ACTIVITIES OF THE NATIONAL ACADEMY OF SCIENCES IN RELATION TO THE
RADIATION EFFECTS RESEARCH FOUNDATION

Final Progress Report

March 1, 1990 – September 30, 1997

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INTRODUCTION AND BACKGROUND

During the period of this grant, the analyses of studies conducted at the Radiation Effects Research Foundation (RERF) in Hiroshima and Nagasaki, Japan, have continued to provide important information contributing to understanding of the late somatic and genetic effects resulting from exposures of human populations to ionizing radiations. Around the world, governmental agencies and learned bodies continue to rely on the results of these important studies as the basis for radiation risk assessments and radiation protective standards. It should be noted that the investigations conducted by RERF are the only opportunity in existence for determining the late biologic effects resulting from a single exposure to ionizing radiation ranging from very low to high doses. Evidence of the progress that has been made during the period of this grant is the significant number of manuscripts that have been published in the scientific literature by a dedicated RERF staff, many written in collaboration with scientists from various countries including the United States.

The funds of this grant represent the major contribution of the United States in this binational project, which for many years was a 50/50 agreement between the United States and the Japanese Government. The National Academy of Sciences, through its operating structure of the National Research Council, Commission on Life Sciences (NAS), and Board on Radiation Effects Research (BRER), has provided oversight and management for the United States' contribution to this important research project. However, budgetary uncertainties were introduced in 1995-1996, and were coupled with proposed changes in management on the American side. This has impacted negatively on the American staffing at RERF, contributing at least in part to the departure of some key individuals and resulting in a decreased morale. Significant reductions in funding have made it difficult to recruit replacements in key positions. A strengthening Japanese yen resulted in fewer yen be converted from U.S. dollars. Furthermore, an agreement between the two governments reduced the number of American permanent directors to one, requiring the combining of the titles of Vice-Chairman and Chief of Research into one position.

However, despite the turmoil brought about by the budgetary uncertainties and staffing changes, the follow-up of the various RERF study cohorts has continued and remains very important. For example, in one of the cohorts, the Life Span Study (LSS) cohort, approximately 50% of the cohort members are still alive and more than 90% of those who were under the age of 20 at the time of the bombings are still alive. It is especially important to ascertain the late health effects that will occur in what might be a more sensitive component of the exposed population, a component that is now reaching the cancer-prone age.

At the same time (1995-1996) that budgetary uncertainties and a strong yen were impacting negatively on RERF, a Blue Ribbon Panel (BRP) chaired by Dr. Roger Clarke and composed of Japanese, American, and other international scientists, conducted a review of the

scientific program at RERF. The Chief of Research at that time, Dr. Seymour Abrahamson, assisted the RERF staff in preparation for, and participation in, the BRP's review. The BRP final report, submitted by the panel in July, 1996, in general commended the RERF for its research studies, emphasized the importance of the project to human kind, urged that the RERF research programs be further strengthened, and included 21 specific recommendations covering the entire spectrum of RERF activity. Dr. William Schull, who followed Dr. Abrahamson as Chief of Research, coordinated the development of a "Five-Year Strategic Research Plan and Program Management" in response to the panel's report and additional recommendations by the Science Council.

Some of the uncertainties surrounding the management and budget were resolved from the U.S. side and additional staff were recruited by NAS to work at RERF, including a Vice-Chairman and Chief of Research, Dr. Sheldon Wolff, an editor, Ms. Rosalyn Vu, and a biostatistician, Dr. Claire Sherman. Additional changes at RERF included the appointment of a new RERF Chairman, Dr. Shigenobu Nagataki, who succeeded Dr. Itsuzo Shigematsu who retired June 30, 1997, after 16 years of service as RERF Chairman, and appointment of a new Japanese permanent Director, Dr. Senjun Taira. Mr. Kazumasa Kunitoshi was named Chief of Secretariat. In the U.S., DOE's Office of International Health included some new managerial personnel and I became director of BRER in May, 1997. One of my personal objectives of this past year has been to work in collaboration with the RERF and DOE staff to become familiar with the RERF research program, including its investigators, its facilities, and its projects.

This past year represented the 50th anniversary of what was originally the Atomic Bomb Casualty Commission (ABCC) and later became RERF. To commemorate that historic occasion, NAS planned two special events in Washington, D.C. The first was a symposium held April 30, 1997, in conjunction with the Annual Meeting of NAS entitled "A Song Among the Ruins: 50 Years of Japanese/Academy Cooperative Studies of Atomic-Bomb Survivors." The second was a symposium entitled "ABCC/RERF: Commemorating the First 50 Years and Looking to the Future," held at NAS on June 13-14, 1997. This latter symposium included a commemorative session in which two panels were formed to discuss their most memorable highlights, one panel composed of former ABCC staff and a second panel composed of RERF staff. The second session included panels, made up of RERF scientists and invited guest speakers, that focused on the most recent RERF discoveries and future planned research activities. Six topic areas were selected from areas that the Blue Ribbon Panel report had identified as key areas for future development. The proceedings of the first symposium have been published in the *Proceedings of the National Academy of Sciences* (Vol. 95: 5423-5444, 1998) and the second symposium's proceedings will be published by the National Academy Press.

HIGHLIGHTS OF RERF STUDIES

Research at RERF has been focusing on two types of studies—projects that have been long-term and, in most cases, are expected to continue well into the future, commonly designated as "core activities," and projects that are generally time-limited, usually initiated within a single department, and referred to as "specific research activities." In order to initiate any one of the

studies, a research protocol (RP) must be prepared in English and Japanese and submitted to the RERF Research Protocol Committee for approval. Any research protocol involving human subjects must also be approved by the RERF Human Investigation Committee (HIC; is the institutional review board, or IRB). In addition, the actions of the HIC for the latter protocols are also reviewed by the NAS IRB. Since January 1990, 35 new RPs have been approved by the RERF and the total number of currently active RPs is approximately 78. The highlights of some of the various studies will be summarized in this report.

The investigators and staff (totaling 317 in March of 1997—245 in Hiroshima and 72 in Nagasaki) who conducted the studies reside in 6 major departments (clinical studies, genetics, radiobiology, epidemiology, statistics, and information technology). In 1994, a department of epidemiologic pathology, responsible for the conduct of pathology studies and the tumor and tissue registries, was merged with the Department of Epidemiology. Several of the studies are conducted by investigators from several departments. For example, and as indicated in the BRP report, one of the most important multidisciplinary programs is the molecular epidemiology of cancer which requires interdepartmental and interdisciplinary collaboration. The members of the Department of Statistics play an important role in the design and analysis of data for virtually all of the RERF activities. The Information Technology Department (ITD) provides support for all of the departments. During this grant, RERF has completed a transition from a host-computer environment to a distributed processing system centering on Unix workstations. The former department chief was an NAS employee; she has departed from RERF and has not been replaced. Despite having a shortage of technical computer staff, the (ITD) has adjusted well to the new computer system and has verified that RERF does not expect to have a year-2000 problem and does not project any significant computer equipment requirements in the next few years.

Adult Health Studies

Biennial examinations initiated in 1958 have been continued to determine the types of diseases and abnormalities in physiologically- or biochemically-determined values that might have occurred as a consequence of previous exposure to ionizing radiation. These studies focus on the Adult Health Study (AHS) cohort. As of the fall of 1996, more than 9,200 of the 17,397 exposed members of the AHS were still alive. About 8,000 of those individuals are living in the clinical-contact catchment area, and almost 80% of this latter group participated in the recent 19th cycle of AHS examinations.

Through AHS, RERF has accumulated an enormous body of data on serial medical examinations, with and without the superimposed radiation aspects, which increases with time. The AHS clinical exams provide an important point of direct contact with the survivors and function as a source of biologic materials for many of the various interdepartmental special studies. The major elements of the AHS can be categorized as

- characterization of cancer types in relation to various confounders of radiation effects,
- radiation-related noncancer diseases,
- benign tumors,
- cardiovascular disease,

- aging,
- medical dosimetry,
- psychosocial changes associated with exposure to radiation, and
- radiation- or age-related changes in other physiologic endpoints.

Particularly noteworthy is the accumulating evidence that cardiovascular mortality may have a positive radiation-dose response. Similarly intriguing and potentially important relationships have arisen from the clinical studies of hyperparathyroidism and serum levels of parathormone, calcium, and alkaline phosphatase. Those results suggest that significant deviations in calcium metabolism may be a direct effect of radiation exposure and raises further questions about bone density and osteoporosis among survivors. Another unexpected finding was the retrospective evidence that radiation exposure is associated with premature menopause and this, in turn, may result in earlier onset of other physiologic conditions such as an increase in cholesterol levels and cardiovascular disease.

Some additional important highlights include

- significant dose-response relationships have been detected for noncancer endpoints such as thyroid disease, myoma uteri, and chronic hepatitis and/or liver cirrhosis,
- significant dose-response relationships have been detected for cancers of the stomach, colon, urinary bladder, and female breast, and for leukemia,
- basal cell carcinoma and senile keratosis were found to be increased in the population exposed to radiation,
- the AHS provides the population base for late-effects studies in cytology, genetics, immunology, radiobiology, and medical dosimetry,
- in the 18th biennial-exam cycle, a total of 3,920 cohort members from Hiroshima and 2,429 from Nagasaki were examined,
- data from cycles 1-14 have been analyzed and reported in AHS Report 7, and
- storage of serum (72,000 frozen and 63,000 freeze-dried samples) and other biologic materials such as lymphocytes has been a high priority.

To improve health information retrieval, a mail survey followed by telephone contact of nonresponders was introduced in 1995 in Hiroshima, and in 1996 in Nagasaki. In both cities, the response rate over the past 3 surveys was approximately 85%. The response rates were 70% and 80% for those members who refused to participate in the biennial medical examinations and those who migrated out of the contact area, respectively. The results indicate that the data collection on morbidity has become more complete upon the introduction of the new system, and future analyses of data on morbidity of various diseases may give answers regarding the association between morbidity and previous exposure to ionizing radiation.

Life-Span Studies

Two major goals of the Life-Span Studies (LSS) are (1) to ascertain whether those exposed individuals who survived (an original cohort of 93,000) continue to survive as long as the nonexposed (27,000) and whether any diminution of their life expectancy is a function of radiation exposure, and (2) to determine whether or not increased mortality has occurred in children who were exposed in utero. The extensive analysis of the cancer mortality data has been published as LSS Report 12 Part 1 and in *Radiation Research* (Vol. 146: 1-27, 1996). The

analysis of noncancer mortality for 1950-1990 is being completed and will be published in LSS Report 12 Part 2. Mortality data from 1950-1995 will be published in LSS Report 13 before the year 2000. The present analyses continue to demonstrate a small, but statistically significant increase for noncancer diseases in the irradiated population and significant excess mortality is observed for circulatory, digestive, and respiratory diseases. It seems unlikely that the effects are a result of presently recognizable biases, despite the lack of a plausible biologic mechanism and the fact that the observed excess is small.

For the studies of the populations exposed in utero, it was decided that analysis of mortality and morbidity should be based on data from the combined in utero mortality and clinical cohorts. This increased the number of in utero subjects by about 30%. The results of the analysis of cancer mortality in the in utero and childhood exposure cohorts through the end of 1992 will be published in *Radiation Research* in 1997. Despite the small number of cancer deaths among the cohort members exposed in utero, there is, especially for women, a radiation-related excess risk of solid cancer after the age of 17. Those risks are similar to the risks seen for LSS cohort members who were 6 years of age or less at the time of exposure. A manuscript on cancer incidence in the in utero and childhood exposure cohorts is in preparation and analyses of general mortality are in progress. Since the members of that cohort are approaching 50 years of age, death and cancer incidence rates are increasing rapidly and the next 3-5 years of the study will be especially important.

Immunology Studies

Investigators in the Radiobiology Department have been applying precursor-frequency analysis to lymphocyte function in order to clarify whether there are radiation-induced alterations in immune function. In addition, they are cryopreserving live blood cells from members of the AHS. The results of the measurements of immune functions suggest that there is a dose-dependent increase in B cells and a dose-dependent decrease in CD4⁺ helper T cells and previous irradiation might have affected the development of T and B cells, possibly leading to long-term impairment of mean T-cell function. Blood cells from 165 Hiroshima cohort members and 19 Nagasaki cohort members have been cryopreserved. A typing method using polymerase chain reaction (PCR) and DNA extracted from lymphocytes has been used to conduct HLA typing rapidly on a large number of samples at low cost. A possible population bias in the frequency of HLA types is being investigated in samples from high-dose survivors since the frequency of DQA1*0103 males appears to decrease with increasing radiation dose.

Cell Biology Studies

Members of the Radiobiology Department are also conducting molecular studies related to investigate potential mechanisms for radiation-induced changes. They have established a SCID-hu mouse model for analysis of human epilation and human thyroid tissue and for specifically examining radiation-induced oncogene activation in human thyroid. They have also perfected a method for direct sequencing of the p53 gene from archival paraffin sections and have analyzed the mutational changes of the p53 suppressor gene, specifically exons 5-8. The frequency of cases with p53 point mutations was found to increase in a dose-dependent manner. The Radiobiology Department was selected as the first department to undergo review by an

international panel in 1998, in accordance with a recommendation of the BRP and the RERF Science Council. This review process will look carefully at the ongoing activities in the Radiobiology Department and will provide advice to RERF regarding future areas of focus and investigation.

Biochemical Genetics and Cytogenetics

The Genetics Department has been focusing on two major areas of investigation: (1) a biochemical genetics program centering on the detection of gene-mutational events and development of the requisite technologies to explore those events; and (2) a cytogenetics program which focuses on chromosomal abnormalities in survivors and their offspring. Cyclosporin A treatment has been used to establish cell lines from members of 100 families, which in turn, have provided DNA for analyses. A goal is to establish cell lines from 1,000 parent-child trios, with half of the trios including at least one proximally exposed parent. Chromosome aberrations, mainly translocations, are being examined in peripheral lymphocytes from survivors using the fluorescence in situ hybridization (FISH) technique and a total of approximately 494 Hiroshima survivors. An attempt is being made to identify markers in studies to elucidate the association between radiation exposure and hypertension. A pilot study is screening for deletion/duplication mutations.

Studies of the F₁ Generation

The RERF Scientific Council did not fully endorse the recommendation of the BRP calling for studies of the offspring of survivors (F₁ generation) to clarify radiation-induced genetic effects in relation to the occurrence of common multifactorial diseases. Council did recommend a carefully planned pilot study including (1) clinical examination of the F₁ adults who were previously examined in a biochemical genetics study, particularly those whose parents were exposed to a high dose, and (2) a mail questionnaire survey. The Japanese Government has agreed to bear the full cost of the AHS and F₁ studies.

Atomic-Bomb Dosimetry

A task force at RERF continues to collect exposed materials for new and refined measurements of thermal- and fast-neutron activation and thermoluminescence measurements of gamma kerma. A database is under development in the Statistics Department for all samples collected and for all reported measurements relevant to the atomic-bomb dosimetry. Three principal concerns are (1) an apparent discrepancy between relatively recent measurements and computed estimates of neutron doses in Hiroshima, (2) any changes in the estimate of the gamma doses that might result from any changes in the estimates in the neutron doses, and (3) probable over-estimations of doses for the factory workers in Nagasaki. In addition, approximately 680 teeth have been received from survivors and efforts are underway to estimate doses by means of electron-spin resonance measurements of tooth enamel. At this time, 100 teeth from 69 survivors have been measured. Biologic measurements of lymphocyte chromosome aberrations will be made in the same teeth donors. Chromosome analyses have been completed for 61 of those donors.

CONCLUSIONS

The number of RERF publications supported in part by this contract and which describe the results of the studies summarized below is approximately 80 per year (84, 80, and 83 for the years 1995, 1996, and 1997, respectively).