RERF update RERF

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

Volume 6, Issue 1 Hiroshima & Nagasaki Spring 1994

RERF Chairman Receives Gold Medal from Royal Swedish Academy of Sciences

In early January, the Royal Swedish Academy of Sciences awarded to RERF Chairman **Itsuzo Shigematsu** a gold medal for distinguished service in the field of radiation protection. **Roger Clarke**, chairman of the International Commission on Radiological Protection's (ICRP) Main Commission, presented the award to Shigematsu at the 18th International Congress of Radiology, held this year in Singapore.

The award, which is usually presented once every 4 years, honors a person who has rendered distinguished service in the field of international radiation protection during the previous decade.

The tradition began in 1962 at the recommendation of **Rolf M Sievert**, a Swedish radiation physicist and former chairman of the ICRP's Main Commission. (Sievert's name has since been given to the international radiation unit for expressing "equivalent dose" and "effective dose.") After consulting with the ICRP's Main Commission, three nominees for the gold medal are selected.

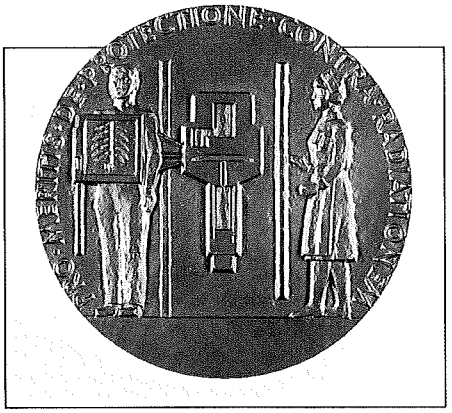
"I received this award because of the achievements of RERF's staff. I am their representative," said Shigematsu, who is now serving his fourth 4-year term as RERF chairman. "Belatedly I wish to express my deepest appreciation to all the people associated with RERF who have congratulated me."

Shigematsu is the second Japanese scientist to be honored by the Royal Swedish Academy. **Shinji Takahashi**, former president of the Aichi Cancer Center, received the award posthumously in 1985. Other previous recipients of the gold medal were **W Binks** and **KZ Morgan** (1962), **WV Mayneord** (1965), **LS Taylor** (1973), **EE Pochin** (1981), and **B Lindell** (1989).

Shigematsu is a member of the World Health Organization's (WHO) Expert Advisory Panel, and until recently he was a member of the ICRP's Main Commission.

In 1990, he chaired the International Chernobyl Project's (ICP) International Advisory Committee. The ICP, a year-long study conducted under the auspices of the International Atomic Energy Agency with expert counsel drawn from various countries and organizations of the United Nations system and the European Union, corroborated the earlier local findings regarding the environmental and health situation in areas of the former Soviet Union affected by the Chernobyl nuclear-power-plant accident. Several RERF staff members also participated in the ICP.

A graduate of Tokyo and Harvard universities, Shigematsu was director of the National Institute of Public Health's Department of Epidemiology from 1966–1981, where he is now a professor emeritus. In 1981, he became the third chairman of RERF. ❑



The Royal Swedish Academy of Sciences' Radiation Protection Fund gold medal.

The chairman of the International Commission on Radiological Protection's Main Commission, Roger Clarke (left), presents the Royal Swedish Academy of Sciences' Radiation Protection Fund gold medal to RERF Chairman Itsuzo Shigematsu.

In This Issue

Perspectives

The Budget Crisis at RERF

by Mortimer L Mendelsohn, Vice Chairman

The 1994 Japanese Fiscal Year (FY94) began on 1 April, but the US and Japanese governments have yet to agree on the RERF budget for the year. The representatives of the two governments are scheduled to meet again in May, in the hopes of reaching agreement.

The primary cause for this problem is the tight federal budgets of the Clinton Administration, coupled to the roughly 15% reduction in the value of the dollar relative to the yen in the past 2 years. From the beginning of the negotiations, the US Department of Energy (DOE) has taken an unyielding position that, in effect, is asking RERF to reduce its operations by 22% for FY94. The corresponding responsible agency in Japan, the Ministry of Health and Welfare (MHW), has countered with the largest reduction that it thinks is possible according to Japanese law and style of management. However, this reduction is about half of what DOE wants. Even if the governments can somehow converge at the level offered by the MHW, RERF faces the loss of 35 people in 1 year, including a drop from 6 to 4 directors, and an almost halving of the number of Americans. This would be accompanied by a dramatic reduction of the operating budget for supplies, equipment, and communication. As an example, the very existence of *RERF Update* is severely threatened.

It is ironic that this should be happening during the 50th anniversary year of the atomic bombings and at a time of impressive research productivity, as epitomized by publication of a supplement to the February issue of the journal *Radiation Research*, which is devoted to RERF's latest cancer-incidence studies. From the historical and the scientific points of view, this is definitely not the time to be phasing out the Foundation or severely restricting its activities. Amazingly, 52% of the survivors who were initially defined as the Life Span Study cohort in 1950 are still alive. Furthermore, 86% of the survivors who were less than 30 years old at the time of the bombings are alive, leaving the youngest and probably most sensitive of the exposed still largely unaccounted for in terms of cancer mortality. With another 10 or so years of commitment to cancer-incidence and life-span mortality studies, we should be able to define the radiation risk to all ages of survivor, allowing construction of the risk profile of any particular irradiated population over any particular time span. It is imperative that RERF remains intact if for no other reason than to accomplish this end.

Similar arguments for continuation can be made for other aspects of RERF work in which immediate access to the survivors is crucial to understanding the radiation biology of this uniquely exposed population. The periodic examination of the survivors within the recently modernized Adult Health Study (AHS) is a prime example. The AHS is uncovering a fascinating variety of hitherto unknown physiological and medical radiobiological effects in the survivors and simultaneously remarkably documenting the aging and evolving Japanese control population. Similarly, the biological dosimetry being done at RERF is unmatched anywhere in the world. It functions locally as a critically important approach toward understanding the city differences and the biological susceptibility of the survivors, and it functions in general as a tool for broad application throughout the fields of epidemiology and human toxicology.

The Hiroshima Laboratory

Given the current financial circumstances, there may well be some aspects of RERF work that are suitable for delay or even export, even though they are exemplary and important science and are best done in the setting of RERF. Such studies can be carried out remotely, in place and time, because of the availability of appropriately stored or retrievable materials. Examples of this type of work include estimates of heritable mutation, organ-specific pathology and epidemiology, and continued death-certificate surveillance of the offspring of the survivors.

Regardless what research continues and what can be reduced or postponed, the social and legal structures under which RERF operates must be respected. RERF management may not discharge long-serving, diligent employees or reduce their traditional benefits. Thus, although management has the power to terminate programs, we cannot eliminate the people and thereby save the associated costs. Restructuring can be done, but only at a pace dictated by the natural turnover of personnel at RERF.

In the spirit of Japan, RERF must be regarded as an institutional living treasure. The clearest reason is because of its primary role in radiation and cancer biology and in the developing field of human risk assessment. Less well known, but of rapidly growing importance, is its international role in training and advising other nations as they face large-scale radiation and toxicological accidents. Surely RERF's two wealthy sponsors recognize the importance of this treasure and their responsibility to it. The whole world is hoping that they will find a way to support the program properly and thereby allow the continued flowering of this unique resource. ❑

Cancer Incidence in Atomic-bomb Survivors

A special issue of the journal* Radiation Research, *published in February, is devoted to RERF analyses of cancer incidence, a complement to RERF's periodic Life Span Study reports that focus on mortality among the atomic-bomb survivors.

by Kiyohiko Mabuchi, Department of Epidemiology, RERF, and Dale Preston, Department of Statistics, RERF

Editor's note: Complete bibliographic information for all four papers published in this special issue can be found on page 12 of Update.

The RERF Life Span Study (LSS), comprising 93,000 atomic-bomb (A-bomb) survivors and 27,000 unexposed persons, is a major source of epidemiological data for cancer-risk assessment. Periodic analyses of LSS mortality data have been published by RERF, beginning in 1961. However, the few reports addressing cancer incidence have almost exclusively dealt with selected individual cancer sites. Four RERF reports published in a special issue of *Radiation Research* in February provide the first comprehensive overview of cancer incidence in the LSS. What follows is a brief summary of this four-part special issue.

Use of the tumor registries

Part I, by K Mabuchi et al, describes the methodological aspects of the Hiroshima and Nagasaki tumor registries and addresses data-quality issues relevant to the incidence studies, in the context of the LSS cohort. Population-based tumor registries, established in 1958 in Hiroshima and Nagasaki, are characterized by active case ascertainment based on abstracting medical records at local hospitals. Efforts to improve the quality and usefulness of this cancer-incidence data already have been described by K Mabuchi and M Soda in *RERF Update* 2(2):5–6, 1990.

The quality of the Hiroshima and Nagasaki registries ranks among the best in Japan and is comparable to registries established in other countries, because of a death-certificate-only rate of less than 9% and a histological verification rate greater than 70%. LSS cancer cases identified from the registries were reviewed and processed using standardized procedures to ensure complete ascertainment, data quality, and consistency. Special studies and monitoring programs were introduced. The analyses performed indicated the uniformity of the data across various strata, justifying the use of incidence data for cancer risk assessment in the LSS.

Solid tumors

Solid-cancer-incidence data are presented in Part II, by D Thompson et al. Included in the analyses are 8613 first occurrences of primary solid tumors diagnosed among 79,972 individuals during the period 1958–87. A standard set of analyses based on a general excess-relative-risk (ERR) model was performed for all cancer sites as well as for each of 21 organs or systems, using Dosimetry System 1986 (DS86) organ doses. Analyses performed for each cancer site involved fitting of a set of models: the background model with no dose effect, a linear-dose-response model with no effect modifiers, a linear-quadratic dose-response model with no effect modifiers, and a series of linear-dose-response models that included each of the covariates (sex, age at exposure, time since exposure, attained age, and city) individually as effect modifiers. Because the tumor registries ascertain cancers in the registry catchment areas only, an adjustment was made for the effect of migration (*RERF Update* 3[3]:10, 1991).

> ***'The quality of the Hiroshima and Nagasaki registries is comparable to registries established in other countries.'***

Part II begins with the analysis of all solid-tumor-incidence data. For all cancer sites, a strong linear dose response was found, with no significant difference between the responses for Hiroshima and Nagasaki. The ERR is about twice as high for females as for males and decreases with increasing age at radiation exposure, as previously found in the mortality studies. ERR for all solid tumors decreased with time for the groups exposed when young but remained virtually constant for the cohorts exposed when older; averaged over all ages at exposure, ERR decreased with time since exposure.

Part II also describes the results of cancer-site-specific analyses. In agreement with the previous findings, a statistically significant excess risk was found for cancers of the stomach, colon, lung, breast, ovary, urinary bladder, and thyroid. An effect of A-bomb radiation on salivary-gland tumors was also observed, strengthening earlier incidence findings. For the first time in the LSS cohort, radiation has been associated with liver cancer and nonmelanoma skin cancer. No significant dose response was found for cancers of the oral cavity and pharynx, esophagus, rectum, gallbladder, pancreas, larynx, uterine corpus and cervix, prostate, kidney and renal pelvis. No city differences were found for any of the cancer sites examined; females had a significantly higher ERR compared with males, for cancers of the respiratory system, including the lung, and cancers of the urinary system. The ERR decreased with increasing age at exposure for the following cancer sites: salivary glands, stomach, nonmelanoma skin, breast, and thyroid.

Leukemia, lymphoma, and multiple myeloma

Leukemia incidence has been of interest since the earliest studies of A-bomb survivors, and the analysis of the incidence data on leukemia as well as on cancers of the

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Cancer Incidence

continued from page 3

lymphoid tissues is presented in Part III, by D Preston et al. This analysis adds 9 additional years of follow-up for leukemia and 12 for multiple myeloma to the last comprehensive incidence reports on these cancers, and it is the first analysis of lymphoma incidence in the LSS cohort. Unlike Part II, which is based solely on solid-tumor data from the Hiroshima and Nagasaki tumor registries, Part III also includes incident cases ascertained from the leukemia registry. The availability of the leukemia-registry data made it possible to extend the study period back to 1950. The total numbers of cases diagnosed during the present study period (1950–87) are 290 for leukemia, 229 for lymphoma, and 73 for multiple myeloma, with analyses restricted to the first occurrences of primary tumors among the residents of Hiroshima and Nagasaki assigned DS86 dose estimates between 0 Gy and 4 Gy.

Time-dependent models for the excess absolute risk were applied for all the studied diseases and for specific leukemia types, including acute lymphocytic leukemia (ALL), acute myelogenous leukemia (AML), chronic myelocytic leukemia (CML), and adult T-cell leukemia (ATL), which is endemic in Nagasaki. Too few cases of chronic lymphocytic leukemia were found to allow meaningful statistical analysis. The report emphasizes the importance of considering age, time, and sex, as well as specific leukemia types, in estimating risk. Strong evidence exists of radiation-induced risks for all types of leukemia except ATL, but significant leukemia-type differences in dose response and patterns of risk by age at exposure, sex, and time since exposure have been found. The AML dose-response function was nonlinear, whereas no evidence against nonlinearity was found for the other types of leukemia. The results suggest that men and women differ significantly with regard to the level and temporal patterns of the excess risk. The present analysis shows no evidence of an excess risk of multiple myeloma, whereas weak evidence was found of an increased risk of non-Hodgkin's lymphoma in men.

Comparing incidence and mortality data

The significance of considering incidence data in risk assessment is made clear by comparing the major differences between incidence and mortality findings, highlighted in Part IV, by E Ron et al. The incidence data derived from the Hiroshima and Nagasaki tumor registries are limited to the period after 1958 and the catchment area of the registries, whereas mortality data are available through nationwide family registries, dating from 1950 onward. During the period 1958–87 in Hiroshima and Nagasaki, 9014 first-primary-incident tumor cases (including hematopoietic cancers) were identified among the LSS cohort members, compared with 7308 deaths nationwide attributable to cancer for the period of 1950–87 and 5859 cancer deaths for 1958–87 in Hiroshima and Nagasaki. For certain cancer sites, such as the oral cavity and pharynx, skin, breast, female and male genital organs, urinary bladder, and thyroid, the number of incident cases was more than double the number of mortality cases. The overall conclusions, regarding which cancer sites provide significant evidence of dose response, are consistent for incidence and mortality data. Both incidence and mortality data show significant excess risks for all solid cancers of the stomach, colon, liver (defined as primary liver cancer or liver cancer not otherwise specified on the death certificate), lung, breast, ovary, and urinary bladder; no significant risk is seen for cancers of the pharynx, rectum, gallbladder, pancreas, nasal cavity, larynx, uterus, prostate, or kidney in either the incidence or mortality series. Disagreements are confined to the risk of esophageal cancer—significantly elevated on the basis of mortality data—but not on the basis of incidence data and the risk of nonmelanoma skin cancer, which is significantly elevated only on the basis of incidence data. Cancers of the salivary glands and thyroid, found to be in excess in the incidence series, were not considered in the earlier mortality analyses.

> ***'The virtually complete ascertainment of deaths among the LSS and other RERF cohorts . . . is one of the major strengths of the RERF follow-up investigations.'***

For all solid tumors, the estimated ERR based on incidence data is about 40% higher than the mortality-based ERR. Furthermore, the incidence-based EAR is 2.7 times higher than the mortality-based estimate. For some cancer sites, the differences between the risks for incidence and mortality are greater. These differences reflect several factors but are largely due to the better representation in the incidence series of relatively nonfatal cancers, such as breast, thyroid, and skin cancers.

Both incidence and mortality data are important

These recently completed comprehensive analyses of the LSS cancer-incidence data provide valuable new information on the cancer risk associated with radiation. Especially for fatal cancers, incidence data support the major LSS mortality findings, emphasizing the importance of continued mortality surveillance of A-bomb survivors. The virtually complete ascertainment of deaths among the LSS and other RERF cohorts by means of the unique *koseki** system is one of the major strengths of the RERF follow-up investigations. Incidence data are not problem free and are liable to bias unless special care is taken to collect the data systematically.

The present studies demonstrate the usefulness of the tumor-registry-based incidence data, which are crucial to fully evaluating the full impact of radiation effects. Incidence data provide a powerful means of evaluating the risk at the time of disease onset and provide information more useful for cancer etiology. In view of the rapid progress in the treatment and control of cancer, the importance of continued incidence surveillance will increase. With the availability of the two complementary sets of cancer data—incidence and mortality, a broader spectrum of research on radiation effects and risk assessment is now possible. ❑

** In Japan, the birth and death of family members are recorded in official records as required by law. Through an arrangement with government agencies, RERF and its predecessor, the Atomic Bomb Casualty Commission, have been permitted access to these records.*

The Origin of Clonal Chromosome Aberrations

Clonality of chromosome aberrations in peripheral-blood lymphocytes has been seen among high-dose atomic-bomb survivors. This report describes the first confirmed case of their stem-cell origin and the implications of mutation assays as lifetime biodosimeters.

by Y Kusunoki, Y Kodama, Y Hirai, N Nakamura, and M Akiyama, Department of Radiobiology, RERF

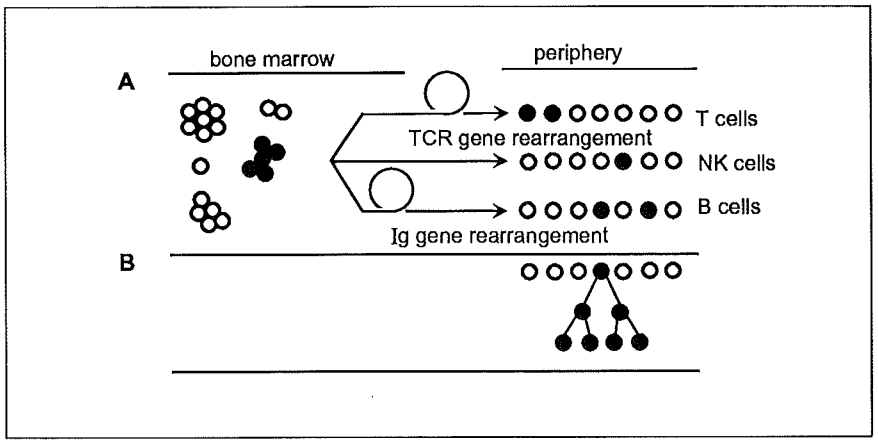

FIGURE REVISED BY K KANEOKA

Figure. Two alternative mechanisms for the clonal manifestation of a chromosome aberration observed in peripheral-blood lymphocytes. A. Clonal proliferation of an aberration-bearing stem cell in bone marrow, producing lymphocytes of various lineages with identical chromosome aberration(s), shown as filled circles. B. Clonal proliferation, probably by antigen stimulation, of an aberration-bearing mature lymphocyte in the periphery, producing lymphocytes carrying identical chromosome aberration(s) shown as filled circles. In mechanism B, the lymphocyte lineages and T-cell-receptor (TCR) gene rearrangements or immunoglobulin (Ig) gene rearrangements of the monoclonally derived cells are identical. NK cells = natural-killer cells. Open circles are normal cells.

The frequency of chromosome aberrations in peripheral-blood lymphocytes has been measured to biologically evaluate radiation doses received by humans. Among the high-dose atomic-bomb (A-bomb) survivors, clonal chromosome changes have been encountered either repeatedly in the same donor—but at different times—or in three or more cells from one blood sample. Scrutiny of such clonal aberrations is likely to provide valuable information on the clonal proliferation of human bone-marrow stem cells, in addition to information on possible biases in reconstructing A-bomb doses based on the frequency of cells bearing chromosome aberrations or mutations at specific genes.

In this brief report, we describe a chromosome aberration shared by several percent of phytohemagglutinin-stimulated (PHA-stimulated) lymphocytes from one A-bomb survivor (Kusunoki et al, *Blood*, in press). We found that a single stem cell proliferated, differentiated, and was finally able to reconstitute about 10% of both T- and B-cell colonies randomly established from this survivor. Our results suggest that in humans, some stem cells have an enormous capacity to multiply, with a single cell able to reconstitute up to several percent of the lymphoid system, as seen in rodents.

Methods

The examinee was exposed when 20 years old to an estimated Dosimetry System 1986 (DS86) dose of A-bomb radiation of 1.95 Gy. Cytogenetic analysis consistently showed that 30–40% of cells in PHA culture (that is, T and natural-killer cells, but not B cells) carried various chromosome aberrations. A subset of 3–8% of the cells had the identical aberration [two reciprocal translocations, t(4;6),t(5;13)], beginning with the first examination in 1980 and persisting in subsequent years.

Because it is virtually impossible that the different cells containing the same two translocations were of independent origin, they must have come from the same clone. This clone could originate either from a single bone-marrow stem cell or from a mature, antigen-stimulated peripheral T cell (see the Figure above).

To ascertain the origin of this aberration, peripheral-blood lymphocytes were first propagated monoclonally (that is, by colony formation) at random to establish many T- and B-lymphocyte colonies for subsequent analyses.

Major findings

Chromosome analysis of 71 T-cell colonies ($CD4^+$, $CD8^+$, or $CD4^-8^-$) showed that 43 bore various chromosome aberrations and that among these, 6 carried the t(4;6),t(5;13) reciprocal translocations. Among the 58 independent colonies of B cells transformed by the Epstein-Barr virus, 31 contained various aberrations and, unexpectedly, 7 carried the same t(4;6),t(5;13) translocations. Because mature T lymphocytes are most unlikely to redifferentiate into B cells, or vice versa, the presence of the identical pair of translocations in T and B lineages required that the initial event occurred in a precursor cell.

Supportive evidence derives from the patterns of the rearrangements of T-cell-receptor (TCR) genes or immunoglobulin (Ig) genes, which were different among the colonies. These TCR- and Ig-gene rearrangements, which determine the antigen specificity of the cells, occur during differentiation of T and B cells, respectively. Thus, t(4;6),t(5;13) cells must have been present when these differentiations occurred.

Interleukin-2 production and cytotoxic activity are general characteristics of $CD4^+$ (helper/inducer T) and $CD8^+$ (suppressor/cytotoxic T) lymphocytes, respectively. Among the six T-cell colonies bearing a

continued on next page

Origin of Aberrations

continued from page 5

t(4;6),t(5;13) aberration, four were $CD4^+$ and two were $CD8^+$, all functionally normal in this regard. Persistence of the t(4;6),t(5;13) cells since 1980 at an almost constant frequency suggests that these cells are not likely to have monoclonally propagated because of a growth advantage, for example, caused by a preleukemic condition.

Although the possibility of spontaneous origin cannot be totally excluded (that is, the pre-radiation-exposure condition cannot be determined), the generation of two translocations within a cell appears more likely to be radiogenic. Indeed, most of the survivors so far identified as having clonal aberrations are from the high-dose (≥2 Gy) group (personal communication with A Awa, Department of Genetics, RERF, Hiroshima, 1994).

The ability of a single stem cell in the bone marrow of a human adult to produce progeny attaining several percent of the total lymphocyte population, that is, on the order of 10^{11} to 10^{12} lymphocytes, is impressive. In the present case, the t(4;6),t(5;13) aberration probably occurred in a stem cell that later became one of the largest clones. Indeed, in this survivor, two additional aberrations occurred in both T and B cells, but less frequently.

The number of stem-cell clones

Two sources of information on stem-cell clones are available. Awa reported that about 10% (7/71) of the high-dose survivors bore three or more cells with an identical aberration in PHA cultures of peripheral lymphocytes (*Chromosomes and Cancer*, edited by JL German, New York, John Wiley, 1974, pp 637–74). The average frequency of lymphocytes with various chromosome aberrations in the PHA culture was about 15% among the 71 survivors.

Amenomori et al examined 100 metaphases in PHA culture from peripheral-blood lymphocytes and 10 metaphases (on the average) in myeloid cell culture from bone marrow for each of 21 high-dose survivors (*Exp Hematol* 16:849–54, 1988). In two survivors, possibly identical aberrations were observed in both PHA and myeloid cultures. The average frequency of aberrant cells in PHA culture was 23% among these 21 survivors.

Since the spectrum of the various clone sizes is not known, we assume here for simplicity that the size of active stem-cell clones is the same. In the first study, by Awa, for each clone among N active clones to be sampled x times in 100 cells scored, the probability is described by the binomial function

$$p_x = {}_{100}C_x[1-(1/N)]^{100-x}(1/N)^x.$$

Thus, for any aberrant clone to be sampled three times or more,

$$p = 0.15N(1 - p_0 - p_1 - p_2).$$

In the second study, by Amenomori et al, the probability of any clone being sampled among both 100 cells in PHA culture and 10 myeloid cells is

$$0.23N(100/N)(10/N).$$

The computed number N was 450 in the Awa study and 2400 in the Amenomori study. Although the confidence intervals are much larger in the latter study because only two cases were found, the two independent estimates agreed within an order of magnitude. The apparently smaller estimate obtained using the first approach (that is, clonal aberrations in PHA culture only) might be an indication of a significant contribution of clonal propagation to the population of mature lymphocytes, possibly after antigen stimulation in the periphery. Further studies on additional cases to test for the presence of peripheral clones should clarify this issue.

The above estimates probably represent the minimum numbers of the largest clones in bone marrow. Smaller clones, for example, one-tenth the size of the largest ones, would not be properly detected unless 1000 or more metaphases were examined for each individual. Such smaller clones are likely to be much more abundant, as should be the total number of active stem-cell clones. Further, the above estimates are derived from survivors who received a high whole-body dose of radiation (about 2 Gy or more), and the surviving fraction of the stem cells would be below 10% (mean inactivation dose, D_0, is reportedly about 1 Gy). This severe depletion of the stem-cell pool could have caused an apparent increase in average clone size if tissue recovery is managed preferentially by proliferation of active stem cells at the time of irradiation, in which case the calculated number is undoubtedly an underestimate. In contrast, if the recovery is aided by an excess of previously dormant stem cells, which would be otherwise quiescent, the radiation exposure would not have caused an undue increase in clone size distribution. Currently available data do not allow us to distinguish between the two alternatives. Future studies on the relationship between the estimated size of aberrant clones and radiation dose may clarify whether the recovery process involves mainly active stem cells or previously dormant cells as well.

Implications for lifetime biodosimetry using blood cells

To date, the three T-lymphocyte assays employed for the quantitative measurement of mutant frequency (HPRT, HLA, and TCR loci) have not shown a clear dose-response relationship in the A-bomb survivors. Initially, we assumed that the mutants were not neutral in vivo and were negatively selected over time. However, we now suggest an additional possibility: the decay of lymphocyte mutant frequency over time might be a common characteristic essentially independent of the markers studied.

By means of a lymphocyte surface marker, peripheral-blood T lymphocytes are operationally classified into two approximately equal subpopulations, CD45RA marker-positive (naive T) and CD45RO marker-positive (memory T) cells. Naive T cells are defined as cells that had not encountered or responded to antigen stimulation. Most CD45RA-positive cells appear to be direct descendants of precursor stem cells and are replenished continuously throughout life.

To serve as a lifetime biologic dosimeter, the naive T cells must satisfy two conditions. First, they must be derived from a sufficiently large number of stem-cell clones, 10^6 or more. Otherwise, a "jackpot-type" event (an occasional large "payoff-type" event) might occur, and dose response would fluctuate extensively many years after irradiation because the mutation-induction rate at the HPRT locus, for example, is on the order of 10^{-5}/Gy. Second, the number of descendants of each clone should not vary extensively.

Although we know little about the clone size spectrum, current infor-

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News Briefs

✓ Research Staff News

Hiroshima

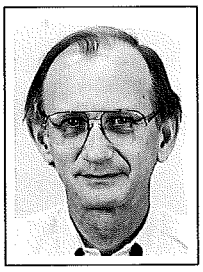
Department of Statistics: On 1 March, **Donald A Pierce** was promoted to senior scientist and **John B Cologne** to associate senior scientist.

Department of Radiobiology: **Yuko Hirai** of the Laboratory of Immunology was promoted to senior scientist on 1 March.

Research scientist **Takashi Ito** is spending 2 years at the University of California at San Diego. He will conduct research on cell differentiation and proliferation in the laboratory of **James T Kadonaga**.

Research Information Center: In the fall, **Timothy Demarest** joined the Information Systems Laboratory as a research scientist. He comes to RERF from HJ Ford Associates of Arlington, Virginia. He will provide support for personal-computer hardware and software, networking, interface to the UNIX environment, and application systems development.

Hirai



Pierce

✓ Attendance at International Meetings

In Vienna, 1–4 March, Epidemiology Chief **Kiyohiko Mabuchi** attended a meeting of an International Atomic Energy Agency advisory group that is updating information on thyroid effects caused by the Chernobyl accident. Researchers from Belarus, France, Germany, Italy, Japan, the Russian Federation, Switzerland, Ukraine, the US, and the UK represented various disciplines, including epidemiology, clinical medicine, and dosimetry.

From 7–11 March in Vienna, Mabuchi and RERF Department of Statistics Chief **Dale Preston** attended the 43rd session of the United Nations Scientific Committee on the Effects of Atomic Radiation. Epidemiological studies of radiation carcinogenesis was one major topic of discussion.

✓ Former Department Chief Honored

In October, **Howard B Hamilton**, former chief of the RERF Department of Clinical Laboratories, was unanimously elected an honorary member of the Japan Society of Human Genetics. ❑

Origin of Aberrations

continued from page 6

mation suggests that naive T cells could satisfy the two conditions only with difficulty. Namely, if the clones of active stem cells are the same size, then the total number of the clones may not reach 10^6, whereas if the clone size varies, the first requirement may be satisfied but not the second. Such a structure, however, will not seriously affect the frequency of stable chromosome aberrations because the whole genome is the target and the induction rate is sufficiently high (about 10% per gray).

The CD45RO-positive memory-T cells do not disappear over time but remain in the body for many years to provide an immunologic repertoire against a wide spectrum of foreign antigens. Because they constitute about 50% of total T lymphocytes, the pool size of which is huge, memory T cells appear to fulfill the two basic requirements for measuring mutant frequency as an indicator of biodosimetry.

However, evidence now exists that a peripheral T cell (defined by the identical TCR-gene rearrangement) proliferates extensively—for example, one billionfold—to occupy 1 out of 1000 peripheral lymphocytes (Nicklas et al, *Environ Mol Mutagen* 12:271–84, 1988) or even more (Kusunoki et al, *Blood* 79:2965–72, 1992, and *Eur J Immunol* 23:2735–9, 1993; Dellabona et al, *J Exp Med* 177:1763–71, 1993). Thus, the major fraction of peripheral T cells might also comprise on the order of 10^6 clones, a number probably large enough to provide immunologic defense against various foreign antigens and to allow measurement of chromosome-aberration frequency. But, again, the number of such clones might not be large enough for quantitative determination of mutant frequency at specific loci as a lifetime biodosimeter. In addition, and more importantly, more than 48 years have passed since A-bomb-radiation exposure, and varying histories for the expansion and curtailment of each memory-T-cell population after antigen stimulation have seriously confounded the estimation of mutant frequency caused by radiation exposure.

In contrast to the lymphocyte assays of somatic mutation, the erythrocyte assay at the glycophorin-A (GPA) locus has been shown to detect radiation exposure for A-bomb survivors more than 40 years later. The target cells of the GPA assay are the nucleated erythroid precursor cells in bone marrow. Thus, the number of long-lived stem-cell clones of erythroid lineage would be larger than the number of cells of lymphoid lineage and would be large enough to record dose-dependent radiation effects. However, extensive overdispersion of the GPA mutant frequency was observed among the moderate- to high-dose donors (Langlois et al, *Science* 236:445–8, 1987). Some of the high-dose survivors did show a 40% or higher frequency of chromosome aberrations in PHA culture but no increase in GPA mutant frequency (Akiyama et al, *Mutation and the Environment*, edited by ML Mendelsohn and RJ Albertini, New York, Wiley-Liss, 1990, pp 69–80). Therefore, the stem-cell pool in the erythroid lineage of the survivors probably also suffered extensive depletion and was too small to record properly the dose effect after high-dose exposures. In view of the induction rate of GPA mutations (about 2×10^{-5}/Gy), the number of long-lived precursor clones in the active erythroid lineage appears to be on the order of 10^6 under normal conditions.

In summary, the frequencies of both chromosome aberrations and specific locus mutations in lymphocytes appear equally useful for biodosimetric purposes because of the huge numbers of lymphocytes in vivo. However, the structure of the lymphocyte pool clearly seems to have more effect on the mutation assay than on the chromosome assay when the lymphocytes are used for lifetime dosimetry. The present study employing clone size distribution provides important insights into the kinetics and size of the lymphocyte-precursor pool. More data will undoubtedly refine our understanding of this issue. ❑

How Much Does Accuracy of Information about Shielding for Individual Survivors Influence Dosimetry Error?

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

A long-term cytogenetic survey on the atomic-bomb (A-bomb) survivors has shown that radiation-induced stable chromosome aberrations persist in vivo without changes in their frequency for many decades. Among detectable stable chromosome aberrations, translocations, which are the major contributors to the dose-response relationship, are mostly seen. Such translocations can now be detected to a large extent using the conventional staining method and also using G-banding analysis for more precise identification of translocations. This report describes the additional information derived from analysis of G-band data regarding the dose-response relationship for translocation frequencies in Adult Health Study (AHS) subjects in Hiroshima.

The subjects were 37 Hiroshima survivors with estimated Dosimetry System 1986 (DS86) doses (kerma) ranging from 0–4 Gy. Metaphase slides were treated with a 0.2% trysin solution and stained with diluted Giemsa for G-banding, according to the method of Seabright et al (*Lancet* 2:971–2, 1971). One hundred metaphases per sample were scored for the presence of translocation-type aberrations. The study showed generally good agreement between translocation frequency and the radiation dose of individual survivors. As emphasized in our previous reports, we also noted an overdispersion of aberration frequencies relative to individual doses (Awa, *J Radiat Res* 32(suppl):265–74, 1991). To test whether the observed overdispersion is associated with any uncertainty in radiation-dose estimates for individual survivors, translocation frequencies determined by G-band analysis were further classified into several shielding categories.

Figure 1 shows the plots obtained from those survivors either exposed in the open totally unshielded (code number 01, in the 9-parameter method for DS86 dose estimates) or exposed in the open but shielded by a nearby Japanese building (07). The range of variation seems to be wider for this group of survivors. Figure 2 shows the plots of translocation frequencies obtained from survivors exposed inside a Japanese house (03) or tenement (05). The range of dispersion becomes narrower for these survivors inside a building than for the survivors exposed in the open. The sample size of the present study is so small that no conclusive evidence has yet been found of a relationship between the frequencies of translocations and the DS86 dose estimates. However, this suggests that the dose estimates of survivors inside Japanese houses are more accurate than the dose estimates of survivors exposed in the open.

Further detailed study is needed of the accuracy of available shielding information for estimating doses to individual survivors. Recent advances in the technique of fluorescence in-situ hybridization (FISH) with whole-chromosome probes to paint specific target chromosomes allow rapid detection of translocations, as described by Lucas et al (*Int J Radiat Biol* 62:53–63, 1992), and analyses of translocation frequencies using FISH are now underway at RERF. ❑

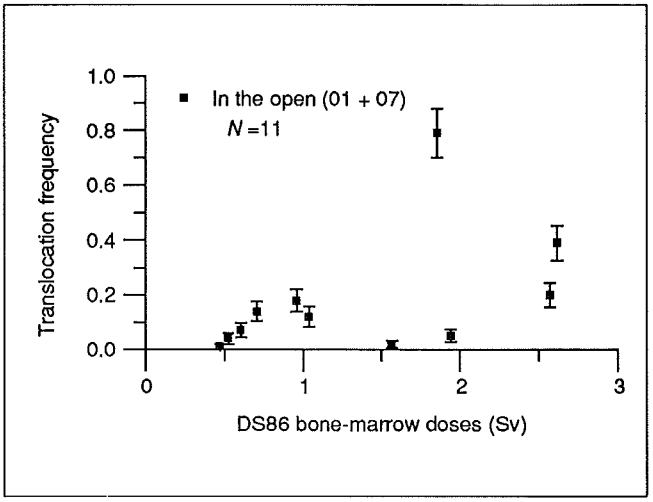


Figure 1. Translocation frequencies measured using G-band analysis for individual survivors either exposed in the open and unshielded (code number 01) or exposed in the open but shielded by a nearby Japanese building (code number 07), plotted against Dosimetry System 1986 (DS86) bone-marrow doses with a neutron relative biological effectiveness of 10. N = the number of survivors.

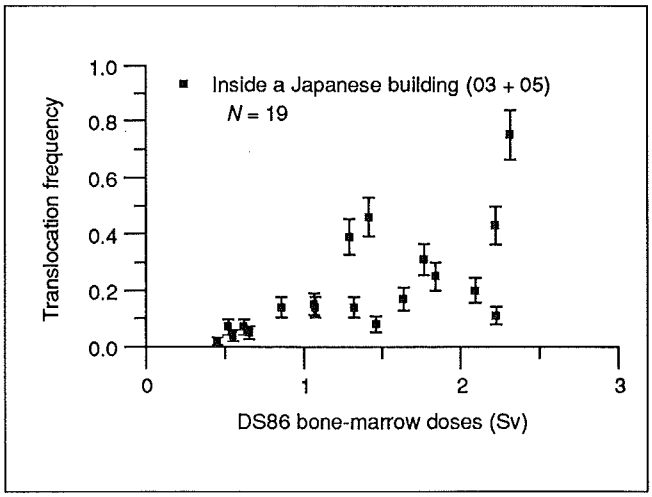


Figure 2. Translocation frequencies measured using G-band analysis for individual survivors exposed inside a Japanese house or tenement (code numbers 03 and 05). N = the number of survivors.

Miller's Memories of ABCC–RERF, 1953–1990: Part 2

The anecdotes of a longtime ABCC–RERF associate continue.

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

Editor's note: Part 1 of Robert Miller's recollections appeared in the previous issue of RERF Update *(5[4]:7–9, 1993).*

PHOTO COURTESY OF HATSUKO YOKOYAMA

When the "Hiroshima maidens" journeyed to the United States for medical treatment in 1955, Hatsuko Yokoyama (seated in the front row to the right of the girl with braids), an ABCC Department of Medicine staff member, served as the cultural liaison.

Problems in scientific communication

I stayed at ABCC an extra 6 months and rushed to prepare a report on findings among children in the decade after the bombings for presentation at the spring meeting of the pediatric research societies in the US. I am still shocked that the paper was not accepted for presentation, perhaps because it was not a conventional subject for pediatric research. A similar experience occurred in Japan. At the special quadrennial meeting of the Japan Medical Association, as a distinguished foreign visitor, I was scheduled to speak on the late effects of the atomic bombings on children. ABCC had long been accused of withholding information, so here was a chance to show we had nothing to hide. Virtually no one came to my lecture because at the same time there was a lecture on *ekiri,* a common life-threatening diarrheal disease thought to be unique to children in Japan. Ten years later, on the 20th anniversary of the bombings, journalists searched for something new to report and discovered the effects of exposure on the fetal brain.

Matrimonial pursuits

The 6-month extension allowed me another pursuit—of my future wife. I had purposely signed a 1-year contract because I thought I would probably be socially limited in Japan. I had no clue that Japanese women would be so attractive. The main tourists to Japan had been millionaires, who had not spread the word as later visitors did. For me the fairest of all was **Haruko Nakagawa**, whose personality has blended with mine for 39 years so far. She had been given an English name at a New Year's Day luncheon at the Bachelor's Officers Quarters, the predecessor of Hijiyama Hall, which was built in 1953. Someone suggested that for foreigners she needed a name that was easier to remember. *Holly* seemed the diminutive of Haruko and was appropriate to the Christmas season. She accepted it after first objecting that it is a man's name, like Harry Truman. Seven weeks later we were married at the US consulate in Kobe. The day we married the roof fell in—the roof of the *hondori* [the covered shopping street] in Hiroshima had been built to hold 6 inches of snow and on that day 7 inches of snow fell.

The 'Hiroshima maidens'

Just before we left for home in May 1955, **Norman Cousins**, editor of *The Saturday Review of Literature,* and **William M Hitzig**, an internist, came to Hiroshima to select 25 young women to bring to New York for surgery to diminish their disfiguring keloids due to burns. Cousins and Hitzig were late in looking for someone to serve as a cultural liaison for the "Hiroshima maidens" while they were in the hospital and between admissions, when they were to live with nearby Quaker families. While visiting the Department of Medicine at ABCC, Cousins mentioned the need for such a person as he stood beside the desk of the perfect candidate, **Hatsuko Yokoyama** (known to the American staff as Helen), who was performing just that function for ABCC internists and their patients. Helen, born in the US, had graduated from UCLA with a degree in psychology and had returned to Japan. Her initial uncertainty about accompanying the Hiroshima maidens was overcome when she met them and saw their plight. Her travel documents were in order, so she could leave immediately. In New York there were, as expected, many problems during the course of the year, as we learned during visits with Helen that have since been partially described in two excellent books, *The Hiroshima Maidens*, by **Rodney Barker**, and *Faces of Hiroshima*, by **Anne Chisholm**. I wish that Helen, who lives in retirement near Hiroshima, had written the story behind their stories, known only to her. Without her, the heroic endeavor would likely have failed, as it did subsequently when others tried to repeat it.

continued on next page

Miller's Memories, 1953–1990: Part 2

continued from page 9

National Academy of Sciences, 1955–1957

We returned to Rochester, NY, in early June 1955, and I was unemployed for 4 months because no one needed a pediatrician who specialized in radiation effects. The field was too narrow. Word came that **Tax Connell** was leaving his position as the National Academy of Sciences (NAS) professional associate for ABCC. I assumed the position on a month-to-month basis and stayed for 2 years. My boss was **R Keith Cannan**, a biochemist and a superb administrator. He was chairman of the NAS Division of Medical Sciences and a master of committee management. He sat in on many committee sessions, making suggestions that moved the deliberations along and, when necessary, rewrote reports that would have fallen short of the Academy's high standard. He was a wonderful mentor.

Just after I arrived at NAS, he and the three-person Francis Committee left for Japan, where ABCC was near collapse scientifically. **Thomas Francis Jr** had just finished the landmark field trials of the Salk polio vaccine. He was an expert in acute-disease epidemiology, but could he adapt to the idea of long-term studies of chronic diseases? The other two members of the team were **Seymour Jablon**, a statistician in the Medical Follow-up Branch of NAS, and **Felix Moore**, chief statistician at the National Heart Institute. Previous advisors to ABCC had been academic medical specialists whose visits to the clinics in Japan were more ceremonial than substantive. Cannan, a basic scientist, was the first to appreciate that ABCC needed expert advice on epidemiology. The Francis Committee spent 3 weeks collecting information and then formulated the scientific design that still serves as the basis for the studies of the Radiation Effects Research Foundation. It was a stunning consultative success.

In 1957 the name of **George B Darling**, professor of epidemiology at Yale University, arose as a candidate for the directorship of ABCC. Cannan spoke to him about scientific and administrative matters, and I told him and his wife about life in Japan. They accepted the offer for 2 years and stayed 15. Darling implemented the recommendations of the Francis Committee and greatly improved not only productivity but also congeniality at ABCC. The contributions of Cannan, the Francis Committee, and Darling have been covered from other points of view in *RERF Update* by **S Jablon** (3[1]:5–7, 1991), **H Maki** (3[3]:7, 1991), and **K Joji** (ibid, p 8).

Cannan also arranged for rotation of staff from academic departments in the US through ABCC. Yale provided internists, UCLA pathologists, and NAS biostatisticians. He went to his friend, **James Shannon**, director of the National Institutes of Health (NIH), and arranged for public-health officers recruited to NIH to be assigned as junior staff members to ABCC for 2 years. Among them were **Robert M Heyssel**, who went on to become executive vice president and director of Johns Hopkins Hospital, and **Gerard N Burrow**, who is now dean of the Yale Medical School. My job was to provide Cannan with medical advice, to speak on radiation effects found at ABCC, and to recruit staff from the US.

From my experience in Japan, I realized my interest was in epidemiology, which is relatively rare among physicians. By brief formal training in this field, I could broaden my horizons. Going back to school, though, was unthinkable. Then **James V Neel** visited Cannan to tell of his idea, with **William J Schull**, of comparing the health of children of consanguineous marriages [eg, marriages between cousins] with that of outbred children who had been among the 72,000 people examined in the ABCC genetics study, but in the non-exposed group. At the time, about 7% of marriages in Japan were between cousins. About 3800 inbred children and an equal number of outbred children would have comprehensive medical examinations. A chief of pediatrics was needed to help with the planning, for 1 year in Ann Arbor, to be followed by a year each in Hiroshima and Nagasaki, and then back to Ann Arbor for a year in analyzing and reporting on a study of my own. During the first year in Ann Arbor, I would be a candidate for a master's degree in public health, and during the last year would write a dissertation to qualify for a doctorate degree in public health. Cannan invited me to a farewell luncheon at the Cosmos Club, just the two of us and our wives. About 20 members of the division were there—truly a surprise party. We left for Ann Arbor in September 1957. ❑

In 1955, ABCC colleagues and friends (including physician and well-known author Michihiko Hachiya, seen in the background between the Millers) bid farewell to the author, left, and his bride, Holly.

Editor's note: Robert W Miller's recollections will be continued in an upcoming issue of RERF Update.

Multiple Cancers in the Atomic-bomb Survivors

by Thanne P Rose, Department of Epidemiology, RERF

In most populations, about 3–6% of cancers are second primary tumors occurring after first primary tumors. The identification of second primary tumors in the Life Span Study (LSS) cohort is made possible through the systematic ascertainment of all tumors through the Hiroshima and Nagasaki tumor registries. The LSS cancer-incidence cohort includes any member of the LSS cohort with at least one primary solid tumor diagnosed during 1958–89 who resided in Hiroshima or Nagasaki prefectures at the time of diagnosis. The criteria used to determine independent second primary tumors are patterned after those used in the US Surveillance, Epidemiology, and End Results (SEER) program: a definite picture of malignancy, a distinct tumor, and the exclusion of metastatic disease.

The LSS solid-cancer-incidence data for 1958–89 includes 9398 individuals, of whom 631 had more than one cancer diagnosed. Of these 631, the following second diagnoses were made: 21 hematopoietic cancers (leukemias, lymphomas, and myelomas), 14 benign solid tumors (excluding brain/central-nervous-system benign tumors), 77 occult tumors, 146 simultaneously diagnosed second primaries, and 408 solid primary tumors. Of 4118 males with a first primary, 3.9% (161/4118) had a second primary, compared with females, 4.7% (247/5280) of whom had a second primary tumor.

Figures 1 and 2 show the distribution of common sites of first and second primaries for males and females in this cohort. As shown in Figure 1, cancers of the gastrointestinal and respiratory tracts (stomach, lung, liver, and colon) in males are the most common cancer sites for first and second primaries. Also, males have other tobacco-related cancers such as esophageal and oral-cavity tumors. Figure 2 shows females to have a similar distribution of gastrointestinal and respiratory tumors, except that gynecologic cancers such as breast and cervical cancers are also quite common. Brain tumors are relatively rare in most adult populations, amounting to about 1–2% of total first cancers. Among females in this cohort, brain tumors make up 1.8% of total first primaries and 3.6% of the total second primaries. In general, a higher percentage of individuals with only one primary tumor tend to be diagnosed with cancers more likely to be fatal, such as cancer of the pancreas or liver. Conversely, first cancers of the thyroid or skin—cancers with a more favorable prognosis—are seen in more individuals with two primaries.

Work is in progress to determine the excess risk among atomic-bomb survivors of having a second tumor, given what we know about the excess risk of having a first tumor (D Thompson et al, *Radiat Res* 137:S17–S67, 1994; see related article on p 3). ❑

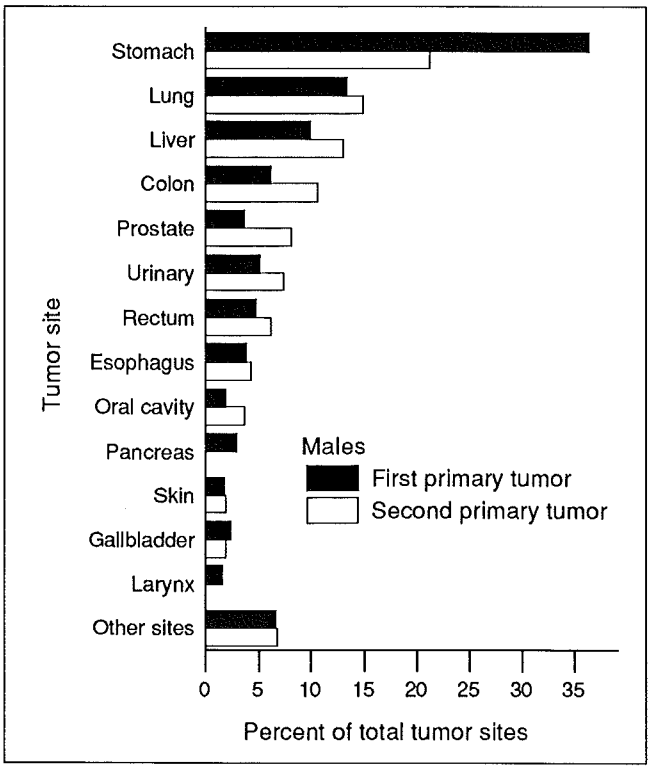


Figure 1. Distribution of solid-tumor sites for first and second primaries for males. Site categories that have less than 1.5% of the total tumors are combined into "other sites."

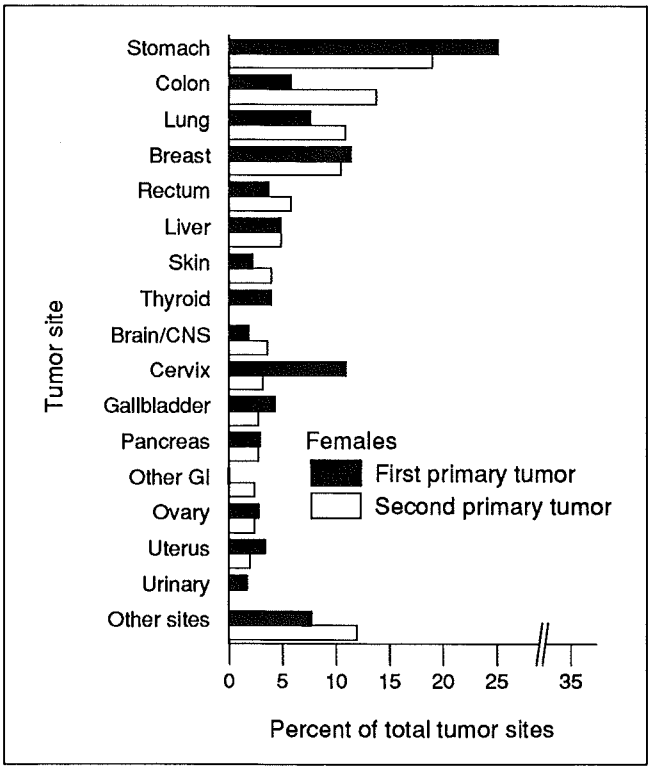


Figure 2. Distribution of solid-tumor sites for first and second primaries for females. Site categories that have less than 1.5% of the total tumors are combined into "other sites." CNS = central nervous system; GI = gastrointestinal.

Recent Scientific Publications

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

Publications in the Open Literature

Editor's note: The following four papers were published as a supplement to Radiation Research *Volume 137 (February 1994). For summaries of these papers, see p 3.*

Cancer incidence in atomic bomb survivors. Part I: Use of the tumor registries in Hiroshima and Nagasaki for incidence studies. K Mabuchi, M Soda, E Ron, M Tokunaga, S Ochikubo, S Sugimoto, T Ikeda, M Terasaki, DL Preston, DE Thompson. *Radiat Res* 137:S1–S16, 1994 (based on RERF Commentary and Review 3-91).

Cancer incidence in atomic bomb survivors. Part II: Solid tumors, 1958–87. DE Thompson, K Mabuchi, E Ron, M Soda, M Tokunaga, S Ochikubo, S Sugimoto, T Ikeda, M Terasaki, S Izumi, DL Preston. *Radiat Res* 137:S17–S67, 1994 (based on RERF Technical Report 5-92).

Cancer incidence in atomic bomb survivors. Part III: Leukemia, lymphoma, and multiple myeloma, 1950–87. DL Preston, S Kusumi, M Tomonaga, S Izumi, E Ron, A Kuramoto, N Kamada, H Dohy, T Matsuo, H Nonaka, DE Thompson, M Soda, K Mabuchi. *Radiat Res* 137:S68–S97, 1994 (based on RERF Technical Report 24-92).

Cancer incidence in atomic bomb survivors. Part IV: Comparison of cancer incidence and mortality. E Ron, DL Preston, K Mabuchi, DE Thompson, M Soda. *Radiat Res* 137:S98–S112, 1994 (based on RERF Manuscript 11-93).

Duplication detection in Japanese Duchenne muscular dystrophy patients and identification of carriers with partial gene deletions using pulsed-field gel electrophoresis. M Kodaira, K Hiyama, T Karakawa, H Kameo, C Satoh. *Hum Genet* 92:237–43, 1993 (based on RERF Manuscript 7-93).

DNA samples from 21 unrelated Japanese patients with Duchenne muscular dystrophy (DMD) with nondeletion-type abnormality in the dystrophin gene and three samples from possible deletion carriers were analyzed using pulsed-field gel electrophoresis (PFGE). Among the 21 patients, 7 were found to carry partial duplications of the dystrophin gene spanning 50–400 kb. Of these 7 patients, 4 carried duplications corresponding to the major hot-spot regions for deletions (7.5–8.5 kb from the 5′ end of cDNA), whereas 2 cases contained duplications in a region about 10 kb from the 5′ end of cDNA, where causative mutations are reported to be rare. Only 1 case was found to contain a duplication of a region about 1 kb from the 5′ end of cDNA, which is the reported duplication prone region. A combination of Southern blot analyses of conventional agarose gel electrophoresis and PFGE was confirmed to be useful, not only for detecting duplications and deletions, per se, but also for identifying carriers in the affected family.

Intragenic recombination at the human phosphoglucomutase 1 locus: Predictions fulfilled. N Takahashi, JV Neel. *Proc Natl Acad Sci USA* 90:10725–9, 1993 (based on RERF Manuscript 21-93).

In 1982, we advanced a phylogeny that attributed eight alleles of the phosphoglucomutase 1 locus (*PGM1*) to three independent mutations in a primal allele, followed by four intragenic recombination events involving these mutants [Takahashi N, Neel JV, Satoh C, Nishizaki J, Masunari N. (1982) *Proc Natl Acad Sci USA* 79:6636–6640]. The recent description of a cDNA probe for this locus [Whitehouse DB, Putt W, Lovegrove JU, Morrison K, Hollyoake M, Fox MF, Hopkinson DA, Edwards YH. (1992) *Proc Natl Acad Sci USA* 89, 411–415] now renders it possible to test the validity of this phylogeny. cDNAs of *PGM1* reverse-transcribed from mRNAs obtained from Japanese individuals possessing eight different electrophoretically defined alleles (*PGM1*1+, PGM1*1–, PGM1*2+, PGM1*2–, PGM1*3+, PGM1*3–, PGM1*7+, PGM1*7–*) were amplified by PCR and the sequences were determined. Only three different base substitutions were identified when *PGM1*+* was taken as the reference allele, as follows: an A to T transversion at residue 265, a C to T transition at residue 723, and a T to C transition at residue 1320. The second of these substitutions creates a *Bgl* II restriction enzyme site and the third creates an *Nla* III site. At the amino acid level, these substitutions alter amino acid 67 from Lys to Met, amino acid 220 from Arg to Cys, and amino acid 419 from Tyr to His, respectively. These mutations resulted in the electrophoretic properties defining *PGM1*7+*, the *PGM1*2+*, and the *PGM1*1–* alleles, respectively. Subsequent intragenic recombinational events resulted in the remaining four alleles. For two of these latter alleles (*PGM1*7–* and *PGM1*3*), more than one type of intragenic crossover can produce the allele. These findings verify the predicted phylogeny and provide a case study in the evolution of complexity at a genetic locus. ❑

RERF update RERF

This quarterly newsletter is published by the Radiation Effects Research Foundation (formerly the Atomic Bomb Casualty Commission), established in April 1975 as a private, nonprofit Japanese foundation. It is supported equally by the Government of Japan through the Ministry of Health and Welfare and the Government of the United States through the National Academy of Sciences under contract with the Department of Energy.

RERF conducts research and studies—for peaceful purposes—on the medical effects of radiation on humans with a view toward contributing to the maintenance of the health and welfare of atomic-bomb survivors and to the enhancement of the health of all mankind.

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Editorial Staff

Editor in chief: S Abrahamson
Managing editor: B Magura
Assistant editor: R Masterson
Proofreader: Y Shimokawa
Production assistants: F Maruyama, K Konami, S Harachi
Photographers: J Takayama, Y Ogasawara

Mailing Address

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

Facsimile

81-82-263-7279

E-mail

RERF Update, c/o B Magura
magura@rerf.or.jp