放影研 RERF update
Radiation Effects Research Foundation News and Views
Hiroshima and Nagasaki, Japan
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RERF conducts research and studies—for peaceful purposes—on the medical effects of radiation on humans with a view toward contributing to the maintenance of the health and welfare of atomic-bomb survivors and to the enhancement of the health of all mankind.

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Editorial Policy

Contributions to Update *receive editorial review only and do not receive scientific peer review. The opinions expressed herein are those of the authors only and do not reflect RERF policies or positions.*

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The 38th Board of Directors Meeting

The annual meeting of the Board of Directors was held on June 18–19, 2003 in the auditorium of the Hiroshima Laboratory with 23 participants including directors, supervisors, a scientific councilor, and observers. Current issues of RERF management and budget were discussed.

In opening remarks, RERF Chairman Dr. Burton G. Bennett cited the on-going mission and the high level of research activities of RERF, paid a tribute to and expressed his resolve to support A-bomb survivors, and requested the directors and sponsors to continue their active involvement and support of the important work.

Subsequently, the minutes of the previous Board of Directors meeting (37th, Washington, DC) were approved. The meeting proceeded to a status report and to items for information on the agenda.

In the status report of RERF, Dr. Bennett summarized recent research accomplishments and pointed out several issues to be addressed in the future, such as data accessibility, further development of future plans, and establishment of a consortium in cooperation with universities in the US and Japan. He also explained the points of difference between the DS86 and the new dosimetry system DS02, and said that the final report of the US-Japan Working Groups on the new dosimetry evaluation would be published by RERF within the year.

Dr. Senjun Taira, RERF Vice Chairman, reported on the progress in the clinical study of survivors' children and on activities of RERF involving international collaboration. Dr. Eiichi Tahara, Chief of Research, gave an overview of the external research grants that had been granted to RERF researchers.

RERF Chief of Secretariat, Mr. Masaharu Yoshikawa, reported on the present personnel status, the FY2002 salary revision, and the FY2003 Labor Union negotiations.

Along with the scheduled agenda items, Drs. Bennett and Taira reported on the issues of journal subscriptions and travel reimbursements. After sudden bankruptcy of its journal subscription agent, RERF faced a considerable loss on payments already made. Fortunately, however, many publishers agreed to honor these subscriptions without further payment. It was further reported that measures were being taken to revise the RERF travel regulations to avoid excessive, although authorized, travel reimbursements and to base payments on actual, often low-cost fares now widely available.

Concerning the issues proposed by the members of the Board, a lively discussion was held on the management system for external research grants and whether or not an internal audit of these ought to be conducted by the supervisor. As a result of the discussion, it was unanimously agreed that a centralized management system would be established; however, it was decided to continue to examine whether or not an internal audit of external grants ought to be conducted.

Discussions were also held on the policy on the use of biological materials, recruitment of young research scientists and statisticians, and the future planning.

For the items for deliberation and action, Scientific Councilor Ohtsura Niwa gave a summary report on the recommendations of the 30th meeting of the Scientific Council, and Dr. Tahara presented the responses to these recommendations.

Subsequently, discussions were held on the FY2002 research activities report and audit, the FY2003 research activities plans, the FY2002 settlement of accounts and audit, the FY2003 working budget, and the FY2004 provisional budget plan, all of which were approved by the Board of Directors.

Lastly, election of the directors and others were held. As for the directors, Dr. Takefumi Kondo was reappointed. Dr. Samuel H. Wilson (Deputy Director, National Institute of Environmental Health Sciences, National Institute of Health) was elected as a successor to Dr. Richard B. Setlow. It was reported that Mr. Masaaki Kuniyasu (former officer of the Ministry of Foreign Affairs) and Dr. Paul L. Ziemer (Professor Emeritus of Purdue University) were elected directors in the preceding month via a mail ballot effective 1 June 2003 as successors to Mr. Kazuaki Arichi and Dr. Jonathan M. Samet, who had continued to serve as directors after the expiration of their terms on 30 June 2002. With regard to the supervisors, while Mr. David Williams was reappointed, it was agreed to have Dr. Tomio Hirohata continue to fulfill his duties even after completion of his term until his successor assumes his/her post.

As for the scientific councilors, Dr. Teruhiko Yoshida (Chief, Genetics Division, National Cancer Center Research Institute) and Dr. Roy E. Shore (Pro-

fessor, Department of Environmental Medicine, New York University School of Medicine) were elected as successors to Dr. Yusuke Nakamura and Dr. J. Martin Brown, respectively. Also, Dr. Shinkan Tokudome (Professor in Health Promotion and Preventive Medicine, Nagoya City University Graduate School of Medical Sciences) was elected as a successor to Dr. Hiroyuki Shimizu, who had expressed his intention to resign, effective 1 July 2003. Each of them will assume his post as scientific councilor on July 1, 2003.

It was agreed that the next meeting of the Board of Directors would be held on June 23–25, 2004 at the Hiroshima Laboratory.

List of Participants

Permanent Directors:
Burton G. Bennett, Chairman
Senjun Taira, Vice Chairman
Eiichi Tahara, Permanent Director and Chief of Research

Visiting Directors:
Hiromichi Matsudaira, Consultant, Radiation Effects Association
Takefumi Kondo, Member, Pollution-related Health Damage Compensation Grievance Board, Ministry of the Environment, Guest Professor, Keio University School of Medicine
Masaaki Kuniyasu, Former Ambassador Extraordinary and Plenipotentiary to the Republic of Portugal
Richard B. Setlow, Senior Biophysicist, Biology Department, Brookhaven National Laboratory, Adjunct Professor, Biochemistry and Cell Biology Department, State University of New York at Stony Brook
John E. Burris, President, Beloit College
Paul L. Ziemer, Professor Emeritus, Purdue University

Supervisors:
Tomio Hirohata, Professor Emeritus, Department of Public Health, Faculty of Medicine, Kyushu University
David Williams, Senior Financial Advisor, National Academy of Sciences (NAS)

Scientific Councilor:
Ohtsura Niwa, Professor, Kyoto University Radiation Biology Center

Representatives of Supporting Agencies:
Masami Kato, Deputy Director, General Affairs Division, Health Service Bureau, Ministry of Health, Labour and Welfare
Steven V. Cary, Deputy Assistant Secretary for Health Studies, Department of Energy (DOE)
Kevin Maher, Minister-Counselor for Environment, Science and Technology, Embassy of the United States of America
Steve M. Dyokas, Scientific and Technical Affairs Officer, Environment, Science and Technology Office, Embassy of the United States of America
Nicole Nelson-Jean, Energy Attaché, Director, DOE Asia Office, Embassy of the United States of America
Yoshimi Tamada, Assistant, DOE Tokyo Office, Embassy of the United States of America
Warren R. Muir, Executive Director, Division on Earth and Life Studies, National Research Council, NAS
Evan B. Douple, Director, Board on Radiation Effects Research, Division on Earth and Life Studies, National Research Council, NAS

Secretariat:
Charles A. Waldren, Chief Scientist
Masaharu Yoshikawa, Chief of Secretariat
Richard D. Sperry, Administrative Advisor, Secretariat

Observers:
Gen Suzuki, Chief, Department of Clinical Studies, Hiroshima
Kei Nakachi, Chief, Department of Radiobiology/Molecular Epidemiology
Kazunori Kodama, Chief, Department of Epidemiology, Hiroshima
Hiroaki Katayama, Chief, Department of Information Technology

The 30th Meeting of RERF Scientific Council

The 30th meeting of the Scientific Council was held on March 10–12, 2003, in Hiroshima. The meeting was co-chaired by Drs. Martin Brown and Yusuke Nakamura. In addition to reviewing as usual the scientific program of the RERF, a specific aim was an in-depth review of the Department of Radiobiology/Molecular Epidemiology. After RERF Chairman Dr. Burton Bennett extended greetings and introductory remarks, Chief of Research Dr. Eiichi Tahara presented a general report of RERF research. Dr. Tahara emphasized the need for RERF to move into new areas of research focused on, but not limited to, radiation-related research. He pointed out that the peak of cancer mortality in the Life Span Study (LSS) will

not occur until around 2015, thereby emphasizing the importance of continuing to follow the survivors. He also presented a new comprehensive strategy for molecular analysis of all newly diagnosed cancers and for obtaining archival tissue samples from the survivors.

Presentations were then made by all departments. In addition to overviews given by department chiefs, the following more specific presentations were made:

- Hepatocellular carcinoma risk, hepatitis and radiation exposure (Saeko Fujiwara, Clinical Studies)
- Ophthalmologic study of atomic-bomb survivors (Kazuo Neriishi, Clinical Studies)
- Thyroid autoantibodies (Misa Imaizumi, Clinical Studies, Nagasaki)
- Sjogren's syndrome (Ayumi Hida, Clinical Studies, Nagasaki)
- Does A-bomb exposure increase oxidative stress after 55 years? (Gen Suzuki, Clinical Studies)
- Genetic effects of radiation in mice by 2D-DNA (Junichi Asakawa, Genetics)
- Progress of array CGH (Norio Takahashi, Genetics)
- Search for genetic instability in lymphocytes (Kazuo Ohtaki, Genetics)
- Why does *in utero* exposure not induce chromosome aberrations (Nori Nakamura, Genetics)
- Study of breast cancer using stored serum samples (Gerald Sharp, Epidemiology)
- Fruit-vegetable intake and cancer mortality in LSS (Catherine Sauvaget, Epidemiology)
- Data cleaning of mail survey information (Fumiyoshi Kasagi, Epidemiology)
- Age-period-cohort model for Hiroshima Tumor Registry data (Kojiro Koyama, Epidemiology)
- Progress report on F_1 mail survey (Akihiko Suyama, Epidemiology, Nagasaki)
- Implementation of DS02 (Shoichiro Fujita and Harry Cullings, Statistics)
- Issues of bias due to selection by survival in LSS (Donald Pierce, Statistics)
- Estimating radiation risk from dose-matched studies (John Cologne, Statistics)
- Design of stratified case-control studies of diabetes and genetic polymorphisms (Eiji Nakashima, Statistics)
- Overview of immunological studies on radiation effects (Seishi Kyoizumi, Radiobiology/Molecular Epidemiology)
- Immunogenetic background in development of diabetes among A-bomb survivors (Tomonori Hayashi, Radiobiology/Molecular Epidemiology)
- Overview of molecular studies of breast and thyroid cancers (Yuko Hirai, Radiobiology/Molecular Epidemiology)

There was then a two-hour round-table discussion on future plans of the Radiobiology/Molecular Epidemiology Department. Topic 1 was the immunogenome, and Topic 2 was molecular analyses of solid cancers among atomic-bomb survivors.

The Scientific Council continues to support the core mission of RERF to study effects of radiation exposure on atomic-bomb survivors. They also support expansion of the core mission, but suggest that the nature of this expansion be based on thorough evaluation of research priorities in relation to its contribution to the mission of RERF, funding bases, and resources. The Council's general recommendations were as follows:

- Recruiting of replacements for senior people leaving in the next 1–2 years, especially from the Statistics Department, needs to be given highest possible priority.
- The publication rate of many RERF scientists should be higher. It is recommended that at least once per year the chief of each department review with each professional staff plans for publication of their research.
- RERF investigators are encouraged to apply for outside funding, one of the items to be discussed in the annual review of each scientist.
- The Council is concerned that in some cases an overly long internal review process for publications discourages scientists from writing up their work. It recommends that every effort be made to restrict this review process to no longer than one month.
- The Council is concerned about potential conflict of interest when a director of RERF is also a principal investigator of a research project that involves significant use of RERF resources (more than two Ph.D. level staff). It recommends that any such arrangement require the director in question to recuse himself from the process of approval of the research protocol (RP), and that final approval of the RP by the Board of Directors of RERF should be required.
- All RPs other than pilot projects should be subject to external review by at least one past/present member of the Scientific Council, as a supplement to the normal review process.
- With rare exceptions, every RP should have a statistician as a co-investigator. The intent is that the statistician would be included as a full partner in the research, and be actively involved in formulating the study design as well as in analyzing and interpreting the findings.
- The Council feels that there was insufficient time for in-depth study of departments being reviewed under the aegis of Multinational Peer Reviews. It recommends that a different process be developed that will allow more time for review and interaction with the scientists.

- The Council remains concerned about the number of participants in the F_1 Study, particularly the low anticipated numbers of those with one parent having exposure above 1 Sv. Experience to date suggests that only 77% of the expected participants in clinical examinations are attending, which would result in a total of 10,000 or fewer participants. Greater effort is needed to attract participants and to include participants from outside of the catchment area.

Extensive evaluations and recommendations were also made for each research department.

Members of the Scientific Council

Yusuke Nakamura, Director, Human Genome Center, Institute of Medical Science, University of Tokyo
Yasuhito Sasaki, President, National Institute of Radiological Sciences
Ohtsura Niwa, Director, Radiation Biology Center, Kyoto University
Hiroyuki Shimizu, Professor, Department of Public Health, Gifu University School of Medicine
Toshitada Takahashi, Director, Aichi Cancer Center Research Institute
J. Martin Brown, Professor and Division Chairman, Division of Radiation Biology, Department of Radiation Oncology, Stanford University School of Medicine
Theodore L. Phillips, Professor and Chairman, Department of Radiation Oncology, Cancer Center, School of Medicine, University of California, San Francisco
Gloria M. Petersen, Professor of Clinical Epidemiology, Mayo Medical School
Clarice R. Weinberg, Chief, Biostatistics Branch, Environmental Diseases and Medicine Program, National Institute of Environmental Health Sciences
Joel S. Bedford, Professor, Department of Radiological Health Sciences, Graduate Faculty of Cellular and Molecular Biology, Colorado State University

International Workshop: Immunological Homeostasis in Inflammatory Response and Disease Development

On January 16 and 17, 2004, RERF hosted at its Hiroshima Laboratory a workshop on the subject of immunological homeostasis. This is the mechanism by which the immune system responds to invasive foreign substances, such as infectious germs, then returns to its original state except for its memory of the foreign substance. Without this mechanism, the immune system would also target the body's own normal tissue and result in a state of continuous inflammation. Discussions at the workshop focused on how immunological homeostasis deteriorates due to aging and how radiation exposure is associated with disease occurrence in atomic-bomb survivors. Key research questions involve how immunological homeostasis is maintained and how the genetic determinants of immunity are related to disease development.

The first day featured a special lecture by Professor Abul K. Abbas of the University of California, San Francisco. He described T-cell regulation of immune functions—from the T cells' initial response to their complex regulatory mechanism involving a large number of molecules and cells. Following that lecture there was a topical session, "T- and B-cell homeostasis and disease development," at which presentations were made by Drs. Toshiaki Ohteki (Akita University), Hajime Karasuyama (Tokyo Metropolitan Institute of Medical Science), Paul J. Martin (Fred Hutchinson Cancer Research Center, Seattle), and Yoichiro Kusunoki and Seishi Kyoizumi (RERF Radiobiology/Molecular Epidemiology Department).

The second day began with another special lecture, given by Professor Tadatsugu Taniguchi of the University of Tokyo. He spoke on regulation of immune response by interferon. After that, the second topical session, "Innate immunity, inflammation and disease," featured presentations by Drs. Shigeo Koyasu (Keio University) and Gen Suzuki (RERF Clinical Studies Department). The third topical session, "Genetic approaches to human inflammatory diseases," included presentations by Drs. Eric G. Wright (Dundee University, UK), Katsushi Tokunaga (University of Tokyo), and Kei Nakachi and Tomonori Hayashi (RERF Radiobiology/Molecular Epidemiology Department). The workshop concluded with a general overview and closing remarks by Dr. Charles A. Waldren, RERF Chief Scientist.

Dr. Yoichiro Kusunoki, Chief of the Immunology Laboratory of RERF's Department of Radiobiology/Molecular Epidemiology, said a number of suggestions beneficial to RERF's future immunological research activities arose out of the talks and discussions. He also expressed his appreciation to the RERF directors, especially Chief of Research Dr. Eiichi Tahara, for their support of the workshop.

Staff News

Dr. Frederic Lagarde joined the Statistics Department in June 2003. He was previously in Biostatistics at the Karolinska Institute, Stockholm, where he received his Ph.D. and was subsequently involved in studies of residential exposures to radon. Mr. Douglas Solvie joined RERF in January 2004 as Assistant to Chief of Secretariat, replacing Mr. Richard Sperry as liaison for the National Academy of Sciences (NAS) in regard to their financial interests at RERF. A substantial number of new scientific staff joined RERF in April 2004, and details will be provided in the next issue of *Update*.

Mr. Sperry retired in June 2003 following 45 years of service at ABCC, NAS, and RERF. As noted, his primary function is being taken over by Mr. Solvie. Ms. Margaret Irwin resigned in July 2003, following several years of work organizing the ABCC-RERF archives. Dr. Gerald Sharp resigned in November 2003 to take a position at the US National Institute of Allergy and Infectious Diseases to carry out research in their HIV/AIDS projects. Dr. Shoichiro Fujita retired in December 2002 and was re-employed on a temporary basis to continue his work.

Current Status of Dosimetry Revision

The dosimetry system revision from DS86 to DS02 was completed in March 2004. The last three issues of *RERF Update* have contained columns summarizing the developing status of the revision, and the Spring 2003 issue carried a full article by Cullings and Fujita explaining much of the background and development. An RERF paper[1] is in press at *Radiation Research* describing how the revision affects radiation risk estimates for solid cancer and leukemia. Datasets for various RERF cohorts including the new dose estimates are available to RERF workers through the database access system EasyClick.

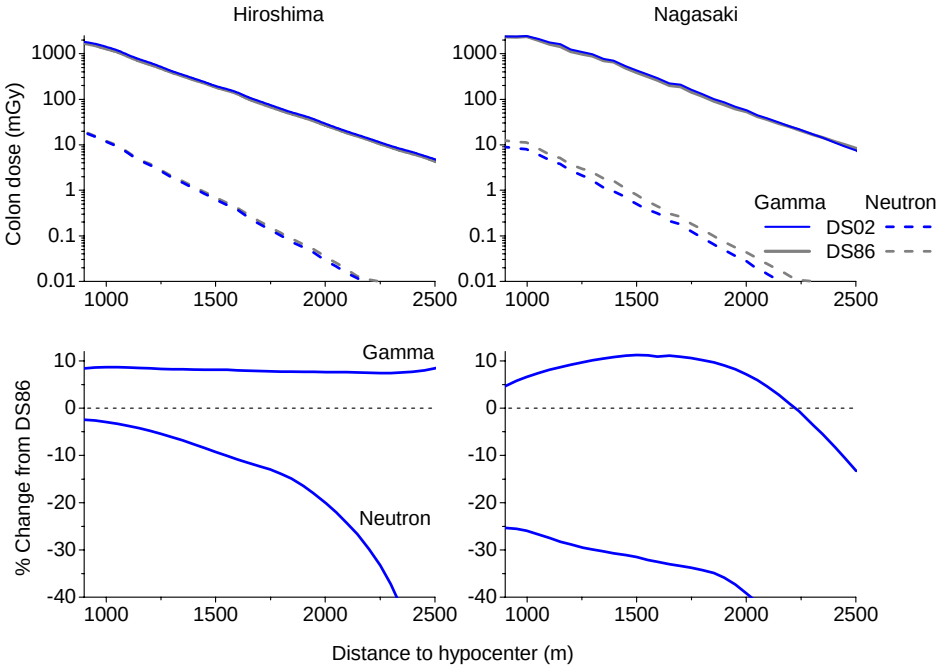
Several years of intensifying concerns about the need for revision culminated in a 2001 National Research Council Report recommending that the revisions be undertaken, directed as for DS86 by a Bi-National Dosimetry Committee largely external to RERF. A group of about 30 physicists from Japan, the U.S. and Germany, assisted by RERF statisticians, contributed enormous and varied efforts leading to the basic DS02 system that was approved in March 2003. For the next year RERF scientists, research assistants, and Master File Section staff carried out the extensive work necessary to implement the new system. Documentation of DS02, prepared by those who developed the system, will be in a forthcoming volume published by RERF.

The primary impetus for the revision was indications from activation measurements in exposed materials that DS86 Hiroshima neutron estimates at distances greater than 1.5 km might be much too low. However, after a thorough reconsideration of bomb source terms, radiation transport calculations, experimental errors in the activation measurements, and additional samples using refined or new methods, there was agreement that this was not the case. Thus DS02 came to be a progressive refinement of DS86, improving on it in many details but largely confirmatory in nature. In addition to many improvements in shielding calculations, source term adjustments and improved radiation transport calculations resulted in changes in dose estimates summarized by the figure here. Gamma-ray estimates are increased by about 8–10% in distance ranges relevant to risk estimation, and neutron estimates are decreased. This means that the ratio of neutron to gamma-ray dose estimates is smaller than in the past. Thus adjusting for the higher biological effect of neutrons to estimate gamma-ray risks has become less of an issue than before, and estimation of neutron risks has become even less feasible.

The RERF paper[1] in press concludes that cancer risk estimates are decreased by about 8% due to the dosimetry change, with negligible change in the apparent shape of the dose response or the age-time patterns of risk. Work is underway to update the methods to allow for random errors in dose estimates. This is far enough along to indicate that such changes will not appreciably affect the conclusions of that paper. Although there had been some promise that DS02 would substantially reduce problems with dose estimates for Nagasaki factory workers, which can be seen from both chromosome aberration and cancer data to be too large, this improvement did not materialize.

A feature of the DS02 implementation is that dose estimates have newly been assigned to a large number of persons related to RERF cohorts. Some details on this are given in the Facts & Figures section of this *Update* issue. Although most of these new dose estimates are zero, the improvement will provide for substantially improved analysis of data on the F_1 and *in utero* cohorts.

Summary of gamma-ray and neutron survivor colon dose estimates, and their relative changes with dosimetry revision, for each city



Reference

1. Preston DL, Pierce DA, Shimizu Y, Cullings HM, Fujita S, Funamoto S, Kodama K: Effect of recent atomic bomb survivor dosimetry changes on cancer mortality risk estimates. (Radiat Res, in press)

Long-term Effects of A-bomb Radiation on the Immune System: Beyond a Half Century

Yoichiro Kusunoki, Chief, Immunology Laboratory, Department of Radiobiology/Molecular Epidemiology, **Tomonori Hayashi**, Senior Scientist, Department of Radiobiology/Molecular Epidemiology, **Masayuki Hakoda**, Chief, Division of Clinical Laboratories, Department of Clinical Studies, **Gen Suzuki**, Chief, Department of Clinical Studies, **Kei Nakachi**, Chief, Department of Radiobiology/Molecular Epidemiology, and **Seishi Kyoizumi**, Assistant Chief, Department of Radiobiology/Molecular Epidemiology

Introduction

More than 50 years after exposure, we still have no clear answers as to how A-bomb radiation has caused biological effects in humans and how these effects seem to lead to many different diseases including noncancer diseases as well as cancer. Radiation-related cancer has been observed for a very long time, but recently there have emerged clear associations among A-bomb survivors between radiation dose and the death rate of most major noncancer diseases.[1,2] Mechanisms for radiation-related cancer, although not totally understood, are much clearer than those for radiation-related noncancer diseases, where in fact almost nothing is known. An interesting hypothesis is that radiation effects on the immune system may be in part involved in these radiation-related diseases, especially for noncancer diseases. Recent developments in immunological science have paved the way to explain many human diseases as abnormalities in the immune system. Therefore, to gain further insights into the mechanisms of radiation-induced diseases, it is necessary to study the possible origin of these radiation-associated disorders from the immunological point of view (Figure1). Exposure to radiation is thought to affect host immune surveillance, but little is known about the direct relationship between radiation effect on the immune system and disease development. Immunological studies at RERF are aimed at obtaining better understanding of the possible relationships between the damaging effects of radiation on the immune system and the subsequent development of radiation-induced diseases.

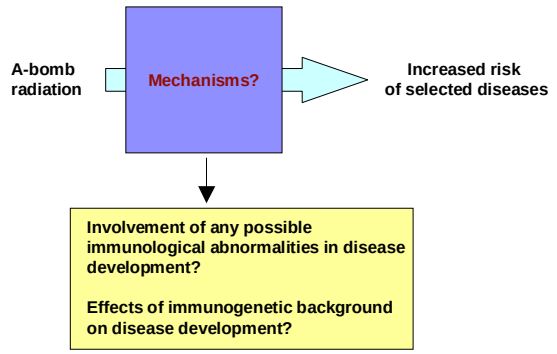


Figure 1. Immunological approaches to investigation of the mechanisms on the development of radiation-related diseases.

Does acute radiation-induced damage of the immune system lead to disease development?

The immune system was dose-dependently damaged in A-bomb survivors at the time of exposure, mainly due to radiation-induced cell death. Several months after radiation exposure, following cell repopulation, the hematopoietic system had nearly recovered from the damage in the survivors.[3,4] However, even 50 years after radiation exposure there still remain lymphocyte and hematopoietic stem cell populations that bear radiation-induced DNA damage, such as somatic mutations and chromosome aberrations, in the survivors' hematolymphoid systems.[5–15] In addition, we can still observe significant effects of the previous radiation exposure on lymphoid cell composition and function in the immune system of the survivors (Figure 2).[16–25] Since most of these effects appear as small, few percent changes per 1 Gy of exposure (Table 1), one can not easily draw the scenario that such changes in the immune system may lead to succumbing to any particular diseases. Nevertheless, it may be possible that even immunological changes (if the alterations last for more than several decades) may have led to increased risks of diseases that we

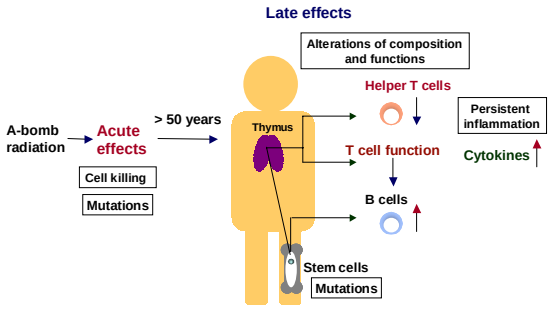


Figure 2. Acute and late effects of A-bomb radiation on the human immune system.

frequently observe in the A-bomb survivor population. We suppose that the more compromised the immune competence becomes in an individual from consequences of aging and/or radiation exposure, the higher the disease risk will likely be for the individual (Figure 3).

Immunological alterations observed in A-bomb survivors

Immunological alterations that we have observed in A-bomb survivors are listed in Tables 1 and 2. T-cell functions, such as responses to mitogens (phytohemagglutinin-dependent proliferation,[16] interleukin (IL)-2-producing cell frequency[19]), alloantigens,[17] and superantigen staphylococcal enterotoxin[23] appear to be consistently lower in the survivors, due to reduction in the number of T cells as a consequence of insufficient supply of new T cells. These functional alterations agree well with observations of lymphocyte composition (Table 1), that is, a decrease in the CD4 helper T-cell population, especially naïve CD4 T cells.[22–25] A similar decrease in the number of naïve CD4 T-cell population was also observed in other studies such as follow-up studies of radiotherapy patients.[26] A proportion of memory CD4 T cells did not show significant changes with radiation exposure.[22,24,25] In contrast to the CD4 T-cell population, CD8 T-cell population of A-bomb survivors showed significant

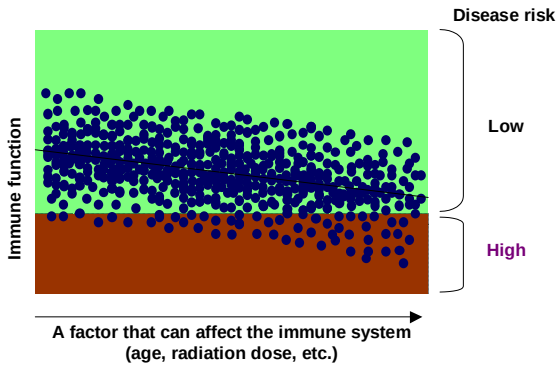


Figure 3. A schematic model explaining how a slight immunological change may have caused an increased risk of disease. Each blue circle represents each individual value for any given immunological parameter, and the orange line indicates the regression line between value for the immunological parameter and an appropriate environmental factor such as radiation dose. The lower value for the immunological parameter an individual has become to possess as consequences of aging and/or radiation exposure, the higher disease risk the individual is likely to have.

Table 1. Comparing effects of sex, age, radiation dose on the percentages of lymphocyte subsets in peripheral blood lymphocyte fractions of A-bomb survivors

Lymphocyte subsets	Effects		
	Sex	Age (10 years)	Radiation (Gy)
T cells			
CD4 total	F > M (5.3%)[a]	Decrease (5.0%)	Decrease (2.0%)
naïve	F > M (3.3%)	Decrease (7.5%)	Decrease (4.5%)
memory	F > M (8.2%)	NS[b]	NS
CD8 total	NS	NS	NS
naïve	F > M (18.5%)	Decrease (42.3%)	Decrease (7.7%)
memory	NS	Increase (7.3%)	Increase (5.6%)[c]
B cells	F > M (5.3%)	Decrease (7.3%)	Increase (8.5%)
NK cells	M > F (20.3%)	Increase (20.7%)	NS

[a](% change), [b]not significant, [c]suggestive

Table 2. Late effects of A-bomb radiation on immune functions

Cell type	Function	Radiation effect	Reference
T cells	PHA response	Decrease	*Radiat Res* 93:572 (1983)
	MLR	Decrease	*Radiat Res* 117:26 (1989)
	IL-2 production	Decrease	*Radiat Res* 155:81 (2001)
	SAg response	Decrease	*Radiat Res* 158:715 (2002)
B cells	Ab production (serum levels)	Increase	*Radiat Res* 137:89 (1994)
	RF	Increase	
NK cells	K562 cell lysis	Not significant	*Radiat Res* 116:343 (1988)

reductions in the proportion of naïve cells but also a significant increase in that of memory T cells.[25] As for B-cell population, the number of B cells, as well as B-cell functions such as serum IgM, IgG, and IgA levels (ref. 21 and Hayashi *et al*, submitted), anti-EB virus antibody,[20] and prevalence of rheumatoid factor[21] are significantly higher in the exposed persons. The reason why B-cell immune responses are enhanced in the survivors is unclear. It may be that increased inflammatory reactions due to deficit of helper T cells are involved in the enhanced B-cell responses of the survivors. With regard to innate immunity, however, the proportion and cytotoxic activity of natural killer (NK) cells showed no significant effect of A-bomb radiation.[27]

Possible alterations in lymphocyte function of A-bomb survivors

RERF's immunologists have proposed the hypothesis that A-bomb radiation acted as a trigger to reduce cellular immune responses controlled by Th1 cells but to augment humoral immune responses controlled by Th2 cells.[28] That the ratio Th1/Th2 is fundamental is a well-known paradigm in immunology. The above hypothesis has been tested by measuring the levels of plasma cytokines that are related to either Th1- or Th2-dominant status and by enumerating the numbers of Th1 and Th2 cells in the peripheral blood using a chemokine receptor (CXCR3) and a prostaglandin D receptor (CRTH2) as their cell surface markers, respectively.[29] Results obtained in recent years provided indications that radiation-dose dependent elevations of cytokine levels are apparent not only for a Th2-related cytokine, IL-6, but also for Th1-related cytokines, IFN-γ and TNF-α (Hayashi *et al*, submitted), indicating enhanced production of inflammatory cytokines irrelevant to Th1/Th2 imbalance in A-bomb survivors. Furthermore, there has been no significant effect of A-bomb radiation on the ratio between Th1 and Th2 cells (Kusunoki, unpublished observation). It is therefore unlikely that A-bomb radiation has induced a long-lasting alteration in the host immunity controlled by Th1 and Th2 cells even though a possible impairment of the ability of T cells to produce IL-2 has been suggested in A-bomb survivors.[19] Recent studies have indicated that $CD4^+CD25^+$ regulatory T cells play crucial roles in suppression of the host immune responses, especially of those to self-antigents.[30] NKT cells are also suggested to play pivotal roles in the interplay between innate and acquired immune responses in which the direction of T-cell function polarization is determined.[31] It remains to be determined whether radiation exposure affects these important lymphocyte subsets.

Possible perturbation of T-cell homeostasis in A-bomb survivors

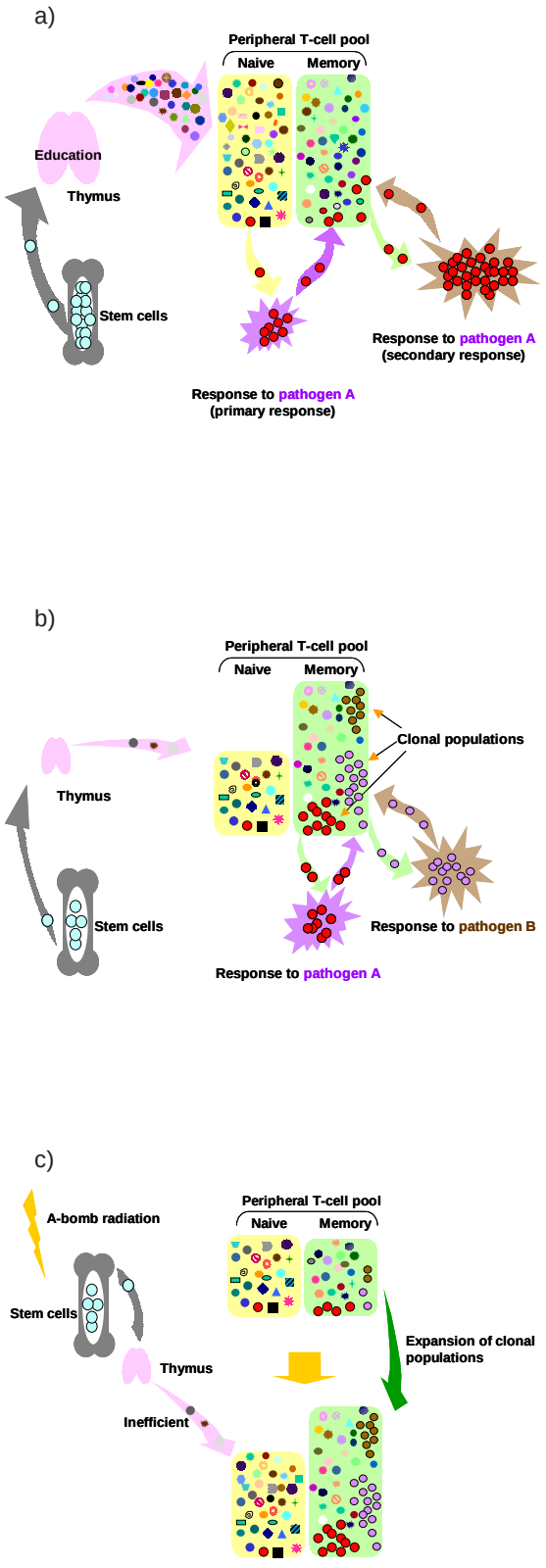
In the T-cell system, a constant supply and diverse repertoire of lymphocytes are maintained, despite the emergence of new lymphocytes and tremendous expansion of individual clones that may occur during responses to antigens. This homeostasis in the T-cell system is achieved by the balance between renewal and death among naïve and memory T cells, and the sizes of these T-cell populations are maintained independently (Figure 4a).[30] Maintenance of both naïve and memory T-cell pools is important for the body to protect against intrusions by pathogens. However, the ability to maintain both pools is believed to decline with age. In older persons, the size of the naïve T-cell pool becomes smaller due to reduced production of new T cells in the thymus, and responses to antigens are subsequently impaired as compared with younger individuals (Figure 4b).[33–35] Although the entrance of naïve cells into the memory T-cell pool becomes rare, the size of memory T-cell pool is kept constant regardless of age. However, some fractions of cells preferentially proliferate, and clonally expanded populations frequently arise in the memory T-cell pool of older individuals. The existence of clonal populations that make up a large portion of the memory T-cell pool may result in deviation of immune responses to antigens.

Both naïve CD4 and CD8 T-cell pools of A-bomb survivors are not likely to be appropriately maintained because of lower numbers of naïve CD4 and CD8 T cells than in unexposed controls of the same age,[25] even 50 years after the bombing. This may indicate that the naïve T-cell pool has insufficiently recovered after radiation-induced damage of the T-cell system and has not reached the normal level in size (Figure 4c). In contrast, memory T-cell pools of A-bomb survivors appeared to be almost normal (CD4) or larger (CD8) in size.[25] However, we have recently demonstrated that the extent of T-cell receptor repertoire deviation in memory CD4 T cells significantly increased with radiation doses to which the survivors were exposed (Figure 5).[24] Because the repertoire deviation in memory CD4 T cells was frequently associated with the presence of a large size of clonal populations, we speculate that A-bomb radiation may have resulted in preferential expansion of memory CD4 T-cell clones that might have existed at the time of the bombing (Figure 4c). Thus, our current interpretation of the long-lasting abnormality in the T-cell systems of survivors is that the previous radiation exposures have 1) reduced the ability to produce new T cells and 2) impaired the maintenance of helper T-cell memory. The reduction in the size of naïve T-cell populations may compromise the ability of the host to defend against an intrusion by pathogens to which the host has not previously been exposed. The impaired maintenance of memory T-cell populations may lead to reduced abilities to prevent recurrent infection by pathogens and to control latently infected microbes.

Disease development in A-bomb survivors through inflammatory responses

It has been already reported that there are statistically significant associations between inflammatory

Figure 4. T-cell homeostasis is likely to be perturbed by aging or radiation exposure.



a) T-cell homeostasis involves the maintenance of a balance between renewal and death among the naïve and memory T-cell populations. The naïve T-cell pool is primarily maintained by the inflow of T-cell populations that acquired diverse receptors for recognition of various kinds of peptides associated with self MHC molecules in the thymus (education). Once the immune system encounters an antigen, a population of T cells in the naïve T-cell pool will recognize the antigen and proliferate, but most of the cells that proliferate will die and only a few of them will enter the memory T-cell pool after the immune response has run its course (primary response). T cells in the memory pool can be recalled by antigens that have previously been encountered by the immune system (secondary response). A secondary response is usually more rapid and vigorous than a primary response. Only a few memory T cells return to the memory pool after the secondary immune response has run its course. The renewal rate of a memory T-cell population is believed to be much higher than that of the naïve T-cell population.

b) Our ability to maintain both naïve and memory T-cell pools is believed to decline with aging. In older people, the naïve T-cell pool becomes reduced in size as a result of diminishing rates of production of new T cells in the thymus; their responses to antigens begins to be impaired in comparison with those of younger individuals. Although fewer naïve T cells move into the memory T-cell pool, the size of the memory T-cell pool is nonetheless maintained in aging individuals. However, some cells proliferate preferentially, and clonally expanded populations frequently appear to arise in the memory T-cell pools of older individuals. Thus clonal populations often come to represent a considerable percentage of the memory T-cell pool, and this may lead to a distorted array of immune responses to antigens.

c) Perturbation of T-cell homeostasis in A-bomb survivors could be considered as accelerated aging. A-bomb radiation exposure may have damaged the ability of thymus to produce naïve T cells and subsequently resulted in reduced size of the naïve T-cell pool, which may be associated with increased risk of infection-associated diseases such as myocardial infarction. The maintenance of memory T-cell pool may have been also perturbed by A-bomb radiation exposure. Although the size of memory T-cell pool was not reduced by A-bomb radiation exposure, emergence of clonal expansions of a part of memory T-cell population has been frequently observed in the memory T-cell populations of A-bomb survivors.

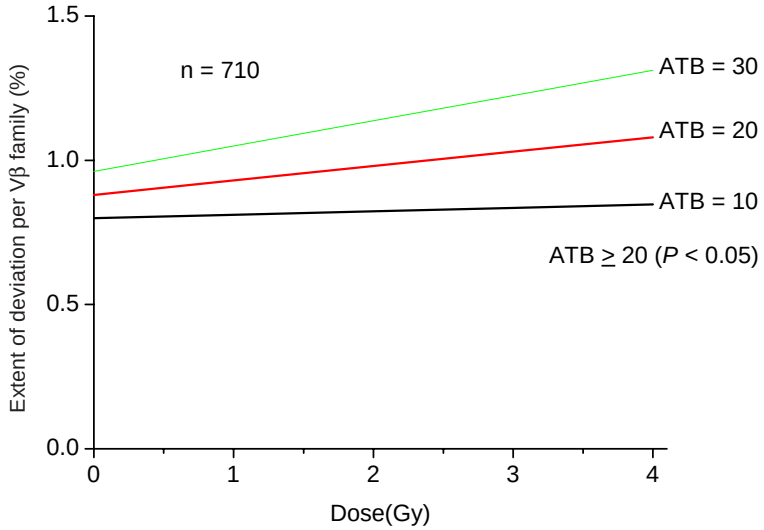


Figure 5. Evaluation of T-cell repertoire of memory CD4 T-cell population by determining to what extent any individual's value for the percentages of T cells expressing specific TCR Vβ families deviated from the average value for all subjects. The T-cell receptor repertoire in the memory CD4 T-cell populations diverged significantly from the population average for counterpart families especially in individuals who had been exposed to higher doses and were at least 20 years of age at the time of the bombing (ATB).

biomarkers (leukocyte count, erythrocyte sedimentation rate, alpha 1 globulins, alpha 2 globulins, and sialic acid) and radiation dose in A-bomb survivors.[36] To test whether defects in CD4 helper T-cell activities in A-bomb survivors are related to inflammatory responses, we recently measured the levels of inflammatory cytokines and C-reactive proteins (CRP) in plasma samples from a large group of survivors.[37] There was a strong correlation between IL-6 and CRP levels. Interestingly, the plasma IL-6 level appeared to correlate negatively with the percentages of peripheral blood CD4 T cells. We found that both IL-6 and CRP levels appeared to have increased with increased radiation dose. These results may indicate that pre-clinical inflammatory status is linked in some way to the decrease in CD4 T-cell count, suggesting that immunological changes may have caused some diseases through inflammatory responses. To investigate this possibility, we examined whether any immunological changes were associated with the pathogenesis of cardiovascular diseases including myocardial infarction (MI), since recent studies provide evidence that inflammation plays a role in this type of cardiovascular disease and since a dose-dependent increase in relative risk of MI has been observed in the Adult Health Study (AHS) cohort. Adjusting for dose, the prevalence of MI was significantly higher in individuals who had reduced CD4 T-cell percentages (Figure 6).[38] Furthermore, the IL-6 levels appeared to be significantly higher in survivors with a history of MI than in those without such a history. A similar result was also found in levels of CRP (Figure 7). [37] These results indicate that MI in A-bomb survivors may be at least in part due to their having reduced numbers of CD4 helper T cells, and hence to their having a diminished ability to mount an immune defense against infections of a type which may be implicated in the etiology of atherosclerosis (Figure 8).

Could genetic background be involved in disease risks of A-bomb survivors?

It is quite apparent that there are large individual variations in the levels of immunological and inflammatory markers (e.g., Figures 6 and 7) and that only a part of individuals who show reduced immune functions and/or elevated inflammatory biomarkers develop particular diseases. Both immune and inflammatory responses are controlled by a series of genes that are genetically polymorphic. Thus, one can hypothesize that individual immunogenetic background may determine individual susceptibility to diseases. A careful analysis of the data obtained from a previous study of AHS subjects suggested that there was a significant positive correlation between prevalence of type 2 diabetes and radiation dose in individuals who were less than 20 years of age at the time of exposure to the A-bomb in Hiroshima.[37] One especially important genetic factor that can affect host immune responses appears to be the major histocompatibility complex (*MHC*) locus, which in humans is referred to as the *HLA* (for Human Leukocyte Antigens) locus. We used *HLA class II* typing data obtained from a subset of the same survivors to determine whether there was any evidence of a relationship between the development of diabetes and *HLA class II* type that might also be associated with the estimated doses of A-bomb radiation that they

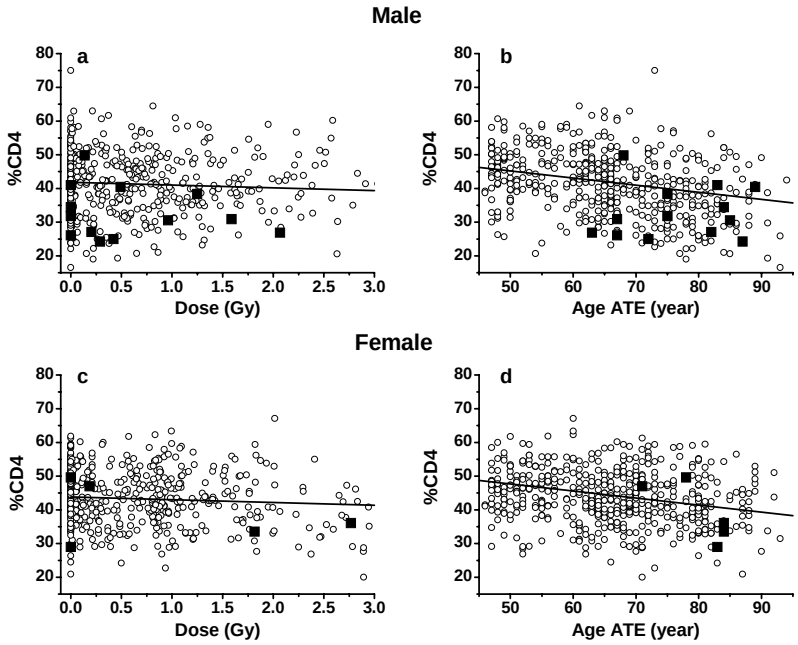


Figure 6. Proportion of peripheral blood CD4 T cells in A-bomb survivors with histories of myocardial infarction (MI, closed squares) and those without such histories (open circles). Lines denote regression lines between CD4 T-cell proportion and radiation dose (a and c) or age (b and d), after adjusting the proportion for 66-year-old male (a) and female (c) survivors or unexposed males (b) and females (d), respectively. CD4 T-cell proportion is significantly ($P < 0.01$) higher in females than males and decreased with age ($P < 0.01$) and dose ($P < 0.01$). Proportion of CD4 T cells is significantly ($P = 0.02$) lower in survivors with myocardial infarction than those without.

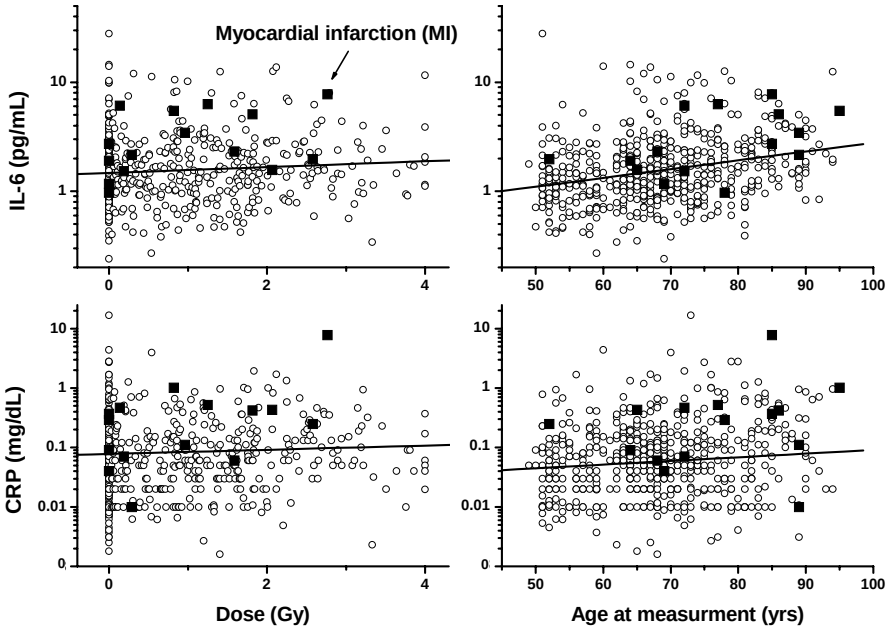


Figure 7. Plasma IL-6 (upper panels) and CRP (lower panels) levels in A-bomb survivors with histories of MI (closed squares) and those without such histories (open circles). Lines denote regression lines between IL-6 level and radiation dose or age and, between CRP level and radiation dose or age. Inflammatory markers, IL-6 and CRP, increased with radiation dose ($P < 0.01$) or age ($P < 0.01$). Adjusting for dose, history of MI was associated with higher IL-6 and CRP ($P < 0.05$).

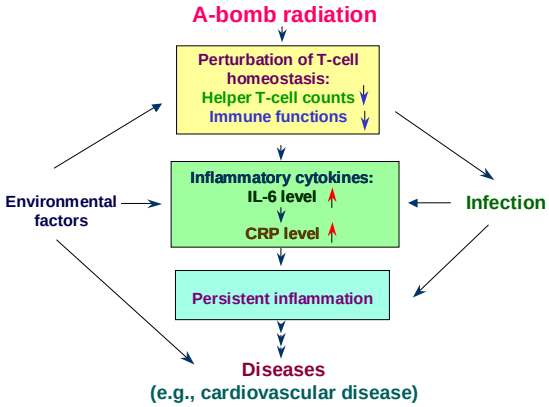


Figure 8. A hypothesis of the immunological mechanism on the disease development in A-bomb survivors. A-bomb radiation may have perturbed T-cell homeostasis and resulted in deficits of helper T-cell counts that are associated with reduced immune functions. Such abnormalities in the T-cell system may cause long-lasting inflammation that may lead to the development of diseases such as cardiovascular diseases. Infections and other environmental factors such as lifestyles may certainly interact with the process of disease development.

received.[34] We found that there appear to be significant differences in diabetes prevalence between exposed and low-dose or non-exposed survivors with different *HLA DQA1* and *DRB1* alleles. Thus, for example, the odds ratios (ORs) for the most heavily exposed (>1.5 Gy) group of survivors who had either *DQA1*0401* and *DRB1*08* alleles or *DQA1*0301* and *DRB1*09* alleles were significantly higher than the ORs observed for either unexposed controls or survivors in the low dose group, whereas there were no comparable dose-dependent increases in diabetes incidence among equivalently exposed survivors who were not carrying either *DQA1*0401* and *DRB1*08* or *DQA1*0301* and *DRB1*09* (Figure 9). These findings suggest that certain *HLA class II* genes (or possibly even certain closely-linked gene or genes) regulate one or more components of the immune system that are an important influence on the likelihood of diabetes development among the younger (<20 year-old) and more heavily exposed A-bomb survivors. We believe this is the first report of differences in apparent radiation risk for some disease, according to individual genetic backgrounds.

Such an immunogenetic approach may provide us a new clue to determine the mechanisms by which radiation exposures cause diseases. A finding based on genetic differences in individuals should be more defi-

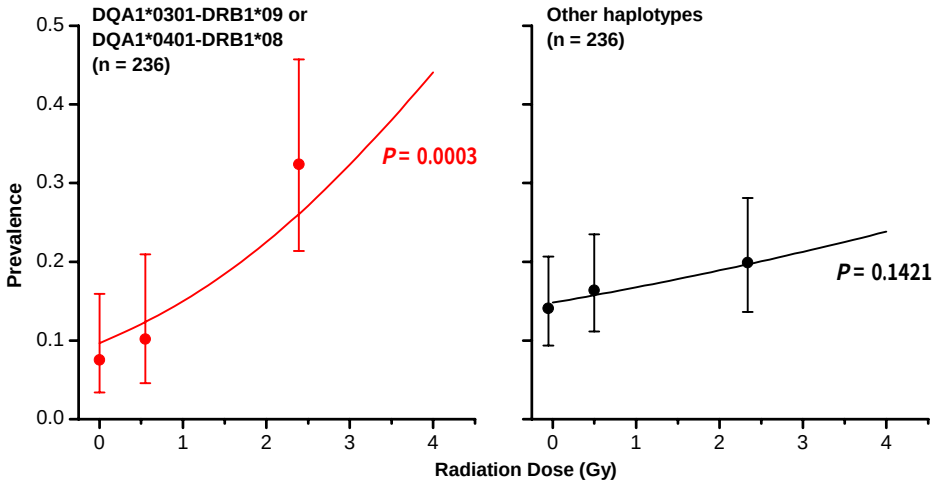


Figure 9. Cumulative prevalence rates of diabetes by *HLA* haplotyping in radiation dose categories. Prevalence of diabetes increased with higher radiation dose categories among individuals who have either the *DQA1*0301-DRB1*09* or *DQA1*0401-DRB1*08* haplotype (trend $P = 0.0003$). No significant association was found between radiation and diabetes among individuals who have neither the *DQA1*0301-DRB1*09* alleles nor the *DQA1*0401-DRB1*08* haplotype (trend $P = 0.14$). The prevalence of diabetes among individuals with these haplotypes was significantly higher than that among individuals without these haplotypes ($P = 0.03$).

nite than that based on conventional phenotypical observations. In other words, if a genetic difference in individual immunogenome can explain a difference in individual susceptibility to a disease, one can argue that there is a possible immunological mechanism in the development of this particular disease.

Future directions in RERF's immunology studies

To address the questions of how A-bomb radiation has caused biological effects in humans and many different diseases, the immunologists at RERF have made three hypotheses (Figure 10). The first hypothesis is that A-bomb radiation may have accelerated immunological aging by perturbing T-cell homeostasis. To test this hypothesis, we have begun determining the number of T cells that contain T-cell receptor-rearrangement excision circles (TRECs), and also measuring the lengths of telomere repeats in blood leukocytes (see RP 4-02[41]). To gain a better understanding of the mechanisms involved in radiation-induced perturbation of T-cell homeostasis, we also plan to investigate the processes of T-cell reconstitution following radiation-induced damage, using a number of potentially valuable animal models.

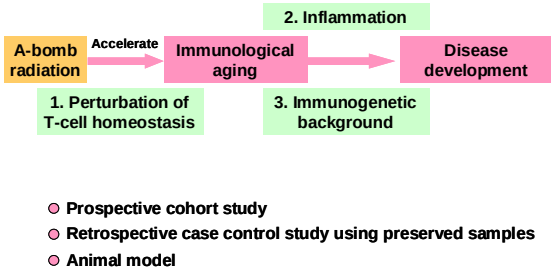


Figure 10. Strategies of RERF's immunology study.

The second hypothesis is that A-bomb radiation may have induced long-lasting inflammation that may lead to disease development. We believe that RERF's multidimensional research environment will make it possible to carry out a comprehensive investigation of the immunological mechanisms underlying disease development in A-bomb survivors. Data obtained from comparative measurements of serum cytokine levels as well as of surface markers for lymphocyte subsets in the survivors will be referred to onsets of various diseases in the survivors, both prospectively and retrospectively. Inflammatory response, mediated by immune cells, is thought to be a key mechanism in the development of various lifestyle-associated diseases, such as diabetes, coronary heart disease, and several cancers. We will investigate whether there are any interactions between immune inflammatory mediators (such as pro-inflammatory cytokines, IL-1, IL-6, TNF-α, etc.) and lifestyle factors in the development of these diseases among A-bomb survivors.

We also hypothesize that individual immunogenetic background may determine individual susceptibility to succumbing to diseases. To test this hypothesis, we would like to utilize the results that have been achieved in the human genome project and in the current progress of molecular immunology. RERF's studies provide immunological data as well as clinical and epidemiological data on the health status and mortality in a fixed A-bomb survivor cohort. In addition, blood lymphocytes of approximately 7,000 survivors have been preserved, and these samples are quite useful for genome analyses. Thus, we will examine the genotypes of a series of genes that are closely involved in host immune and inflammatory responses among A-bomb survivors using preserved blood samples, and comprehensively analyze their associations with diseases and radiation exposure.

Glossary

Adapted, with permission from Elsevier, from pp. 468–99 of Cellular and Molecular Immunology, *4th Ed., Abbas A, Lichtman AH, Pober J (eds), W.B. Saunders, Philadelphia, 2000.*

Acquired immunity. The form of immunity by lymphocytes that is stimulated by exposure to infectious agents. In contrast to innate immunity, acquired immunity is characterized by exquisite specificity for distinct macromolecules and "memory" which is the ability to respond more vigorously to repeated exposure to the same microbe.

Alloantigen. A cell or tissue antigen that is present in some members of a species and not others, that is recognized as foreign on an allograft. Alloantigens are usually products of polymorphic genes.

B cell. The only cell type capable of producing antibody molecules. B cells develop in the bone marrow, and mature B cells are found mainly in lymphoid follicles in secondary lymphoid tissues such as lymph nodes and spleen, in bone marrow, and in low numbers in the circulation.

CD4 T cell (helper T cell). The functional subset of T cells whose main effector functions are to activate macrophages in cell-mediated immune responses and promote B-cell antibody production in humoral immune responses. These effector functions are mediated by secreted cytokines and by T-cell binding to macrophages or B cells.

CD8 T cell (cytotoxic T cell). A type of T cell whose major effector function is to recognize and kill host cells infected with viruses or other intracellular microbes.

Chemokines. A large family of structurally homologous, low molecular weight cytokines that stimulate leukocyte movement and regulate the migration of leukocytes from blood to tissues.

CRP (C-reactive protein). A member of the pentraxin family of plasma proteins involved in innate immune responses to bacterial infections. CRP in an acute phase reactant, and it binds to the capsule of pneumococcal bacteria. CRP also binds to C1q and may thereby activate complement or act as an opsonin by interacting with phagocyte C1q receptors.

Cytokines. Proteins produced by many different cell types that mediate inflammatory and immune reactions. Cytokines are principal mediators of communications between cells of the immune system.

Haplotype. The set of alleles inherited from one parent and therefore on one chromosome.

HLA (human leukocyte antigens). Major histocompatibility complex (MHC) molecules (see below) expressed on the surface of human cells.

Immune system. The molecules, cells, tissues, and organs that collectively function to provide immunity, or protection against foreign organisms.

Innate immunity. Protection against infections that relies on mechanisms that exist before infection, are capable of rapid responses to microbes, and react in essentially the same way to repeated infections. The innate immune system includes epithelial barriers; phagocytic cells (neutrophils, macrophages); natural killer cells; the complement system; and cytokines, largely made by mononuclear phagocytes, that regulate and coordinate many of the activities of the cells of innate immunity.

IFN-γ (interferon-γ). A cytokine produced by T cells and NK cells whose principal function is to activate macrophages in both innate immune responses and cell-mediated immune responses.

IL-1 (interleukin-1). A cytokine produced mainly by activated mononuclear phagocytes whose principal function is to mediate host inflammatory responses in innate immunity (e.g., induction of endothelial cell adhesion molecules, stimulation of chemokine production by endothelial cells and macrophages, stimulation of the synthesis of acute phase reactants by the liver, induction of fever).

IL-2 (interleukin-2). A cytokine produced by antigen-activated T cells that acts to stimulate T-cell proliferation and also potentiates the apoptotic cell death of antigen-activated cells. Thus IL-2 is required for both the induction and self-regulation of T-cell mediated immune responses. IL-2 also stimulates the proliferation and effector functions of NK and B cells.

IL-4 (interleukin-4). A cytokine produced by the Th2 subset of CD4 helper T cells whose functions include induction of differentiation of Th2 cells from naïve CD4 T cells, stimulation of IgE production by B cells, and suppression of IFN-γ-dependent macrophage functions.

IL-5 (interleukin-5). A cytokine produced by the Th2 cells and activated by mast cells. IL-5 stimulates IgA production by B cells and activates eosinophils that contribute to many of pathogenic processes in allergic diseases.

IL-6 (interleukin-6). A cytokine produced by many cell types and functions in both innate and acquired (T- and B-cell mediated) immunity. IL-6 stimulates the synthesis of acute phase proteins (such as CRP) by hepatocytes, as well as the growth of antibody-producing B cells.

Memory T cells. T cells that mediate rapid and enhanced (i.e., memory or recall) responses to second and subsequent exposure to antigens. Memory T cells are produced by antigen stimulation of naïve T cells and survive in a functionally quiescent state for many years after the antigen is eliminated.

MHC (major histocompatibility complex). A large genetic locus that includes the highly polymorphic genes encoding the peptide-binding molecules recognized by T cells. Two structurally distinct types of MHC molecules exist. Class I MHC (HLA-A, B, and C in human) molecules are present on most nucleated cells, bind peptides derived from cytosolic proteins, and are recognized by CD8 T cells. Class II MHC (HLA-DR, DQ, and DP in human) molecules are restricted largely to professional antigen-presenting cells (macrophages, dendritic cells, B cells), bind peptides derived from endocytosed proteins, and are recognized by CD4 T cells.

MLR (mixed lymphocyte reaction). An in vitro reaction of alloreactive T cells from one individual against MHC antigens on blood cells from another individual. The MLR involves proliferation of and cytokine secretion by both CD4 and CD8 T cells and is used as a screening test to assess the compatibility of a potential graft recipient with a potential donor.

Naïve T cell. A mature T cell that has not previously encountered an antigen, nor is the progeny of an antigen-stimulated mature T cell. When naïve T cells are stimulated by antigen, they differentiate into effector cells. Naïve T cells have surface markers and recirculation patterns that are distinct from those of previously activated T cells.

NK (natural killer) cells. A subset of bone marrow-derived lymphocytes, distinct from B or T cells, that function in innate immune responses to kill microbe-infected cells by direct lytic mechanisms and by secreting IFN-γ. NK cells do not express clonally distributed antigen receptors like Ig receptors or TCRs, and their activation is regulated by a combination of cell surface stimulatory and inhibitory receptors, the latter recognizing self-MHC molecules.

PHA (phytohemagglutinin). A carbohydrate-binding protein, or lectin, produced by plants that cross-links human T-cell surface molecules, including the T-cell receptor, thereby inducing polyclonal activation of T cells. PHA is frequently used in experimental immunology to study T-cell activation. In clinical medicine, PHA is used to assess whether a person's T cells are functional or to induce T-cell mitosis for the purpose of generating karyotypic data.

Superantigen (SAg). Proteins that bind to and activate all the T cells in an individual that express a particular set or family of T-cell receptor (TCR) genes. Several staphylococcal enterotoxins are superantigens. Their importance lies in their ability to activate many T cells, which results in large amounts of cytokine production and a clinical syndrome that is similar to septic shock.

T cell. The cell type that mediates cell-mediated immune responses in the acquired immune system. T cells mature in the thymus, circulate in the blood, populate secondary lymphoid tissues, and are recruited to peripheral sites of antigen exposure. They express antigen receptors (TCRs) that recognize peptide fragments of foreign proteins bound to self-major histocompatibility complex (MHC) molecules. Functional subsets of T cells include CD4 helper and CD8 cytotoxic T cells.

Th1 cells. A functional subset of helper T cells that secretes a particular set of cytokines, including IFN-γ, and whose principal function is to stimulate phagocyte-mediated defense against infections, especially with intracellular microbes.

Th2 cells. A functional subset of helper T cells that secretes a particular set of cytokines, including IL-4 and IL-5, and whose principal functions are to stimulate IgE and IgA productions by B cells and eosinophil/mast cell-mediated immune reactions and to downregulate Th1 responses.

Thymus. A bilobed organ situated in the anterior mediastinum, which is the site of maturation of T cells from bone marrow-derived precursors. Thymic tissue is divided into an outer cortex and an inner medulla and contains stromal thymic epithelial cells, macrophages, dendritic cells, and numerous T-cell precursors (thymocytes) at various stages of maturation.

TNF-α (tumor necrosis factor-α). A cytokine produced mainly by activated mononuclear phagocytes that functions to stimulate the recruitment of neutrophils and monocytes to sites of infection and to activate these cells to eradicate microbes. TNF-α produced in large amounts has systemic effects, including induction of fever, synthesis of acute phase proteins by the liver, and cachexia. TNF-β is a closely related cytokine with identical biologic effects to TNF-α but is produced by T cells.

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Ethics Issues in Human Health Research

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Introduction

At present, ethical issues figure very prominently in research studies involving human subjects. Although informal discussions on bioethical issues between doctors and patients have always taken place, full-scale, organizational discussions on ethical issues involved in medical care began about 20 years ago in Japan. Ethical committees began to be established to discuss ethical issues from an objective viewpoint after the issue of *in vitro* fertilization arose at the Tokushima University School of Medicine in 1982. These committees were first established in an effort to create bodies comparable to institutional review boards (IRB) in the United States. On the agenda in those days were mainly ethical issues arising from clinical situations, such as *in vitro* fertilization and organ transplantation.

When did the debate on ethical issues in scientific research begin? It is no exaggeration to say that until quite recently there were virtually no ethical regulations or requirements for "studies on human beings" funded by the research grants offered by the Ministry of Education, Culture, Sports, Science and Technology (MEXT) or the Ministry of Health, Labour and Welfare (MHLW). Only very recently did discussions on the ethical issues involved in studies on genes begin in Japan, with guidelines issued jointly by three ministries and review procedures adopted by research institutes that included the establishment of ethics committees based on the guidelines. Guidelines for epidemiological studies have also been published recently.

I am involved in research and studies conducted at the Radiation Effects Research Foundation (RERF). I gave a keynote lecture at the 14th annual meeting of the Japan Association for Bioethics (November 2002), focusing on examples from RERF and taking heed of social trends, including invasion of privacy and enhancement of researcher awareness of ethical issues, partly in order to present problems from the viewpoint of someone involved in ethical issues, with the intent of raising this issue at the meeting. This paper is based on that lecture.

Before discussing the main subject, I will describe the research conducted at RERF on the effects of atomic-bomb radiation on human beings.

I. Establishment of ABCC-RERF

In 1945, atomic bombs were used in warfare for the first time in human history, and Hiroshima and Nagasaki became the targets. About 114,000 individuals were killed directly by the bomb in Hiroshima, and about 70,000 in Nagasaki. Those who survived the bombings have suffered from various late effects on health from their exposure to radiation from the bombs.

The bomb dropped on Hiroshima was a uranium bomb called "Little Boy." This type of bomb is no longer produced. The one dropped on Nagasaki was a plutonium bomb called "Fat Man." This is the type of bomb that is still currently produced. I do not know why different types of bombs were dropped on Hiroshima and Nagasaki. Some people say it was to test two types of atomic bombs developed in the United States and to investigate the destructive power each had on human beings and materials by dropping them on different places. What is certain is that different types of atomic bombs release different amounts of gamma rays and neutrons, exerting different effects on humans.

On August 6 and 9, atomic bombs were dropped on Hiroshima and Nagasaki, respectively. The bombs exploded, producing a mushroom cloud, and the blasts and heat rays generated by the roughly 7,000°C fireballs burned out everything near by, including humans and buildings.

Shortly after the bombings, the United States sent a group of experts to Hiroshima and Nagasaki to investigate the damage caused by the bombs. Some Japanese experts joined the group, forming the so-called "US-Japan Joint Commission." It was Dr. Masao Tsuzuki of the School of Medicine, the University of Tokyo, who served as a coordinator of as many as 90 Japanese and American scientists who participated in the investigation.

The investigation began on September 8, 1945, and its report was submitted to then US president Harry Truman. President Truman, in response, directed the US National Academy of Sciences-National Research Council (NAS-NRC) to conduct studies of the late effects of atomic-bomb radiation, and the Atomic Bomb Casualty Commission (ABCC), RERF's predecessor, was established in March 1947.

II. Research at ABCC–RERF

Epidemiological research was the core research activity at ABCC. The study cohorts for the epidemiological studies were first selected from among the atomic-bomb survivors based on information obtained from the supplementary questionnaire for atomic-bomb survivors conducted as part of the 1950 national census to survey their actual conditions at that time. Of the 284,000 individuals from whom information was obtained, 120,000 were selected to form a cohort for the Life Span Study (LSS). The mortality study of that cohort has been continued up to the present time. About 60,000 individuals have already died, and epidemiological studies are being carried out to investigate the relationship of radiation dose to their causes of death and other issues.

In addition to the LSS, ABCC-RERF has conducted the Adult Health Study (AHS) through biennial health examinations of about 20,000 individuals extracted from the LSS cohort. Other study cohorts include a cohort of about 3,600 *in utero* atomic-bomb survivors and a cohort of about 88,000 second-generation atomic-bomb survivors.

These studies show that the incidence of leukemia and other types of cancer is higher among atomic-bomb survivors than among unexposed individuals. Studies on the relationship between radiation dose and development of diseases have also been conducted, and RERF's study results have been used as important data in establishing radiation protection standards.

The relative risk for radiation-induced cancer death has been shown to be highest for leukemia, and it is higher for breast cancer in those exposed at young age compared with other solid cancers. Quantitative risk estimates and dose and age-related relationships for leukemia and solid cancers following radiation exposure have been derived from the ABCC-RERF data.

ABCC, which had conducted these studies, was reorganized into the Radiation Effects Research Foundation in 1975 as a private nonprofit organization authorized by the former Ministry of Health and Welfare and the Ministry of Foreign Affairs, allowing the studies of atomic-bomb survivors to continue for a long period of time. The US and Japanese governments agreed to equally fund RERF, enabling RERF to take over ABCC's programs.

Rarely have I heard that previously in Japan, there was a practice of having review committees review research protocols (RPs) before studies were initiated. RERF, however, has adopted an American system, under which an RP that researchers have developed is reviewed for its quality before the research project in question can be initiated. During the days of ABCC, 316 RPs were approved after review, and 218 RPs since ABCC was reorganized into RERF.

RERF, which succeeded ABCC, has continued the RP review system and has had RPs reviewed by the Research Protocol Review Committee before initiation of research projects. However, only the scientific aspects were reviewed and no ethical aspects were considered. In 1972, the Tuskegee incident came to light, and this triggered the movement at RERF to review studies from the viewpoint of protection of human rights.

III. Tuskegee study and IRB

The Tuskegee incident was, so to speak, a human experiment conducted in Macon County, Alabama, beginning in 1932, in which 399 African-American males who had syphilis were left purposely untreated so that the natural course of untreated syphilis could be observed.

In 1929, venereal diseases, including syphilis, were quite prevalent in the United States. The Julius Rosenwald Fund, a Chicago-based charity, initiated a project to eradicate venereal diseases with the support of the United States Public Health Service (USPHS). They chose Macon, Alabama, one of the counties where syphilis was most prevalent in the United States, and carried out a survey of syphilis on African-American males in this county, where 82% of its population was African-American. In the county was a famous university called Tuskegee University, after which the study was named. It was found out through this survey that the incidence of syphilis in Macon County was 36%, the highest in the United States. The Fund began treating 3,694 syphilis patients with Neosalvarsan.

In the same year, the Great Depression began. The Fund ran short of funds, and was left with no other choice but to withdraw its financial support from the charity project before completion. Then, the USPHS took over and scaled the project down from medical treatment to a study.

In this survey, 399 African-American males who had never been treated for syphilis were identified. Although penicillin was developed and made widely available in the 1940's, those subjects of the Tuskegee study were never administered penicillin in the 1940's, 50's, or even 60's. The objective of this study was clearly to observe the natural course of untreated syphilis. Physicians wanted to know how untreated syphilis would progress. This is quite conceivable, considering the tide of medical science of those days. I would like to emphasize, however, that serious ethical problems were involved here.

Around 1966, Peter Buxton, a young physician newly employed at the USPHS, became suspicious about the Tuskegee study and, after investigation,

began criticizing the officials who had been carrying it out. In July 1972, an Associated Press reporter, Jean Heller, a friend of Buxton's, wrote an article about the Tuskegee study. The article was published on the front page of newspapers throughout the country, bringing the incident to light. Finally, in November of the same year, the Secretary of Health, Education, and Welfare, Casper Weinberger issued an official command to terminate the study.

The Tuskegee incident can be summarized once more from an ethical viewpoint as follows:

1) The study was conducted in total disregard of obtaining informed consent;
2) The physicians left the patients untreated and observed the natural course of untreated syphilis regardless of their duty to cure diseases, and;
3) The medical society helped the study.

These are some of the ethical problems that came to light. Before this incident was disclosed, no ethical regulation had been enforced in the fields of research even in the United States. In those days, there were movements to establish ethics committees only for such issues as organ transplantation and *in vitro* fertilization, and Senator Edward Kennedy held public hearings to arouse public opinion. However, there was a deep-rooted belief that medical care should be left in the hands of physicians, since they are experts, and lawyers or representatives of citizens could not be accepted as ethics committee members. The Tuskegee incident changed public opinion in the United States dramatically and the arrangements have been changed, requiring inclusion of representatives of study subjects, such as lawyers and citizens, in ethics committees.

As a result of the incident, a law, which requires the establishment of IRBs that consist not only of physicians but also experts in other fields for all studies involving human subjects, was established and enforced in the United States in 1974.

IV. Establishment of RERF Human Investigation Committee and its activities

Thus the US government legislated an act requiring research institutes to establish IRBs and have them review all federally funded projects involving human subjects before those projects are initiated. Since RERF receives one-half of its funds from the US government, it has been requested by NAS to establish a committee to review the ethical aspects of studies and protect human rights. In response, then Chief of Research Dr. Stuart Finch and Permanent Director Dr. Masuo Takabe began preparations for establishment of the RERF Human Investigation Committee (HIC) in July 1976. With this in the background, RERF has continued to submit reports of the HIC's reviews of research protocols to NAS.

There is a document in the RERF archives, in which it is recorded that the HIC members were appointed in August 1976. However, there is no clear description as to whether the first HIC discussion was held in the form of an actual meeting or by means of exchanging written communications; what remains is only a copy of the letter sent to NAS saying that the HIC discussed the "Assurance of protection of human rights for the Nagasaki tumor registry plan."

At that time, the HIC was composed of a permanent director who served as its chairman, seven RERF employees, and one non-RERF lawyer. Figure 1 is an RERF official document, "Draft Action Form," drawn up to convene an HIC meeting in April 1977. It is clear that the HIC was established in August 1976 and met in April 1977. This probably is the first committee established in Japan to protect human rights in "studies involving human subjects." For some reason, however, this fact is not well known. A book on ethics issues says that the first ethics committee in Japan is the one established at Tokushima University in December 1982. I believe that the RERF HIC must be the first ethics committee in Japan, as it was established five years earlier.

RERF's "Operational Procedures of RERF Human Investigation Committee" stipulates in the "Range of work" that the HIC shall review matters

Figure 1. Draft Action Form to approve the Human Investigation Committee at RERF on April 15, 1977, the first documented ethical committee meeting in Japan.

pertaining to protection of human rights 1) as seen from the ethical points of view and from the universally accepted concept, 2) in the handling of biological materials including blood and biopsy sections, and 3) in the handling of investigation records.

Presently the HIC includes two non-RERF experts, because the IRBs are obligated to include experts other than physicians when ethical issues are dealt with, as mentioned earlier. Participation of individuals outside RERF as its members carries a high degree of significance in many senses.

The followings are some of the noteworthy examples of actual cases discussed by the RERF HIC. One case concerns consent for storage of blood samples; that is, what course of action should we take to use the blood samples of deceased donors in the absence of their informed consent. Another example concerns the amount of blood to be drawn. The present regulations stipulate that blood cannot be drawn in an amount of more than 30 ml. Another issue that the HIC has addressed involved non-RERF researchers' use of RERF stored research samples by taking the samples out of RERF for collaborative studies.

As mentioned above, RERF has well organized regulations concerning review of ethical issues involved in research projects. Dr. Kazumasa Hoshino wrote in his book that the percentage of universities that have ethics committees had increased from 35% in 1985, nine years after the RERF HIC was established, to 94% in 1988. However, most of these ethics committees mainly address issues involved in organ transplantation, *in vitro* fertilization, and other issues of clinical medicine. Only recently were ethical guidelines developed for genome and epidemiological research.

V. Ethical problems RERF has faced

While RERF has mainly studied and examined atomic-bomb survivors, genetic studies of second-generation atomic-bomb survivors have also been conducted, such as studies of chromosome aberrations and abnormal development. No genetic effects of radiation have been found in these studies so far.

However, the average age of second-generation atomic-bomb survivors reached 42 years in or around 1996, the age at which they are prone to develop lifestyle diseases. Therefore, the RERF Scientific Council recommended that RERF study the relationship between lifestyle diseases (i.e., multifactorial diseases such as hypertension, diabetes, and heart diseases) among these individuals and genetic effects, if any. In response, RERF initiated the study.

A study plan was developed to select second-generation atomic-bomb survivors living either in Hiroshima or Nagasaki City or their surrounding areas from the full second-generation survivor (F_1) cohort of about 88,000 second-generation atomic-bomb survivors, carry out a mail survey on about 24,000 individuals, conduct health examinations of those who wish to undergo health examinations, store blood and urine samples for future genetic studies, and to study the relationship between lifestyle diseases and radiation effects (Figure 2).

The ethical problem that RERF faced erupted when RERF began obtaining family register (*koseki*) attachments from local governments before initiation of the study in 1997 to locate 24,000 second-generation atomic-bomb survivors so that questionnaires could be mailed. The mass media (Asahi Newspaper) created a commotion by exaggerated reporting, claiming that it would be a violation of those survivors' privacy. It came as a

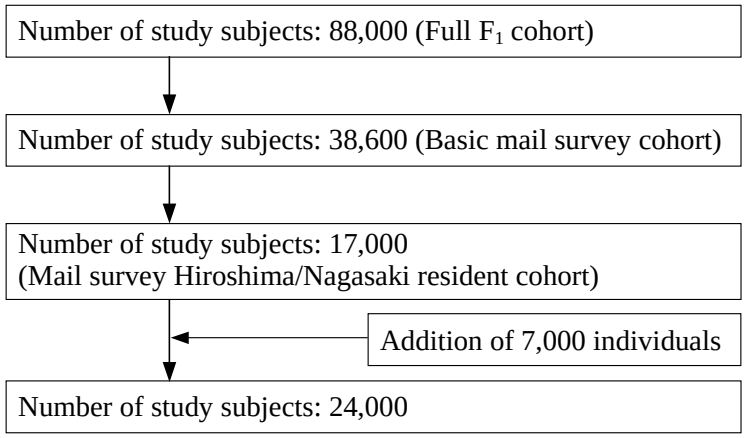

Figure 2. Number of subjects in health effects study of the children of atomic-bomb survivors. Of 88,000 persons in the full F_1 cohort, about 24,000 were selected for a mail questionnaire survey.

surprise to us, because RERF had followed the required legal procedures to obtain *koseki* attachments. In response, RERF held the first meeting with the Hiroshima Prefecture Second Generation A-bomb Victims Liaison Council in November of the same year to explain to them the objectives of the study.

The Council's arguments can be summarized as follows:
1) It is a gross invasion of privacy for RERF to obtain *koseki* attachments without the knowledge or consent of second-generation atomic-bomb survivors themselves.
2) This study could create discrimination.
3) RERF, which has been criticized for examining atomic-bomb survivors without giving medical care (since the days of ABCC, its predecessor), hiding unfavorable data, and giving data only to America, is utterly untrustworthy.
4) RERF must apologize.

The mass media at that time published articles in concert, as if RERF were a devil. Listening to the arguments of study subjects, I became keenly aware that studies, depending on approaches, could create problems such as discrimination and invasion of privacy. Thus, RERF actively began to hold as many talks with those groups as possible.

At one of the talks with them, we told them that there would be no point in having discussions, if they were against the study itself, and we asked if they were absolutely against the study. They replied that they were not against it *per se* and that they wanted RERF to fully explain the objectives and listen to them in good faith. Therefore, RERF made the following proposals:
1) RERF will formulate a third party "scientific committee" consisting of non-RERF experts to incorporate opinions of learned and experienced persons outside RERF in deciding the nature and design of the study.
2) RERF will establish a third party "ethics committee," aside from the HIC, to review ethical issues, such as discrimination and privacy, involved in the study of second-generation atomic-bomb survivors.
3) The *koseki* attachments obtained will be stored safely and carefully in a safe installed in a room accessible to only those concerned until the issue is settled.
4) RERF will study the relationship between radiation exposure and lifestyle diseases strictly scientifically.

As mentioned above, RERF reviewed and discussed the study plans while deepening mutual understanding with the groups concerned. All these efforts were made because the study of second-generation atomic-bomb survivors would be the first study of this kind in the world, an important study that could be done only by RERF. It took us as many as four years to initiate the study, as we waited for second-generation atomic-bomb survivors to understand the importance of the study.

As we made progress in the preparation of the study, the following four ethical problems were identified and became the focus of discussions:
1) What considerations should be given to the feelings that recipients of the questionnaire might have when they receive it by mail?
2) Recipients of the questionnaire might wonder why and how they were selected.
3) Many prospective study subjects do not know that their parents are LSS cohort members.
4) Questionnaires could cause family problems to those who have been hiding the fact that their parents were atomic-bomb survivors.

The Ethics Committee for the Health Effects Study of the Children of Atomic-bomb Survivors discussed other issues in addition from various angles. The Ethics Committee also reviewed the design and other details of this study carefully. One example of the suggestions we incorporated in the study plan was to add such a note as "The following questions are asked to obtain information on health and living habits. We have no intention to meddle in your private life. Please answer them up to the point you don't mind." to the delicate questions that could invade privacy, such as the questions about "Present marital status, occupation and education," and "Pregnancy, childbirth and child rearing (ladies only)."

Another issue the Committee discussed was the name of the sender for the purpose of minimizing the discomfort the recipients might experience when they receive the questionnaires. In response, we formulated several proposals for our return address, including or excluding the name of RERF and the Second-Generation Secretariat. It was decided that use of the RERF address only would be most appropriate. The study is going smoothly, although it requires attention to the smallest detail by the staff in the front line.

The pilot study was followed by the first full-scale mail survey, the results of which are shown in Table 1. The initial mailing of questionnaires was sent to a total of 4,355 individuals in Hiroshima and Nagasaki, of whom 3,118 replied. Of these respondents, 2,213 expressed their willingness at varying degrees to undergo health examinations. This allowed the initiation of the first study.

VI. Mutual trust underlying ethical issues

The genetic studies conducted at RERF have not shown genetic effects of radiation. Some individuals wondered what RERF wanted to study after so many years had passed since the atomic bombing. There were others who were afraid that genetic effects or abnormalities, if any, could lead to discrimination.

Table 1. The first full-scale mail survey: Summary of responses (as of 16 November 2001)

	Results	Both cities	Hiroshima	Nagasaki
1	Responded and willing to participate in health examinations	1,840	1,219	621
2	Responded but refused to participate in health examinations	467	342	125
3	Responded but not decided to participate in health examinations	346	244	102
4	Responded but wrote reasons for refusing to participate in health examinations	1	0	1
5	Refused (No response, etc.)	21	19	2
6	Address unknown	399	251	148
7	Deceased	5	5	0
8	Participation not possible	12	6	0
9	Responded but left blank the question about participation in health examinations	27	16	11
	Total	3,118	2,102	1,016

We have learned through the course of the health effects study of the children of atomic-bomb survivors that possible problems, such as violation of privacy and disadvantages to study subjects, can be prevented by showing some consideration.

However, there is concern that the study, if it shows the involvement of genetic effects of radiation in diseases among the second-generation atomic-bomb survivors, would create discrimination against the study participants or bring disadvantages to them when the results are published.

Yet we must accept the results obtained from a scientific study and publish them without distortion. Of course, the data must be objectively presented and interpreted with some sensitivity to alleviate any individual or group concerns. Depending on the results obtained, the study could cause a serious social problem. What judgment should the Ethics Committee make?

I have never heard of ethics committees, either in Japan or abroad, going so far as to discuss how study results should be handled. Of course, there have been studies that were judged to generate results unfavorable to study subjects and thus were called off before their initiation at RERF, and I believe other research institutes and universities have experienced similar cases.

Many geneticists "predict" that "no effects will be found" from the study of second-generation atomic-bomb survivors. If we can say that no effects are found from the study, it will be a relief to them and eliminate discrimination, if any, making the study worthwhile. However, what should we do if some effects are found? It is a matter of grave importance, and it will probably be settled through discussions with the parties concerned.

The term "ethical issues" is used casually; however, I keenly feel that there are many important problems that need to be discussed and resolved. The studies involving human subjects would be impossible without coordination of efforts and mutual trust between the party being studied and the party conducting the study. In other words, it is probably correct to say that we must not conduct studies if mutual trust has not been established. How to proceed with the building of mutual trust between these two parties seems to be the starting point of resolving ethical issues.

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Facts and Figures

New Dosimetry Roster

The current status of the new dosimetry system DS02 is presented elsewhere in this issue of *Update*. In the process of RERF implementation of DS02 substantial improvements have been made in addition to the changes in the basic system itself. These efforts resulted in the creation of dosimetry roster of 250,000 people, whose doses are of interest to RERF, containing the best available information on exposure status and shielding established from a review of all relevant data sources. A large number of persons have newly-assigned dose estimates, mainly zero, which will lead to improved analyses.

The roster includes not only the Life Span Study (LSS) cohort members, but (a) mothers of the *in utero* cohort, (b) parents of those included in the F_1 mortality and laboratory study cohorts, and (c) parents of F_1 members of the early ABCC study (GE-3) of pregnancy outcomes. Because of the previous lack of a comprehensive roster, dose estimates were often treated as unknown for some members of cohorts (a)–(c) even though RERF records contained sufficient information to assign doses. Also, in some cases different sources were used in dose computations for various studies, leading to inconsistencies. The development of the more complete roster has no affect on estimates for the LSS. The table below summarizes the current dose estimation status for the overlapping groups mentioned above. Most of the 113,000 people added to the roster were unexposed or received doses of less than 1 mGy. As with DS02, doses are not assigned to proximal survivors unless they are known to have been exposed in a standard house or have detailed shielding information of a type handled by the dosimetry system.

There is an important distinction between the *In-City Unknown Dose* and *No Information* groups. The *Unknown Dose* group includes survivors who were close enough to the hypocenters to have received doses in excess of 10 mGy but for whom doses cannot be computed because of the complexity or lack of information regarding their shielding conditions. The mean distance from the hypocenter for survivors in this group is about 1.6 km, where the mean survivor dose is about 0.17 Sv. The *No Information* group comprises people for whom there is no information on shielding or location. Most of this group are F_1 parents where the other parent has been assigned a dose. These were largely unexposed persons, and can sometimes be used as such in analyses even though a dose has not been officially assigned to them.

	In City				Not in City		No Info	Total	Change
	Known	Change	Unknown	Change	Zero Dose	Change			
LSS	86,671	39	7,070	–39	26,580	0	0	120,321	0
In Utero Mother	2,693	344	248	–42	727	524	699	4,367	1,525
F_1 Parent	42,832	2,126	3,705	–27	42,714	36,393	10,153	99,404	48,645
F_1 GE-3 Parent	32,293	10,697	3,557	1,260	72,428	67,583	760	109,038	80,300
Other Groups	12,964	8,342	973	363	2,133	2,133	17	16,087	10,855
All Groups	125,399	20,757	10,520	1,568	106,702	80,122	10,996	253,617	113,443

Hiroshima Memorial to Norman Cousins

–The common language of humanity–

On August 2, 2003, a memorial to the late Norman Cousins was dedicated in the Peace Memorial Park in Hiroshima. Mr. Cousins (1915–1990), as editor of the Saturday Review, involved himself in the peace movement of the post-World War II world. He showed particular compassion for the survivors of the atomic bombings, arranging adoptions of orphans, scholarships and the medical treatment in New York for 25 young women who had facial keloids (or severe skin burns), who became known as the Hiroshima Maidens. Staff members of ABCC were able to help Mr. Cousins in this humanitarian work, especially Hatsuko Yokoyama, ABCC clinical staff member and Japanese American (second generation), who served as chaperone for the group in New York in 1955. Perhaps because of this connection, RERF was part of the memorial dedication ceremony. RERF staff members made a financial contribution to the monument.

Those who made short remarks or greetings at the memorial ceremony included the Presidents of the Hiroshima Medical Associations, Dr. Shizuteru Usui (city) and Dr. Koso Sanada (prefecture), the Governor of Hiroshima Prefecture, Yuzan Fujita, Hiroshima Mayor, Tadatoshi Akiba, Chairman of the Prefecture Assembly, Atsumi Nitta, Chairman of the Hiroshima City Council, Tadamasa Asao, and RERF Chairman, Burton Bennett.

A special part of the ceremony was made by family members of Mr. Cousins, who had come from the US and Israel: Andrea Cousins, daughter, Sarah Cousins Shapiro, daughter, and Shigeko Sasamori, adopted daughter and one of the Hiroshima Maidens. They eloquently expressed the strong feelings of common humanity that unites us all.

In order to inform a wider audience of this event, the statements by the RERF Chairman and by Sarah Cousins Shapiro are included below. We are all pleased that the deeds of Norman Cousins will be remembered and the ideals that found life in Hiroshima will be permanently honored.

Statement by Burton Bennett, Chairman of RERF:

The atomic bombings of Hiroshima and Nagasaki caused indescribable death and destruction and left the survivors with lives forever changed by trauma and injuries. If ever care and compassion were required in this world, it was needed in the aftermath of those events.

Fortunately there were individuals who did demonstrate compassion and who provided support for care and recovery. Norman Cousins was one of those who responded to the desperate needs. To remember those deeds and to keep alive the spirit of compassion that he demonstrated, this monument is dedicated.

Former colleagues of mine at the Radiation Effects Research Foundation and its predecessor, ABCC, were able to assist Mr. Cousins in his humanitarian work. We have the greatest respect for the survivors and their families and have always wished to contribute to their welfare and well-being.

I am grateful for this opportunity to acknowledge in the presence of family members of Norman Cousins, who have come to Hiroshima for this ceremony, our gratitude for the deeds of Mr. Cousins and for the ideals that he upheld.

On behalf of my colleagues at RERF, I wish to express to all of the survivors of the atomic bombings our determination to maintain the spirit of care and compassion that is enshrined in this monument. We will bear this in heart and mind as we in continue our scientific studies in Hiroshima and Nagasaki. We would like to contribute to the good health of all of you and promote an enduring peace throughout the world.

Statement of Sarah Cousins Shapiro:

A few years before he died, my father wrote his daughters a letter.

He asked us not to think anything was pending or that he was having premonitions, but something had come up, he said, in the course of attending to his will, and he didn't wish to make such a decision without discussing it with us beforehand. Upon his death, the letter informed us, he would like his ashes to be scattered over Hiroshima.

This announcement presented me with a daughter's most profound dilemma. First of all, it was unbearable to hear my father speak of his own death. I was a mother already myself at that point, but the childhood belief that my parents *had* to live forever had never left me, and I was ashamed to admit the possibility that one day this thing would come to be.

Secondly, I didn't want his ashes to be scattered here. When the unthinkable day would arrive that he wouldn't be with us anymore, I wanted to be able to visit his grave, and wanted my children to visit his grave. As a little girl, I had said goodbye to him and my mother many times when they traveled to Japan, yet as an adult I found myself unwilling to consider letting go of him in this way forever.

Thirdly, and most importantly, cremation contradicts Jewish tradition. According to the Torah, the relationship between body and soul is a mystery ultimately known only to God, and Judaism teaches us to return the soul to its Creator by returning the body, dust to dust, to the earth from whence it came.

With anguish and apology, I wrote back to my father all of these things. He answered at once that he accepted my reasons, and that I should please put my mind at rest, he would do as I asked.

Last week my family and I visited my father's grave, and the significance for us of that privilege is beyond my ability to convey. Yet it was not in that cemetery in America, where he and my mother are buried, that I can best feel his spirit but here, today, with you. For it is in Hiroshima that my father saw the ideals and values he cherished come alive; that our lives on this small planet are a constant miracle, and our capacity for regeneration far beyond what we imagine; that it is every human being's responsibility to justify that gift; that it is possible to reach out across all the differences of culture which seem to divide us, and recognize the vastness of all that we share.

One morning here in Hiroshima thirteen years ago, my mother and I stepped into the hotel elevator, exchanging small nods of acknowledgement with the Japanese woman who was standing inside. In the four or five seconds down to the lobby, we were feeling the customary awkwardness strangers usually feel when facing each other in an elevator, whereupon she turned and with a little smile bowed to us in the customary manner, and we bowed back. Then we got off and never saw her again.

It was an unremarkable event but the image of that woman's face has stayed with me until today, as has the memory of the way that traditional gesture of respect restored for us our inherent human dignity. We couldn't say anything, because we didn't share a language, but her gesture instantly gave back to us that which in Hebrew is called *tzelem Elokim*, the divine image in which each human being is created. The divine image is not anything having to do with the physical body, but is, rather, the godliness within all of us which only becomes visible when we strive to emulate the infinite kindness of our Creator.

A few minutes away from our home in Jerusalem, my sons-in-law learn at a yeshiva, a school of Jewish learning, all of whose students were saved in World War II by Chiune Sugihara. As you surely know, Sugihara issued visas to this large group of Jews to escape Germany, thereby putting himself in extreme danger. He served as a lifeline to people who could not have been more different from himself culturally, saving the lives of hundreds of people whose children and grandchildren and great-grandchildren are alive today, thanks to him. He, like my father, had eyes to perceive the humanity of people who seemed to be so foreign. In Israel today, Sugihara is someone to whom we are eternally grateful. Gratitude is a common language. Suffering is a common language. Joy is a common language.

I stand before you now knowing how happy it would make my mother and father to see us today with you in Hiroshima they loved. I don't know how to thank you for the opportunity you have given me to honor them in this way. It is a joy to be here together with my sisters Andrea and Shigeko, and on behalf of my sisters Amy and Candis, who could not be here, to remember the deeds of my father and perpetuate the ideals which found life in this place.

Research Protocol Approved 2003

RP 1-03 A Study of Gene Polymorphisms and Their Possible Role in the Development of Diabetes in the Adult Health Study Population
Hayashi T, Fujiwara S, Kusunoki Y, Kyoizumi S, Hakoda M, Nakanishi S, Nakashima E, Takahashi N, Akahoshi M, Suzuki G, MacPhee DG, Nakachi K

The purpose of this study is to analyze the relationships between a certain genotype-related diabetes prevalence and dose in all the cases and controls available for study and determine whether differences in the frequency of any particular genotypes between Hiroshima and Nagasaki survivors may be the reason why a significant association between diabetes prevalence and radiation dose is observed in the Hiroshima but not Nagasaki survivors. In this study, it is focused on the major histocompatibility complex (*MHC*) locus, as an especially important genetic factor, which in humans is referred to as the human leukocyte antigen (*HLA*) locus and the tumor necrosis factor A (*TNFA*) gene, which includes polymorphic genes that map in the *HLA* gene cluster and appears to involve with the expression of TNF-a and with the development of diabetes. We therefore plan to analyze *HLA* (*DQA1*, *DQB1*, and *DRB1*) genotypes and *TNFA* gene polymorphisms of total 3,226 Adult Health Study (AHS) subjects composed of diabetic cases (Hiroshima 627 and Nagasaki 269 subjects) and controls (Hiroshima 1,254 and Nagasaki 1,076 subjects). We will also begin by measuring autoantibodies against glutamic acid decarboxylase (GAD), tyrosine phosphatase IA-2, and insulin as many as possible of survivors who develop diabetes in order to determine the clinical characteristics of those diabetes. From the results of the newly-typed Hiroshima and Nagasaki subjects in this study, we should be in a very good position to specify the clinical feature of an *HLA*-linked diabetes subtype, of which prevalence has been influenced by radiation exposure.

Recent Publications

(Japanese): the original article is in Japanese.
(Bilingual): the original article is in both English and Japanese.
(JTr): a Japanese translation is available.

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