RERF update RERF

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

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19th Scientific Council Convenes in Hiroshima

RERF's Scientific Council met at the Hiroshima Laboratory, 24–26 March, continuing the tradition of annual reviews of RERF's research activities. Cochaired by **Toshiyuki Kumatori** (Radiation Effects Association) and **Mortimer Mendelsohn** (Lawrence Livermore National Laboratory), the council also reviewed a recently completed planning report that outlines the Foundation's major research directions for the next 5 years.

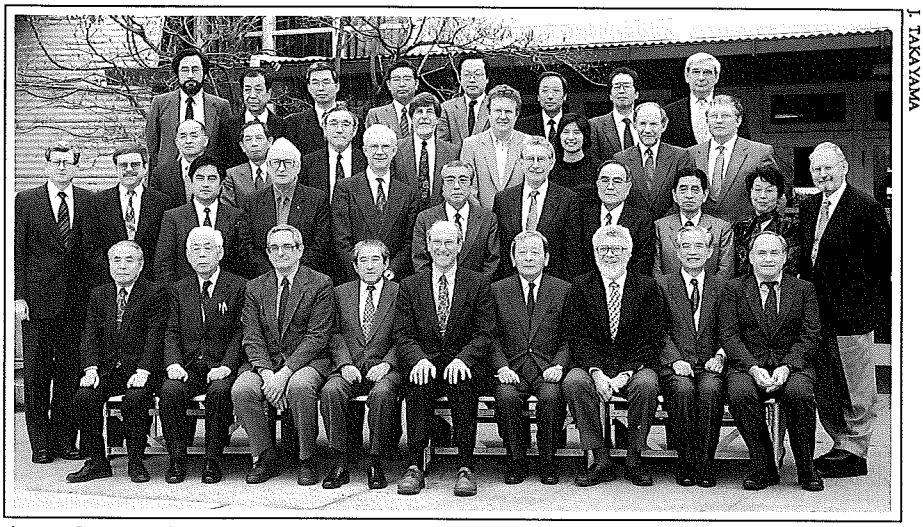
Research scientists briefly described to the council the progress achieved in a number of areas, highlights of which are listed below:

♦ The understanding of how radiation might have enhanced the risk of **cardiovascular disease in A-bomb survivors**, an effect that the council now finds to be well established, after initial hesitation with respect to other possible explanations.

♦ Continued development and application of **biological dosimeters** (eg, by use of somatic mutation markers and application of "chromosome painting" techniques for the detection of chromosomal aberrations). The council noted that RERF is a most appropriate place to do this kind of research.

♦ Development of **new techniques to measure any potential mutations at the DNA level** in the offspring of A-bomb survivors. According to the Scientific Council, these studies may profit greatly from collaborative efforts with other scientists outside RERF, including involvement in human genome activities.

♦ Studies concerning a possibly **decreased susceptibility in A-bomb survivors** to the late effects of radiation, research that so far has failed to provide any indication that the survivors are a selected, more radioresistant population than the population at large.



J. TAKAYAMA

Attendees of the 19th Scientific Council included, front row (from left): Shigefumi Okada, Ei Matsunaga, Clark Heath, Toshiyuki Kumatori, Mortimer Mendelsohn, Eisei Ishikawa, Leonard Herzenberg, Kunio Aoki, and Lon White. Second row (from left): Richard Sperry, John Burris, Hiroyuki Doi, J. W. Thiessen, Paul Ziemer, Itsuzo Shigematsu, Warren Sinclair, Kazuaki Arichi, Akira Shishido, Chiyoko Satoh, and Seymour Abrahamson. Third row (from left): Kenjiro Yokoro, Yutaka Hasegawa, Tomoyuki Kono, James Trosko, Dale Preston, Jill Ohara, David Williams, and Harry Pettengill. Top row (from left): Takeo Honda, Katsutaro Shimaoka, Yoshisada Shibata, Akio Awa, Kazunori Kodama, Mitoshi Akiyama, Kiyohiko Mabuchi, and Charles W. Edington.

♦ New research into **model systems for the study of human radiosensitivity** through hybridization of cells from severe combined immunodeficient mice—a highly radiosensitive species—with human cells. (We will report on this research in an upcoming issue of *RERF Update*.)

♦ Advances in **statistical and epidemiologic studies**, with landmark publications on cancer incidence and its comparison with cancer mortality studies soon to appear in a special issue of *Radiation Research*. (Readers of *Update* will be informed of these studies as they develop.)

♦ New research in the field of **"molecular epidemiology"** to search for molecular footprints in the tumors of A-bomb survivors that might be unique to radiation as compared to other cancer-causing agents.

The Scientific Council expressed its satisfaction with the progress made during the past year. At a press conference following the meeting, Kumatori noted that during his 15-year tenure as a scientific councilor, he had seen a continual improvement in the quality of RERF's research efforts. Mendelsohn was particularly impressed with the new research initiatives developed at RERF—such as the molecular oncology studies—that continue to establish RERF's place in the forefront of human radiation research.

This year marked the last time that Kumatori and Mendelsohn will cochair the council meeting. Mendelsohn will join RERF as a permanent director this summer (after 11 years as cochairman), and Kumatori felt that it was time for him to step down, after continual service since the founding of RERF. ❑

Perspectives

The Never-ending Debate: Threshold or No Threshold?

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

One way to become unpopular quickly is to discuss a controversial subject, especially when it concerns a field in which two opposite positions are equally strongly defended: no matter what you say, there is at least one party very unhappy with your opinion. The effects from low-level radiation exposure are such a field, with the no-threshold hypothesis right at the center. This issue of *Update*, which includes three articles pertaining to certain aspects of threshold, is as good a place as any to bring up the old controversy again.

I don't think there is any other subject in radiobiology that is so emotionally charged as the linear-no-threshold theory, as it is most commonly referred to. True, linearity is not necessarily connected with a no-threshold assumption, but historically it is, and the two are still mentioned in one breath more often than not. This may be because, at one time, only high-dose data being available for consideration, assumptions had to be made about extrapolation to low doses to serve as a basis for the derivation of radiation-protection standards, and strict proportionality between dose and effect appeared to be most appropriate for the purpose—or the least inappropriate. Constraining the linearity to start at $D = 0$ was considered a most suitable assumption given the need for a cautionary approach.

All this is well and good, but both linearity and the actual existence of a threshold have been put to the test on numerous occasions. For theorists, a linear-quadratic dose-effect relationship is de rigueur, because a model for it can be derived from simple suppositions with respect to DNA damage and cell killing, and it is liked by radiobiologists and radiation protection people because it allows a method for the derivation of low-dose/low-dose-rate radiation effectiveness, the slope of the linear part of the curve at low doses being its measure. It is interesting that RERF's newest cancer incidence data (to be published this year) generally appear to give more credence to a linear relationship over a range up to a few gray, with no indication of a quadratic component. Two clear-cut exceptions are the leukemias and skin cancer, which show either a low-slope linear segment followed by a quadratic component, or a no-effect zone of up to a few hundred (leukemia) or a thousand (skin cancer) milligray, followed by a linear increase above that dose level. The choice between the two is not so much a matter of statistics, but of belief: both dose-effect behaviors look equally likely. It is extremely interesting to note (although subject to confirmation) that different leukemia types demonstrate a different dose-effect behavior at low doses, with a clear threshold only for acute myeloid leukemia (see the article by **Randy L. Carter** on p 9 of this issue).

There are some flies in the ointment, however. The *mortality data* (Y. Shimizu et al, *Radiat Res* 118:502–24, 1989), although consistent with linearity for all solid cancers taken together, show "too little" or no effect of low-dose radiation up to a few hundred milligray for a number of cancers, eg, gastrointestinal cancers, breast cancer, and lung cancer. The *cancer incidence data* (D. Thompson et al, RERF TR 5-92, in press), on the other hand, show a rather perfect linearity, all the way from (or near) zero dose. The comparative analysis of these two data sets is still ongoing, so it is too early to draw conclusions with respect to the existence or likelihood of a threshold. Nevertheless, even a solidification of the evidence for strict linearity for cancer induction raises some interesting is-

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News Briefs

✓ Scientific Councilors Meet at Hiroshima Laboratory

The 19th annual gathering of RERF's council of scientific advisors occurred at the Hiroshima Laboratory, 24–26 March, continuing the tradition of regular program reviews (see related story on p 1).

The following councilors attended this year's meeting: **Kunio Aoki**, Aichi Cancer Center, Nagoya; **Eisei Ishikawa**, Jikeikai University School of Medicine, Tokyo; **Toshiyuki Kumatori**, Radiation Effects Association, Tokyo; **Clark W. Heath Jr**, American Cancer Society; **Leonard A. Herzenberg**, Stanford University School of Medicine; **Ei Matsunaga**, National Institute of Genetics, Mishima; **Mortimer L. Mendelsohn**, Lawrence Livermore National Laboratory; and **Shigefumi Okada**, University of Tokyo.

Observers at the meeting included: **Paul Ziemer** and **Harry Pettengill**, US Department of Energy; **Seymour Abrahamson**, University of Wisconsin; **John E. Burris**, **Charles W. Edington**, and **David Williams**, US National Research Council; **Hiroyuki Doi**, Japanese Ministry of Health and Welfare; **Akira Shishido**, Japanese National Institute of Health; **Warren K. Sinclair**, National Council on Radiation Protection (US); and **Lon R. White**, US National Institute on Aging.

✓ RERF Newsletter Now Sent to 41 Countries

As of 1 January, *RERF Update*, which was first published in the spring of 1989, is being distributed to nearly 900 subscribers in 41 countries. The following countries have 10 or more subscribers: United States (316), Japan (255), Commonwealth of Independent States (60), United Kingdom (51), Germany (24), People's Republic of China (23), France (21), The Netherlands (14), Switzerland (12), India (11), and Sweden (10).

✓ Chinese Scientists Visit RERF

In late January, four scientists from the People's Republic of China met with RERF representatives to discuss an ongoing Chinese study of the Guangdong region, reputed to have elevated levels of background radiation. The visitors were **Wei Lüxin**, Ministry of Public Health, Beijing; and **Wang Fang Neng**, **Qiu Xi Qia**, and **Kuang Wen Rao**, Occupational Diseases Prevention and Treatment Center, Guangzhou.

✓ 'Hiroshima International Council for the Health Care of the Radiation-exposed' Continues to Fund Training and Consulting

As part of its ongoing effort to provide access to local expertise in matters

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Does Radiation Cause Cancer?

The author discusses the multistage aspects of cancer formation and how acute irradiation may affect these processes.

by James E. Trosko, RERF Chief of Research

What an outrageous question! With an enormous amount of experimental animal and human epidemiological data showing that a wide variety of cancers appear after exposure to various kinds of radiation, one could hardly question the conclusion that radiation does "cause" cancer. But wait! Our understanding of carcinogenesis today leads us to believe that it is a multistage, multimechanistic process, involving the interaction of many external and endogenous factors. Consequently, it is misleading to assume that any single factor or "carcinogen"—chemical or physical—"causes" cancer. The key word here is *cause*.

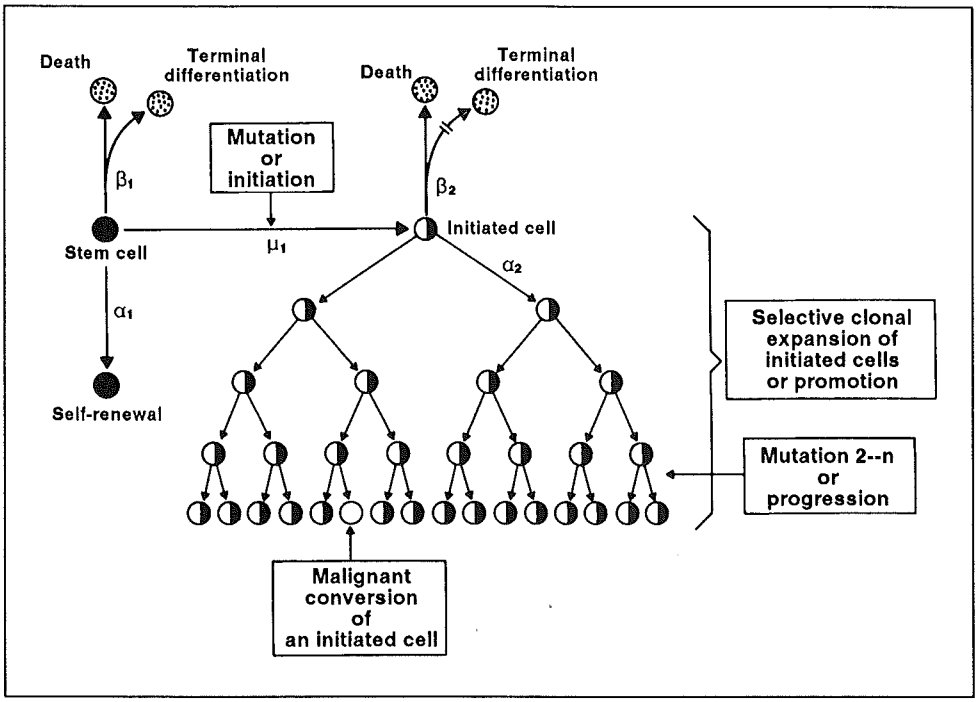

Figure 1. The initiation-promotion-progression model of carcinogenesis. β_1, rate of terminal differentiation and death of stem cell; β_2, rate of death, but not of terminal differentiation of the initiated cell (⊣ ↦); α_1, rate of cell division of stem cells; α_2, rate of cell division of initiated cells; μ_1, rate of the molecular event leading to initiation (ie, possibly mutation); and μ_2, rate at which the second event occurs within an initiated cell.

Carcinogenesis involves many steps and mechanisms, with the interaction of external determinants such as chemical and physical pollutants, medication/drugs, mutagenic and epigenetic agents—as these may occur in the diet or as workplace and environmental pollutants—and endogenous factors related to genetic background, sex, developmental stage, number of stem or progenitor cells that give rise to cancer, DNA repair systems, hormones, growth factors, oncogenes, tumor suppressor genes, and antimetastasis genes.

Carcinogenesis as a multistep, multimechanistic process

Currently, the multistage model of carcinogenesis, derived from whole animal experimental studies, seems to be a plausible model for human carcinogenesis. This model indicates that the first step in carcinogenesis—the initiation stage—is irreversible. The observation that mutagens appear to be effective initiators implicates mutagenesis as the mechanism underlying the initiation stage. The fact that the initiation process appears to be irreversible is also consistent with the hypothesis that mutagenesis is at least one mechanism of initiation. Stable epigenetic repression or activation of genes may be another.

Most cancer studies have been consistent with the clonal theory of cancer, ie, the assumption that cancer arises from changes initiated in one cell (Figure 1). Therefore, the second step in carcinogenesis—the promotion stage—appears to involve the clonal expansion of an initiated stem cell, which, because it is unable to terminally differentiate, accumulates as a focus of nonterminally differentiated cells. Examples of such foci might be papillomas of the skin, enzyme-altered foci of the liver, polyps of the colon, and nodules of the breast. Obviously, this process must require stimulation of cell division (ie, it must be mitogenic), at least with respect to the initiated cell. As demonstrated in experimental animals, this stage is potentially interruptable and reversible.

If one of these promoted, initiated cells acquires additional genetic alterations (eg, other mutations, stable epigenetic changes) that allow the cell to become promoter-independent, invasive, and metastatic, then the third step of carcinogenesis—the conversion or progression stage—has occurred. This step also appears to be irreversible. Given the observations that mutagens appear to affect this stage, mutagenesis as well as stable epigenetic events could be applicable mechanisms for progression.

Genetic aspects of carcinogenesis

While it has seemed surprising to many laypersons and scientists that genes play a role in carcinogenesis, it has not been so for geneticists, who have known this for decades. Recent discoveries have identified two classes of genes in all normal mammalian cells: "proto-oncogenes" and "tumor suppressor" genes (RA Weinberg, *Science* 254:1138–46, 1991). In general, "proto-onco-

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Cancer Causes

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genes" seem to code for growth factors, growth factor receptors, transmembrane mitogenic signalling elements, and nuclear transcriptional factors. They seem to be involved in regulating the proliferation and differentiation of cells. Stable activation of these proto-oncogenes, by abnormal gene expression, amplification, or mutations, converts them to "oncogenes" and, depending on other events, can transform the phenotype of the cell to a premalignant or malignant cell.

The other event needed for the activated oncogene to convert the cell to a malignant cell seems to be the deactivation of tumor suppressor (and possibly antitumor invasive and anti-tumor metastasis) genes. These tumor suppressor genes appear to code for proteins that either negate or inhibit the function of proto-oncogenes and oncogenes. Therefore, conceptually, if the function of proto-oncogenes and oncogenes is to prepare cells to proliferate and invade tissue, the tumor suppressor genes function as "brakes" and keep the progenitor cells in a quiescent state. In a normal cell, the specific expressed oncogenes and tumor suppressor genes are in a "yin/yang" state of balance.

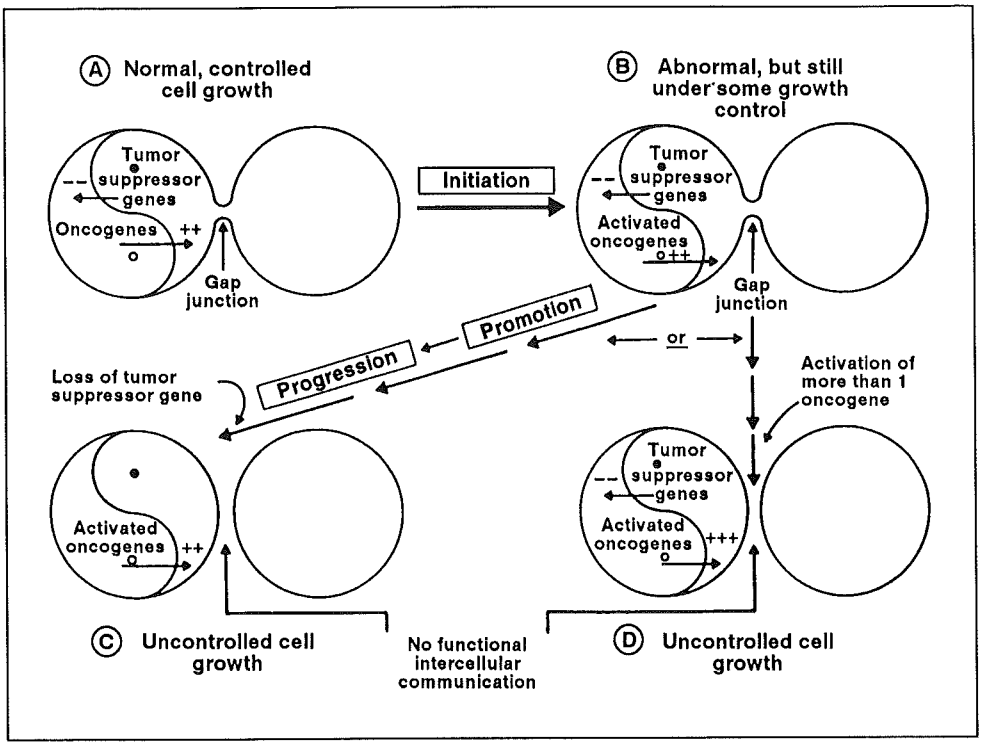


Figure 2. The yin/yang model of oncogenes and tumor suppressor genes in the control of cell growth depicts the balance between positive factors that stimulate growth and negative factors that suppress growth. In the quiescent state of a normal cell that is contact inhibited (solid tissue) or suppressed by extracellular regulators (soft tissues), the two factors balance out. During the initiation-promotion-progression process of carcinogenesis, activation of oncogenes could occur, followed by clonal expansion of these cells. The loss of tumor suppressor genes by mutation or by deletion allows the cell to enter the progression phase by stimulation of cell growth or by inability to respond to negative growth control (ie, growth inhibition). The role of gap junctional intercellular communication (for cells in solid tissues) is speculated to be down-regulated by oncogenes and up-regulated by tumor suppressor genes.

How do the different factors fit together?

If carcinogenesis is a multistep process, with each stage affected by different mechanisms (eg, there are many ways to cause mutations; many mechanisms lead to mitogenesis), how could a single exposure to ionizing radiation "cause" cancer? For those who harbor the idea that ionizing radiation "causes" cancer, does it not seem incredible that after an acute exposure, radiation would not only have to activate one or more oncogenes, as well as inactivate suppressor genes, it would also have to initiate, promote, or clonally expand that cell manyfold and then convert one of those initiated cells by mutating other genes to have invasive and metastatic abilities by a series of independent events in a single cell?

Would it not be more informative to ask questions such as: "Which step(s) of carcinogenesis might be affected by ionizing radiation?"; "By what mechanisms might ionizing radiation initiate, promote, or bring about progression of carcinogenesis?"; "Does ionizing radiation activate oncogenes?"; and "Does ionizing radiation deactivate tumor suppressor genes?" Moreover, does a linear-no threshold model describe the underlying mechanisms of the multistage nature of carcinogenesis, especially the promotion or mitogenic step? A recent review of chemical carcinogenic studies appears to indicate a no-effect, threshold level for the role of the mitogenic process, primarily linked to the promotion or clonal expansion of the initiated cell (S Cohen and L Ellwein, *Cancer Res* 52:6493–505, 1991). Serious examination, as suggested in an accompanying article by **V. P. Bond** (see p 7), must be considered. By rephrasing the problem, specific testable hypotheses, using these concepts and molecular technologies, might provide new insights into how (in our case) exposure to A-bomb radiation could have contributed to the process of carcinogenesis.

Epidemiologists involved in determining the risks of radiation exposure use the term "confounding factors" for factors, such as age at exposure, time elapsed since exposure, sex, reproductive history, diet, postirradiation therapy, etc, that are known to be associated with "modifying" the radiation response. In the context of the carcinogenic process outlined above, the term "confounding factors" is very misleading. In fact, the term ought to be "contributing factors," with radiation being only one of these factors.

Oncogenes, tumor suppressor genes, and intercellular communication

The initiation/promotion/progression hypothesis of carcinogenesis is an operational concept derived from whole-animal experiments, having no implied underlying molecular mechanism. Independently, the oncogene/tumor suppressor gene hypothesis is a concept derived empirically from molecular in vivo and in vitro studies. However, to date no viable cellular mechanism has been offered as to how the various oncogenes and tumor suppressor genes might function to convert a contact-inhibitable progenitor cell to a cancer cell, ie, one that is not contact-inhibitable and unable to terminally differentiate.

In a multicellular organism, tight regulation of a cell's ability to proliferate and to differentiate must occur.

Various intercellular communication mechanisms, such as extracellular communication via growth factors, hormones, or gap-junctional intercellular communication (GJIC) via ions and small molecules through gap-junction channels, appear to be directly associated with the regulation of cell growth and differentiation. Since the major phenotypic dysfunctions of cancer cells seem to be the lack of contact inhibition and loss of growth control and the ability to terminally differentiate, it would be reasonable to speculate that intercellular communication has been disrupted during the carcinogenic process. Indeed, many if not all cancer cells have abnormal homologous or selective communication characteristics. Many chemical tumor promoters, oncogenes, and growth factors also inhibit intercellular communication, whereas the few antitumor agents and anticarcinogens seem to up-regulate GJIC (JE Trosko et al, *Pathobiology* 58:265–78, 1990; JE Trosko et al, *Radiat Res* 123:241–51, 1990). One tumor suppressor gene has been associated with a gap-junction gene (SW Lee et al, *Proc Natl Acad Sci USA* 88:2825–9, 1991). These circumstantial, but completely independent, observations are consistent with the hypothesis that the oncogene/suppressor gene function modulates GJIC, which, in turn, modulates a cell's ability to proliferate or differentiate.

The role of ionizing radiation in carcinogenesis

The question now arises as to how radiation might affect one or more of the mechanisms underlying the initiation, promotion, and progression phases of carcinogenesis.

Radiation: a weak initiator

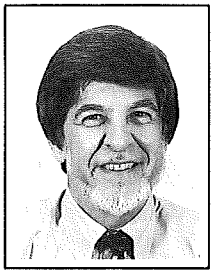
The current weight of the evidence indicates that ionizing radiation is a rather weak point mutagen but a good clastogen (inducer of chromosome breaks, deletions, and rearrangements). At high enough doses, this translates into radiation being a good cytotoxicant since chromosome deletions and many types of chromosome rearrangements are lethal. In contrast, given the oncogene/tumor suppressor gene paradigm, where a balance between proto-oncogenes and tumor suppressor genes is needed for normal growth control and differentiation (see Figure 2), ionizing radiation might generally be predicted to be a rather weak "activator" of oncogenes but a strong "deactivator" of tumor suppressor genes, except possibly by causing rearrangement of normal proto-oncogenes causing them to be abnormally and stably expressed.

Radiation as a promoter

If ionizing radiation is to be a promoter, ie, a stimulant of the clonal expansion of initiated cells, it must be given at a high enough dose to cause significant cell killing, which, in turn, would induce compensatory hyperplasia. If one of the surviving stem cells were to have been previously initiated by some other environmental mutagen or initiated by the radiation itself, then regenerative or compensatory hyperplasia could be seen as "promotion." If the dose were too high, the ionizing radiation would start to kill some of the preexisting or newly induced initiated cells, thereby decreasing the cancer incidence and increasing the likelihood of early death of the organism.

Radiation as a progressor

If the exposed individual has preexisting initiated and promoted clones of cells (as we all must: the older we get, the more of these we should have), then ionizing radiation, as an effective gene and chromosome deletion mutagen, might be expected to be a relatively good tumor suppressor gene "deactivator."



Trosko

Assuming that stem cells are the target cells for carcinogenesis, then the risk that the initiation step of carcinogenesis occurs from a single exposure to ionizing radiation is influenced by the number of these stem cells. Some tissues will have relatively stable numbers of these cells during aging (eg, skin and the lining of the GI tract), whereas others, such as the breast, liver, and brain tissues, may have decreasing numbers of stem cells (due to many intrinsic and extrinsic factors that I won't discuss here).

On the other hand, depending on previous exposure to other point mutagens that might initiate (activate oncogenes) and promote (age might be an important factor here), ionizing radiation might be a good "progressor." The interaction of sunlight exposure and ionizing radiation in skin cells of older individuals, in sun-exposed and non-sun-exposed areas, might be a test of this hypothesis, since UV radiation is a good point mutagen and skin carcinogen (presumed initiator and activator of oncogenes, promoter via its ability to kill cells, and progressor by its ability to deactivate tumor suppressor genes by point mutations).

Does radiation "cause" cancer?

Clearly, radiation is a contributing factor. How it contributes in the multistage process of carcinogenesis is not yet known; however, radiation does seem to be a *weak initiator*, both by its ability to induce chromosome rearrangements (to activate oncogenes) and by its weak point mutagenic potential. At higher doses, radiation might act as an *indirect promoter* of preexisting initiated stem cells by its ability to induce regenerative hyperplasia via its cell-killing effects. Finally, because of its ability to delete genes and chromosomes, it should be *effective as a deactivator of tumor suppressor genes* and therefore should act as a *progressor* at the late stages of carcinogenesis.

All this does not imply that ionizing radiation is unimportant in bringing about cancer. However, only by knowing the mechanisms by which ionizing radiation influences this complex disease process can we hope to develop meaningful risk estimates from studies of populations and individuals exposed to radiation, especially at low doses where the greatest uncertainties exist. Clearly, epidemiological and statistical analyses of radiation-exposed populations are critical and necessary. So are basic and fundamental studies of radiation effects on molecules, cells, and animals. In addition, the future demands a greater interaction among epidemiologists and radiation molecular and cell biologists for better hypothesis design, testing, and interpretion of epidemiologic studies. At the same time, epidemiological findings should stimulate laboratory research to explain the results. The emerging field of molecular epidemiology may provide the stimulus for this union (PG Shields and CC Harris, *J Am Med Assoc* 266: 681–7, 1991). At RERF, we are developing plans to move in this direction. ❑

*Note added in proof: Three recent papers (D Zhu et al, **Proc Natl Acad Sci USA 88:1883–7, 1991; PP Mehta et al, J Membrane Biol 124:207–25, 1991; B Ehlibali et al, Proc Natl Acad Sci USA 88:10701–5, 1991**) have demonstrated that noncommunicating cancer cells, when transfected with expressible gap-junction genes, had restored cell-to-cell communication and normal growth patterns.*

More about RBE and Dose-response Functions

Editor's note: This letter to the editor comments on the article "RBE and Dose-response Functions" by D. Preston and R. Sposto (RERF Update 3[3]:3–4, 1991).

We cannot agree with several statements Preston and Sposto made.

1) It is said that "...even for relatively simple dose-response functions, the RBE varies with dose in a complex manner." It may be a matter of opinion whether a second-order equation is "complex," but it is more important that the form of the relation has been found to be the same in effects on higher organisms ranging from plants to humans. Do Preston and Sposto know of any exceptions? It also holds for effects where the criteria for dose response must be arbitrary, such as the opacification of the murine lens of the eye, where it was shown to apply for more than three orders of magnitude of the neutron dose.

2) It is not necessary that with a constant RBE the dose-response functions for gamma and neutron radiation be linear. All that is required is that they have the same shape, ie, that in a logarithmic plot they can be made to coincide by a shift parallel to the dose axis. Thus, while the *dose response* may be "complex" (as it is very likely to be in carcinogenesis), the *RBE relation* remains simple. An example applies to low doses and lung tumors in mice (H Rossi, *Radiat Res* 84:401, 1980). Thus a change of the criterion for chromosome damage can change the dose-response function but not the RBE relation. Furthermore, if the "effect" is in fact a combination of diverse but statistically independent effects (eg, "all nonleukemic cancers"), the constants (g, c, and n in our equations) are merely weighted over ages.

There are, however, complications when there is coherence (statistical correlation) between effects. This is evident at high doses in the example of the lung tumors. It is probably due to an interaction between cell transformation and cell killing and a neutron RBE that is higher for the former compared with the latter. This interaction is not likely to be very important in the Japanese situation because the neutron doses were low relative to the gamma-ray doses.

As far as we can see, the bivariate fraction is merely designed as a device to achieve coincidence between the data for the two cities. We hope that Preston and Sposto will provide it explicitly because it should conform to our quantity H. It would therefore be possible to extract RBE_M (the limiting RBE at low doses), which is of great practical as well as of theoretical interest.

—H. H. Rossi and M. Zaider

Preston and Sposto Reply:

We would like to thank Drs Rossi and Zaider for their response to our article on dose-response functions and RBEs. Their main point appears to be that the RBE function has the advantage of being largely independent of the response criterion. We understand this independence to mean that if $g(n)$ is the gamma dose that has *precisely the same biological effect* as neutron dose n, the RBE function would be the same regardless of how one *measured* the effect. This invariance of the RBE seems of limited usefulness in many applications of the RBE concept since exposure-response situations often differ in ways that make it difficult, if not impossible, to specify the meaning of identical biological effects. For example, in the case of comparisons of radiation risk estimates from Hiroshima and Nagasaki, *equal effects* can be defined in different ways even if we ignore the problems caused by differences in the age and sex distributions of the populations in the two cities. For example, consider an effect for which the zero dose rates in Hiroshima and Nagasaki are 0.01 and 0.02, respectively. Following a dose of (g_H, n_H) in Hiroshima the rate for this outcome is increased to 0.02, whereas in Nagasaki a dose of (g_N, n_N) increases the risk to 0.04. Are these considered equivalent effects? The relative increase is the same, but the absolute increase in Nagasaki is twice that for Hiroshima.

With regard to some of the specific points raised in their letter, we agree that the definition of the RBE function implies a constant RBE whenever the logarithms of the gamma and neutron responses differ by a constant, ie, when the ratio of the dose-response functions is constant. We do not consider the use of general dose-response models to be "a device to achieve coincidence between the data for the two cities." Our belief is that if one is interested in dose-response or RBE functions one should use the data in as direct a manner as possible and that undue reliance on simple intercity comparisons only serves to complicate the problem. We plan to publish more on dose-response functions and RBE estimation in the near future. ❑

RERF Reports Available Upon Request

RERF Update lists technical reports, as well as reports in the Commentary and Review Series, usually on the last pages of each issue. Readers often inquire why they have not yet received copies of these listed reports. Reports that are "approved" should be considered as "in press" publications that may not yet be available for distribution. As soon as they are printed, they will be distributed to those on the appropriate mailing lists.

Readers interested in receiving reports should select one or more of the following subject categories: radiation effects on humans; reanalyses using the DS86 dose estimates; Life Span Study—cancer and noncancer mortality; Adult Health Study—disease incidence and aging; genetic studies—chromosome abnormalities, biochemical genetics; in utero radiation exposure (mental retardation); cancer epidemiology—tumor registries, histopathology; radiobiology; A-bomb dosimetry; and statistical methodologies.

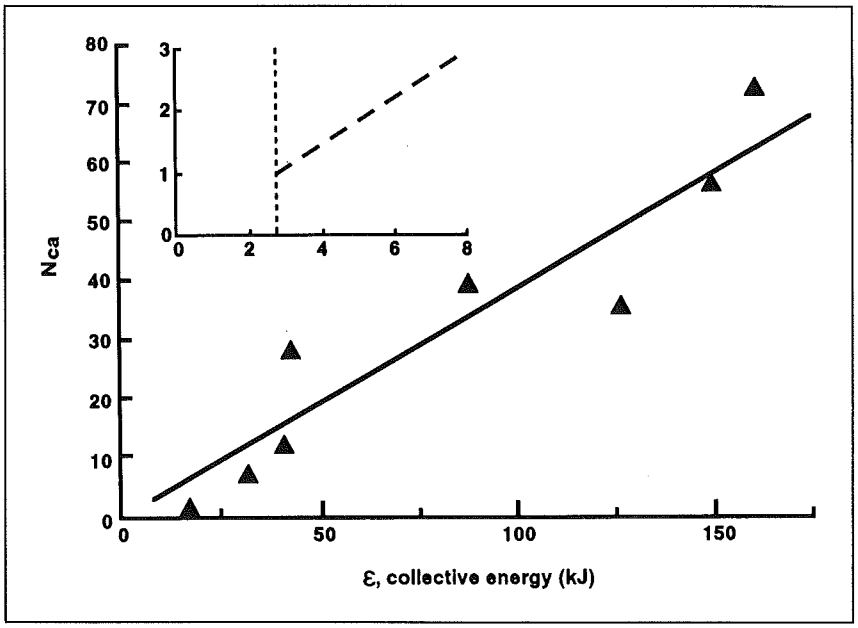
Please send your name, address, and subject area(s) to Chief, RERF Publication and Documentation Center, 5-2 Hijiyama Park, Minami-ku, Hiroshima, 732 Japan. Fax: 81-82-263-7279. ❑

An Empirically Determined Energy Threshold for Radiation-attributable Cancer

by V. P. Bond, Medical Department, Brookhaven National Laboratory, Brookhaven, NY

Every radiobiologist and radioepidemiologist has had the following experience: regardless of the criterion of biological effect, decreasing the energy concentration—ie, the absorbed dose, D—results in a level being reached at or below which no radiation-attributable excess biological responses can be observed. A common practice is to include more subjects at that data point, in order to "improve the statistics" so an excess can be observed without increasing the absorbed dose.

However, inadequately appreciated is the fact that, as the number of subjects included at a given (low) value of D increases, the energy content of the system, ε, increases proportionately: more responses cannot be obtained without the expenditure of additional energy. Although the limiting absorbed dose below which an excess in response cannot be observed constitutes an empirical "threshold," this is not useful because it varies with the number of subjects irradiated.



Excess cancers (N_{ca}) plotted against administered dose, ε. Enlargement of the lower end of the curve shows a threshold at about 3 kJ.

Dose versus collective energy

The significance of the above is that it is the total or collective energy, ε, in the entire system or subsystem, in units of joule (or, alternatively and if the mean mass is known, cell · Gy or person · Gy), that is the "true" dose upon which the severity of biological effect depends. This thesis is supported by the dictionary definition of dose as ε and not D; by historical usage of the word and concept of dose in medicine and toxicology, and by the long-standing use of person · Gy in radioepidemiology and radiation protection practice. Although an average value of D may be adequate when used for early acute effects, eg, in radiotherapy in which the focus is on a particular relatively uniformly irradiated tumor, organ, or organism, it has also long been recognized that ε to the mass m of normal tissues, in units of kg · Gy (ie, joule), and not D alone, must be kept small to minimize the chance of unacceptable side effects.

However, radioepidemiology and radiation protection constitute public health problems. Thus, as contrasted with medicine (including toxicology) in which the focus is on care of the individual patient, the responsibility is for the health and well-being of a defined population regarded as a single entity. A radiation-related public health problem exists when a population has become irradiated as a result of a single macro-irradiation event (eg, the atomic bombings, the Chernobyl accident, or a year of occupational exposure), in which a randomly or quasi-randomly determined broad range of doses, D, with widely differing numbers of persons at each dose point, is the inevitable consequence. Here, unlike in toxicology, both D and m must be considered explicitly at each data point, in the form of $m \cdot D = \varepsilon$, in order to describe fully (and thus predict) the severity of effect in terms of the actual number of excess cancers in the exposed population or subpopulation.

Excess cancers related to collective energy

Radioepidemiological functions using ε have been constructed recently, using the radiation-attributable solid cancer data, ie, total cancers minus baseline incidence, from studies of the atomic bomb survivors. The assumed linear function for the actual number of observed cancers as a function of ε is shown in the figure. As indicated in the figure insert, the curve is abruptly truncated at the level of one cancer, at an average value for ε of about 3 kJ (50 person · Gy). This is because it is not possible to have a fraction of a cancer. Although not shown here, a plot of ε/cancer vs D demonstrated that the average energy requirement for one cancer is invariant to very low values of D (VP Bond et al, *Proc Natl Acad Sci USA* 88:8666–70, 1991; VP Bond, 1991 Taylor Lecture, Bethesda, Md, NCRP). Thus, unlike the cutoff in a dose-response curve, the stability of the cutoff in ε permits its use as an empirically determined threshold or *de minimis* point below which there should be no cause for regulatory concern. However, the 3-kJ threshold must be considered as minimal because one excess cancer has little statistical credibility: much more energy would have to be absorbed in the system before it could be stated with confidence that an ap-

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Energy Threshold

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parent excess over the baseline number of cancers is in fact attributable to the irradiation and not to baseline causes.

Minimum collective energy for one cancer

For purposes of orientation with respect to the effectiveness of collective energy, the 3 kJ necessary for one cancer, if delivered to one person weighing 70 kg, would be some 12 times greater than the acutely lethal amount (ie, radiation is much more efficient in causing an acute death, rather than death from a cancer). At the low-dose end, a person receiving 1 mGy to the entire body would have received some 50,000 times less than the average requirement for one cancer. The possibility of this small amount of radiation causing a cancer is so remote as to constitute speculation.

The thesis that the risk from low-level irradiation is linear to the lowest doses, ie, the "linear-no-threshold" hypothesis, is based upon the usual absorbed dose-response curve. A key point is that "risk," as it is used in this context (actually, a probability and not conventional risk), is no more than a synonym for observed excess incidence. Thus, below the level at which an actual excess of cancers can be observed empirically, there is no basis for "extrapolated" values, be they termed excess incidence or risk. All such values can be only hypothetical. That such risk extrapolation is frequently done is in itself testimony to the presence of an empirical threshold, as is the fact that the smallest dose groups among the atomic bomb survivors, with no excess cancers, have been used as an unirradiated comparison population.

The ε-response curve precludes the downward extrapolation encouraged by the usual dose-response curve. Because the ordinate of the ε-response curve is the absolute value for excess cancers, and not a ratio, no basis for such downward extrapolation, under the rubric of risk, is provided. That the threshold is inviolate can also be seen by considering a value of ε below this level. Although the inclusion of additional persons could result in an observable excess of cancers, the additional energy would force relocation of the point to a position well above the threshold.

The consequences of the "linear-no-threshold" hypothesis are frequently expressed in words to the effect that "...any amount of radiation, however small, can be harmful or even lethal." Perhaps the strongest defense of the hypothesis lies in the argument that, at even the lowest dose levels, an excess of cancers will appear if a great enough number of subjects is included. However, with the demonstration that the relevant "amount" is ε and not D, this argument is rendered invalid. It becomes highly misleading to infer that a small dose D may well result in a cancer, unless it is also made clear that, for this to actually happen, ε at that small value of D must equal or exceed the relatively large threshold value.

Linearity

Although dose-response curves for both human and animal tumors have been described as being "consistent with linearity," the principal evidence for the hypothesis lies with response data from single-cell systems. These systems lack the systemic defense mechanisms of the mammal, which may well have evolved over eons of exposure to background radiation, some of which may "seek and destroy" fully transformed cells that are capable of producing an overt cancer. Possible mechanisms include adaptive cell responses, hormesis (LE Feinendegen, *Phys Med Biol* 35:597–612, 1990), and immunologic processes. It is quite possible that some of these mechanisms may easily become saturated, so as to be maximally effective at the low dose rates invariably present naturally; less so with the higher doses and dose rates provided only relatively recently by manmade sources.

Low-level radiation epidemiology

The results of the most recent of several studies of large populations exposed to low-level radiation, ie, the 10-year "Matanoski study" of nuclear shipyard workers in which accumulated dose was within occupational exposure limits, were the same as those of most similar studies (GM Matanoski, *Health effects of low-level radiation in shipyard workers*, Dept of Epidemiology, Johns Hopkins University, Baltimore, Md, June 1991). There was no excess of attributable cancers, and the death rate from all causes was significantly lower than that for the comparison population. Such results may be explained in part by arguments from molecular and cellular oncology that are put forth in a companion article by **James E. Trosko** on p 3. Because several genetic alterations in a single cell are required during the multistep, multimechanism, "initiation, promotion, progression" process of carcinogenesis, a low-level *acute* radiation exposure would not be expected to be able to bring about all the needed steps. Other factors, before or after the low-level acute exposure, would be necessary for completing the process.

For *chronic* low-level exposure, the mutagenic potential, albeit low, rather than the mitogenic potential related to compensatory hyperplasia due to the cytotoxic effects of radiation (which at low dose would be insignificant), might contribute to either the initiation or progression steps. If this exposure initiated a cell, it would have to be promoted or multiplied by endogenous or exogenous agents and would have to acquire other genetic alterations due to either additional radiation or other carcinogenic agents. If cells initiated and promoted by other carcinogens exist before chronic low-level exposure starts, the low-level exposure might, with a low probability, contribute to the progression phase. In effect, the radiation might be a contributor to one or more, but not all, steps required to complete the carcinogenic process.

Consequences of the no-threshold approach

The final point is quasi-philosophical in nature. In nearly all walks of life, action is based on what can actually be demonstrated or on repeatedly validated theory. With radiation, this practice is reversed, and action is based on a hypothesis that is belied by actual empirical observations, and that is neither proved nor provable because of statistical limitations (also, one cannot prove the negative). As noted above, newer findings provide possible bases for a threshold. The question must then be asked seriously: to what extent does this strict adherence to one unproved hypothesis indicating no threshold—which is counter to other, opposing unproved biological hypotheses and extensive empirical observations pointing to a threshold—constitute defensible science or conservatism carried to unwarranted extremes? This particularly when so much is at stake, eg, the stifling restrictiveness of exposure limits, costly litigation in radiation-cancer lawsuits, limitations on the use of radiation in medicine, restrictions on the availability of badly needed energy sources, and widespread and severe anxiety where none is warranted. ❑

Low-dose Leukemogenic Effects of A-bomb Irradiation

The effect of low dose on acute lymphocytic and chronic myeloid leukemias is qualitatively different from that on acute myeloid leukemia.

by Randy L. Carter, RERF Department of Statistics

In a previous issue of *RERF Update* (3[4]:5–6, 1991), we summarized several results from our study of the relative effects of atomic bomb irradiation on four major leukemia types: acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), chronic myeloid leukemia (CML), and "OTHER" (M. Tomonaga et al, RERF TR 9-91, in press). One of these results led to the suggestion that "kerma values less than 50 mGy and probably as low as 16 mGy apparently produced excess cases of ALL and CML (see table), whereas kerma values greater than 50 mGy and probably at least 229 mGy were required to produce excesses in AML." Considering the practical importance of low-dose radiation effects, this statement merits further discussion.

Reclassification of leukemia cases

In 1987, a panel of hematologists attempted to reclassify leukemia cases in the RERF leukemia registry using up-to-date diagnostic criteria. The French-American-British (FAB) classification system was used to distinguish several types of acute leukemia. Among survivors who were within 9 km of the hypocenters ATB, 766 cases of leukemia were observed. Sufficient hematological and pathological preparations were available to reclassify 493 of the 766 cases. Of these, 413 had been assigned DS86 dose estimates, roughly twice the number of cases in the RERF Life Span Study (LSS) with assigned dose estimates. We applied a type of proportional incidence analysis to data from these 413 cases (see N Breslow and N Day, *Statistical Methods in Cancer Research*, Vol 2, Lyon, IARC, 1987, pp 45–6). This analysis allowed us to estimate the relative risk of exposure for ALL and CML divided by that for AML from case data only and, hence, to compare the effects of exposure on ALL and CML to that on AML.

Proportional incidence analyses

We presented estimated ratios of relative risks (RRRs) by exposure category and period in the table accompanying our previous *Update* article. For ALL and CML, the ratios were significantly greater than 1 during early periods even in the lowest exposure category, 1–49 mGy, which had a mean dose of 16 mGy. On the presumption that low-dose radiation does not produce a deficit of AML risk, we suggested that "kerma values less than 50 mGy and probably as low as 16 mGy apparently produced excesses of ALL and CML." The RRR estimates on which this suggestion was based were derived from a complex modeling of observed proportions of ALL, CML, OTHER, and AML among the 413 reclassified leukemia cases with DS86 estimates. It is instructive to consider the issue of low-dose effects using a simplified, model-free, proportional incidence analysis. In this simplified analysis, I used data before 1970 because there is a clear exposure-level-by-time interaction effect on excess incidence. The effects of exposure were much greater in the early period than later. After 1970 the dose response was relatively weak.

Two hundred ninety-one of the 413 cases available for analysis occurred before 1970. Of these, 132 had shielded kerma estimates of 0, and 23 had estimates between 1 and 49 mGy. The distributions of these into ALL, CML, and AML subtypes were 12 (9%), 17 (13%), and 70 (53%) and 5 (22%), 8 (35%), and 9 (39%), respectively. The percentage of ALL more than doubled from no dose to low dose, whereas that of CML nearly tripled. Corresponding drops in the percentages of AML from 53% to 39% and OTHER, including cases of ATL in Nagasaki, from 25% to 4% were observed. The relative risk of ALL, for example, divided by that of AML for the low-dose category is estimated by the generalized odds ratio (5 + 9) + (12 + 70) = 3.24 (see RERF TR 9-91, Appendix, for details). An approximate 95% lower bound is 1.14. Similarly, the estimated RRR for CML relative to AML for this exposure category is (8 + 9) + (17 + 70) = 3.66 with a 95% lower bound of 1.23. These results provide indirect evidence that there was an excess relative risk of ALL and CML among survivors exposed to less than 50 mGy.

Potential biases

It should be noted that proportional incidence analyses such as that described above can be seriously biased by differential exclusion of leukemia types in case ascertainment. In this analysis, for example, such biases would be present if cases of ALL and CML, but not AML, among exposed survivors were more likely to enter the leukemia registry than among those in the 0 shielded kerma group. This is not likely as the registry is believed to contain the vast majority of all leukemia cases that occurred in Hiroshima and Nagasaki after the bombings, whether exposed or not. Such a bias would also exist if the effect of exposure on the distribution of reclassified cases into the four leukemia types were different than the effect on cases that could not be reclassified—that is, if there were an exposure-dependent selection bias in reclassification. A statistical analysis, however, showed that the effect of exposure category on the distribution of reclassified cases was not significantly different than that on the distribution of cases that were not reclassified. Thus, there is no apparent source of bias in our proportional incidence analysis results. Nevertheless, these results alone should not be viewed as definitive as they provide only indirect evidence for a low-dose radiation effect. They should be viewed, instead, as hypothesis-generating results to be tested with cohort data.

The matter of threshold: analyses of LSS cohort data

Subsequent to our previous *Update* article, I performed analyses of LSS cohort data to assess the issue of low-dose effects on leukemia incidence. Results were consistent with our earlier suggestion of a low-dose effect.

The essential question is whether there is a threshold dose below which ionizing radiation has no leukemogenic

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Low-dose Leukemogenic Effects

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effect. In this regard, it is interesting to note that the relative risk of all leukemias, due to low-dose exposure (1–49 mGy), calculated from raw incidence rates from pre-1970 LSS data, is 0.99. The corresponding relative risk for ALL is 2.64 and that for CML is 2.22. For AML and OTHER, these raw relative risks were 0.91 and 0.61, respectively. Thus, simple statistics calculated from LSS cohort data are consistent with the suggestion from "case only" data that there may be a threshold for AML and OTHER but not for CML and ALL.

To address the question of a threshold dose for AML more thoroughly, using the 83 primary AMLs that occurred in the LSS in Hiroshima or Nagasaki between 1950 and 1980, I fit a segmented linear model for excess rates with a break at 500 mGy, allowing both slopes to be modified by age ATB, time, and age ATB by time. This model was then reduced to a threshold model with a threshold at 500 mGy with no significant increase in deviance ($p > .15$). Thus, there is no evidence against a threshold dose of 500 mGy for AML. To the contrary, the threshold model fit the data better than the best-fitting linear-quadratic model, which was concave. Estimated incidence rates from the threshold model were 2.71, 2.67, 2.78, 8.70, and 35.96 for exposure categories 0, 1–49, 50–499, 500–1,499, and ≥1,500, respectively. Corresponding raw incidence rates were 2.91, 2.64, 2.57, 9.76, and 31.96, based on 25, 17, 13, 13, and 15 cases, respectively.

It is difficult to adequately assess the threshold issue for ALL and CML separately because of the small number of cases in the LSS. Thus, ALL and CML were combined to address this question. All primary CMLs and ALLs observed in the LSS in Hiroshima and Nagasaki between 1950 and 1980 ($n = 85$) were used for model fitting. First, a linear model including DS86 shielded kerma with a threshold at 50 mGy and dose-effect modifiers city, sex, age ATB, and time since exposure was fit. Then a term involving the logarithm of shielded kerma was added to allow a convex dose response in the low-dose range. The convex model provided a nearly significantly better fit than the threshold model ($p = .056$) suggesting no threshold.

Based on this nonlinear model, incidence estimates in the 0, 1–49, 50–499, 500–1,499, and ≥1,500 exposure categories were 1.25, 2.09, 4.75, 13.69, and 39.79, respectively. The corresponding estimates from a purely linear model were 1.57, 1.85, 4.48, 13.47, and 44.75. Raw incidence rates for these exposure categories were 1.40, 2.02, 4.16, 13.51, and 44.75, based on 12, 13, 21, 18, and 21 cases, respectively. Relative risk estimates for the 1–49 mGy exposure category from raw data, from the linear-logarithmic model, and from the linear model were 1.44, 1.67, and 1.18, respectively.

Raw incidence rates before 1970 were 0.81, 1.96, 4.70, 16.67, and 53.03 for the five exposure categories, respectively. Corresponding estimates from the linear and linear-logrithmic models were 1.10, 1.44, 4.73, 16.44, and 51.69, and 0.86, 1.68, 4.83, 16.48, and 50.71, respectively. Thus, pre-1970 relative risk estimates for the 1–49 mGy exposure category from raw incidence, from linear-logarithmic model estimates, and from linear model estimates were 2.42, 1.95, and 1.31, respectively.

Results from the linear-logarithmic model analysis of CML-ALL incidence presented above must be viewed with some caution as they were obtained from analyses to test hypotheses generated by our proportional incidence analysis of an overlapping data set. Thus, whether these results can be generalized is far from certain as they could be sample specific. A linear model is less likely to produce sample-specific incidence and relative risk estimates and, hence, seems to be the best suited for application to practical issues. Thus, estimated incidence rates for the 0 and 1–49 mGy exposure categories that were derived from the linear model including terms for city, sex, age ATB, and time-since-exposure effects in addition to DS86 shielded kerma are presented by period and exposure category in the table. At the very least, these results suggest interesting hypotheses to be tested in other cohorts.

Recommendations and summary

When checking for low-dose effects, investigators should focus on ALL and CML. Furthermore, if sample sizes are too small to allow reliable estimation of dose by time interactions, then such investigations should also focus on a period when excess rates are expected to be high. Inclusion of times after most of the excess has already disappeared may obscure the effect by introducing data on which exposure level has little or no effect.

In summary, both reclassified cases and the LSS cohort data suggest that there was an A-bomb radiation-induced excess of CML and ALL at very low exposures. The linear model with no threshold that produced estimates in the table seems appropriate for practical use. In contrast, both data sets are consistent with a threshold at about 500 mGy for AML. Similar hypotheses should be tested in other cohort studies. ❑

Editor's note: This topic will be discussed in greater detail in an upcoming RERF report.

Low-dose incidence (cases per 100,000 person-years) and relative risk estimates from Life Span Study cohort data for chronic myeloid leukemia and acute lymphocytic leukemia combined.

Source of estimate	Shielded kerma (mGy)		Period							
			1950–55	1956–60	1961–65	1966–70	1971–75	1976–80	Pre-1970	Overall
Raw data	0	Cases	0	1	0	4	4	3	5	12
		Incidence	0.00	0.64	0.00	2.91	3.14	2.56	0.81	1.40
	1–49	Cases	0	4	1	4	3	1	9	13
		Incidence	0.00	3.42	0.91	3.90	3.14	1.13	1.96	2.02
		Relative risk	–	5.34	∞	1.34	1.00	0.44	2.42	1.44
Linear model	0	Incidence	0.64	0.91	1.26	1.73	2.37	3.19	1.10	1.57
	1–49	Incidence	1.32	1.23	1.44	1.85	2.45	3.30	1.44	1.85
		Relative risk	2.06	1.35	1.14	1.07	1.03	1.03	1.31	1.18

J. TAKAYAMA

✓ Ten Years of Leadership Fêted

On 17 December, 190 community leaders, professional colleagues, and RERF staff members gathered to honor Itsuzo Shigematsu, who is beginning his 11th year as RERF chairman. Shown ceremonially cracking open the banquet's cask of rice wine are, from left, RERF Chief of Research James Trosko; Toshinaga Sakai, Labor Union of Autonomous Government Employees; Shigematsu and his wife, Yoshie; Hiroshima Deputy Mayor Takayoshi Fukushima; and RERF Consultant Emeritus Iwao Yasuda.

related to radiation research and medicine, the local philanthropic group known as HICARE, whose president is RERF Chairman **Itsuzo Shigematsu**, sponsored the following training opportunities or consultative trips abroad:

✈RERF Research Scientists Join Medical Team Dispatched Overseas

Kazuo Neriishi, RERF Division of Medicine chief; **Toshio Seyama**, RERF Department of Radiobiology; and **Yukiko Shimizu**, RERF Department of Epidemiology, participated with other scientists from Hiroshima in a 10-day mission to the republics of Russia, Ukraine, and Belarus, where the late effects of radiation exposure resulting from the Chernobyl nuclear power plant accident are continuing to be studied. Health examination systems and the incidence of cancer and leukemia in the areas were reviewed at research institutes in Moscow, Kiev, and Minsk.

✈Geriatric Physician Trains Locally

Dean Norman, clinical director of geriatric research education at the West Los Angeles Veterans Administration Medical Center, spent most of the month of February at facilities in Hiroshima, including RERF. Focusing on the effect of aging and environmental stress on immunotoxicology and infectious diseases, Norman hopes to participate in A-bomb survivor health care upon his return to the United States.

✓ Research Staff News

Hiroshima

Department of Epidemiology: **Thanne P. Rose** joined RERF to study multiple primary tumors and benign tumors among the members of the Life Span Study. She comes to RERF from the University of California–Los Angeles Cancer Center.

Research Information Center: **Robert L. Allen** has joined the Information Systems Laboratory to help implement the development of data bases on Sun workstations. He was previously employed by Contel Corporation, where he was a data base administrator for 7 years.

Department of Statistics: Research scientist **Michael Væth** of Denmark has returned to RERF for his second 2-year stay. An associate professor of biostatistics at the Århus University Medical School, he will participate in ongoing statistical analyses of RERF's cancer mortality and cancer incidence data.

Department of Radiobiology: Research scientist **Seishi Kyoizumi** has returned to the Laboratory of Immunology after a 2-year extended sabbatical at

continued on next page

✓ A-bomb Materials Committee Visits US

At the request of the Japanese Ministry of Health and Welfare (JMHW), a five-person delegation recently visited the United States to evaluate the existence and availability of documents and other materials related to the atomic bomb explosions and their effects. The delegation consisted of **Atsushi Kuramoto** (Hiroshima University), **Yutaka Okumura** (Nagasaki University), **Yutaka Hasegawa** and **J. W. Thiessen** (RERF), and **Akitsugu Yamamoto** (JMHW). They visited the Armed Forces Institute of Pathology, the National Archives, the National Academy of Sciences, the Smithsonian Institution, and the US Department of Energy in Washington, DC, and the Texas Medical Center Library in Houston.

This effort is part of the activities to plan for an (as yet unnamed) international documentation and information center as part of the 50th anniversary of the atomic bomb explosions in Japan. Future follow-up visits and first visits to other institutions in the US are being planned.

J. W. THIESSEN

The Japanese delegation (standing, from left, Yamamoto, Kuramoto, Okumura, and Hasegawa) with Sarah Heald and Stanley Goldberg, Smithsonian Department of History of Science and Technology.

F_1 Mortality and Cancer Incidence Data Released on Disk

Mortality and cancer incidence data for the RERF F_1 mortality sample are now available on high-density 3.5- or 5.25-inch floppy disks (MS-DOS-formatted) for users outside RERF. The disk contains the following three files: F_1 mortality data for 1946–85, F_1 cancer incidence data for ages <20 years at diagnosis for 1946–82, and descriptions of the data and file format including disease groupings with ICD codes.

The population consists of 67,586 subjects who are offspring of atomic bomb survivors having assigned DS86 doses. This population is identical to that used in the analysis described by Y. Yoshimoto et al (*Radiat Res* 32:327–51, 1991). The mortality data cover the period from 1 May 1946 through 31 December 1985, classified by 11 major causes of death as presented in Y. Yoshimoto et al (RERF TR 1-91). The cancer incidence data covering the period from 1 May 1946 through 31 December 1982 include leukemia and cancer with different degrees of presumed heritability as reported by Y. Yoshimoto et al (RERF TR 4-90; *Am J Hum Genet* 46:1041–52, 1990).

The disk contains two separate data sets, one organized by conjoint parental gonadal dose groups and the other by both paternal and maternal gonadal dose groups. Parental gonadal doses are based on calculations in sievert with an RBE of 20 for neutrons, and mean doses—conjoint, paternal, and maternal—are provided in millisievert.

Each record in the main files contains data for a single cell in a cross-tabulation over city, sex, year of birth, parental gonadal dose (conjoint, paternal, and maternal), and attained age. For each cell, data are provided on person-years (for both mortality and cancer incidence analysis), and mean number of years between the atomic bombings and birth, as well as parental mean dose, number of deaths, and number of incident cancer cases.

All fields are separated by at least one blank so that the file can be easily read by any program able to read blank-delimited ASCII files. FORTRAN formats also can be used.

Persons interested in obtaining a copy of this data set on disk should contact the RERF Publication and Documentation Center, 5-2 Hijiyama Park, Minami-ku, Hiroshima, 732 Japan (facsimile: 81-82-263-7279). The cost per disk is US$50. Please specify the type of disk desired. ❑

News Briefs

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Systemix Inc, Palo Alto, Calif, where he further refined a way to study the differentiation of human hemopoietic stem cells by transplanting these cells into severe combined immunodeficient mice.

Research scientist **Keisuke S. Iwamoto** has begun a 2-year stay in the Laboratory of Cell Biology, where he will study the molecular mechanism of radiation carcinogenesis as it relates to tumor suppressor genes. He comes to the Foundation from Prof. **Amos Norman**'s lab at the Laboratory of Biomedical and Environmental Sciences at the University of California–Los Angeles.

PHOTO COURTESY OF US EMBASSY

✓ RERF Directors Meet US Secretary of Energy

From left, RERF Chairman Itsuzo Shigematsu and RERF Vice Chairman J. W. Thiessen are introduced to US Secretary of Energy Admiral James D. Watkins, USN (ret), by US Department of Energy principal representative Milton Eaton of the US Embassy. In the background overseeing the introductions is US Ambassador to Japan Michael H. Armacost, who hosted a reception for Watkins during his visit to Tokyo in December.

Publication and Documentation Center: **Jeanette Nakada** has joined the Editorial and Publications Section as an English editor, specializing in the development of desktop publishing applications in English and Japanese. She formerly worked for Aspen Publishers, Inc, of Gaithersburg, Md, as a newsletter and journal editor.

Robert Masterson has also joined the Editorial and Publications Section as an English editor. He comes to RERF from Lawrence Berkeley Laboratory, where he had been a supervisor and senior writer/editor.

✓ Highlights of the RERF Lecture Program

Takashi Sugimura's lecture on the multiple steps of carcinogenesis and their impact on cancer prevention—which had been scheduled for December—was delivered on 27 January. He is the former president of the National Cancer Center, Tokyo.

On 28 January, **Wei Lüxin**, Ministry of Public Health, Beijing, discussed the epidemiological studies of a high background radiation area in Yangjiang, People's Republic of China.

Suzanne Ho, Chinese University of Hong Kong, spoke about the epidemiology of aging in Hong Kong on 4 February.

On 16 March, **Geoffrey R. Howe**, National Cancer Institute of Canada, spoke about the use of fluoroscopy in Canada.

On 15 April, **Jolyon H. Hendry**, Christie Hospital, Manchester, UK, spoke about cellular repair after high- and low-LET irradiations. ❑

Facts & Figures

A Look at Estimated Relative Risks

The conventional summary estimates of the estimated relative risk (ERR) included in many RERF reports are often viewed as providing a general purpose summary of radiation risk. These statistics are regression estimates based on a model which does not allow for the effects of sex or other factors which affect the ERR.

Although these values do provide a useful, simple summary of the risk, it is important to recognize that the estimation procedure gives relatively more weight to the experience of older survivors because they account for a high proportion of the deaths. Table 1 contrasts the conventional estimates for the Life Span Study (LSS) 1958–87 cancer incidence data for selected organ systems with those computed by 1) weighting age ATB-specific risk estimates with the cohort age-ATB distribution and 2) weighting age-ATB and sex-specific risks with the cohort age-ATB and sex distribution. Table 2 describes the age-ATB and sex distribution of the LSS in 1958. Table 3 contains the age-ATB and sex-specific risk estimates used in computing the averages in Table 1. As this example illustrates, the use of weights that reflect the actual composition of the cohort can lead to fairly substantial changes in the risk estimates. Because of the unusual sex and age distribution in the LSS, use of weights which reflect other populations of interest lead to further changes in the estimates. For example, if one uses weights based upon the sex and age distribution of the 1985 Japanese population shown in Table 2, the age-ATB and sex-adjusted rates for the sites considered here are 0.5, 1.2, 1.6, and 2.7. ❑

Table 1. Average estimated relative risks at 1 Gy computed using different methods

Type of estimate	Digestive system	Respiratory system	Urinary tract	Thyroid
Conventional	0.39	0.81	1.21	2.04
Age ATB-adjusted	0.52	0.79	1.42	2.70
Age ATB- and sex-adjusted	0.61	1.43	1.87	3.70

Table 2. Population distributions

Age-ATB categories (yr)	Life Span Study, 1958		Japan, 1985	
	Men	Women	Men	Women
0–19	0.19	0.22	0.15	0.14
20–39	0.08	0.22	0.15	0.15
≥40	0.12	0.17	0.19	0.22

Table 3. Estimates of age-ATB and sex-specific relative risks at 1 Gy

Age-ATB categories (yr)	Digestive system			Respiratory system			Urinary tract			Thyroid		
	Men	Women	Both sexes	Men	Women	Both sexes	Men	Women	Both sexes	Men	Women	Both sexes
0–19	0.53	1.35	0.79	0.19	3.14	0.73	1.46	1.70	1.56	11.97	5.04	5.84
20–29	0.39	0.51	0.45	0.48	1.47	0.91	1.06	3.48	1.86	0.00	1.31	1.02
≥40	0.11	0.32	0.19	0.41	1.74	0.76	0.25	1.98	0.76	0.00	0.16	0.00
All ages	0.32	0.66	0.39	0.36	2.05	0.81	0.86	2.34	1.21	3.61	1.84	2.04

Never-ending Debate

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sues, apart from the need to explain more fully why there is biological plausibility for either a threshold, or no threshold, or for either depending on cancer type. More importantly, if it is true that there are at least two different types of dose response, what is the explanation of this from a mechanistic point of view?

Both **V. P. Bond** and **James E. Trosko** in their articles in this issue of *Update* address the matter of threshold, one directly, the other implicitly. Bond argues that, from a collective-dose point of view, there is a minimum energy requirement for the production of one cancer, which he estimates to be on the order of 3 kilojoule or 50 person · gray. This amount of energy effectively represents a threshold value, it being impossible to have a fraction of a cancer. Trosko analyses the mechanics of carcinogenesis, in which radiation, according to him—particularly at low doses—plays only a small part, making it necessary for other nonradiation-related factors to play theirs in order to produce a cancer. In addition, he mentions a few of the processes involved in gene expression, some of which, I add, may well be nonlinear and with a threshold (even though mutagenesis per se may be a nonthreshold phenomenon).

If I have a problem with Bond's approach, it is not with his logic but with the interrelationship between his line of reasoning and Trosko's, or, in other words, with the biological substrate to which Bond's argument applies. Do both say the same thing in different words? If so, it seems to me that it needs to be retold in a common language, before widespread acceptance of a "real" threshold is to be expected, assuming (probably naively) that such judgments are made on scientific grounds only. One thing stands out after reading Bond's and Trosko's articles: both appear to agree that it is impossible to quantify the attributable risk from radiation exposure in any individual case. Is this, in effect, the death blow to the "probability of causation" concept?

In the Winter 1990–91 issue of *Update*, I argued that the shape of the dose-response curve at low doses may well be found in the RERF data sets as these develop over the years. The newest data on cancer incidence, and the results of ongoing special studies on individual cancer types (such as the one discussed by Carter) provide us, indeed, with important insights and shed light on the old question: "Threshold...or not?" ❑

Recent Scientific Publications

Editor's note: The reports listed have been approved, and will be distributed as soon as they are printed.

Approved Technical Reports

Joint analysis of site-specific cancer risks for the atomic bomb survivors. DA Pierce, DL Preston. RERF TR 17-91.

Statistical methods are presented for joint analysis of site-specific cancer risks for the atomic bomb survivors. Previous analyses of these data, aside from that on leukemia, have been made either without regard to cancer type or separately for types or classes of cancers. Clearly, analyses without regard to cancer type are less than satisfactory. The primary advantages of joint analysis rather than separate analyses are that (a) models can be fitted with parameters common to cancer types that can allow more precise estimation of effects of interest, (b) significance tests can be used to compare type-specific risks, and (c) a clearer understanding may be obtained of risk-modification factors such as sex, age at exposure, and time since exposure. Joint analysis is straightforward, entailing primarily the incorporation of another factor for cancer type in the usual cross-tabulation of the data for analysis. The use of these methods is illustrated in an analysis of three classes of cancer studied by the BEIR V Committee: digestive, respiratory, and other solid tumors. Based on this analysis, some criticism is made of the BEIR V-preferred models. Because the proposed methods are applicable to models for either relative or absolute risks, some comments on the use of explicit models for the absolute excess risk are also given. Although some of the gains from joint analysis are apparent from the results here, it will be important to use these methods with a more suitable choice of cancer classes and for cancer incidence data for which the diagnoses are more accurate.

Radiation-related ophthalmologic changes and aging among the atomic bomb survivors: a reanalysis. M Otake, SC Finch, K Choshi, I Takaku, H Mishima, T Takase. RERF TR 18-91.

The relationship of ionizing radiation to the age-related ophthalmologic findings of the 1978–80 ophthalmologic examination of atomic bomb (A-bomb) survivors has been reanalyzed using DS86 eye organ dose estimates. The main purpose of this reevaluation was to determine whether age and radiation exposure, as measured by the revised dosimetry information (DS86), have additive, synergistic, or antagonistic effects. The data in this study are limited to axial opacities and posterior subcapsular changes, for which a definite radiation-induced effect has been observed in the A-bomb survivors.

The best model fitting axial opacities gives a significant positive effect for both linear dose response and linear age-related regression coefficients and a significant negative effect for an interaction between radiation dose and age. Such a negative interaction implies an antagonistic effect in that the relative risks with relation to radiation exposure doses become smaller with an increase in age. The magnitudes of the log relative risks in persons 40, 50, 60, and 70 years old at the time of examination (ATE) were 8.2-, 6.4-, 4.6-, and 2.8-fold higher, respectively, than in persons age 80 ATE. The relative risks for axial opacities in persons 40 years old ATE were 1.5/1 Sv, 2.3/2 Sv, 3.4/3 Sv, and 7.8/5 Sv, but the risks in persons 80 years old ATE were 1.0, 1.1, 1.2, and 1.3, respectively. This phenomenon suggests that the lenses of younger persons are more sensitive to radiation than are those of older persons. On the other hand, the best fitting relationship for posterior subcapsular changes suggested a linear-quadratic dose response and a linear age-related effect. The quadratic estimate of radiation dose squared showed a highly significant effect with a negative trend, but the negative quadratic estimate had almost no contributive value within an appropriative dose area because it was extremely small. These data suggest an additive relationship between aging and radiation for the induction of posterior subcapsular changes, and they also indicate that there is no distinct evidence of a radiation-induced aging effect. The radiation-related relative risks increase with a log linearity, as 1.7/1 Sv, 3.0/2 Sv, 5.1/3 Sv, and 14.3/5 Sv. The relative risks for axial opacities and posterior subcapsular changes based on an assumed threshold of 1.5 Sv are briefly described in the Discussion.

Decreased visual acuity and accommodation with increasing age were comparable in both exposed and control subjects, with the age-related decrease in visual acuity being greater than that of accommodation.

Adult Health Study Report 7: radiation effects in noncancer disease incidence, Hiroshima and Nagasaki, 1958–86 (cycles 1–14). FL Wong, M Yamada, H Sasaki, K Kodama, S Akiba, K Shimaoka, Y Hosoda. RERF TR 1-92.

Using the longitudinal data of the Adult Health Study (AHS) cohort collected during 1958–86, we examined the relationship between exposure to ionizing radiation and the incidence of 24 selected nonmalignant disorders. Cases were ascertained through the three-digit International Classification of Diseases codes contained in the AHS subjects' data base. The most appropriate organ dose from the DS86 dosimetry system was used. Since the exact disease onset time could not be determined without a review of patient charts, the midpoint between the date of the exam when the disease was diagnosed and the date of the previous disease-free exam was used as an estimate for each subject. A significant dose-response relationship was detected for hypothyroidism, chronic lymphocytic thyroiditis, nontoxic nodular goiter, chronic hepatitis and liver cirrhosis, and myoma uteri. Suggestive evidence was obtained for thyrotoxicosis. An inverse relationship with radiation exposure dose was also observed for glaucoma. The evidence of radiation effects detected in chronic lymphocytic thyroiditis is questionable because of the presence of a city effect indicating a lack of dose response in Nagasaki. This is most likely due to differences in the diagnostic procedures between the cities and not to the quality of radiation. Dose-response relationships were not detected for stroke or for coronary heart disease. Although an increased incidence of cataract was detected in the first decade of the AHS program among those exposed at an early age, further investigation suggests that the results are more likely due to incomplete removal of prevalent cases diagnosed before the beginning of the AHS follow-up. It is hoped that the results provided in this report will call attention to disorders that merit further detailed investigations so that current findings may be confirmed or disproved.

M-proteinemia in atomic bomb survivors. K Neriishi, Y Yoshimoto, RL Carter, T Matsuo, M Ichimaru, M Mikami, T Abe, K Fujimura, A Kuramoto. RERF TR 2-92.

An analysis was conducted of monoclonal gammopathy (M-proteinemia) in relation to atomic bomb (A-bomb) radiation exposure of members of the Adult Health Study (AHS) in Hiroshima and Nagasaki examined between October 1979 and September 1981 and between June 1985 and May 1987. Thirty-one cases of M-proteinemia were detected among 8,796 subjects (mean age = 58.3 years) studied in the first survey, whereas 68 cases were found among 7,350 subjects in the second survey (mean age = 61.9 years). M-proteinemia is a pathologic state of immunoglobulin overproduction from plasma cells, and the clinical course of the disease is not well known. Among the 31 cases of M-proteinemia found in the first survey, 9 individuals (29%) died before the second survey due to multiple myeloma (2), lung cancer (1), colon cancer (1), myocardial infarction (2), heart failure (1), cerebral bleeding (1), and pneumonia (1). Among 8 individuals with benign monoclonal gammopathy (BMG) who had been examined in both surveys, 4 developed suppression of residual immunoglobulin(s), suggesting the progression of M-proteinemia.

Recent Scientific Publications

The overall relative risks of M-proteinemia in A-bomb survivors in the two surveys were not significantly increased with increasing radiation dose. Only BMG in 1985–87 showed a suggestive increase with radiation exposure. The relative risk of BMG in 1985–87 was 2.64 in the group exposed to 0.01–0.49 Gy and 2.14 in the ≥0.50 Gy group (95% confidence intervals = 0.90–8.82 and 0.69–7.31, respectively).

Further observation is required because most A-bomb survivors are now reaching the age of highest risk for M-proteinemia.

Approved Research Protocols

Evaluation of radiation doses of atomic bomb survivors in Hiroshima using tooth samples. Part 2: Measurements using electron spin resonance. N Nakamura, M Iwasaki, K Niwa, C Miyazawa, S Sawada, Y Kodama, AA Awa, S Umeki, Y Kusunoki, S Fujita, M Akiyama. **RERF RP 1-92.**

It is now possible to quantitatively measure gamma-ray doses recorded in the enamel of human teeth using electron spin resonance. In the present study, we propose to use this technique to estimate the radiation doses of atomic bomb survivors in Hiroshima using teeth collected as part of RP 10-86. In addition, chromosome abberation frequencies in lymphocytes and mutant red blood cell frequencies will be measured for the tooth donors.

Studies on ovarian tumor incidence among the RERF Extended Life Span Study cohort, 1950–87. Shoji Tokuoka, Kioko Kawai, K Inai, Y Shimizu, E Nakashima, M Tokunaga, M Soda, K Mabuchi, CE Land. **RERF RP 2-92.**

In general, reports concerning the risk of development of ovarian tumors due to exposure to radiation are few. However, a significant increase in mortality from ovarian cancer with increasing dose was found among females in the RERF Extended Life Span Study (LSS) cohort during 1950–85, and the latest incidence data also demonstrated a significant dose response for ovarian cancer incidence in the same population.

The proposed study will assess, under the RERF guidelines for the conduct of site-specific cancer incidence studies, risks of malignant and benign ovarian tumors in females of the extended LSS cohort and examine the shape of the dose-response curve, the effect of such modifiers as city, age at the time of bombings, attained age, time after exposure and histological subtype, upon extending the study period through 1987 and identifying more cases. Basically, tumor cases will be identified from the autopsy records, surgical pathology records, and death certificates maintained at RERF, as well as from the tumor and tissue registries of Hiroshima and Nagasaki. Consideration will also be given to detecting and collecting cases from the autopsy and surgical pathology records maintained at major medical organizations in both cities.

Approved Commentary and Review

Correcting for catchment area nonresidency in tumor registry-based cohort studies. R Sposto, DL Preston. **RERF CR 1-92.**

We discuss the effect of catchment area nonresidency on estimates of cancer incidence from a tumor-registry-based cohort study and demonstrate that a relatively simple correction is possible in the context of Poisson regression analysis if individual residency histories or the probabilities of residency are known. A comparison of a complete data maximum likelihood analysis with several Poisson regression analyses demonstrates the adequacy of the simple correction in a large simulated data set. We compare analyses of stomach cancer incidence from the Radiation Effects Research Foundation tumor registry with and without the correction. We also discuss some implications of including cases identified only on the basis of death certificates.

Publications in the Open Literature

Following is a partial listing of the papers included in the Volume 32 supplement of the Journal of Radiation Research (March 1991). The rest of the contents was listed in the preceding issue (RERF Update 3[4]:16, 1991).

Somatic cell mutations in atomic bomb survivors. M Akiyama, N Nakamura, M Hakoda, S Kyoizumi, J Kushiro, Y Hirai, Y Kusunoki. *J Radiat Res* (Tokyo) 32S:278–82, 1991.

Radiation cataract. M Otake, WJ Schull. *J Radiat Res* (Tokyo) 32S:283–93, 1991.

Mortality and cancer risk among the offspring (F_1) of atomic bomb survivors. Y Yoshimoto, K Mabuchi. *J Radiat Res* (Tokyo) 32S:294–300, 1991.

Overview of immunological studies on A-bomb survivors. M Akiyama, Y Kusunoki, S Kyoizumi. *J Radiat Res* (Tokyo) 32S:301–9, 1991.

Aging. H Sasaki, K Kodama, M Yamada. *J Radiat Res* (Tokyo) 32S:310–26, 1991.

Current summary of lymphocyte survival study. N Nakamura, M Akiyama, S Kyoizumi, Y Kusunoki. *J Radiat Res* (Tokyo) 32S:327–9, 1991.

X-ray sensitivity of fibroblast cell strains derived from atomic bomb survivors with and without breast cancer. S Ban, RB Setlow, H Ezaki, T Hiraoka, M Yamane, M Nishiki, K Dohi. *J Radiat Res* (Tokyo) 32S:330–8, 1991. (RERF TR 6-90)

Interactive effects between radiation and other factors on cancer risk among A-bomb survivors—an overview of RERF studies. S Akiba. *J Radiat Res* (Tokyo) 32S:339–46, 1991.

The children of parents exposed to atomic bombs: estimates of the genetic doubling dose of radiation for humans. JV Neel, WJ Schull, AA Awa, C Satoh, H Kato, M Otake, Y Yoshimoto. *J Radiat Res* (Tokyo) 32S:347–74, 1991.

Future research in epidemiology and statistics at RERF. K Mabuchi, DL Preston. *J Radiat Res* (Tokyo) 32S:375–77, 1991.

Biochemical genetics study. C Satoh. *J Radiat Res* (Tokyo) 32S:378–84, 1991.

Future studies of the prenatally exposed survivors. WJ Schull, M Otake. *J Radiat Res* (Tokyo) 32S:385–93, 1991.

Future perspective of radiobiological studies. M Akiyama, N Nakamura. *J Radiat Res* (Tokyo) 32S:394, 1991.

A review of forty-five years' study of Hiroshima and Nagasaki atomic bomb survivors. Summary and conclusions. S Abrahamson. *J Radiat Res* (Tokyo) 32S:395–412, 1991.

Biological effectiveness of neutrons from Hiroshima bomb replica: results of a collaborative

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Recent Scientific Publications

cytogenetic study. RL Dobson, T Straume, AV Carrano, JL Minkler, LL Deaven, LG Littlefield, AA Awa. *Radiat Res* 128:143–9, 1991.

Editor's note: Other articles in the scientific literature follow:

Evaluation of four somatic mutation assays for biological dosimetry of radiation-exposed people including atomic bomb survivors. N Nakamura, S Umeki, Y Hirai, S Kyoizumi, J Kushiro, Y Kusunoki, M Akiyama. In: *New Horizons in Biological Dosimetry.* New York, Wiley-Liss, 1991. pp 341–50.

Frequency of mutant T lymphocytes defective in the expression of the T-cell antigen receptor gene among radiation-exposed people. S Kyoizumi, S Umeki, M Akiyama, Y Hirai, Y Kusunoki, N Nakamura, K Endoh, J Konishi, MS Sasaki, T Mori, S Fujita, JB Cologne. *Mutat Res* 265:173–80, 1992. (RERF TR 10-90)

An estimate of the magnitude of random errors in the DS86 dosimetry from data on chromosome aberrations and severe epilation. R Sposto, DO Stram, AA Awa. *Radiat Res* 128:157–69, 1991. (RERF TR 7-90)

Flow cytometric measurements of somatic cell mutations in Thorotrast patients. S Umeki, S Kyoizumi, Y Kusunoki, N Nakamura, MS Sasaki, T Mori, Y Ishikawa, JB Cologne, M Akiyama. *Jpn J Cancer Res* 82:1349–53, 1991. (RERF TR 16-91)

Calibration of $Mg_2SiO_4(Tb)$ thermoluminescent dosimeters for use in determining diagnostic x-ray doses to Adult Health Study participants. K Kato, S Antoku, S Sawada, WJ Russell. *Am Assoc Phys Med* 18:928–33, 1991. (RERF TR 11-89) ❑

International Oral Presentations

The 8th International Congress of Human Genetics, Washington, DC, 6–11 October 1991.

- *Detection of reverse mutation from HP*2 to HP*1 in human somatic and sperm cells using PCR.* J Asakawa, N Nakamura, M Kodaira, C Satoh.
- *Characterization of genes encoding phosphoglycerate kinase 1 (PGK1) variants in children of atomic bomb survivors.* C Satoh, J Asakawa, N Takahashi, K Hiyama.
- *Denaturing gradient gel electrophoresis of PCR-amplified DNA fragments for detection of variation in DNA.* N Takahashi, C Satoh, J Asakawa, M Kodaira, K Hiyama.

International Conference on Osteoporosis, Kobe, Japan, 5–7 November 1991

- *Vertebral fracture prevalence is lower among Japanese in Hawaii compared to Japan and American Caucasians.* S Fujiwara, LJ Melton, PD Ross, JW Davis, YK Yhee, RS Epstein, K Kodama, RD Wasnich.

Cellular Responses to Environmental DNA Damage, Banff, Canada, 1–6 December 1991

- *Host variation in radiosensitivity among A-bomb survivors.* S Ban, JB Cologne.

Japanese–German Joint Workshop on Thorotrast Late Effects, Tokyo, 11 January 1992

- *Flow-cytometric measurements of somatic cell mutations in Thorotrast patients.* M Akiyama.

International Conference on Radiation Effects and Protection, Mito, Japan, 18–20 March 1992

- *Detection of radiation-induced translocations in A-bomb survivors using the fluorescence in situ hybridization (FISH) method. Results of a collaborative study.* AA Awa, Y Kodama, M Nakano, K Ohtaki, JN Lucas, JW Gray.
- *Somatic mutation at the TCR loci as a biological dosimeter of radiation-exposed people.* S Umeki, Y Kusunoki, K Endoh, K Ohama, T Kodama, M Yamakido, M Akiyama.
- *BCR-ABL fusion genes are inducible by X-irradiation in vitro.* T Ito, T Seyama, T Mizuno, T Hayashi, K Kohi, N Nakamura, M Akiyama.
- *Health risks of atomic bomb survivors: the experiences of those exposed in utero or early in childhood.* Y Yoshimoto, M Soda, K Mabuchi.
- *Leukemia incidence in the atomic bomb survivor Life Span Study, 1950–87.* D Preston.

Radiation and Society Symposium, San Francisco, 5–10 April 1992

- *Studies of children in utero during atomic bomb detonations.* Y Yoshimoto, M Soda, WJ Schull, K Mabuchi.

The XIth International Conference on Calcium Regulating Hormones, Florence, Italy, 24–29 April 1992

- *Effect of radiation exposure on calcium metabolism.* S Fujiwara, R Sposto, M Shiraki, N Yokoyama, H Sasaki, K Kodama, Y Hosoda. ❑

RERF update RERF

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Editorial Staff:
Editor-in-chief: J. W. Thiessen
Managing editor: Beth Magura
Assistant editor: Michael Edington
Production asst: Fumie Maruyama
Photographer: Junso Takayama

Mailing Address:
RERF Update
5-2 Hijiyama Park
Minami-ku, Hiroshima
732 Japan

Facsimile: 81-82-263-7279