RERF update RERF

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

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Funding Agencies Commission Review Panel

As endorsed by RERF's Scientific Council and Board of Directors, in October 1995 the Foundation's funding agencies—the Japanese Ministry of Health and Welfare (MHW) and the US Department of Energy (DOE)—appointed a review committee consisting of internationally prominent experts in the field of radiation research to seek recommendations regarding RERF's research directions for the next 2 decades.

The nine-member group met at the Hiroshima Laboratory, 5–7 February, and at the Nagasaki Laboratory on 8 February. This so-called Blue Ribbon Panel heard overviews presented by RERF's research and support departments, after which informal discussions with researchers followed.

The committee met a second time in May at the National Radiological Protection Board (NRPB) headquarters in the United Kingdom.

On 2 July, the NRPB's Roger H Clarke, chairman of the Blue Ribbon Panel, presented its recommendations regarding the future of RERF's research program. He addressed MHW and DOE representatives and the RERF directors and research staff in separate sessions held at the Hiroshima Laboratory.

The full Blue Ribbon Panel report, *Review of the Radiation Effects Research Foundation*, written in English, has been posted on the World Wide Web (WWW) by the DOE at http://www.eh.doe.gov/ihp/rerf. A Japanese translation is posted on the RERF WWW site at http://www.rerf.or.jp/nihongo/news/bluereco.htm. (See p 3 of this issue of *Update* for summarized conclusions and recommendations.)

Earlier review panel advice instrumental to ABCC–RERF

Two previous program reviews (also discussed on p 2), undertaken by the Francis Committee (20 October–9 November 1955) and the Crow Committee (13–21 February 1975), are credited with prospectively charting the research course still followed today.

The Francis Committee's pivotal recommendations led to the establishment of fixed study cohorts—each well defined in terms of a priori criteria independent of the effects under study and consisting of persons with widely ranging radiation exposures, characteristics that have facilitated effective intracohort comparisons. These cohorts are the Life Span Study (LSS) for mortality follow-up, the Adult Health Study (AHS) for the clinical examination program, the in utero study of those exposed during gestation, and the F_1 study of children born to exposed parents.

"The careful establishment of fixed cohorts along with the aim of limiting analyses to them rather than allowing more opportunistic gathering of data has been a cornerstone of the ABCC–RERF investigations," commented Vice Chairman William J Schull, who has participated in the studies since the late 1940s. "As a result, the difficulties inherent in observational studies have been minimized and results are accepted with a remarkable level of confidence by the scientific community."

Before ABCC's reorganization into RERF, the Crow Committee was convened to review ongoing research protocols and to assess the need for introducing new technology to monitor the possible late effects of atomic-bomb radiation on somatic and germline cells in the atomic-bomb survivors and their offspring. ❑

Commemorative Events Honor Deceased

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This year's commemorative ceremony in Nagasaki's Peace Park on 9 August was attended by an estimated 25,000 persons.

Marking the 51st anniversary of the atomic bombings, annual commemorative events in Hiroshima (6 August) and Nagasaki (9 August) attracted an estimated 75,000 persons to the cities.

Japanese Prime Minister Ryutaro Hashimoto attended the ceremonies, as did the mayors of both cities—Iccho Itoh of Nagasaki and Takashi Hiraoka of Hiroshima.

In Hiroshima, Chairman Itsuzo Shigematsu and Vice Chairman William J Schull represented RERF at the Peace Park ceremonies. In Nagasaki, Permanent Director Yutaka Hasegawa, who is director in charge of the Nagasaki Laboratory, attended on behalf of RERF.

In both cities, the times of detonation are marked by the ringing of temple and church bells and a moment of silent contemplation. ❑

In This Issue

Perspectives

Periodic Program Reviews and the Re-emergence of Past Ideas

by William J Schull, RERF Chief of Research and* Update *Editor in Chief

Since their inception in 1947 the studies of the survivors of the atomic bombings have undergone numerous reviews, but of these three have been particularly important: the evaluations of the Francis Committee in 1955, the Crow Committee in 1975, and more recently, the Blue Ribbon Panel in 1996. Each review came at a critical time in the history of the studies and of the institution charged with their implementation, and each offered perceptive recommendations.

In 1955, Thomas Francis Jr, a distinguished epidemiologist, was sent to Japan at the instigation of R Keith Cannan of the National Academy of Sciences–National Research Council (NAS–NRC) to evaluate the scientific program and to recommend changes, if these seemed warranted. Francis was accompanied by Felix E Moore, a biostatistician at the National Heart Institute, and Seymour Jablon, a member of the Veterans' Follow-up Agency of the NAS–NRC. The program they suggested, which was adopted in principle by an ad hoc conference convened by NAS in Washington in November 1955, has sustained the activities of the Atomic Bomb Casualty Commission and RERF for more than 4 decades.

Critical of what was perceived to be a lack of continuity in direction and investigative leadership, and cognizant of the need to increase programmatic stability, integration of purpose and effort, the committee recommended sweeping changes. They argued that the individual studies had to serve the whole, and this could only be done by unifying them through a focus on a common set of survivors. Accordingly, the new research strategy they proposed, termed the "Unified Central Program," included a mortality surveillance, a clinical study to assess health and morbidity, and a program of autopsies. The former two were to center upon fixed samples of survivors and suitably age-, gender-, and city-matched comparison persons, whereas the last would entail the pathological study of as many deceased individuals from the mortality sample as practical. Their recommendations had the merit of anchoring the studies on fixed samples, rather than the "open," constantly changing populations of these two cities as had previously been done. Thus, migration into and out of the cities, which plagued earlier assessments, would loom less large as a possible source of confusion or error.

To support the clinical program, they suggested establishing an epidemiological detection network to provide current information on the health status of members of the clinical study sample through a system of weekly health reports on the status of sample members or immediate notification of the Commission in the event of significant illness or death. They contended this network would serve two other purposes as well; it would yield information regarding the migration of individuals within the study groups and provide ". . .a continuing and close relationship between ABCC and the members of the study groups." These ends were to be achieved through the designation of a series of lay observers who would have under their supervision another 15 to 20 sample members, all living in the neighborhood. If a member of a group moved to another location within the city, he or she was to be assigned to the monitor in the new neighborhood.

This was a novel suggestion. First, health networks of this nature were nonexistent in Japan and rare elsewhere. However, their acceptability to the survivors was uncertain, since they could easily be seen as an intrusion on privacy. Second, the proposed network was unwittingly tantamount to recreating the neighborhood associations that had existed before and during the war and had been used by the military oligarchy to stifle dissent and to mobilize the population. These uses had led to their disbanding by the Occupation authorities. This recommendation was never implemented partly for the reasons previously advanced and partly because of concern about the quality of the information that might be obtained.

In the early 1970s, after the value of the yen was permitted to float, a budgetary crisis arose. The program's cost increased greatly, mainly due to the declining value of the dollar, imposing serious fiscal problems on the US funding source, the Energy Research and Development Agency (ERDA). To stem the costs, negotiations were begun, largely by James Liverman, to establish a larger funding and administrative role in the studies for the Japanese government, specifically the Ministry of Health and Welfare. Arrangements were made that ultimately gave rise to the present RERF, but before the new Foundation came into existence formally another committee, known as the Crow Committee after its chairman, James F Crow, a distinguished geneticist, reviewed the research program.

While this committee strongly urged continuing the studies, and ringingly endorsed specific research initiatives, such as the mortality and morbidity surveillances, it did recommend changes—some of emphasis and some more fundamental. The committee urged the Foundation to stop soliciting autopsies. Although endorsing the Adult Health Study, it recommended greater emphasis on objective laboratory determinations and the institution of cancer screening. These were seen as promoting public acceptance of the study and as a way to use personnel better. Unlike the Francis Committee, this one called attention to the need to continue the studies of mortality among the survivors' children and to begin the program in biochemical genetics that had been proposed but had not yet been implemented. The committee also recommended continuing efforts to characterize better the radiation exposures of the survivors—stemming from the atomic bombings and from medical sources. The Crow Committee also suggested that the Foundation complement its studies on humans with grants and contracts to universities and other institutions for laboratory and animal research. Only one such award was ever made, namely, to the late Terumi Mukai at the University of Kyushu. These specific recommendations were clearly seen as secondary to the ". . .overriding recommendation. . .that the basic elements of the ABCC program continue under the Foundation."

In this issue, the recommendations of the most recent external review—the first truly international one—are described in detail. Now RERF is preparing to implement these recommendations with the concurrence of its Scientific Council and the support of its funding agencies. ❑

Report of the Blue Ribbon Panel

Summary of Conclusions and Recommendations

Editor's note: On 2 July 1996, Blue Ribbon Panel Chairman Roger H Clarke presented a 54-page report, titled Review of the Radiation Effects Research Foundation. *The following summary has been extracted from this report.*

The population

The population studies at RERF are unique not only because of the type of exposure received by such large numbers of subjects, but also because the quality of the information recorded about each individual is extremely high. It seems unlikely that a comparable opportunity to study the effects of ionising radiation on health in such a detailed way will present itself in the future: and even if it does, it will take 50 years to accrue as much information as now exists at RERF.

Review of the scientific programme

Epidemiology

The data held by the Departments of Epidemiology are of enormous importance, not only for assessing the effects of radiation on health, but also for determining the influence of various lifestyle factors on health and their interactions with radiation exposure. There is currently insufficient effort available to analyse the data and present reports, and much of the potentially valuable information collected has so far not been fully utilised.

Recommendation 1. We recommend that the Departments of Epidemiology should continue to collect data on mortality and cancer incidence and that they be strengthened. The management of RERF should give these studies the highest priority in view of the size and scope of the data. In addition, research should be carried out by collaborating with epidemiologists from other institutions both in Japan and elsewhere, so that the full range of potentially valuable information already collected can be analysed.

Statistics

Highly successful work has been performed in the Department of Statistics, which is a source of great strength for the entire organisation. Its input has been essential in making the accumulated data sets the worldwide basis for the estimation of human radiation risks.

Recommendation 2. We recommend that the Department of Statistics should continue to produce analyses of the risks of radiation exposure in collaboration with the Epidemiology Departments and that the high quality of the research in the Statistics Department be maintained.

Recommendation 3. We recommend that the Department of Statistics should continue to make available basic data sets on mortality and cancer incidence for analysis by other groups. This should now be extended to making available those data sets relating to mental retardation, IQ, and related outcomes of exposure in utero.

Information technology

Efficient data management and computing are the backbones to the success of research at RERF. The Panel believes that RERF has taken the right strategic decisions with respect to computing infrastructure, and the

continued on next page

Nine Review Panel Members Hail from Six Countries

The Blue Ribbon Panel members were as follows:

Roger H Clarke, panel chairman. Director, National Radiological Protection Board, United Kingdom, and chairman, Main Commission, International Commission on Radiological Protection

Herbert L Abrams, professor, Department of Radiology, Stanford University School of Medicine, USA

Dan Beninson, chairman, Argentine National Commission on Atomic Energy, and formerly chairman, International Commission on Radiological Protection

Valerie Beral, chief, Cancer Epidemiology Unit, Imperial Cancer Research Fund, United Kingdom

Jack H Geiger, senior professor, Department of Community Health and Social Medicine, City University of New York Medical School, USA

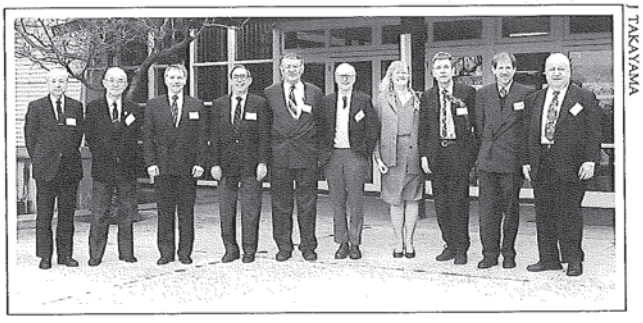
Albrecht Kellerer, director, Gesellschaft für Strahlung Forschung, Institute on Environmental and Health Research, Germany

Keith H Lokan, director, Australian Radiation Laboratory, and a member of the International Commission on Radiological Protection

Wataru Mori, president, Japanese Association of Medical Sciences, and formerly president, University of Tokyo

Tadao Shimao, president, Japan Anti-tuberculosis Association, and Japanese chairman, US–Japan Medical Cooperation Committee

Colin Muirhead, panel executive secretary, National Radiological Protection Board, United Kingdom ❑



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Members of the Blue Ribbon Panel, which met at the RERF laboratories, 5-8 February 1996 (see story on page 1): from left, Wataru Mori, Tadao Shimao, Roger H Clarke, Jack H Geiger, Keith H Lokan, Herbert L Abrams, Valerie Beral, Albrecht Kellerer, Colin Muirhead, and Dan Beninson.

Report of the Blue Ribbon Panel: Conclusions and Recommendations

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Department has gone about implementing them with considerable skill and intelligence. Impressive progress has been made over the last few years in creating a central linked database.

Recommendation 4. We recommend that strong support continue to be given to the Department of Information Technology because it is essential that the large body of data collected over many decades is properly stored, documented and accessible to researchers at RERF.

Clinical studies

The importance and merit of the research lies largely in the size and quality of follow-up of the LSS and AHS populations, the quality of the epidemiology and statistics as they relate to the LSS and AHS groups, and the continuing assessment of in utero exposed survivors. The role of the Departments of Clinical Studies is central to attaining many of the goals of all divisions.

'It seems unlikely that a comparable opportunity to study the effects of ionising radiation on health in such a detailed way will present itself in the future: and even if it does, it will take 50 years to accrue as much information as now exists at RERF.'

The content and quality of the research lies in the collaborative role that the Departments play with all other Departments:

- by providing clinical data on fatal and nonfatal carcinomas and on noncancer effects of radiation exposure;
- by enabling in-depth investigations of associations to be observed in the LSS;
- by furnishing a unique pool of serum, plasma and lymphocyte samples; and
- by providing an essential bridge function to the survivors.

Recommendation 5. We recommend that while many of the Clinical Studies projects under way should be extended, the programme should be critically reviewed so that those which are not promising are discontinued. The continuing surveillance of the cohort who were children in 1945 and are now adults is likely to be revealing, since radiation sensitivity may be highest in the young.

Recommendation 6. We recognise that the AHS is vital to the well-being of the survivors, and we recommend that this important service continue, since we believe it has led to their high level of cooperation with RERF. As the population ages and health problems become more complex, consideration needs to be given to ensuring that the voluntary participation remains high.

Genetics

While molecular biology investigations will enable the most detailed determinations to be undertaken, and will thus be the focus of future work, there is nevertheless need to continue—and even to extend—the more conventional studies of the health of the offspring (F_1 generation). They will also have continued importance because it remains uncertain at what point molecular studies can come sufficiently close to the resolution of the problem of multifactorial hereditary damage produced by radiation.

It does now appear that there can be a more complete chain linking the evolving physics dosimetry and individual data on location at the time of the bombing to chromosome data, to tooth data, and data from solid state dosimetry on other objects, such as building materials, ceramics, or jewelry. While dosimetry has traditionally not been the task of RERF, these new interconnections will be very important for validating the DS86 dosimetry system.

Recommendation 7. We recommend that the studies on the health of the offspring (F_1 generation) of the survivors continue, since they may elucidate data on multifactorial disease while also providing direct benefit to the survivors and their offspring.

Recommendation 8. We recommend the preservation of biological samples for FISH analysis and for ESR, together with the documentation that will be needed to compare dose estimates based on biological samples with those from physics assessments.

Recommendation 9. We recommend the continuation of the storage of biological materials and associated documentation for future molecular genetic studies.

Recommendation 10. We recommend that the most advanced methods and expertise in cytogenetics continue to be available at RERF.

Radiobiology

The archives of tumour and normal tissue material for molecular and biological studies from A-bomb survivors are of great importance in view of developments in molecular biology, and the extension and upkeep of the repositories is a central task for RERF.

The particular strengths of the immunology studies at RERF are the repeated observations in groups of A-bomb survivors that extend over sufficiently long periods to demonstrate the effects of aging, and the combined effect of aging and radiation exposure on the immune competence of T-cells. Recent studies on clonal expansion are of special interest.

Somatic mutation systems are applicable for biological dosimetry when exposures are recent, but the mutations are not sufficiently persistent to provide reliable information on exposures that occurred in the distant past.

The establishment of causality in epidemiological studies requires several conditions in addition to a strong association. Among these conditions the postulation of a plausible mechanism is essential. This postulation, in the form of a mechanistic model, is also the basis for extrapolations beyond the observations, particularly at very low values of the cause.

It is clear, therefore, that RERF radiation risk studies will always be related, explicitly or implicitly, to mechanisms and models. The spectacular increase in the understanding of the cancer process on the basis of molecular genetics indicates that models will evolve in this direction. While it does not seem appropriate to specifically include modellers in the staff of RERF, it

would be very important that the implications of data from experimental studies are kept under review as they may influence the research strategy of the Foundation.

Recommendation 11. We recommend that the Radiobiology Department should focus on molecular epidemiology and immunology and that strong links should be forged between RERF and the relevant groups around the world involved in modelling the carcinogenic process.

Future activities

Recommendation 12. We recommend that the LSS research programme should continue until the survivor cohort has died, so as to provide an authentic and complete assessment of the neoplastic and non-neoplastic effects of radiation. We also recognise that there are both medical and social aspects of the AHS that are of direct benefit to the promotion of the health of the A-bomb survivors and their offspring.

'. . . overall strategic planning and a firm commitment to fairly detailed programme management are needed to secure the best outcomes in the present (worldwide) climate of constrained resources.'

Recommendation 13. We recommend consideration be given to further investigation into the health of the offspring (F_1 cohort) since it may well yield valuable information on genetic effects, especially when conducted together with research using the new molecular genetics techniques.

Recommendation 14. We recommend that the recently initiated work on the molecular mechanisms of carcinogenesis should be focussed to elicit the shape of the dose-response curve at low doses of radiation.

Recommendation 15. RERF has a valuable source of surgical and autopsy specimens and, serum, plasma and lymphocyte samples, and we recommend that an explicit policy be developed over the management and ethics of the provision of biological samples for use in research, especially outside RERF.

Strategic planning and programme management

Programme management in a research environment such as RERF requires a deftness of touch to ensure that the processes are not so formalised and heavy-handed that they obstruct the development of new ideas. Nevertheless, it has been the experience in other establishments that overall strategic planning and a firm commitment to fairly detailed programme management are needed to secure the best outcomes in the present (worldwide) climate of constrained resources. In practical terms, the plan will reach down to the individual Departments, which will need to articulate their own priorities and plans to manage their own programmes, in accordance with the general strategic goals. The process is an interactive one, with the experience and thinking of the Departments contributing to and sharing ownership of the overall strategic plan.

It is important for the continued productivity and success of the RERF programme that external peer review on an intensive basis be established, with a committee of experts chosen from each discipline to review each of the programmes once every 5 years. The external review committee should have time to assess individual protocols, to review them in concert with the investigators, and then to make recommendations about the future direction of the programme. This mechanism would not only stimulate investigators to improve their projects by exposing them to concentrated critique and discussion with outstanding experts in the field, but would also encourage them to discontinue projects that seemed nonproductive.

Recommendation 16. In the context of the current organisational structure, we recommend that successive 5-year Strategic Plans, with annual updates, be developed and offered through the Executive Committee for approval by the Board of Directors.

Recommendation 17. We also recommend a new peer review process be established with multinational teams reviewing each Department every 5 years, each team being chaired, for example, by a different member of the Scientific Council.

Recommendation 18. We recommend that the Scientific Council takes a more active role with a closer involvement in the assessment and guidance of RERF. Its membership should reflect all of the major disciplines involved in the work of RERF. We further recommend that appointment to the Council be for 5-year terms, with no more than a single reappointment, and that two members retire each year.

National and international collaborations

While RERF is internationally known as a centre for radiation research, the results of its diverse programmes need to be more widely disseminated both in Japan and in the global scientific community. In order to continue the core research programmes of RERF, as well as the collaborative studies, recruiting and maintaining a strong and motivated scientific staff is a vital objective. It would be advantageous to seek short term appointments from other institutions in Japan, as well as to strengthen interactions with universities, especially those in the locality, and to enter into some additional formal overseas arrangements.

Recommendation 19. We recommend that consideration be given to formal links being established, or strengthened, to universities or other research institutions in Japan and especially to the universities in Hiroshima and Nagasaki, with RERF Department Chiefs having visiting or part-time Professorships and undertaking teaching commitments together with PhD students being involved on projects at RERF.

Recommendation 20. In addition to the bilateral arrangements between Japan and the US, we recommend that consideration be given to RERF entering into formal programmes of exchange of research fellows with other countries, and with regional or international bodies.

Recommendation 21. We recommend that, in view of the accumulated knowledge at RERF, it be developed as an Information Centre to promote informed public understanding of the risks of radiation. ❑

Invited Commentary

The International Role of RERF

Among investigations providing the basis for radiation protection standards worldwide, the atomic-bomb survivor study is the most long-standing and extensive ever undertaken.

by Warren K Sinclair, president emeritus, US National Council on Radiation Protection and Measurements, and RERF visiting director

Editor's note: This article is abridged from a talk given at ceremonies held in June 1995 in Hiroshima and Nagasaki to mark RERF's 20th anniversary. Attending the event were present and past employees, as well as representatives of citizen's groups, the local and national governments, RERF's funding agencies, and the US National Academy of Sciences.

We are here this afternoon to celebrate the 20th year since the Radiation Effects Research Foundation (RERF) was founded, thus beginning the unique Japanese–American collaboration that succeeded 27 years of atomic-bomb survivor studies conducted by the Atomic Bomb Casualty Commission (ABCC). These studies have led to what we now recognize, worldwide, as the most informative findings on the delayed effects of ionizing radiation on man ever obtained.

'Discovery' of radiation

This year is 1995 which marks a century of man's awareness of ionizing radiation as a factor in his life. Röntgen discovered x rays in 1895 and put them to manifold use at once, including in medicine. In 1896, Becquerel discovered the radioactivity of uranium, which was followed by the discovery of other radioactive substances, such as radium by Marie Curie. Obviously, radioactivity and ionizing radiation have been present naturally in the universe since the beginning of time, but man finally became aware of them just 100 years ago. The discovery of radioactivity opened the field of nuclear physics and quickly led Rutherford and others to an understanding of the structure and composition of the atom and, indeed, of nuclei themselves.

Today we recognize that radiation is an inevitable part of our lives and that natural background radiation is ubiquitous on Earth. It consists of radon exposure, external terrestrial exposure, internal radionuclides, and cosmic radiation which results in a dose to the individual of about 3 mSv per year (*NCRP Report 93*, Bethesda, Maryland, USA, 1987). Assuming linearity at low doses, the risk of cancer associated with natural background may be of the order of 1% (ie, about 1/20th of the cancer risk due to all other causes). In the US, individuals receive on average about another 0.6 mSv per year from manmade sources, mainly medical.

Sinclair

Putting radiation to work

Man also has put ionizing radiation to a broad range of uses, including industrial, agricultural, medical, and nuclear power, thus providing the opportunity for further exposure to manmade sources (International Atomic Energy Agency, *Highlights of Activities,* IAEA, Vienna, 1993). With these uses—some involving large amounts of radiation and radioactivity, comes the inevitability of accidents. However, in spite of widespread use, comparatively few fatal accidents have occurred in radiation work. By 1995, a total of 389 accidents had taken place—some 3,000 persons exposed significantly and 112 fatalities (not counting possible later cancer deaths) (Radiation Emergency Assistance Center/ Training Site Accident Registries, Oak Ridge Institute for Science and Education, Oak Ridge, Tennessee, USA, 1995).

> *'I regard the binational RERF as a great move forward in Japanese and American science. . . . I am very proud of it.'*
>
> *—James Liverman, 1995*

These activities occupationally expose radiation workers (about 4 million worldwide) to an average of about 2 mSv per year, which is about equal to a doubling of natural background radiation except for radon. This effectively doubles the radiogenic component of their risk.

The good news about radiation protection is that in the US, while the number of workers has grown from about 500,000 persons to 2,000,000 between 1960 and 1990, the average dose of those exposed has decreased by more than a factor of 2 because of the "as low as reasonably achievable" philosophy and other radiation protection pressures. In the US nuclear industry, the decrease has been more rapid and greater—more than a factor of 3 (from over 6 mSv/y on average in 1980 to under 2 mSv/y on average in 1990).

Except for accidents involving high doses, radiation protection today is not concerned with direct deterministic effects—erythema, cataract, sterility—because the low doses involved in most occupational settings are below the thresholds for these effects. However, stochastic effects—cancer and genetic effects—may be caused at low frequency after low-dose exposures. The major radiation protection question is: "What is the frequency (or risk) of cancer after a specific low dose of ionizing radiation?"

Source of most radiation risk information: atomic-bomb survivors

All of our information on these risks comes from exposed human populations, of which by far the most important are the survivors of the atomic bombings at Hiroshima and Nagasaki, although some medically exposed populations and some occupationally exposed populations provide important complementary information.

Cancer induction after ionizing radiation is, of course, a delayed effect. Leukemia has a minimum latency of 2 years and a peak incidence at about 6–8 years. Solid tumors have a minimum latency of about 5–10 years,

and thereafter incidence rises as the natural cancer rate increases with age at least up to 40 years after exposure.

Internationally, the responsibility of informing the world community on risk estimates for induced cancer is undertaken by the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) and, in the US, by the Advisory Committee on the Biological Effects of Ionizing Radiation (BEIR) of the US National Academy of Sciences (NAS). These bodies consider the relevant worldwide data from exposed populations and estimate the risk. Internationally, the International Commission on Radiological Protection (ICRP) and in the US the National Council on Radiation Protection and Measurements (NCRP)—informal professional bodies—use these risk estimates as the basis for recommendations on limits of exposure for workers and the public. Governments usually frame their radiation safety legislation on the ICRP and NCRP recommendations.

Table 1. Summary of the UNSCEAR estimates of fatal cancer risk coefficients (percent per sievert)

Tissue	1958	1964	1972	1977	1988[a]	1994[a]
Bone marrow	0.2–0.5	0.01–0.02[b]	0.15–0.40	0.20–0.50	1.0	1.1
Breast	–	–	0.06–0.20	0.50	0.9	1.0
Lung	–	–	0.10–0.40	0.25–0.50	2.2	2.5
Thyroid	–	0.16	0.40	0.10	0.8[c]	0.8[d]
Stomach	–	–	–	–	1.9	1.4
Liver	–	–	–	–	–	1.2
Brain	–	–	–	–	–	–
Salivary glands	–	–	–	0.10–0.15[e] (organs pooled)	–	–
Large intestine	–	–	–	–	–	–
Small intestine	–	–	–	–	1.2	0.6
Bone	–	–	0.40	–	–	–
Esophagus	–	–	–	–	0.5	0.5
Bladder	–	–	–	–	0.6	0.3
Pancreas	–	–	–	–	–	–
Rectum	–	–	–	0.02–0.05[e] (organs pooled)	–	–
Mucosa of cranial sinuses	–	–	–	–	–	–
Lymphatic tissue	–	–	–	–	–	–
Skin	–	–	–	–	–	–
Other, remainder	–	–	–	Low	2.4	3.5
Estimated total	–	–	–	1.0–2.5	10.7	12.0

[a] Multiplicative projection, Life Span Study

[b] Per year

[c] Incidence from *NCRP Report 80*

[d] Life Span Study incidence data

[e] Incidence

I have been personally involved with UNSCEAR from the 1977 report onwards and with the ICRP since 1977 (especially during the drafting of the ICRP 1990 recommendations), and I also have been president of the NCRP through most of that period. Consequently, I have considered these radiation risks from both international and national viewpoints.

The largely US-funded ABCC and, more recently, the RERF have assessed the epidemiological data on excess cancer deaths in their program approximately every 4 years, beginning in 1961. These data have formed the basis of input to UNSCEAR and BEIR periodically. It warrants noting that a risk estimate is actually a risk coefficient, ie, the number of excess cancers per unit population divided by the dose causing the excess. Thus, the dose also is important and also has been evaluated carefully at intervals for the RERF program, stimulated by both NCRP and NAS committees. The latest revision, known as Dosimetry System 1986, was approved for use at RERF by both US and Japanese national dosimetry committees.

The extent of the cancer risk information available to UNSCEAR has increased over time (Table 1), derived mainly from the ABCC–RERF Life Span Study (LSS) but supported by some other studies. Information has increased through the years so that a single value for leukemia risk in 1958 has evolved into individual risks for about 10 organs and a "remainder" in 1994. The estimated lifetime risk (high dose rate) for all cancers was about 10%–12%/Sv in the 1988 and 1994 reports. I believe that will not differ greatly when *LSS Report 12,* which incorporates data up through 1990, is completed and published in 1996 [Pierce et al, *Radiat Res* 146:1–27, 1996]. BEIR committee evaluations follow a pattern similar to those of UNSCEAR and generally have found similar risks.

Why is the RERF Life Span Study more important than any other radiation-related study?

A summary of the number of cancer deaths altogether as of 1985 indicates 339 excess cancer deaths among about 6,000 cancer deaths. This is not a large number statisti-

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The International Role of RERF

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cally, especially when it is broken down into individual cancer sites.

Nevertheless, the LSS, because of the number of persons involved and the range of doses received (up to high doses), has more power than any other study to do the following:

- to produce risk estimates for total cancer, mortality, and incidence;
- to produce risk estimates for 10–20 individual organs;
- to demonstrate the shape of the dose response;
- to find the lowest doses for which there are statistically significant risks (*LSS Report 11*: 0.2 Sv; *LSS Report 12*: 0.05 Sv);
- to examine the effect of variables such as age and sex;
- to follow the fate of the youngest cohorts: 0–9 years old and 10–19 years old at the time of the bombings;
- to demonstrate latency and whether the risk of solid tumors decreases with time; and
- to demonstrate cancer risks in sensitive groups such as fetuses.

We are now beginning to see in the early and imprecise results of occupational studies (from the US, UK, and Russia) risk data that are similar to those from the LSS, as interpreted by the ICRP (UNSCEAR, 1994). This is important confirmation.

It is not only for total risk estimation that the LSS is so powerful. The 1994 UNSCEAR report also considered risks by individual site from all sources as completely as possible. For some sites, such as the breast, the number of sources is extensive. The average risk derived from all studies is about the same as the LSS value, the standard against which all other studies are measured.

The RERF LSS not only has all this power with respect to cancer induction but it also yields information on noncancer effects as well, including acute effects, mental retardation among those exposed in utero, delayed noncancer effects, and genetic effects. Note that here I am focusing on the human effects studies arising from the LSS program. I am not addressing the entire RERF research program which includes the important radiobiological and other studies that have always been a part of the program.

Table 2. Decrease in numbers of atomic-bomb survivors in the youngest cohorts (percent alive)

Age ATB[a] (y)	Year							
	1950	1990	1995	2000	2005	2010	2015	2020
0–9	100	94.0	92.3	89.7	85.8	80.1	71.3	58.3
10–19	100	86.3	82.6	77.1	68.6	55.8	38.6	20.6

[a] *At the time of the bombings*
Note: Calculations by Dale Preston, RERF Department of Statistics, June 1995.

Applications of the cancer mortality risk data

The RERF LSS risk data are invariably the standard for risk estimates and form the basis for the following:

- standards for radiation workers;
- standards for the public;
- probability of causation assessment in a wide variety of circumstances;
- assessing the impact of accidents;
- assessing the risk to the public of environmental exposures;
- assessing the risk to soldiers and others exposed to tests, etc; and
- assessing effects on special groups, eg, fetuses (mental retardation, etc).

Probably the most important single application is the underlying basis of low-dose radiation protection standards. The change in risk estimates based on RERF LSS data collected up through 1988 caused the ICRP (and NCRP) to lower limits for workers in 1990 for the first time in over 30 years from an average of 50 mSv/y to an average of 20 mSv/y. Limits for the public were similarly lowered.

The Future

For the data up through 1985, only 39% of the LSS population had died and been evaluated. For *LSS Report 12*, which covers the data up through 1990, the figure is about 44%. The change in percentages expected in the future can be calculated easily from the characteristics of the Japanese population (in 1990).

The most important groups, about which we so far know little, are the 0- to 9-year-old group and the 10- to 19-year-old group. The population demographics with respect to these groups are shown in Table 2. In 1990, only 6% and 14% of these two groups had died and could be evaluated. By the year 2010, 44% of the 10- to 19-year-old group are projected to have been evaluated, as compared with only 20% of the youngest (0- to 9-year-old) group.

In my view the epidemiological and statistical study must continue at least until that time and in modified form perhaps even longer.

Long-term projects require enormous patience on the part of everyone concerned: the study subjects, the scientists, the managers, and the funding sources, ie, the Japanese Ministry of Health and Welfare and the US Department of Energy. The latter especially has had severe funding pressures mainly, but not solely, because of fluctuations in the yen–dollar exchange rate. In spite of these difficulties, the RERF program must continue strongly for the sake of future world knowledge.

It is fitting, in this 20th year, to quote James Liverman, who, in 1975 as assistant administrator of DOE's predecessor (the Energy Research and Development Agency), was instrumental on the US side in bringing about this unique binational research foundation. "I regard the binational RERF as a great move forward in Japanese and American science. . . . I am very proud of it," he said in June 1995.

In closing, let me say that the RERF staff has not only made a great success of this ongoing binational project but it has contributed enormously and uniquely to the worldwide knowledge of radiation-induced cancer and to many other delayed effects as well. Without you and the splendid cooperation of the atomic-bomb survivors, the world scientific community would still be floundering on this important subject. However, we still have much to learn, especially about the youngest groups of survivors.

Thank you for what you have done so far. I wish you godspeed in what you will do for the world scientific community tomorrow. ❑

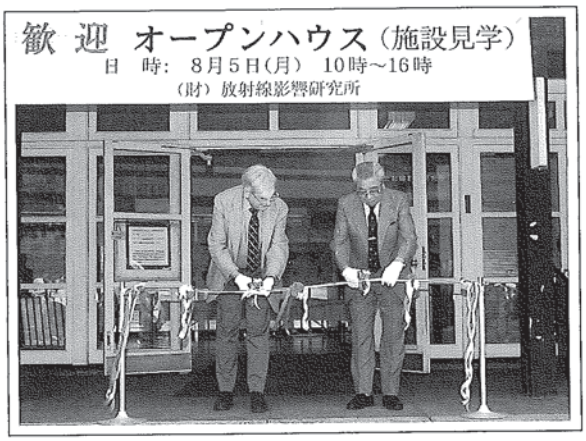
News Briefs

✓ Second Hiroshima Laboratory Open House Attracts Interest

The RERF Hiroshima Laboratory hosted 718 visitors at its second public open house, 5 August, the day before citywide activities to commemorate the 51st anniversary of the atomic bombing of Hiroshima.

Both Japanese citizens and foreign visitors to the city were welcomed at the Hiroshima Laboratory open house, held from 10:00 to 16:00. Although most explanations were conducted in Japanese, English-speaking staff members were on hand to assist visitors from outside Japan. Visitors were offered chances to have a blood pressure reading taken, to view laboratory specimens through a microscope, and to access the Internet using the laboratory's computer network.

Last year, 897 visitors took the opportunity to stroll through the small complex of quonset-hut style buildings on the weekend, keeping researchers and general staff busy answering questions and tending displays throughout the day.



J TAKAYAMA

Clockwise from below: (1) Laboratory technicians explain about cryopreservation of biological tissues. (2) Research scientist Kazuo Neriishi of the Department of Clinical Studies hosts a question-and-answer session adjacent to rooms where atomic-bomb survivor health examinations are conducted. (3) A ribbon cutting ceremony by Chairman Itsuzo Shigematsu, right, and Vice Chairman William J Schull officially begins the Hiroshima Laboratory open house on 5 August.

✓ Board of Directors Gathers

The 30th meeting of the RERF Board of Directors was held 5–7 June at the Hiroshima Laboratory. In addition to the four permanent directors, the following visiting directors attended the meeting: **Kazuaki Arichi**, Japan Institute of International Affairs; **Patricia A Buffler**, University of California School of Public Health; **Seymour Jablon**, US National Cancer Institute; **Toshiyuki Kumatori**, Radiation Effects Association; **Masumi Oike**, National Social Insurance Societies Association; and **Warren K Sinclair**, US National Council on Radiation Protection and Measurements.

✓ Scientific Council Convenes in November

The 23rd meeting of the RERF Scientific Council convened 13–15 November at the Beckman Center in Irvine, California, to deliberate upon the recommendations of the Blue Ribbon Panel (see articles on pp 1 and 3) and plans for the next 5 years.

Members of the RERF Scientific Council are as follows: **Curtis C Harris**, US National Cancer Institute; **Clark W Heath Jr**, American Cancer Society; **Tomio Hirohata**, Kyushu University Faculty of Medicine and Nakamuragakuen University; **Eisei Ishikawa**, Jikei University School of Medicine; **John B Little**, Harvard University School of Public Health; **Hiromichi Matsudaira**, National Institute of Radiological Sciences and Research Development Corporation of Japan; **Ei Matsunaga**, National Institute of Genetics; **Arno G Motulsky**, University of Washington School of Medicine; **Shigefumi Okada**, University of Tokyo; and **Susan Preston-Martin**, University of Southern California School of Medicine.

✓ US National Research Council Honors Department Chief

Information Technology Department Chief **Jill L Ohara** received a US National Research Council (NRC) Staff Performance Award in August for her long service and dedication to RERF. Ohara's successful coordination of the conversion from a mainframe computing system to a networked system of Unix workstations and personal computers 15 months ahead of the original target date, which resulted in substantial cost savings for RERF, was cited as especially noteworthy by **Paul Gilman**, executive director, Commission on Life Sciences, NRC.

✓ Research Staff News

William J Schull was appointed vice chairman on 28 June. Chief of Research **Seymour Abrahamson** returned to the United States on 14 July. **Sheldon Wolff** will assume the chief of research responsibilities in January.

Nagasaki

With the closing of the Nagasaki Laboratory's Department of Radiobiology, the following transfers to the Hiroshima Laboratory occurred as of 1 April: **Masahiro Itoh** joined the Laboratory of Cytogenetics, Department of Genetics. **Kiyohiro Hamatani** joined the Laboratory of Cell Biology, Department of Radiobiology.

Research scientist **Masumi Abe**, formerly of the Nagasaki Department of Radiobiology, resigned from RERF in March. He is now a research scientist at the National Institute of Radiological Sciences, Chiba.

Department of Clinical Studies: As of 1 August 1996, **Tan Tominaga** is acting chief, Division of Clinical Laboratories. He is concurrently a research scientist in the Division of Medicine and the industrial health physician.

Hiroshima

Department of Statistics: Assistant Chief **Masanori Otake** retired on 31 March. He now is a professor at Okayama University. **Fumiyoshi Kasagi** was promoted to associate senior scientist on 1 September 1995.

Department of Epidemiology: Research scientist **Yasuhiko Yoshimoto** resigned on 31 August. He is now a research scientist at the National Institute of Radiological Sciences, Chiba.

Information Technology Department: Information Systems Laboratory research scientist **Timothy Demarest** resigned in September. He is now a systems administrator at ArrayComm, Inc, San Jose, California.

Publication and Documentation Center: **Beth Magura**, chief editor, resigned on 18 November. In January 1997, she will be employed at Digital Equipment Corporation, Littleton, Massachusetts, as a senior technical editor. ❑

A Quick Look at *Life Span Study Report 12, Part I*

The latest review of cancer mortality among the atomic-bomb survivors employed improved analytical methods to clarify the age-time patterns of excess cancer risk.

by Donald Pierce, Yukiko Shimizu, and Kiyohiko Mabuchi, RERF Department of Epidemiology, and Dale Preston, RERF Department of Statistics

The Life Span Study (LSS) report on cancer mortality through 1990 was published in the July issue of *Radiation Research* (see p 16 for the summary). This latest report extends the previous LSS report by including 5 more years of follow-up, along with the addition of about 10,000 subjects recently assigned computed dose estimates. Some highlights of the report follow.

Tables 1 and 2 provide an overview of the excess cancer mortality. All analyses in the LSS report use doses in sievert based on a neutron relative biological effectiveness of 10. The expected background refers to estimated numbers of cancer deaths that would be expected for this cohort between 1950 and 1990 had there been no radiation exposure. The estimated excess is the difference between the observed numbers and this expected background; this is a random quantity, and the negative values seen in some low-dose categories are within normal sampling variation for an excess risk of zero. Although the excess relative risk depends on age at exposure and sex, these tables give a rough idea of the levels of risk by dose categories. The mean colon and marrow doses for those in the cohort with significant exposures was about 0.2 Sv. We estimate that within our follow-up, there have been about 334 excess deaths from solid cancers and about 87 from leukemia. We note that according to imprecise assessments the cohort considered here may contain about half of all survivors with significant radiation exposures.

Note that in contrast to leukemia, about 25% of the excess solid cancer deaths occurred in the last 5 years; for those exposed as children, this figure is nearly 50%. That excess solid cancer risks persist for so long—most likely throughout lifetime even for those exposed as children—has been one of the most important findings of the RERF cancer studies. This was generally unanticipated, and the evidence for such prolonged risks only gradually emerged during the past 2 decades. A primary emphasis of the report is to take advantage of the continued follow-up and improved analytical methods to clarify the age-time patterns of excess cancer risks.

Figure 1 portrays the age-specific excess relative risk

Table 1. Observed and expected deaths for solid cancers

		1950–1990			1986–1990		
Colon dose (Sv)	Subjects	Observed deaths	Expected background	Excess deaths	Observed deaths	Expected background	Excess deaths
0 (<0.005)	36,459	3,013	3,055	–42	489	496	–7
0.005–0.1	32,849	2,795	2,710	85	443	428	15
0.1–0.2	5,467	504	486	18	90	74	16
0.2–0.5	6,308	632	555	77	106	85	21
0.5–1.0	3,202	336	263	73	48	42	6
1.0–2.0	1,608	215	131	84	40	22	18
>2.0	679	83	44	39	11	7	4
Total	86,572	7,578	7,244	334	1,227	1,154	73

Table 2. Observed and expected deaths for leukemia

		1950–1990			1986–1990		
Marrow dose (Sv)	Subjects	Observed deaths	Expected background	Excess deaths	Observed deaths	Expected background	Excess deaths
0 (<0.005)	35,458	73	64	9	12	10	2
0.005–0.1	32,915	59	62	–3	6	9	–3
0.1–0.2	5,613	11	11	0	0	2	–2
0.2–0.5	6,342	27	12	15	4	2	2
0.5–1.0	3,425	23	7	16	2	1	1
1.0–2.0	1,914	26	4	22	1	1	0
>2.0	905	30	2	28	3	0	3
Total	86,572	249	162	87	28	25	3

(ERR) per sievert, ie, the ratio of excess to background age-specific mortality rates. These are given for each sex and for ages at exposure 10, 30, and 50 years. The ERR for females is larger than for males because the excess absolute rates (EAR) for cancer death are similar for the sexes, whereas the females have much smaller background rates. For those exposed at ages 30 and 50 years, the ERR for each sex has been fairly constant over the follow-up, but at levels that depend on age at exposure. That is, for those exposed as adults, the EAR has increased with age rather proportionately to the age increase in background rates. For those exposed as children, the EAR was initially quite high, but has decreased during follow-up. The large EAR at young ages is the result of dividing a fairly small EAR by a quite small background rate. The declining ERR means that the age-time increase in the EAR has been less rapid than the age increase of the background rates. The extent of this decrease—in particular, the level of ERR early in the follow-up—is imprecisely estimated, and, in fact, the statistical significance of a decrease is marginal.

In this report, increased emphasis has been placed on description of the age-time-sex patterns in the EAR. Although for some time, the primary numerical risk estimates have been for the ERR, and we continue this by giving ERR estimates specific to sex and age at exposure, we have found that a clearer understanding of the data results from giving increased attention to the EAR.

Figure 2 portrays the EARs resulting from multiplication of the ERRs of Figure 1 by age- and sex-specific background rates. The sex differences seen in this plot are not statistically significant, and the age-at-exposure differences only marginally so. This provides a clearer indication of the excess rate for those exposed as children, which is seen to be rather small during the current follow-up as compared to those exposed as adults and to increase with age or time. It is commonly said, based essentially on what is seen in Figure 1, that children are more sensitive to radiation than adults. Although it is true that they have had larger ERRs during much of the follow-up, the patterns seen in Figure 2 should be considered in evaluating such statements.

A single curve passing through these EAR patterns, illustrated later in this article, provides an adequate description of the data. That is, to a useful approximation, the age-specific excess absolute cancer death rates are the same for both sexes and do not depend on age at exposure. Following a minimal latent period of 5–10 years, an individual's excess risk can be thought of as depending only on his or her current age. If one fits a single curve through these patterns and divides this EAR by the age- and sex-specific background rates, the result is a single curve for each sex which corresponds closely

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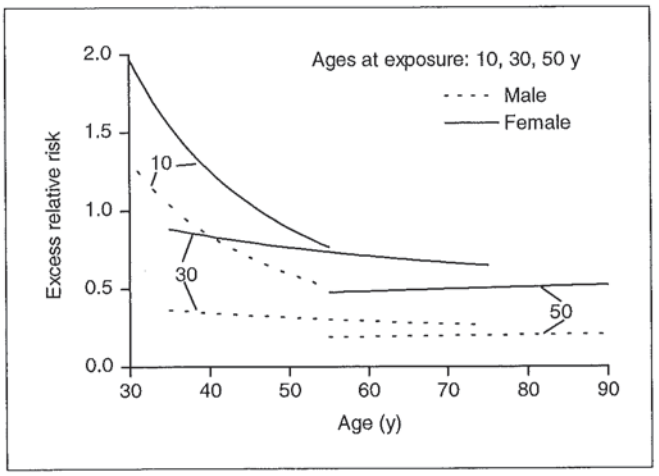

Above: Figure 1. Excess relative risk per sievert for solid cancer as a function of age for atomic-bomb survivors exposed at 10, 30, or 50 years of age.

Below: Figure 2. Excess absolute solid cancer rate per sievert as a function of age for atomic-bomb survivors exposed at 10, 30 and 50 years of age.

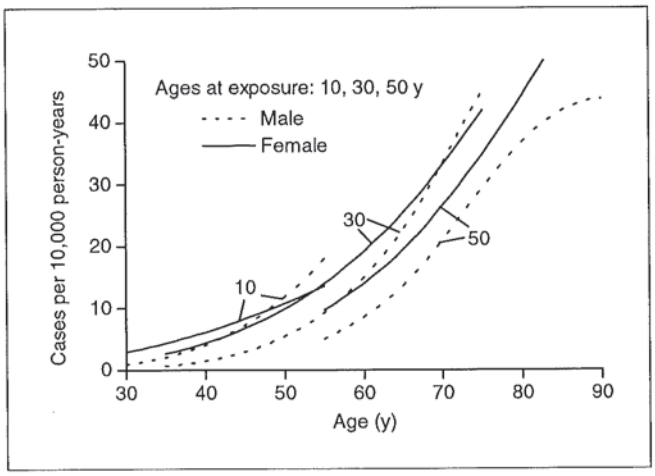

Table 3. Lifetime excess risk estimates for solid cancer at 1 Sv colon dose

Age at exposure (y)	Sex	Projected lifetime risk at 1 Sv	Life lost per excess death (y)	Background risk
10	Male	.12	15	.26
	Female	.16	20	.19
30	Male	.10	12	.28
	Female	.14	13	.20
50	Male	.03	10	.18
	Female	.05	11	.15

Table 4. Lifetime excess risk estimates for leukemia at 1 Sv marrow dose

Age at exposure (y)	Sex	Projected lifetime risk at 1 Sv	Life lost per excess death (y)	Background risk
10	Male	.014	48	.010
	Female	.009	54	.003
30	Male	.015	33	.008
	Female	.008	21	.004
50	Male	.009	13	.004
	Female	.007	13	.003

Cancer Mortality Data Available for Analysis Soon

Several data sets on cancer mortality among the atomic-bomb survivors, 1950–1990, that were used in the analyses published in *Life Span Study Report 12, Part I* (Pierce et al, *Radiat Res* 146:1–27, 1996; see summary on p 16) will be available soon. These include detailed cross-tabulations of the solid cancer and leukemia data similar to those used for the *Report 12* analyses and 54 supplementary summary tables of site-specific risk estimates for cancers of 18 organs or organ systems. The package includes extensive documentation of the contents of the data files and supplementary tables along with a table of conversion factors that can be used to transform colon doses to approximate other organ doses for use in site-specific analyses. Also included are AMFIT command and log files that illustrate how to fit the primary models and reproduce several of the key tables in the report.

The solid cancer file includes data on cancer deaths for 28 specific sites or organ systems together with aggregate data on deaths from all causes and some additional groups of cancers. The leukemia file includes data on deaths attributed to leukemia, lymphoma, and multiple myeloma. These files summarize the LSS mortality data for the 86,572 survivors with Dosimetry System 1986 dose estimates in detailed tabulations that contain data on person-years, case counts, dose, and other factors stratified by city, sex, age-at-exposure, attained age, and calendar year. Each file contains about 17,000 records.

The supplementary tables include three tables for each of the 18 sites or groups of sites considered. The first table in each set presents parameter estimates and significance tests based on a standard series of simple models used to examine the nature of the dose response and effect modification. The issues considered include the shape of the dose response and the effects of sex, age, and time on the excess risk. Results are given in terms of excess relative risks for all sites and excess absolute rates for sites with relatively large numbers of cases. The second and third tables for each site present observed and expected cases and person-years stratified by sex, dose, and time period or age at exposure.

The data sets and supplementary tables will soon be available on 2 DOS 3.5-inch floppy disks. Plans are underway to enable downloading of the data via RERF's World Wide Web site (http://www.rerf.or.jp).

The data files are fixed-format ASCII text files with data items separated by blanks. The files can be read by most spreadsheet, database, or statistical analysis programs. The files are being distributed as compressed self-extracting archives created using PKZip. Supplementary tables are contained in a single Microsoft Excel workbook. Printed versions of the 54 supplementary tables can be requested from RERF.

Send requests and inquiries to the RERF Publication and Documentation Center, 5-2 Hijiyama Park, Minami-ku, Hiroshima, 732 Japan. Fax: 81-82-261-3197. Internet email: pub-info@rerf.or.jp.

The LSS cancer incidence data and data from *LSS Report 10* and *LSS Report 11* are still available on disk and will be available for downloading via the RERF WWW site in the future. ❑

A Quick Look at *LSS Report 12, Part I*

continued from page 11

to the three line segments shown in Figure 1. Thus, one may also think of the ERR for each sex as depending only on age, rather than on age at exposure.

The age-time patterns of excess risk for leukemia are complicated, but as has been clear for some time the significant leukemia risks occurred much earlier in the follow-up, with substantial risk even before 1950.

These age-time patterns of excess risk are potentially important in understanding the biological mechanisms of radiation-related cancer, and they also provide a basis for projecting lifetime risks for the cohort. Tables 3 and 4 (see p 11) give estimated lifetime risks by sex and age at exposure. Projection beyond the current follow-up is mainly an issue only for solid cancers in the case of those exposed as children. In *LSS Report 12*, four methods were used for such projections, but only an intermediate one is given here. The sex differences seen for solid cancers reflect largely that females live longer. The larger solid cancer risk for those exposed as children is substantially due to their having elevated risk for a greater portion of their lives. Because the leukemia dose response is somewhat nonlinear, excess lifetime risk estimates for it at low doses, say 0.1 Sv, are about 50% of that predicted by simple linear extrapolation.

Finally, here and in *LSS Report 12*, there is substantial emphasis on describing excess risk at a dose of 1 Sv. Among those in our cohort with significant exposures, the mean dose is about 0.20 Sv. Figure 3 places in clearer perspective the excess cancer mortality risks for atomic-bomb survivors, in general, by presenting excess risks at 0.20 Sv. For this, we have used the simple EAR description which was discussed above. For perspective, we present the age-sex-specific background rates for those age 30 years at exposure. We emphasize, however, that the EAR shown in Figure 3 is applicable to all ages at exposure, beginning after some minimal latent period of about 10 years following exposure. ❑

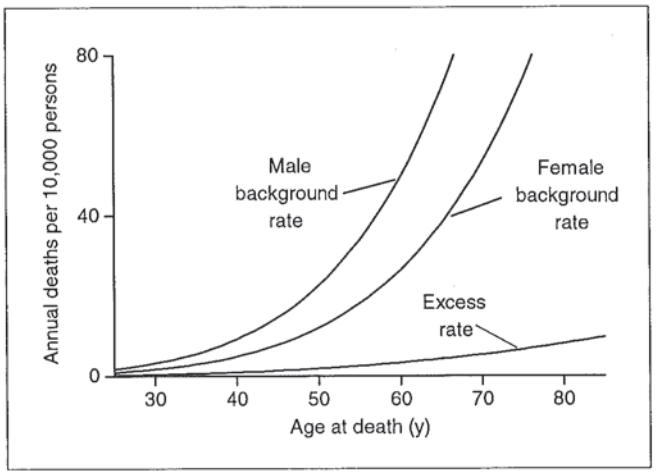

Figure 3. Background and excess solid cancer rates as a function of age for a survivor exposed at age 30 to a radiation dose of 0.20 sievert—the mean dose for survivors considered to have received a significant exposure.

Recent Scientific Publications

Editor's note: In this section of RERF Update, *selected summaries of journal articles based on approved RERF manuscripts accompany the complete journal-article citations. Other summaries from selected journal articles published by RERF researchers may also be included here occasionally. Variation in title or text styles reflects different journal styles.* J *after the citation means a Japanese version will be available. Reprints, when available, can be obtained from the RERF Publication and Documentation Center, 5-2 Hijiyama Park, Minami-ku, Hiroshima, 732 Japan. Facsimile: 81-82-263-7279 or 81-82-261-3197. Internet email address:* pub-info@rerf.or.jp. *Limited publication information is now available via RERF's World Wide Web site:* http://www.rerf.or.jp

Publications in the Scientific Literature

Cytogenetic and immunologic identification of clonal expansion of stem cells into T and B lymphocytes in one atomic-bomb survivor. Y Kusunoki, Y Kodama, Y Hirai, S Kyoizumi, N Nakamura, M Akiyama. *Blood* 86:2106–12, 1995.

Chromosome aberration frequency in peripheral blood lymphocytes is elevated in radiation-exposed people, and identical karyotypic changes are not infrequently encountered in one blood sample as well as in separate samples from the same donor. Such clonal propagation originates either from a single immature stem cell able to expand and differentiate into several cell types or from a single mature lymphocyte able to expand after antigen stimulation in vivo. In the present study, a total 71 T-lymphocyte and 58 B-lymphocyte colonies were established from one atomic-bomb survivor, who showed a persistent clonal aberration t(4; 6), t(5; 13) in phytohemagglutinin culture of peripheral lymphocytes. Nearly 10% of the colonies (6 T-lymphocyte and 7 B-lymphocyte colonies) showed the same chromosome abnormality. Southern blot analyses of the T-cell-receptor or Ig heavy-chain gene showed all different rearrangement patterns among T- or B-lymphocyte colonies, respectively. Thus, the chromosome aberration occurred in a precursor cell before differentiation into T and B lineages and was not derived from monoclonal proliferation of mature T or B lymphocytes in the periphery. To confirm the issue, cells from erythroid burst-forming unit (BFU-E) colonies were examined by the chromosome-painting method. Two translocations, one between chromosomes 5 and 13 and the other between chromosomes 4 and one of group C, perfectly consistent with the t(4;6), t(5; 13), were found in about 10% of the cells. The results imply that a single stem cell of an adult is capable of generating long-lived myeloid and lymphoid progeny amounting to several percent of the total population of circulating lymphocytes and hematopoietic progenitors.

Vertebral fracture prevalence in women in Hiroshima compared to Caucasians or Japanese in the US. PD Ross, S Fujiwara, C Huang, JW Davis, RS Epstein, RD Wasnich, K Kodama, LJ Melton. *Int J Epidemiol* 24:1171–7, 1995. J

Background. Although vertebral fractures are very common among elderly Caucasian women, no studies have compared the prevalence to that among Asian populations. Any observed differences in prevalence might lead to the identification of important environmental and/or genetic factors. We therefore compared the prevalence of vertebral fractures among US Caucasians to native Japanese and Japanese immigrants in Hawaii using a standardized approach.

Methods. Spinal radiographs of women aged ≥50 years were obtained from native Japanese in Hiroshima, Japanese-Americans in Hawaii, and North American Caucasians in Minnesota between 1982 and 1991. Fractures were defined as vertebral heights >3 standard deviations (SD) below the vertebra-specific mean.

Results. Compared to Japanese-Americans, odds ratios (OR) and 95% confidence intervals (CI) for prevalent vertebral fractures were 1.8 (95% CI: 1.3–2.5) for native Japanese women and 1.5 (95% CI: 1.1–2.1) for Minnesota Caucasians. The OR tended to be higher when comparing the prevalence of two or more fractures per person: OR = 3.2 (95% CI: 2.0–5.3) for native Japanese and OR = 1.9 (95% CI: 1.2–3.2) for Minnesota Caucasians. Similar results were observed for native Japanese using a fracture definition of ≥4 SD below the mean, but the OR for Caucasians was reduced to 1.2 (95% CI: 0.6–2.3).

Conclusion. The observation that, among these three populations, hip fracture incidence is lowest but spine fracture prevalence is greatest among native Japanese suggests that different risk factors may be responsible.

Mutant frequency at the *HPRT* locus in peripheral blood T-lymphocytes of atomic bomb survivors. Y Hirai, Y Kusunoki, S Kyoizumi, AA Awa, DJ Pawel, N Nakamura, M Akiyama. *Mutat Res* 329:183–96, 1995.

The mutant frequency at the hypoxanthine-guanine phosphoribosyltransferase locus in peripheral blood lymphocytes was measured for 254 atomic bomb survivors (171 exposed and 83 control survivors) by a colony assay using recombinant human interleukin-2. Weak but significant effects were detected for atomic bomb radiation dose and smoking status at the time of examination but not for age and sex. However, the slope of the dose-response curve is quite small, and the smoking effect would not have been significant without the inclusion of data from just three individuals with extremely high mutant frequencies. The weakness of the dose response is at least partly due to the time lapse of 50 years since radiation exposore. Among the 254 survivors, 23 had chromosome aberration data in lymphocytes and the dose response was highly significant. However, the correlation between the mutant frequency and the proportion of cells with aberrations was not significant. It was concluded that the lymphocyte mutation assay is presently not sensitive enough for biological dosimetry of radiation exposure in the survivors.

Relationship between cataracts and epilation in atomic bomb survivors. K Neriishi, FL Wong, E Nakashima, M Otake, K Kodama, K Choshi. *Radiat Res* 144:107–13, 1995.

Among 1713 atomic bomb survivors who underwent ophthalmological examinations from 1963–1964, the risk of cataract formation per unit dose of radiation was significantly greater for those who reported hair loss of 67% or more after exposure (the epilation group) than for those who reported less or no hair loss (the no-epilation group) ($P < 0.01$). Such an epilation effect has also been associated with leukemia mortality and the frequency of chromosome aberrations. Although this might be interpreted as indicating differential sensitivity to radiation between the epilation group and the no-epilation group, it could also be explained by imprecision in dose estimates. We have calculated that a 48% random error in DS86 dose estimates could be in accordance with the dose-response relationship for the prevalence of cataracts in the epilation group or the no-epilation group. Possible mechanisms for variation in radiosensitivity are discussed.

Recombination activating gene (RAG)-1 and 2 encoding proteins expressed by the baculovirus system. R Araki, M Kaku, M Itoh, K Hamatani, T Usui, M Abe. *Acta Med Nagasaki* 41:43–7, 1996.

We have been attempting to obtain mouse recombination activating gene-1

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Recent Scientific Publications

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(RAG-1) and RAG-2 protein for biochemical analyses. First of all, we obtained truncated products of these genes expressed and purified using the *E. coli* expression system and then established the polyclonal and monoclonal antibodies by means of *E. coli* expressed peptides as antigens. Subsequently, whole RAG-1 and RAG-2 gene products were expressed the baculovirus expression system. Since it has been difficult to achieve the significant gene expression of full-length cDNA, we employed the glutathione S-transferase (GST)-fused gene-expression system which facilitated the massive expression of gene products. This system was also advantageous in that we could detect the expressed protein molecules not only with anti-RAG antibody but also with anti-GST antibody.

Incidence of benign gastrointestinal tumors among atomic bomb survivors. E Ron, FL Wong, K Mabuchi. *Am J Epidemiol* 142:68–75, 1995. J

Using the Hiroshima and Nagasaki tumor and tissue registries, benign tumors of the stomach, colon, and rectum were identified among members of the Life Span Study cohort of atomic bomb survivors. During the period 1958–1989, a total of 470 cases with histologically confirmed benign gastrointestinal tumors (163 stomach, 215 colon, and 92 rectum) were identified among approximately 80,000 Life Span Study members with known radiation doses, who were alive in 1958. Restricting the analysis to adenomatous tumors not detected at autopsy, a dose-response relation was observed for stomach tumors (excess relative risk at 1 sievert (ERR_{1Sv} 0.53; 95% confidence interval (CI) −0.01 to 1.43). However, there was little evidence of a dose response for colon tumors (ERR_{1Sv} = 0.14; 95% CI −0.20 to 0.76), and no evidence was present for rectal tumors (ERR_{1Sv} = −0.25; 95% CI undetermined to 0.80). The excess relative risk (ERR) for benign tumors of the stomach is consistent with the excess found for stomach cancer. For cancer of the rectum, the dose response was not significant, but the point estimate of the excess relative risk was positive. The excess relative risk for benign colon tumors is less than that reported for colon cancer (ERR_{1Sv} = 0.72). The authors observed a dramatic increase in colon tumors detected after 1985, suggesting that the relatively recent introduction of colonoscopy may be influencing these results.

Lack of effects of atomic bomb radiation on genetic instability of tandem-repetitive elements in human germ cells. M Kodaira, C Satoh, K Hiyama, K Toyama. *Am J Hum Genet* 57:1275–83, 1995.

In a pilot study to detect the potential effects of atomic bomb radiation on germline instability, we screened 64 children from 50 exposed families and 60 from 50 control families for mutations at six minisatellite loci by using Southern blot analysis with Pc-1, λTM-18, ChdTC-15, pλg3, λMS-1, and CEB-1 probes. In the exposed families, one or both parents received a radiation dose >0.01 Sv. Among the 64 children, only one child had parents who were both exposed. Thus, of a total of 128 gametes that produced the 64 children, 65 gametes were derived from exposed parents and 63 were from unexposed parents, the latter being included in a group of 183 unexposed gametes used for calculating mutation rates. The average parental gonadal dose for the 65 gametes was 1.9 Sv. We detected a total of 28 mutations at the *pλg3*, *λMS-1*, and *CEB-1* loci, but no mutations at the *Pc-1*, *λTM-18*, and *ChdTC-15* loci. We detected 6 mutations in 390 alleles of the 65 exposed gametes and 22 mutations in 1098 alleles of the 183 gametes from the unexposed parents. The mean mutation rate per locus per gamete in these six minisatellite loci was 1.5% in the exposed parents and 2.0% in the unexposed parents. We observed no significant difference in mutation rates in the children of the exposed and the unexposed parents (P = .37, Fisher's exact probability test).

Prevalence of hepatitis B surface antigen, hepatitis B e antigen and antibody, and antigen subtypes in atomic bomb survivors. K Neriishi, S Akiba, T Amano, T Ogino, K Kodama. *Radiat Res* 144:215–21, 1995.

On the basis of previous studies showing an association between hepatitis B surface antigen (HBsAg) positivity and radiation exposure in atomic bomb (A-bomb) survivors, we investigated further the active state of hepatitis B virus (HBV) infection by incorporating tests for hepatitis B e antigen (HBeAg) and hepatitis B e antibody (anti-HBe) and HBsAg subtypes into our biennial health examinations. Among 6548 A-bomb survivors for whom HBsAg was assayed between July 1979 and July 1981, 129 persons were HBsAg positive. HBeAg and anti-HBe were measured in 104 of these persons and subtypes of HBsAg in 98 persons. Among those exposed to radiation (average liver dose 0.58 Sv), the odds ratio of HBsAg positivity tended to increase with radiation dose (P for trend = 0.024). The P values for association between the prevalence of HB e antigen and radiation dose and between the prevalence of anti-HBe and radiation dose were 0.094 and 0.17, respectively. The HB antigen subtype adr was predominant over other subtypes in both Hiroshima and Nagasaki, but the distribution of subtypes did not seem to differ in relation to radiation dose. These results suggested that A-bomb survivors remain in an active state of HBV infection and that the mechanism(s) of seroconversion may be impaired.

Mutation frequency in human blood cells increases with age. M Akiyama, S Kyoizumi, Y Hirai, Y Kusunoki, KS Iwamoto, N Nakamura. *Mutat Res* 338:141–9, 1995.

Using either the colony formation assay or flow cytometry, it is feasible to measure the frequency of rare mutant lymphocytes or erythrocytes in human peripheral blood. Accordingly, we have investigated the mutant cell frequencies of the hypoxanthine-guanine phosphoribosyltransferase and T-cell receptor genes in T lymphocytes and of the glycophorin A gene in erythrocytes of several hundred persons aged 0–96 years. The mutant frequency of every one of these genes increased significantly with age. A simple accumulation of mutations in hematopoietic stem cells over time may explain the age-dependent increase in the frequency of glycophorin A mutants. In contrast, a balance between mutant cell generation and loss should be taken into account for the mechanism of the increase of T-cell mutations.

Effects of menopause on trends of serum cholesterol, blood pressure, and body mass index. M Akahoshi, M Soda, E Nakashima, K Shimaoka, S Seto, K Yano. *Circulation* 94:61–6, 1996.

Background. To elucidate the impact of menopause on coronary risk factors, we determined the trends of serum cholesterol (mg/dL), blood pressure (BP, mm Hg), and body mass index (BMI, kg/m^2) and investigated whether menopause affects these trends in women in Nagasaki, Japan.

Methods and Results. Trends of cholesterol, systolic BP (SBP), and BMI from 9 years before menopause through 9 years after menopause in 579 women with natural menopause (ranging in age from 40.2 ± 3.1 to 57.9 ± 3.1 years; age at menopause, 49.4 ± 3.0 years) and 134 women with surgical menopause (hysterectomy with or without bilateral oophorectomy; ranging in age from 34.9 ± 4.5 to 51.7 ± 5.1 years; age at menopause, 42.9 ± 5.0 years) and those in 579 and 134 age- and time-matched male subjects (ranging in age from 40.1 ± 3.1 to 57.8 ± 3.2 years and from 35.2 ± 4.5 to 51.6 ± 5.0 years, respectively) in Nagasaki were determined by rearrangement of the data from 1958 to 1989 with time of menopause as the datum line. Although cholesterol tended to increase with age in both sexes, it increased signifi-

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cantly in women from 3 years before natural menopause to 1 year after natural menopause and from 1 year before surgical menopause to 1 year after surgical menopause. SBP and BMI did not exhibit a significant increase in relation to natural or surgical menopause. In male subjects, no significant increase of cholesterol, SBP, or BMI was observed at the age corresponding to natural or surgical menopause.

Conclusions. Natural menopause and surgical menopause exert an effect only on cholesterol, and an increase in cholesterol precedes natural menopause by 3 years and occurs at the time of surgical menopause.

Late effects of radiation on the human immune system: an overview of immune response among the atomic-bomb survivors. M Akiyama. *Int J Radiat Biol* 68:497–508, 1995.

The studies of the late effects of atomic-bomb (A-bomb) radiation on the immune system were started about 20 years after the bombings in 1945. The most remarkable late effects of radiation are the functional and quantitative abnormalities of T and B cells in survivors exposed to high doses (≥1.0 Gy). Abnormalities of T-cell immunity include (1) a decreased proportion of $CD3^+$ T cells in peripheral blood lymphocytes, particularly the proportion of $CD4^+$ $CD45RA^+$ naive T cells (study period 1987–91); (2) an increased frequency of $CD4^-$ and $CD8^-$ (double negative) αβ T cells (1987–91); and (3) functional defects in T-cell responses to mitogens and alloantigens (1974–85). B-cell abnormalities include: (1) a significant increase in the proportion of B cells among peripheral lymphocytes (1987–91); (2) an increase in serum immunoglobulin A levels in females and immunoglobulin M and the incidence of rheumatoid factor in both sexes (1987–89); and (3) an increased level of anti-Epstein-Barr virus antibody titer (1987–90). In contrast, suggestive ($0.05 < p < 0.1$) or not significant ($p > 0.1$) dose effects were observed for the number and function of natural killer cells (1983–91), and benign monoclonal gammopathy (1979–87). In addition, studies initiated sooner after the bombing such as the incidence of autoimmune diseases (1958–87), systemic bacterial infections (1954–67), and granulocyte functions (1947–79) also show little dose-effects. Thus, A-bomb radiation induced the alteration of the balance/interaction between the T- and B-cell subsets—specifically, a decrease in the T-cell population and an increase in the B-cell population in the periphery.

Somatic cell mutations at the glycophorin A locus in erythrocytes of atomic bomb survivors: implications for radiation carcinogenesis. S Kyoizumi, M Akiyama, JB Cologne, K Tanabe, N Nakamura, AA Awa, Y Hirai, Y Kusunoki, S Umeki. *Radiat Res* 146:43–52, 1996.

To clarify the relationship between somatic cell mutations and radiation exposure, the frequency of hemizygous mutant erythrocytes at the glycophorin A (GPA) locus was measured by flow cytometry for 1,226 heterozygous atomic bomb (A-bomb) survivors in Hiroshima and Nagasaki. For statistical analysis, both GPA mutant frequency and radiation dose were log-transformed to normalize skewed distributions of these variables. The GPA mutant frequency increased slightly but significantly with age at testing and with the number of cigarettes smoked. Also, mutant frequency was significantly higher in males than in females even with adjustment for smoking and was higher in Hiroshima than in Nagasaki. These characteristics of background GPA mutant frequency are qualitatively similar to those of background solid cancer incidence or mortality obtained from previous epidemiological studies of survivors. An analysis of the mutant frequency dose response using a descriptive model showed that the doubling dose is about 1.20 Sv [95% confidence interval (CI): 0.95–1.56], whereas the minimum dose for detecting a significant increase in mutant frequency is about 0.24 Sv (95% CI: 0.041–0.51). No significant effects of sex, city or age at the time of exposure on the dose response were detected. Interestingly, the doubling dose of the GPA mutant frequency was similar to that of solid cancer incidence in A-bomb survivors. This observation is in line with the hypothesis that radiation-induced somatic cell mutations are the major cause of excess cancer risk after radiation exposure. Furthermore, the dose response was significantly higher in persons previously or subsequently diagnosed with cancer than in cancer-free individuals. This may suggest an earlier onset of cancer due to elevated mutant frequency or a higher radiation sensitivity in the cancer group, although the possibility of dosimetry errors should be considered. The findings obtained in the present study suggest that the GPA mutant frequency may reflect the cancer risk among people exposed to radiation.

Determinants of vertebral fracture prevalence among native Japanese women and women of Japanese descent living in Hawaii. C Huang, PD Ross, S Fujiwara, JW Davis, RS Epstein, K Kodama, RD Wasnich. *Bone* 18:437–42, 1996.

Age-adjusted prevalence of vertebral fracture has been reported to be higher among native Japanese women than among women of Japanese descent living in Hawaii. In this cross-sectional population-based study, we examined a variety of potential risk factors for associations with prevalent vertebral fractures and investigated whether these factors could explain the difference in vertebral fracture prevalence between native Japanese and Japanese-American women. Spine radiographs and data on spine bone mineral density (BMD) and other potential risk factors were collected among 802 Japanese women aged 50–88 years living in Hiroshima and 840 Japanese-American women aged 52–88 years living in Hawaii. In logistic regression analysis, BMD was a major predictor of prevalent vertebral fracture. In linear regression models, weight, age, and menstrual history (age at menopause or years between menarche and menopause) were significantly associated with BMD and thus might contribute to fracture risk indirectly through their effects on BMD. However, age and menstrual history provided additional and complementary information about fracture prevalence after adjusting for BMD. These variables together explained much of the difference in vertebral fracture prevalence between the two study populations. We conclude that the observed difference in age-adjusted prevalence of spine fracture between native Japanese and Japanese-American women was accounted for primarily by the differences in BMD, duration of estrogen exposure, and/or duration of estrogen deficiency. Thus, current BMD is a major but not the sole risk factor for vertebral fractures. Age-related and menopause-related mechanisms may also play an important role in spine fracture independent of BMD.

Activation of telomerase in human lymphocytes and hematopoietic progenitor cells. K Hiyama, Y Hirai, S Kyoizumi, M Akiyama, E Hiyama, MA Piatyszek, JW Shay, S Ishioka, M Yamakido. *J Immunol* 155:3711–5, 1995.

This is the first report describing up-regulation of telomerase activity in human normal cells. Telomerase, a ribonucleoprotein enzyme, has been thought to be involved in maintaining telomere length stability in germline and most cancer cells, but not in normal cells. However, in the present study, we demonstrate that telomerase activity is detectable at low levels in normal human T and B cells, increases by in vitro mitogenic stimulation, increases in hematopoietic progenitor cells upon their proliferation and differentiation, and decreases with aging. Understanding the regulation of telomerase activity in normal

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cells may provide important insights not only into the mechanisms of normal cellular senescence but also into the mechanisms of telomerase activity deregulation as part of cancer development.

Studies of the mortality of atomic bomb survivors. Report 12, Part I. Cancer: 1950–1990. DA Pierce, Y Shimizu, DL Preston, M Vaeth, K Mabuchi. *Radiat Res* 146:1–27, 1996. J

This continues the series of periodic general reports on cancer mortality in the cohort of A-bomb survivors followed by the Radiation Effects Research Foundation. The follow-up is extended by the 5 years 1986–1990, and analysis includes an additional 10,500 survivors with recently estimated radiation doses. Together these extensions add about 550,000 person-years of follow-up. The cohort analyzed consists of 86,572 subjects, of which about 60% have dose estimates of at least 0.005 Sv. During 1950–1990 there have been 3086 and 4741 cancer deaths for the less than and greater than 0.005 Sv groups, respectively. It is estimated that among these there have been approximately 420 excess cancer deaths during 1950–1990, of which about 85 were due to leukemia. For cancers other than leukemia (solid cancers), about 25% of the excess deaths in 1950–1990 occurred during the last 5 years; for those exposed as children this figure is nearly 50%. For leukemia only about 3% of the excess deaths in 1950–1990 occurred in the last 5 years. Whereas most of the excess for leukemia occurred in the first 15 years after exposure, for solid cancers the pattern of excess risk is apparently more like a life-long elevation of the natural age-specific cancer risk. Taking advantage of the lengthening follow-up, increased attention is given to clarifying temporal patterns of the excess cancer risk. Emphasis is placed on describing these patterns in terms of absolute excess risk, as well as relative risk. For example: (a) although it is becoming clearer that the excess relative risk for those exposed as children has declined over the follow-up, the excess absolute risk has increased rapidly with time; and (b) although the excess relative risk at a given age depends substantially on sex and age at exposure, the age-specific excess absolute risk depends little on these factors. The primary estimates of excess risk are now given as specific to sex and age at exposure, and these include projections of dose-specific lifetime risks for this cohort. The excess lifetime risk per sievert for solid cancers for those exposed at age 30 is estimated at 0.10 and 0.14 for males and females, respectively. Those exposed at age 50 have about one-third these risks. Projection of lifetime risks for those exposed at age 10 is more uncertain. Under a reasonable set of assumptions, estimates for this group range from about 1.0–1.8 times the estimates for those exposed at age 30. The excess lifetime risk for leukemia at 1 Sv for those exposed at either 10 or 30 years is estimated as about 0.015 and 0.008 for males and females, respectively. Those exposed at age 50 have about two-thirds that risk. Excess risks for solid cancer appear quite linear up to about 3 Sv, but for leukemia apparent nonlinearity in dose results in risks at 0.1 Sv estimated at about 1/20 of those for 1.0 Sv. Site-specific risk estimates are given, but it is urged that great care be taken in interpreting these, because most of their variation can be explained simply by imprecision in the estimates.

Incidence of salivary gland tumors among atomic bomb survivors, 1950–1987. Evaluation of radiation-related risk. CE Land, T Saku, Y Hayashi, O Takahara, H Matsuura, S Tokuoka, M Tokunaga, K Mabuchi. *Radiat Res* 146:28–36, 1996. J

A wide-ranging search for benign and malignant tumors of the major and minor salivary glands among members of the Life Span Study sample of the Radiation Effects Research Foundation identified 41 malignant and 94 benign incident tumors, including 14 malignant and 12 benign tumors of the minor salivary gland, plus 10 major gland tumors of unknown behavior. Dose-response analyses found statistically significant increases in risk with increasing A-bomb dose for both cancer and benign tumors. Estimated relative risks at 1 Sv weighted tissue kerma (RR_{1Sv} with 90% confidence interval in parentheses) were 4.5 (2.5–8.5) for cancer and 1.7 (1.1–2.7) for benign tumors. When analyzed by histological subtype within these two broad groups, it appeared that most of the dose response for malignant tumors was provided by an exceptionally strong dose response for mucoepidermoid carcinoma [11 exposed cases with dose estimates, RR_{1Sv} = 9.3 (3.5–30.6)], and most or all of that for benign tumors corresponded to Warthin's tumor [12 cases, RR_{1Sv} = 4.1 (1.6–11.3)]. There was a marginal dose response for malignant tumors other than mucoepidermoid carcinoma [RR_{1Sv} = 2.4 (0.99–5.7)] but no significant trend for benign tumors other than Warthin's tumor [RR_{1Sv} = 1.3 (0.9–2.2)]. Re-examination of the original data from published studies of other irradiated populations may shed new light on the remarkable type specificity of the salivary tumor dose response observed in the present study.

Analysis of a chromosome aberration data with measurement error from atomic-bomb survivors: utilization of large-scale external information. E Nakashima, K Ohtaki. *Jpn J Biometrics* 16:19–36, 1995.

Overdispersion data of chromosome-aberration rates from atomic-bomb survivors were analyzed by the quasi-likelihood/pseudolikelihood (QL/PL) estimating equation method (Breslow 1990). The variance function was composed of two extra-binomial variations: one is an intra-individual correlation, the other is a variation from dosimetry error. This dose-error-variance component was derived using the quasi-structural method (Pierce, Stram, Vaeth and Schafer 1992) that incorporates large-scale external dosimetry information. Using the results of fitting the QL/PL estimating equation, the Wald test revealed that the dose-estimation error is a significant source of overdispersion.

A simple reductionist model for cancer risk in atom bomb survivors. ML Mendelsohn. In: *Modeling of Biological Effects and Risks of Radiation Exposure* (NIRS Symposium Series No. 26). Ed by J Inaba, S Kobayashi. Chiba, Japan, National Institute of Radiological Sciences, 1995. pp 185–92.

1) In data from the atom bomb survivors of Hiroshima and Nagasaki, the roughly linear-quadratic radiation dose responses for chromosome aberration and leukemia correspond closely to each other, as do the linear dose responses for gene mutation and solid cancer incidence.

2) In view of the increasing evidence for multiple oncogene and suppressor gene changes in human cancer, as well as the evidence that human cancer rate is often proportional to age to the power of 6 or so, it is postulated that the radiation has contributed one and only one oncogenic mutational event to the radiation induced cancers.

3) The radiation induced cancers should therefore display a cancer rate versus age relationship that has a power of n–1, where n is the power for the corresponding background cancers.

4) It is shown that this is precisely what is happening in the collective solid cancer incidence of the atom bomb survivors.

Correlation between systolic blood pressure and physical development in adolescence. M Akahoshi, M Soda, RL Carter, E Nakashima, K Shimaoka, S Seto, K Yano. *Am J Epidemiol* 144:51–8, 1996.

Although the close relation between blood pressure and physical development in adolescence has been established in

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cross-sectional and comparative cross-sectional studies, the entire trend of systolic blood pressure (SBP) during adolescence has not been elucidated in conjunction with physical development in a longitudinal study. Blood pressure (mmHg), body weight (kg), and body height (m) were measured annually for 418 subjects in Hiroshima and Nagasaki, Japan, from age 10 (1955 or 1956) through 18 years (1963 or 1964). The Gompertz growth model was used to determine the velocity of weight increase (VEL) during that age period. The relations between SBP from age 10 to 18 and VEL, weight, height, body mass index (BMI; weight/height^2, kg/m^2), and the age at which the measurements were made were investigated individually using random-coefficient growth-curve analysis. The SBP trend for the 10- to 18-year age period could be shown by the following prediction equations: for the 163 Hiroshima males, SBP = 82.38 + 0.89 VEL at age 1.15 years prior to the current examination (VEL (*age* – 1.15)) + 1.40 BMI; for the 57 Nagasaki males, SBP = 92.70 + 1.07 VEL (*age* – 1.15) + 0.79 BMI; for the 148 Hiroshima females, SBP = 104.88 + 1.63 VEL (*age* – 1.15) + 0.05 BMI; for the 50 Nagasaki females, SBP = 113.62 + 1.67 VEL (*age* – 1.15) – 0.59 BMI. VEL 1.15 years prior to the current examination was significantly and positively related to SBP in each city by sex group ($p < 0.01$), and current BMI was significantly related to SBP for males in Hiroshima ($p < 0.01$) and nearly so in Nagasaki ($p = 0.06$), but not for females in either city ($p = 0.84$ and 0.13, respectively). Because the plot of VEL was a convex curve, SBP peaked approximately 1–2 years after the peak in VEL and then decreased in both sexes. The entire SBP trend during adolescence can be expressed as an equation of VEL and BMI in males and of VEL in females. SBP does not increase linearly with age.

Gain-of-function p53 mutations enhance alteration of the T-cell receptor following X-irradiation, independently of the cell cycle and cell survival. KS Iwamoto, T Mizuno, T Ito, N Tsuyama, S Kyoizumi, T Seyama. *Cancer Research* 56:3862–5, 1996.

Missense mutations are by the far the most common types of mutations found in p53 of human tumors, suggesting that mutant p53 proteins function either by abrogating wild-type function or by gaining new oncogenic functions. To distinguish between the dominant-negative effect and gain of new function of p53 missense mutants, we measured the ability of transfected missense mutant p53s in p53-null Jurkat cells to alter T-cell receptor (TCR) surface expression. The TCR is a key signal transduction moiety common to T lymphocytes and is one of the major sites for aberrations in T-cell leukemias/lymphomas. Three p53 mutants(248^{trp}, 249^{ser}, and 273^{his}) enhanced the frequency of TCR mutants after graded doses of X-radiation compared to null p53 parent- and wild-type p53-possessing normal lymphocytes; the parent Jurkat and normal lymphocyte showed no difference. These enhancements were not the results of a change in radiosensitivity or in G_1, checkpoint arrest characteristics. Therefore, the creation of this mutator phenotype by missense-type p53 mutations implies that a more direct mechanism, apart from changes of cell cycle kinetics or cell death, may be responsible for the selection of certain p53 point mutations, which eventually result in the tumorigenesis of the cell.

Prevalence of skin neoplasms among the atomic bomb survivors. M Yamada, K Kodama, S Fujita, M Akahoshi, S Yamada, R Hirose, M Hori. *Radiat Res* 146: 223–6, 1996. J

About 7,000 atomic bomb (A-bomb) survivors from Hiroshima and Nagasaki who participate in the Radiation Effects Research Foundation (RERF) Adult Health Study (AHS) were examined to define the relationship between skin neoplasms and exposure to ionizing radiation. Careful clinical inspection of the skin was undertaken to detect not only skin cancer but precancerous lesions such as senile keratosis. Five cases of basal cell carcinoma, five cases of senile keratosis and one case of Bowen's disease were confirmed histologically among 5955 A-bomb survivors for whom Dosimetry System 1986 (DS86) dose estimates are available. The relationship between the combined prevalence of skin cancer and precancerous lesions and DS86 dose was examined together with other factors that might affect skin neoplasms including occupational exposure to ultraviolet (UV) rays, age, sex and city. The prevalence of basal cell carcinoma and senile keratosis increased as the DS86 dose increased. The prevalence of skin cancer and senile keratosis among persons engaged in work involving frequent exposure to UV rays was higher than among those who were not engaged in such work. Sex and city were not significantly related to those skin diseases. Odds ratios of skin neoplasm for a 1-Gy dose, occupational exposure to UV rays and age at time of examination (in 10-year increments) are 1.7, 5.9 and 1.9, respectively.

Spontaneous immortalization of cultured skin fibroblasts obtained from a high-dose atomic bomb survivor. T Honda, N Sadamori, Mitsuo Oshimura, I Horikawa, H Omura, K Komatsu, M Watanabe. *Mutation Research* 354:15–26, 1996.

Two immortal fibroblastic cell strains (substrains) were established by culturing healthy skin cells obtained from a high-dose atomic bomb survivor (female, age 76 years, 5.14 Gy) for more than 4 years. Designated FM-U and FM-M, the two substrains share the same marker chromosome, t(5q – ;6p +), but are karyotypically different, possessing hypodiploid chromosome numbers (39–43) in the former and hypertriploid (69–76) in the latter. Thus far, the two strains have passed through 117 and 156 subcultures or more than 230 and 310 cumulative population doublings, respectively, each passage requiring 4–6 days in the former and 3–4 days in the latter. In the process of immortalization, sequential rearrangement among various chromosomes presumably due to telomeric and interstitial telomeric fusions took place following the telomere shortening, particularly in the senescence and postsenescence phase cells. Of particular interest is the fact that loss of heterozygosity (LOH) of the p53 gene was demonstrated in these immortalized cell populations. In addition, the allelic patterns of the LOH of p53 differed. Further evidence indicative of infinite proliferation was demonstrated in both strains, such as the telomere elongation and the significantly low frequency of cells possessing dicentric chromosomes.

Normal D–J_H rearranged products of the IgH gene in SCID mouse bone marrow. R Araki, M Itoh, K Hamatani, M Abe. *International Immunology* 8(7):1045–53, 1996.

SCID mice are profoundly immunodeficient, resulting from an inability to carry out the V(D)J recombination reaction during both B cell and T cell development. Recently, however, it was revealed that normal rearrangement frequently did occur in the TCR δ and γ chain loci in the SCID thymus. To evaluate whether the normal rearrangement occurring in SCID is a T-cell-specific phenomenon, we directly cloned using PCR the D_{Q52}–J_{H2} and $D_{FL16.1}$–J_{H2} rearranged segments of the IgH gene from SCID bone marrow. The subsequent analysis revealed that normal V(D)J recombination occurred in a significant number of the analyzed clones. By quantitative Southern hybridization it was shown that the quantity of normal D_{Q52}–J_{H2} joints existing in the SCID bone marrow is ~4–7% that in normal bone marrow. D–J_H rearrangement in SCID mice and normal mice differs in the frequency

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of nucleotide insertion (N insertion). Although most of the normal mouse clones exhibited N insertion in the D–J_H rearrangement, in SCID mouse clones N insertion was identified in only a few D–J_H rearrangements. Furthermore, in several normal rearranged clones, the recombination occurred at the short homologous sequence. These observations suggest that the V(D)J recombination of IgH normally occurs at the early stage of SCID B cell development, just as TCR gene rearrangement occurs during SCID T cell development. Furthermore, the features of rearranged products isolated from SCID bone marrow cells were remarkably similar to those from leaky SCID mice.

Feasibility of using decades-old archival tissues in molecular oncology/epidemiology. KS Iwamoto, T Mizuno, T Ito, M Akiyama, N Takeichi, K Mabuchi, T Seyama. *Am J Pathol* 149:399–406, 1996.

Archival tissues are a bountiful resource for various studies. Polymerase chain reaction permits the use of such tissues for molecular biological analyses of disease causation. However, a comprehensive study using a large number of decades-old samples (20 or more years) for molecular oncology/epidemiology has never been shown to be feasible. We have relied upon the unique tumor registry of atomic bomb survivors to show that such studies are possible using 275 hepatocellular carcinoma and 41 skin cancer cases. We used 23 relatively recent thyroid papillary carcinoma cases from persons living in the vicinity of the Chernobyl nuclear reactor accident for comparison. Degradation of DNA is severe in autopsy hepatocellular carcinoma samples but can be compensated for by decreasing the polymerase chain reaction product size. Increasing the amount of DNA that is used by a factor of 8 improved amplification efficiency from approximately 60 to 80%. Age of the samples was not as great a problem as was the source of procurement. The extracted DNA can be used for all types of assays that require polymerase chain reaction amplification, such as restriction fragment length polymorphism, single-strand conformation polymorphism, and direct sequencing.

Hypothesis: "Rogue cell"-type chromosomal damage in lymphocytes is associated with infection with the JC human polyoma virus and has implications for oncogenesis. JV Neel, EO Major, AA Awa, T Glover, A Burgess, R Traub, B Curfman, C Satoh. *Proc Natl Acad Sci USA* 93:2690–5, 1996.

Growth suppressive efficacy of human LAK cells against human lung cancer implanted into SCID mice. S Teraoka, S Kyoizumi, T Suzuki, M Yamakido, M Akiyama. *Int J Oncol* 6:1271–7, 1995.

A novel SCID mouse model for studying spontaneous metastasis of human lung cancer to human tissue. S Teraoka, S Kyoizumi, T Seyama, M Yamakido, M Akiyama. *Jpn J Cancer Res* 86:419–23, 1995.

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