (LSS) of the atomic-bomb (A-bomb) survivors following high-dose-rate exposure using a dose and dose-rate effectiveness factor (DDREF) of 2, chosen by the ICRP and NCRP.

Uncertainties in risk estimates derived from the LSS can be grouped into five main categories: epidemiology, dosimetry, projection to lifetime, transfer between populations, and extrapolation to low dose and dose rate.

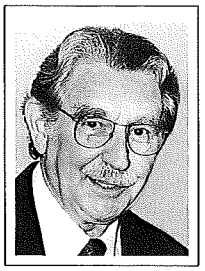
Epidemiological uncertainties

Epidemiological uncertainties include the statistical uncertainties associated with deriving the relatively few excess cancers (339) among a background of cancers resulting from all causes (5936), until 1985, in the 75,991 persons in the RERF Dosimetry System 1986 (DS86) sample. Also, since mortality data are based on death certificates, underreporting of deaths attributable to cancer, especially among older persons, gives rise to a significant error. The BEIR III committee used a factor of 1.23 to correct for this. But in its 1988 report, the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) made no correction, and, in its BEIR V report, the BEIR committee made no correction either.

Recently, researchers at RERF have examined the effect of diagnostic misclassification on noncancer and cancer mortality and have found that the excess relative risk for cancer should be increased by 13% for this reason (Sposto et al, *Biometrics* 48:605–17, 1992). The LSS sample, while representing a good cross section of all ages, may be somewhat unrepresentative in other ways, although probably less so than many clinical samples.

Dosimetrical uncertainties

Dosimetrical uncertainties include random and systematic errors in the dosimetry which have been estimated to be of the order of 25–40%. Jablon (ABCC Technical Report 23-71), Gilbert et al (RERF Technical Report 12-82) and Pierce et al (*Radiat Res* 123:275–84, 1990) noted that these errors lead to bias errors in the risks, causing them to be smaller than the true risks in the higher dose range. This persistent bias in the dose-response curve would, if corrected for, require an increase in risk of 6–17% for all dose points and 4–11% if dose points above 4 Gy were eliminated.



Sinclair

The neutron component in DS86 is about 1–2% of the absorbed organ dose in Hiroshima depending on organ site, distance, etc. Applying an average relative biological effectiveness (RBE) of 10 would cause the neutron equivalent dose to be about 10% of the total equivalent dose. Clearly, uncertainty is associated with this assignment.

The issue of the presence of "excess" thermal neutrons at distances in Hiroshima has caused much recent speculation (Preston et al, *RERF Update* 4[4]:5, 1993). If more neutrons were to be added at Hiroshima, agreement between the two cities on risk and on cytogenetic data would become distinctly poorer.

Projection to lifetime risk

Projecting from the observed population (39% of the total in 1985) to the lifetime of the entire population is one of the greatest potential uncertainties in our current estimates of lifetime risk.

The A-bomb survivor data for total cancer and for some individual organs, when classified by individual age groups, show that the excess relative risk (ERR) is approximately constant with time, even though a simple plot of ERR vs time for all age groups shows that the gross ERR for all solid cancers is still increasing.

In a different approach, Kellerer and Barclay (*Radiat Prot Dos* 41:273–81, 1992) suggested that attained age might be a better parameter than age at exposure for the dependence of sensitivity on age. Present data are complete only for the older ages in the population, and thus it is not possible yet to discriminate between these two models. If the attained-age model should ultimately prove correct, the presently used age-at-exposure model would overproject perhaps by as much as a factor of 2.

Uncertainty due to transfer between populations

Because of differing natural cancer rates among various populations in the world, it is difficult to know how to transfer risks from the exposed Japanese population to other populations. Transfer could be done either multiplicatively or additively.

In view of the uncertainties involved, the ICRP transferred the risk for individual organs by both the multiplicative and additive models and averaged the result, thus minimizing the potential error from this source. Fortunately, the ICRP average of five populations and the US estimate of the fractional organ risks do not differ greatly.

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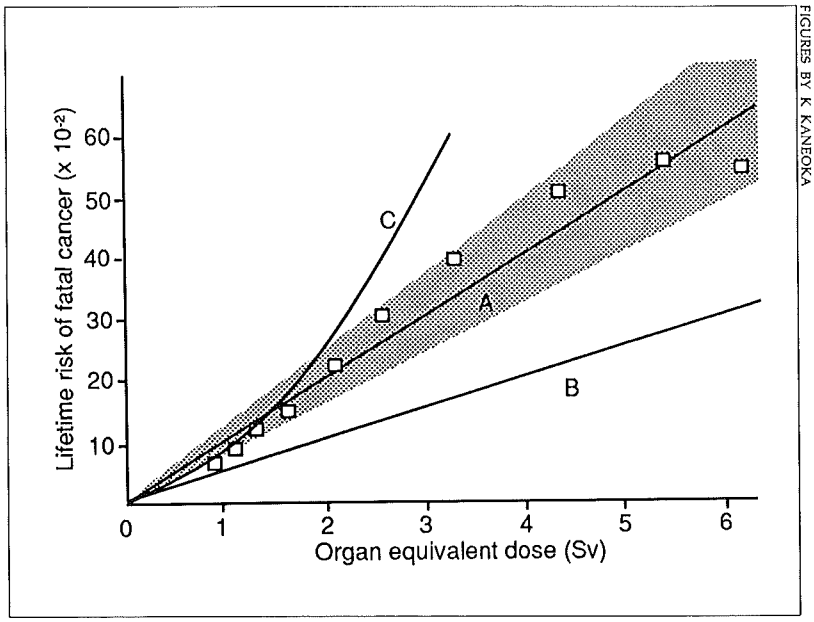
Uncertainty resulting from extrapolation to low dose rate

Many radiobiological phenomena involving low linear-energy-transfer radiations show reduced effectiveness for low dose rates as compared to high dose rates. In view of all these laboratory data (*NCRP Report 64*, 1980; UNSCEAR, 1993) and considering some less-definitive human information, the ICRP used an effectiveness DDREF of 2. NCRP would have preferred a larger value—perhaps 2 to 3 (and thus lower risk estimates), but accepted the ICRP value.

Dose response for solid tumors among the A-bomb survivors

A serious problem for choosing a value of the DDREF is that of the dose response for the solid-tumor data from the A-bomb survivors. For leukemia (which is about 10% of the total risk), the dose-response curve is best fit by a linear-quadratic expression that is compatible with a DDREF of 2 to 2.5. However, the other 90% of the risk is due to solid tumors that collectively are best fitted with a linear curve. This response can be stretched within the statistics of the data to include a DDREF of about 2 for mortality, but only to about 1.4 for the incidence data. Clearly, the linear fit over a dose range up to 4 Gy or 5 Gy is just that—a fit. It does not imply single-hit kinetics or any other mechanism. Furthermore, it is a composite of many different individual tumor responses. Again, a low-dose-rate response could actually be a linear curve of lower slope over the observed dose range. Nevertheless in the low-dose region, somewhere the high-dose-rate curve and the low-dose-rate curve must become the same, when there is less than one event per cellular target and no dose-rate effects can occur. Presumably this occurs at doses lower—possibly *much* lower—than present data provides.



FIGURES BY K KANEOKA

Figure 1. Curve A represents the "observed" high-dose-rate Japanese data line **(slope 10×10^{-2} Sv^{-1}).** ***Curve B represents the ICRP risk line obtained with a dose and dose-rate effectiveness factor (DDREF) of 2, viz,*** **5×10^{-2} Sv^{-1}.** ***Curve C is the beginning of a curve of incidence vs*** **$\alpha D + 0.83\alpha D^2$,** ***not corrected for cell killing. The set of points (squares) is for*** **$(\alpha D + 0.83\alpha D^2)K \cdot f(D)$,** ***ie, the linear quadratic with the experimental cell-killing values*** **$K \cdot f(D)$**. ***The set of points begins below curve A, fits well over a range, and then begins to level off. It could be reasonably fitted by the 10%-per-sievert line (see the 95% confidence limits on curve A), but its initial slope is only 5% per sievert, equivalent to a DDREF of 2; ie, within the limits of error, we could have an initial slope of only 5% per sievert, derived apparently from data that with a good linear fit yield 10% per sievert.***

I want to point out another way in which a lower slope (and thus a significant DDREF) can be reconciled with the apparent linear slope of the Japanese solid-tumor data. In some clearly defined circumstances, in-vitro cell killing at higher doses can account for a decreased incidence of transformation. Indeed, the slope of the decrement in transformation can be shown to be the same as that of a cell-killing curve. In the much more complex circumstances applying to intact tissues in vivo such a simple influence of cell killing is not to be expected. Nevertheless, cell killing can be expected to play some role in limiting the number of viable cells at risk for cancer induction. Has cell killing been sufficiently considered in the assessment of the Japanese data? Here is one possible approach.

Let us suppose, simplistically, that the incidence of fatal cancer with dose is strictly a linear-quadratic $I = \alpha D + \beta D^2$ and that what we observe is this incidence modified by a cell-killing term, $K \cdot f(D)$, which is a function of dose [ie, $I = (\alpha D + \beta D^2) K \cdot f(D)$]. Let us assume values for the parameters: α = 5% per sievert for the risk at low doses in a total population; a cross-over dose (ie, $\alpha D = \beta D^2$) of 1.2 Gy (a reasonable value); and thus $\beta = \alpha \div 1.2$ or 0.83α. Then take for $K \cdot f(D)$ values from an experimental mammalian cell-survival curve for single cells in culture, eg, V79 cells exposed to cobalt-60 γ rays from Hill et al (*Radiat Res* 113:278–88, 1988). The situation then is shown in Figure 1. This admittedly oversimplified and rather crude example shows that a lower initial slope than appears at first applicable could be possible, and it could account for a reasonably low value of DDREF, such as 2. The existence of a lower-than-linear initial slope in the low-dose region is further confirmed by a recent analysis by Shimizu et al (*RERF Update* 4[3]:3–4, 1992) of the region below 0.5 Sv. The relative risk for solid cancers is greater than 1 down to a dose of 0.02 Sv (ie, 20 mSv). Also, the analysis of data at less than 0.5 Sv leads to a linear slope somewhat lower than for the slope of the linear response for all the data up to 4 Sv. This is in concert with the linear-quadratic response and cell-killing notion described above.

Does a threshold for induced cancer exist?

While it is true that in view of conflicting sources of information and statistical uncertainties a threshold for induced cancer cannot be entirely ruled out, I nevertheless want to make a few points about the issue of a threshold. Although it is possible to imagine a line of lower slope than the 10% per sievert high-dose-rate line derived from the Japanese data as being the true situation for low dose rate, as we have shown above, a threshold is much more difficult to explain. It involves a discontinuity that requires, in my view, a new process operative only at low doses that somehow leads to the dotted portions of curves A and B, as shown in the expanded low-dose portion of Figure 2. It is

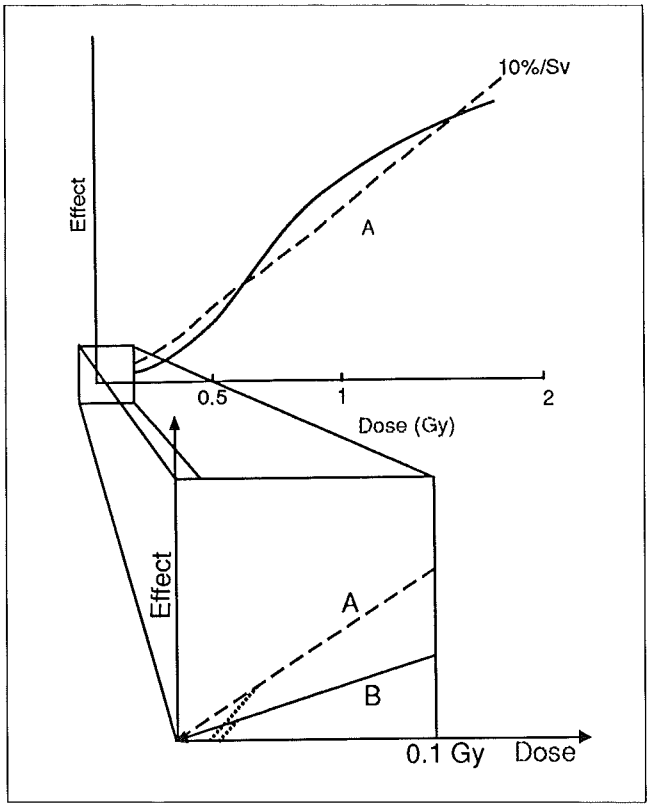


Figure 2. Effect vs dose, expanded in the low-dose region. Line A (- - - -) is linear, line B (——) is linear quadratic, and the dotted lines represent possible response.

not impossible to imagine such a process, and indeed something like it has been shown by S Wolff and colleagues for a transient repair effect for chromosome-aberration induction in human lymphocytes at low doses (Shadley et al, *Radiat Res* 111:511–17, 1987). However, this phenomenon has not seemed either to last very long or to be generally applicable to, eg, the case of cancer induction.

Some outstanding laboratory studies of the dose response in the low-dose region are noteworthy. One by Lloyd et al (*Int J Rad Biol* 61:335–43, 1992) involves the study by six laboratories of chromosome aberrations in lymphocytes that found linearity in dose vs effect down to 20 mGy. Some studies in the past have extended to even lower doses, notably Sparrow et al (*Science* 176:916–18, 1972) with pink mutations in *Tradescantia* that extend to 2.5 mGy of x rays and 0.1 mGy of neutrons. When plotted on a linear scale, the x-ray data still show linearity. Also Bateman et al (*Radiat Res* 51:381–90, 1972) studied lens opacities after neutron doses as low as 0.22 mGy and found that controls differed significantly.

Thus, we may ask at what dose levels are thresholds expected to start? We seem to have measured linearity in some systems to about 2 mGy of x rays and to 1/10th of a milligray for neutrons. Is there any reason to suppose linearity will not continue to even lower doses? At very low doses and therefore very low risks, does it matter if a nominal threshold exists? Both the doses and the risks would be regarded by many as negligible. In my view, given the stochastic nature of the process, it is sounder to accept the nonthreshold hypothesis and describe the risk as negligible at very low doses than to argue for a threshold.

Low-dose epidemiological studies

Over the years, a multitude of low-dose epidemiological studies have raised many questions about radiation effects in humans but have individually contributed relatively little to risk estimation for a variety of reasons. However, recently low-dose studies on workers in the United Kingdom and also in Russia, as well as one environmental study in Russia, have contributed some new numbers. A comparison with the Hiroshima–Nagasaki-derived estimates indicate that the UK study has a higher leukemia risk, which is partially balanced by the negative result from a smaller US study. The two Russian studies, while based on rather uncertain data up to now, appear to be in concert with the derived high-dose values. More data of this type, even though it has very wide confidence intervals, would be extremely useful for radiation protection. A proposed study of all US workers at nuclear-power plants could be most valuable but has so far not been initiated. The scientific community and perhaps especially the NCRP should press to see that this takes place. Such a study and its potential incorporation in a larger worldwide study under the aegis of the International Agency for Research on Cancer (IARC), Lyon, could be a most important step for radiation protection. In the meantime, it seems that a less ambitious but also useful study will be done by IARC, combining the US, UK, French, and Canadian data.

Table 1. Summary of possible ways that uncertainties might affect risk estimates

Factors related to uncertainties	Approximate contribution
In support of higher risk estimates	
Dosimetry bias errors	+10%
Underreporting	+13%
Projection directly from current data	+?%
In support of lower risk estimates	
Dosimetry—more neutrons at Hiroshima	? –(13–22)%
Projection, eg, attained age	? –(25–50)%
Of equal impact for higher or lower risk estimates	
Transfer between populations	? 25–50%
Dose response and extrapolation	? 50%

Radiation protection recommendations

Given all the above, where does the NCRP stand with its current recommendations? Overall, I think the uncertainties are about as likely to lead to higher risk estimates as lower, see Table 1 (though I tend to favor them being lower, mainly because of the possibility of overprojection). In the future, I hope they lead to lower risk estimates because, in fact, the ICRP in 1990 (*Publication 60*) did not aim for a higher "level of ambition" for radiation protection than in 1977, ie, the relationship of the total detriment to the limits is about the same. NCRP went a little further with its guidance in 1987 (*Report 91*) and its limit in 1993 (*Report 116*). Furthermore, the NCRP base of comparison with worker risks is updated to the present. In any case, I would rather find that the present risk estimates are a little too high so that when they are next used as the basis of recommendations—perhaps in the early years of the new century—changes might not be needed because the risks would be in concert with other normal worker risks at that time.

Thus, in my opinion, the ICRP in 1990 and the NCRP in 1987 and in 1993, even more so, have correctly lowered occupational and public limits in response to our best present information on risk estimates despite the many uncertainties in these estimates. ❑

Assessing Radiation Dose Recorded in Tooth Enamel

Electron-spin resonance measurements of extracted teeth donated by atomic-bomb survivors correlate fairly well with the lymphocyte chromosome-aberration frequencies for these same donors.

by N Nakamura,[1] M Iwasaki,[2] C Miyazawa,[3] M Akiyama,[4] and AA Awa[1]

Radiation's "fingerprints" remain in certain materials for quite a long time. For example, thermoluminescence has been used to measure atomic-bomb (A-bomb) γ-ray doses using ceramic roof tiles in Hiroshima and Nagasaki more than 40 years after the bombings.

In the technique known as electron spin resonance (ESR) (also called electron paramagnetic resonance), radiation-induced radicals (ie, unpaired electrons) absorb microwaves when subjected to certain strengths of magnetic field. Different radicals (either atoms or molecules) have their own magnetic-field strength for the absorption. In liquid, radicals disappear quickly; but in solids, eg, in the calcified tissues of the human body such as bones and teeth, radicals can not freely move around and are much more stable. Because bones are continuously remodeled and are not readily accessible, mainly teeth have been used in ESR studies to date. (However, ESR dose estimates obtained from the bones of legs amputated due to radiation necrosis after accidental exposure have been reported [Desrosiers, *Health Phys* 61:859–61, 1991]). Enamel, the covering of the tooth surface, consists mostly of hydroxyapatite (a compound of crystalline structure consisting of calcium and phosphate) and is free from any metabolism. Tooth enamel is a unique inorganic body structure.

Although laboratory studies about ESR have been published since the 1960s, in the past decade ESR has received renewed attention. In Japan, M Ikeya of Osaka University has actively promoted ESR studies (eg, Ikeya et al, *Jpn J Appl Phys* 23:697–9, 1985; Ishii and Ikeya, *Jpn J Appl Phys* 29:871–5, 1990). A series of ESR studies on tooth enamel from mainly Nagasaki A-bomb survivors has been published by S Okajima's research group at Nagasaki University (Tatsumi et al, *J Hiroshima Med Assn* 41:382–5, 1988 [in Japanese]; *J Radiat Res* 29:88, 1988 [English abstract]). These results have not been compared with individual Dosimetry System 1986 (DS86) dose estimates.

Departments of [1]Genetics and [4]Radiobiology, RERF; Departments of [2]Dental Radiology and [3]Preventive Dentistry, School of Dentistry, Ohu University, Kooriyama.

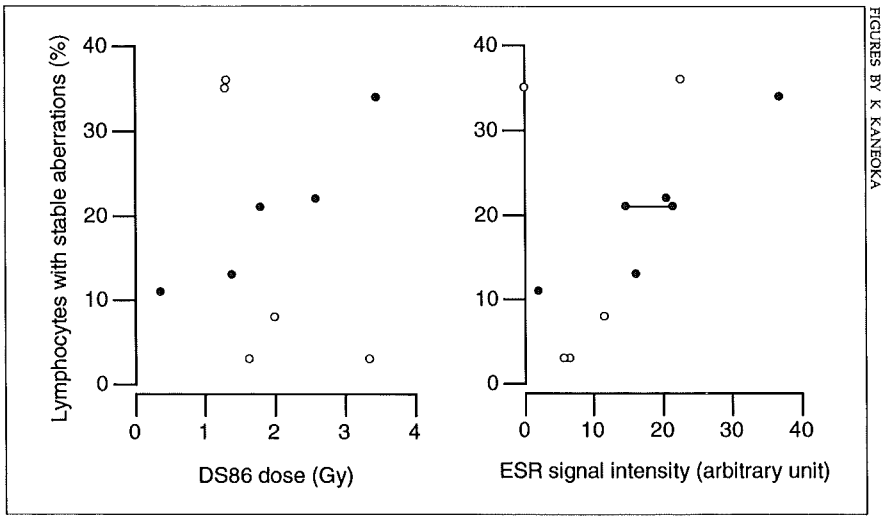


Figure. (Left) Frequency of lymphocytes bearing stable-type chromosome aberration(s) plotted against Dosimetry System 1986 (DS86) total dose. (Right) Frequency of lymphocytes bearing stable-type chromosome aberration(s) plotted against ESR signal intensity of tooth enamel. Because each sample contains a different amount of enamel, the measured signal intensity was corrected by dividing with the weight. The black circles represent five cases that are close to the average in chromosome-aberration dose response in our large cohort. The two black circles connected with a line represent the results of two teeth from the same donor. The five open circles are so-called outliers, although such individuals are not common. The ESR signal shown here is for outer halves of the samples.

Current knowledge about ESR of tooth enamel

- It seems that CO_3^{3-} radicals are being measured.
- Photon-energy dependence is evident, eg, 40-keV x rays generate an ESR signal per unit dose more than five times greater than cobalt-60 γ rays (Tatsumi et al, *J Hiroshima Med Assn* 39:418–22, 1986 [in Japanese]; Iwasaki et al, *Radioisotopes* 40:421–4, 1991).
- Compared to γ rays, neutrons are much less effective in producing ESR signals (Tatsumi, *Filmbadge News* 125:1–9, 1986 [in Japanese]; Iwasaki et al, unpublished observation, 1991).
- Observed ESR signal intensity is linearly proportional to the mass of enamel examined (Iwasaki et al, *Ohu University Dental J* 17:95–100, 1990).
- No dose-rate effect was observed after in-vitro exposure to γ rays with dose rates ranging from 225–0.33 R/min (Iwasaki et al, *Radioisotopes* 41:642–4, 1992).
- Irradiation of enamel samples in vitro, either in dry conditions or in water, produced identical ESR signal intensities (*ibid*).
- Enamel grain sizes of 0.5–1.4 mm in diameter are preferred (Iwasaki et al, *Radioisotopes* 42:470–3, 1993).

The Hiroshima ESR project

In Hiroshima, we began to request donations of extracted teeth from RERF's Adult Health Study partici-

News Briefs

✓ Research Staff News

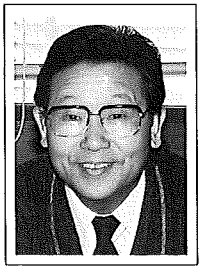
Permanent directors **Tomoyuki Kono**, chief of the Secretariat, and **Seymour Abrahamson**, chief of research, retired on 30 June as part of RERF's cost-reduction measures. **Yasukiyo Hirano** is now chief of the Secretariat.

Katsutaro Shimaoka retired as associate chief of research, Nagasaki Laboratory, after serving since October 1986. Former Department of Genetics Chief **Akio Awa** is now an associate chief of research, based at the Hiroshima Laboratory.

Hiroshima

Department of Genetics: **Chiyoko Satoh** is now chief of the department. **Norio Takahashi**, chief of the Radioisotope Facility, is also chief of the Laboratory of Biochemical Genetics. **Nori Nakamura** is assistant department chief and chief of the Laboratory of Cytogenetics.

Department of Radiobiology: In January, **Toshio Seyama** was promoted to assistant department chief. He is concurrently chief of the Laboratory of Cell Biology. Associate senior scientist **Seishi Kyoizumi** was promoted to chief of the Laboratory of Immunology on 1 February.



Awa

Department of Epidemiology: **Yasuhiko Yoshimoto**, who is chief of the Epidemiologic Analysis Laboratory, was promoted to senior scientist on 1 April. Department of Statistics senior scientist **Donald Pierce** is concurrently assigned to the Epidemiology Department. Research scientist **Thanne P Rose** completed her 2-year stay at RERF and returned to the US on 30 June.

Department of Epidemiologic Pathology: Assistant Department Chief **Yasuyuki Fujita** is concurrently serving as acting chief of the Tumor and Tissue Registry Office.

Department of Statistics: Senior scientist **Shoichiro Fujita** is chief of the Statistical Analysis Office. Research scientist **David Pawel** completed his 2-year term at RERF and returned to the US on 2 August.

Department of Clinical Studies: **Saeko Fujiwara**, senior scientist, is concurrently assigned to the Division of Radiology. Research scientist **Michiko Yamada**, Division of Medicine, was promoted to associate senior scientist on 1 April.

✓ In Memoriam: Felix E Moore

Felix E Moore, a member of the Francis Committee, died in Reno, Nevada, on 27 November 1993 at the age of 81. In 1955, along with fellow committee members **Thomas Francis Jr** and **Seymour Jablon**, Moore spent 3 weeks reviewing the research program of RERF's predecessor, the Atomic Bomb Casualty Commission. The scientific design formulated then still serves as the basis for the Foundation's studies today (see ABCC Technical Report 33-59). ❑

Tooth Enamel

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pants in 1986. Since that time, 300 teeth have been collected, but only about 30% were found to be suitable for enamel separation and subsequent ESR measurement.

We have learned that enamel must be carefully separated from dentin because dentin produces a large background signal and is very ineffective in producing a radiation-related signal. A disc-shaped diamond cutter with running water is currently used to isolate enamel after slicing a tooth. Imagine slicing the crust off of a piece of toast. This method, which is tedious and requires great skill, produces quite satisfactory results. (This method will be described in detail in the near future.)

One unsolved problem is how to evaluate the contribution to dose from dental x rays (which have an effective energy of 30 keV or less). As mentioned above, such low-energy photons are much more effective than cobalt-60 γ rays and thus may contribute significantly to the ESR signal while actually contributing little to the dose. To assess dental x-ray dose, each tooth is divided in half—one half from the inside of the mouth and the other from the outside. Because panoramic photographs were not common in the past, we assume that most of the diagnostic dental x rays struck the outside of the tooth. Whenever a larger ESR signal is seen in the outer half than in the inner half of the tooth, we are particularly cautious in interpreting the results for that donor.

Preliminary results for 11 samples from 10 donors are presented in the figure. Note that the current ESR measurements do not include any in-vitro γ irradiation of known doses. Thus, the ESR results may not necessarily correspond linearly with dose because each tooth may respond to radiation somewhat differently. Nevertheless, several interesting features are apparent. First, the two black circles connected with a line represent the results of two teeth from the same donor. The discrepancy seems mostly derived from dental x rays, because inner halves of the two teeth gave almost identical signal intensities (not shown) and are close to the lower value in the figure. Second, the chromosome-aberration data correlate quite well with the ESR data. In other words, no outliers are apparent. Third, one exceptional case has been noted. The tooth of a survivor whose DS86 assigned dose is 1.3 Gy and who has a 35% frequency of lymphocytes with chromosome aberration(s) showed no sign of radiation exposure! That particular sample was a wisdom tooth, known to be formed much later than other human teeth, and the tooth donor was 15 years of age at the time of the bombing. Because individual variation in the development of wisdom teeth is quite wide, we do not know if the tooth in question was really underdeveloped at the time of exposure in 1945. We hope to examine another type of tooth from this donor in the future.

Future prospects

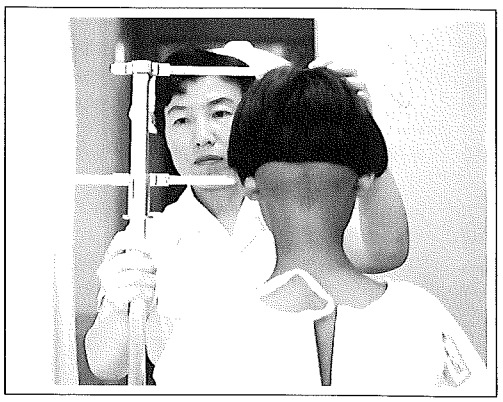
In view of the applicability of ESR for dating fossil teeth, eg, from early *Homo sapiens* (Tiemei et al, *Nature* 368:55–6, 1994), it seems likely that tooth enamel can properly accumulate radiation doses imparted at extremely low dose rates. This means that human teeth may be distinctive natural biodosimeters not only for acute radiation exposures but also for repeated small doses or chronic γ-ray exposures of radiation workers and people residing in contaminated environments. At RERF, we intend to coordinate the ESR of tooth enamel with our lymphocyte chromosome-aberration studies that employ the fluorescence-in-situ-hybridization method. ❑

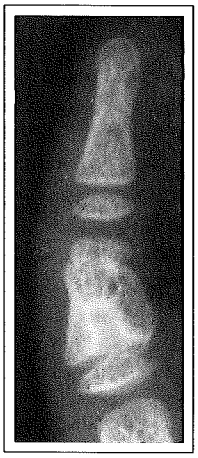
Miller's Memories of ABCC–RERF, 1953–1990: Part 3

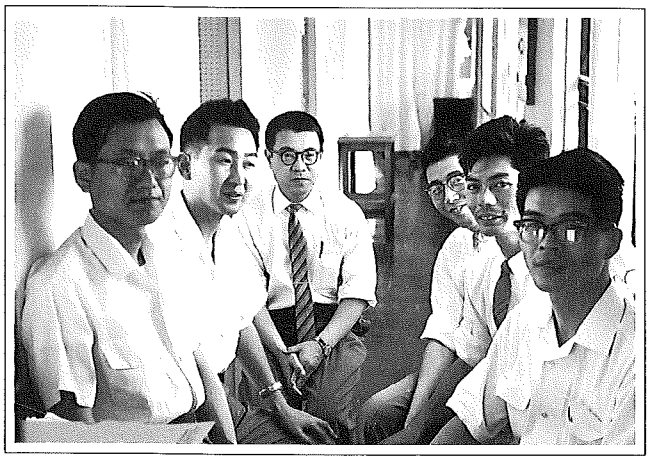
The anecdotes of a longtime ABCC–RERF associate are concluded in this issue.

by Robert W Miller, Clinical Epidemiology Branch, National Cancer Institute, Bethesda, Maryland

Editor's note: Part 1 of Robert Miller's recollections appeared in RERF Update *5(4):7–9, 1993, and Part 2 was published in* RERF Update *6(1):9–10, 1994. On 27 April, Miller became a scientist emeritus at the National Cancer Institute.*







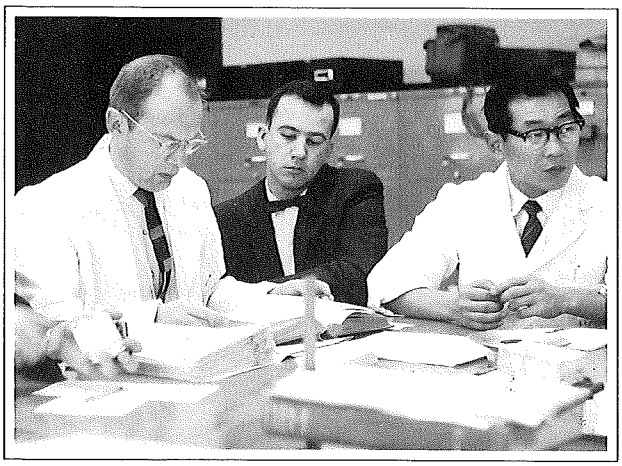
PHOTOS COURTESY OF ROBERT W MILLER

At left, anthropometrics being collected, 1959–60. Below left, a malformed bone of the little finger, nicknamed "geisha finger" because of its x-ray shadow, unusually common in Japanese children. Below right, in 1959–60, at the Nagasaki Laboratory, pediatricians in the Child Health Survey. From left, Hiromi Tanaka; Kanji Ito; Shotaro Neriishi; Norio Fujiki, a hematologist and geneticist; Munetaka Miyake; and Noboru Yanai.

Child Health Survey, 1957–61

Jim Neel is a very talented organizer of large field studies. Advance planning would prepare us all to "hit the ground running." Three young Japanese faculty members joined us and helped make the connections needed for approvals in Japan. Jim made sure everyone there who should know our plans was informed—from members of the Ministry of Health and Welfare and academic leaders, through officials of the local governments, to teachers and parents. We reviewed the literature, developed the procedures and tests to be used, met with key Japanese geneticists who visited Ann Arbor, and sidestepped some unexpected obstacles. Going back to school was as bad as I expected, but tailoring my activities to those of Neel's Genetics Department diminished, or at least justified, the pain.

We did hit the ground running. We quickly recruited an excellent staff of Japanese pediatricians, nurses, psychometric testers, and patient contactors. At least one of them, **Masanori Otake**, is still at RERF, where he built a career in biostatistics. Within 2 weeks, we were seeing 40 patients a day in the clinic. We finished in Hiroshima on schedule and soon after had a full clinic in Nagasaki.



Morning review of the previous day's medical charts for the Child Health Survey, 1958. From left: Jim Neel, and dentists Jerry D Niswander and Chokudo Sujaku.

My project was to be on a form of parasitism that caused 10% eosinophilia in 1 out of 4 Hiroshima children in 1955. When we returned in 1958, Japan had changed its agricultural practices, and the medical problem was gone. So I changed my topic to disturbances in visual acuity. My thought was that vision depends on perfect formation of the components of the eye, and imperfections due to inbreeding would be detectable by vision tests. This proved to be true, but overall the effects of inbreeding were not biologically significant except in families with known recessive traits—infrequent even in the large sample studied.

Some cases were unusually interesting. One tall girl only 8 years old almost pressed her eye to the page of a book as she waited to be examined. She had Marfan's syndrome, as did nine other members of her family, who were among the tallest people in Nagasaki. Another child's heart beat could not be heard until we listened to the right side of his chest. His little sister was peering at us from the end of the examining table. We listened to her chest and found she also had situs inversus. Both families were reported in the Japanese

literature. All families were sent a letter describing the findings 4 days after the clinic visit.

When reviewing x-ray films of the hand as a measure of maturation, we often noticed a malformed bone in the middle of the little finger. Its formal name is brachymesophalangy, but we called it "*geisha* finger" because of its x-ray image (see accompanying photo on p 8). Formal study by our group showed that in Japan it occurred in 10% of boys and 17% of girls, compared with about 3% in both sexes in the US.

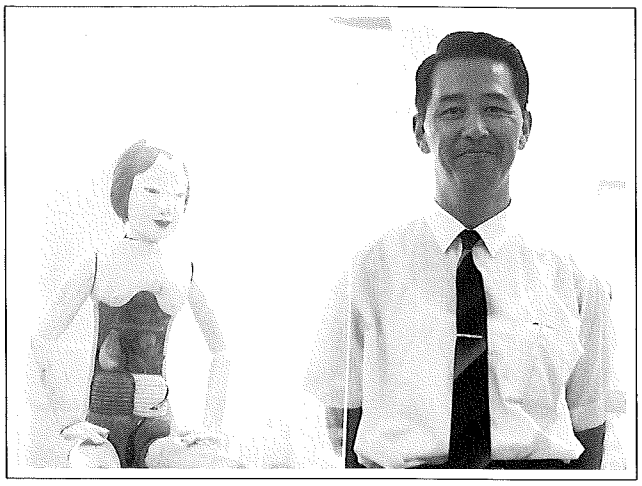
My thesis was accepted at the end of my second year at the University of Michigan. During that time, as Jim Neel reviewed the medical records he found they were detailed enough for him to use appendectomy scars as a measure of susceptibility to infection. There were no differences between inbred and outbred children.

Of the four Japanese pediatricians who worked with us in addition to **Shotaro Neriishi**, two obtained fellowships at Buffalo (NY) Children's Hospital and one at Johns Hopkins University in Baltimore. I recently learned that our pediatrician from Kyushu University paved the way for five others from his school to follow him to Buffalo. One is now chairman of the pediatrics department at Kyushu University, and another is chairman at the school in Saga. Meanwhile Jim Neel helped establish studies of human genetics in Japan through the nucleus of young medical geneticists who worked with us.

National Cancer Institute, 1961 to the present

My natural place in epidemiology seemed to be in the study of birth defects, and the best opportunity proved to be at the US National Cancer Institute (NCI). I sought to use all of the information I had acquired—about pediatrics, radiation effects, and epidemiology—in the most clinical way possible. My lack of knowledge about cancer etiology may have been an advantage: I had no preconceptions about it. Very little attention had been given to childhood cancer etiology, and we made quick progress by means of descriptive studies of mortality (by age and race in particular) and by finding associations of certain cancers with specific birth defects. The syndromes we delineated or studied have since led to the identification of tumor-suppressor genes: Wilms' tumor of the kidney and congenital absence of the iris of the eye, neurofibromatosis types 1 and 2, trilateral retinoblastoma (involving both eyes and the pineal gland), and the Li–Fraumeni cancer syndrome. Study of these rarities have led to understanding of how a substantial proportion of common cancers develop—cancers of the breast, colon, bone, and lung, among others. These findings belied the advice given to us 25 years ago: don't study rare cancers because they have no public-health significance, and don't study genetics because it can't be fixed.

At a dinner party in 1964 in Bethesda, Maryland, I met a genealogist who thought that **Hideo Nishimura**, a teratologist and professor of anatomy at Kyoto University, and I would have common interests. Soon after, when Dr Nishimura visited Washington, we met, and we hit upon the idea of organizing a US–Japan workshop on teratology and childhood cancer in Tokyo. Although the National Science Foundation was funding only basic research, it approved our application for support of travel for five Americans, supplemented by others from ABCC (**George Darling**, **Iwao Moriyama**, **William J Schull** and **Kenneth** and **Marie-Louise Johnson**). Japanese funding came from the Japan Society for the Promotion of Science (JSPS). It proved to be a landmark meeting, for it encouraged the Japanese to extend their areawide childhood cancer registry in Tokyo to five other metropolitan centers, it set the style for a long series of US–Japan workshops on cancer, and it introduced teratologists from the two countries to each other, which led to many exchange visits by senior scientists, training of young Japanese in the US, and to increased studies of normal and abnormal development of human embryos. Three years later Dr Nishimura organized a Pan-Asian workshop in Kyoto on research methods in teratology, which produced an excellent set of proceedings and established Japan as an international force in teratology. Dr Nishimura was elected to the Japan Academy (Science) a few years ago.



Michihiro Miyanishi in 1967 poses beside an antique Japanese anatomic teaching figurine. As an intern, his question to a single patient led to the discovery that wartime mustard-gas workers were developing respiratory-tract cancer at high rates.

"These findings belied the advice given to us 25 years ago: don't study rare cancers because they have no public-health significance, and don't study genetics because it can't be fixed."

During a visit to Hiroshima at about this time, I met Dr **Michihiro Miyanishi** of Hiroshima University, who worked part time at ABCC, and learned that, as an intern, he had asked a 30-year-old patient a seemingly naive question, "Why, when you are so young, do you have lung cancer?" The patient replied that it was probably because he had worked 10 years earlier during World War II at a plant on Okunojima that made mustard gas. Miyanishi and his professor, **Sunao Wada**, later a senior consultant to ABCC, visited the island and found another 18 former mustard-gas workers with respiratory-tract cancer. The study was not population-based and had not been reported in an international journal. We provided a modest 2-year contract that called for the fullest ascertainment possible of those exposed to the several poison gases made there and for determination of the frequency of cancer among the former workers. We published the results in *Lancet* in 1968: 33 deaths from

continued on next page

Miller's Memories, Part 3

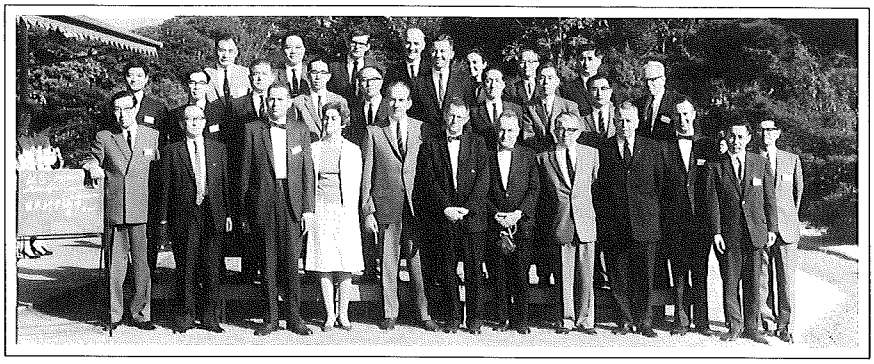
continued from page 9

cancer of the respiratory tract as compared with 0.9 expected. Since then the number of cases has risen to more than 75.

In 1971 the yen–dollar exchange rate fell sharply, and ABCC faced a fiscal crisis in meeting its expenses in Japan. At that time NCI had a year-end surplus of funds, and by formulating new tasks to be pursued at ABCC, we were able to make a contract that bridged the financial gap over the next 3 years. One purpose was to develop a visiting fellowship program in epidemiology for young Japanese who were faculty members in departments of public health. They would come to the US for a summer course in epidemiology and/or spend 4–6 weeks visiting NCI and other epidemiologic units. The balance of the year was spent in Hiroshima in the ABCC Department of Epidemiology and Biostatistics working on a research project. Among the former fellows are **Takesumi Yoshimura** of the medical school in Kitakyushu, **Kenichi Nakamura** of Showa University, **Kuniomi Nakamura** of the National Institute of Industrial Health, and **Mitoshi Akiyama**, RERF Department of Radiobiology chief, who trained in immunology. The other new endeavor was to establish a tumor-tissue registry to monitor the occurrence of cancer in Hiroshima and Nagasaki. The physicians in Hiroshima were interested, but it took time before several holdouts joined in and completed the coverage. The reluctant doctors in Nagasaki did not participate until the value of the system in Hiroshima was evident.

In 1972 we happened to be in Hiroshima when George Darling retired, and we participated in the celebration of his 15 years at the helm of ABCC. During the following year, when he was a Fogarty Scholar at NIH, I suggested to **Richard Remington**, dean of the School of Public Health at the University of Michigan, that he consider Dr Darling for an endowed lectureship on international public health. Instead he was awarded an honorary degree.

In February 1975, I was a member of the Crow Committee, which evaluated the accomplishment and potential of research at ABCC just before it became RERF. A comprehensive report was prepared (JF Crow et al, ABCC Technical Report 21-75), but it was impossible to match the impact of the report by the Francis Committee 20 years earlier (see "Miller's Memories, Part 2," *RERF Update* 6[1]:9–10, 1994). The most memorable event of this visit was my departure from Hiroshima on a wintery night. Alone on the train platform on my 20th wedding anniversary I watched the snow falling gently. A soft voice called to me from behind. It was **Celina Rappaport**, who had come to say goodbye in place of her father [then ABCC–RERF business administrator **Mick Rappaport**], who was ill.



Attendees of the US–Japan workshop on teratology and childhood cancer held in Tokyo in 1965 included the author (front row, sixth from the left) and co-organizer Hideo Nishimura (front row, second from right). Also pictured are ABCC Director George Darling (first row, fourth from right), present RERF Scientific Councilor Ei Matsunaga (second row, third from right), then RERF staff members Kenneth and Marie-Louise Johnson (back row, fourth and fifth from the left, respectively), and former RERF Permanent Director William J Schull (back row, third from the left).

Postscript

In 1974 NCI had entered an agreement with JSPS to establish a US–Japan Cooperative Cancer Research Program, which provided for short-term exchanges of mid-level scientists, of materials such as drugs, and of ideas—through numerous workshops. Since 1979 the program has involved four subject areas: etiology and carcinogenesis, biology and diagnosis, treatment, and interdisciplinary studies. **Haruo Sugano,** president of the Cancer Institute in Tokyo, and I have been the coordinators of the interdisciplinary area. We have had two workshops per year featuring differences in cancer occurrence in the two countries. There have been three on lymphoma and other lymphocytic diseases, which are of interest because the Japanese have lower rates for B-cell lymphoma but higher rates of autoimmune disease than do US Caucasians. Whatever protects against B-cell lymphoma in Japanese seems to predispose them to autoimmune diseases. **Koji Nanba** of Hiroshima University made good use of the tumor-tissue registries to show that the rates of lymphoma in Japan differ greatly from US rates.

We have held four workshops on biostatistics that proved to be especially beneficial to RERF. Three were in Hiroshima, because it is the biostatistical center of Japan—few academic positions for biostatisticians exist elsewhere. Our objective was to enhance interest in the field. **David Hoel**'s attendance at one of these workshops led him to spend two terms at RERF as a director and to accept several Fellows from Japan for training at the National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina. **Takashi Yanagawa** of Kyushu University, who has trained extensively in the US and Australia, has emerged as the Japanese leader of the workshops. I co-organized the first of the series with his mentor, **Akio Kudo,** who said to me midway through the program, "You have to realize, Dr Miller, that in Japan mathematics is 2000 years old and medicine is only 200 years old. You can't rush them into a marriage."

In 1981, after serving on various committees of ABCC–RERF, I was appointed to the Scientific Council, which made it possible for me to return annually for 9 years, enabling me to keep abreast of developments, offer suggestions about new studies, and provide the council with an institutional memory going back more than 30 years. My career and those of others who have served ABCC–RERF have been well served in return. On-the-job experience there has produced a small army of radiation experts, epidemiologists, biostatisticians, and human geneticists for Japan and the US. ❑

Estimating Doses to Servicemen Stationed Near Hiroshima

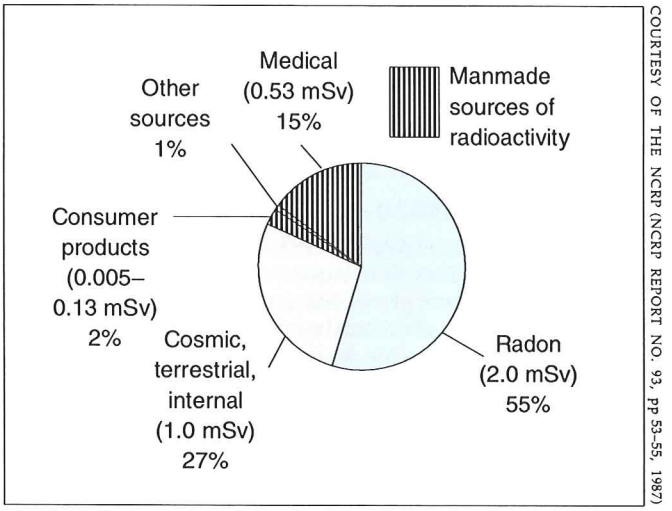
by Shoichiro Fujita, Department of Statistics

In recent months, RERF's chief of research has responded to various inquiries from former Australian servicemen who, during the post-World War II occupation of Japan, had spent time in Hiroshima.

Although doses to the atomic-bomb (A-bomb) survivors are attributed mostly to the direct radiations produced by the weapons, residual radioactivity was produced by neutron activation of soil near the hypocenters and by radioactive fallout of activation and fission products from the clouds formed by the explosions. The Dosimetry System 1986, used to estimate doses, is derived from the direct, instantaneous A-bomb radiation and does not include individual dose estimates from the aforementioned residual radiation components.

The upper limits of possible doses from induced radioactivity and fallout have been presented in the *US–Japan Joint Reassessment of Atomic Bomb Radiation Dosimetry in Hiroshima and Nagasaki. Final Report.* (Vol 1, 1987, Hiroshima, RERF, pp 205–226).

The estimated maximum absorbed doses from cumulative fallout are 120–240 mGy in the Nishiyama area of Nagasaki and 6–20 mGy in the Koi-Takasu area of Hiroshima. Those from cumulative induced radioactivity near the hypocenters are 180–240 mGy in Nagasaki and about 500 mGy in Hiroshima. Both types of exposure declined as time passed: after 1 day, the cumulative exposure decreased by about one-third and after a week to a few percent. The exposure rate from induced radioactivity rapidly decreased with distance from the hypocenter. (A detailed calculation of this has been published in *US–Japan Joint Reassessment of Atomic Bomb Radiation Dosimetry in Hiroshima and Nagasaki. Final Report*, Vol 2, Hiroshima, RERF, pp 342–351.)



COURTESY OF THE NCRP (NCRP REPORT NO. 93, PP 53–55, 1987)

During their 2-year stays in the Hiroshima area beginning a few months after the atomic bombing, Australian servicemen received estimated radiation doses ranging from 0.05–0.2 mGy to 1.2 mGy. The figure above shows, for comparison, the annual doses received per capita in the US from naturally occurring and manmade sources of radioactivity, often referred to as "background" radiation. The total yearly dose is approximately 3.6 mSv (≅3.6 mGy), ie, 1.6 to 40 times greater than the doses received by the servicemen in 2 years. Thus, for a 70-year-old man, the risk of developing cancer from naturally occurring background radiation is about 700 times greater than from the dose received in Hiroshima.

Exposures (dose rate in roentgen per hour) were measured during the first 3 months after the explosions, providing the basis for these dose estimates. The fission-product decay was calculated as $t^{-1.2}$ with time t in hour. Then, by simple calculation, the cumulative dose from entry time t to infinity, $D(t,\infty)$, into a specific area is equal to $5t^{-0.2}$. The ratio of $D(t,\infty)$ to $D(1,\infty)$ is calculated as $t^{-0.2}$. Finally, the dose $D(t_1,t_2)$ in a specific area from time t_1 to t_2 is calculated as $(t_1^{-0.2} - t_2^{-0.2}) \times D(1,\infty)$ (see the estimates of $D(1,\infty)$ in the previous paragraph).

The estimated dose to Australians stationed in the nearby city of Kure from the beginning of December 1945 for about 2 years, who came to Hiroshima about 4 days a month and spent some time in the high fallout zone, is calculated as 6–20 mGy × D(2784 h; 21,048 h) × (4 days ÷ 30 days). The latter is calculated as (0.205 – 0.137) × (4 ÷ 30) = 0.009, and the estimated upper limit dose range is 0.05–0.2 mGy.

For another group that came to the area in January 1946 and was stationed near the fallout area of Koi (western Hiroshima) for 2 years, $D(t_1,t_2)$ = D(3528 h; 21,048 h) = 0.195 – 0.137 = 0.058. Multiplying by 20 mGy, the maximum dose is estimated to be 1.2 mGy.

To estimate individual doses from induced radioactivity requires knowledge of a person's movements in time and proximity to hypocenter after the detonations. The time of entry into contaminated areas and the history of movement within the areas are needed to calculate the exposure rates and cumulative doses to persons involved. ❑

Scientific Council

continued from page 1

cell lacks a nucleus, molecular analysis of any presumed mutation is not possible. Recently, radiobiology researchers at RERF have isolated reticulocytes—precursors of red blood cells—that occur at low frequency. Analyses of their nucleic acids have shown that individual mutant cells lack either the M or N gene messenger RNA—clearly demonstrating true gene mutation.

Clinical studies

An array of pilot studies have been undertaken during the past year to determine the most effective ways of maintaining health surveillance of Adult Health Study participants—particularly those over the age of 70 years whose age-associated infirmities are of great interest. A mixture of approaches, including annual examinations when possible, telephone and mail surveys, coverage of selected large hospitals, and access to MHW records, may be employed to create a more-comprehensive surveillance network. ❑

Recent Scientific Publications

Editor's note: As announced in the Summer 1993 issue of RERF Update, *the RERF Technical Report Series, begun in 1959, will be terminated after the processing of 1992 manuscripts is complete. Henceforth, summaries of journal articles based on approved RERF manuscripts will accompany the complete journal citation. Other selected summaries of interest will also be published occasionally. Reprints, when available, can be obtained from the RERF Publication and Documentation Center, 5-2 Hijiyama Park, Minami-ku, Hiroshima, 732 Japan.*

Publications in the Open Literature

Frequency of reciprocal translocations and dicentrics induced in human blood lymphocytes by X-irradiation as determined by fluorescence *in situ* hybridization. M Nakano, E Nakashima, DJ Pawel, Y Kodama, AA Awa. *Int J Radiat Biol* 64:565–9, 1993 (based on RERF Manuscript 26-93).

This study was designed to test the scoring efficiency of reciprocal translocations and dicentrics induced by X-irradiation *in vitro* using the fluorescence *in situ* hybridization (FISH) technique. An excess was found in the frequencies of reciprocal translocations relative to those of dicentrics by measurement with FISH at the first cell division after irradiation (translocation:dicentric ≈ 60:40). However, when the same metaphases were also evaluated sequentially by a conventional staining method, the ratio of about 50:50 was restored. This was due in part to misclassification of certain dicentrics as reciprocal translocations by the FISH technique.

Frequent occurrence of *in vivo* clonal expansion of CD4⁻ CD8⁻ T cells bearing T cell receptor αβ chains in adult humans. Y Kusunoki, Y Hirai, T Hayashi, S Kyoizumi, K Takahashi, Y Morishita, Y Kodama, M Akiyama. *Eur J Immunol* 23:2735–9, 1993 (based on RERF Manuscript 3-94).

We have previously reported 2 cases of healthy men showing *in vivo* monoclonal expansion of mature CD4⁻ CD8⁻ αβ T cells. In the present study, an additional 3 adults were found to exhibit such an expansion, among a total 464 adult donors studied. These 5 individuals were otherwise physiologically normal, with no history of severe illness and autoimmune disease at the time of examination. To investigate the mechanisms of the clonal expansion, further characterization of the clonal cells was attempted. No apparent preference for usage of the T cell receptor β chain variable region was observed in the clonal T cells. These clonal T cells showed lectin-dependent or redirected antibody-dependent cell-mediated cytotoxicities, whereas they could not lyse autologous lymphoblastoid cell lines. Failure of Fas antigen expression was not observed for any of these clones. These results suggest that clonal expansion of CD4⁻ CD8⁻ αβ T cells frequently occurs in the periphery without any T cell abnormalities.

Analysis of somatic cell mutations at the glycophorin A locus in atomic bomb survivors: a comparative study of assay methods. RG Langlois, M Akiyama, Y Kusunoki, BR DuPont, DH Moore II, WL Bigbee, SG Grant, RH Jensen. *Radiat Res* 136:111–7, 1993 (based on RERF Manuscript 5-94).

The glycophorin A (GPA) assay for *in vivo* somatic cell mutations was performed on blood samples from 39 survivors of the atomic bomb at Hiroshima. Parallel analyses were performed at two laboratories using three different GPA assay methods to enumerate cells lacking expression of either the M- or N-allele of GPA. All assay methods yielded significant dose-dependent increases in hemizygous GPA variant cell frequencies (VFs) and smaller increases in homozygous VFs. The slopes of the fitted linear dose-response functions did not differ significantly among assay methods used in the present study, or from slopes obtained in a study reported previously. The version of the assay described most recently (BR6) appears best suited for future studies because the assay has a higher precision than earlier methods. Variant frequencies from different assay methods measuring the same variant cell type agreed with each other better than with the estimated dose, suggesting that the imprecision in the assay is not primarily responsible for VFs that differ from the fitted dose response. Consistent deviations from the dose response were seen for some individuals, suggesting either errors in dose estimates for these individuals or interindividual differences in susceptibility or other exposures. For the study population as a whole, however, discrepancies between assays for M-loss and N-loss variants suggest stochastic factors may have an important effect on individual VFs for A-bomb survivors.

Role of somatic mutations for risk evaluation of various high risk cancer groups. M Akiyama, S Umeki, Y Kusunoki, S Kyoizumi, N Nakamura, T Mori, Y Ishikawa. In: *Proceedings of Fukui Workshop on Health Risks: Perspectives and Research.* Ed by T Sugahara, K Torizuka, S Kobayashi, Y Ishii. Kyoto, Health Research Foundation, 1993. pp 172–5.

Autoantibodies and immunoglobulins among atomic bomb survivors. S Fujiwara, RL Carter, M Akiyama, M Akahoshi, K Kodama, K Shimaoka, M Yamakido. *Radiat Res* 137:89–95, 1994 (based on RERF Technical Report 4-92).

Levels of parathyroid hormone and calcitonin in serum among atomic bomb survivors. S Fujiwara, R Sposto, M Shiraki, N Yokoyama, H Sasaki, K Kodama, K Shimaoka. *Radiat Res* 137:96–103, 1994 (based on RERF Technical Report 18-92). ❑

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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