RERF update RERF

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

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Shigematsu To Continue as RERF Chairman

Itsuzo Shigematsu's unprecedented third four-year term as RERF chairman was unanimously approved at the Foundation's 23rd board of directors meeting, held 21–23 June in Nagasaki and Hirado.

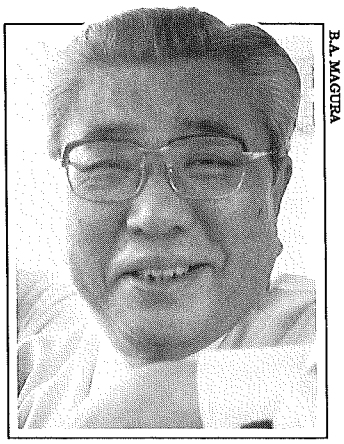
Shigematsu became the third RERF chairman in July 1981, after serving for 15 years as chief of the Institute of Public Health's Department of Epidemiology.

During the past eight years, he has been instrumental in promoting joint research ventures between the Foundation and local research and medical organizations, thus greatly improving RERF's relationship with the communities of Hiroshima and Nagasaki.

Shigematsu has also played a leading role in proposing that the entire population of 360,000 survivors be included in the 1985 Atomic Bomb Survivors Actual Status Survey, sponsored by the Ministry of Health and Welfare. This has led to the clarification of health problems and sociological issues among atomic bomb survivors throughout Japan, thus contributing to the promotion of governmental measures for their benefit.

The 12-member board of directors also unanimously approved the recommendations of the 1989 Scientific Council and those of the workshops on immunology (see *RERF Update* 1(1):5) and radiation carcinogenesis (see page 6 of this issue).

Foremost among the Scientific Council recommendations was continued emphasis on cancer incidence studies. It is felt that the greater accuracy of tumor registry diagnoses as compared to death certificate diagnoses used in the mortality studies may result in a greater yield of tumors that will improve the resolution and significance of RERF's risk calculations. The two methods of collecting data have important complementarities, thus their combined use is likely to increase the power of RERF's future analyses.



B.A. MAGURA

Shigematsu

Further progress will depend on verifying that A-bomb survivor tumor incidence and mortality data are being reliably collected by the registries. Hence, a proposal was made to create and continually update an address database for better monitoring of the 120,000 Life Span Study subjects.

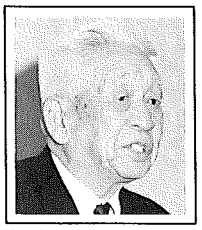
Amidst ongoing work on determining the uncertainties in the survivors' physical dosimetry, the council encouraged continuation of the recent biological approaches, which during the past year have added the influence of epilation into the assessment of dosimetry error and the estimation of true dose. (See page 5 for a discussion of this topic.)

Of course, the use of biological dosimetry must acknowledge possible differences in radiation sensitivity, particularly as a function of dose. However, the hypothesis that A-bomb survivors may be biased toward low radiation sensitivity has not yet been demonstrated at RERF. Studies of the radiosensitivity of lymphocytes using in vitro radiation and cell killing found no evidence of differential sensitivity among different dose groups of survivors. Other studies, including the assessment of micronuclei in lymphocytes, are now in progress. ❑

In Memoriam: RERF Mourns Passing of Former Director

Working in a university laboratory only 700 meters from hypocenter, former RERF Director Raisuke Shirabe considered it a miracle that he survived the atomic bombing of Nagasaki. Forty-four years later, RERF mourns the passing of a man who gave unstintingly of his professional and teaching skills to better the lot of his fellow survivors.

Soon after the bombing, Shirabe established a rescue team for treatment of the injured. Working under trying circumstances with limited resources—and preoccupied with the survivors' immediate needs—Shirabe, who himself suffered from acute radiation illness, and his associates accumulated a body of data that provided an important basis for understanding the nature and dimension of the catastrophe that overwhelmed Nagasaki on 9 August 1945.



Shirabe

An honorary RERF consultant until his death on 15 April, Shirabe served as a visiting director at the Nagasaki Laboratory from 1975 to 1983. He was a stalwart supporter of ABCC–RERF since the late 1940s when collaborative US–Japan research efforts began.

"There was a warmth, a gentleness, a humbleness to the man that pervaded everything about him," recalls former RERF Permanent Director Jack Schull. "Through almost 40 years of association, I never heard him utter an unkind word, nor seek to diminish anyone. His passing pulls one more thread from the scant fabric that remains of Nagasaki in the immediate postwar years—soon all will just be a memory."

A Faculty of Medicine graduate of Tokyo Imperial University, Shirabe was decorated by the Japanese Government in 1971 and received numerous civic honors for his contributions to the health and welfare of the A-bomb survivors. After his death, the city of Nagasaki conferred upon him honorary citizenship—only the seventh such award ever granted.

As a continual reminder of his eminent services to the Foundation, a sculpted portrait of Shirabe will be erected at the main entrance of the Nagasaki Laboratory. Unveiling ceremonies will take place later this year. ❑

DS86—Where Do We Stand?

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

As we reported in the spring issue of *RERF Update*, a three-day binational dosimetry workshop was held in Honolulu in March to discuss some of the remaining work to be done on the Dosimetry System 1986, widely known as DS86. In this issue of *Update*, we give rather extensive coverage to some rather evident questions that one may raise: To what extent is DS86 incomplete? Will additions and modifications change DS86 so as to create another "new and improved" system of dosimetry? Will a total re-reassessment of the radiation effects database be necessary, resulting in a further change of the radiation risk estimates?

Let me try to address some of these questions here. I believe it is fair to say that DS86 is the product of the most advanced dosimetric evaluation of the A-bomb survivors for a long time to come; that it represents a great improvement over T65D; but also, that it is not perfect. It was acknowledged from the outset that we would attempt to answer questions related to how imperfect the final product would be. By necessity, the major work in the uncertainty analysis had to be at the end of the total effort, and we are right in the middle of it now.

Two presentations on uncertainties in DS86 were made in Honolulu, and articles in this issue of *RERF Update* by **Dean Kaul** and **Dan Stram** reflect these presentations. Of course, it is still too early for an in-depth assessment of the uncertainty issue. But it was interesting for at least this observer to note that the analytical and biostatistical approaches presented appeared to arrive at compatible outcomes. Given the totally different methods used, this is quite surprising, and gives hope that we may develop complementary ways of dealing with this critically important issue. You will doubtlessly hear more on this subject in the future.

As far as additions and modifications to DS86 are concerned, **Shoichiro Fujita** describes in this issue three versions of DS86: the original one—directly implemented from DS86 as described in the two volumes representing the final report of the US–Japan Joint Reassessment of Atomic Bomb Radiation Dosimetry in Hiroshima and Nagasaki (RERF, 1987)—and two subsequent versions. Although they are known around RERF as versions 1, 2 and 3, in software terminology they should probably be called something like 1.0, 1.1, and 1.2, i.e., they incorporate improvements and additions that do not substantially alter DS86 as such.


J.W. THIESSEN

Among those attending the US–Japan dose reassessment workshop were (from left) Itsuzo Shigematsu, Dale Preston, Edgar Mendelsohn, Bill Loewe, James Schulman, Alvin Weinberg and Eizo Tajima.

It is clear now that a few additional versions may be necessary in the future, in an attempt to assign dose estimates to as many survivors as scientifically justifiable. For 6,000 "proximal survivors," DS86 estimates are unavailable. Half of these had no T65D estimate either, so it appears unlikely that the available information on location, shielding conditions, etc., will be adequate to derive any reliable dose estimate. For the remaining 3,000 survivors, additional analyses may result in usable dose estimates. This is not too critical for Hiroshima, where proximally exposed survivors with unknown doses are only 6.5% of the total. But in Nagasaki, where nearly 29% of the proximal survivors have unknown doses, the situation is of some urgency.

In a few months, a meeting will be held at RERF in Hiroshima to evaluate the possibility of further extending DS86. We will keep you posted on the results of that evaluation also. ❑

News Briefs

✓ RERF Physicians Consult with A-bomb Survivors in US

Kazunori Kodama, Hideo Sasaki and **Tadaaki Watanabe**, of the departments of Clinical Studies and Epidemiology, will conduct consultations with A-bomb survivors in the US from 13 June to 12 July. This is part of an ongoing program, sponsored by the Hiroshima Prefectural Medical Association, to provide continual monitoring of A-bomb survivors outside of Japan.

✓ RERF Scientists Participate in Black Rain Reassessment

Based on reviews of published literature and surveys of survivors, recent reports by a former department chief of the Japan Meteorological Research Institute indicate that the area affected by black rain after the atomic bombing in Hiroshima may have been from two to four times greater than previously estimated.

RERF Chairman **Itsuzo Shigematsu**, Genetics Department Chief **Akio A. Awa** and Radiobiology Department Chief **Mitoshi Akiyama** are among 11 specialists appointed by the local government to consider how issues related to black rain can be clarified more than 40 years after the bombing.

Since the local government has asked that areas affected by heavy black rainfall be included in the officially designated disaster-stricken area, the committee will seek a scientific basis for undertaking such a change.

Future efforts will focus upon statistical reevaluation of fallout surveys conducted by RERF and other institutions at the request of the Ministry of Health and Welfare in 1976 and 1978. The accuracy of computer simulations based on photographs of the A-bomb mushroom cloud in Hiroshima has also been discussed, and a similar method has been suggested for analyzing the extent of black rain in Nagasaki.

Assessment of residual radioactivity in the black rain-affected areas and observations of chromosomal aberrations or somatic cell mutations are viewed pessimistically as methods of analysis due to confounding factors, such as fallout from atmospheric nuclear weapons testing and medical radiation exposures.

✓ *National Geographic* Cites RERF

Months of research, including a stopover in Hiroshima and a visit to RERF, resulted in the article "Living with radiation," published in the April 1989 issue of *National Geographic* magazine, which has a circulation of more than 10.5 million worldwide. RERF Vice-Chairman **J.W. Thiessen** and Genetics Chief **Akio A. Awa** were quoted in the article in regard to the health effects of ionizing radiation exposure as a result of the atomic bombings.

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Versions of DS86

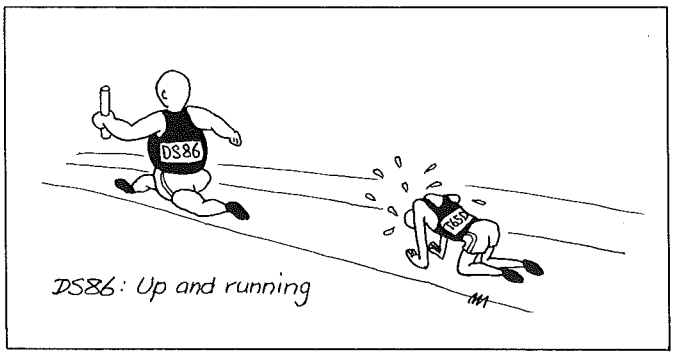
'Extending' DS86 allows dose assessment for about 1,200 survivors in Nagasaki who were shielded in factories and by terrain and for about 10,000 distal survivors who were in the open

by Shoichiro Fujita
RERF Department of Statistics

In March 1986, US and Japanese dosimetry committees approved a new system of dosimetry to replace the tentative system known as T65D which had been used as a basis for risk assessment until that time. The description of the new system, given the name "DS86," together with the scientific basis for it, was published by RERF in 1987. Computer codes were developed immediately to implement DS86 on RERF's NEC ACOS-750 computer. The following describes the versions of this dosimetry system from the inception of computer implementation.

Version 1: DS86 was installed in early 1986, and covered all survivors with detailed shielding histories who were at distances less than 2,500 meters from the hypocenter at the time of the bombings, and who were unshielded or shielded by Japanese-style houses or tenements. It enabled the computation of free-in-air tissue kerma, tissue kerma adjusted for the effects of shielding by housing (sometimes loosely called "shielded kerma"), and absorbed doses, all of these for neutrons and gamma radiation. Calculations were possible for males and females; standing, sitting, or in a prone position, in either frontal, rear, right or left orientation; for three age classes (< 3, 3–12, and > 12 years); and for a number of organs (12 for males and 14 for females): active bone marrow, bladder, bone, brain, breast, eyes, intestinal tract, liver, lungs, ovaries, pancreas, stomach, testes, thyroid gland, and uterus. In addition, DS86 allowed the output of energy-dependent fluence distributions for each organ dose component, i.e., prompt gamma radiation and neutrons, delayed gamma and neutron radiation, and secondary gammas from prompt and delayed neutrons created by the shielding and from interactions in the body. It turned out that the system was able to compute kerma and dose for 23,422 of the 28,743 survivors (81%) who had been within 2,500 meters of hypocenter in the ABCC/RERF Master Sample for which detailed shielding data were available. This included 18,526 of the 23,420 survivors (79%) in the Life Span Study (LSS) cohort used in most analyses of radiation effects among A-bomb survivors.

Because DS86 requires the availability of detailed shielding information, and only covers survivors within 2,500 meters, it was necessary to "extend" DS86 to enable the assessment of the doses of survivors, at all distances, for which no detailed shielding information was available. The method developed for this purpose became known as the "indirect DS86." It relies on the use of free-in-air-kerma regression models, and the application of average transmission factors for given classes of shielding, rather than the individual-specific ones used in the "direct DS86."

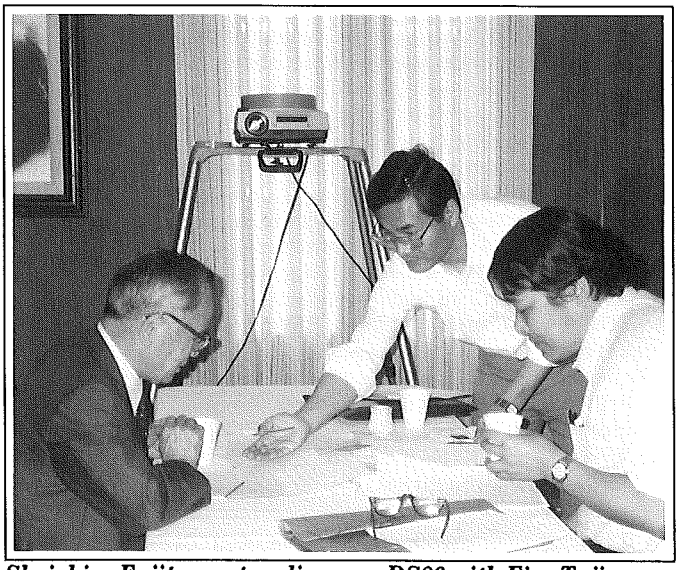


The indirect DS86 produces only kerma and dose, as broken down above, but no fluences. Altogether, 71,367 survivors (of whom 57,567 are in the LSS cohort) were added to the number of direct estimates given earlier.

Version 2: Early on, the system was slightly modified to correct software errors in the original version. It produced only minor changes in dose estimates, and concerned primarily direct DS86 organ doses for breast, ovary and uterus in adults, and all organ doses for the age group below three. Average transmission factors used in the indirect DS86 were also recalculated. Enhancements to the system permitted calculation of special cases, specifically factory workers and survivors shielded by terrain (all of them in Nagasaki), but these enhancements were not implemented until version 3 was prepared. Therefore, the number of survivors covered did not change between versions 1 and 2.

Version 3: Most recently (in May 1989), kerma and doses for Nagasaki survivors shielded in factories (361) and by terrain (815) were included (all direct DS86). New indirect estimates were made for 10,034 distal survivors who were in the open. Kerma and dose estimates for all Nagasaki survivors were recalculated and slightly reduced (1%) because of modifying the calculation of slant distance from the epicenter to each survivor, which reflects a sea-level correction.

After the latest version, DS86 covers 105,995 survivors for which T65D estimates were available, 93,741 of whom are in the LSS cohort. Eighty-eight percent of the proximal survivors and 97% of the distal survivors now have kerma and dose estimates. Future efforts will be directed to the inclusion of more special cases in the proximal group: those who were shielded in concrete buildings, in air-raid shelters, and in other complex shielding situations. It appears already, however, that this may produce dose estimates for at best 3,000 survivors, and will require considerable effort and time. ❑



J.W. THOMPSEN

Shoichiro Fujita, center, discusses DS86 with Eizo Tajima, left, and Masaharu Hoshi at the binational dosimetry workshop held in Honolulu earlier this year.

Uncertainty Analysis of the DS86 Dosimetry System

by Dean C. Kaul
Science Applications International Corporation

The DS86 dosimetry system was created in a joint effort by US and Japanese scientists to assign radiation dose values to A-bomb survivors. The system provides a description of the local radiation field, accounts for the effect of shielding, and determines the transmission of the radiation into 15 internal organs for each survivor. It does this based on a complex model, which interprets information from the A-bomb Survivor Master File, including distance from the hypocenter, shielding posture, and survivor age and orientation. That model is based in turn on a series of assumptions and calculations, which, along with the data from the Master File, are subject to uncertainty. As a result, the epidemiological process must consider two aspects of uncertainty—that associated with the occurrence of an observed endpoint in a sample of limited size and that associated with the dose assigned to the survivors in that sample. This article describes efforts to estimate the latter.

Each assumption and calculation constituent to the DS86 model contributes a portion of the uncertainty in the dose values which the system calculates. Therefore, in the process of developing DS86, care has been taken to estimate the uncertainty in each input parameter or calculational process which affects the dose and to determine the sensitivity of the dose to such uncertainties. This has been done to permit the assessment of the overall uncertainty required for the epidemiological process and to determine whether there is any single source of uncertainty which dominates the total and may be amenable to reduction through further research. A list of the separate factors contributing to the uncertainty of DS86 dose values is given in Table 1. The associated uncertainty values are applicable to the total dose and correspond to one standard deviation of the mean as a percent of the mean, which is often referred to as a fractional standard deviation (FSD) or coefficient of variation. These values are representative of those which apply to a survivor located 1,500 meters from the hypocenter; some vary with distance. They are assembled from contributions for each radiation component, i.e., prompt neutrons, prompt gamma rays, secondary gamma rays, etc. For an individual factor, these contributions are generally highly correlated. However, it is assumed that there is no correlation between the various factors.

There are two aspects of the information in Table 1 which are of significance. First, four factors dominate total uncertainty. These are weapon yield, air transport calculation methodology, survivor coordinates and shielding assignment. The uncertainty value associated with air transport does not include the impact of discrepancies between calculated and measured neutron activation, which are currently under investigation. Inclusion of such uncertainties, taken at face value, would increase the value very slightly, to 10%, because the neutron dose is very small. However, if the reference quantity were changed from dose to dose equivalent (Q=10), the uncertainty value associated with this factor would increase to 24%. The uncertainty in survivor coordinates includes contributions from the resolution of the reported data, map error and error attributable to survivor recall. The uncertainty value above is representative of those proximal survivors whose shielding is described using the so-called nine-parameter model. These persons constitute one-half of all proximal survivors and one-quarter of the total cohort. However, as indicated by the values in parentheses, the uncertainty due to shielding assignment is subject to wide variations, with values ranging from 10% to 35%, depending on the applicable shielding model. Thus, the total uncertainty can vary from approximately 29% to 45%.

The second aspect of significance in Table 1 is that uncertainties can be divided into two types, systematic and random. Systematic uncertainties are those which apply identically to each survivor, such as that associated with weapon yield, while random uncertainties are those which apply to each survivor independently of any other survivor, such as that associated with survivor location. Vaeth and Stram (*RERF Update* 1(1):4) have described how random uncertainties can affect analysis of linear dose-response relationships. Assuming a random uncertainty of 35%, they report an increase in the estimate of excess relative risk of all cancers except leukemia of 13% over an estimate which makes no allowance for random dosimetry error. The data in Table 1 indicate that there is a wide range of random errors among survivors. However, the distribution of errors within this range is not uniform. In the proximal group, those whose shielding is best characterized, approximately half have random uncertainties between 25% to 30%. The survivors in the distal group, those whose shielding is poorly characterized and who make up approximately 69% of the total, have random uncertainties of approximately 42%. This indicates the need to stratify the uncertainty analysis so that these large variations in uncertainty can be properly taken into account in epidemiological studies.

Table 1. Factors contributing to uncertainty in A-bomb survivor absorbed dose.

Factors	Absorbed Dose Uncertainties (FSD[%])		
	Total	*Systematic*	*Random*
Yield	9.2	9.2	
Neutron output	2.5	2.5	
Air density & moisture	2.8	2.8	
Air cross sections	4.4	4.4	
Hydrodynamic model	4.0	4.0	
Fission product source	2.5	2.5	
Air transport calculation method	8.6	8.6	
Burst height	0.7	0.7	
Hypocenter location	1.9		1.9
Survivor coordinates	21.0		21.0
House materials	4.3		4.3
Shielding assignment	15.5 (10 to 35)		15.5 (10 to 35)
Shielding calculation method	4.5		4.5
Phantom materials & orientation	5.8		5.8
Organ dose calculation method	4.5		4.5
Total	31.5 (29.2 to 44.5)	14.7	27.9 (25.2 to 42.0)

The uncertainty values associated with DS86 may be found in the DS86 final report (RERF, 1987) and have been summarized by Kaul and Egbert (SAIC-88/1014, 1988 draft). The latter report is currently being revised to address the issue of stratification and to include uncertainty contributions from the survivor data base. Finally, the creators of DS86 are working with RERF statisticians to perfect the survivor dosimetry uncertainty assessments and their application in epidemiological studies, including the manner in which systematic uncertainties can be taken into account in the epidemiological process. ❑

Radiosensitivity or Dosimetry Error?

Observed relationships between acute and late effects of radiation exposure in the Hiroshima–Nagasaki data

by Daniel O. Stram
RERF Department of Statistics

Recently, considerable attention at RERF has been focused upon the apparent existence of associations between early and late effects of radiation exposure, which are in evidence after adjustment for level of radiation exposure using the DS86 dose estimates. For example, a significant association between the occurrence of severe epilation and the subsequent risk of leukemia mortality has been reported (RERF technical report, submitted). In that analysis, the excess relative risk of leukemia mortality in the follow-up period 1950–1988 was estimated to be more than twice as great among survivors who reported the occurrence of severe epilation within 60 days of the bombings, as compared to survivors with identical DS86 dose estimates, who did not report such epilation. In other data sets too, associations between the occurrence of epilation and late effects have been detected. The figure below illustrates this phenomenon in chromosome aberration data collected over the period 1968–1980 for 1,028 Adult Health Study participants. In Figure 1, the proportion of circulating lymphocytes (usually from a sample of 100 cells per survivor) with at least one stable chromosome aberration is plotted against DS86 estimated dose. The figure depicts, separately, the average chromosome aberration dose response for survivors who reported the occurrence of severe epilation (▲) and for those reporting no severe epilation (■). Reports of occurrence of severe epilation are, of course, more common at high dose than at low dose, but at all dose levels above about 1 Sv, there are survivors who reported, and who did not report, severe epilation. The implication of the figure is that at any given estimated dose level, subjects who reported severe epilation have on average approximately twice the chromosome aberrations of those who did not report severe epilation.

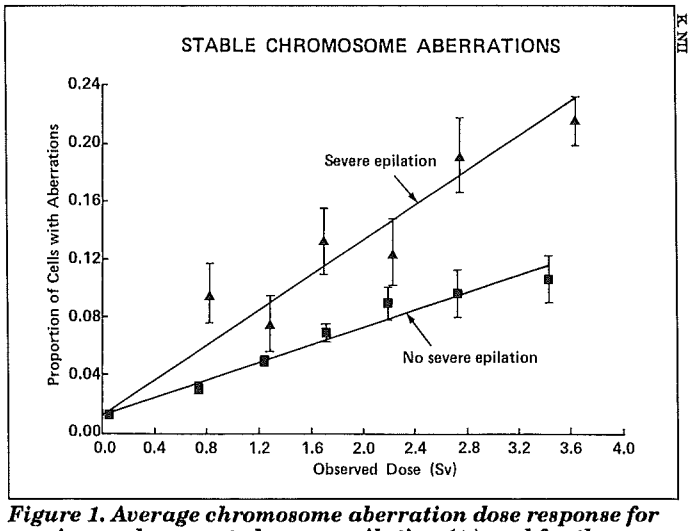
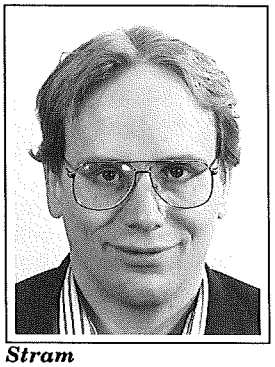


Figure 1. Average chromosome aberration dose response for survivors who reported severe epilation (▲) and for those who did not report severe epilation (■).

RERF's interest is whether these apparent associations between epilation and leukemia mortality, and epilation and chromosome aberrations, represent real evidence for epilation occurrence as an indicator of differential radiosensitivity, or are artifacts of random errors in the DS86 dose estimates. Since the probability of occurrence of all three—leukemia, chromosome aberrations, and epilation—increases with true, rather than estimated, radiation exposure, substantial dosimetry error can induce a false association between epilation and the other outcomes which persists after correction for estimated exposure. That is, random error in the individual dose estimates could perhaps be the sole cause of the leukemia finding and of the observed differences in chromosome aberration dose response, by epilation group, as depicted in the figure.



Stram

Whether or not induced association due to random dosimetry error is the sole cause of the apparent differential dose responses by epilation group, it must be at least a contributing cause. Working with models discussed by Pierce et al (RERF TR 2-89, also described by Vaeth and Stram in the previous issue of *RERF Update*), statisticians at RERF have been attempting to compute the amount of induced association between outcome variables such as epilation and chromosome aberrations which can be expected to be produced, given a specified amount of dosimetry error. Tentative results, now in preparation as an RERF technical report, indicate that random dosimetry errors as large as 40%–45% may be required to fully explain the discrepancy in dose response, as depicted in the figure.

In order to arrive at conclusions like these, the approach taken is to try to incorporate a model for the probability of epilation occurrence as a function of dose into the statistical framework described by Pierce et al. The epilation models used have been patterned after results of the analysis of epilation occurrence in the LSS data given by Stram and Mizuno (*Radiat Res* 117:93–113, 1989). In oversimplified terms, what happens is that two "adjusted dose estimates" are calculated for survivors at a given DS86 dose, one for those who reported severe epilation and another for those who did not. For those who reported epilation, this adjusted dose is higher than for those who did not. The degree to which the adjusted dose differs by epilation group is a function of the amount of dosimetry error assumed to exist in the DS86 system. What appears to occur is that when the amount of assumed measurement error in these calculations is in the range 40%–45% the resulting difference in "adjusted dose" by epilation group closely matches the observed differences in chromosome aberration dose response. On this basis, the statisticians conclude that dose errors in this range are required to explain the so-called "epilation effect" evident in the figure as being an artifact of random error-induced association.

In the final analysis, however, the question of whether associations in the chromosome aberration or leukemia mortality data are indicative of differential radiosensitivity, or are merely by-products of dosimetry error, is also a biological one. Work has begun to see whether a biological basis for differences in radiation sensitivity, related to epilation occurrence, can be established. Concurrently with the biological work, the need for further statistical analysis is anticipated. If random dosimetry error, rather than differential radiosensitivity, is really at the root of these associations, then similar associations should be detectable in many other data sets as well. A review of existing data sets, to see if they are basically in agreement with the results of the epilation and chromosome aberration analysis, is being planned. ❑

Experts Focus on Carcinogenesis Research

As the third of four workshops designed to steer the Foundation toward promising avenues of future research, the Radiation Carcinogenesis Workshop—held 16–18 March—brought eight expert panelists to Hiroshima to interact with RERF's scientific staff, as well as representatives of sponsoring and collaborating institutions who had earlier attended RERF's annual Scientific Council meeting. Scientists from the Soviet Union and the People's Republic of China also attended.

Based primarily upon the concepts and technology of modern molecular biology, unprecedented growth is occurring in mankind's knowledge of the mechanisms involved in carcinogenesis. Workshop members noted that RERF's scientific staff has been effectively using this information in exploiting the Foundation's unique research opportunities in well-designed experiments and surveys.

An overview of the workshop recommendations follows:

Overall research planning

◆ Specific scientific priorities should be set for the next 4–5 years. Creation of a forward planning document, under the aegis of the chief of research, could fill a gap in the present formal research agenda, thus providing a basis for measuring progress during the next few years.

◆ Systematic examination of the fundamental sources of variation in cancer risk among A-bomb survivors was recommended, including time-response parameters, such as latency and duration of effect and their relation to background incidence and mortality; target organs and tissues; dose and exposure characteristics; age at the time of the bombings and other host characteristics; and exposure to carcinogens and modifying factors associated with life-style and environment.

Radiation susceptibility

◆ Severe epilation among some A-bomb survivors may be closely associated with leukemia development, thus providing a possible predictor of cancer susceptibility. To further investigate the occurrence of other acute symptoms, sources at RERF, such as the Joint Commission records on individual casualties, should be examined.

◆ Other indices of individual sensitivity should be sought in addition to the chromosomal changes and interphase death of skin and blood cells that are already under study at RERF.

◆ Differences among organs and tissues as related to susceptibility to radiogenic cancer should be considered. All aspects of discrepancies between biological and physical dosimetry should be explored.

◆ Age at the time of the bombings is known to be an important determinant of cancer susceptibility. New data on A-bomb survivors exposed before 10 years of age show a very high incidence of cancer, although in utero irradiation has not yet been observed to result in a high frequency of cancer in either man or mouse. Since the youngest A-bomb survivors are just entering the age interval of high cancer risk, continued study of this population was recommended. Similar considerations should be applied to cancer incidence in the first filial generation born to survivors.

◆ Since it is well documented that many types of cancer are closely related to life-style, it was deemed urgent that A-bomb survivors be informed of the importance of nutrition in reducing their cancer risk. Examining endocrine status may also be useful in correlating cancer development with nutritional status.

◆ Hormonal status may greatly affect cancer development, not only in endocrine organs but also in many other tissues. Continued investigation of the relationship between serum levels of relevant hormones and other factors, as well as the development of breast and thyroid cancers was recommended. The study of other hormones and endogenously produced factors that control growth and differentiation should be considered.

◆ Since the relationship between immune function and cancer is not well understood, immunological studies of survivors should be continued—even if they are not yet specifically related to cancer. Efforts should focus on carcinogenesis, since studies of immune functions of cancer patients are not unique to RERF.

◆ Investigating the role of tobacco as a major risk factor in lung cancer development should continue. Current data suggest an additive effect of smoking and radiation exposure. In particular, RERF should communicate to the Adult Health Study population the potential benefits of smoking cessation.

◆ Long-term records of chromosomal abnormalities possessed by RERF present an opportunity to search for markers that indicate increased cancer risk among the exposed survivors. Will it be possible to relate the degree or nature of the cytogenetic abnormality to subsequent cancer?

Integrating epidemiology with cellular and molecular studies

◆ During the developmental stages of future case-control studies, the scientific potential of combining cytogenetic and molecular biologic components with epidemiologic approaches should be examined thoroughly, requiring the interaction of specialists in both areas.

Mechanism studies

◆ To detect alterations relevant to malignant transformation, new techniques should be introduced at RERF. Restriction fragment length polymorphisms and finger-prints using adequate DNA probes are available to detect fine differences between tumor cells and normal cells. In situ hybridization should also be incorporated into cytogenetic analyses. Techniques for use at different loci in cancer-prone cells are necessary to assess possible links between mutagenesis and carcinogenesis.

◆ Detecting chromosome aberrations is vital to RERF's research, so assessing the merit of "chromosome painting" should continue.

◆ Identifying an oncogene change that is specific to radiation would be an important development, but one that is unlikely. Hence, workshop members advised that the role of oncogene-based experiments will require constant evaluation.

◆ The association between the loss of an allele and a specific cancer may identify a gene that influences susceptibility. Since knowledge and technology related to the function and control of genes is expanding rapidly, RERF must increase contacts with other laboratories specializing in molecular biology.

Models

◆ Extensive epidemiologic and cytogenetic studies have resulted in dose-response curves for A-bomb survivor mortality due to various types of cancers and chromosome aberrations. Derivation of the most appropriate dose-response functions awaits final determination of the physical doses to the survivors. Workshop members recommended the prompt resolution of controversy related to the neutron component of DS86.

continued on next page

Policies Control Access to A-bomb Survivor Data

by Yutaka Hasegawa
RERF Permanent Director

During the 40-year history of ABCC/RERF, the unique nature of the atomic bomb survivor data maintained at RERF has often stimulated interest from outside researchers. As a result, questions about confidentiality and proper use of RERF data sometimes arise.

International Oral Presentations

Asia–Pacific Osteoporosis Conference, Honolulu, 4–8 March 1989. *Study on risk factors of vertebral compression fractures.* S Fujiwara, S Mizuno, Y Hosoda.

The Second International Conference on Preventive Cardiology and the 29th Annual Meeting of the American Heart Association Council on Epidemiology, Washington, D.C., 18–22 June 1989. *Cholesterol and coronary heart disease in a Japanese population—A 26-year follow-up study.* K Kodama, H Sasaki, Y Shimizu, H Kato, M Akahoshi, Y Hosoda.

The 18th Annual Meeting of the European Thyroid Association, Copenhagen, Denmark, 26–30 June 1989. *Low level radiation may be involved in the development of chronic thyroiditis in young females.* S Nagataki, K Shimaoka, S Inoue, H Hirayu, M Izumi.

Following are the major aspects of RERF's policy:

◆ A-bomb survivors can obtain their own health records and radiation exposure data by submitting a written request.

◆ Outside researchers who plan to conduct studies on late A-bomb effects may use RERF data after filing the appropriate form. Confidential information on individual survivors, such as name, address, age, occupation, and economic status, will not be released without written consent of the survivor or a survivor's legal representative. If access to the requested data conflicts with an ongoing RERF study, the request may be denied.

◆ Full-time RERF professional staff members have complete access to A-bomb survivor data. However, they must submit a written pledge stating that they will not release individual A-bomb survivor data to anyone outside of RERF without the written consent of individual survivors or their legal representatives.

◆ Part-time professional staff members also have complete access to A-bomb survivor data. However, this data must not be removed from RERF, except in the form of aggregate tables or figures or as "nonindividual" data.

All studies conducted by part-time professional staff must be based on approved RERF research protocols, the results of which must be published as an RERF technical report regardless whether such results will eventually be published in the open literature. The source of the data must be acknowledged whenever study results are published or reported orally.

Part-time professional staff members are requested to submit a written pledge agreeing to the preceding conditions. ❑

Program Reviews
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◆ Are certain histological types of tumors specific to radiation and even to the type of radiation, i.e., gamma rays or neutrons? Tumor specimens should be reexamined and the late appearance of other tumors, such as skin tumors, should be evaluated.

◆ Updating the classification of leukemias deserves high priority. Do the dose-response curves for chronic myelocytic leukemia and acute leukemia differ?

◆ A variety of dose-response relationships, as well as relative vs absolute risk and time-response models, should be tested while exploring the role of promoting factors, such as smoking, nutrition, and aging. Although a single exposure to ionizing radiation is recognized as a carcinogenesis initiator, its possible promoting effect should also be studied.

◆ Intercity comparisons should be given high priority to provide insights into the influence of life-style, environmental factors and the frequency of viral infections on tumor types.

◆ Dose-response curves for cancer should be reexamined on the basis of cancer incidence, for which diagnosis is considered superior, rather than on mortality. Major efforts should be made to correct for the effects of survivor migration on estimates of cancer incidence.

Collection and storage of specimens

◆ Due to the speed at which members of RERF's study population are being lost through aging or migration, the collection and preservation of tissues, cells and body fluids should receive the highest priority. The explosive development of powerful investigative methods requires appropriately frozen or viable cells, such as blood lymphocytes, hair follicle cells, skin fibroblasts and specimens of normal and tumor tissue. ❑

Radiation Carcinogenesis Workshop Participants

Arthur C. Upton (cochairman), Institute of Environmental Medicine, New York University
Kenjiro Yokoro (cochairman), Research Institute for Nuclear Medicine and Biology, Hiroshima University
Gilbert W. Beebe, Clinical Epidemiology Branch, National Cancer Institute, Bethesda, Md.
Roswell K. Boutwell, McArdle Laboratory for Cancer Research, University of Wisconsin, Madison, Wisc.
R.J. Michael Fry, Biology Division, Oak Ridge National Laboratory, Oak Ridge, Tenn.
Hiromichi Matsudaira, National Institute of Radiological Sciences, Chiba
Taisei Nomura, Department of Fundamental Radiological Sciences, Osaka University School of Medicine
Hiroshi Tanooka, Department of Radiation Biology, National Cancer Center Research Institute, Tokyo

Invited Observers

John E. Burris, National Research Council, Washington, D.C.
Charles W. Edington, National Research Council, Washington, D.C.
Stuart C. Finch, UMDNJ/Robert Wood Johnson Medical School, Camden, N.J.
Michito Ichimaru, Atomic Disease Institute, Nagasaki University
Marie-Louise Johnson, Benedictine Hospital, Kingston, N.Y.
Sohei Kondo, Atomic Energy Research Institute, Kinki University, Osaka
Toshiyuki Kumatori, Radiation Effects Association, Tokyo
Atsushi Kuramoto, Research Institute for Nuclear Medicine and Biology, Hiroshima University
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Feedback

Comments on 'A Radiobiological Rationale for Applying RBE to Neutron Exposures in A-bomb Data'

At low exposures, it is well known in regard to mutation as the end point or induction of cancer that the dose-response curves are linear for both gamma rays and neutrons. And in the dose range 0–0.3 Gy, the ratio of the slopes of these two radiations (i.e., the RBE) in any mammalian cell systems does not exceed a value of 10 or so—at least for mutational events at the cellular level. The deduction of an RBE of 26 for D_γ of 0.31 Gy and D_n of 0.001 Gy is not tenable, based on the cytogenetic end point of the chromosome aberration yield. Gross chromosome aberrations, as scored under the microscope, lead to cell death, and these cells in vivo do not survive to propagate as mutants and induce cancer. In fact, the RBE of cell death has been too liberally used to arrive at cancer induction, which is not correct. The chromosome aberration yield is a good method as a dosimeter for exposure and not as a predictor of cancer induction. As we are looking for cancer incidence among A-bomb survivors, I do not subscribe to the approach indicated by S. Abrahamson [*RERF Update* 1(1):3].

—U. Madhvanath

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Reply to Dr. Madhvanath

U. Madhvanath presents an interesting issue, viz., that cell death resulting from chromosome aberrations may cause an overestimate of RBE. It is true that the frequency of this event induced per unit dose is often greater than the frequency of other genetic end points per unit dose, such as reciprocal translocation or mutation induction. However, it is not clear to me that this will be reflected as a greater RBE relative to other end points.

The real point of his letter—and I take issue with it—is his statement that ". . .RBE in any mammalian cell systems does not exceed a value of 10 or so—at least for mutational events at the cellular level."

I will cite from a publication of the National Council on Radiation Protection and Measurements, *Influence of Radiation Quality (LET) on Relative Biological Effectiveness* (in press), which contains an extensive review of the literature.

With respect to HGPRT mutations, "the cultured human cells show a maximum RBE for mutation induction somewhat less than the current maximum Q value of 20." In human–hamster hybrids: "The RBE for mutation induction at the a^1 locus, however, ranged from 30 for 0.33 MeV to 4.2 for 14 MeV neutrons at or around the lowest levels of effect examined." (In my original note, the neutron energy was 0.7 MeV from which the neutron:gamma RBEs were estimated.)

For fission neutrons vs cobalt-60 gamma rays, depending on the manner of neutron delivery, i.e., single acute, weekly doses, or daily small doses, the RBEs for reciprocal translocations induced in mouse spermatogonia were 5–10, 15–35, and 45–75, respectively. RBEs for specific locus mutations induction in mouse spermatogonia are in the range of 20. In the maturing mouse oocyte, there may be a wide range of RBE values (14–70), depending on the age of the female at exposure.

For mammalian carcinogenesis, the report states ". . .that for tumors in which the dose response characteristics are sufficiently defined to derive RBE values, the range is not as wide but substantial variability still remains (20 to 60)."

When extrapolation is made from high neutron doses where the curve is bending down, the RBE estimates will tend to be underestimates. Thus RBE maximums result when the linear portions of the neutron and gamma-ray curves are compared.

—Seymour Abrahamson
RERF Chief of Research

Postscript: I received additional comments directly from **Harald Rossi**, Upper Nyack, N.Y., and from **Harold Wyckoff** and **Bill Beckner**, NCRP, Bethesda, Md. Referring to *ICRU Report 40*, Rossi indicates that the RBEs should be higher than the ones I have shown for pure neutrons, and lower for the indicated n/γ mixtures. Wyckoff and Becker point out that I have given no consideration to the possibility of a decrease in RBE and absorbed dose with depth in the body; this would produce an appreciably lower value of the dose equivalent for deeper lying organs. They refer to a letter to the editor in the July issue of the journal *Health Physics* for more detail.

Clearly, the suggestion that I have made can only be the beginning of a longer discussion, and should lead to the design of a more appropriate model by people better qualified in neutron dosimetry and radiobiology than I am. All I wanted to do is point out that a constant RBE over the entire dose range is incorrect, using some biological data to illustrate my point. I gladly cede to others to develop this thought into a more robust product! ❑

News Briefs

continued from page 2

✓ Epidemiology Chief Speaks to UN Conference

In late April, **Hiroo Kato**, chief of the RERF Department of Epidemiology, spoke about the medical effects of the atomic bombings to participants of a United Nations disarmament conference. Representing 30 countries, the group visited Hiroshima after its meeting in Kyoto.

✓ Film on Atomic Bombing of Hiroshima to be Revised

As chairman of the A-bomb Film Production Committee, RERF Chairman **Itsuzo Shigematsu** is participating in the production of a revised documentary chronicling the atomic bombing of Hiroshima. Shown to visitors at the city's Peace Memorial Hall, it will also depict the city's recovery, the rise of anti-nuclear activism, Hiroshima's military role during World War II and the Tokyo Tribunal sessions. The 30-minute documentary, produced in both English and Japanese, will be available for purchase or rental as 16-mm film or VHS format videotape.

✓ New RERF Scientific Councilors Appointed

At its meeting in late June, the RERF board of directors appointed to the Scientific Council **Kunio Aoki**, dean of Nagoya University's School of Medicine; **Curtis C. Harris**, chief of the National Cancer Institute's Laboratory of Human Carcinogenesis; and **Clark W. Heath Jr.**, the American Cancer Society's vice president for epidemiology and statistics. They replace outgoing councilors **Masanori Kuratsune**, **Donovan J. Thompson** and **Robert W. Miller**.

✓ Reprint Requests Received from 34 Countries

During the past year, 457 requests were received for reprints of RERF articles in the open scientific literature. The US tops the list with 110 requests. Other top-ranking countries were East Germany—48 requests, Czechoslovakia—35, Japan—27, West Germany—26, the Soviet Union—23, Bulgaria—23, Poland—23, France—18, and Hungary—13.

✓ Indonesian Trains at Nagasaki Lab

Djoko T. Iskandar, a biology lecturer at Indonesia's Bandon Institute of Technology Department of Science, spent 40 days studying techniques for analyzing human chromosome karyotypes under the supervision of **Takeo Honda**, chief of the Nagasaki Laboratory's Department of Radiobiology. ❑

Recent Scientific Publications

Editor's Note:

Beginning with the first report of 1989, the format and style of the RERF Technical Report Series were changed. To better inform the scientific community in a more timely fashion, RERF technical reports will no longer be published in the traditional Japanese–English bilingual format, but will be made available in both languages as separate publications. Selected reports of a highly specialized nature will be produced only in English, along with a Japanese summary.

Approved Technical Reports

Allowing for random errors in radiation exposure estimates for the atomic bomb survivor data. DA Pierce, DO Stram, M Vaeth. **RERF TR 2-89.**

The presence of nonsystematic errors in the individual radiation exposure estimates for the atomic bomb survivors results in underestimation of radiation effects in dose-response analyses and also distorts estimates of the shape of the dose-response curve. Statistical methods are presented which will adjust for these biases for linear and quadratic dose-response models, provided that a valid statistical model for the exposure estimation errors is available. This latter qualification is important; less than would be desired is currently known about the nature and magnitude of the errors. Emphasis is placed on clarifying the rather subtle statistical issues involved. The methods involve downward adjustment of dosimetry system estimates, but this is not to imply that these estimates are biased; rather this is part of the dose-response analysis to remove biases in the risk estimates.

Primary focus in this report is on linear dose-response models, but methods for linear-quadratic models are also indicated. Some plausible models for the exposure estimation errors are considered, with a substantial range in magnitude of errors, and sensitivity analysis of the resulting bias corrections is provided. It is found that unbiased estimates of linear excess risk for cancer mortality, for these error models, are about 5%–15% greater than estimates making no allowance for such errors. The upper end of this range is reduced to about 10% if, as is commonly done, some survivors with extremely high exposure estimates are eliminated from the analysis. Since the range is not extremely wide and since the statistical issues—although difficult—seem clear enough to proceed, it is recommended that some adjustment of the type proposed here now be made in most analyses.

A specific error model in the central range of those considered is tentatively proposed for such adjustments. No information specific to the new DS86 dosimetry is used in this recommendation, even though it will be important to bring such information to bear on DS86 as soon as possible. To a large extent the revision in dosimetry was intended to correct systematic errors affecting large groups of survivors, whereas the methods here pertain only to nonsystematic errors resulting largely from inadequacies in information about location and shielding of individual survivors—input common to old and new dosimetry systems. For further accrual of information regarding precision of the new dosimetry system to be most useful, it is critical that attention be given to the rather subtle statistical issues involved. In particular, it is critical to distinguish between the distribution of estimates or those at a given true exposure, and the distribution of true exposure for those having a given estimate.

Smoking and serum proteins in atomic bomb survivors in Hiroshima. DO Stram, S Akiba, K Neriishi, RG Stevens, Y Hosoda. **RERF TR 3-89.**

Associations of smoking habit with serum levels of total protein as well as protein fractions were studied in a population consisting of 4,739 atomic bomb survivors and unexposed control subjects in Hiroshima who participated in the 1979–81 period of the Adult Health Study, an on-going health follow-up program of RERF.

Smoking was strongly related to serum protein concentration after correction for age, sex, and body mass index. Among current smokers as compared to nonsmokers, levels of total protein, β globulin, and γ globulin were significantly lower (p), and levels of α_1 and α_2 globulin were significantly higher (p). For serum albumin levels, a decrease was also noted but it failed to attain statistical significance. Exsmokers were indistinguishable from nonsmokers in terms of the serum protein levels analyzed in this paper. With an increase in daily cigarette consumption, monotonic increases of serum levels were observed only in α_1 globulin. Duration of smoking (years) was related to increased α_1 and α_2 globulin. Smoking duration was also associated with albumin level but the trend was not monotonic. The radiation exposure effect on serum protein level was significant in several instances but was in general much smaller than the smoking effect. Its inclusion in the regression models did not noticeably affect the association between smoking and serum proteins.

Radiation-related posterior lenticular opacities in Hiroshima and Nagasaki atomic bomb survivors based on T65DR and DS86 dosimetry systems. M Otake, WJ Schull. **RERF TR 4-89.**

This paper investigates the quantitative relationship of ionizing radiation to the occurrence of posterior lenticular opacities among the survivors of the atomic bombings of Hiroshima and Nagasaki, as suggested by the DS86 dosimetry system. DS86 doses are available for 1,983 (93.4%) of the 2,124 A-bomb survivors analyzed in 1982. The DS86 kerma neutron component for Hiroshima survivors is much less than its comparable T65DR component, but is still 4.2-fold higher (0.38 Gy at 6 Gy) than that in Nagasaki (0.09 Gy at 6 Gy). Thus, if the eye is especially sensitive to neutrons, some useful information on neutron effects may yet be discernible, particularly in Hiroshima. The dose-response relationship has been evaluated as a function of the separately estimated gamma-ray and neutron doses. Among several different dose-response models with and without two thresholds, we have selected the one with the smallest χ^2 or the largest log likelihood value associated with the goodness of fit. The best fit is a linear gamma-linear neutron relationship which assumes different thresholds for the two types of radiation.

In the DS86 system, both gamma-ray and neutron regression coefficients for the best-fitting model are positive and highly significant for the estimated energy deposited in the eye, here termed the eye organ dose. The DS86 gamma regression coefficient is almost the same as that associated with the T65DR kerma gamma, the ratio of the two coefficients being 1.1 (95% confidence limits: 0.5–2.3) for DS86 kerma in the individual data. If the risks based on the DS86 eye organ dose and DS86 kerma are compared, the ratio is 1.3 (0.6–2.8). However, the risk estimates associated with neutron exposure are 6.4-fold (2.2–19.2) higher for the DS86 kerma than for the T65DR kerma and 1.6-fold (0.5–5.2) higher for the DS86 eye organ dose than for the DS86 kerma.

The relative biological effectiveness (RBE) values based on the individual gamma and neutron components of the DS86 eye organ dose are estimated to be $32.4 + 0.73/(D_n - 0.06) \geq 0$ with the 95% confidence limits ranging from 11.8 to $88.8 + 1.39/(D_n - 0.06) \geq 0$, where D_n is the neutron dose in gray. When such a threshold for the neutron dose is used, the RBE estimates are 105 at 0.01 Gy when D_n is 0.07 Gy, 40 at 0.10 Gy when D_n is 0.16 Gy, 36 at 0.20 Gy when D_n is 0.26 Gy, 35 at 0.30 Gy when D_n is 0.36 Gy and so on. The RBE value with the 95% lower bound suggests the constant to be 12. It should be noted that we cannot estimate the RBE when D_n is less than or equal to 0.06 Gy based on the restriction of $(D_n - 0.06) \geq 0$.

In any case, these values strongly suggest that the neutron component could be more important for the eyes than for other sites of the body. If we take into consideration the 95% lower bound of the neutron threshold including zero, we estimate the RBE values as $32.4 + 0.73/D_n$ with a range from 11.8 to $88.8 + 1.39/D_n$. Finally, it is interesting to observe that a linear-quadratic gamma and linear neutron model with two thresholds, which fits the data less well, produces very similar estimates of the two thresholds as the linear gamma-linear neutron-response model. In this model, however, the regression coefficient associated with the quadratic gamma response is not significantly negative.

A chromosome study of 6-thioguanine-resistant mutants in T lymphocytes of Hiroshima atomic bomb survivors. Y Kodama, M Hakoda, H Shimba, AA Awa, M Akiyama. **RERF TR 5-89.**

Cytogenetic characterizations were made of lymphocyte colonies established from somatic mutation assays for 6-thioguanine (TG) resistance in Hiroshima atomic bomb survivors. G-banded chromosomes were analyzed in both TG-resistant (TG^r) and wild-type (not TG-selected) colonies. In-

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Recent Scientific Publications

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cluded were 45 TG^r and 19 wild-type colonies derived from proximally exposed A-bomb survivors, as well as colonies from distally exposed control individuals who were not exposed to a significant level of A-bomb radiation (18 TG^r and 9 wild-type colonies). Various structural and numerical abnormalities of chromosomes were observed in both TG^r and wild-type colonies. Aberrations of the X chromosome, on which the hypoxanthine guanine phosphoribosyltransferase (HPRT) locus is present, were found in six colonies: two resistant colonies from controls [45,X/46,XX;46,X,ins(X)], three resistant colonies [45,X/46,XX/46,X,+mar; 46,X,t(Xq+;14q–);46,Y,t(Xq–;5q+)], and one wild-type colony [45,X/47,XXX] from proximally exposed persons. In cases with exchange aberrations, each of the break points on the X chromosome was situated proximally to band q26 where the HPRT locus is known to be assigned. DNA replicating patterns were also studied, and it was found that abnormal X chromosomes showed early replicating patterns, while normal X chromosomes showed late replicating patterns.

Expression of proto-oncogenes in non-Hodgkin's lymphomas by in situ hybridization with biotinylated DNA probes. K Hamatani, K Yoshida, M Abe, H Kondo, K Shimaoka, H Shiku, M Akiyama. **RERF TR 6-89.**

Expression of six proto-oncogenes (*fos*, *myc*, *myb*, Ki-*ras*, Ha-*ras*, and N-*ras*) in 43 cases of non-Hodgkin's lymphoma was analyzed by means of in situ hybridization. Biotinylated DNA probes of the six oncogenes and those of the immunoglobulin H-chain (*IgH*) gene and the T cell receptor-chain (*TCR*) gene were used. The results of in situ hybridization performed under blind conditions by *IgH* and *TCR* gene probes were compatible with those of typing by cell surface markers. The nuclear protein-related proto-oncogenes, *fos*, *myc*, and *myb*, were expressed in about 70%–80% of all cases regardless of phenotypes, histology or histologic grade. On the contrary, genes of the *ras* family were expressed in fewer cases except for the Ki-*ras* gene which was more frequently expressed by cases of the T cell immunophenotype with a high malignancy grade. The results of dot hybridization with RNA extracted from some cases were compatible with those of in situ hybridization, further demonstrating the specificity of in situ hybridization.

The shape of the cancer mortality dose-response curve for the atomic bomb survivors. DA Pierce, M Vaeth. **RERF TR 7-89.**

The shape of the cancer mortality dose-response in the atomic bomb survivor data is analyzed in the context of linear-quadratic models. Results are given for all cancers except leukemia as a group, for leukemia, and for combined inferences assuming common curvature. Since there is substantial information aside from these data suggesting a dose-response concave from above, the emphasis here is not on estimating the best-fitting dose-response curve, but rather on assessing the maximal extent of curvature under linear-quadratic models which is consistent with the data. Such inferences are substantially affected by imprecision in the dose estimates, and methods are applied which make explicit allowances for biases due to this. The primary means used here to express the extent of curvature is the factor by which linear risk estimates should be divided to arrive at appropriate low-dose risk estimates. Influential committees have in the past recommended ranges of 2–10 and of 1.5–3 for such a factor. Results here suggest that values greater than about 2 are at least moderately inconsistent with these data, within the context of linear-quadratic models. It is emphasized, however, that there is little direct information in these data regarding low-dose risks; the inferences here depend strongly on the link between low-dose and high-dose risks provided by the assumption of a linear-quadratic model.

Frequency of variant erythrocytes at the glycophorin A locus in two Bloom's syndrome patients. S Kyoizumi, N Nakamura, H Takebe, K Tatsumi, J German, M Akiyama. **RERF TR 8-89.**

Blood type MN is determined by a glycoprotein called glycophorin A (GPA), which exists on the surface of erythrocytes and the difference between the M and N types is derived from the presence of two different amino acids at the amino terminal portion. Using a pair of fluorescence-labeled monoclonal antibodies specific to each GPA, somatic mutations in erythrocytes of MN heterozygotes at the GPA-M and -N alleles can be quantitatively determined by a flow sorter. Our results for two Bloom's syndrome (BS) patients showed that variants either lost expression of one allele (simple gene inactivation or loss) or expressed only one allele at twice the normal level (most probably somatic recombination), occurring at a frequency of about 1–3 per 10^3 erythrocytes. The flow cytometric patterns of erythrocytes from the BS patients showed a typical smear of variants bearing intermediate levels of expression of one GPA allele, indicating the real variant frequency is even greater than measured. On the other hand, the parents heterozygous for the BS gene showed variant frequencies which are within the normal range ($1–8 \times 10^{-5}$). These data strongly supported the hypothesis that cancer proneness of BS patients is due to their increased frequency of spontaneous mutations and somatic recombinations.

Approved Research Protocol

Incidence of radiation-related skin lesions in the Adult Health Study populations of Hiroshima and Nagasaki, 1958–89. K Migita, M Yamada, K Kodama, Y Hosoda, K Shimaoka, K Mabuchi, M Soda, N Sadamori, M Kishikawa, DE Thompson, SC Finch. **RERF RP 6-89.**

The entire Adult Health Study (AHS) sample in both Hiroshima and Nagasaki will be thoroughly investigated for any malignant lesions, precancerous lesions, or any other possible radiation-related dermatologic changes which may have occurred since the inception of the AHS program in 1958. The information sources to be used will include the tumor and tissue registries, surgical pathology and autopsy information, AHS medical records, and any other medical information available to RERF. Histologic verification of specific lesions will be obtained whenever possible. For patients who are alive, as much information as possible on past skin lesions will be collected by means of a medical questionnaire.

Publications in the Open Literature

Analysis of the DS86 atomic bomb radiation dosimetry methods using data on severe epilation. DO Stram, S Mizuno. *Radiat Res* 117:93–113, 1989.

Molecular analyses of in vivo HPRT mutant T cells from atomic bomb survivors. M Hakoda, Y Hirai, S Kyoizumi, M Akiyama. *Environ Mutagen* 13:25–33, 1989.

The Radiation Effects Research Foundation of Hiroshima–Nagasaki. S Abrahamson. *Interdependent World* 8:2–3, 1989.

Problems in radiographic detection and diagnosis of lung cancer. N Hayabuchi, WJ Russell, J Murakami. *Acta Radiologica* 30:163–7, 1989. ❑

RERF **update** RERF

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