DOE/NAS/RERF-6

RADIATION EFFECTS RESEARCH FOUNDATION

FIVE YEAR

STRATEGIC RESEARCH PLAN

AND

PROGRAM MANAGEMENT, 1997-2001

SUBMITTED BY THE RERF EXECUTIVE COMMITTEE

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DISCLAIMER

FOREWORD

The Foundation recognizes that it functions in a climate of limited resources, and if these resources are to be used cost-effectively and if the Foundation is to fulfill its mission efficiently, there is a need for continued program planning and management. To conduct all of the research that is deemed important within the current funding level and probable future ones, priorities must be established, some research activities will need to be redirected or terminated, and recruitment of additional scientific personnel may be necessary. The intent of this document is to provide a framework for the establishment of research priorities to guide the allocation of resources and the recruitment of personnel.

Organization of this Strategic Research Plan and Program Management Document

This Strategic Research Plan and Program Management document will give an overview of the origin of the Foundation, its management structure, its mission, its research programs, and its resources. This will be followed by a listing of program objectives, current major research activities and those projected in the next five years, and the related resource requirements for each of the major research departments. This section will be followed by an enumeration of resource and personnel requirements as they relate to the administrative, computer-related, publication and documentation, and radioisotopic services necessary to support the research program. Finally, there will be a section on the maintenance of an adequate infrastructure and a summary and set of conclusions which will also act as the executive summary of this document. Annexes will provide ancillary information too detailed for enclosure in the body of the report.

There are many reasons why a strategic research plan and program management document is timely and necessary. However, the salient ones are the following:

- The members of RERF's survivor cohorts are aging, and the number of cohort members who remain alive will decrease markedly over the next few years. The research program and data collection procedures must reflect these changes. (See Annex A for the current size of the cohort and projections to the year 2020).

- The revolution in biomedical research in the last several decades has opened avenues of research of potentially great relevance to RERF and the understanding of the biological bases of radiation-related damage.

- Recent years and the next several have seen or will see a significant loss in personnel, largely through retirement. This situation requires renewed emphasis on optimizing the proportions of manpower devoted to research and support functions, and the development of innovative ways of achieving the Foundation's aims without increasing the general staff while maintaining a sound level of scientific personnel, for example, through the judicious use of personal services contracts.

- A series of workshops recommended by the Foundation's Scientific Council were conducted between 1988 and 1993 (see Annex B). The recommendations from these workshops have affected RERF's current research and are influencing plans for future research initiatives.

Assumptions used in developing this planning document

In this assessment of the Foundation's needs to support its scientific program, the Executive Committee felt it necessary to adopt certain self-imposed restrictions:

- It was assumed that budgetary limitations will prevent a significant expansion of the Foundation as a whole, that is, the level of support provided by its two funding agencies for research will remain more or less constant (with inflationary increases only).

- It was further assumed that it was critically important to maintain the appropriate array of professional, technical, and clerical skills needed to implement the research.

Within these limitations, the Committee believes that its research activities can still expand through increasing efficiency, through savings created by retirements, and, where possible, through transfer of general personnel positions to research-oriented ones.

The Executive Committee has carefully considered which of all potentially desirable research activities *could only be carried out* by the Foundation, which *could best be carried out* by the Foundation, and which *could be carried out elsewhere*, possibly on a collaborative basis. Prioritization along these lines will avoid the inclusion of research that is not specific to the Foundation's needs and potential, and will therefore reduce needed resources to only those that are most appropriate to RERF.

THE FOUNDATION

In the summer of 1945, the residents of Hiroshima and Nagasaki were in all probability, representative of a typical, heterogeneous wartime population of individuals in Japan. In August of that year, atomic bombs were detonated over these two cities. Soon thereafter a group of Japanese and American scientists, known as the Joint Commission for the Investigation of the Effects of the Atomic Bomb, began the task of assessing the physical damage wrought by the bombings and of identifying the early health effects of exposure to atomic radiation. This Commission, in its final report, strongly recommended the establishment, under civilian auspices, of a program of research to evaluate the long-term health consequences of exposure to ionizing radiation. In November 1946, President Truman approved a directive to the US National Academy of Sciences-National Research Council (NAS-NRC) to initiate the long-term investigation recommended by the Joint Commission. With funding provided by the Atomic Energy Commission (AEC), now the Department of Energy (DOE), the NAS-NRC established the Atomic Bomb Casualty Commission (ABCC) in March 1947, and research began shortly thereafter. The Government of Japan, through the Japanese National Institute of Health, became a partner in this endeavor.

In 1975, the Radiation Effects Research Foundation (RERF) was established and assumed the responsibilities of the ABCC. This private, nonprofit Foundation, a *zaidan hôjin*, is incorporated under Japanese law and its research is equally funded by the Governments of Japan and the United States, through the Ministry of Health and Welfare (MHW) and through the Department of Energy and the National Academy of Sciences, respectively. Administratively, the Foundation is governed by a Board of Directors consisting of 12 individuals, six of whom are Japanese citizens and six of whom are United States citizens. The day-to-day operations are managed by an Executive Committee consisting of four permanent members of the Board of Directors, two from Japan and two from the US, each of whom resides in Japan. The Permanent Directors consist of a Chairman, a Vice Chairman, a Chief of Research, and one other Director, who functions as the head of the Foundation's Nagasaki laboratory. The responsibilities of these individuals, their terms of office, and the like are specified in the Foundation's charter, known as the Act of Endowment.

Functionally, the Foundation consists of five major research departments, namely, the Departments of Clinical Studies, Epidemiology, Genetics, Radiobiology, and Statistics, supported by the Information Technology Department (ITD), the Publication and Documentation Center (PDC), a Radioisotope Facility, and a Secretariat. The ITD is responsible for the maintenance of the computational capabilities of the Foundation; whereas the Publication and Documentation Center and Secretariat are responsible for the publications (print and online) emanating from the Foundation and the administrative details relating to budgeting, personnel, purchasing, and public affairs, respectively. The Radioisotope Facility serves as a resource for those departments, such as Genetics and Radiobiology, requiring the use of radioisotopic materials.

The clinical, epidemiological, statistical, and other investigations are conducted in two laboratories, one in Hiroshima and the other in Nagasaki. The management of both laboratories is the responsibility of the Executive Committee, and the research activities conducted in the two laboratories are coordinated by the Chief of Research. To help conduct RERF's research activities properly there is a series of standing committees such as the Research Protocol and

Human Investigation committees. Review of the research program and recommendations on the relevance and scientific quality of ongoing investigations, as well as future research directions, are provided to the Board of Directors on an annual basis by a Scientific Council. This Council is composed of ten experts in areas of research relevant to RERF, five of whom are from Japan and five of whom are from the United States. As in the instance of the Board of Directors, the process of selection of these individuals, their terms of office, and their responsibilities are specified in the Act of Endowment. In addition, over the last eight years, the Council has been instrumental in the organization of a series of workshops in specific areas of research to provide guidance on promising approaches for possible implementation in the research programs and many of their recommendations have been implemented. (See Annex B for a listing of the recent workshops.)

As of 1 April 1996, the Foundation had 335 employees, 258 in Hiroshima and 77 in Nagasaki. Of these 47 represented the professional research staff, 43 in Hiroshima and 4 in Nagasaki.

The Foundation is housed in Hiroshima in a complex of nine interconnected two-story structures with a gross area of 9,681 square meters (about 105,400 square feet); whereas in Nagasaki, the Foundation occupies a four story building with a gross area of 2,643 square meters (28,780 square feet). The facility in Nagasaki is relatively new, but the bulk of the one in Hiroshima was built in 1950 and is now barely adequate for the Foundation's research needs.

To conduct a broadly based research program involving the collection, processing, and analysis of extensive data on mortality and morbidity in a population as large as that of the survivors and their children, RERF has developed an organization plan (see Figure 1) for the coordination of epidemiological, clinical, and laboratory research conducted in two widely separated laboratories. This plan is periodically reviewed by the Board of Directors and revised as circumstances warrant.

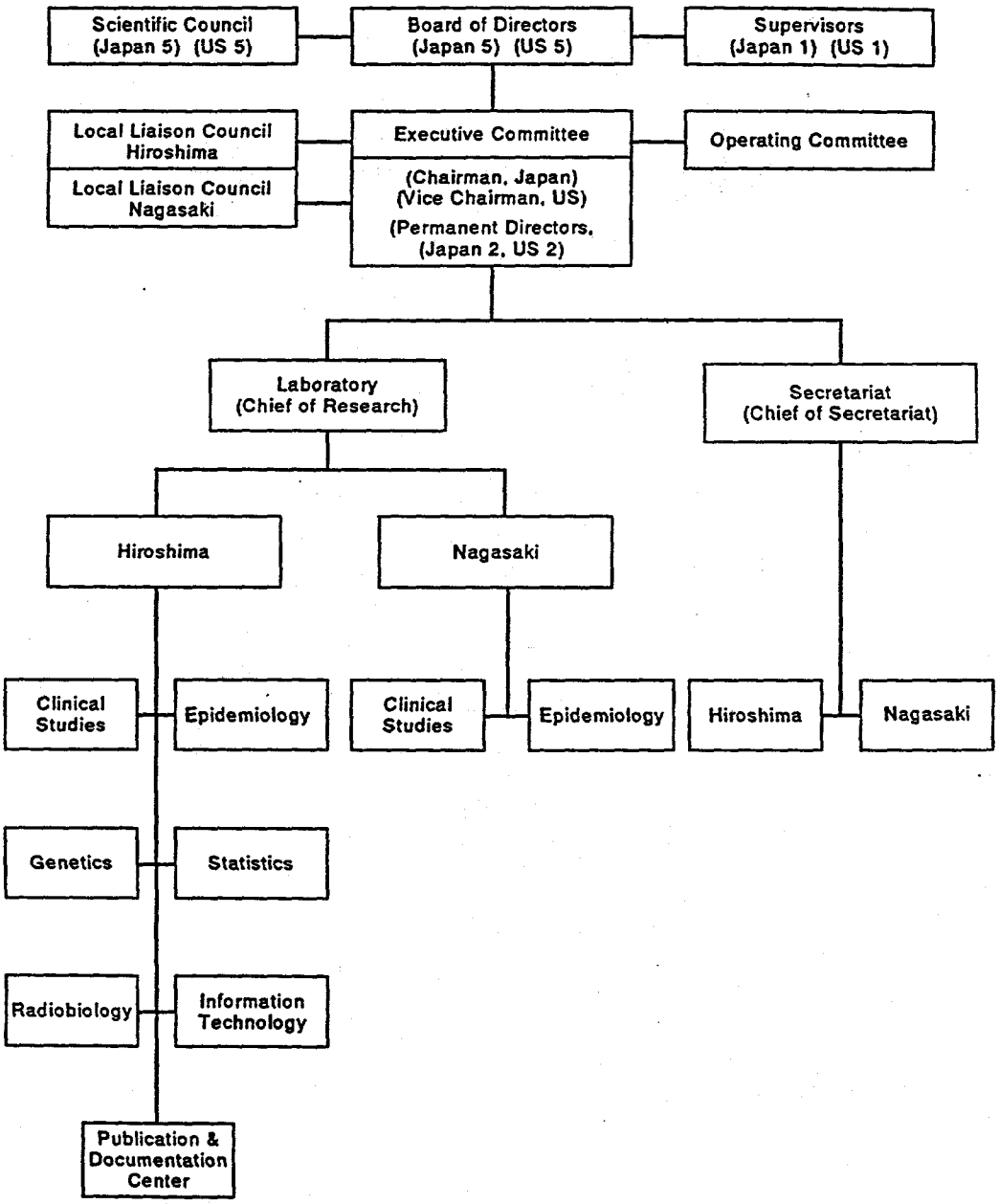
It is important to note that the investigations conducted by the Foundation are the only opportunity in existence for determining the late biological effects resulting from a single exposure to ionizing radiation ranging from very low to high doses. The results obtained in these investigations provide information that will lead to improved health care for the survivors as well as individuals who may be exposed to ionizing radiation elsewhere. Furthermore, the results of these investigations are of fundamental importance to an understanding of the effects of ionizing radiation on human beings and are, therefore, essential for estimating radiation risk and setting safe standards for occupational, medical, and general population exposures. Indeed, the data accumulated by the Foundation is the major source of information on which the standards established by national and international radiation protection bodies rest.

RESEARCH GOALS AND OBJECTIVES

The unique nature and long-term follow-up of this exposed population have provided invaluable information on the early and late health effects of radiation exposure. (See Annex C for some recent summaries of the findings to date.) To ensure that these investigations continue in a productive manner and are focused on radiobiological and health-related issues of importance to the scientific and medical community and the concerned public, it is essential that a careful,

Figure 1.

Organization



continuing evaluation of the research program be made, future directions determined or revised as need arises, and research priorities established. This strategic research plan has been developed to achieve these ends.

To carry out its responsibilities in an orderly and scientifically sound manner and to be responsive to its charter, the broad goals of the Foundation are:

- To determine the late health effects, both somatic and genetic, produced in human beings from exposure to ionizing radiation.

- To obtain information on the temporal pattern of cancer expression and other radiation-related effects and on the role of biological and environmental factors which may modify the effects resulting from exposure to ionizing radiation.

The strategy for addressing these goals is implicit in the following general research objectives:

- To conduct long-term epidemiological studies of a fixed sample of exposed and unexposed individuals to determine the frequency-dose relationships of morbidity and mortality resulting from radiation exposure and to obtain information on the differential sensitivity of various tissues.

- To conduct case-control and other special investigations on cancer induced in specific tissues or organs to determine the cell types affected and the effects of modifying factors.

- To conduct research in molecular and cellular biology to detect somatic mutation, cell transformation, changes in immunological competence and other biological events for use in understanding and estimating radiation risk.

- To utilize all available sensitive and cost-effective approaches for measuring heritable mutation in the children of exposed and unexposed individuals, and for assessing the public health impact of these mutations.

All research at the Foundation aimed at these goals takes place under published research protocols that must obtain the approval of the Chief of Research, the Research Protocol Committee, the Human Investigation Committee, and the Chairman of the Foundation before they are activated. These protocols are of two kinds, the so-called platform protocols that guide the major or core research activities of the Foundation, and special research protocols. The core activities commonly involve more than one department and are collaborative; whereas the specific research activities may or may not be collaborative. A listing of the currently active protocols will be found in Annex I. Of primary importance to the Foundation are, of course, the core activities since ultimately they are the raison d'etre of the institution.

RESEARCH PROGRAM STRATEGY

To conduct a successful long-term epidemiological investigation which addresses the goals of RERF, data must be collected on a continuing, prospective basis using specified samples of

exposed individuals and a matched group of unexposed individuals when a need for a comparison with the latter arises. These data must be collected in a systematic and epidemiologically acceptable manner to reduce the chance of bias or ambiguity affecting interpretation of the results observed.

The first major program to be initiated by ABCC was the Genetics Program, which included observations on the occurrence of major congenital abnormalities, sex, birth weight, viability at birth, and survival during the neonatal period of all newborn infants in Hiroshima and Nagasaki. The study, which began in 1947 and continued until 1954, encompassed some 76,626 infants, with reexamination of a subsample of approximately 20,000 of these infants at age 8-10 months. Although this major clinical program was terminated in 1954, the cohort thus established, with subsequent additions, has been followed for survival since that time, as the F_1 Mortality Study.

Most of the early studies on the survivors themselves were essentially ad hoc, each investigator usually establishing his own study population. In 1955 the Francis Committee reviewed the research on exposed (and unexposed) persons at ABCC and urged the adoption of a Unified Study Program as a permanent research guide. The committee's recommendations were approved and have since provided the basis for much of the current epidemiological and clinical follow-up of the survivors in Hiroshima and Nagasaki. In 1975, prior to the establishment of RERF, a second committee, known as the Crow Committee, reviewed the program and recommended continued investigation of this unique population.

Implementation of the Francis Committee recommendations resulted in the establishment of four major fixed cohorts:

- the Life Span Study (LSS) cohort of survivors and an unexposed comparison group who were alive at the time of the bombings;

- the Adult Health Study (AHS) cohort (a subset of the LSS cohort), whose members are encouraged to participate in a program of standardized biennial clinical examinations carried out at RERF;

- the in-utero (IU) cohort of individuals who were exposed in-utero and matched controls; and

- the F_1 cohort of children born between June 1946 and December 1984 to exposed or unexposed parents.

Follow-up of these cohorts is central to the work of the Foundation. The primary follow-up programs are:

- mortality ascertainment for most members of all of the cohorts through the Japanese family registration (*koseki*) system;

- ascertainment of cancer morbidity through linkage of the cohorts with the Hiroshima and Nagasaki tumor and tissue registries, which are managed by RERF;

- a special registry (the Leukemia Registry) of cases of leukemia and malignant diseases of the hematopoietic system;

- the offering of standardized biennial clinical examinations for members of the AHS cohort and a (fixed) subset of the IU cohort;

- a mail- and telephone-based morbidity surveillance system for AHS cohort members;

- occasional mail surveys carried out within the LSS cohort; and

- an autopsy program (active from about 1960 through the early 1980's but currently inactive).

Analyses of data from the RERF cohorts make use of individual dose estimates. The basic methods used to compute these estimates were originally developed by researchers at Oak Ridge and other national laboratories. The current dosimetry system, DS86, was the result of a binational effort to reassess the physical data and refine the theoretical models that formed the basis for the dosimetry system (T65D) that had been in use at ABCC and RERF since the late 1960's. Japanese and US scientists are currently working to deal with discrepancies between DS86 Hiroshima neutron dose estimates and neutron doses inferred from physical measurements and some biases suggested by RERF biodosimetric data. It is likely that this effort will lead to revised dosimetry within the next five years. As in the past, RERF researchers will be responsible for adapting and applying the new dosimetry for use with the survivors.

CURRENT STATUS OF THE RERF COHORTS

In this section we present some information on each of the major cohorts at this time. This discussion provides a limited amount of historical information about the creation of the cohorts since the primary focus concerns the nature of these cohorts today.

The Life Span Study cohort

The LSS cohort was constructed from a Master Sample of about 284,000 Japanese atomic bomb survivors (159,000 in Hiroshima and 125,000 in Nagasaki) developed from a special nationwide enumeration of A-bomb survivors carried out as a part of the 1950 National Census. As initially defined, the LSS included all survivors in the Master Sample who were within 2000 m of the hypocenter at the time of the bombings (ATB) and alive and residing in Hiroshima or Nagasaki on 1 October 1950 and who met certain other criteria necessary to ensure complete mortality follow-up. There were originally two age and sex matched comparison groups who met the residency and other criteria deemed necessary for adequate follow-up. One of these groups was composed of individuals who were exposed in the cities at distances of 2,500 to 10,000 m from the hypocenter ATB and the other group consisted of individuals who were not in the cities at the time of the bombing. With the introduction of individual dose estimates, the cohort was extended to include all persons in the Master Sample who were within 2,500 m of the hypocenter ATB. Finally, in the early 1980's all remaining distal survivors in Nagasaki (2,500 - 10,000 m from the hypocenter) were added to the LSS to increase the size of the relatively small Nagasaki internal comparison group. With these additions, there are now 120,321 individuals in the LSS

cohort, including 93,473 who were in one or the other of the two cities at the time of the bombing.

As of the fall of 1996, the mortality follow-up records indicate that 49% of the cohort members have died and less than 200 individuals have been lost to follow-up (primarily due to migration out of Japan). The average age of the surviving members of the cohort is 65.4 years. When broken down by age at exposure, it is seen that lifetime follow-up is essentially complete for cohort members who were at least 50 years old at the time of exposure, while more than 90% of those who were under the age of 20 ATB are still alive. (See Annex A.)

The Adult Health Study (AHS) cohort

The AHS cohort is a subset of the LSS cohort. This subset was so defined as to include all members (4,990 individuals) in the original LSS cohort who were within 2000 m of the hypocenter and who reported one or more of the cardinal symptoms associated with acute radiation sickness, that is, epilation, oropharyngeal lesions, and purpura. Three age and sex matched control groups were chosen from among (1) the survivors within 2,000 meters who reported no acute radiation symptoms, (2) survivors who were at distances of 2,500 to 10,000 m from the hypocenter ATB, and (3) unexposed LSS cohort members. With the introduction of individual dose estimates the AHS cohort was augmented by the addition of all remaining members (2,436 persons) of the LSS whose T65D shielded kerma dose estimate was greater than 1 Gy. The examination schedule was set so that in any one month a more or less representative cross section of the entire population would visit the clinic. These examinations are now in the 19th cycle; however, over time, attrition has reduced the population to about 50% of the original sample.

As of the fall of 1996 more than 9,200 of the 17,397 exposed members of the AHS are still alive and about 8,000 of these individuals are living in the clinical contacting catchment area. Among this latter group almost 80% participated in the most recent cycle of AHS examinations.

In Utero Sample

The in-utero cohort was assembled from a roster of more than 10,000 individuals whose date of birth was between the date of the bombings and May 1946. This roster was developed from Hiroshima and Nagasaki birth records, records of early ABCC studies, and data from a special survey conducted in conjunction with the 1960 Japanese national census. As currently defined, the cohort includes data from two overlapping samples: a clinical sample defined in the late 1950's and a mortality cohort defined in the early 1960's. As with the other cohorts these two groups were defined in terms of a core set of individuals whose mothers were close (within 1,500 m for the clinical and 2,000 m for the mortality samples) together with age and sex matched groups of more distal or unexposed people. The cohort includes 3,654 individuals of whom 1,192 were exposed at distances of less than 2,000 m of the hypocenter while 1,356 were exposed at distances of 2,000 to 10,000 m. Complete mortality follow-up is available for all members of the IU cohort other than the 59 individuals who were lost to follow-up due to emigration from Japan or a failure to locate the *koseki* records. There are 755 in-utero survivors who have been included in analyses of IQ and school performance but are not in the main IU cohort. Consideration is being given to initiating routine mortality follow-up for these people. A total of 1,021 members

of the IU cohort are invited to participate in the AHS examinations. (This group overlaps but is not the same as the IU clinical cohort whose members were asked to come to ABCC for annual examinations during their late childhood and adolescence.)

Because of the age of members of this cohort (51 or 52 years in the fall of 1996), there have been few deaths (434) at this time. More than one-third of these occurred during the first few months of life.

The F_1 cohort

The original F_1 cohort included 53,518 children born to survivors between 1 June 1946 and 31 December 1958 selected from among the 76,626 children identified in the course of the Genetics Program that ran from 1947 through 1953 or from other sources, generally the birth records. The F_1 cohort was subsequently extended to include the children of virtually all proximally exposed members of the Life Span Study cohort and the children of some distally exposed members of this cohort. At this time the cohort includes 88,484 persons. However, mortality follow-up is not being carried out for 11,760 cohort members who were selected for some special clinical studies. Follow-up of these individuals should begin within the next year. As of the fall of 1996, 5,316 members of the F_1 cohort are known to have died and 1,434 cohort members have been lost to follow-up. Most of the deaths were infant deaths. The average age of the surviving cohort members is currently about 38 years. As is discussed below, a mail survey of the full F_1 cohort and a small study of the feasibility of an F_1 clinical examination program are being planned.

THE STRUCTURE OF RESEARCH AT THE FOUNDATION

Research at the Foundation can be seen as a matrix with one dimension, the spectrum of health effects resulting from exposure to ionizing radiation, and the other, the disciplinary skills, represented by the research departments, needed to identify and understand the biological events that subtend these effects. This duality of aims is implicit in the Unified Program of research recommended by the Francis Committee and the need to focus most, if not all of the research effort on the fixed samples described above. This focus implies in turn that much of the research is integrative and necessarily collaborative. Indeed, no one of the major research departments at the Foundation stands fully alone; each requires the help of the others either in data collection and management, their analysis, or their biological interpretation. The collaboration can, of course, vary in form. It is instructive, therefore, in describing the Foundation's program of research to view it from both the programmatic perspective and the individual departmental contributions since one illustrates the inherently collaborative nature and broad sweep of much of the research and the other illuminates the individual departmental contributions.

Cancer Studies

Cancer is the best established, and most important late effect of exposure to ionizing radiation among the atomic bomb survivors and other exposed populations. There are, however, several important issues remaining unclear regarding the nature of cancer risk.

Major LSS reports

The series of general reports on cancer mortality and the recent collection of reports on cancer incidence in the atomic bomb survivors in the LSS are the most visible and influential products of the Foundation's research efforts. As previously stated, lifetime follow-up is essentially complete for cohort members who were 50 years of age or older at the time of the bombings, but for those survivors who were less than 20 years of age then 90% are still alive and are now at, or on the verge of, ages of rapid increases in spontaneous cancer rates. While the total number of cancer cases among those exposed as children is not yet large, the data indicate that, despite a possible decrease in the excess relative risks, excess cancer rates associated with the radiation exposure are continuing to increase. The number of cancer cases in the youngest members of the LSS can be expected to double every 5 to 10 years until well into the next century. Thus, additional follow-up and analyses of these data are central to the development of a comprehensive assessment of the long term impact of radiation exposure on cancer risks in the survivors.

During the next five years we will produce a new comprehensive cancer mortality report (LSS Report 13) covering the period from 1950 through 1995 as well as an updated report on solid cancer incidence covering the period from 1987 through at least the end of 1992. While there will undoubtedly continue to be a need for both mortality- and incidence-based risk assessments, efforts will be made to present a more integrated, comprehensive picture of the incidence and mortality data. As these analyses are completed we will continue to make the detailed data sets available to other researchers.

Site-specific incidence studies

The general LSS Reports provide useful summaries of cancer risks in the LSS. However, they cannot provide an in-depth look at the nature of cancer risks for specific tumor types or subtypes. To address this problem, RERF researchers in collaboration with the local medical community and some support from the US National Cancer Institute (NCI) have carried out a number of studies of cancer incidence at specific sites. These studies involve the identification of potential LSS cases from a variety of sources (including tumor and tissue registry records, death certificates, and autopsy reports) using broadly defined selection criteria. The medical records and, where possible, pathologic material for candidate cases are screened by a panel of pathologists in order to arrive at a consensus diagnosis. Cases identified in this way are then analyzed to assess cancer risks.

The results of site-specific studies on cancers of the breast and salivary glands have been published. Reports on skin, CNS tumors, and liver cancer will be completed soon. Over the next several years studies of thyroid cancer, lung cancer, lymphoid malignancies, and an update of the breast cancer series will be completed.

In contrast to the general LSS Reports, which appear in radiation-related journals, we are seeking to publish the results of the site-specific incidence studies in the more general medical literature to increase awareness of the RERF findings in the broader scientific community.

Patterns of excess cancer incidence among those exposed in childhood

As noted above, the excess relative risks associated with radiation exposure among the

youngest survivors are higher than those for other age groups and the data suggest that these relative risks may be decreasing with time. These findings have led to a widely held view that people exposed as children are particularly sensitive to radiation effects. However, for most solid cancers excess absolute rates, at a given attained age, appear to be quite similar to those exposed as adults. This may not be the case for some tumors, notably breast and other endocrine tumors. As those exposed as children reach ages at which rates of cancer increase dramatically it will be possible to carry out more detailed analyses of the nature of solid cancer risks among these survivors. Thus, as in earlier RERF reports on the shape of the dose response and on temporal patterns in the excess solid cancer risk, we will produce a short report focused on solid cancer incidence following childhood exposures. This project is being undertaken in collaboration with NCI.

Issues in modeling excess cancer risks in the LSS

The analysis of the LSS cancer mortality data continues to raise a variety of interesting and challenging statistical problems. A number of innovative methods have been developed to analyze the LSS data. These include extensions of classical regression models for survival analysis to allow for efficient estimation in large cohorts using general relative and absolute risk models, procedures to adjust for biases resulting from random errors in individual dose estimates and to allow for the impact of migration in the analysis of the tumor registry data, and methods for the joint analysis of data on multiple causes.

There is an increasing interest in the application of biologically-motivated models to the data on radiation and cancer risks. Over the next year or so we expect to complete work on a generalization of the Armitage-Doll multistage model that provides some useful insights into the age and time patterns of the excess risk seen in exposed survivors. We are working on the application of the Moolgavkar-Venzon-Knudson two-stage model to the LSS cancer data.

Because of the strong interest in the nature of the dose response at low doses, there is a need to consider more flexible alternatives to linearity than the simple quadratic and threshold models generally used. This will involve the development of regression-adjusted nonparametric smoothers.

Over the next two years studies of inter-site variability in radiation-associated excess cancer incidence and of the comparison of relative risk and absolute rate models in the description of excess cancer risks will be completed.

Effect modification by nonradiation factors

Use of data from the mail surveys conducted by ABCC-RERF over the past 30 years has largely been limited to assessments of smoking and lung cancer risks. However, these surveys also include information on alcohol consumption, nutrition, reproductive history, and socioeconomic factors. Additional cross-sectional and longitudinal data on non-radiation factors have been obtained directly from participants in the AHS examinations. The serum samples from AHS participants that have been collected and stored are also a valuable resource for the study of nonradiation risk factors and for molecular epidemiological studies.

Use of these mail survey and clinical data has been limited in part by the problems in collating data from the various sources. This problem is being addressed as a part of efforts (discussed further below) to modernize the RERF research database. Thus over the next few years we plan to undertake a number of projects that will make more extensive use of the mail survey data. These studies include updated analyses of smoking and the incidence of lung or other smoking-related cancers in the LSS, new analyses of alcohol consumption and liver cancer incidence, and analyses of the impact of socioeconomic factors on comparisons of the exposed and unexposed (not-in-city) groups.

Over the next five years we will conduct a series of case-control studies nested in the AHS to investigate the impact of nonradiation factors on some common but generally nonfatal cancers (breast, thyroid, and skin). The mail survey and clinical data will be useful either directly (as a source of data on risk factors) or indirectly (by providing information enabling more efficient matching of cases and controls) in the design and analysis of such nested case-control studies.

Radiation and benign tumor incidence

Recent AHS data have suggested that there may be radiation-related increases in the risk of various benign tumors including myoma uteri and parathyroid adenoma among AHS participants. A study of the prevalence of uterine myoma based on ultrasonographic examination will be published within a year and reports on the prevalence of several other benign tumors (liver hemangioma, and ovarian tumor) observed using ultrasound will be completed within the next two to three years. Consideration is also being given to the conduct of a study of benign thyroid tumors and other thyroid disorders among Hiroshima AHS participants. If it is deemed feasible, this study would serve to complement the Nagasaki thyroid study, which indicated radiation-related increases in risks for these conditions. Within the next year a 10-year incidence study on hyperparathyroidism among AHS participants will be completed. It is hoped that this study will provide some hints as to the reason for the elevated serum calcium and parathyroid hormone levels in heavily exposed survivors.

Cancer incidence and mortality in the in-utero and F_1 cohorts

A major report on cancer mortality in the in-utero cohort for the period from 1950 through 1992 is now in press. This report will be supplemented within the next year by reports on cancer incidence and general mortality patterns in this cohort. In view of the age of the in-utero population, the number of cancer cases can be expected to increase dramatically with five additional years of follow-up. Thus it would be appropriate to produce an updated report on cancer mortality and incidence in the cohort in about five years.

Mortality follow-up for the F_1 cohort will be extended to include all people who have been selected for the BGS study. Once this is done a new report on cancer incidence and mortality in the cohort will be prepared. This report should be completed within about three years.

Pooling of RERF data with data from other cohorts

While the atomic bomb studies are a major source of information on risk assessment, they cannot address all of the important issues on radiation risks. Comparison of the data on the A-

bomb survivors with that from other exposed populations enables us to examine some of these issues, such as dose rate effects and risk transfer. Under the terms of a contract with the NCI, RERF is working with Russian and US scientists on documenting, updating, and improving the data on cohorts of Russian nuclear workers and the general population exposed to large radiation doses as a result of low-dose rate chronic exposures from the operation of the Mayak plutonium production plant located in the Southern Urals. An important part of this work will be the preparation of initial reports on cancer risk estimates for these cohorts together with some (limited) comparison of these estimates with those seen in the LSS. The initial contract will continue until September of 1998. This contract may be extended for several more years depending upon the results of current work and the availability of funds.

Work being carried out at RERF on a multi-population comparison of breast cancer risks following radiation exposure in six cohorts, including the LSS, should be completed within the next year.

Trends in Hiroshima and Nagasaki cancer incidence

As noted earlier, RERF operates tumor registries in cooperation with the medical associations in Hiroshima city and Nagasaki city and prefecture. The linkage between these general population registries, which are regarded as among the best in Japan, and the LSS, in-utero, and F_1 cohort data is important to the conduct of RERF research. The registries also provide useful information on cancer risks in the Hiroshima and Nagasaki populations. While the Hiroshima and Nagasaki registry data are routinely published in IARC's *Cancer Incidence in Five Continents* volumes, the effort devoted to analysis and publication of these data has been limited (especially in Hiroshima). Over the next five years we will produce a series of short bilingual reports on trends in cancer incidence in these cities and develop procedures for the routine production of summary reports on the status of the registries and the nature of the accumulating data.

Noncancer Studies

Noncancer mortality dose response

The evidence for a significant association between radiation and noncancer mortality is becoming stronger as the follow-up of the LSS cohort continues. Excess risks are seen not only for cardiovascular disease mortality but also for other broad categories of noncancer disease mortality. LSS Report 12 Part 2, which will be completed within the next year, will describe the basic nature of this effect while addressing the uncertainties and limitations of the mortality data. Over the next five years it will be important to extend the mortality follow-up through at least 1995 and to carry out further investigations aimed at clarifying, to the extent possible, issues related to the shape of the dose response and patterns of the excess risk with regard to sex, age and time. Additional follow-up may also help to determine if there are cause-specific differences in risk. Because of the paucity of known biological mechanisms for a radiation effect on noncancer disease we must continue to look for factors that might lead to a spurious association between radiation exposure and noncancer disease mortality in the LSS.

There is a highly significant excess risk for noncancer diseases of the blood, with the

excess relative risk per Sv being larger than for any of the solid tumors. A review of these cases is being undertaken in collaboration with the hematologists associated with the Leukemia Registry. Results of this review should be available in one to two years.

Cardiovascular disease

The AHS data enable us to assess the incidence and prevalence of specific cardiovascular diseases and to undertake analyses of conventional risk factors, and thus are essential for the development of a better understanding of radiation effects on cardiovascular disease (and other noncancer diseases). Studies of AHS data on the incidence of cardiovascular disease and stroke will continue beyond the next five years. Analysis of data on various CVD risk factors and related-endpoints obtained from shorter term studies such as the prevalence of aortic and abdominal arch calcification, isolated systolic hypertension, retinal arteriosclerosis, and coagulation rates have all provided evidence of radiation effects. A major objective for the next few years is to publish initial reports on the first 30 years of follow-up and other findings.

These studies are currently being supplemented with studies of the rate of sudden death, the prevalence of peripheral vascular disease (as determined by pulse wave velocity and ankle-arm blood pressure ratio), plasma fibrinogen levels, and new analyses of conventional risk factors, including blood pressure and cholesterol. Research is being planned on several additional risk factors, including case-control studies of *H. influenzae* and homocysteine and the prevalence of latent atherosclerosis (as determined by ultrasonographic examination of the thickness of the carotid artery).

RERF has had a productive, long-term involvement in the Ni-Hon-San study of cardiovascular disease among Japanese in Japan and the US. This collaboration with the Honolulu Heart Program will continue through the next five years and should lead to several publications on general cardiovascular disease epidemiology.

Noncancer effects hypothesis generation

Because of the lack of a known biological basis for a radiation effect on noncancer morbidity, there is a need to develop ideas and, if possible, testable hypotheses regarding this issue. A workshop, such as that proposed by NAS, that would bring together RERF researchers and scientists from a broad range of disciplines to learn about RERF's findings and to discuss and develop ideas for future research in this area should take place in the near future. This will permit us to develop contacts for future collaboration and may inspire others to undertake research in this area. In addition to such a workshop, we need to establish a continuing dialog involving RERF staff and other scientists (particularly those at Geniken in Hiroshima and Nagasaki University) in order to focus more attention on this issue.

Liver disease

These studies will provide important data relevant to the interpretation of the finding of a radiation-related increased incidence of liver cancer and other liver diseases in the LSS and AHS. The serum assay-based study of the relationship between hepatitis-B and hepatitis-C virus infection and radiation dose, initiated in 1993, will be completed within the next two years.

We plan to investigate the feasibility and power of a nested case-control study using stored sera to compare HCV infection rates and subtypes prior to the diagnosis of liver cancer or cirrhosis and to look for interactions between radiation dose and HCV infection. Of particular interest is the recent report that HCV infection can mask the concurrent presence of HBV infection, leading to an underestimation of the prevalence of the latter infection. Similar studies on HBV infection have been reported, but in the light of the finding just cited may have to be redone.

Longitudinal analysis of clinical and laboratory measurement data

The recent report of an association between radiation and age-related changes in cholesterol levels illustrates the usefulness of modern analytical methods in the study of longitudinal clinical data. These methods will be developed further and applied to other blood chemistry and hematology data as well as to blood pressure and other clinical measurements. We will also consider how these methods might be applied in analyses of longitudinal data from electrocardiograms.

Menopause

Analyses of the Nagasaki menopause incidence study indicate that a decrease in age at menopause is associated with increased radiation dose. A report on these results will be completed in the coming year. The Nagasaki findings have led to the initiation of a longitudinal study of FSH and estradiol levels in peri-menopausal women to characterize better the relationship between self-reported menopause and underlying hormonal changes. Data collection for this study will continue through 1997 with analyses to be conducted in the following two or three years. In Nagasaki, longitudinal observations on peri-menopausal changes in relationship to serum cholesterol and estradiol will continue for the next five years.

Aging

A study of the relationship between age-related changes in cognitive function and radiation dose has been underway since 1992. This study also includes comparison of data on AHS participants with that for Japanese-Americans in Honolulu and Seattle (NI-HON-SEA study). Data collection will continue for about one more year with analyses taking place over the subsequent three years.

Osteoporosis is a common age-related disorder influenced by menopause and parathyroid hormone levels which have been shown to be associated with radiation exposure in the AHS. Dual photon absorptiometric measurements of spinal bone density of AHS participants, made since 1989, suggest that bone density increases as radiation dose increases. In order to provide a more definitive result, measurements of spine and hip bone mineral density using dual X-ray absorptiometry supplemented with data on total body composition are being obtained for selected AHS participants. An analysis of the baseline data is being carried out at this time. As data on these subjects are obtained in future AHS examinations longitudinal analyses of age-related changes in bone mineral density will be made. Data from this study will also be used in the NI-HON-SAN collaboration.

Estimates of physiological age were computed for AHS participants on the basis of grip strength, skin elasticity and other factors measured in the 1970-72 AHS exam cycle. These estimates are being used as covariates in an analysis of rates of mortality and morbidity during the following 20 year period. This analysis should be completed within a year. A new assessment of physiologic age based on a broader battery of measurements is being planned.

Molecular epidemiology

With some effort RERF can play a unique and important role in the search for evidence of so-called finger prints associated with radiation-induced cancers. Work has begun on PCR analyses of the ras and p53 genes using preserved and fresh skin, thyroid, and liver cancer tissues. In the light of recent advances and the relatively large radiation effects for breast and thyroid cancer, studies of tissues from breast and thyroid cancer cases among the high dose survivors have the potential to yield important results. It may also be useful to supplement the search for characteristic gene alterations in cancer cells with a search for evidence of specific mutations associated with cancer development in the blood of cancer-free survivors.

The success of such studies depends heavily on our ability to obtain appropriate samples for LSS cohort members who are diagnosed with cancer. It is possible to obtain archival material through the tissue registries in Hiroshima and Nagasaki; however, better methods are needed to ensure the availability of the necessary materials from newly diagnosed cases. To facilitate this end RERF is seeking support from the local medical community for the establishment of a community-wide tissue/DNA bank in Hiroshima. This bank would maintain tissue specimens or preserved DNA that could serve as a resource for all groups in Hiroshima engaged in studies of the molecular mechanisms of carcinogenesis.

It is important to keep abreast of the rapid progress in knowledge of the molecular basis of cancer. The pace at which this field is developing suggests that future studies may be more important than anything that can be done today. This suggests in turn that it would be worthwhile for RERF scientists to work, possibly in collaboration with other groups, on the development of methods to maintain a broad spectrum of DNA in a form that could be used in future studies. Such samples would be particularly useful when it becomes possible to scan the entire genome for evidence of possible changes.

In view of RERF's limited resources it is important for us to develop a general research plan that defines specific projects that can be done at RERF as well as projects where collaboration is important and establishes mechanisms for seeking this collaboration and, where necessary, support.

Immunology

One of the major sources of tissues from the A-bomb survivors is from the on-going collection of blood samples. This supply of viable cells from the survivors is a resource for the study of many diseases including those with immune system dysfunction. Reduced immune function can potentially lead to a variety of pathologic consequences including cancer, which is known to show heightened risk among the survivors. RERF has a matchless opportunity to investigate the late effects of radiation exposure on the immune system.

We plan to continue our studies of the features and mechanisms of radiation-induced disorders in the hematolymphoid system at the cellular and molecular levels. These studies include radiation effects on the distribution of T-cell subsets in the survivors and of radiation effects on endocrine and hematopoietic growth factor levels as well as the study of stem cells, the progenitors of cells which constitute the immune system.

Heritable Mutations

Permanent lymphocyte cell line cultures

The 1984 Genetic Study Conference endorsed an RERF plan to establish immortalized B-lymphocyte cell lines from 1000 families (500 with at least one parent exposed within 2,000 m). A sampling plan was drafted based on the T65D dosimetry. At this time the Biochemical Genetics Laboratory has established cell lines for 800 families (1600 parents and 1200 children) based on this plan. With the introduction of DS86 doses it was discovered that dose estimates were unavailable for one or more of the parents in the remaining families. Over the next two years 200 additional Hiroshima and Nagasaki families for whom the parental doses are known will be identified and efforts commenced to establish cell lines for these families in order to achieve the goal of 1000 families. This is the largest cohort-based sample for the detection of radiation effects on the human germline anywhere in the world.

Pilot studies of methods for the detection of deletion–insertion–rearrangement mutations (D/I/R)

Methods for genome-level (DNA) analyses are developing rapidly. It is likely that the next five years will see the development of new markers and increasingly powerful methods that can be used in the search for evidence of mutation in the children of the survivors. At this time, we are examining several promising approaches. In each approach, mutations are detected by comparison of a child's gel with that of his or her parents. Indications of a mutation include the absence or dislocation of bands or spots as well as changes in intensity. As we learn of (or develop) additional methods it may be necessary to initiate new pilot studies, in conjunction with researchers outside of RERF when necessary.

Mutations at minisatellite loci

An initial study of 100 families will be extended by the addition of 100 families in order to provide information for further comparisons of the RERF data with the results of a Belarus-UK study (Dubrova et al 1996, Satoh et al 1996) that has been interpreted as providing evidence of an excess of such mutations among Chernobyl victims.

Chemiluminescent bands on Southern filters

Employing a quantitative analysis of chemiluminescent bands on Southern filters, material from the 200 families used in the minisatellite studies will also be screened for evidence of mutation using DNA probes that correspond to the human counterparts of the seven mouse-specific loci and other loci including genes that are suspected to be related to several common chronic diseases, such as hypertension, diabetes mellitus, and hereditary nonpolyposis colorectal cancer.

Two-dimensional electrophoresis (2-DE) methods

The Biochemical Genetics Laboratory has developed a 2-DE technique based on ^{32}P-labeled DNA digests created with three sets of restriction enzymes. This method produces three gels per individual having a total number of roughly 2000 spots (fragments) that are suitable for D/I/R mutation detection. A study using DNA samples from 200 BALB/c mice derived from irradiated spermatogonia, conducted primarily to prove that the 2-DE technique is capable of detecting mutations, will be completed within a year. This study will be followed by an investigation of DNA from the 200 pilot study families. It is expected that this pilot study will take at least five years to complete. If the spontaneous mutation rate is 1×10^{-5} / fragment / generation, we would expect to detect five mutations in the 120 children of the 100 control families.

The study (even in its preliminary phase) involves collaboration of a number of groups, including: the Cytogenetics Laboratory for efforts to localize putative mutations and their normal counterparts using FISH or other techniques, the Information Technology Department for help in data management and software conversion/development, the Department of Statistics in dealing with the pattern recognition and other problems arising in the analyses of these complex data. RERF's long-term collaboration with the University of Michigan is also an essential component of this program.

Genetic markers of hypertension

In accordance with the recommendations of the Blue Ribbon Panel, a protocol is being developed for a pilot study to assess markers for genes potentially associated with hypertension. This study, which will include 200 AHS participants (100 normal and 100 with hypertension as defined by the 1993 WHO/ISH guidelines), will make use of DNA from lymphocytes obtained during the routine AHS examination.

F_1 mail survey and health study feasibility

In response to the recommendations of the Blue Ribbon Panel, we are preparing detailed plans to carry out a mail survey of all surviving members of the F_1 cohort and to conduct a small scale study of the feasibility of an ongoing program for ascertainment of disease and disability in the cohort. The mail survey will provide data that can be used to obtain baseline (self-reported) information on health status and serve as a source of risk factor data that can be used in future analyses of cancer mortality and incidence in this cohort. The small clinical study (500 people) will include biochemical genetic studies of several genes related to common diseases (e.g., hypertension and diabetes). The mail survey and clinical feasibility study will last about two years and will be followed by a workshop to determine what additional studies, if any, should be carried out by RERF.

Genetic epidemiology (family studies)

Efforts are currently underway to define a database of family relationships within the LSS, in-utero, and F_1 cohorts. The initial focus is on the families of breast cancer patients in order to

look for evidence of genetic predisposition among women who were diagnosed with breast cancer before the age of 35. Data on family relationships in the RERF cohorts and the extensive epidemiological and clinical follow-up data for the cohort members will be a unique resource in the study of the impact of genetic factors on disease. Continued development and use of this resource requires support and collaboration with groups outside of RERF who are active in this area. Progress will be highly dependent on the availability of personnel and special financial support.

Dosimetry

Biodosimetric studies

Over the past thirty years, RERF has played a central role in the development and assessment of biomarkers of radiation exposure, including structural chromosome aberrations (using conventional staining, G-banding, and most recently FISH methods); mutation assays (including GPA, T-Cell receptor, HPRT, and others); and electron spin resonance (ESR) of tooth enamel. The availability of physical dose estimates, DS86, makes RERF one of the most important centers for developing and assessing various long-term biological dosimeters useful in other populations. As for the mutation assays, only the GPA assay can detect radiation exposure that occurred several decades earlier. However, the frequency of GPA mutants varies widely and thus the GPA assay has not proven to be a useful alternative to the cytogenetic method of estimating individual doses although it can be valuable in estimating collective dose. Therefore, little, if any, work on the development or application of somatic mutation assays will be done during the next few years, and the extensive programs for the analysis of chromosome aberrations in the survivors using conventional and G-band analyses have also ended. However, these cytogenetic studies, as corroborated by our recent work on ESR of 100 teeth and cytogenetic tests of the tooth donors, are useful in estimating individual doses, and the recently introduced FISH method is even more effective. Accordingly, we plan to obtain FISH data on an additional 1,000 survivors over the next five years. Our aim is two-fold, namely, (1) to clarify the possible systematic bias in the DS86 dose estimates according to shielding category and (2) to determine the extent of random errors among individuals. We hope to supplement this activity with a program to obtain FISH data from all unsampled AHS participants who were under 20 years of age ATB with DS86 dose estimates in excess of 0.6 Gy (about 1,500 persons) and all parents of families selected for molecular heritable mutation screening studies. ESR analyses of 100 additional samples that are currently available will be carried out in the next year. Efforts to obtain more tooth samples (and, when possible, FISH data) from AHS cohort members in Hiroshima will continue.

Over the next few years effort will be directed toward a variety of comprehensive analyses and comparisons of existing biodosimetric data. These analyses will include: an analysis of all available data from the conventional chromosome aberration studies including assessments of more detailed data (e.g. interchromosomal:intrachromosomal aberration ratios); continued comparison of ESR, chromosome aberration data and GPA data as well as comparison of the correlation between these biological markers and the physical (DS86) dose estimates.

While further analyses of the nature of the dose response for the various assays are important, recent comparisons of the ESR and cytogenetic data demonstrate that the data are also

useful for the detection of errors in individual dose estimates. More importantly, the biodosimetric data will become increasingly important for the identification of potential systematic biases and the characterization of uncertainties in the physical dose estimates. For example, the chromosome aberration data suggest that DS86 dose estimates for Nagasaki factory workers may be too high by a factor of two or more.

Revision of the DS86 dosimetry system

Ten years after its introduction, there is increasing evidence of systematic errors in DS86 dose estimates. Much attention has been focused on a distance-dependent discrepancy between measured and calculated values for neutrons in Hiroshima. While estimates based on the best available information suggest that these changes will have little impact on cancer risk estimates derived from the survivor data, the fact that these discrepancies exist has led to some serious questions about the validity of RERF risk estimates. There is also, as noted above, biodosimetric data suggesting that doses may be over-estimated for Nagasaki factory workers (who account for 30-40% of Nagasaki survivors with DS86 doses in excess of 0.5 Gy). It is expected that within the next two to three years the US and Japan senior atomic bomb survivor dosimetry committees will accept a revised dosimetry that will modify the Hiroshima neutrons and, hopefully, address the factory worker problem. Once a consensus has been reached the current RERF dosimetry programs will be revised and doses recomputed for all survivors. This will involve a considerable effort on the part of members of the Department of Statistics and ITD over a period of six months to a year followed by reassessments of the major findings regarding cancer and other risks.

To prepare for the revised DS86 system, to make the basic dosimetry data more easily available (including shielding histories and acute effects), and to resolve several basic questions about exposure status for some in-utero mothers and F_1 parents, we have been working to reorganize and better document the dosimetry data. This effort, which has also included moving the DS86 system to the new RERF computer system, was begun several years ago and will continue for another year. This project should lead to the incorporation of all of the basic dosimetry data into the RERF research database and to a report that thoroughly describes and documents these data.

Database Development

Continued development and documentation of core research database

The introduction of distributed computing has led to great progress in the development of a modern, unified research database. The new database is built around a newly created master list of over 700,000 individuals including all members of the major and minor RERF study cohorts as well as people registered in the tumor and tissue registries. The new system has simplified data handling for the mortality and cancer incidence follow-up and led to improvements in data quality through the elimination of redundant copies of data items. Using the new system researchers have quick direct access to current RERF data and can easily link their data to other items in the system to obtain data needed for analysis using standard statistical programs. At this time the database includes demographic, cohort membership, mortality follow-up, basic dosimetry, and tumor and tissue registry data. However, much additional work is needed to ensure that the database fully serves RERF's research needs. These activities include the development of improved

documentation (on paper and online) and the implementation of additional consistency checks to ensure data quality along with an effort to make researchers more aware of the capability and accessibility of the new system. In addition to these activities, much of the work on database development over the next several years will focus on the areas mentioned in the following subsections.

Clinical follow-up data

These complex and voluminous data include longitudinal information on clinical contacting, routine measurement and laboratory test results, the results of special tests, diagnostic information, and more. Work has progressed on the development of the basic design of the clinical follow-up data tables to be added to the core database. This database will include data on the AHS examinations but also data from other special examinations of the in-utero and F_1 cohorts. It is hoped that the design and implementation of the major tables (focusing on the AHS data) will be completed in a year or two but the effort to incorporate all of the clinical follow-up data can be expected to take several additional years. In addition to incorporating these data to the RERF research database, a modernized version of the AHS patient tracking and clinical management system is being developed that will serve as the front-end for continued updating of the clinical data.

Laboratory data

The data collected in the course of RERF's cytogenetic, biochemical genetic, and radiobiological studies are stored in computer files, laboratory notebooks and other formats. It is not practical to add all of these data into the new database at once. However, as new analyses of archival data are undertaken or new programs are introduced we will incorporate these data in the main research database. At the present time the conventional chromosome aberration data are being cleaned and linked to the core database. Over the next year data on other biodosimetric studies will be added to the system.

The DNA studies being carried out in the Biochemical Genetics Laboratory will generate large amounts of data and analyses will be highly computer-intensive. Thus, there is a need to develop methods for the storage and management of these data. An interdepartmental effort will be undertaken to develop effective methods for handling these data.

Detailed dosimetry data

As noted earlier, efforts are underway to add all of the basic dosimetric data (survivor location, shielding history, and acute effects data) into the research database. This work has involved developing consistency checks and procedures for resolving differences in data from different sources. The basic work on this project has been completed and the new dosimetry data tables should be ready for formal addition to the main database within a few months. Work on documentation of these data will continue for about a year.

Unified inventory of stored samples

Over the last 30+ years more than 120,000 sera and other biological specimens have been

collected and stored for use in future studies. Advances in molecular biology are increasing the value of this unique resource. At present there is no single inventory of these samples. Over the next two to three years we will develop a unified inventory of stored samples. This inventory will be a part of the research database and will be useful in facilitating the planning and conduct of case-control and family studies that employ stored samples and managing this resource more effectively.

Current Status and Future Plans for RERF Follow-up Programs

Mortality ascertainment (koseki check)

RERF carries out a program of active mortality ascertainment for all members of the LSS and most members of the in-utero and F_1 cohorts. As noted earlier, plans are being developed to extend the mortality follow-up to include the 11,760 F_1 cohort members who are not currently included in the routine follow-up. Death certificate information for survivors whose *honseki* (place of family registration) is in Hiroshima or Nagasaki is routinely received by RERF. For cohort members whose honseki is not in either of the cities, requests for information are sent to the appropriate office once every three years. Because of the decreasing number of surviving members of the LSS cohort and more efficient procedures for handling the data, it should be possible to obtain information on vital status and cause of death every two years, especially for members of the LSS cohort.

Hiroshima and Nagasaki tumor and tissue registries

RERF manages the population-based Hiroshima city and Nagasaki city and prefectural tumor registries. These registries are recognized as among the best in Japan. The Foundation's role in the management of these registries has allowed us to create and maintain a direct link between the cancer registry data and the RERF cohorts. Without this connection the increasingly important analyses of cancer incidence among survivors and their children would be difficult, if not impossible. The development of the RERF research database has strengthened the linkage between the tumor registries and the LSS cohorts and further development of the database will make this linkage even more useful. Over the next five years we hope to develop increasingly efficient and effective means for obtaining data on cancer incidence among residents of Hiroshima and Nagasaki.

While it is essential for RERF to continue to play a central role in the management of the tumor and tissue registries, we are working closely with the Hiroshima prefectural government and Hiroshima Medical Association on plans for the development of a new Hiroshima prefectural tumor registry and on the inclusion of the Hiroshima tumor and tissue registry database as an integral part of the proposed new Hiroshima cancer center. It is hoped that in conjunction with these efforts RERF can take a leading role in the creation of a regional tissue bank that would serve as a resource for molecular epidemiological studies carried out at RERF or other institutions, such as Hiroshima University and the Hiroshima Red Cross Hospital. As these plans develop, it should be possible to begin discussions with Nagasaki University and other related groups about the establishment of a similar system in Nagasaki.

The tumor registries are community resources and it is essential that more effort be

devoted to the presentation and analysis of the accumulated data in ways that benefit the communities. Steps are being taken to analyze trends for selected cancer types and to publish regular, standardized summaries of the tumor registry data in a format that will be useful to physicians and others.

Leukemia registry

Special efforts to collect data on cases of leukemia and other hematopoietic malignancies occurring among the survivors were begun by local physicians and ABCC in the late 1940's. Over time these efforts evolved into the Leukemia registry. In recent years virtually all ascertainment of leukemia and related disorders is being done through the tumor registry. It is now felt that the tumor registries are adequate for the identification of new cases of leukemia and related malignant conditions. Hematologists and others associated with the leukemia registry are currently involved in a review of survivor deaths attributed to blood diseases other than leukemia as well as an effort to reclassify all potential LSS lymphoma and myeloma cases using modern diagnostic criteria. Over the next five years we plan to incorporate all of the historical leukemia registry data into the research database.

Standardized biennial clinical examinations

Since 1958 RERF has been giving standardized medical examinations to all participating members of the AHS survivor and in-utero cohorts. This examination currently consists of a complete physical examination that includes systolic and diastolic blood pressures, electrocardiography, radiography, abdominal and thyroid ultrasonography as well as special tests of bone mineral density and cognitive function. Data are also collected on smoking and drinking habits, diet, and other factors. Overall participation remains high (almost 80% of those who were still living in the clinical contacting area participated in the most recent examination cycle). Home visits and hospital examinations are conducted for those survivors too infirm or incapacitated to participate in examinations at the Foundation's clinic. Participation rates do tend to decline sharply among the oldest groups of survivors, and as a consequence of this, thought is being given to plans to increase the examination frequency for some of the older individuals as well as to the development of cost-effective methods of special morbidity surveillance (see next item).

Special one-time examinations have been carried out for selected subsets of the RERF cohorts. The major examination programs, included annual examinations during 1956-63 of in-utero cohort members during adolescence; special examinations of almost 25,000 F_1 cohort members for the biochemical and cytogenetics studies; and most recently the ongoing examinations of the F_1 cohort members and parents in conjunction with the establishment of permanent lymphocyte cell cultures for future genetic studies. As discussed later, plans are being developed to conduct clinical examinations on a limited number of F_1 cohort members in order to assess the feasibility of an ongoing clinical examination program for a subset of the F_1 cohort members.

AHS mail- and telephone-based morbidity surveillance

In response to the recommendations of the 1993 Health Monitoring Workshop, a new AHS morbidity surveillance system was introduced in 1995. This system involves a short mail

survey with subsequent telephone contact at six month intervals. Thus far, response rates have exceeded 90%. To validate the information obtained from this survey a system of periodic hospital and home visits by physicians or public health nurses within the regular two year examination cycle should be introduced.

Mail surveys

Since 1965 a number of mail surveys have been carried out on the LSS or AHS cohorts. These surveys provide important data on risk factors that cannot be determined by means of the routine mortality surveillance program. As described elsewhere, in response to the recommendations of the Blue Ribbon Panel, a new mail survey of F_1 cohort members will be carried out within the next few years.

RESEARCH PLANS BY DEPARTMENT

Research at the Foundation centers on two broad fronts, namely, those programs that will presumably continue well into the future, such as the periodic reports on mortality and cancer incidence in the LSS sample, and are commonly designated as the "core activities," and those programs, the "specific research activities," that are initiated within a single department and are generally time-limited. As previously noted, the core activities are set forth in the so-called "platform protocols" whereas the specific research activities are described in individual research protocols. Largely for convenience, we describe departmental research activities on an individual departmental basis.

Departments of Clinical Studies

The AHS biennial examinations initiated in 1958 continue. The primary purposes of these examinations have been to determine the types of diseases and abnormalities in physiologically or biochemically determined values that may have occurred as a consequence of previous exposure to ionizing radiation and to collate this information with other life experiences and death. The AHS clinical examination is the only point of direct contact with the survivors and functions as a source of biological materials for various special studies.

The AHS has greatly increased in importance in recent years as a result of the accumulation of an enormous body of data on serial medical examinations, with and without the superimposed radiation aspects. Particularly noteworthy is the accumulating evidence that cardiovascular mortality may have a positive radiation-dose response. This potentially important and largely unexpected relationship could never be properly studied using death certificate data alone. Similarly intriguing and potentially important relationships arise from the clinical studies on hyperparathyroidism and serum levels of parahormone, calcium, and alkaline phosphatase. These results suggest that significant deviation in calcium metabolism may be a direct radiation effect and raise further questions about bone density and osteoporosis among the survivors. Still another unexpected finding is the retrospective evidence that radiation 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. However, given the age of the survivors, the window of time for such studies is growing shorter, and it is imperative that these opportunities be exploited soon.

The major research elements in the Department's investigations of the AHS sample can be categorized as follows: (1) characterization of cancer types in relation to various confounders of radiation effects, (2) radiation-related noncancer diseases (benign tumors, cardiovascular diseases, and other chronic diseases), (3) aging associated with exposure, (4) radiation-related changes in physiological, biochemical, and hematological measurements, (5) medical dosimetry, (6) psychosocial changes associated with exposure, and (7) health status of the in-utero exposed.

Program objectives

1. To provide biennial comprehensive medical examinations to the AHS cohort subjects to determine disease occurrence and longitudinal changes in physiological or biochemical parameters in relation to exposure to ionizing radiation and to relate this information to effects on life span.

2. To conduct special in-depth studies to determine the association between ionizing radiation and various health outcomes taking into account the possible effects of other health determinants (for example, life-style factors, physiological and biochemical determinants, prior health history, and menstrual and reproductive history for women).

3. To collect and store biological materials for basic science uses.

4. To utilize the accumulated data for epidemiological purposes in general.

Major research activities in the next five years

A. Core activities (Hiroshima and Nagasaki)

Priority 1

A-1. Basic AHS examination (RP 2-75):

The AHS clinical examinations will be continued in their usual format, but to optimize the quality and quantity of the clinical information considering the aging of the population, a new method of morbidity surveillance was introduced in Hiroshima and Nagasaki in 1995 based on the recommendation of the Health Monitoring Workshop in 1993. This method, with modifications if warranted, will be continued. The new morbidity surveillance consists of a mail survey followed by telephone contact every six months. Since its introduction, the response rate has been more than 90%. To validate the information obtained through this new surveillance program, a system of periodic hospital and home visits by either physicians or public health nurses within the examination cycles should be begun as soon as possible. The utility of introducing an annual health examination for older AHS members, such as those who are 70 years old or older, will also be carefully assessed both from the standpoint of the health of the study participants and research needs.

A-2. Application of new methods of longitudinal data analysis:

A new method of analysis of longitudinal epidemiological data (which takes fuller advantage of the 38 years of accumulated serial measurements than is possible with cross sectional analyses) is being developed with support from staff members of the Departments of Statistics and Epidemiology. The creation of a new AHS database (diseases and measurements) for this type of analysis is currently underway.

A-3. Collection and storage of biological materials:

Collection and storage of biological materials, such as serum, plasma, and lymphocytes, will be continued with some modification of the method of storage, if necessary. The collection of teeth extracted for health reasons will be continued to provide materials for ESR measurements through the new AHS surveillance system.

A-4. Improvement of clinical examination procedures:

In addition to the above, clinical examination procedures of recognized benefit to the study participants, such as early cancer detection or health guidance, that will provide more services to the AHS participants as recommended by the Blue Ribbon Panel, will be updated and broadened to maintain a high level of AHS subject participation. However, it is unrealistic to seek to obtain such equipment as a CT scanner or MRI, and where such tests are needed, they should be performed through collaboration with local medical institutions.

Research plan for the next one year (A1-A4):
The plan to produce *AHS Report 8* will be developed. In this report, the study period will be extended to 1994 and analytic methods will place greater emphasis on confounding and bias due to long-term follow-up, migration and nonparticipation. The creation of the new AHS database will be completed. A plan to improve services to AHS participants will be developed.

Research plan for the next three years (A1-A4):
The *AHS report 8* will be completed and the results published. The new information obtained through the AHS surveillance program should become available for use in AHS Report 9. Comprehensive clinical examination procedures of recognized benefit to the study participants will be introduced in an effort to provide more services to the participants.

B. Special research activities (Hiroshima)

Priority 1

B-1. Benign tumors:

a) Hyperparathyroidism (RP 11-86, 2-89):

Screening for hyperparathyroidism, by measuring serum calcium level, has been underway since 1986. Continued screening will provide not only incidence data on

hyperparathyroidism but could also offer a clue to the cause of the slightly elevated levels of serum calcium and parathyroid hormone seen among survivors exposed to higher radiation doses..

Research plan for the next one year:
Data collection for a 10-year incidence study will be completed.

Research plan for the next three years:
The incidence of hyperparathyroidism will be analyzed for radiation effect, using the data accumulated in the 10 years from 1988 to 1997.

In collaboration with the Department of Radiobiology, a protocol for a molecular biological study (PRAD gene analysis) will be developed to elucidate the etiological mechanism underlying parathyroid adenoma and elevated levels of serum calcium and parathyroid hormone among individuals exposed to radiation.

b) Other benign tumor study (RP 6-86):

Systematic detection of various benign tumors such as myoma uteri, ovarian tumor, and liver hemangioma are being undertaken using abdominal ultrasonographic techniques.

Research plan for the next one year:
Results of the prevalence study of uterine myoma will be published.

Analysis of the prevalence of liver hemangioma and ovarian tumor determined by ultrasonography will be completed.

c) Benign thyroid tumors:

In Nagasaki, thyroid tumors and disorders were screened for by means of physical examination, ultrasonography, and thyroid function tests from 1984 to 1987.

Research plan for the next one year:
The feasibility of studying benign thyroid tumors or thyroid disorders in Hiroshima will be examined.

Research plan for the next three years:
If the decision is made to initiate a thyroid study in Hiroshima, a research plan will be developed and data collection begun.

B-2. Cardiovascular disease study (RP 4-85):

A longitudinal cardiovascular study has been underway since 1965, and the results of this study, covering the period of 1958-1990, suggest a positive radiation effect on the incidence of myocardial infarction (MI). The estimated relative risk (RR) at 1 Gy is 1.17 (p=0.02, 95% confidence interval: 1.01-1.36). In a Cox regression analysis including such factors as age, sex, blood pressure, and cholesterol, it was found that exposure dose still

remained a significant factor, though the association was less than that with age, sex, or blood pressure, suggesting that atomic bomb radiation may be involved in the occurrence of MI. In addition, the different endpoints of atherosclerosis available in the AHS database, such as the prevalence of aortic arch calcification, calcification of the abdominal aorta, blood coagulability, the prevalence of isolated systolic hypertension, and the prevalence of retinal arteriosclerosis, were analyzed and all of these endpoints suggested the presence of radiation effects. Studies in progress include those on sudden death and detection of peripheral vascular disease by pulse wave velocity (PWV) measurements and ankle-arm blood pressure ratio using Doppler equipment. The analysis of radiation effects on conventional risk factors, such as blood pressure and cholesterol levels, has been underway for some time. An analysis of plasma fibrinogen is also underway as a part of the NI-HON-SAN Study, which will be described in more detail later. Studies on new risk factors, such as *H. influenzae* infection and homocysteine will be undertaken in the near future either in cross-sectional fashion or by a nested case-control study using stored sera. The feasibility of ultrasonographic measurement of the wall thickness of the carotid artery to detect latent atherosclerosis will be explored. The incidence studies on myocardial infarction and stroke will continue beyond the next five-year period because the necessary information can be obtained through routine AHS data collection and it is worthwhile to continue to try to understand the underlying mechanisms. The other studies are conducted over shorter periods, such as two years.

Research plan for the next one year:
Manuscripts on myocardial infarction, isolated systolic hypertension, calcification of the aortic arch, and pulse wave velocity will be prepared and submitted for journal publication. The analysis of plasma fibrinogen will be completed. Data collection on ankle-arm blood pressure will be completed. The feasibility of studies of new risk factors will be carefully assessed.

Research plan for the next three years:
Data collection on the incidence of myocardial infarction and stroke will continue. Results on plasma fibrinogen will be published. If new proposed studies turn out to be feasible, data collection will be initiated.

B-3. Studies of liver disease (RP 9-92):

Previous studies have shown a higher prevalence of hepatitis B surface (HBs) antigen in highly exposed subjects, but no difference in the prevalence of anti-HBs antibody was observed between the two groups.

With the availability of the serum assay for hepatitis-Be antigen (HBe) and hepatitis-C virus antibody (HCV), a study of liver diseases, such as chronic hepatitis or liver cirrhosis, was initiated in 1993 to determine the relationship between radiation dose and the prevalence of infection by B and C hepatitis virus in the AHS sample.

Research plan for the next one year:
Measurements and analysis of the data on HCV antibody, and HB antigen and antibodies will be completed.

Research plan for the next three years:
The design of a nested case-control study using stored serum will be developed. Using stored serum collected before onset of hepatoma or liver cirrhosis, the prevalence of HCV or subtypes of HCV in cases and controls will be compared.

Priority 2

B-4. Cancer study (RP 2-75):

Cancers continue to be one of the most prevalent diseases among AHS subjects. For example, from 1969 through 1991, approximately 800 gastric cancers, 280 lung cancers, and 200 breast cancers were found among the AHS subjects in Hiroshima.

Cancer screening will continue to be one of the objectives of the AHS, and special emphasis will be placed on screening for cancers which are often not fatal, such as skin, breast, and thyroid. A new analysis including potential confounders and risk modifiers using the information obtained by various questionnaires and clinical measurements at the time of the routine AHS examinations, such as dietary factors and medications, will be initiated. A case-control study will be conducted on various cancers related to nutrients, hormones and potential carcinogens such as viral infections using stored serum. This study will continue beyond the next five years because all of the necessary information is obtained through routine AHS operations.

Research plan for the next one year:
An attempt will be made to create a new data set for longitudinal analysis using currently available information on confounders and/or risk modifiers. An inventory will be initiated of stored sera for each cancer case for use in future case-control studies.

Research plan for the next three years:
If a new data set is constructed, longitudinal analysis will be initiated to identify confounders or risk modifiers of radiation in cancers among atomic bomb survivors. Once the inventory of stored sera on cancer cases is completed, similar steps will be taken for controls. Then, a comprehensive study method will be developed including noncancer diseases for nested case-control studies.

B-5. Aging and radiation:

Priority 1

a) Osteoporosis study (RP 3-91):

Osteoporosis is a common aging-related disorder among Japanese, and bone density is influenced by premature menopause and parathyroid hormone levels which are known to be radiation-related. Measurement of spinal bone density using dual photon absorptiometry has been underway since 1989, and the results suggest a significant positive relationship between radiation exposure and spinal bone mineral density. However, the apparent increase in bone mass measurements may have been a confounding

effect caused by calcification of the abdominal aorta which is positively associated with radiation dose. To solve this problem, bone mineral density in the spine and hip using dual X-ray absorptiometry was begun in 1994. Total body composition (fat, lean body mass, bone) among the selected AHS samples has been measured using the same equipment.

Research plan for the next one year:
Radiation effects on bone mineral density and body composition including various potential risk factors will be analyzed.

Research plan for the next three years:
A longitudinal analysis will be undertaken to look at the radiation effects on changes in bone density with aging.

b) Senile dementia (RP 5-92):

A dementia study was begun in 1992 to assess the association between radiation exposure and a decline in cognitive function and to determine whether the prevalence of senile dementia increases as radiation dose increases. The epidemiological survey method being used was developed through international collaboration under a program known as the NI-HON-SEA study, which will be described later. This study may make it possible to examine the effects of ionizing radiation on the mature central nervous system.

Research plan for the next one year:
Cognitive function tests have been conducted on about 70% of AHS participants at this time; the remainder will be tested next year.

Research plan for the next three years:
Case ascertainment of senile dementia by a neurologist will be complete, and the results of an analysis of the data will be written up for publication.

c) Menopause study (RP 5-93):

Menopause is a general biological marker of aging in women. Information on age at menopause has been obtained in past epidemiological surveys in Hiroshima and Nagasaki. In Nagasaki, self-reported date of last menstrual period has been routinely obtained at the time of the biennial chest X-ray examinations. Incidence of menopause among Nagasaki participants was analyzed in 1993 using this self-reported information. The results suggest that the higher exposed group experienced an earlier onset of menopause. A longitudinal study using hormone measurements as an indicator of menopause was initiated in 1994 and is expected to take four years to complete. The subjects of this prospective study are premenopausal women who were younger than 10 years old or were in-utero when exposed to A-bomb radiation..

Research plan for the next one year:
The level of two important perimenopausal hormones (FSH and estradiol) will be measured every six months until 1997.

Research plan for the next three years:
The relationship between radiation exposure and the levels of these perimenopausal hormones will be analyzed.

Priority 2

d) Physiologic aging study (RP 4-86):

Accelerated aging resulting from irradiation has been a scientific concern for several decades. Earlier studies of the AHS participants have failed to reveal evidence of such an effect; however, these studies were conducted almost twenty years ago. It is important, therefore, to repeat them using a broader battery of physiological measures and several endpoints that reflect aging. The endpoints to be used for analysis are the incidence of myocardial infarction and stroke, cardiovascular mortality, and the prevalence of aortic arch calcification. The physiological measurements to be used are hand grip strength and skin elasticity which are measured as part of the routine AHS examinations in Hiroshima.

Research plan for the next one year:
Data analysis will be carried out using new endpoints, and a manuscript will be prepared.

Research plan for the next three years:
A new research plan including the use of new statistical methods will be developed.

B-6. Medical dosimetry (RP 7-86, 8-86):

Information on exposure to X-irradiation (radiological examinations at ABCC/RERF, radiological examinations elsewhere, and radiation therapy) has been obtained in the course of the AHS examinations. The examination of ionizing radiation exposure for medical reasons may facilitate assessment of the role of medical X-ray exposures in the follow-up studies of the A-bomb survivors. However, this is an issue which requires careful consideration since it will be difficult to incorporate these data into the various analyses conducted at RERF.

Research plan for the next one year:
Data collection will continue.

B-7. Psychosocial studies and others (RP 2-75):

Few studies have been done on the psychosocial effects of exposure to the atomic bombing, although it is well recognized that they vary greatly in association with socioeconomic factors. Nonetheless, it is possible that psychosocial factors may have influenced the occurrence of disease or at least the stage of development when disease is recognized.

Research plan for the next one year:
A study will be designed to assess the frequency and nature of the social and psychological problems experienced by the survivors with the cooperation of psychological specialists.

The possibility of international collaboration with scientists at the State University of New York will be explored.

B-8. Measurements:

Priority 1

a) AHS Clinical measurements (RP 2-75)

In the AHS, an enormous amount of information has been obtained on laboratory measurements, and it has now become possible to analyze the changes in these measurements over time. In collaboration with the Department of Statistics, growth curve analyses of the information on total serum cholesterol and blood pressure showed that heavily exposed individuals had higher levels of total serum cholesterol. This elevated cholesterol level associated with radiation exposure may have been one of the confounding factors in the increased cardiovascular morbidity and mortality seen among atomic bomb survivors.

Research plan for the next one year:
Results of the longitudinal analyses of cholesterol and blood pressure will be published. The other longitudinal data, including height, weight, and hematological information, accumulated since 1958 will be analyzed.

Research plan for the next three years:
Autoanalyzers for biochemical measurements were introduced into the Hiroshima Clinical Laboratory in 1986 and into Nagasaki in 1987. Longitudinal analyses will be performed on twenty different biochemical measurements accumulated from 1987 to 1996.

Priority 2

b) Benign monoclonal gammopathy (RP 6-85):

Benign monoclonal gammopathy has been shown to be suggestively related to radiation dose, a finding of potential importance since this disease has the possibility of being transformed into multiple myeloma. Screening with protein electrophoresis will be continued for detection of cases with monoclonal spike. Cases will be further tested for confirmation.

Research plan for the next one year:
Screening by protein electrophoresis will continue as before.

Research plan for the next three years:
The study of the incidence of this condition will be summarized and the results published.

B-9. National and international collaboration (RP 4-85, 5-92, 3-91):

There are three major international collaborations underway in Hiroshima. These are the

NI-HON-SAN Study, the NI-HON-SEA Study, and the Japan-Hawaii Osteoporosis Study. All of these studies have been beneficial to RERF because the epidemiological methods developed through collaboration have been applied to other radiation research, and they have been producing important results in elucidating effects of radiation on noncancer diseases.

At its outset, the NI-HON-SAN Study was a study of cardiovascular diseases among Japanese men and men of Japanese descent living in Honolulu and San Francisco. It was initiated in 1965. Although follow-up of the San Francisco cohort ceased in the mid-1970s, the Japanese and Hawaiian cohorts are still being studied. A symposium to commemorate the study's 30th anniversary was held on 2 September 1996 in Hiroshima.

The NI-HON-SEA Study is a study of senile dementia among Japanese men living in Japan and men of Japanese descent living in Honolulu and Seattle. It began in 1992.

The Japan-Hawaii Osteoporosis Study was initiated in 1991.

We have been involved in several national collaborative studies sponsored by the Ministry of Health and Welfare. Through these collaborations, it has been possible for us to develop epidemiological methods to study radiation effects on noncancer diseases and to provide diagnostic services to AHS participants that otherwise would not have been possible. For example, we have been able to obtain free use of a modern bone mineral densitometer to conduct studies of osteoporosis as part of a national collaborative study.

Research plan for the next one year:

NI-HON-SAN Study: Results of comparisons of mortality, glucose intolerance, and fibrinogen levels will be summarized and published.

NI-HON-SEA Study: Data sets will be created to compare the prevalence of senile dementia in the different study cohorts.

Japan-Hawaii Osteoporosis Study: In collaboration with the Hawaii Osteoporosis Center, a comparative study of bone mass, bone loss, and potential risk factors of osteoporosis among Japanese and Japanese-Americans will be analyzed.

Research plan for the next three years:

NI-HON-SAN Study: Results of comparisons of ankle-arm blood pressure index, EKG changes, and pulmonary function will be summarized and published.

NI-HON-SEA Study: Results will be summarized and published.

Japan-Hawaii Osteoporosis Study: Results will be summarized and published.

C. New research initiatives (Hiroshima)

Priority 1

C-1. Molecular epidemiological study:

There are many studies describing the importance of oncogenes and tumor suppressors in the development of malignant disorders, but the role of ionizing radiation in the activation or suppression of these genes is still unclear. In addition, recent studies suggest that some of these genes may be involved in the development of atherosclerosis. A molecular epidemiological study on the AHS population will be initiated with inter-departmental collaboration to examine these issues. For this study, collection of fresh biological materials from surgery, such as tissues of cancers, benign tumors, blood vessels and skin, is desirable through a more intensive morbidity surveillance, in addition to the preservation of lymphocytes of the AHS subjects.

Research plan for the next one year:
A study plan will be developed.

Research plan for the next three years:
If a study is thought to be beneficial for RERF, collection of biological materials will be initiated and appropriate techniques for their use will be developed.

C-2. Feasibility of an F_1 clinical study

In response to the recommendations of the Blue Ribbon Panel, the feasibility of a full-scale study of chronic disease among the F_1 will begin with a mail survey involving all members of the F_1 mortality cohort, to be followed by the clinical examination of a small set of these individuals, about 500 persons, and biochemical genetic studies of several genes known to be related to common chronic diseases.

Research plan for the next one year:
The feasibility study will last for two years.

Research plan for the next three years:
A workshop will be convened to determine whether a full-scale study should be conducted.

Priority 2

C-3. Lenticular opacities:

A new system of grading the degree of lenticular opacification, developed by the research group at NASA, will be introduced and grading will be done using illustrations from the cases of cataracts detected in previous ophthalmological surveys. This will be part of an international collaboration with NASA that aims to test hypotheses regarding the relationship between degree of opacification and radiation dose. For those survivors who were young at the time of the bombing and have not been included in previous surveys, we will consider the use of stereolaminographic images of the lens to provide a more objective and permanent basis for the evaluation of changes that may occur in the future.

Research plan for the next one year:
A study plan will be developed.

Research plan for the next three years:
If the study plan is thought to be beneficial, data collection will be initiated.

Project time lines (Hiroshima)

	1997	1998	1999	2000	2,001.00
Core program: AHS (RP 2-75)	➡	➡	➡	➡	➡
Special studies					
Cancer study (RP2-75)	➡	➡	➡	➡	➡
Parathyroid (RP11-86)	➡	➡	➡	➡	➡
Other benign tumor (RP6-86)	➡	➡	➡		
Cardiovascular (RP4-85)	➡	➡	➡	➡	➡
Liver disease (RP9-92)	➡				
Aging and radiation					
Osteoporosis (RP3-89)	➡	➡	➡	➡	
Dementia	➡	➡	➡		
Physiologic aging (RP4-86)	➡	➡	➡		
Menopause (RP5-93)	➡	➡			
Medical dosimetry (RP7-86,8-86)	➡	➡	➡	➡	➡
Psychosocial (RP2-75)	➡	➡	➡		
Monoclonal gammopathy (RP6-85)	➡	➡	➡		
National-international collaboration					
NI-HON-SAN (RP4-85)	➡	➡	➡	➡	➡
NI-HON-SEA (RP5-92)	➡	➡	➡		
Osteoporosis (RP3-91)	➡	➡	➡		
Molecular epidemiology	➡	➡	➡	➡	➡
Cataract		➡	➡	➡	➡

Personnel requirements (Hiroshima)

Year	1996	1997	1998	1999	2000	2001
Research Scientists*	6 (5+0.5 x2)	6	6	6	6	6
Assistant Adm. Chief	1	1	1	1	1	1
Nurses*	9	8	7	7	7	7
Technicians (X-ray)	3	3	3	3	3	3
Technicians (Lab)	8.5	8	8	8	8	8
Contactors*,#	9	11	12	12	12	12
Clerks+	13	12	12	12	12	12
Total	49.5	49	49	49	49	49

*: If clinical examination of the F_1 is introduced, the number of physicians, nurses and contactors must be increased.
#: Replacement should be made by nurse or public health nurses.
Need more contactors due to aging of the population and newly introduced surveillance program.
+: Replacement should be made by research assistants.

Space requirements (m^2) (Hiroshima)

	1996	1997	1998	1999	2000	2001
Administration	134.50					
Medicine	78.50					
Nursing	185.30					
Radiology	169.21					
Clinical Lab	236.06	+10*	+30**			
Contacting	59.80					
General affairs	286.83					
Total	1,150.20					1,190.20

* : Room for hematology currently in use needs expansion for smooth daily operation.
**: Additional space for storage of serum and plasma is needed.

Equipment budget (Hiroshima) (x ¥ 1,000)

Fiscal year	1997	1998	1999	2000	2001
Laboratory equipment	3,760	2,533	13,528	0	7,283
Computer equipment	4,612	1,952	2,682	712	4,282

D. Special research activities (Nagasaki)

Priority 1

D-1. Effects of menopause on risk factors for ischemic heart disease - a longitudinal study of the Nagasaki Adult Health Study sample (RP 1-95).

The purpose of this study is to look for an association between perimenopausal changes in the level of total serum cholesterol and its fractions and changes in serum estradiol. The results of this study will produce hypotheses on cardiovascular mortality and its relationship to radiation dose in women, because radiation seems to accelerate the onset of menopause, that is, radiation may cause earlier deterioration of the atherogenic cholesterol profiles.

At the outset of the study 63 of 73 study participants had not yet experienced menopause. This study will continue for 4 to 6 years.

D-2. The Nagasaki Department of Clinical Studies will implement all RPs except for RP 4-86, RP 3-89, RP 3-90, RP 3-91, RP 6-92, and RP 2-95 in the same manner as conducted by the Hiroshima Clinical Studies Department.

Project time lines (Nagasaki)

Project	1997	1998	1999	2000	2001
Menopause	⇒	⇒	⇒	⇒	⇒

Personnel requirements (Nagasaki)

Fiscal Year	1997	1998	1999	2000	2001
Physicians[1]	2.5	2.5	2.5	2.5	2.5
X-ray technicians	3	3	3	3	3
Clinical Laboratory	9	9	9	9	9
Nursing Section	5	5	5	5	5
Contacting Section	9	9	9	9	9
Administration	9	9	9	9	9

[1] Dr. Midori Soda is included as half-time in the Nagasaki Department of Clinical Studies.

Space requirements (m^2) (Nagasaki)[1]

Fiscal Year	1997	1998	1999	2000	2001
Internal Medicine	73	73	73	73	73
X-ray	171	171	171	171	171
Clinical Laboratory	298	298	298	298	298
Nursing Section	143	143	143	143	143
Contacting Section	81	81	81	81	81
Administration	103	103	103	103	103

[1] Personnel strength and floor space must be expanded if a full-scale study of chronic disease among the F_1 is initiated.

Equipment budget (Nagasaki) (x ¥ 1,000)

Fiscal Year	1997	1998	1999	2000	2001
Laboratory	19045	0	0	3000	0
Computer Equip.	1072	1052	2252	452	852

[1] The standard equipment budget was calculated on the basis of the present cost of the respective pieces of equipment. Annual inflation and price increases due to equipment upgrading may affect this five-year projection. Equipment approaching the end of its working life may malfunction and would also alter this estimate as would the initiation of new research protocols.

Departments of Epidemiology

Until the mid-1980s, epidemiology, statistics, and computing were combined in a single Department of Epidemiology and Statistics at the Foundation. It became clear, however, that this was neither an efficient nor cost-effective organization of resources and skills. During 1984-85, these disciplines were established as independent research or support departments. In 1994, the Departments of Epidemiologic Pathology, responsible for the conduct of pathology studies and the tumor and tissue registries, were merged with the Departments of Epidemiology.

Program objectives

The Departments of Epidemiology play a central role in the conduct of the long-term follow-up of the three cohorts, LSS, in-utero, and F_1. The follow-up of these cohorts has long relied on mortality surveillance through the use of the nationwide family registration system, the *koseki*. Recently, cancer incidence data from improved tumor registries in Hiroshima and Nagasaki have become available on these cohorts, adding new dimensions to our studies of radiation cancer risks. Continued follow-up of these cohorts is essential in clarifying the temporal patterns of cancer risk as young subjects reach ages when background cancer risk is increased. In addition, the emerging excess noncancer mortality risk is of particular concern as the nature of the risk is still unclear. Although the numerous mail surveys conducted in the LSS provide potentially valuable data on the role of nonradiation risk factors, little effort has been made to incorporate these data into RERF analyses. We must place increased emphasis on the studies of nonradiation risk factors in relation to cancer and noncancer disease risks.

Because of the nature of the RERF research, the Departments of Epidemiology should and will play a key role in the design and conduct of various interdepartmental research activities. As indicated in the Blue Ribbon Panel report, one of the most important multidisciplinary programs at the present time is the molecular epidemiology of cancer, which will require close interdepartmental and interdisciplinary communication. In addition, the Departments of Epidemiology must also play a more active role in generating new ideas for studies to answer questions arising from the ongoing epidemiological studies, which are being conducted in collaboration with other RERF departments or outside research groups.

The epidemiological research activities in Hiroshima and Nagasaki are carried out following common research protocols and procedures. The professional staff in the Department of Epidemiology in Hiroshima currently consists of three epidemiologists supplemented by one

pathology consultant and one visiting pathology investigator. The professional staff in the Nagasaki Department of Epidemiology consists of one epidemiologist and one physician. The epidemiology staff work closely with the staff in the Department of Statistics in study design, data analysis, and preparation of major reports; they also work with the Departments of Statistics and Information Technology in database design and development.

A. Core activities

The core activities of the Epidemiology research program are as follows:

A-1. Publication of periodic general reports

The Departments of Epidemiology working together with the Department of Statistics will continue to produce periodic and specific reports on cancer and noncancer mortality as well as cancer incidence resulting from continued follow-up of the LSS, in-utero and F_1 cohorts. In view of the uncertainty regarding the cancer risk for the young survivors, continued follow-up of the LSS and in-utero cohorts in the next decade and beyond is considered critical. Principal periodic reports that are expected within the next 5 years include LSS Report 13 on updated cancer and noncancer mortality (through 1995), an updated LSS cancer incidence report (through 1992 or later), an in-utero cancer incidence report, and F_1 mortality and cancer incidence reports.

Investigations of the noncancer mortality data will be particularly challenging because of the multiplicity of factors that must be considered and the paucity of relevant biological models. As the survivors age, further follow-up of the cohort will provide increasingly useful information on this important question. At the same time, it will be equally important to define working hypotheses to account for the excess noncancer disease risks and to develop and carry out research programs in collaboration with other RERF departments and outside research groups.

A-2. Conduct of site-specific cancer studies

Several site-specific cancer studies are currently active. These studies are designed to provide detailed data on pathological features of tumors associated with radiation exposure accompanied by in-depth risk analysis, providing insights into the biological bases of radiation-induced tumorigenesis. A number of reports from this series of site-specific cancer studies will be forthcoming in the next several years.

A-3. Continued management of the Hiroshima and Nagasaki tumor and tissue registries, and development of a tissue bank

The Foundation continues to manage the Hiroshima and Nagasaki tumor and tissue registries which provide high-quality cancer incidence data. They are among the few registries in Japan whose incidence data have been included in several volumes of *Cancer Incidence in Five Continents* (by IARC/IACR), a worldwide compilation of cancer incidence data. The LSS cancer incidence data published in 1993 and 1994 and the current series of site-specific cancer incidence studies would not have been possible

without RERF's direct involvement in the registry operations. While we will continue to publish the Hiroshima and Nagasaki incidence data in future volumes of the above IARC/IACR monograph series, it is important that we also produce our own comprehensive and more detailed analyses of population-based cancer incidence data.

RERF, together with the local medical societies, also continues to manage the tissue registries. These registries have the potential to be developed into a tissue bank linked to the LSS, which will be a tremendously valuable source for molecular oncology studies. Therefore, the Departments of Epidemiology must continue to be involved in the management and further development of the tumor and tissue registries.

A-4. Design and conduct of case-control and other special studies to address specific questions

The Epidemiology department also conducts ad hoc case-control or other studies to investigate specific hypotheses prompted by regular analyses of the A-bomb survivor data or other research developments. Such studies involve personal interviews to elicit specific information, make use of existing information, or require biological samples such as tissues and frozen sera. Case-control studies nested in the cohort are particularly useful for providing answers to the questions of current interest. Illustrative examples include studies of liver cancer and viral hepatitis infection (ongoing), breast cancer and detailed reproductive history (completed), and stomach cancer and serum ferritin (completed). The Department will continue to generate new studies of this kind to gain insights into the nature of cancer and noncancer diseases.

A-5. Studies of radiation and nonradiation factors using mail survey data

During the course of the LSS follow-up several mail surveys have been conducted to obtain epidemiological information on lifestyle factors such as smoking, alcohol intake, diet, and occupation. To date use of this information has been limited to the smoking data as related to cancer. Studies of conventional risk factors are also critically important in elucidating the nature of the excess noncancer vascular, digestive, and respiratory diseases. While some work has been done in the last few years, further effort should be devoted to the study of nonradiation risk factors.

These studies are covered by the following platform research protocols:

Priority 1

Research plan for RERF studies of the life span of A-bomb survivors, Hiroshima and Nagasaki (RP 1-75)

Research plan for RERF studies of the potential genetic effects of atomic radiation: Hiroshima and Nagasaki, Part 1. Mortality study of children born to atomic bomb survivors (RP 4-75)

Tumor registry study in Hiroshima and Nagasaki (RP 18-61)

Detection of leukemia and related disorders (RP 29-60)

Pathology studies in Hiroshima and Nagasaki, revised research plan (RP 5-89: Formerly RP 3-75)

Guidelines for the conduct of site-specific cancer incidence studies among A-bomb survivors, Hiroshima and Nagasaki (RP 9-88)

B. Special research activities

B-1: Site-specific cancer studies

Under the platform protocols regarding tumor and leukemia registries (RP 18-61, RP 29-60) and pathology studies (RP 5-89, RP 9-88), various site-specific cancer studies are now under way. Standardized pathology reviews are conducted by panels of pathologists (from Hiroshima and Nagasaki) using contemporary classification schemes, and special effort is made to ascertain cases beyond those routinely reported to the tumor and tissue registries. Pathology slides and tissue blocks obtained for these studies facilitate the conduct of molecular epidemiological studies. These site-specific studies in various stages of completion are summarized in the next table, followed by a description of the objectives for each study.

Priority 1

Incidence of lymphoid malignancies among the atomic bomb survivors, 1950-90 (RP 3-94):

This study is designed to provide more definitive data on the rather inconsistent evidence thus far available on the risk of lymphoid malignancies in the LSS. The objective is to investigate all lymphopoietic tumors (lymphomas, multiple myeloma, lymphocytic leukemias) between 1950 and 1990 in the LSS. Emphasis is on the confirmation and classification of cases using modern techniques. The study involves both hematologists and pathologists engaged in lymphoid tumor research. Non-Hodgkin's lymphomas are classified by immuno-histochemical studies into T- or B-cell lymphomas, and the diagnosis of adult T-cell leukemia is based on detection of proviral DNA of HTLV-I using archived tissues.

Studies of lung cancer incidence among the atomic bomb survivors, 1950-90 (RP 1-94):

Lung cancer is a late effect of radiation exposure, but several specific issues and questions remain to be addressed. These include the specificity of various cell types involved in radiation- versus smoking-related cancers, confounding and joint effects of smoking in relation to radiation exposure, delineation of the temporal trend with allowance given to the age-at-exposure and attained-age effects. ICRP also has recently published a new report on lung cancer risk from inhaled radionuclides modeled on an anatomical basis in terms of lung "compartments." New information on anatomical distribution of lung cancers resulting from uniformly distributed radiation may be useful for evaluating the ICRP model. This RP was developed to address these questions and issues.

Current and Planned Site-specific Cancer Studies

Site	Year study began	Specific objectives	Current status/Plan
		Currently active	
Liver	1990	Incidence; role of hepatitis infection (case-control)	Preliminary results presented at Jpn. Soc. Path. Mtg., '96; Paper on incidence to be submitted within a year; HCV assays in progress
Salivary gland	1991	Benign & malignant tumors; major & minor glands	Results presented at Jpn. Soc. Path. Mtg., '95 One paper published; another submitted; To be completed within a year
Skin	1991	Cell types and UV effect	Results presented at Jpn. Soc. Path. Mtg., '95; Data presented One paper submitted; another paper in preparation;To be completed within a year
Thyroid	1991	Benign & malignant tumors; microcarcinomas	Ready for analysis; Papers to be prepared in the next 2-3 years
Ovary	1992	Benign & malignant tumors	Preliminary results presented at Jpn. Soc. Path. Mtg., '96; Analysis in progress; To be completed in 2-3 years
Nervous system	1992	Neurilemmoma, meningioma, pituitary tumors; benign and malignant	Results presented at Jpn. Soc. Path. Mtg., "95 Two papers in preparation; To be completed within a year
Breast	1993	Update of the continuing series; risk for young women	Paper in preparation; To be completed within a year
Lung	1994	Topographic distribution, cell types and smoking; time trend	Pathology review in progress; Expected to be completed in 4-5 years
Lymphoid	1994	Lymphoma, multiple myeloma; T-cell and B-cell origin	Pathology review started; Expected to be completed in 4-5 years
		Planned	
Colon		Different sub-sites; parallel molecular study	To be started
Stomach		Histological subtypes; EB virus infection	To be started
Bone/connective tissues		Bone tumors	To be started

Breast cancer incidence study among atomic bomb survivors, 1950-90 (RP 6-93):

This is the latest (started in 1993) of a series of breast cancer incidence surveys, extending the follow-up through 1990. Data collection for this series has been completed, adding 261 newly accessed cases (250 for the period of 1986-1990 and 11 prior to 1986). Of these, 58 cases were exposed at <10 years of age, and this should strengthen risk estimates for this age-at-exposure group.

Incidence of tumors of the central nervous system among A-bomb survivors (RP 4-92):

In the recent solid cancer incidence report, a suggestive dose response was found among those survivors exposed at ages <20 years for tumors of the nervous system except for the brain. These findings prompted the present study. The objective is to ascertain malignant and benign tumors of the central nervous system in the LSS from 1950 to 1987.

Studies of ovarian tumor incidence among the RERF extended Life Span Study cohort, 1950-87 (RP 2-92):

The present study extends the previous ovarian cancer series by 7 years (through 1987) and also includes a systematic ascertainment of benign tumors.

Studies of thyroid tumor incidence among the RERF extended Life Span Study cohort, Hiroshima and Nagasaki, 1950-87 (RP 6-91):

This investigation was started in 1991 with the aim of updating and expanding the earlier thyroid cancer incidence series (through 1979), including both benign and malignant tumor cases diagnosed between 1950 and 1987. The increased number of cases over the extended study period should allow more detailed risk analyses than were available previously.

Studies of skin cancer incidence among the RERF extended Life Span Study cohort, Hiroshima and Nagasaki, 1950-87 (RP 2-91):

The completeness of the ascertainment of skin cancer from the tumor registries is questionable and diagnoses of skin cancer are highly variable among physicians and pathologists. The present study is designed to provide extended case-finding and a standardized pathology review for histological typing of skin tumors. All work related to case ascertainment that began in 1991 has been completed, and analyses have almost been completed. A significant dose response is demonstrated for basal cell carcinoma but not for squamous cell carcinoma of the skin. Noteworthy is the absence of a suspected combined effect of UV and ionizing radiation exposure and a strong effect of age at exposure on basal cell carcinoma.

Studies of salivary gland tumors among the RERF extended Life Span Study cohort, Hiroshima and Nagasaki, 1959-87 (RP 1-91):

This study was initiated in 1991. The objective was to study both benign and malignant

tumors of the major and minor salivary glands diagnosed between 1950 and 1987. All phases of the study are virtually completed. Analysis shows a significant dose response for both benign and malignant tumors. Most of the dose response for malignant tumors is provided by an exceptionally strong dose response for a particular type, mucoepidermoid carcinoma, and most or all of the dose response is attributable to Warthin's tumor.

Primary liver cancer incidence study among atomic bomb survivors, Hiroshima and Nagasaki, 1958-1987 (RP 5-90):

Since diagnostic misclassification is a major concern for liver cancer, the primary objective of this study is to assess the relationship between atomic bomb radiation and liver cancer based on data confirmed by a panel of pathologists. Another objective is to investigate, in a nested case-control study, the possible role of HBV, and possibly HCV, infection in radiation-related liver cancer. The pathology review extends from histologic classification of liver cancer to diagnosis of any accompanying liver cirrhosis and testing for HBV markers. In the companion study conducted in the Department of Radiobiology (RP 5-90), molecular techniques are being used to characterize the HB and HC viruses more precisely.

B-2: Case-control studies in progress

In addition, case-control studies are being conducted to investigate factors other than radiation exposure that may interact with radiation. Information is obtained, primarily by retrospective interview, on personal habits, and other life-style factors, medical history, reproductive factors, and other suspected cancer risk factors.

Priority 1

Interaction between radiation dose and host factors. An epidemiological case-control study of female breast cancer in atomic bomb survivors (RP 14-79):

This study, started in 1979, continues to investigate reproductive and other known risk factors in association with radiation. In a study of 196 breast cancer cases and 566 controls, the risk was found to be positively associated with age at first full-term pregnancy, in agreement with the literature; whereas negative, and partially independent, associations were observed with number of births and total cumulative period of breast feeding. Significant positive associations were also found with history of treatment for dysmenorrhea and uterine or ovarian surgery. Neither age at menarche nor age at menopause was significantly associated with breast cancer. Multiplicative relationships were found between radiation exposure and age at first full-term pregnancy, number of children, and cumulative total period of lactation.

A plan is underway to revise this case-control study by adding reproductive and family information from various Master-File documents kept at RERF (an example of a record-based case-control study).

Priority 2

Thyroid cancer (RP 12-85):

The study includes 365 cases with histologically diagnosed thyroid cancer and their matched controls. Personal interviews have been completed to obtain retrospective information on major risk factors such as diet and nutrition, reproductive experiences and previous medical history. Factors that have been found to be associated with thyroid cancer are: history of cancer in sisters, previous histories of goiter, tonsillectomy, ovariectomy, and breast disease, and increased body mass index. Analysis is almost completed, and a paper is being prepared for publication. Data from this study are included in a pooled analysis of thyroid case-control data from various countries undertaken by the NCI.

Priority 3

Nutrients and cancer (RP 11-85); hormones and cancer (RP 10-85):

These two studies utilize stored sera for nutritional and hormonal assays. Preliminary analysis shows a relationship between total estradiol and breast cancer risk. Following the first paper on serum ferritin and stomach cancer risk (TR 14-89), the second paper on serum selenium and zinc in association with the subsequent development of lung and stomach cancer was published (*Cancer Epidemiology, Biomarkers & Prevention*). In this study of 208 cases with stomach cancer, and 77 cases with lung cancer and matched controls, a slightly increased risk of lung cancer was found to be associated with low serum levels of selenium but little association was found with either lung or stomach cancer across normal selenium or zinc ranges. A paper on breast and other cancers in relation to hormone assays is under preparation and is expected to be completed shortly.

C. New research activities anticipated in the next 5 years

As mentioned above, a number of important specific issues have been identified through the follow-up of the major cohorts. These are summarized below:

Cancer

Increased cancer risks have been clearly substantiated as a late effect of radiation exposure among the survivors. However, several issues regarding cancer risk remain to be clarified.

- Cancer risk among the young: The temporal pattern of cancer risk among the survivors exposed as children, that is before the age of 10, as they reach the ages at which background cancer risk is increased.

- Confounding and modifying effects of nonradiation factors: Because smoking and other life-style factors are important determinants of cancer, cardiovascular and other diseases, more research is needed to study the possible confounding and modifying of effects of nonradiation factors. This is an area which has received little attention in the past and will require collaboration with researchers in other RERF departments and outside RERF.

- Mechanistic models for radiation-induced cancer: Initial attempts by Donald Pierce and Mortimer Mendelsohn to develop a mechanistic model for radiation-induced cancer using the LSS data have provided some interesting and useful insights into how to interpret the age and time dependence seen in the solid cancer risks. There is also increasing interest in other biologically motivated models for radiation carcinogenesis. These models may provide useful insights into temporal patterns, sex differences and other aspects of the radiation-induced excess risk. While most of the developmental work will rely on the Statistics staff, RERF provides an environment for close interaction with radiation biologists. More effort at RERF along these lines of research seems warranted.

- Organ-specific cancer risks: Observed differences in site-specific cancer risks are difficult to interpret because of statistical variability and the relatively small excess number of cases involved. The joint analysis approach initiated by the Department of Statistics on this issue is promising and will be further pursued working with members of the Departments of Epidemiology.

- Incidence vs mortality: While mortality follow-up will continue to be the primary basis of risk assessment, cancer incidence patterns will play an increasingly important role, especially for breast, thyroid, and other less fatal cancers. The availability of both cancer mortality and incidence data now enables us to provide more comprehensive assessment of the radiation risk, starting from cancer onset to death. However, it has also become necessary to pay attention to how to interpret results from mortality and incidence data. It is important to develop methods to provide an integrated presentation of the mortality and incidence data. It will be useful too to develop measures of detriment using both results. While some work has already been done on mortality/incidence comparison and risk of second primary cancers, much more work is needed in this area.

Noncancer diseases

The evidence of an excess noncancer mortality risk in the LSS data is becoming more compelling. Thus, another outstanding issue is further characterization of the noncancer risks in the LSS.

- Working with the Department of Statistics, we will attempt to clarify essential characteristics of the noncancer excess including such issues as the shape of the dose response, patterns of risk by age, sex, and time, etc. Since the excess risk appears to be continuing, we can expect that further follow-up will make possible more detailed analyses and improve characterization of these risks.

- The AHS is the source of clinical data on diseases and laboratory measurements that are immensely useful for characterizing noncancer events. Therefore, it will be essential that we work with the Departments of Clinical Studies and Statistics to develop studies that integrate the LSS and AHS data on radiation effects on noncancer endpoints.

Some other important questions to be examined are as follows:

- Misclassification: We have already shown that the misclassification of cancer to noncancer

on death certificates contributes only a fraction of the observed excess noncancer mortality and that a noncancer excess exists even after the correction for such misclassification. More work is needed to learn how best to deal with misclassification between different noncancer diseases and how this misclassification affects the risk estimates.

- Confounding, biases and indirect effects: Whether the observed noncancer excess mortality results from confounding or indirect effects of other factors, selective or other biases, remains a central question. While all available data should be used to examine these issues, new ideas are also needed to initiate new research and analyses.

- Plausible disease mechanisms: A serious problem with the noncancer risk is the paucity of biological models for radiation induction of noncancer diseases at low dose levels. This is an area in which the development of new innovative research ideas requires close interaction with biologists and clinical investigators. Such collaborations should help us generate and test hypotheses regarding plausible mechanisms for the effects.

New research will be generated in the following areas. These topics are not covered under the existing platform or individual research protocols, but new specific RPs will be developed as needed.

Priority 1

Molecular epidemiology of cancer

As mentioned in the Blue Ribbon Panel recommendations, research on molecular oncology requires specific hypotheses or models that can be tested in this unique population of radiation exposed individuals. Contributions from the Departments of Epidemiology will be several-fold.

First, because of the involvement of the departments in the tumor and tissue registries and their long-standing relationships with the local medical communities, we must take a leading role in establishing collection and management procedures for tissues and other biological samples to ensure that appropriate samples are available for this research. It will be essential that we develop as the first step an efficient database management system, in collaboration with ITD and others, to catalogue all available tissues together with relevant information linked to the RERF cohorts. Second, the Departments of Epidemiology should provide intellectual input by identifying important research questions based on the ongoing analysis of cancer data and by being involved in study design, analysis, and interpretations of the results.

F_1 mail survey

As part of the planned clinical examination of the F_1 population, the Departments of Epidemiology will be involved in a mail survey on this cohort. It is anticipated that basic information obtained from this mail survey will provide data useful for assessing the feasibility of a full-scale investigation and the factors which may be considered as confounders in future analyses of the mortality and morbidity data and reproductive

performance among the F_1 cohort.

Site-specific cancer studies

Most of the currently active site-specific cancer incidence studies will be completed within the next few years. As they are completed, new studies will be initiated to update the case series or to investigate additional tumor sites of interest. These include such sites as colon, stomach, and bone and connective tissues (see table).

Priority 2

Family pedigree studies and genetic epidemiology

The setting in which the three RERF cohorts were established presents a unique opportunity for identifying family members within these cohorts and conducting a long-term prospective follow-up of the role of genetic and other familial factors in the occurrence of cancer and other common, chronic diseases. Some preliminary work has been undertaken in collaboration with the Departments of Statistics, Clinical Studies and Information Technology to set up a family pedigree database. In view of the evidence relating genetic predisposition for breast cancer, a pilot study is now underway to construct family pedigrees for young breast cancer patients as well as older breast cancer patients (as a comparison group). To obtain useful results, more formal research protocols will be developed in association with geneticists and statisticians. To implement this research may require the additional help of individuals who are familiar with Japanese kinship terms in establishing genealogical relationships and the use of the koseki records to verify the stated relationships.

Personnel requirements (Hiroshima)

In the last few years, the number of epidemiologists in the department's professional staff in Hiroshima has decreased from 6 (4 Japanese and 2 US) to 3 (Japanese only), while that in Nagasaki has remained at 2 (both Japanese). In view of the ongoing and anticipated research activities, the current size is woefully inadequate. The minimum staff requirement for Hiroshima is 6 professionals as it was in 1994. Because of the generally high level of epidemiologists trained in the US and some European countries, efforts are underway to recruit two epidemiologists through NAS. We also plan to recruit one Japanese epidemiologist. Finally, in anticipation of the retirement of the current Department Chief in 5 years, we should begin to consider the recruitment of another Japanese M.D. or Ph.D. level epidemiologist.

The Epidemiology support staff for Hiroshima has also decreased in size and currently consists of 35 full-time and 4 part-time employees. The support staff provides research assistance (data preparation, tabulation and analyses), technical assistance (the management of the Master-File and tumor registry database, the abstraction of medical records for the tumor registry operation, and histo-pathology work for specific cancer studies), clerical work (Master-File and tumor registry) and secretarial and administrative assistance. The current total size of 39 is adequate.

Area	Current	1997	1998	1999	2000	2001
			Fiscal Year			
			Research scientists			
Epidemiology	1.5	4.5	4.5	4.5	4.5	4.5
Tumor registry	1.5	1.5	1.5	1.5	1.5	1.5
Total	3	6	6	6	6	6
			Support staff			
Research assistants	3	3	3	3	3	3
Master File	17 (1)[1]	18	18	18	18	18
Tumor registry	11 (2)	13	13	13	13	13
Pathology	2 (1)	3	3	3	3	3
Administration	2	2	2	2	2	2
Total	35 (4)	39	39	39	39	39

[1] Part-time employees shown in parentheses.

Space requirements (m^2) (Hiroshima)

Area	Current	1997	1998	1999	2000	2001
			Fiscal Year			
Research scientists	73	105	105	105	105	105
Administration	18	20	20	20	20	20
Research assistants	20	20	20	20	20	20
Master File	307	210	210	210	210	210
Tumor registry	112	210	210	210	210	210
Pathology	181	180	180	180	180	180
Other Support[1]	57	40	40	40	40	40
Total	768	785	785	785	785	785

[1] Includes half of the area of the conference, computer, and copier rooms which are shared with the Department of Statistics and of the visiting scientists office, which is also shared with Statistics.

Equipment budget (Hiroshima) (x ¥ 1,000)

Computer hardware and software are the primary equipment used by the Epidemiology staff. A three-year schedule for the replacement of computers and a continuing need to expand network storage capacity have been assumed. It also is assumed that replacing or upgrading hardware and software will occur on a regular basis. In addition, laboratory equipment for the Pathology Laboratory will be needed.

Hiroshima, Research and Administrative

Budget category	Fiscal Year 1997	1998	1999	2000	2001
Computer hardware replacement/upgrade[1]	6,060	6,000	6,200	6,140	6,140
New computer hardware and software[2]	660	780	640	760	760
Pathology lab	970+	150	150	150	150
Total	7,690	6,930	6,990	7,050	7,050

1. There are currently 26 PCS, of which 8 will be replaced each year.
2. There are currently 7 printers, one of which will be replaced each year. Also one new PC will be added each year.
\+ Incubator, microtome, cleaner

Hiroshima, Research

Budget category	Fiscal Year 1997	1998	1999	2000	2001
Computer hardware replacement/upgrade[1]	4,292	4,200	4,390	4,298	4,348
New computer hardware and software[2]	549	617	536	608	608
Pathology lab[3]	970+	150	150	150	150
Total	5,811	4,967	5,076	5,056	5,106

1. 75% use for research assumed.
2. 75% use for research assumed.
3. 100% use for research assumed.

Personnel requirements (Nagasaki)

There are two Japanese professional staff in Nagasaki and the size is appropriate. However, we need one research assistant who has a sound knowledge of epidemiology, statistics and the computer sciences, and who will be expected to obtain a Ph.D. within 5 years.

The epidemiology support staff for Nagasaki has decreased in size and currently consists of 20 full-time employees. The support staff provides technical assistance (the maintenance of the computer system, the management of the Master-File and tumor registry database, the

abstraction of medical records for the tumor registry operation, the histopathology work for cancer studies, etc.), clerical work (Master-File and tumor registry) and secretarial and administrative assistance. The current total size of 20 should be increased to 21 through the employment of the one additional research assistant mentioned above.

Nagasaki

	Fiscal Year					
Area	Current	1997	1998	1999	2000	2001
	Research scientists					
Epidemiology	0.8	0.8	0.8	0.8	0.8	0.8
Statistics	0.2	0.2	0.2	0.2	0.2	0.2
Tumor registry	0.8	0.8	0.8	0.8	0.8	0.8
Clinics	0.2	0.2	0.2	0.2	0.2	0.2
Total	2	2	2	2	2	2
	Support staff					
Research assistant	0	1	1	1	1	1
Master File	9	9	9	9	9	9
Tumor registry	6	6	6	6	6	6
Pathology	3	3	3	3	3	3
Computer technicians	2	2	2	2	2	2
Total	20	21	21	21	21	21

Space requirements (m^2) (Nagasaki)

	Fiscal Year					
Area	Current	1997	1998	1999	2000	2001
Research scientists	28*	50	50	50	50	50
Research assistant	0	10	10	10	10	10
Master File	146	146	146	146	146	146
Tumor registry	61	70	70	70	70	70
Pathology	82	82	82	82	82	82
Computer technicians	18	22	22	22	22	22
Other Support[1]	96	96	96	96	96	96
Total	431	476	476	476	476	476

[1] Includes space for data and document storage ($52m^2$), network communication servers and equipment ($18m^2$) and underground storage of pathology samples ($26m^2$).

Equipment budget (Nagasaki) (x ¥ 1,000)

Budget category	Fiscal Year				
	1997	1998	1999	2000	2001
Computer hardware replacement/upgrade	2,570	2,500	1,000	0	3,000
additional	570				
Printer replacement/upgrade	1,900	700	1,500	700	1,900
Software upgrade	968	144	1,044	144	1,044
additional	190				
Pathology lab	1,618	30	30	30	30
Total	7,816	3,374	3,574	874	5,974

Survey Expenses (x ¥ 1,000)

				Projection					
	1993	1994	1995	1996	1997	1998	1999	2000	2001
Mortality surveillance									
Hiroshima	13,509	13,524	13,450	17,082	17,000	17,850	17,850	18,740	18,740
Nagasaki	7,489	7,337	7,423	11,294	11,000	11,550	11,550	12,130	12,130
Total	20,998	20,861	20,873	28,376	28,000	29,400	29,400	30,870	30,870
Tissue registry									
Hiroshima	12,000	12,000	12,000	12,000	12,000	12,000	12,000	12,000	12,000
Nagasaki	12,000	12,000	12,000	12,000	12,000	12,000	12,000	12,000	12,000
Total	24,000	24,000	24,000	24,000	24,000	24,000	24,000	24,000	24,000
F1 mail survey Hiroshima & Nagasaki					13,300	13,300	13,300	13,000	
Grand Total				52,376	65,300	66,700	66,700	68,170	54,870

1) Mortality surveillance: Projections based on a 5% biennial increase in fees for koseki request plus postage.
2) F1 mail survey: Estimates for 71,000 subjects currently alive, costs include survey form, envelope, labels and postage for residence check (¥6,350); fees for koseki (¥24,880); and postage for koseki and mailing (twice on the average)(¥22,050) for 71,000 subjects (alive)(Total: ¥53,280) equally distributed over the four year period 1997-2000.

Construction of LSS-based Family Pedigree Database

Hiroshima and Nagasaki Combined Estimates (x ¥ 1,000)

	Current	1997	1998	1999	2000	2001
Koseki check		19,450	19,450	19,400	19,400	19,400
Supplies		150	150	140	140	140
Total		19,600	19,600	19,540	19,540	19,540

Estimates for 120,000 subjects based on fees for original koseki and postage (¥97,100) and supplies (¥720) equally distributed over the 5-year period 1997-2001.

Department of Genetics

The current research activities of the Department of Genetics have two major thrusts, namely, a cytogenetics program that focuses on the occurrence of chromosomal abnormalities in the survivors as well as their offspring, and a biochemical genetics program that centers on the detection of gene-mutational events and the development of the requisite technology to achieve this end. These two programs have been carried out by the Cytogenetics Laboratory and the Laboratory of Biochemical Genetics, respectively.

In the past, screening for chromosomal abnormalities and gene mutations occurring in germ cells were carried out in the two laboratories by examining the children of the survivors selected from the same F_1 cohort. However, in the last 10 years, the cytogenetics program focused on screening for somatic chromosome abnormalities in the survivors in order to establish biological dosimetry as an alternative to physical dose estimation through the application of electron spin resonance (ESR) of tooth enamel obtained from the survivors. The efforts of the biochemical genetics program have been concentrated on developing technologies for the detection of germ cell DNA mutations in the children of the survivors and establishing cell lines from 1000 parent-child trios, with half of the trios including at least one proximally exposed parent.

In the next five years, in each program, on-going projects will be continued. In addition, the FISH (fluorescence in situ hybridization) technique will be utilized for the physical localization of unreported genes or new mutations in specific genes detected in the biochemical genetics program by using single probes of DNA fragments and a subsample of the 1000 trios whose lymphocytes and cell lines have been stored in our cell bank for the biochemical genetics program will be examined for the detection of chromosomal germline mutations.

The Cytogenetics Program

The research objectives of the Cytogenetics Laboratory are two fold. First, to collect cytogenetic information on the survivors and to use this information to strengthen the DS86 dose estimates, either by validating them or by indicating possible biases in them. Second, to determine by means of the F_1 cytogenetic studies whether parental exposure to A-bomb radiation caused an increased frequency of chromosomal abnormalities in their progeny. Since these aims entail

different studies, we describe them separately.

Cytogenetic studies of the survivors

Past experience has confirmed that the conventional Giemsa staining method can detect nearly two-thirds of all reciprocal translocations. However, even with the best technique and highly qualified investigators, the chromosome aberration data on each survivor scatter quite widely when regressed on the individual DS86 doses. This statistical "overdispersion" could be attributable to two possible sources of error, one physical and the other biological. The former includes errors in the physical estimation of the DS86 dose itself and in the interview information regarding location and shielding conditions ATB. The latter includes possible differences in radioresponse among individuals due to genetic factors, age ATB, sex, and life-style, including smoking habits, for example. To estimate the relative contributions of these possible confounding factors, it has long been considered desirable to estimate dose using another biodosimetric marker independent of the cytogenetic results.

The frequency of mutations in somatic cells was once considered a good candidate, and several assays were investigated by the Department of Radiobiology to see if they could serve as alternative biodosimetric tools. However, among some five different assays, only the glycophorin A (GPA) assay in erythrocytes can detect exposures to radiation that occurred several decades earlier. Furthermore, the overdispersion of mutant frequency is even greater than that seen in the chromosome data, most likely due to a "jackpot-type" event (an occasional large "payoff-type" event) stemming from the relatively small number of bone marrow stem cells (the target cells for mutation by radiation exposure revealed by the GPA assay) which are actively producing mature red blood cells. Thus, the erythrocyte-based GPA mutation assay does not seem capable of serving as an alternative tool for biodosimetry on individuals.

Electron spin resonance (ESR) to detect radicals in tooth enamel has been used by a number of laboratories as another indicator of past radiation exposure. Since installation of ESR equipment in the cytogenetics laboratory (January 1995), 100 teeth selected from over 300 samples donated during the past nearly 10 years have been examined. The results show a close association with the cytogenetic data from the tooth donors, and the ESR method appears to be a promising alternative means to estimate individual doses, which in turn supports the cytogenetic data on the survivors. Since ESR can be applied only to extracted teeth whereas chromosome tests require only 1 to 2 ml of blood that can be readily obtained from most of the survivors, ESR cannot supplant cytogenetic tests but serves to reemphasize the value of the latter.

Major research activities in the next five years

A. Core activities

Priority 1

A-1. FISH examination of Hiroshima and Nagasaki survivors (RP 8-93):

A recent summary of the cytogenetic data on over 2000 survivors revealed two important issues with respect to the accuracy of the dose estimates based on physical grounds.

First, the dose-response relationship for Nagasaki survivors exposed in factories was unusually shallow, only one-half as steep as that for the survivors exposed in Japanese houses. This implies that the DS86 system overestimated the doses of these workers. Second, among the survivors exposed in Japanese houses, the dose responses were similar in both cities, but the Hiroshima curve is consistently above the Nagasaki one, suggesting the possibility of a small systematic error in the calculation of the DS86 doses. However, because the conventional staining method used in cytogenetic studies is known to be affected by observer bias (the Hiroshima and Nagasaki survivors were examined separately in the two laboratories by different investigators), we need to confirm these findings using FISH, the most objective method of scoring stable-type chromosome aberrations. This will be undertaken in the Hiroshima laboratory exclusively.

In 1994, collection of blood samples began with the aim of applying the FISH technique to about 200 survivors a year for five years. In 1995, the sampling scheme was extended to include an additional 200 survivors of specific interest (for example, tooth donors for ESR, carriers of clonal chromosomal aberrations, and mothers of the in utero exposed). Further extension is planned in the near future to maximize sampling of those survivors who were below 20 years of age ATB and have DS86 doses of about 0.5 Gy or more. (The total number of subjects will be about 1,500.)

The motivation for this large scale survey comes from our recent finding, based on tooth enamel ESR and the cytogenetic data on the tooth donors, that the cytogenetic data are closely related to the real radiation dose. To document the apparently higher proclivity of the youngest cohort to develop excess cancers, evaluation of biases in DS86 dose estimates is critical and only cytogenetic data can provide the necessary information. For this purpose, information on middle to high dose survivors is important not only because they have the higher risks for cancer but also the fraction of LSS cohort members with such doses included in the AHS is larger (the fraction is 85% for those with DS86 doses of above 1 Gy).

B. Special research activities

Priority 1

B-1. Characterization of the ESR assay (RP 1-92):

Because the ESR assay is rather new, laboratory techniques differ in the various steps of the assay procedure. Creation of international guidelines for standardization of the assay is in progress, and we are eager to compare our technique with that of others to reduce possible laboratory-specific errors in estimating the dose. The major advantage of the ESR assay is that the measurement itself is not destructive and the same specimen can be repeatedly measured. ESR results for the first 100 tooth samples along with the cytogenetic data on the tooth donors will be published in 1997.

We propose to examine an additional 100 teeth in the future and to couple this examination with the FISH technique using lymphocytes from the tooth donors to strengthen the current results. At the same time, tooth collection will continue.

B-2. Clonal chromosome aberrations (RP 8-93):

In the past studies using conventional staining methods, some 20 survivors were identified who carry identical chromosome changes in 3 or more lymphocytes, defined as clonal aberrations. A priori, clonal expansion can occur in two ways. Either the stem cells proliferated extensively and produced a large number of progeny or the mature lymphocytes proliferated after being stimulated by certain antigen(s). In the former case, clonal aberrations are expected to be seen mainly in naive T cells ($CD45RA^+$), whereas in the latter case, mainly in memory T cells ($CD45RO^+$). Studies using separated lymphocytes ($CD45RA^+$ or $CD45RO^+$) are in progress and results will be obtained within 2 years.

Depending upon the findings, further detailed examinations (for example, $CD4^+$ vs $CD8^+$ lymphocytes) may be necessary. This research will be performed in collaboration with the Department of Radiobiology.

B-3. FISH examination of exposed parent(s) in the F_1 molecular genetics study sample (RP 8-93):

We now know that the DS86 dose estimates contain potentially systematic errors. Because the molecular genetics study sample is a small subsample of the AHS cohort, and a considerable fraction of the high dose survivors in Nagasaki consists of factory workers whose DS86 doses seem to be overestimated, it would be prudent to examine the exposed parent(s) with assigned DS86 doses above a certain level (say, 1 Gy) for the chromosome aberration frequency of lymphocytes to validate their gonadal doses. Because most of the exposed parents are in the AHS, they will be included in the routine FISH examination and the total number of parents examined will be about 200. This study will require at least one AHS examination cycle (two years) or possibly two (four years), and the participation of the Departments of Clinical Studies.

B-4. Detailed comparison of ESR dose with DS86 dose (RP 1-92):

The 100 tooth samples that have been examined by ESR were derived from 69 survivors. The ESR estimated tooth dose and DS86 kerma dose show a positive correlation, but considerable variation exists. In some cases, the chromosome data and the ESR data fit one another closely but deviate substantially from the DS86 estimates. As previously said, these discrepancies are likely to be due to errors in the information on survivor location ATB and are most likely unrelated to errors in the program designed to compute the DS86 dose. It would be useful to scrutinize the relationships among ESR dose, cytogenetic information, and DS86 dose in the remaining cases so that consistent deviations related to shielding conditions and other factors can be detected.

Priority 2

B-5. Scrutiny of ESR and DS86 doses for tooth donors (RP 1-92):

As mentioned in the previous section, ESR data are the first physical measurements of

gamma dose on individual survivors, and they should be carefully compared with the DS86 estimates. In 1995, Dean C. Kaul (SAIC) expressed an interest in the DS86 dose information on the tooth donors. A collaborative program with SAIC would be valuable if the necessary internal administrative agreements can be reached.

B-6. Domain structure of chromosomes in interphase nuclei (RP 8-93):

Brenner's hypothesis states that the ratio of interchromosomal versus intrachromosomal aberrations, termed the F-value, decreases from over 10 to nearly 5 as the LET of radiation increases. Current data, both in vivo and in vitro, obtained in the Cytogenetics Laboratory do not seem compatible with this hypothesis. There is no evidence that "the majority of the effective dose received by individuals in Hiroshima ... came from neutrons" as described by Brenner (1996), but the most recent tooth enamel ESR versus translocation data show that the majority of the cytogenetic effects are due to gamma-ray exposure.

Because the hypothesis is derived from the domain structure of chromosomes in interphase nuclei, several approaches from independent angles should be helpful to understand the issue. For example, do reciprocal translocations occur randomly among chromosomes? Do inactive X chromosomes in females undergo translocation less frequently? Are translocation breakpoints distributed homogeneously throughout a chromosome arm? Most of these questions can be answered by careful analysis of data presently available (both by G-band and FISH), and no extensive new experiments are required.

B-7. Research on genetic instability

Recent studies, both in vivo and in vitro, suggest that radiation exposure causes genetic instability in cells. We plan two approaches. One is to carefully examine previously collected G-band data to see if cells which have undergone a chromosomal change have an increased chance of having a second change. Second, if radiation exposure can cause instability which lasts for the lifetime of the individual, the frequency of unstable aberrations (dicentrics) would be expected to increase with dose. Scrutiny of the previously collected large set of cytogenetic data based on conventional staining procedures should provide an answer to this.

B-8. Assessment of errors in the DS86 system

As previously stated, recent ESR results on tooth enamel revealed that the ESR estimated dose more closely correlates with chromosome aberration data on the tooth donors than DS86 estimates. This finding along with in vitro studies indicate that chromosome data are good measures of the true dose. The extensive body of cytogenetic data collected in the past should be reviewed to estimate the distribution of true dose at different levels of DS86 dose.

Cytogenetic studies of the children of the survivors

Using conventional staining methods, an extensive cytogenetic survey was conducted in the past involving nearly 16,000 F_1 persons (8,000 born to exposed parent(s) and 8,000 to the unexposed). The results showed only one de novo autosomal mutation in each group, although not all of the parents of aberration-carrying individuals could be cytogenetically examined. Thus, no evidence of a radiation effect on the germ cells has been observed so far.

Major research activities in the next five years

Priority 1

C-1. Examination of EBV-transformed B-cell lines by the G-banding method

Because the previously used conventional staining method can detect only gross structural changes and is not suitable for detecting small deletions, it will be necessary to apply the G-banding method which can detect small changes.

EBV-transformed B-cell lines established from trios of families for molecular genetic studies in the Laboratory of Biochemical Genetics would be an appropriate source of materials, both in terms of sample size, estimated gonadal dose, and availability of cells from the parents. The work will require 3 to 4 years.

Priority 2

C-2. Development of FISH using a single probe

One application of the FISH technique is mapping using a single gene probe or a probe for a specific DNA segment. In the future, in the Laboratory of Biochemical Genetics, we anticipate that mutant genes will be detected using molecular analysis of the children born to the survivors. FISH mapping of the mutated gene would be useful in characterizing the mutation.

Project time lines (Cytogenetics)

Fiscal Year	1997	1998	1999	2000	2001
1. FISH examination of survivors	⇒	⇒	⇒	⇒	⇒
2. FISH by a single probe	⇒	⇒			
3. Chromosome domain structure	⇒	⇒			
4. Genetic instability	⇒	⇒			
5. Assessment of DS86 errors	⇒	⇒			

Biochemical Genetics Program

The primary objective of the biochemical genetics program is to determine whether an increase in mutations measurable at the molecular level has occurred in the children born to A-bomb exposed parents in Hiroshima and Nagasaki.

Past and recent accomplishments

Extensive studies of the children of the survivors of the atomic bombings of Hiroshima and Nagasaki, using various endpoints such as untoward pregnancy outcomes, mortality, chromosome aberrations, and gene mutations screened at the protein level, have thus far yielded no statistically significant increases in genetic effects compared to a control population.

Because it is important to determine the mutation rate induced by radiation in this unique population, detecting mutations at the DNA level has been explored in a feasibility study. Establishment of cell lines from parent-child trios was recommended by the Genetic Study Conference held in 1984. It is anticipated that immortalized B-lymphocyte cell lines from 1000 families, one-half of them from a proximally exposed parent(s), will be maintained at RERF. Cell lines from 800 families composed of 1600 parents having DS86 estimates and 1200 children are now in the cell bank. This is the largest properly selected population in the world for the detection of radiation effects on human germline mutations. The Human Germline Mutagenesis Workshop held in 1991 recommended starting a pilot study using 100 families (50 exposed and 50 control families), a subsample of the 800 families, to compare various types of DNA as potential targets for the detection of germinal mutations with various techniques, because there was no information about the genes sensitive to radiation-induced mutagenesis. In keeping with this recommendation, microsatellites, minisatellites and various functional single-copy sequences in 124 children and both parents of the 100 families have been examined to determine whether deletion/insertion/rearrangement (D/I/R) type mutations or mutations causing other types of quantitative changes, all commonly produced by radiation, as well as nucleotide substitutions, exist at higher frequency in the children of the exposed parents.

Preliminary studies have failed to reveal a significant difference between the children of the exposed and the control parents in the mutation rates at the microsatellite and the minisatellite loci, both of which are repetitive sequences dispersed through the human genome.

We have developed two techniques to screen for D/I/R type mutations in single-copy sequences. One is the quantitative measurement of intensities of chemiluminescent bands on Southern filters and the other is the two-dimensional electrophoresis (2-DE) of DNA digests followed by a quantitative image analysis of ^{32}P-labeled spots. Each technique can detect a 50% decrease or increase in band intensity or spot intensity that is derived from the D/I/R events on the totality of a single allele. Thus, these techniques are suitable to detect a fresh D/I/R type mutation because a fresh mutation would usually be detected in a heterozygote for a normal and a variant allele.

Major research activities in the next five years

A. Core activities

Priority 1

A-1. Pilot studies for the detection of D/I/R type mutations

In addition to the original 100 families, a new set of 100 families (50 exposed and 50

control families) will be selected and screened for mutations at the minisatellite loci during the first two years. It is important to use a larger body of data to confirm our preliminary results, which showed no effect of A-bomb radiation on genetic instability at the minisatellite loci in human germ cells obtained from the original 100 families, including children derived from 65 exposed gametes with a mean dose of 1.9 Sv. We have assumed that the 65 gametes received, on average, the doubling dose estimated by Neel et al. (1990)), namely, 1.7-2.2 Sv. For a locus with a spontaneous mutation rate of 0.02 per gamete, which is the mean mutation rate of the six minisatellite loci examined in the previous study, using standard power function statistics (a Type I error of 0.05 and a Type II error of 0.2), we calculate that we would need to survey two samples (exposed and unexposed) of 1,188 germ cells each to observe a significant difference at the 0.05 level.

By examining 60 children from an additional 50 exposed families, each one of them having one exposed parent and the mean gonadal dose of the parent being 1.9 Sv, it is anticipated that we can examine the required number of alleles for each sample. Dubrova et al. reported that mutation rates at minisatellite loci in 79 children of parents who lived in heavily polluted areas of Belarus after the Chernobyl accident were twice that of 105 control children from the United Kingdom although the estimated individual dose from external and internal chronic exposure to ^{137}Cs of inhabitants of those areas was less than 5 mSv per year. By comparing their data with our new data based on the projected additional sampling, it may be possible to determine whether there is a difference in the biological effects of radiation between acute external exposure and chronic internal exposure.

The pilot study for the screening of D/I/R mutations will be carried out with the quantitative measurement of intensities of chemiluminescent bands on Southern filters on two hundred families (the original 100 families and the new 100 families). Probes to be used are DNA fragments from the human counterparts of the seven mouse specific loci, other genes located nearby, and genes supposedly related to common chronic diseases such as hypertension, diabetes mellitus and hereditary nonpolyposis colorectal cancer (HNPCC).

The 2-DE technique will be used in the pilot study. DNA samples from the 200 families will be examined using this technique after digestion with three sets of restriction enzymes, that is, NotI/EcoRV-HinfI (NotI/EcoRV and HinfI being used before and after the first dimensional electrophoresis, respectively), NotI/EcoRV-PvuII and NotI/EcoRV/PvuII-HinfI, products of each set of enzymes being different from those produced with the other two sets of enzymes. These three kinds of DNA digests labeled with ^{32}P from one individual will be electrophoresed separately, and the resulting three gels will be quantitatively analyzed. A total of 2000 spots (fragments) will be suitable for the detection of the D/I/R type mutations among 6000 spots (fragments) visualized on the three autoradiograms from the three gels. With the current research design (2000 diploid fragments scored on three gels per individual), 5 mutations would be detected in 120 children from 100 control families, if we assume that the spontaneous mutation rate is 1×10^{-5}/fragment/generation.

Image analysis is an essential part of any 2-DE study of DNA fragments, and this will

require support of the Information Technology Department (ITD) in the rewriting of the 2-DE software developed at the University of Michigan and currently in use in the Department of Genetics. This software was developed for older computer operating systems and cannot be readily used with the system upgrades that have occurred and that are contemplated in future computer system upgrades at RERF. In addition, to organize the data from the various DNA examinations and perform analyses, support from the ITD and the Department of Statistics will be required.

Physical localization of mutant genes and their normal counterparts will be carried out using the FISH technique in collaboration with the Cytogenetics Laboratory. To understand the characteristics (physical nature and functional effects) of new mutations, not only molecular biological data but also physical data are essential.

In each of the 100 exposed families, at least one parent belongs to the most heavily exposed group among the approximately 400 exposed parents on whom permanent cell lines have been established. Therefore, if the mutation rate detected in the children of the exposed group is significantly higher than that in the children of the control group, and the efficiency of the technique we propose is sufficiently high to warrant screening a larger number of samples, the study will be expanded to determine the dose response relationship. However, if there is no significant difference in the mutation rates between the two groups or the efficiency of the technique is too low, the study will not be continued and new methods will be introduced or developed.

A-2. Culture of permanent lymphocyte cell lines as sources of biological samples for the study of germ cell mutations

Initially, families for this program were selected on the basis of T65DR doses since the DS86 system did not exist when the original selections were made. Some of the cell lines already established are from families including parents whose DS86 doses are unavailable. New families where parental DS86 doses exist will be selected and cell lines will be established keeping the original goal of 1000 families in mind. This means we shall try to add 200 families in Hiroshima and Nagasaki over the next two years.

In the beginning of the pilot study for the detection of mutations, DNA extracted from cell lines established from members of the 100 families, a subsample of the 1000 families of the cell-line project, was used. However, recently, in order not to exhaust the cell lines, portions of the cell lines have been proliferated and the resulting "re-cultured cell lines" have been used for routine purposes. For the additional new 100 families to be examined in the pilot study, "re-cultured cell lines" will be produced and they will be used as sources of DNA.

B. Special research activities

Priority 1

B-1. A feasibility study on the ascertainment of disease and disability among offspring of the survivors (Feasibility of F_1 health study)

The Blue Ribbon Panel urged that consideration be given to the feasibility of studying diseases and disabilities of late onset among the offspring (F_1 generation) of the survivors. A protocol for the feasibility study has been written. It includes a mail questionnaire survey for a total of 82,000 F_1 (F_1 Mortality Sample and the so-called BGS Extension Samples), physical examination of approximately 500 F_1 (F_1 reporting chronic illness and those not doing so) in the Departments of Clinical Studies, and analyses of genes related to common diseases such as hypertension and diabetes mellitus in approximately 50 F_1. It is anticipated that it will take two years to complete the study. As soon as the results of the feasibility study are obtained, a workshop will be held to determine whether a full-scale study is practical and warranted. This feasibility study will be carried out as a collaborative undertaking involving the Departments of Clinical Studies, Epidemiology, Statistics and Genetics.

B-2. Assessment of detectability of germ cell mutations by the 2-DE technique (Detectability of mutations by 2-DE: Approved by Chief of Research Donald Harkness on 14 March 1995)

A pilot study, which was begun in 1996 for the assessment of detectability of the 2-DE technique of radiation-induced germ cell mutations in mammals, will be continued for one more year. DNA samples from 100 control mice (BALB/c) and from two groups of 100 F_1 mice, one derived from spermatogonia irradiated with 3 Gy and the other from spermatogonia irradiated with 5 Gy, are being examined with the 2-DE technique after digestion with two sets of restriction enzymes (NotI/EcoRV-HinfI and NotI/EcoRV-PvuII). The search for D/I/R type mutations that result in spots with 50% decreased intensity at the normal positions among 1000 spots on a gel are being carried out using quantitative image analysis. Among DNA samples from 43 F_1 mice of 5 Gy irradiated male parents, examined in 1996, one mutation was detected. Results of the study will provide basic information for the estimation of the number of children of A-bomb survivors that should be examined in order to obtain statistically significant results.

B-3. Pilot study to evaluate various markers in potential candidate genes associated with hypertension. (Pilot study for the hypertension markers)

Suggestive radiation-related increases in cardiovascular disease incidence and the prevalence of aortic arch calcification and systolic hypertension have been reported. The Blue Ribbon Panel states that further studies are required to confirm a real association between radiation exposure and atherosclerosis. This indicates the importance of studying at the molecular level the hypertension observed in the AHS population. A protocol is being prepared for a pilot study to evaluate several markers in potential candidate genes associated with hypertension. Some 100 individuals each from the normal group and the hypertension group, defined by the 1993 WHO/ISH classification among the participants of the AHS, will be examined for their polymorphic markers in several candidate genes. DNA will be extracted from lymphocytes in the blood samples obtained in the biennial physical examination conducted at the Departments of Clinical Studies. Because some AHS participants with hypertension are parents of the cell line project for the germinal mutation study, family studies for the potential markers associated with hypertension can be carried out if the need arises.

Project time lines (Biochemical Genetics)

Project	1996	1997	1998	1999	2000	2001
Feasibility for F_1-health study		⇒	⇒			
Detectability of mutations by 2-DE	⇒	⇒				
Pilot study for the hypertension markers		⇒	⇒			

Personnel Requirements (Department of Genetics)

Fiscal Year	1996	1997	1998	1999	2000	2001
Research Scientists						
Cytogenetics	5	5	5	5	5	5
Biochem. Genet.	4+0.5[1]	5	5	5	5	5
Technicians						
Cytogenetics	5	6	6	6	6	6
Biochem. Genet.	11[2]	12	12	12	12	12
Clerks						
Cytogenetics	1	1	2	2	2	2
Biochem. Genet.	2.2[3]	3	3	3	3	3

[1] One visiting scientist (Dr. Murakami) is concurrently assigned to the Departments of Genetics (50%) and Clinical Studies (50%). Her employment as a permanent research scientist is required.
[2] One young technician retired at the end of FY95 and no replacement has been made.
[3] One clerk is assigned to the Department of Genetics (20%) and the Publication & Documentation Center (80%).

Space requirements (m^2) (Department of Genetics)

Fiscal Year	1996	1997	1998	1999	2000	2001
Bench Research						
Cytogenetics	146.2	146.2	146.2	146.2	146.2	146.2
Biochem. Genet.	402[1]	442	442	442	442	442
Support Space						
Offices cytogenetics	73.2	83.2[2]	83.2	83.2	83.2	83.2
Biochem. Genet.[3]	100	100	100	100	100	100
Slide Storage(Cytogenetics)	7.3	17.3[4,5]	17.3	17.3	17.3	17.3
Storage Space(Biochem Genet.)..	23	23	23	23	23	23
Total						
Cytogenetics	226.7	246.7	246	246.7	246.7	246.7
Biochem. Genetics.	525	565	565	565	565	565
Grand Total	751.7	811.7	811.7	811.7	811.7	811.7

[1] Some corridor space where various research equipment, refrigerators and incubators are installed for daily use is included.
[2] Computer space (+10 m^2).
[3] Space used for image analysis of the 2-DE gels and other types of gel analyses is included.
[4] Nagasaki slide storage (+10 m^2).
[5] Space for liquid nitrogen tanks, deep freezers and glassware for experiments.

Equipment Budget (× ¥ 1,000)

Fiscal Year		1997	1998	1999	2000	2001
Equipment						
Routine	Laboratory[1]	2,149	3,695	4,789	0	0
Replacement	Computer[1]	2,641	326	1,127	1,116	2,929
	Computer[2]	421	326	560	588	533
Routine New	Computer[1]	2,200	850	890	930	490
	Computer[2,3]	600	150	155	160	50
Major New Acquisitions/Repl.		13,000[4,5]	5,000[6]	22,880[7]	0	0
Total		21,011	10,347	30,381	2,794	4,002
Lab Supplies/Reagents[8]		24,000	26,400	28,800	31,200	33,600

[1] Laboratory and computer equipment for research purpose. For computer, 80% of the cost for hardware and 50% of that for software are included in this category.
[2] Equipment for administrative/service-related. For computer, 20% of the cost for hardware and 50% of that for software are included in this category.
[3] All new hard disks are for research purposes.
[4] Software for 2-DE Analysis (¥10,000,000): For 2-DE analysis, the software developed at the University of Michigan has been used. It was developed for older computers and cannot be readily used with the upgrades that have occurred. If a computer scientist outside of the RERF rewrites the program, the estimated cost is about ¥10,000,000.
[5] Pulsed Field Gel Electrophoresis Apparatus (¥3,000,000): DNA digests are electrophoresed by this apparatus for the detection of deletion mutations in DNA by quantitation of band-intensity on a Southern filter. One of the two apparatuses which we have been using for these 8 years is broken and cannot be repaired because the parts are unavailable. A new apparatus is essential to the continuation of our research.
[6] Photon camera (¥5,000,000): For the quantification of the intensity of chemiluminescent bands on a Southern filter and for the detection of deletion mutations, images of the bands on the filter are taken by photon camera. The sensitivity to photons of the camera we have been using for the past 5 years is decreasing. The old camera should be replaced by a new one.
[7] Bio-Imaging Analyzer with Imaging Plates and Cassettes (¥22,880,000): In the 2-DE analysis, the spot pattern on a gel is visualized by making an autoradiogram which requires at least two weeks or more. This will be a big problem in the screening for mutations using the 2-DE technique. By using this image analyzer, the problem will be solved and the accuracy of the measurement of spot intensity will be much improved because it has high sensitivity for radioactivity.
[8] A 10% yearly increase is included.

Department of Radiobiology

The Department of Radiobiology came into existence in August 1985 at the time of the

reorganization of the Foundation's Department of Pathology. The primary objectives of the department are to determine the late effects of exposure to ionizing radiation on immune system function, on somatic cell mutation and altered gene expression; on cell survival and transformation; and to maintain serum and tissue resources for epidemiological, histo-pathological, and radiobiological investigations.

Recent achievements

The Department of Radiobiology has conducted research in three areas, namely, immunology, somatic mutation, and molecular oncology. Recent achievements in these areas can be summarized as follows:

a). The immunologic studies have revealed that among atomic-bomb survivors immune function, such as mitogen and alloantigen responsiveness of T-cells, lymphocyte subpopulation numbers, and anti-Epstein-Barr virus immunity, is still compromised fifty years after the atomic bombings.

b). The department has established various mutation assays, namely, the HPRT, HLA, Fcγ RIII, TCR, and GPA assays, and applied these to ascertain radiation doses among atomic bomb survivors and to estimate the risk of cancer development. These studies have shown that the somatic mutation frequency at the glycophorin A locus increases with increasing dose of A-bomb radiation, suggesting that various diseases among the A-bomb survivors, including cancer, develop in part from genetic alterations induced by radiation.

c). The molecular oncology/epidemiology study was initiated six years ago to elucidate possible unique molecular finger prints in cancers among A-bomb survivors. Technical problems in using formalin-fixed paraffin-embedded samples from the A-bomb survivors have been resolved. The molecular analyses of liver cancer and skin cancer are on going.

In addition to the above mentioned studies, new research areas have been opened up to understand the precise mechanisms of radiation-induced damage, which might be important in cancer development. It is now evident that alterations of cancer-specific genes, such as RET oncogene activation and BCR-ABL translocation, can be induced by radiation.

Program objectives

The survivors of the atomic bombings represent a population of individuals who have been exposed to a wide range of doses of ionizing radiation; therefore, the primary objective of RERF has been to ascertain the effects that might have been produced in the exposed individuals and their children as a result of exposure to A-bomb radiation, and to relate these changes to dose and to the subsequent health effects which may have occurred. Consequently, until recently, research at RERF has focused primarily on the long-term epidemiological studies of A-bomb survivors to ascertain morbidity and mortality of the exposed population, specific investigations on health-related effects that might be related to radiation exposure, and genetic studies to ascertain the mutation rate resulting from radiation exposure in the children of the survivors but clearly there is a need for molecular and cellular studies aimed at revealing the underlying bases of this morbidity and mortality. It is thus important to bear in mind that if the Foundation is to achieve

its goals it must necessarily maintain a balance between mechanistic studies aimed at understanding the biological bases of radiation-induced changes and the statistical description of risk. It behooves the Foundation, therefore, to establish a credible and strong program in molecular and cellular research if the biological origin of radiation-related damage is to be understood.

Accordingly, the mission of the Department of Radiobiology is to study the molecular mechanisms of radiation-induced carcinogenesis in A-bomb survivors. We also believe that it is our mission to clarify what the biological effects of radiation are on human health and why and how disease is induced as a consequent process.

Major projects in the next five years.

In the coming 5 years, as we explain in the next several pages, some current studies will be phased out, others will be continued, and new ones will be introduced. The determination of the fate of these studies will be based on their relevance to several factors. Simultaneously the department will concentrate its energy on three major core activities, namely, molecular epidemiology, molecular oncology, and immunology.

The studies will be prioritized by the direct impact they are projected to have on these three core fields. That is, the highest priority studies will be the ones that can potentially produce supportive evidence for the radiogenic etiology of diseases occurring in the A-bomb survivors via damage of key molecules and their pathways.

A. Molecular epidemiology

A major objective of the molecular epidemiological study is to identify radiation-induced gene alterations in cancer and normal tissues of A-bomb survivors, and thereby to provide significant insights into the molecular mechanisms of human radiation carcinogenesis and disease development. To accomplish this goal, we will analyze cancer-associated genes such as oncogenes and tumor suppressor genes in archival and surgical specimens of normal and tumor tissues obtained from A-bomb survivors.

Molecular epidemiology at RERF combines powerful data analysis methods for revealing trends in disease development among the A-bomb survivors with state-of-the-art techniques in molecular biology. Such a partnership of disciplines can produce the first line of attack for understanding the mechanisms behind the observed human diseases following exposure to the A-bomb radiation. There are now many epidemiological studies demonstrating an effect of the A-bomb on the survivors; and with these results are hypotheses that try to explain them. For example one belief is that cancer incidence is heightened among the exposed because the radiation inflicted damage to the DNA of cells led to the loss of function of some crucial genes that controlled growth. But what are these genes? In which tissues are they most affected? Why does sex, age ATB, dose of exposure make a difference? There are no clear answers to these and many other questions. Generation of some of these answers may help in the treatment and prevention of diseases in numerous groups such as other radiation exposed people, chemically exposed people, and cancer patients, as well as in the A-bomb population. But study of the A-bomb survivor population, because of its size and because it and its tissues have been so well catalogued

and followed up for nearly a lifetime, will provide the best opportunities for such analyses.

The large repository of archival tissues makes possible extensive retrospective molecular epidemiological studies. As indicated in the following table, high priority studies will include those cases showing the highest relative risk with sufficient number of high dose, histologically verified samples such as the female breast, thyroid, and skin. Because analysis of these cancers, given that 33 of 43, 12 of 17, and 15 of 22 breast, thyroid, and skin cancers, respectively, are due to radiation, have the highest probability of producing the most statistically significant difference between the exposed and control groups.

Estimation of the cancer cases due to radiation

Cancer site	ERR 1 Sv	0.01 - 0.99 Sv			1.0 Sv			
		mean dose	No. of cases	Fraction of cases due to radiation	mean dose	No. of cases	Fraction of cases due to radiation	HV (%)
Female Breast	1.6	0.18	252	0.22	2.01	43	0.76	96.7
Thyroid	1.2	0.17	115	0.16	1.83	17	0.69	93.3
Skin	1.0	0.18	76	0.15	2.22	22	0.69	96.4
Bladder	1.0	0.16	108	0.14	1.63	7	0.62	82.9
Ovary	0.99	0.16	60	0.14	1.65	6	0.62	84.2
Colon	0.72	0.16	201	0.10	1.63	22	0.54	80.7
Liver	0.49	0.16	262	0.07	1.72	22	0.46	38.8
Stomach	0.32	0.16	1227	0.05	1.71	80	0.35	72.8
Prostate	0.29	0.16	56	0.04	1.61	5	0.32	85.7

HV: Histological verifications; Mabuchi, et al., RERF CR3-91; Thompson, et al., RERF TR5-92

Core activities (Molecular epidemiology)

A-1. Oncogenes and tumor suppressor genes in A-bomb survivors with cancer (RP 7-92, 3-93, 7-93, 2-94):

Cancer development is believed to be a multi-step process. The steps are not known but major roles appear to be played by oncogenes and tumor suppressor genes. The former act to accelerate cell growth and the latter to suppress it. Radiation can potentially damage either or both which can lead to uncontrolled growth -- a hallmark of cancer. Such damage is presumed to be the key in the increased risk of various cancers in the survivors. One especially important gene to study is p53 because it is the most commonly mutated gene in human cancers suggesting that it is a major player in multi-step carcinogenesis. Differences in the frequencies of mutations or types of mutation between the exposed and unexposed are anticipated.

A-2. Tissue collection

The success of such studies depends heavily on our ability to obtain appropriate samples

from LSS cohort members who are diagnosed with cancer. It is possible to obtain archival material through the tissue registries in Hiroshima and Nagasaki; however better methods are needed to ensure the availability of the necessary materials from newly diagnosed cases. To achieve this end RERF is seeking support from the local medical community for the establishment of a community-wide tissue/DNA bank in Hiroshima. This bank would maintain tissue specimens or preserved DNA that could serve as a resource for all groups in Hiroshima engaged in studies of the molecular mechanisms of carcinogenesis.

Tissues to be collected will have to have an associated RP describing their use. Once the collected tissue samples are registered in the "tissue bank", they will be available for use internally or by outside collaborators. Registration will include entry of the tissues into a database that will catalogue and link them to relevant RERF cohorts.

A-3. Molecular analyses

The usefulness of preserved tissue specimens from A-bomb survivors has been demonstrated by means of the PCR method. PCR is a method for the amplification of DNA by over a million-fold. Thus PCR makes it possible to study the genes of A-bomb survivor using microscopic quantities of archival tissues from as far back as 1950.

A-3-1. *Skin cancer (RP3-93):*

We have already prepared DNA from 60 tissue samples of skin cancer and are currently analyzing the ras and p53 genes. We will continue this analysis and start an analysis of the patched gene, which has been cloned and found to be frequently mutated in skin cancer.

A-3-2. *Liver cancer (RP2-94):*

In addition to skin cancer, molecular analyses of liver cancer (total sample number is 800) are on going. Currently studies of mutation in the p53 tumor suppressor gene and genomic integration of the hepatitis B and C viruses are being carried out. It may take two more years to complete these analyses.

A-3-3. Thyroid cancer (RP7-93):

Thyroid cancer should also be analyzed at the molecular level since it is among the cancers with the highest risk seen in the A-bomb survivors, implying that this cancer may be one of the best candidates for the identification of an A-bomb radiation-induced unique fingerprint, if such exists. Thyroid samples will be analyzed for aberrations in RET by immunohistochemistry using monoclonal antibodies against the RET proteins, which is not expressed in normal thyroid tissues.

A-3-4. Female breast cancer (RP7-92):

Breast cancer has one of the highest increased risks in the survivors. The risk is even higher for those survivors exposed at a young age with an ERR at 1 Sv of 3.21 and 2.61

for age ATB of 0 - 9 years and 10 - 19 years, respectively. Moreover, breast cancer is a potential familial cancer that may predispose some women to radiogenic breast malignancies. These studies will be complemented by research on the genetic background of cancer patients among the A-bomb survivors (see special research activity B). BRCA1 and 2 have so far shown the best prospects as genes in the cause of the disease.

Breast samples will be screened for BRCA1 mutations by immunohistochemistry since antibodies to detect mutations are commercially available.

A-5-5. Others

Salivary cancer is another important candidate for analysis at the molecular level, since it has been revealed recently that the ERR is 3.47 at 1 Sv which makes it the highest risk cancer among the survivors. Specific salivary gland cancer related genes are currently unknown. At present p53 may be the best candidate.

Special research activities (Molecular epidemiology)

Priority 1

B. Genetic background of cancer patients among A-bomb survivors

It is suspected that certain genetic backgrounds may be involved in radiation carcinogenesis. The genes involved in some cancer prone diseases, such as those associated with the recessively inherited ataxia telangiectasia (AT) and the dominantly inherited hereditary non-polyposis colon cancer (HNPCC), in which individuals who possess abnormalities in these genes have high susceptibility to radiation damage and high genetic instability, will be surveyed to define the involvement of genetic background in cancer development among A-bomb survivors.

Individuals who were exposed at young ATB and developed early breast cancer will have priority in the survey of such gene mutations. A strong association has been reported between radiation-induced chromosomal damage and breast cancer in cells from AT heterozygotes, and thus peripheral lymphocytes would seem a logical starting point in this screening activity. Screening will be done using available antibodies for the ATM and BRCA1 gene products. Suspect cases will then be molecularly analyzed at the gene level by sequencing. The total number of cases to be initially screened will be 200 breast cancer patients among the survivors. If mutations are detected, family members will be tested. This study will be an interdepartmental collaboration with the Departments of Clinical Studies, Epidemiology and Statistics.

Priority 2

C. Molecular analyses of non-cancer diseases in A-bomb survivors

Epidemiological studies are beginning to reveal increased risks in various non-cancer diseases such as myoma uteri, atherosclerosis and hyperparathyroidism among the A-

bomb survivors. It is expected that this trend will increase with the aging of the survivor population. As the target genes become evident, molecular analyses will be required to illuminate the mechanisms.

C-1. Parathyroid disease

In parathyroid disease one candidate gene is PRAD1. PRAD1 is a mutant gene caused by a translocation of a gene associated with a cell growth regulating factor and the gene that regulates parathyroid stimulating hormone expression. This will be a cooperative study with the Department of Clinical Studies.

C-2. Atherosclerosis

In atherosclerosis one possibility is the ras oncogene. Screening will be conducted by immunohistochemistry. This study will be in collaboration with the Department of Clinical Studies.

B. Molecular Oncology

Molecular oncology is closely related to molecular epidemiology. Whereas the latter produces trends of molecular changes in radiogenic cancers, the former provides the explanation or mechanism for how these changes work to cause cancer. Such results will supply the direct evidence for the carcinogenic effect of A-bomb exposure on the survivors. Knowledge of the mechanism will allow improved management of exposure to ionizing radiation as well as provide information in the treatment and prevention of related diseases.

As stated earlier, molecular epidemiology will provide much of the basis for other molecular studies. To delve deeper into the mechanisms, more manipulative experiments will be necessary. Manipulations will include working with live human cells from the A-bomb survivors, other human populations, and with human tissues in animal models, in that order of priority. Live cells are necessary to recreate as accurately as possible the events and responses of the cells in the survivors after A-bomb exposure. In the light of recent advances and the relatively large radiation effects for breast and thyroid cancer, studies of tissues from breast and thyroid cancer cases among the high dose survivors have the potential to yield important results. It may also be useful to supplement the search for characteristic gene alterations in cancer cells with a search for evidence of specific mutations associated with cancer development in the blood of cancer-free survivors.

The Blue Ribbon panel emphasized the necessity to determine the shape of the dose-response curve for radiation carcinogenesis at low doses of radiation. The recommendation suggested initiation of a molecular oncological study to clarify the molecular mechanisms in human radiation carcinogenesis.

Core activities (Molecular oncology)

A. Alterations in cancer-associated genes among A-bomb survivors

It was observed in the recent somatic mutation study that the GPA mutation frequencies increased with increasing A-bomb radiation doses, and the dose-response curve is very similar to that for solid tumor incidence among the A-bomb survivors. We can expect that since radiation may cause DNA damage randomly in the cell, cancer-related gene alteration could have been induced and remained in the cells of the A-bomb survivors. Based on the multi-step carcinogenesis theory, it may be suspected that cells carrying cancer-related gene alterations and proteins exist in blood cells among the A-bomb survivors.

A-1. Detection of the cells carrying mutations

Recent advances in flow cytometry make it possible to analyze translocation of cancer-associated genes by in-cell PCR methods using fluorescent primers. BCR-ABL and Bcl2 translocations are both associated with blood malignancies and can be detected in peripheral blood lymphocytes by this method.

Newly developed antibodies against oncogenes and tumor suppressor gene products will be used to detect cells carrying cancer-associated gene alterations in the blood among A-bomb survivors. This technique can demonstrate the existence of mutant gene products or changes in levels of normal gene products which may be especially pertinent in cases of deletion of tumor suppressor genes like p53 and possibly the ataxia telangiectasia mutated (ATM) gene. The projected number of samples to be studied is a 300 (control and high risk group). These approaches could provide meaningful information for understanding the molecular mechanisms of human radiation carcinogenesis and cancer risk estimation.

Special research activities (Molecular oncology)

Priority 1

B. Human radiation carcinogenesis (RP 18-81):

Strategically, not only are studies directly looking at tissues from the A-bomb survivors important, but studies taking advantage of experimental models could be very helpful in interpreting effects on the survivors. In the experimental system we have developed, we can examine the first and consequent events occurring in the cell at the cellular and molecular levels which may have crucial roles in human carcinogenesis.

B-1. Models

The severe combined immunodeficient (SCID) mouse-human chimera makes it possible to study radiation effects on humans in vivo, and thereby provide more relevant and meaningful information than those obtained in vitro or from other non-human animal models. We have already established a transplantation system of normal human tissues (skin, intestine, thyroid and bone marrow) to SCID mice which preserves in situ histology, structure and function. These models will be improved so that they are as close to the human situation as possible and will be applied to the studies on radiation response (see

B-2) and radiation carcinogenesis (see B-3) described below.

B-2. Radiation Response

We will analyze cellular and molecular changes in human tissue/cell after radiation exposure, especially at low doses. This system will enable us to follow the various molecular changes in vivo in human tissues following irradiation. For example, this model demonstrated the dose-response and cellular mechanism of human radiation-induced epilation, which were not clear from the survivor study. Preliminary findings using the SCID-hu intestine model suggest that human crypt stem cells in the intestine are extremely resistant to radiation-induced apoptosis in comparison to mouse stem cells.

B-3. Radiation Carcinogenesis

The approach will make possible studying the process of carcinogenesis at the molecular level and to specify radiation specific gene alterations which induced cancers in the A-bomb survivors.

B-3-1. Thyroid cancer

We established a model of SCID-hu mice with human thyroid tissue, in which the normal histological features of the human thyroid can be maintained in the mammary fat pads of SCID mice for as long as 1 year. Using this model we will attempt to induce thyroid cancer by radiation. Preliminary data indicate that high-dose X-irradiation induces RET inversions in thyroid grafts, which have often been observed in the thyroid papillary cancers and the childhood thyroid cancer of Chernobyl victims. Furthermore, since the RET inversions were found to be sustained as long as 3 months in the grafts, we will follow-up the development of thyroid cancer in the SCID-hu mice.

B-3-2. Skin cancer

We have already established a SCID-hu mouse model for the analysis of human epilation by implanting human skin. This model will also be applied to human radiation-induced carcinogenesis. This project, unlike the thyroid study where no other laboratory has successfully maintained human tissues in SCID, can be a collaboration with outside researchers such as Professor Taisei Nomura of Osaka University, because his laboratory was the first to succeed with a SCID-hu skin model.

Priority 1

C. Radiation-susceptibility of somatic cells in radiation carcinogenesis (RP 7-87):

It is still unclear whether interindividual variation exists in the susceptibility to radiation, especially in radiation carcinogenesis. Individual variation in susceptibility to radiation carcinogenesis is believed to be partly due to a difference in cellular responses to ionizing radiation.

For analysis of interindividual variation in cellular responses, we will establish assay systems using molecular and flow cytometric techniques for the quantitative analysis of radiation-induced physiological and biochemical changes in key molecules responsible for cell apoptosis, signal transduction, and cell cycle regulation such as in ATP, oxygen radicals and protein phosphorylation.

These measurements will be used to evaluate interindividual variation in 100 non-cancer and 100 cancer patients among A-bomb survivors with the same exposure dose. This will be a collaborative effort with the Departments of Clinical Study, Epidemiology and Statistics.

C. Immunology

A major objective of the immunological study is to demonstrate the late effects of A-bomb radiation exposure and the combined effect of radiation exposure, age and sex on the hematolymphoid system and to identify the relationship between altered immune function and radiation-related disease, especially cancer. A-bomb radiation-induced alterations in the immune system may have caused the development of cancer. To achieve this objective we plan to continue our studies of the features and mechanisms of radiation-induced disorders in the hematolymphoid system at the cellular and molecular levels. These studies include radiation effects on the distribution of T-cell subsets in the survivors and of radiation effects on endocrine and hematopoietic growth factor levels. The survey of immune functions in A-bomb survivors will contribute to the health monitoring of the survivors.

Core activities (Immunology)

A. Disorders in the hematolymphoid system of A-bomb survivors (RP 3-87, 7-89, 2-90, 1-93):

The functionality of the hematolymphoid system is a key measure of the ability of A-bomb survivors to respond to infectious disease. Abnormalities in this system also lead to carcinogenesis and autoimmune disease. Aging, sex and radiation exposure affect immune competence, altering lymphocyte subsets in their number and in their differential responsiveness when challenged by various stimuli. Therefore, study of the hematolymphoid system is crucial to assessing the radiation-induced effects that may affect the long-term health of the survivors.

A-1. T-cell (RP 3-87, 1-93):

Since our previous studies demonstrated age-related dysfunctions of T cells in the high dose exposed, we should focus on the cellular and molecular mechanisms of disorders in T-cell differentiation and function. One of the approaches is the analysis of T-cell receptor (TCR) repertoire in A-bomb survivors, which is currently underway and will be finished within FY96. Another approach is to analyze helper T-cell differentiation into two functionally different subsets, Th1 and Th2, which are believed to have different roles in immunity to pathogens and malignant cells. Th1 helper T cells are mainly involved in cellular immunity; whereas Th2 cells are involved in humoral immunity. Our hypothesis

is that the balance between these two subsets is altered in the exposed. These subsets will be analyzed for about 1,000 Hiroshima survivors by flow cytometry using fluorescence-labeled antibodies to interferon gamma and Interleukin (IL)-4 which are specifically expressed in Th1 and Th2 cells, respectively. This study will take about 3 years. Expression of cytokines and other functional molecules in T-cells will be analyzed at the single cell level by using a combination of PCR and cell sorting techniques, which have been established in our department.

A-2. B-cell and stem cell (RP 3-87, 7-89):

As previously reported, white-blood cell production including B-lymphopoiesis is significantly increased with radiation dose, especially in female survivors. We have also observed a dose-dependent increase in hematopoietic stem cell functions in female A-bomb survivors. Based on these findings, we should focus on the analysis of the molecular mechanism of radiation-associated hyperfunctions of hematopoietic stem cells. We will measure some hematopoietic factors such as stem cell growth factor and IL-6, both associated with white-blood cell production and B-lymphopoiesis. It has been suggested by previous mouse studies that the endocrine system such as sex hormones (estrogen) is involved in the control mechanism of hematopoiesis. It was proposed that the decreased level of estrogen after menopause enhances the production of interleukin 6 and osteoclasts and thereby causes osteoporosis in female. Based on these findings, we will compare the onsets of menopause and these hematopoietic growth factors for about 500 female survivors. This will take about 2 years. This study will be in collaboration with the Department of Clinical Studies.

A-3. Blood cell preservation (RP 2-90):

To ensure that appropriate materials will be available for future studies of the late effects of exposure to A-bomb radiation, and to allow the exploitation of potential future technological advances and scientific discoveries, we are cryopreserving live blood cells from AHS participants in Hiroshima and Nagasaki. From 1990 to 1996, (3 AHS cycles), lymphocytes and granulocytes from 4,420 Hiroshima and 3,766 Nagasaki survivors were cryopreserved. We will continue this effort to complete all AHS participants. In the near future, retrospective study of immunological functions using these cryopreserved materials will be possible for the survivors who eventually develop cancer or other disease.

Special research activities (Immunology)

Priority 1

B. Clonal expansion (RP 3-87, 7-89, 1-93):

B-1. Mutant stem cells

After the atomic bombing, the number of hematopoietic stem cells decreased by cell killing and bone marrow death occurred in many survivors. Several months after the bombing the number of these cells should have returned to the normal level. Clonal expansion of

stem cells should have been involved in this recovery process in many survivors. We will focus our efforts on clonal expansion of hematopoietic stem cells carrying mutations and chromosome aberrations. So far two such cases have been documented by mutation and cytogenetic markers; further study is needed to illustrate that clonal expansion occurs as a result of A-bomb exposure. We will survey such cases using somatic mutations in blood cells (T-cells and granulocytes) as a marker. Stem cell expansion will also be analyzed at the molecular level for $CD34^+$ cells isolated from survivors' peripheral blood by a cell sorter. This work will be in collaboration with the Cytogenetics Laboratory.

B-2. Memory T cells

It has been reported that the frequency of abnormal expansion of memory T-cells increases with aging and this may be related to immunological aging and disease development. Abnormal expansion of memory T-cell clones in the periphery has also been observed in A-bomb survivors and this may be reflected in the radiation-induced T-cell dysfunctions mentioned above (see A-1). We have already screened about 1,000 survivors for their TCR repertoire and found about 50 who demonstrated abnormal expansion of T cells with a unique TCR V alpha or beta family. We will attempt to clarify the molecular mechanisms of clonal expansion of T-cells for these 50 survivors by using molecular biological methods such as single cell PCR.

Priority 1

C. Immunity to tumor-associated viruses in A-bomb survivors

Immunity to tumor-associated viruses in A-bomb survivors is one of the issues to be addressed for understanding interactive causality of radiation exposure and virus infections in cancer development. Radiation-induced alterations in tumor virus immunity might have induced some virus-related cancers in A-bomb survivors.

C-1. Hepatitis C virus (HCV)

Cell-mediated and humoral immune reactions to hepatitis C virus (HCV), which is believed to be directly involved in the development of hepatocellular carcinoma, might be altered in the exposed. In fact, our preliminary study on liver cancer of A-bomb survivors suggests that the integration rate of HCV increased with dose. Proliferative response and killer cell activity of T-cells against a mixture of virus-derived peptides or whole viral proteins will be measured for about 1,000 A-bomb survivors including about 20 HCV carriers in 4 years. This will be a collaborative effort with the Departments of Clinical Studies and Epidemiology and will be an extension of the molecular epidemiology based study of HCC (see core activity A-2-2) in the A-bomb survivors.

C-2. Epstein-Barr Virus (EBV)

The Epstein Barr virus (EBV) is another candidate to be studied because our previous study demonstrated a dose-dependent increase in the level of anti-EBV antibodies. Recent reports suggest the possible involvement of EBV infection in stomach cancer

development. Therefore, alteration of immunity against EBV in the survivors may be related to radiation-induced stomach carcinogenesis. We will measure lymphocyte response against whole EBV in culture for the same subjects as in the HCV studies. Recently developed PCR methods for measuring the frequency of EBV-infected B-lymphocytes in peripheral blood will also be applied in these 1,000 subjects.

Priority 2

D. Somatic mutations (RP 7-88):

As mentioned in the response to the recommendations of the Blue Ribbon Panel, the somatic mutation studies seem to have reached a logical end, because many of the somatic mutation assays are not particularly valuable dosimeters for A-bomb survivors. However, since many scientists still request RERF to measure mutation frequencies in exposed people, maintenance of the mutation assays, albeit at a much reduced level, is necessary for international collaborations. Also, these assays are useful in the assessment of various aspects of aging and cancer risk.

D-1. Follow up study (RP 7-88):

We will follow-up cancer incidence and life span for the survivors (n=2,000), whose GPA mutation frequencies have been measured to determine the relationship between somatic mutation and cancer risk or aging. This study will be carried out at a lesser effort than in the past.

Priority 3

E. Immunity to oncogene products in A-bomb survivors

Recent progress in tumor immunology allows us to assess lymphocyte reactivity to the products of cancer-associated genes such as p53 and ras. Such tumor specific immunity of T-cells may be disordered in the exposed. Proliferative response of T-cells against a mixture of peptide fragments of p53 gene products will be measured for about 1,000 A-bomb survivors, the same subjects as in HCV studies for 4 years. Furthermore, we will explore natural killer cell functions to autologous mutant cells lacking the expression of a single HLA class I allele as a model for natural immunity to transformed cells at an early stage of cancer development.

F. Somatic mutations among the in-utero exposed A-bomb survivors

As yet only a very limited amount of information on the occurrence of somatic mutations among the in utero exposed is available and it is not clear whether they will or will not exhibit a greater sensitivity to ionizing radiation as reflected in an increased frequency of mutation in comparison with the exposed A-bomb survivors. It should be emphasized that, although the fraction of the in-utero exposed to more than 0.1 Sv is 13.9 % of the 3,289 RERF cohort (*in utero* mortality, Clinical, and LSS), it is important to ascertain whether the mutation frequencies are different from those of the exposed. This project

is expected to be finished within four years.

Molecular and cellular biology is a rapidly moving field which requires constant upgrading of technique. For the department of Radiobiology to maintain pace with the rest of the scientific world, new methods of analysis have to be developed as well as introduced.

Establishment of in-cell PCR will allow careful scrutiny of individual cells for studying EBV integration frequency or Bcl2 and BCR-ABL translocation in blood samples, for example. Differential display is a potentially powerful technique that may reveal differences in transcription of various genes between tumor and normal cells. The tumor and normal parts of archival tissue sections can be separated and compared for changes that may have occurred in cancer related genes as a result of A-bomb exposure. A similar comparison technique is comparative genomic hybridization (CGH) which can scan the entire genome for possible changes, such as relatively large (10^7 bp) deletions, in cancer DNA versus normal DNA.

The introduction of new technologies is also important as new problems arise. After arrival of the new confocal microscope system, we will be able to study various new facets of radiation effects on cellular function and cellular structure. New studies that can be initiated are alterations of signal transduction in radiation induced tumors or molecular analysis of a single or a few cells from surgical and paraffin embedded archival tissues of the survivors. Such abilities will help to increase sensitivity and resolution for detection of changes in tissue samples.

Finally, it should be noted that most of the studies in the Department of Radiobiology cannot be performed without collaboration with the Departments of Clinical Studies, Genetics, Epidemiology, and Statistics. In view of RERF's limited resources it is important for us to develop a general research plan that defines specific projects that can be done at RERF and projects on which collaboration is important and establishes mechanisms for seeking this collaboration and, where necessary, support.

Project time lines

	1997	1998	1999	2000	2001
a) Genetic background	⇒	⇒	⇒	⇒	⇒
b) Non-cancer diseases			⇒	⇒	⇒
c) Human carcinogenesis	⇒	⇒	⇒	⇒	⇒
d) Susceptibility to radiation	⇒	⇒	⇒	⇒	⇒
e) Clonal expansion	⇒	⇒	⇒		
f) Viral immunity	⇒	⇒	⇒	⇒	
g) Somatic mutations	⇒	⇒	⇒	⇒	⇒
h) Immunity to oncogene products		⇒	⇒	⇒	⇒
I) Somatic mutation in-utero	⇒	⇒	⇒	⇒	

Personnel requirements

The present staff is barely adequate to conduct the studies in radiobiology outlined above.

In order to perform the studies, the following are needed;

1. a permanent researcher who can conduct molecular and pathological analysis of cancer is essential for molecular epidemiology because identification of tumors is the *sine qua non* of the study.

2. allocation of the proper support staff to the molecular epidemiology program for tissue collection.

Fiscal Year	Present	1997	1998	1999	2000	2001
Research Associates						
Immunology	5	5	4	4	4	4
Molecular epidemiology and oncology	5	6	7	7	8	8
Technicians						
Immunology	10	7	7	5	5	5
Molecular epidemiology and oncology	3	7	8	10	10	10
Technician helpers	2	2	2	2	1	1
Clerks	5	5	4	4	4	4
Total	30	32	32	32	32	32

Space requirements (m^2)

Fiscal Year	(1996)	1997	1998	1999	2000	2001
Bench Research						
Immunology	292	292	292	292	292	292
Molecular epidemiology and oncology	91	200	200	200	200	200
Support Space and Offices	97	157	157	157	157	157

Room G105 (temporarily used by the department of radiobiology; $53m^2$) is not included.

Equipment budget

See Annex J.

Department of Statistics

The Department of Statistics provides expertise to all of the other research departments in the matter of study design, data analysis, and the construction of databases.

Program objectives

The Department of Statistics plays an important role in virtually all RERF research activities. Collaboration and the provision of guidance on statistical analyses and data management to researchers throughout RERF is a major function of the Department of Statistics. An equally important activity of RERF statisticians involves methodological research aimed at improved understanding of the statistical questions raised by the RERF data and the development and implementation of improved statistical methods for analyses of the broad range of data arising from RERF studies. The Department is also playing a leading role in the design of modern databases to make the RERF data more accessible to all RERF researchers. Finally, the Department of Statistics is responsible for management of the dosimetry data and the computation of individual dose estimates.

Major research activities in the next five years

A. Core activities

The core research and analysis activities carried out by the Department of Statistics focus largely on the need for continued analysis and improved presentation of the RERF epidemiological, clinical, and laboratory data. In addition to direct collaborations with other RERF researchers, RERF statisticians are actively involved in research that leads to the development and implementation of statistical methods applicable to the RERF data.

Preparation of the RERF reports on the epidemiologic follow-up of the survivors and their children require significant contributions from both the Departments of Epidemiology and Statistics. As a consequence of the need for more sophisticated statistical analyses and a shortage of epidemiologists, statisticians have taken increasingly central roles in work on LSS reports and other epidemiological studies at RERF. Because of staff reductions in the Department of Statistics we have had to devote an increased proportion of our resources to the epidemiological studies, which has made it difficult for us to address the statistical needs of RERF's clinical and laboratory programs. Over the next few years it will be necessary to maintain (or even slightly increase) our current level of support for the epidemiologic studies, but it is especially important for us to provide a greater level of support for the statistical needs of RERF's clinical and laboratory research programs.

It should be stressed that the work of the department is largely determined by the nature of statistical issues that arise in the course of RERF research. Thus, other than stating that RERF research will continue to be a source of interesting and challenging statistical problems it is difficult to make specific predictions about future statistical research at RERF.

Priority 1

A-1 *Assessment of mortality and cancer morbidity for the LSS, in-utero, and F_1 cohorts*

A significant portion of the work of RERF statisticians is concerned with ongoing analyses of the LSS follow-up data. This work is carried out in close collaboration with members of the Departments of Epidemiology. Over the next year we plan to complete the final

part of LSS Report 12 dealing with noncancer mortality for the period from 1950 through 1990. Within the next three years we intend to produce general summary reports extending mortality data through 1995 and tumor registry-based cancer incidence data through at least 1992. In preparing these updated reports we hope to develop methods for merging the mortality and incidence reports. Members of the in-utero and F_1 cohorts are now reaching ages at which mortality and cancer incidence rates increase markedly. A series of reports on mortality and cancer morbidity among the in-utero exposed will be completed in the coming year. Work on similar reports for the F_1 cohort is underway. It is likely that the in-utero findings will be updated during the coming five years since the number of deaths and cancer cases can be expected to increase rapidly with the lengthening follow-up.

RERF statisticians are also taking a leading role in the analysis and preparation of the reports on cancer risks based on the results of detailed site-specific pathology reviews, including those of the central nervous system (CNS tumors), liver cancer, and thyroid cancer. An important part of the department's work on these studies concerns the development of standards for the management of data arising from these site-specific studies in order to ensure that the findings are reflected in the tumor registry and are available for use in future analyses.

While RERF statisticians, together with members of the Departments of Epidemiology, plan, carry out and report the results of the analyses of these data, the statisticians' most important contributions concern the development and application of analytical methods and software needed to analyze and summarize these data and the development of procedures to address specific problems which arise in the course of work with the RERF data. These problems include: the development of a general class of statistical models that can be used for the description of and inference about patterns in the excess relative risks and excess absolute rates associated with radiation exposure; methods for the joint analysis of site-specific risk data; the development of procedures to adjust for biases in risk estimates caused by random errors in individual dose estimates; development of methods to determine the impact of death certificate misclassification on cancer and noncancer risk estimates; the development of methods to adjust for the impact of migration in analyses of the LSS cancer incidence data; statistical issues related to RBE estimation from the LSS data; and the development and application of "mechanistic" models for radiation carcinogenesis.

As noted below, an effort is now underway to incorporate the data obtained from the various mail surveys into the RERF research database. As this effort progresses it will become possible to make more effective use of these data in analyses of confounding and effect modification in RERF's epidemiological studies.

A-2 *Analysis of Clinical Studies Data*

The clinical data are an important and underutilized RERF resource. The Department of Statistics role in making more effective use of these data includes the application of recent developments in the analysis of complex longitudinal data sets to the RERF data and the development of more effective ways to store and access these data. While some progress

on analysis of these data has been made in recent years, there is a need to devote more of the departmental resources to the issues related to the clinical data. An area of particular importance over the next few years concerns studies that integrate the epidemiological and clinical data related to the finding of an association between radiation exposure and noncancer mortality. These analyses will undoubtedly lead to challenging statistical problems.

A-3 *Analyses of Laboratory Data*

The investigations carried out by the staff of the Departments of Genetics and Radiobiology often require statistical collaboration for planning and analysis. At the present time statisticians are actively involved in comprehensive final analyses of the conventional chromosome aberration data, assessment of the data on various somatic mutation assays, and the provision of advice and support for a broad range of fairly routine statistical analyses carried out by the researchers in the laboratories. Analyses of the laboratory data present a number of challenging statistical problems including issues related to over-dispersion (due to dosimetry error or unmeasured covariates) and correlated data. Over the next few years there will be a need for significant additional statistical support for the analyses of the 2-DE DNA study data (pattern recognition), for the planning and analysis of molecular epidemiological studies, and for work on the comparison of various potential biodosimeters.

A-4 *Database development*

The Department of Statistics has taken a leading role in the design and documentation of the new RERF research database. While the ITD is responsible for the actual implementation of the database, much of the design work involves issues of direct concern to the Department of Statistics. These issues include clarification of study population definitions, specification of contents of and relationships between individual database tables, and the identification of appropriate data sources, and, in some cases, the development of new coding schemes for specific items. At the present time the RERF research database includes most of the epidemiological follow-up data and basic dosimetry data for the major cohorts. Current efforts are focused primarily on the integration of the mail survey, clinical follow-up data, laboratory data and detailed dosimetric data (including shielding history and acute effects data), into the RERF research database.

A-5 *Dosimetry* (Work on dosimetry is covered by RP 18-59, *Shielding Survey and Dosimetry Study.*)

The Department of Statistics is responsible for management of the basic dosimetry data and for the computation of dose estimates for individual survivors. Current work includes the development of an expanded roster of persons whose exposure status is of interest to RERF (in addition to LSS cohort members, this roster includes mothers of in-utero cohort members and parents of F_1 cohort members) and the restructuring of the shielding history and acute effects data. As a part of this effort we are also working on an updated description of cohort definitions and dose estimation procedures. In the decade since the introduction of DS86 a number of questions have been raised about certain aspects of

current survivor dose estimates (including errors in Hiroshima neutron estimates, problems with gamma doses levels in both cities, and possible biases in estimated doses for Nagasaki factory workers). RERF has been asked to develop and maintain a database related to physical measurements as a part of the ongoing reassessment of DS86. It now appears likely that this reassessment will lead to the introduction of a new dosimetry system within the next five years. Even though current efforts to reorganize RERF's basic dosimetric data will make it easier to implement a new dosimetry system, the introduction of the new system will still require significant effort on the part of staff from the Department of Statistics and the ITD.

B. Special research activities

Most of the work of the Department of Statistics arises from projects undertaken in relationship to our core activities which revolve around collaborations with researchers from other departments. At this time there are only five time-limited special research projects and one outside contract for which the department has primary responsibility. While the department will continue to deal with new statistical problems that arise in the course of work related to our core activities, there is little likelihood that department members will initiate new research protocol-based projects in the coming years.

Priority 2

B-1 *Blood groups in Adult Health Study and in-utero ATB subjects, Hiroshima and Nagasaki (RP 63-63):*

The study is intended to examine blood group frequencies in the LSS and to investigate the relationship between serological type and mortality or morbidity for selected diseases. Following a long period of inactivity, a manuscript describing blood group frequencies for members of the AHS and F_1 cohorts has been prepared. Over the next two years we hope to work with members of the Departments of Clinical Studies to plan and conduct analyses of the relationship between blood group and cause-specific mortality.

B-2 *Cancer studies of occupational and environmental radiation exposure in the Mayak Nuclear Facility and the surrounding areas in the South Urals, Russia (NIH Contract N01-CP-51025, Principal Investigators: Preston DL, Mabuchi K, Koshurnkova NA, Kossenko MM).*

When the extent of radioactive contamination at the Mayak Nuclear Facility and the surrounding area became clear, the Foundation was approached to assist in the design and implementation of studies to determine the health consequences of exposure to this contamination. This contract supports joint work with the US National Cancer Institute and scientists at the Branch Laboratory 1 (Ozersk) and the Urals Research Center for Radiation Medicine (Chelyabinsk) in the Russian Federation on improvements to the epidemiological follow-up data risk estimation procedures for the Russian studies. It is hoped that by the end of this three year contract in September 1998 we will be able to complete some solid cancer and leukemia risk assessments for the Mayak worker and Techa River populations. During the first year of the contract, significant progress has

been made on improvements in the quality of the follow-up data for these cohorts. A paper describing the nature of the Techa River cohort just prior to the beginning of the NCI-RERF collaboration including comparison of the demographics of the LSS and Techa River cohorts has been completed.

Priority 3

B-3 *Radiation effects on the brain and central nervous system (RP 5-87 and RP 8-89).*

One of these studies is intended to search for physical evidence of radiation-related damage to the brain among in-utero survivors (RP 5-87) based on magnetic resonance imaging of a small number of in-utero survivors. The second (RP 8-89) was to make use of autopsy material to investigate the late effects of A-bomb exposure on aging of the central nervous system and to obtain basic data which would improve understanding of the anatomic and functional brain changes that may have resulted from atomic bomb exposure. There has been no significant activity associated with either of these projects for several years. Without the active involvement of physicians, pathologists and others responsible for obtaining the cooperation of the in-utero survivors for the first study or the specimens required for the second, these studies cannot continue. With the retirement of the Assistant Department Chief, Masanori Otake, earlier this year, no one at RERF is actively involved in either of these projects. It is unlikely that there will be any progress on either of these projects in the next five years. In view of the current level of support for these projects and the needs of other projects, it would probably be best to terminate them.

Personnel requirements

The number of research scientist positions has decreased from 10 to 7 as a result of retirements and the general cutbacks that have taken place over the past few years without any diminution in the workload. It is likely that we will lose another statistician within the next few months. These losses have seriously reduced our ability to meet RERF's needs for statistical support in all areas, but particularly with regard to analysis of the clinical and laboratory data. Recently we have been able to take some steps to deal with the impact of these losses. These steps include recruiting (through NAS) one or two additional statisticians, seeking approval of the Executive Committee to hire an experienced statistician to work part time under contract on problems related to analysis of the AHS clinical and laboratory data, and contacting statisticians at various Japanese institutions to solicit support (and candidates) for post-doctoral training in the Department of Statistics. Prior efforts to recruit qualified Japanese statisticians have been only moderately productive and as a consequence the Department has had and continues to have a need for a high proportion of non-Japanese statisticians, who tend to turnover frequently. This turnover gives us the flexibility to seek statisticians who can meet current needs, but it also means that we need to have the ability to employ qualified statisticians in anticipation of all upcoming losses.

In view of the nature of the department's work the table below is designed to reflect personnel needs associated with each of the core activities.

Area	Fiscal Year					
	Current	1997	1998	1999	2000	2001
			Research Associates			
Epidemiologic Studies	3	3.5	3.5	4	4	4
Clinical Studies	1	2	2.5	2.75	2.75	2.75
Laboratory Studies	1	1.5	2	2.5	2.5	2.5
Database design	1	1	0.5	0.25	0.25	0.25
Dosimetry	1	1	1.5	0.5	0.5	0.5
Total	*7*	*9*	*10*	*10*	*10*	*10*
			Research Assistants			
Epidemiologic Studies	0.75	0.75	0.75	0.75	0.75	0.75
Clinical Studies	0.5	0.5	0.5	1	1	1
Laboratory Studies	0.25	0.25	0.5	0.5	0.75	0.75
Database design	1	1	0.75	0.5	0.25	0.25
Dosimetry	0.5	0.5	0.5	0.25	0.25	0.25
Total	*3*	*3*	*3*	*3*	*3*	*3*
Clerical	2	2	2	2	2	2

Space requirements (m^2)

The space requirements for the Department of Statistics are summarized in the following table. The totals do not include hallways.

Area	Fiscal Year					
	Current	1997	1998	1999	2000	2001
Office	125†	142	142	142	142	142
Clerical Support	18	18	18	18	18	18
Other Support ‡	57	40	40	40	40	40
Total	*200*	*200*	*200*	*200*	*200*	*200*

† in square meters

‡ Includes half of the area of the conference, computer, and copier rooms which are shared with the Department of Epidemiology and of the visiting scientists office, which is also shared with Epidemiology.

Equipment budget (x ¥ 1,000)

Computer hardware and software are the primary equipment used by the staff of the Department of Statistics. Because of the size and complexity of many RERF data sets it is important for the statisticians to have access to versatile and powerful computers. In preparing these budget estimates a three year schedule for the replacement of computers and a continuing need to expand network storage capacity have been assumed. It has also been assumed that it will be necessary to replace or upgrade other hardware and software on a continuing basis. It should be noted that, as in recent years, Department of Statistics computers that are replaced can usually be used by other departments with less demanding computational needs for additional years. The following table presents estimates of the total costs for computer equipment and software for the Department for the next five years.

	Fiscal Year				
Budget Category	1997	1998	1999	2000	2001
Replacement hardware and software	4,000	4,500	4,215	4,715	4,400
New hardware and software	1,075	775	1,195	875	1,275
Total	5,075	5,275	5,410	5,590	5,675

Since this hardware and software is used for both and administrative purposes, it seems reasonable to assume that some fraction of these costs should be considered as administrative rather than research expenses. Based on the recommendations formulated by the ITD, the following table shows the research portions of the estimated equipment budget.

	Fiscal Year				
Budget Category	1997	1998	1999	2000	2001
Replacement hardware and software	2,700	3,050	2,850	3,220	2,970
New hardware and software	950	650	1,040	720	1,110
Total	3,650	3,700	3,890	3,940	4,080

SUPPORTING SERVICES

Department of Information Technology

Program objectives

The Information Technology Department (ITD) provides the necessary computing and data tools to all RERF departments to support the Foundation's research and administrative activities. Responsibilities are to maintain computer systems and software, manage the RERF research database, provide user support, and introduce new technology as appropriate to meet evolving needs. Although located in Hiroshima, planning, development, and support work extends to the Nagasaki Laboratory, and ITD coordinates activities with the two Nagasaki computer staff in the Department of Epidemiology. ITD also is responsible for operation of the library in Hiroshima, another information service at RERF. The Hiroshima library provides support to the library in Nagasaki as well.

To ensure that computing resources remain relevant and to play a leading role in ascertaining technology and user support needs, a key aspect of ITD activities is to maintain effective liaison with all RERF departments. ITD also must seek collaboration to utilize the technical skills of staff in other departments and that outside RERF to complement and supplement technical capabilities within the department. These are extremely important for making effective progress on multidisciplinary projects such as those involving database design, systems development, and support of laboratory research projects.

Because many of the activities undertaken by ITD reflect its technical support role in research activities, ITD project content within some of the core activity categories will change as research program emphasis evolves and changes. Project content listed below represents known major foci within the upcoming five-year period.

A. Core activities

- *Maintain and keep current the RERF computing environment*

ITD is responsible for the management and maintenance of all personal computers, Unix workstations, disk and tape data storage, printers, scanners, and other peripheral equipment. Network design and support responsibilities include the TCP/IP Ethernet network that links all computing resources within the Hiroshima and Nagasaki laboratories, the communications line linking the two laboratories, and the communications line linking RERF to the Internet. ITD provides maintenance and support of all operating systems, application software, and Internet services for these computer systems. With an increased awareness of the role that computers can play in the workplace, demand for resources and support continues to rise in all departments as they seek ways to automate work activities and increase staff productivity, partially in response to coping with personnel downsizing that has occurred (and continues) at the Foundation. It also is anticipated that the research demand for these resources and services will continue to increase as new research techniques increasingly rely on interfacing computers with laboratory equipment to process data.

ITD staff play an active role in assessing new technology and its relevance to RERF activities. The introduction of new tools to users ensures that the most recent and appropriate technologies are available to enable researchers to work competitively in their research fields and ensures that the RERF computing environment will remain compatible with future computer technology.

The RERF computing system has expanded greatly over the past few years, both within the two laboratories and in terms of outside linkage via connection to the Internet and dial-in lines to RERF. Because all RERF departments now rely quite heavily on computing resources to carry out their work, it is important that efforts be undertaken to review and strengthen system security. This includes additional measures to guard against unauthorized access to the RERF system by outsiders, to maintain confidentiality both within and outside RERF of personal identification data on study participants, and to ensure that appropriate disaster prevention/recovery plans and procedures are in place. These are necessary to protect the unique repository of data accumulated during the existence of ABCC/RERF, minimize system down time, and minimize user productivity loss resulting from damage to equipment, software, and data.

- *Engage in design and implementation efforts for the RERF research database*

As indicated in the Database Development section within The Structure of Research at the Foundation, the installed hardware and software that now comprise the RERF distributed computing system has resulted in great progress in building a new research database using

modern relational database technology. This technology has made it much easier for researchers to access data, link information from different sources, and extract the desired items for analysis. The new system has simplified data flow procedures for much of the mortality and incidence data follow-up activities. This, together with the elimination of redundant data storage, has contributed to improved data quality. The database system also supports direct links with certain analysis software packages, eliminating the need to create interim work files for analysis. However, much work remains to ensure that the database will serve the wide array of research needs at RERF.

Of utmost importance over the next several years is continued development of a comprehensive picture of study participants by clarifying study populations and incorporating more information into the database. As described earlier, more detailed data related to the major cohorts, such as clinical data, mail surveys, and dosimetry will be added. Biological materials collected over the years are a valuable resource for current and future studies. It is important to create a centralized registry of these materials and link it to other study participant data so that these samples are efficiently and effectively shared and used by the different RERF research programs. It also will be important to address both the volume of data and special data management issues that are expected to arise from data generated from the Department of Genetics DNA studies. All database work is being undertaken as a joint effort of the ITD and the departments responsible for collecting and using the data. These efforts involve major input on design issues from the Departments of Statistics and Epidemiology.

Together with developmental activities, it is important to provide information and training that will ensure that researchers are aware of the capability of the system and how to use it. In addition, researchers must have adequate information about the data in order to use it properly. Thus, it also is important to make suitable documentation available on paper and on-line to meet that need. Together with the Departments of Statistics and Epidemiology, ITD will be working toward that end.

- *Develop and maintain application systems*

Application systems are developed, as necessary, to meet specific needs at RERF, but, as much as possible, they are developed using commercial software packages to minimize time- and labor-intensive custom programming and maintenance efforts.

ITD has developed and supported the Adult Health Study (AHS) patient tracking and clinical management system. The hardware and software for this system are over ten years old, and efforts already are underway to develop a replacement system that will be compatible with the new network and software used for all other RERF activities.

ITD developed and currently maintains a name matching system used by the Departments of Epidemiology for its follow-up activities. With this system, individual follow-up information received from outside sources is matched with RERF database records so that mortality and incidence data can be updated accordingly.

ITD provides support to the Department of Statistic management and maintenance of

dosimetry-related data and the system used for computing dose estimates for individual survivors. Increased support for this activity is anticipated because of the likelihood that dosimetry reassessment activities will result in implementation of a new dosimetry system.

A significant increase in programming and data management support will be needed for the Department of Genetics' two-dimensional electrophoresis image analysis of DNA fragments. This work will involve a joint effort among the Departments of Genetics, and Statistics, and ITD.

The development of a new business system has enabled most day-to-day business computing activities to be carried out by staff in the Secretariat. ITD staff continue to play an integral role in troubleshooting, maintenance, and, as necessary, providing some of the more complex enhancements that users are not able to implement on their own.

- *Expand training and information outreach for users*

The distributed computing environment has provided users with direct access to many powerful hardware and software tools. An effective program of training and information dissemination is essential to enable users to make optimal use of these tools. While important initial progress has been made, many important subject areas still need to be covered or further supplemented. Thus, additional emphasis is being placed on organizing additional training courses and information seminars. Planning, preparation of materials, and actual instruction must involve those most familiar with software to ensure training and content is effective and relevant for RERF users. ITD has adopted a multi-departmental approach to this activity and has received collaborative support of departments who have staff expertise in pertinent areas. This has been a very effective way to meet educational needs. The user response to training courses conducted thus far has been overwhelming. Training could be conducted more efficiently and timely if room space and equipment could be expanded to better accommodate participant demand.

ITD also disseminates information to users outside a class or seminar setting. With the recent elimination of RERF's in-house publishing capabilities, ITD uses email and plans to expand its use of the Intranet as a means to providing a greater amount of reference information and announcements in a timely manner.

- *Support expansion of RERF information dissemination to outside communities*

ITD is providing technical support to the Publication and Documentation Center in its use of the Internet World Wide Web to widen accessibility and visibility of RERF's research activities to the outside. The RERF Web pages recently were reorganized and expanded, and information on those pages addresses issues of interest to both the scientific community and the general public. To widen accessibility and to provide a faster and less expensive method of distribution, ITD is working on enhancements that will allow Web users to download RERF public data and documentation files already available on floppy disk, such as those used in analyses conducted for Life Span Study Report 12.

- *Maintain the RERF library and archive*

Much of the institutional memory regarding ABCC and RERF has been and continues to be lost due to the many retirements occurring. Although efforts to establish a centralized archive have been initiated by various groups in the past, currently there exists no institutional archive documenting historical decisions, procedures, and materials that bear significance to the unique activities of the institution and that provide important background perspectives to current research efforts. If RERF is to retain its history, it is important to renew efforts in establishing the archive. The first step would require that RERF obtain outside expertise to obtain guidance in the planning, database cataloging, and management of archives for research institutions. As information services, the library and archive activities ideally should be coordinated and integrated with each other.

Due to staff losses, it has become difficult for the library to keep pace with the work needed to provide journals and books to researchers in a timely fashion. Together with the need to investigate and introduce new services that will give researchers wider access to research information, this provides a strong basis for reassessing library activities. The aim should be to identify the services that researchers find essential to their work and to determine how the library can provide those services effectively. With this information, the Foundation can ascertain what the appropriate resources are in terms of equipment, services, and personnel to meet those needs. This process should include streamlining and modernizing in-house library activities and establishing additional links to outside services for more effective and efficient operation. It will be extremely important to supplement or replace current on-line services with those that provide continuous update of publication and other research reference materials. It would be helpful to seek outside expertise in recent library technology to guide the efforts of library staff. Collaborative support from ITD computing staff will be needed for library and archive efforts.

Personnel requirements

Over approximately the last two years, ITD has lost a total of 5 computer professional/technical staff. This represents a 40% and 60% loss, respectively, among the two fastest growing areas of demand, database management and systems administration. During this period, ITD workload has increased dramatically. With the transition from a mainframe to a distributed computing environment, computing resources have become an integral part of the Foundation infrastructure upon which research, support, and business activities depend. The amount of equipment and software that must be maintained and the demand for support and services continues to grow out of the need to remain competitive on the research front and to automate activities to cope with personnel downsizing occurring throughout the Foundation. The introduction of modern database technology has renewed efforts by both computer and scientific staff to re-examine and reorganize data, and to expand and document the new research database to increase accessibility and usability of data, much of which has never been fully utilized. All these efforts to support research have been hindered because of staff shortages. In other cases, such as providing support for 2-DE image analysis, ITD currently has no personnel resources to undertake application development requirements. Without further action, the situation will worsen rapidly, and many of the core activity needs will go unmet. The department chief will depart at the beginning of 1997, and another two staff will leave within the coming 12 months. Anticipated attrition by 1999 will leave only one-third the original computing staff from two years ago.

To deal with the situation, recruitment is underway through NAS for a department chief and systems administrators. To seek additional personnel and expertise, steps have been taken to explore collaborative and post-graduate research/training relationships with regional Japanese universities. Additional recruitment of experienced database management personnel and qualified Japanese computer technical staff is essential.

Although reassessment of the library has not yet been undertaken, it is evident that establishment of the archive and proper operation and maintenance of the library will require one additional staff for the combined library/archive. During full-scale development and cataloging phases for the archive, additional staff will be required, most likely on a temporary basis.

	Fiscal Year					
Area	Current	1997	1998	1999	2000	2001
Computer	13	16	18	19	19	19
Professional/Technical						
Library/Archives	2	3	3	3	3	3
Clerical Administrative	3	2	2	2	2	2
Total	18	21	23	24	24	24

Space requirements (m^2)

Estimates reflect space for new staff and for the assortment of computers and peripheral equipment in their immediate work area for development, testing, and troubleshooting activities. A small increase in support space is needed to guarantee that all computer servers are installed in a temperature-controlled, restricted access area for security purposes, and to permit use of a projection panel in the training room to provide effective instruction on methods and procedures. Initial archives work most likely can be accommodated in the existing library space. The increase indicated in future years assumes that methods and resources can be introduced that would enable the library to reorganize and economize how it uses its current space, so that once the archive is in the full implementation phase, additional space required to house those materials is minimized.

	Fiscal Year					
Area	Current	1997	1998	1999	2000	2001
Office	180	228	228	228	228	228
Clerical Administrative	31	31	31	31	31	31
Library/Archives	337	337	337	357	357	357
Other Support[1]	166	183	183	183	183	183
Total	714	779	779	799	799	799

[1] includes server, user training, diagnostic workbench, and conference rooms

Equipment budget (x ¥ 1,000)

In the table below, computer hardware and software used by ITD staff to carry out development and support work are distinguished from resources used to provide RERF-wide services to users. In order to perform development, testing, and technical support, it is necessary for ITD to have within the department a variety of equipment and software used in other departments. Estimates are based on a three year schedule for replacement of computers. A faster turnaround is built in for systems administrators, who must troubleshoot problems on new systems installed in other departments. Functional equipment rotated out of service will be used to help keep the training room current, moved to meet needs in other departments, and serve as emergency replacements to minimize down time on critical work activities. Also accounted for is the ongoing need to expand network storage capacity. In the area of RERF-wide services and resources, the regular upgrading and replacement of hardware and software are an essential aspect of maintaining a modern computer environment, ensuring that it keeps pace with future technology developments and provides state-of-the-art tools for research.

	Fiscal Year				
Budget category	1997	1998	1999	2000	2001
ITD staff					
Replacement hardware and software	7800	8520	9095	9095	9550
New hardware and software	1100	900	1155	945	1210
ITD staff total	*8900*	*9420*	*10250*	*10040*	*10760*
RERF-wide services					
Computer and networking hardware/software replacement	36000	36000	37800	37800	39700
Grand Total	44,900	45,420	48,050	47,840	50,460

+ Support fees that cover Unix workstation hardware maintenance contracts, annual software license fees, and network line lease fees are included in the Secretariat operations budget.

Publication and Documentation Center

Dissemination of the findings of the Foundation's research to the scientific and lay communities, nationally and internationally, is centered in the Publication and Documentation Center. Broadly stated, the duties of the Center are the following: editing, production, preservation and management of publications; translation and interpretation services.

Specific roles

(1). Preparation of technical reports on the results of RERF research and studies, and distribution of them to interested organizations as well as to researchers worldwide.

a). Administrative procedures for the review of research manuscripts up to publication thereof in journals; administrative support for research scientists by documentation

of research results and by preserving and making available to them research protocols, abstracts for scientific meeting presentation, and reprints.

b). Publication of English and Japanese Newsletters, annual reports, and bibliographies of publications; management of RERF's World Wide Web site.

c). Proofreading and editing of English manuscripts; translation and interpreting services requested by departments; preparation of figures, diagrams, and slides using computers; photographic activities

Organization (see the following page)

Personnel strength at PDC for the past six years and projection of changes

	Fiscal Years					
	1990	1991	1992	1993	1994	1995
Research	1	2	4	2	2	1
Clerical	30	25	26	28	27	25
Technical	1	0	0	0	0	0

PDC's operational requirements cannot be fulfilled if replacements for retiring employees are not employed. Continued operation at current level requires at least maintenance of the current personnel strength.

Radioisotope Facility

The duties of the RI Facility are 1) management of the facility in accordance with Japanese laws, 2) maintenance of a safe working environment, and 3) summarization and realization of requests from facility users. It should be noted that until recently the Foundation maintained two radioisotope facilities, one in Hiroshima and one in Nagasaki. With the closure of the radiobiology program in Nagasaki, the facility there was no longer needed and was placed on inactive status. It has not, however, been formally closed. Whether it should be closed or merely maintained in an inactive status hinges on two considerations, namely, future use and cost. If this facility should be needed in the future for RERF research purposes, it would be cheaper in the long run to continue to maintain it. At present, the annual maintenance costs are between ¥ 700,000-800,000 but this will diminish in the future. If the facility is formally closed, the space and equipment must be decontaminated in accordance with Japanese regulations. This has been estimated to cost ¥ 8,000,000. Formal closure would, of course, free the space for other uses, and this is an important consideration given the size of the Nagasaki Laboratory. As yet no decision has been made about the fate of this facility.

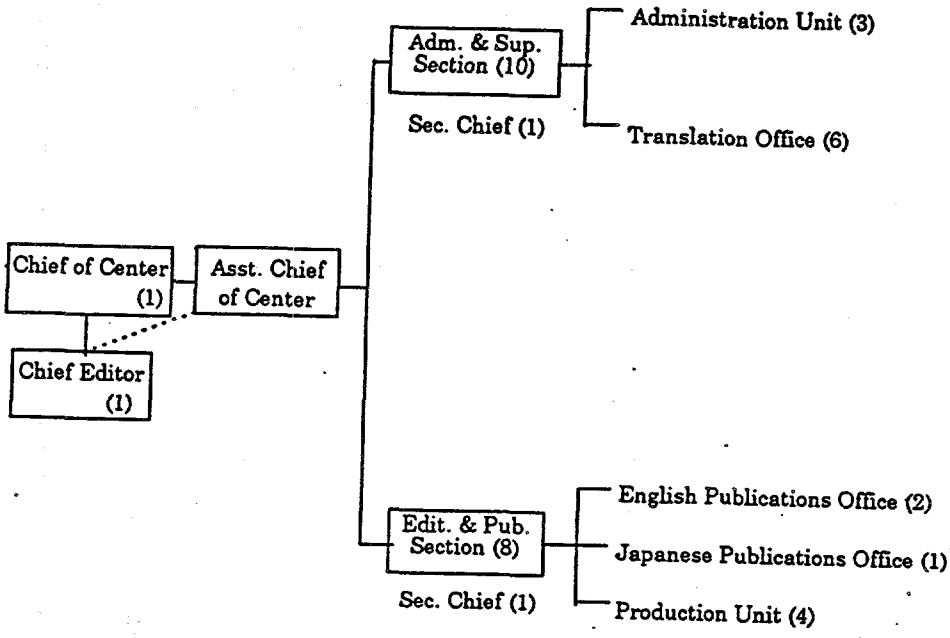
The remarks to follow pertain only to the Hiroshima facility.

Management of the RI facility

The RI Facility is being operated in accordance with various national laws. Detailed record-keeping on many aspects of the RI facility operation (e.g., measurements of air dose rate, concentration of RI in drainage, and the radiation dose to which the user is exposed) is mandated

Present

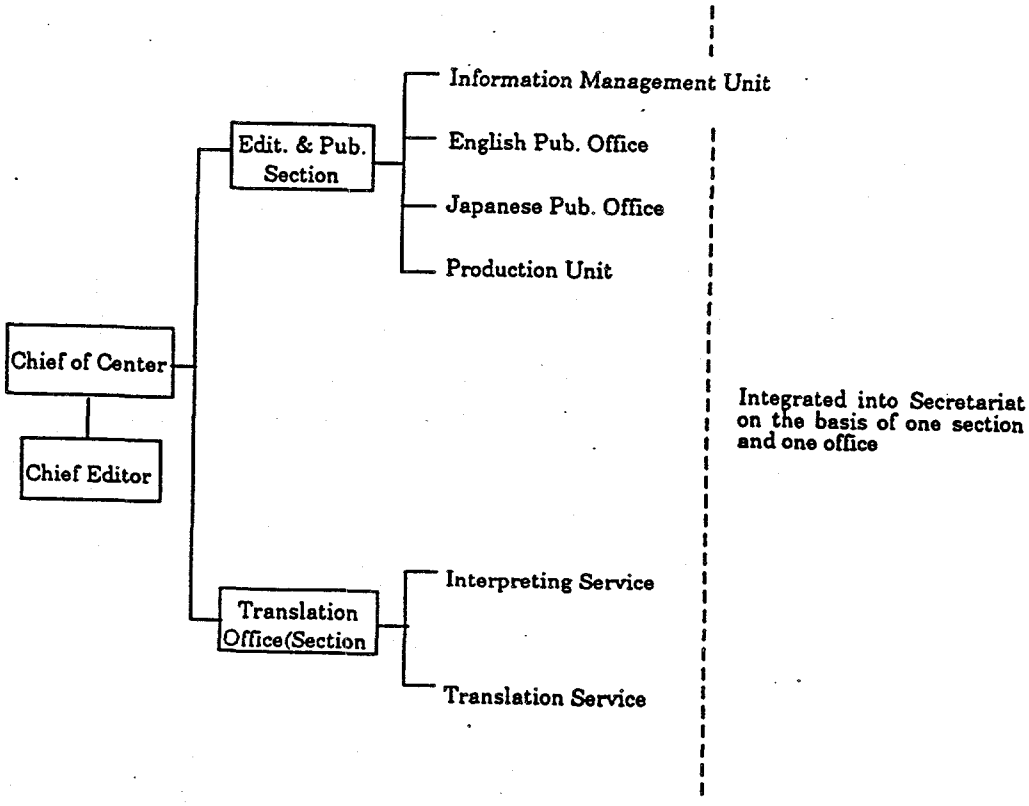
Staff:		
	Professional	1
	Administrative	20
	Total	21



Revised Organizational Structure (draft)

1 January 1998

1 January 1999



by law for safe operation of the facility. It is obligatory to submit summary reports of these data to the Science and Technology Agency. Preparation of these documents has been completely computerized. However, the equipment being used to record and manage these data has exceeded its service life and should be replaced.

Maintenance of a safe working environment

The RI facility supports the activities of the Departments of Clinical Studies, Genetics, and Radiobiology. At present, 31 users are sharing a laboratory space of 75 m^2. Space per user at our laboratory is less than that at laboratories of other institutions. Furthermore, the equipment being used in our laboratory, such as the 2D-DNA electrophoretic apparatus, is larger than usual and occupies more space. In addition, studies being conducted at RERF are mainly conducted on a large scale, and many samples are simultaneously examined. Therefore, lots of different pieces of equipment are used simultaneously. It is dangerous to perform many experiments in such a small place. Expansion of the facility has been requested, but no action has been taken due to a shortage of funds.

Future of RI facility

The RI facility will be used for many aspects of the molecular studies newly proposed by the Blue Ribbon Panel. With future technical developments, it is likely that some of these studies will be less dependent on the RI facility than is present necessary (for example, DNA sequencing, use of the Southern blot method, and chemiluminescent procedures). However, it can be easily imagined that more new experiments will be performed at the RI facility, offsetting the number of experiments that require the use of radioisotopes and will cease due to using the above-mentioned new techniques. Expansion of laboratory space to accommodate these added needs is essential.

Replacement of equipment is also necessary. The current automatic developing machine for X-ray film and the γ-well counter may cease to function at any time. Repair is impossible because no spare parts are available for these old models. One possible option to replacement purchase is to relocate the γ-well counter from the Nagasaki Laboratory to Hiroshima. If this is feasible, measuring contamination on the surface of the equipment and transportation of the equipment to Hiroshima are the only two expenses that must be borne and neither should be unduly onerous.

Renovation of the facility is necessary to satisfy the need to change the type and amount of radioisotopes being used. Installation of a larger drainage tank is especially necessary.

Personnel requirements

Fiscal Year	1996	1997	1998	1999	2000	2001
Research Scientists	0.1[1]	0.1	0.1	0.1	0.1	0.1
Technicians	0.7[2]	1	1	1	1	1

[1] One scientist is concurrently assigned to the Department of Genetics (90%) and the RI Facility (10%).

[2] One technician is concurrently assigned in the RI Facility (70%) and the Department of Clinical Studies (30%).

Space requirements (m^2)

Fiscal Year	1996	1997	1998	1999	2000	2001
Bench Research	75	120*	120	120	120	120
Support Space						
Darkroom	12.5	12.5	12.5	12.5	12.5	12.5
Contamination inspection room	7.7	7.7	7.7	7.7	7.7	7.7
RI depository	5.5	5.5	5.5	5.5	5.5	5.5
Storage disposal room	9.1	9.1	9.1	9.1	9.1	9.1
Waste disposal room	6.8	6.8	6.8	6.8	6.8	6.8
Exhaust facility	9.9	9.9	9.9	9.9	9.9	9.9
Stock room	6.0	6.0	6.0	6.0	6.0	6.0
Office	12.5	12.5	12.5	12.5	12.5	12.5
Total	145	190	190	190	190	190

*: Space for stairs and corridor is included.

Equipment budget (× ¥ 1,000)

Fiscal Year	New/ Repl	Item	Q'ty	Unit Cost	Total
1997	N	PC	1	570	570
	R	Printer	1	220	220
	R	Software version up	1	50	50
1998	R	PC	1	500	500
1999	R	Software version up	2	50	100
2001	R	PC	1	500	500
	R	Printer	1	220	220
	R	Software version up	2	50	100

* Other equipment items requested for each fiscal year are shown in Annex J.

Secretariat

The Secretariat, as the administrative department for the Foundation's operations, is responsible for the procurement of human and material resources required for the smooth conduct of research activities. As of 1 April 1996, the Hiroshima Secretariat was composed of 48

employees in four sections (General Affairs, Personnel, Accounting, and Supply and Property), and the Nagasaki Secretariat of 17 employees in two sections (General Affairs and Accounting).

Organization and personnel strength (as of April 1, 1996)

The numbers in parentheses indicate personnel strength, and "+" indicates section chiefs or other managerial positions.

Secretariat (65)	[Hiroshima]	
	Assistant Chiefs and others (3)	
	General Affairs Sec. (18)	Director's Office (5) +2 General Affairs Unit (7) Document and Archive Unit (2) External Affairs Unit (2)
	Personnel Sec. (6)	Personnel Unit (3) +1 Payroll Unit (2)
	Accounting Sec. (7)	Accounting Unit (3) +1 Receipts & Disbursement Unit (3)
	Supply & Property Sec. (14)	Supply Unit (4) +1 Physical Plant Unit (5) Welfare Unit (4)
	[Nagasaki]	
	Assistant Chief (1)	
	General Affairs Sec. (11)	Public Relations Office (2) +2 General Affairs Unit (4) Employees Unit (3)
	Accounting Sec. (5)	Accounting Unit (2) +1 Supply Unit (2)

Duties

Hiroshima Laboratory

1. General Affairs Section

Administrative duties in support of the Directors' Offices; administrative support for meetings and official functions of the Foundation; management of administrative documents; labor safety and health, security and safety; and external affairs and public relations activities.

2. Personnel Section

Duties concerning employment and dismissal, payroll, social and labor insurance, and administrative procedures for appointment of consultants, etc.

3. Accounting Section

Duties concerning preparation and execution of budget, settlement of accounts, management of cash and special accounts, and management of assets.

4. Supply and Property Section

Duties concerning purchase and management of supplies and equipment, maintenance of the facilities, heat control and energy conservation, employee welfare, and management of lodging facilities of the Foundation.

Nagasaki Laboratory

1. General Affairs Section

Duties corresponding to those discharged by the Hiroshima General Affairs Section and Personnel Section; administrative duties concerning functions of the Foundation; payroll and labor insurance, labor safety and health; and employee welfare.

2. Accounting Section

Duties correspond to those discharged by the Hiroshima Accounting Section and Supply and Property Section; purchase and management of goods; maintenance of facilities; security and safety.

Personnel of Secretariat, Hiroshima and Nagasaki laboratories

(1) Changes of personnel strength (actual) (1990 - 1996)

		1990	1991	1992	1993	1994	1995	1996
Total		93	99	93	90	84	71	65
Total (Hiroshima)		70	76	67	66	62	50	48
Attached to the Secretariat		5	6	4	4	4	3	3
General Affairs Section	Total	24	25	24	22	21	17	18
Personnel Section		6	8	9	8	7	7	6
Accounting Section		6	5	6	7	7	7	7
Supply and Property Section	Total	29	29	24	25	23	16	14
Total (Nagasaki)		23	23	26	24	22	21	17
Attached to the Secretariat		1	1	2	1	2	1	1

General Affairs Section	Total	14	15	16	15	13	13	11
Accounting Section	Total	8	7	8	8	7	7	5

2) Personnel strength required for the next five years

a) Secretariat

The Secretariat will support continued improvement of work procedures to cope with personnel reduction. However, considering the workload of the present organization, a staff of 46 and 14, respectively, for Hiroshima and Nagasaki, 60 in total, is necessary. In the event of relocation to new facilities, personnel strength can be reduced by 7 in the area of security and maintenance of the facilities.

b) Necessary personnel strength by section and projection of change in personnel number (1996 - 2001)

		Necessary personnel	1996			1997			1998			1999			2000			2001			02
			Apr. 1	Ret.	Rep	Apr. 1	Ret.	Rep	Apr. 1	Ret.	Rep	Apr. 1	Ret.	Rep	Apr. 1	Ret.	Rep	Apr. 1	Ret.	Rep	Apr.
Total		60	65	6	0	59	2	0	57	6	0	51	2	0	49	4	0	45	3	0	42
Total (Hiroshima)		46	48	3	0	45	1	0	44	4	0	40	2	0	38	4	0	34	2	0	32
Attached to the Secretariat		1	3	1		2			2			2			2			2			2
General Affairs Sec.	Clerical	15	14			14	1		13			13	1		12	1		11	1		10
	Technical	3	4	1		3			3	1		2	1		1			1			1
	Total	18	18	1	0	17	1	0	16	1	0	15	2	0	13	1	0	12	1	0	11
Personnel Sec.		6	6			6			6	1		5			5	1		4			4
Accounting Sec.		7	7	1		6			6	1		5			5			5			5
Supply & Property Sec.	Clerical	9	9			9			9			9			9	2		7	1		6
	Technical	5	5			5			5	1		4			4			4			4
	Total	14	14	0	0	14	0	0	14	1	0	13	0	0	13	2	0	11	1	0	10
Total (Nagasaki)		14	17	3	0	14	1	0	13	2	0	11	0	0	11	0	0	11	1	0	10
Attached to the Secretariat		1	1			1			1	1		0			0			0			0
General Affairs Sec.	Clerical	7	10	3		7	1		6			6			6			6	1		5
	Technical	1	1			1			1			1			1			1			1
	Total	8	11	3	0	8	1	0	7	0	0	7	0	0	7	0	0	7	1	0	6
Accounting Sec.		5	5			5			5	1		4			4			4			4

Note: "Retirement" in 1996 includes employments, transfers and retirements up to July 1.
Ret. = Retirement; Rep. = Replacement

c) Relationship with duties of the Publication and Documentation Center

Despite the research support aspects of PDC, better results can be expected by removing the division between the duties of the Secretariat and those of PDC. Therefore, in the future, translation which is done at PDC at present and the public relations activities will be put under the charge of the Secretariat together with the Document and Archive Unit and the External Affairs Unit for better utilization of talent. The duties relating to research protocols and technical reports will be placed under the direct charge of the Chief of Research for better coordination of activities. These arrangements should be further discussed. However, they are not considered in the estimation of personnel strength required.

Changes in the Foundation's overall personnel strength

1. Actual changes (1990 - 1996)

Personnel no. as of April 1	Total	Directors	Chief of Secretariat	Research Scientists	General Employees
1990	427	6		57	364
1991	433	6		61	366
1992	437	5		64	368
1993	435	6		62	367
1994	412	6		57	339
1995	373	4	1	48	320
1996	335	4	1	47	283

MAINTENANCE OF AN ADEQUATE INFRASTRUCTURE

Three needs are paramount if the Foundation is to fulfill its mission as set out in the preceding pages. First, there must be adequate staff and these individuals must have the appropriate skills to meet an evolving research program. Second, there must be the requisite equipment to support the research activities of that staff. Finally, there must be sufficient, suitable space in which to house the staff and equipment. Given the recent pace of technological developments it is difficult to project these needs over the next five years with the assurance that is desirable. Nonetheless, some projection is obviously necessary and to make that projection assumptions must be made. We now set out the assumptions that underlie the projections to follow.

Personnel

First, some further reduction in staff from that presently obtaining is possible. However, this assertion tacitly assumes that the future, through increasing use of computer technology, automated laboratory equipment, and better, faster means of communication, will make some current positions that are labor intensive redundant and others less time-consuming. But, it is our view that this reduction should be an orderly one and not so precipitous as to jeopardize the Foundation's research

and capacity to fulfill its charge either in the short or the long run. Accordingly, we have projected staff needs on the assumption that to maintain a viable staff size it will be necessary to replace two out of every three retirements over the next five years. This will amount to a further reduction in staff of about 10% over this period of time; however, the impact of this further loss in personnel must be seen in the context of the 25% reduction that has occurred in the past five years and to which we are still adjusting.

These replacements will be recruited on the basis of demonstrated need and will not be automatically made to the department or unit from which the retiree(s) came. Emphasis will be placed upon technical staff, such X-ray technicians, clinical and research laboratory personnel, and clinical and public health nurses with due allowance for changing workloads with time. However, it is clear that an adequate cadre of support staff is also essential and replacements will be made in the Secretariat, the Information Technology Department, and the Publication and Documentation Center to ensure this end.

Second, there are staff inequities between Hiroshima and Nagasaki that need to be resolved. For example, with the closure of the Radiobiology Department in Nagasaki, all of the technicians employed in this laboratory were transferred to the Clinical Laboratory there. This has resulted in a staff that is actually larger than the one in the Clinical Laboratory in Hiroshima despite the much heavier workload of the latter. These technicians should be offered transfer to Hiroshima or to other positions as retirements occur in lieu of a replacement. Other instances of inequity can be cited.

Third, particularly detrimental to the Foundation's research activities has been the loss of professional employees. Over the past five years, when no replacements of any sort occurred, their number has fallen from 64 to 47. Since it is precisely these employees that are essential to the Foundation's mission we propose increasing this number to 50.

Projected yearly staff changes by broad work categories are given in the tables at the end of this section. These tables should be seen as guides, and not as firm commitments which will, as previously said, be determined by need.

Equipment

Contemporary science rests on increasingly complex and sophisticated equipment both in the laboratory and as a means of communication, data management and analysis. Much of this equipment has, unfortunately, a relatively short useful life, arguably three to five years in most instances. This implies, in turn, that replacements will be necessary periodically. Again, it is our intent to make these replacements on the basis of need and relevance to the current research program. Wherever equipment is outdated for use in one department, if circumstances permit, it will be transferred to another department with less demanding needs.

Clearly high on the list of priorities will be the maintenance of a strong computing capability including the continued cost of transition from a mainframe environment to a distributed system. This is essential not only to research but to the proper administration of that research. As the body of information available at the Foundation grows, which is inevitable, the need for efficient data management grows too. Moreover, significant staff reduction appears possible only if some of the current routine work can be automated, and delegated to computers.

Budget projections for the next quinquennium will be found at the end of this section. These projections set forth personnel and operating costs as well as equipment needs. However, in departure from previous budget projections, equipment expenditures have been divided into those supporting research and those supporting administrative needs. In the past, administrative equipment needs, primarily computing capability, have generally been funded out of operating costs and therefore, not reflected in the overall equipment forecasts. This accounts for much of the seemingly larger equipment projections seen in these tables. It should also be noted that the bulk of the equipment expenditures predicted are for the replacement of outdated apparatus and not new devices, new in the sense of not previously in use at the Foundation.

Space

Although planning for the relocation of the Foundation's facilities in Hiroshima continues, there is as yet no firm date for this to occur. Accordingly, for the purposes of this document, we have assumed that the relocation will not occur in the next five years. However, if this should prove to be incorrect, clearly additional costs over those here projected would occur. It is important to note that the Hiroshima facilities are old, and barely adequate; however, we continue to review space allocations and strive for the most efficient use of the space that is available. This process of review will continue.

Changes of personnel strength
(2/3 replacement of retirements)

		Total	Director	Research Scientist	Clerk	Computer Specialist	B	C	D
FY1996	As of Apr. 1	335	5	47	178	12	16	57	20
	Retirement	10			4		2	3	1
	Replacement	6		3	1		1	1	
FY1997	As of Apr. 1	331	5	50	175	12	15	55	19
	Retirement	30	4	1	18	1		3	3
	Replacement	22	4	1	12	1		2	2
FY1998	As of Apr. 1	323	5	50	169	12	15	54	18
	Retirement	14			10	1	2	1	
	Replacement	9			6	1	1	1	
FY1999	As of Apr. 1	318	5	50	165	12	14	54	18
	Retirement	14	4	1	7	1	1		
	Replacement	11	4	1	5	1			
FY2000	As of Apr. 1	315	5	50	163	12	13	54	18
	Retirement	12			11				1
	Replacement	9			8				1
FY2001	As of Apr. 1	312	5	50	160	12	13	54	18
	Retirement	10		2	7				1
	Replacement	8		2	5				1
FY2002	As of Apr. 1	310	5	50	158	12	13	54	18

1) The expiration of directors' terms of office is considered as mandatory retirements, and replacements for all of the retiring directors will be employed.
2) Number of research scientists is 50 and the replacements for all terminating will be employed.
3) 2/3 of replacement of retirements of general employees will be employed as of 1 April of the next year.
4) B: Technical staff C: Clinical radiology technicians and medical technicians
D: Nurses and public health nurses

Comparison of personnel strength between actual and requested (Total)
(2/3 replacement of retirements)

		Total	Director	Research	General	A	B	C	D
FY1996	as of Apr. 1	335	5	47	283	190	16	57	20
	Retirement	10			10	4	2	3	1
	Sub-total	325	5	47	273	186	14	54	19
	Requested	**331**	**5**	**46.5**	**279.5**	**188**	**11**	**60.5**	**20**
FY1997	Replacement	6		3	3	1	1	1	
	as of Apr. 1	331	5	50	276	187	15	55	19
	Retirement	30	4	1	25	19	0	3	3
	Sub-total	301	1	49	251	168	15	52	16
	Requested	**342.5**	**5**	**50.5**	**287**	**195**	**11**	**62**	**19**
FY1998	Replacement	22	4	1	17	13		2	2
	as of Apr. 1	323	5	50	268	181	15	54	18
	Retirement	14			14	11	2	1	0
	Sub-total	309	5	50	254	170	13	53	18
	Requested	**346.5**	**5**	**51.5**	**290**	**198**	**11**	**63**	**18**
FY1999	Replacement	9			9	7	1	1	
	as of Apr. 1	318	5	50	263	177	14	54	18
	Retirement	14	4	1	9	8	1	0	0
	Sub-total	304	1	49	254	169	13	54	18
	Requested	**348.5**	**5**	**52.5**	**291**	**199**	**11**	**63**	**18**
FY2000	Replacement	11	4	1	6	6			
	as of Apr. 1	315	5	50	260	175	13	54	18
	Retirement	12			12	11	0	0	1
	Sub-total	303	5	50	248	164	13	54	17
	Requested	**347.5**	**5**	**52.5**	**290**	**199**	**10**	**63**	**18**
FY2001	Replacement	9			9	8			1
	as of Apr. 1	312	5	50	257	172	13	54	18
	Retirement	10		2	8	7	0	0	1
	Sub-total	302	5	48	249	165	13	54	17
	Requested	**347.5**	**5**	**52.5**	**290**	**199**	**10**	**63**	**18**

SUMMARY

Investigations have been in progress for 50 years to ascertain the health effects produced by radiation in the survivors of the atomic bombings of Hiroshima and Nagasaki. It is appropriate to ask (1) what the results of these studies have been, (2) what more is to be done, and (3) what changes, if any, are anticipated in the future for RERF. One purpose of this document is to address these issues.

The long-term follow-up of this unique population has provided results of considerable value to the medical as well as the radiobiological community. Significant associations between radiation dose and cancer have been seen among the survivors for most types of cancer, including leukemia, multiple myeloma and cancers of the thyroid, lung, breast, stomach, skin, colon, esophagus, liver, urinary tract, and ovaries. The RERF data provide unique, quantitative information on how these risks are affected by sex, age-at-exposure, and time. The excess relative risks for most solid cancers are found to be higher for men than women and to increase with decreasing age at exposure. There is weak evidence that the high relative risks seen for those exposed as children have decreased with time while the relative risks for those exposed as adults have remained constant. Recent analyses of the LSS data indicate that excess rates increase throughout life and that these rates do not vary much with sex and age-at-exposure. The RERF data also provide evidence of a positive association between radiation dose and noncancer disease mortality. While this effect is small, it does not appear to be an artifact of misclassification of cause of death on death certificates. Clinical studies of cardiovascular disease morbidity and related endpoints have been carried out using the RERF clinical data. The results of these studies also support the notion of a radiation effect on some noncancer diseases. Over the next few years we must develop a more unified approach for combining the epidemiological and clinical data on radiation and noncancer disease morbidity. The presence of dose-dependent developmental effects on survivors who were exposed in-utero is well-documented and it is now becoming clear that radiation exposure is associated with elevated risks of cancer later in life for this group of survivors. If, as seems likely, these risks continue throughout life the coming decades will provide further information on the extent and nature of these risks. It is also important to follow-up earlier findings that the developing human brain is extremely sensitive to teratogenic effects of relatively low doses of ionizing radiation since this vulnerability might manifest itself in earlier onset of cognitive disorders and an increased frequency of senile dementia.

Evidence is still lacking that radiation induces heritable genetic damage in humans. Research with experimental animals, however, has clearly demonstrated that heritable changes are positively associated with radiation exposure. In general, RERF's findings in various genetic studies are as expected if the atomic-bomb radiation exposure has produced mutations. But, to date, the differences between the children of proximally and distally exposed survivors are far from significant. However, none of the strategies to assess mutation risk used thus far has addressed the full gamut of possible genetic damage. For example, the program of clinical examinations of the newborn was designed to identify congenital abnormalities demonstrable soon after birth but could not identify those abnormalities that are not readily detectable until later in life, nor those simply or complexly inherited disabilities that do not manifest themselves until adolescence or later. The latter represent by far the largest proportion of all inherited handicaps, and there has been no systematic program of health examinations of the F_1 after the first year of life which might

detect an increase in these diseases and disorders.

Developments in molecular biology have identified a number of new approaches that will permit mutations at the level of nucleotide bases in DNA to be detected in human populations in the foreseeable future. Although these techniques are not available for use at the present time to monitor human mutation rates, cells from exposed and unexposed parents and their children are being collected now. Some of these cells are being immortalized using the Epstein-Barr virus, cultured, and stored for use when the new molecular approaches to mutation detection can be used cost-effectively.

Continuation of the investigations at RERF will (1) strengthen evidence about the cancer dose-response, (2) clarify the impact of exposure on cancer risks for the survivors exposed as children in-utero, (3) provide additional information on the nature of radiation effects on cardiovascular and other noncancer diseases, and (4) offer new insights into the role of biological and environmental factors on radiation risks.

Initial efforts to develop a database that contains information on family relationships among members of the LSS and other RERF cohorts suggest that these data can be useful for studies of the interaction between hereditary factors and radiation- or nonradiation-related cancer risks. This work will continue during the next five years provided that adequate computing and personnel resources are available.

Public concern over the potential risks of exposure to ionizing radiation shows no sign of abating; indeed it is possibly even greater now than in the past largely due to a series of accidents at nuclear power generating facilities, and increased medical usage. To allay this concern will require greater knowledge of how radiation affects somatic and genetic diseases in human beings. While there are experts in most disciplines related to understanding radiation effects on humans at many institutions all over the world, the Foundation is the only one with many of these experts in one place, and with access to the largest, well-defined and studied population of radiation-exposed individuals. To not maintain this "critical mass" of interested scientists focused on this important human problem would create a serious setback to the Foundation and the successful prosecution of its mission. In addition, with the increasing concern of the effects of environmental chemicals on human health, RERF scientists have the potential to use the information from this unique population to determine how chemical and radiation effects might interact.

With the decrease in the numbers of the A-bomb survivors occurring, and the current lack of sensitive and fully validated techniques to measure mutational effects in both somatic and germ cells, emphasis has been and should continue to be placed on the long-term storage of biological material until appropriate techniques to measure important parameters can be developed. In addition, research should be directed towards the incorporation of new molecular biological approaches in the study of the F_1 generation and the incorporation of new concepts and techniques from molecular and cell biology to study the non-mutagenic mechanisms that may modify radiation effects, aspects that are not, at present, part of the Foundation's current research base.

The development of such new molecular biological techniques; of new conceptual understanding of chronic diseases, including cancer; of the deeper insights into the role of

oncogenes and tumor suppressor genes; and an understanding of chemicals which enhance or suppress tumor growth can be expected to stimulate new laboratory approaches and new epidemiological studies.

研究部門備品要求表 (1996年 ～ 2001年)

Equipment Requests by Research Departments

(単位：千円) (UNIT:¥1,000)

	部・局	DEPARTMENT	FY1996	FY1997	FY1998	FY1999	FY2000	FY2001	合計
	疫学部	EPIDEMIOLOGY	0	7,690	6,930	6,990	7,050	7,050	35,710
	臨床研究部	CLINICAL STUDIES	0	8,372	4,485	16,210	712	11,565	41,344
	遺伝学部	GENETICS	0	21,011	10,347	30,381	2,794	4,002	68,535
	放生部	RADIOBIOLOGY	0	49,412	83,652	20,682	13,572	6,882	174,200
	統計部	STATISTICS	0	5,075	5,275	5,410	5,590	5,675	27,025
	広島合計	HIROSHIMA TOTAL	0	91,560	110,689	79,673	29,718	35,174	346,814
	臨床研究部	CLINICAL STUDIES	0	20,117	1,052	2,252	3,452	852	27,725
	疫学部	EPIDEMIOLOGY	0	6,198	3,344	3,544	844	5,944	19,874
	長崎合計	NAGASAKI TOTAL	0	26,315	4,396	5,796	4,296	6,796	47,599
①	両市合計	BOTH TOTAL	0	117,875	115,085	85,469	34,014	41,970	394,413

サポート部門備品要求表 (1996年 ～ 2001年)

Equipment Requests by Supporting Departments

	部・局	DEPARTMENT	FY1996	FY1997	FY1998	FY1999	FY2000	FY2001	合計
	出版資料センター	PDC	0	8,860	3,640	4,960	2,540	3,200	23,200
	研究情報センター	ITD	0	44,900	45,420	48,050	47,840	50,460	236,670
	放射線同位RI	RI FACILITIES	0	2,500	0	450	360	700	4,010
	事務局	SECRETARIAT	1,770	6,240	8,320	4,690	2,950	1,420	25,390
	広島合計	HIROSHIMA TOTAL	1,770	62,500	57,380	58,150	53,690	55,780	289,270
	事務局	SECRETARIAT	2,720	2,620	440	2,220	1,040	0	9,040
	長崎合計	NAGASAKI TOTAL	2,720	2,620	440	2,220	1,040	0	9,040
②	両市合計	BOTH TOTAL	4,490	65,120	57,820	60,370	54,730	55,780	298,310
①+②	合計		4,490	182,995	172,905	145,839	88,744	97,750	692,723

現金購入	PURCHASE COST	4,490	110,655	86,872	86,021	73,344	87,967	449,349
リース支払い	LEASE CHARGE	0	16,754	36,680	50,533	54,100	56,365	214,431
従来のリース支払	CURRENT LEASE CHARGE	17,095	5,082	5,082	5,082	4,598	2,177	39,116
合計	TOTAL	21,585	132,491	128,634	141,636	132,042	146,509	702,896

コンピューター関係分	For Computer	4,490	94,381	80,017	82,462	73,314	86,797	421,461

ANNEX A

THE PROJECTED SIZE OF THE LIFE SPAN STUDY COHORT, 1995-2020.

	Year					
	1995	2000	2005	2010	2015	2020
Age at exposure (y)						
0-9	16,450	15,990	15,290	14,280	12,710	10,390
10-19	14,500	13,540	12,040	9,800	6,780	3,620
≥ 20	12,800	8,910	5,430	2,710	970	100
Total	43,750	38,440	32,760	26,790	20,460	14,110
Average attained age (y)						
	64.7	67.9	71.3	74.7	78.0	81.3
Average age at time of bombing (y)						
	14.7	12.9	11.3	9.7	8.0	6.3

ANNEX B

WORKSHOPS SINCE 1988

• Radiation susceptibility workshop, 18-20 March 1988	RERF Hiroshima
• Immunology workshop, 28-29 November 1988	RERF Hiroshima
• Radiation carcinogenesis workshop, 16-18 March 1989	RERF Hiroshima
• Aging workshop, 29-31 March 1990	RERF Hiroshima
• Human germline mutagenesis workshop, 12-14 November 1991	RERF Hiroshima
• Health monitoring workshop, 25-27 January 1993	RERF Hiroshima
• US Department of Energy and RERF scientific research activity exchange workshop, 14-16 April 1993	Beckman Center, Irvine, California, USA

ANNEX C

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ANNEX D

MASTER SAMPLE, PROPER AND RESERVE BY EXPOSURE CATEGORY AND CITY

Exposure Group (M)	Proper Part	Reserve Part	Total
HIROSHIMA	90,697	30,403	121,100
0-1999	21,329	4,845	26,174
2000-2499	11,524	3,019	14,543
2500-9999*	36,023	8,455	44,478
10000 or NIC*	21,821	14,084	35,905
NAGASAKI	35,495	7,125	42,620
0-1999	6,801	858	7,659
2000-2499	5,144	805	5,949
2500-9999*	15,642	2,510	18,152
10000 or NIC*	7,908	2,952	10,860
TOTAL	126,192	37,528	163,720
0-1999	28,130	5,703	33,833
2000-2499	16,668	3,824	20,492
2500-9999*	51,665	10,965	62,630
10000 or NIC*	29,729	17,036	46,765

* Matched by sex and age to those exposed between 0 and 1999 meters

ANNEX E

LIFE SPAN STUDY SAMPLE, ORIGINAL AND EXTENDED

City	Original (LSS)	Extended (LSS-E85)
Hiroshima	74,356	82,220
Nagasaki	25,037	37,912
Total	99,393	120,132

ANNEX F

ADULT HEALTH STUDY SAMPLE BY CITY, SEX, AND EXPOSURE GROUP

City and sex	Exposure Group				Total
	With symptoms	Without symptoms	Distal	Not exposed	
HIROSHIMA	3,431	3,417	3,429	3,441	13,718
Male	1,315	1,307	1,309	1,319	5,250
Female	2,116	2,110	2,120	2,122	8,468
NAGASAKI	1,567	1,558	1,559	1,559	6,243
Male	682	676	673	675	2,706
Female	885	882	886	884	3,537
TOTAL	4,998	4,975	4,988	5,000	19,961
Male	1,997	1,983	1,982	1,994	7,956
Female	3,001	2,992	3,006	3,006	12,005

ANNEX G

IN UTERO SAMPLE BY CITY, IDENTIFICATION SOURCE, AND STUDY COHORT MEMBERSHIP

Cohort membership	Source	Hiroshima	Nagasaki	Total
In utero mortality	Birth records	1,104	247	1,351
(only)	ABCC records	183	34	217
	1960 Census	416	62	478
In utero clinical	Birth records	0	0	0
(only)	ABCC records	578	259	837
	1960 Census	0	0	0
In both cohorts	Birth records	515	83	598
	ABCC records	167	6	173
	1960 Census	0	0	0
Total	Birth records	1,619	330	1,949
	ABCC records	928	299	1,227
	1960 Census	416	62	478
Grand total	All sources	2,963	691	3,654

ANNEX H

F_1 MORTALITY SAMPLE, ORIGINAL AND EXTENDED

	City		
Sample	Hiroshima	Nagasaki	Total
Original	34,790	18,731	53,521
Extended	13,225	10,074	23,299
Total	48,015	28,805	76,820

ANNEX I

ACTIVE RESEARCH PROJECTS BY RERF PROGRAM

As of 31 August 1996

LIFE SPAN STUDY

RP	2-61	Study of mortality in children exposed in utero
	1-75	Research plan for RERF study of Life-Span of A-bomb survivors, Hiroshima and Nagasaki
	6-88	Comparative analysis of the LSS population and a cohort of 265,000 Japanese men and women
(Inactive)	4-91	Mail survey on epidemiologic factors in the Extended Life Span Study sample, 1991

ADULT HEALTH STUDY

	2-75	Research plan for RERF Adult Health Study, Hiroshima and Nagasaki

IMMUNOLOGY

	36-63	Blood groups in Adult Health Study and in utero ATB subjects Hiroshima and Nagasaki
(Inactive)	16-81	Establishment of specific reagents for detection of human cancers through in vitro immunologic and biochemical assays
	3-87	Cellular immune function and its relationship to in vitro T-lymphocyte radiosensitivity and MN blood group locus mutation frequency in A-bomb survivors: Precursor frequency analysis of mitogen- and antigen-responsive blood lymphocytes
	7-87	X-ray radiosensitivity of lymphocytes in vitro from A-bomb survivors. Part 3: Transformation of B-cells by Epstein-Barr virus and their cryopreservation (addendum to RP 3-86)
	7-88	Study of somatic mutations at the glycophorin A locus in erythrocytes of atomic bomb survivors
	7-89	Screening of stem cell mutation in lymphoid lineage among A-bomb survivors and its characterization
	9-89	Detecting erthrocyte mutations at the glycophorin A locus in Nagasaki A-

bomb survivors and in Hiroshima area poison gas workers (addendum to RP 7-88)

11-89 A pilot study for detection of somatic mutations at the HLA-A locus in lymphocytes

2-90 Cryopreservation of blood cells from Hiroshima and Nagasaki Adult Health Study participants

4-90 Establishment of a method for HLA-DQ and DP gene typing using the polymerase chain reaction (Inactive)

1-93 Study on T-cell antigen receptor repertoire and hematopoietic progenitor cell activity in peripheral blood of atomic bomb survivors (addendum to RPs 3-87, 4-87 and 7-89)

2-93 Development of assay for somatic mutation at the locus of the neutrophil Fcγ receptor III gene and preliminary study on atomic-bomb survivors

SPECIAL CLINICAL STUDIES

4-85 Incidence and risk factors of coronary heart disease (CHD) in Japanese men living in Japan and Hawaii, 1966-78 (addendum to Research Plan TR 12-71)

6-85 Study of M-proteinemia in the Adult Health Study sample (addendum to RP 9-79)

4-86 Evaluation of index of physiological measurements: A predictor of mortality or morbidity associated with aging

5-86 Dietary habit survey using a simple and computerized diet survey system (addendum to RP 8-83)

11-86 Prevalence of hyperparathyroidism in atomic bomb survivors during AHS cycle 15, Hiroshima and Nagasaki

5-87 Radiation-related damage to the developing human brain

(Inactive) 9-87 The effect of pulmonary function on the subsequent risk of coronary heart disease in Japanese men living in Hiroshima and Nagasaki, Japan and Hawaii, 1966-78 (addendum to RP 4-85)

1-89 Prevalence of radiation-related skin lesions in the Adult Health Study population, Hiroshima and Nagasaki

2-89 Hypercalcemia in A-bomb survivors, Hiroshima and Nagasaki

(addendum to RP 11-86)

3-89 Osteoporosis in Hiroshima atomic bomb survivors

(Inactive) 6-89 Incidence of radiation-related skin lesions in the Adult Health Study populations of Hiroshima and Nagasaki, 1958-89

3-90 The association of serum cholesterol with noncardiovascular mortality and morbidity in the Adult Health Study population

3-91 A comparative study of vertebral fracture prevalence among Japanese, Japanese-Americans in Hawaii, and Caucasians in Minnesota

5-92 Study on senile dementia among the Adult Health Study subjects in Hiroshima and Nagasaki

6-92 Establishment and operation of a system for collecting and storing leukemia cells

9-92 Study of liver diseases in the Adult Health Study sample. Relationship between radiation dose and infection by B and C hepatitis virus

5-93 A longitudinal study of hormone indicators of menopause in female A-bomb survivors of perimenopausal age

1-95 Effects of menopause on risk factors for ischemic heart disease - a longitudinal study of the Nagasaki Adult Health Study sample (addendum to RP 5-93)

2-95 Pilot study: characterization of monoclonal gammopathy by studying the role of BSAP gene in CD19 antigen expression

HISTO-PATHOLOGY

5-89 Pathology studies in Hiroshima and Nagasaki, revised research plan (Formerly RP 3-75)

8-89 Senile changes of the brain in Hiroshima and Nagasaki A-bomb survivors

CELL BIOLOGY

18-81 Pathophysiology and radiation response of human thyroid cells in culture and in grafts in athymic nu/nu mice

7-92 Molecular analysis of the p53 tumor-suppressor gene in breast cancers of

atomic bomb survivors (with addendum)

3-93 Molecular analysis of skin cancers in atomic bomb survivors

7-93 Molecular analysis of thyroid cancers among atomic bomb survivors

2-94 Molecular analysis of hepatocellular carcinoma among atomic-bomb survivors

BIOCHEMICAL GENETICS

5-85 Culture of permanent lymphocyte cell lines as sources of biological samples for investigation of genetic effects of radiation on children of atomic bomb survivors

7-85 Study to develop methods of DNA analysis for detection of mutations in children of atomic bomb survivors

CYTOGENETICS

8-93 Cytogenetic study in the Adult Health Study population by fluorescence in situ hybridization (FISH)

F1 STUDIES

4-75 Research plan for RERF studies of the potential genetic effects of atomic radiation; Hiroshima and Nagasaki. Part 1. Mortality study of children of atomic bomb survivors

SPECIAL CANCER STUDIES

29-60 Detection of leukemia and related disorders

7-76 The value of Adult Health Study family history records in the determination of genetic influences on the development of cancer and other disorders

14-79 Interaction between radiation dose and host factors. An epidemiological case-control study of female breast cancer in atomic bomb survivors

(Inactive) 15-81 Case-control study of lung cancer among atomic bomb survivors

8-85 Incidence study on malignant and benign genital tumors among females,

Hiroshima and Nagasaki, 1950-80

(Inactive) 11-85 Hormone status in relation to cancer: A prospective epidemiologic study using stored sera

2-86 Collection of surgically removed cancer tissues from A-bomb survivors: Special reference to thyroid and breast cancers

6-86 Ultrasonographic screening of Adult Health Study participants to detect cancer and other diseases

9-88 Guidelines for the conduct of site-specific cancer incidence studies among A-bomb survivors, Hiroshima and Nagasaki

5-90 Primary liver cancer incidence study among atomic bomb survivors, 1958-87

1-91 Studies of salivary gland tumors among the RERF Extended Life Span Study cohort, Hiroshima and Nagasaki, 1950-87

2-91 Studies of skin cancer incidence among the RERF Extended Life Span Study cohort, Hiroshima and Nagasaki, 1950-87

6-91 Studies on thyroid tumor incidence among the RERF Extended Life Span Study cohort, 1950-87

2-92 Studies on ovarian tumor incidence among the RERF Extended Life Span Study cohort, 1950-87

4-92 Incidence study of tumors of the central nervous system among atomic-bomb survivors

6-93 Breast cancer incidence study among atomic bomb survivors, 1950-90

1-94 Studies on lung cancer incidence among A-bomb survivors, 1950-90

3-94 Incidence of lymphoid malignancies among A-bomb survivors, 1950-90

A-BOMB DOSIMETRY STUDIES

18-59 Shielding survey and dosimetry study

10-86 Radiation dose estimates using tooth samples. Part 1. Collection of tooth samples from A-bomb exposed people in Hiroshima and Nagasaki

1-92 Radiation dose estimates using tooth samples. Part 2. Use of electron spin resonance on tooth enamel from Hiroshima atomic bomb survivors

MEDICAL DOSIMETRY STUDIES

(Inactive) 7-81 Radiation therapy among Life Span Study subjects

7-86 Doses to Adult Health Study participants from RERF radiological examinations, Hiroshima and Nagasaki

8-86 Ionizing radiation for medical reasons reported by Adult Health Study participants, Hiroshima and Nagasaki

8-87 Organ doses from medical x-ray exposures (addendum to RP 8-84)

5-91 Radiation-therapy-related cancer among Life Span Study subjects (addendum to RP 7-81)

TUMOR REGISTRY AND TISSUE REGISTRY

18-61 Tumor registry study in Hiroshima and Nagasaki [Editor's note: See ABCC Technical Report 2-61 for the full text.]

Following are tissue registry-related protocols that are also listed under the category Special Cancer Studies.

29-60 Detection of leukemia and related disorders

9-88 Guidelines for the conduct of site-specific cancer incidence studies among A-bomb survivors, Hiroshima and Nagasaki

5-90 Primary liver cancer incidence study among atomic bomb survivors, 1958–87

1-91 Studies of salivary gland tumors among the RERF Extended Life Span Study cohort, Hiroshima and Nagasaki, 1950–87

2-91 Studies on skin cancer incidence among the RERF Extended Life Span Study cohort, Hiroshima and Nagasaki, 1950–87

6-91 Studies on thyroid tumor incidence among the RERF Extended Life Span Study cohort, 1950–87

2-92 Studies on ovarian tumor incidence among the RERF Extended Life Span

Study cohort, 1950–87

4-92 Incidence study of tumors of the central nervous system among atomic-bomb survivors

6-93 Breast-cancer incidence among atomic-bomb survivors, 1950–90 (supersedes RP 1-90)

1-94 Studies on lung-cancer incidence among the atomic-bomb survivors, 1950–90

3-94 Incidence of lymphoid malignancies among the atomic-bomb survivors, 1950–90

ANNEX J

ITEMIZED EQUIPMENT LISTS

Department of Clinical Studies

Hiroshima

Fiscal year	New/ Repl	Item	Q'ty	Unit Cost (x¥1000)	Total (x¥1000)
1997	R	Autoclave	1	3,360	3,360
	N	Laser printer	1	400	400
1998	R	Deep freezer	1	2,533	2,533
1999	R	High pressure sterilizer	1	3,358	3,358
	R	Dryer	1	770	770
	R	Ultrasonography	1	9,400	9,400
2001	R	Freeze dryer	1	4,750	4,750
	R	Deep freezer	1	2,533	2,533
			Total		27,104

1. Autoclave (for Departments of Clinical Studies):

   The autoclave currently in use was purchased in 1980 and being used beyond its expected life-span. The early replacement is requested.

2. Personal computer and laser printer (for Departments of Clinical Studies):

   At present, there is no IBM PCs available for research scientists in the department._@ Since there are many research projects to be studied, an early distribution of PCs to some of the key investigators is one of the items with higher priority in the department.

3. Deep freezers (for Departments of Clinical Studies):

   Two of the deep freezers currently in use for storage of biological materials, such as serum and plasma, were purchased in 1972 and 1973. These two freezers have been used beyond their life-span and it is expected to break down in the near future.

4. High pressure sterilizer (for Departments of Clinical Studies, Genetics and Radiobiology):

   The high pressure sterilizer currently in use was purchased in 1986 and being used beyond its

expected life-span. The early replacement is requested.

5. Dryer (for Departments of Clinical Studies, Genetics and Radiobiology):

The dryer for glassware and other laboratory equipments currently in use was purchased in 19 and being used beyond its life-span. The early replacement is requested.

6. Ultrasonography (for Departments of Clinical Studies):

The ultrasonography currently in use was purchased in 1989. Since this is one of the equipme which have been providing direct benefits to the AHS participants, it is requested to replace before it breaks down.

6. Freeze dryer (for Departments of Clinical Studies):

The freeze dryer of serum currently in use was purchased in 1988. Since storage of serum is one of the most important activities in the department, the replacement is requested.

Nagasaki

Fiscal year	New/ Repl	Item	Q'ty	Unit Cost (x¥1000)	Total (x¥1000)
1997	R	Portable ECG	1	1,350	1,350
	R	Autoclave	1	650	650
	R	X-Ray Camera Ident.	1	302	302
	R	X-Ray Microreader	1	550	550
	R	Ultrasonography (Abdomen)	1	8,000	8,000
	R	Magazine for Imaging Camera	1	564	564
	R	Freezer (-40°C)	1	785	785
	R	Freezer (-80°C)	1	1,845	1,845
	R	Refrigerator	2	200	400
	R	Autodiluter	1	1,055	1,055
	R	Oven Drying	1	520	520
	R	Freeze Dryer	1	1,550	1,550
	R	Ampoule Seare	1	314	314
	R	Multi Tube, Ampoule	1	230	230
	R	Centrifuge Refrig	1	930	930
2000	R	ECG	1	3,000	3,000
			Total		22,045

Department of Genetics

Fiscal year	New/ Repl	Item	Q'ty	Unit Cost (x¥1000)	Total (x¥1000)
1997	N	Software for 2-DE Analysis	1	10,000	10,000
	R	Pulsed Field Gel Electrophoresis Apparatus	1	3,000	3,000
	R	Refrigerated Centrifuge	1	1,270	1,270
	R	Refrigerator (with freezer)	1	94	94
	R	Centrifuge (for microtubes)	2	45	90
	R	Spectrophotometer	1	695	695
1998	R	Refrigerator (with freezer)	1	869	869
	R	Autoclave	2	580	1,160
	R	Water bath (with cooling system)	1	379	379
	R	Water bath (with cooling system)	1	447	447
	R	Power supply	4	150	600
	R	Centrifuge	1	240	240
	R	Photon camera	1	5,000	5,000
1999	N	Bio-Imaging Analyzer with Imaging Plates and Cassettes	1	22,880	22,880
	R	PCR equipment	1	4,000	4,000
	R	Water bath (with cooling system)	1	675	675
	R	Refrigerator (with freezer)	1	94	94
			Total		51,493

Department of Radiobiology

Fiscal year	New/ Repl	Item	Q'ty	Unit Cost (x¥1000)	Total (x¥1000)
1997	R	Deep Freezer	1	2,200	2,200
	R	Thermal Cycler	2	850	1,700
	R	Clean Lack for Animal Facility	2	2,650	5,300
	R	Autoclave	1	700	700
		Confocal laser microscope	1	25,000	25,000
	R	X-ray Generator[1]	1	10,000	10,000

1998	R	Thermal Cycler	2	850	1,700
	R	Autoclave	1	700	700
	R	Laser for FACScan	1	1,300	1,300
	R	Laser for FACStar	1	3,500	3,500
	R	Cell Sorter (FACSvantage)[2]	1	75,000	75,000
1999	R	Deep Freezer	1	2,200	2,200
	R	Thermal Cycler	2	850	1,700
	R	Power Supply	2	550	1,100
	R	FACScan[2]	1	15,000	15,000
2000	R	Refrigerated Microcentrifuge	1	900	900
	R	Clean Bench	2	2,200	4,400
	N	Image Analyzer	1	8,000	8,000
2001	R	Fluorescence Microscope	1	2,500	2,500
	R	Thermal Cycler	2	850	1,700
			Total		164,600

Note: (1) The X-ray generator is for interdepartmental use. These items are not included in the total cost. (2) The FACSvantage and FACScan will be obtained on a lease-purchase basis to redu annual equipment costs. The FACSvantage is basically a replacement for an earlier model flow cytometer that is now 13 years old.

A. Deep freezer (-80_‹)

Long term preservation of DNA, RNA and serum of the atomic-bomb survivors are necessary for the molecular epidemiology/oncology and immunology studies. The current equipment (15 years old) should be replaced before it breaks down to assure that the samples are safe.

B. Thermal cycler

Thermal cyclers (program cell cycler) are essential machines for molecular epidemiology/oncology and immunology in the department of radiobiology. These machines can amplify DNA and RNA from very small amounts of materials obtained from A-bomb survivors. Eight machines are currently working in the department of radiobiology. Four of the 8 have been used longer than 5 years. The life span of this machine is 5 years because the cyclic raising and lowering of the temperature causes metal exhaustion.

C. Clean rack for mouse cages

Since the present mouse racks are very old (15 years) and severely deteriorated, they should be

replaced to maintain clean conditions in the cages.

D. Autoclave

The autoclave currently used in the immunology laboratory is seriously deteriorated and should be replaced.

E. X-ray generator

The 250 KV X-ray generator is for interdepartmental use; the current machine is badly in need of repair and cannot be expected to last more than a few years in its present condition, but this model is no longer being manufactured and parts are unavailable to effect the needed repair.

F. Laser tube for the FACScan

A laser tube unit for one of two FACScan flow cytometer should be replaced in FY98, because its expected life will be up within two years.

G. Laser tube for FACStar cell sorter

The laser tube unit for the FACStar should be replaced in FY98, because its expected life will be up within two years. If we can purchase FACS vantage through a lease in FY98, this replacement laser will not be needed.

H. FACS Vantage (dual laser model) cell sorting system

The present cell sorter, FACStar installed in the Radiobiology Department was purchased more than 10 years ago. Because this apparatus often breaks down, it should be replaced as soon as possible. This cell sorter is essential for conducting immunology and molecular oncological studies of A-bomb survivors. Also, it can be used to analyze somatic mutations in exposed people for international collaboration.

I. Power supply

Electrophoresis for detection of point mutation and identification of HLA alleles requires a stable electric power supply. Because, currently, we are using outdated power supplies, some replacements may be needed in a few years.

J. FACScan

The FACScan machine currently used in the Radiobiology Department was installed 8 years ago. Since this apparatus is essential for conducting immunological analyses of lymphocytes from A-bomb survivors, it should be replaced.

K. Refrigerated Microcentrifuge

For studies of molecular oncology/epidemiology, extraction of DNA, RNA and proteins from micro-samples is necessary. Considering the frequency of use, it is expected at least one refrigerated microcentrifuge will break down within a few years, because two of five centrifuges currently used in the Department of Radiobiology is older than 10 years.

L. Clean bench

The clean bench in use in the Immunology Laboratory is used for multiple purposes such as separation, culture and manipulation of the biological materials of A-bomb survivors. This was purchased more than ten years ago and needs to be replaced to assure safety of the staff from biohazardous agents.

M. Image analyzer and video system for microscope

This system is required for precise analysis of cellular functions of lymphocytes and stem cells from the survivors blood. Also, this system is needed for quantitative immunohistochemical analysis of the expression of tumor associated genes in survivors' tumor specimens.

N. Fluorescence Microscope

The microscope in use for 14 years is deteriorated and should be replaced. The fluorescence microscope is essential for cytological and histological examination in the immunological laboratory.

O. Personal Computer

In the Department of Radiobiology, we are currently using 7 PCs in total. Since 6 of them were purchased prior to last year, they should be replaced by new models during the next 5 years. Furthermore, 4 new computers for data analysis, manuscript preparation, literature search and e-mail need to be installed in 4 offices used by research scientists.

Radioisotope Laboratory

Fiscal year	New/ Repl	Item	Q'ty	Unit Cost (x¥1000)	Total (x¥1000)
1997	R	Automatic X-ray Film Processor	1	2,500	2,500
1999	R	GM-Survey Meter	1	450	450
2000	R	Survey Meter with Ionization Chamber	1	360	360
2001	R	Scintillation Survey Meter	1	700	700
			Total		4,010

Publications and Documentation Center

Fiscal Year	New/ Repl	Item	Q'ty	Unit Cost (x¥1000)	Total (x¥1000)
1997	R	PC DX-33	1	500	500
	R	PC DX/66	3	500	1,500
	R	PC P5-90	2	500	1,000
	R	PC P5-166	1	570	570
	R	Printer NEC PR-3000ps/4	1	400	400
	R	Printer JBCC PW5036	1	400	400
		Printer Brother HL-8PSJ	1	400	400
	R	Scanner set	1	410	410
	R	Software	14	50	700
	R	Canon EZPS	1	2,980	2,980
1998	R	Color copier, A Color 635	1	1,500	1,500
	R	Software	7	20	140
	R	PC P5-90	4	500	2,000
1999	R	PC P5-90	2	500	1,000
	R	Printer QMS825PS	1	480	480
	R	Software	10	50	500
	R	Canon EZPS	1	2,980	2,980
2000	R	PC P5-90	3	500	1,500
	R	PC P5-100	1	500	500
	R	Printer Xerox 4150	1	400	400
	R	Software	7	20	140
2001	R	PC P5-133	2	500	1,000
	R	Printer Zerox 4150	1	400	400
	R	Printer Canon LBP-203PS	1	1,300	1,300
	R	Software	10	50	500
			Total		23,200

Secretariat, Hiroshima

Fiscal Year	New/ Repl	Item	Q'ty	Unit Cost (x¥1000)	Total (x¥1000)
Director's Office					
1996	N	Printer	3	400	1,200
1997	N	PC	2	570	1,140
	R	Software	12	50	600
1998	R	PC	2	500	1,000
1999	R	PC	4	500	2,000
2000	R	Printer	2	400	800
	R	Software	14	50	700
2001	R	Printer	3	400	1,200
General Affairs Section					
1997	R	PC	2	500	1,000
	R	Software	8	50	400
1998	R	PC	2	500	1,000
	R	Printer	2	220	440
2000	R	Software	8	50	400
Personnel Section					
1996	N	PC	1	570	570
1997	N	PC	1	570	570
1998	R	PC	2	500	1,000
	R	Printer	2	220	440
2000	R	Printer	1	750	750
	R	Software	6	50	300
Accounting Section					
1997	R	Printer	1	220	220
	R	Software	7	50	350
1998	R	PC	4	500	2,000
	R	Printer	1	220	220
1999	R	PC	3	500	1,500
	R	Printer	1	220	220
	R	Software	7	50	350
2001	R	Printer	1	220	220
Supply & Property Section					
1997	N	PC	3	570	1,710
	R	Software	5	50	250
1998	R	PC	4	500	2,000
	R	Printer	1	220	220
1999	R	Printer	1	220	220
	R	Software	8	50	400
			Total		25,390

Secretariat, Nagasaki

Fiscal Year	New/ Repl	Item	Q'ty	Unit Cost (x¥1000)	Total (x¥1000)
General Affairs Section					
1996	N	PC	2	570	1,140
	N	Printer	1	220	220
1997	R	PC	2	500	1,000
	R	Printer	1	220	220
	R	Software	6	50	300
1998	R	Printer	2	220	440
1999	R	PC	4	500	2,000
2000	R	Printer	1	220	220
	R	Software	8	50	400
Accounting Section					
1996	N	PC	2	570	1,140
	N	Printer	1	220	220
1997	R	PC	2	500	1,000
	R	Software	2	50	100
1999	R	Printer	1	220	220
2000	R	Printer	1	220	220
	R	Software	4	50	200
			Total		9,040

Department of Clinical Studies (Hiroshima)
5-Year Computer Equipment Summary

Year	Item	Qty	Unit Cost	Research Use Total	Admin and Service Use Total
1997	PC DX2-66 (Replace)	3	500	-	1,500
	PC P5-166 (Add)	4	570	1,824	456
	Laser printer (Add)	1	400	320	80
	Basic Software version up	1	50	25	25
	Basic Software version up	5	50	-	250
	Exceed Software version up	2	6	12	-
	Origin Software version up	2	20	40	-
	Corel Draw Soft. version up	2	40	80	-
	Total			**2,301**	**2,311**
1998	PC P5-90 (Replace)	3	500	-	1,500
	Laser printer (Replace)	1	400	-	400
	Exceed Software version up	2	6	12	-
	Origin Software version up	2	20	40	-
	Total			**52**	**1,900**
1999	PC P5-133 (Replace)	1	500	400	100
	PC P5-133 (Replace)	2	500	-	1,000
	Laser printer old Xerox	1	400	-	400
	Basic Software version up	5	50	125	125
	Basic Software version up	8	50	-	400
	Exceed Software version up	2	6	12	-
	Origin Software version up	2	20	40	-
	Corel Draw Soft. version up	2	40	80	-
	Total			**657**	**2,025**
2000	Laser printer (Replace)	1	400	-	400
	Software version up (OS)	5	20	50	50
	Software version up (OS)	8	20	-	160
	Exceed Software version up	2	6	12	-
	Origin Software version up	2	20	40	-
	Total			**102**	**610**
2001	PC P5-166 (Replace)	4	500	1,600	400
	PC P5-166 (Replace)	3	500	-	1,500
	Basic Software version up	5	50	125	125
	Basic Software version up	8	50	-	400
	Exceed Software version up	2	6	12	-
	Origin Software version up	2	20	40	-

	Corel Draw Soft. version up	2	40	80	-
	Total			1,857	2,425
	Grand Total			4,969	9,271

Department of Clinical Studies (Nagasaki)
5-Year Computer Equipment Summary

Year	Item	Qty	Unit Cost	Research Use Total	Admin and Service Use Total
1997	PC DX-33 (Replace)	1	500	-	500
	Laser printer (Replace)	1	220	-	220
	Basic Software version up	3	50	75	75
	Basic Software version up	3	50	-	150
	Exceed Software version up	2	6	12	-
	Origin Software version up	2	20	40	-
	Total			127	945
1998	PC P5-90 (Replace)	1	500	400	100
	PC P5-90 (Replace)	1	500	-	500
	Exceed Software version up	2	6	12	-
	Origin Software version up	2	20	40	-
	Total			452	600
1999	PC P5-133 (Replace)	1	500	400	100
	PC P5-133 (Replace)	2	500	-	1,000
	Laser printer (Replace)	1	400	-	400
	Basic Software version up	3	50	75	75
	Basic Software version up	3	50	-	150
	Exceed Software version up	2	6	12	-
	Origin Software version up	2	20	40	-
	Total			527	1,725
2000	Laser printer (Replace)	1	400	-	400
	Exceed Software version up	2	6	12	-
	Origin Software version up	2	20	40	-
	Total			52	400
2001	PC P5-166 (Replace)	1	500	400	100
	Basic Software version up	3	50	75	75
	Basic Software version up	3	50	-	150
	Exceed Software version up	2	6	12	-
	Origin Software version up	2	20	40	-
	Total			527	325
	Grand Total			1,685	3,995

Department of Epidemiology (Hiroshima)
5-Year Computer Equipment Summary

Year	Item	Qty	Unit Cost	Research Use Total	Admin and Service Use Total
1997	PC replacement	8	500	2,800	1,200
	Printer replacement	1	500	400	100
	New Hardware	1	500	421	79
	Software upgrades	26	60	1,092	468
	New software	4	40	128	32
	Mocrotome (Path)	1	600	600	-
	Incubator (Path)	1	240	240	-
	Paraffin cleaner (Path)	1	130	130	-
	Total			**5,811**	**1,879**
1998	PC replacement	8	500	2,800	1,200
	Printer Replacement	1	500	350	150
	New Hardware	1	500	421	79
	Sofware upgrades	25	60	1,050	450
	New software	7	40	196	84
	Path equipment replacement	1	150	150	-
	Total			**4,967**	**1,963**
1999	PC replacement	8	525	2,940	1,260
	Printer Replacement	1	500	400	100
	New Hardware	1	520	440	80
	Sofware upgrades	25	60	1,050	450
	New software	3	40	96	24
	Path equipment replacement	1	150	150	-
	Total			**5,076**	**1,914**
2000	PC replacement	8	525	2,940	1,260
	Printer Replacement	1	500	350	150
	New Hardware	1	520	440	80
	Sofware upgrades	16	90	1,008	432
	New software	6	40	168	72
	Path equipment replacement	1	150	150	-
	Total			**5,056**	**1,994**
2001	PC replacement	8	525	2,940	1,260
	Printer Replacement	1	500	400	100
	New Hardware	1	520	416	104
	Sofware upgrades	16	90	1,008	432
	New software	6	40	192	48

	Path equipment replacement	1	150	150	-
	Total			**5,106**	**1,944**
	Grand Total			**26,016**	**9,694**

Department of Epidemiology (Nagasaki)
5-Year Computer Equipment Summary

Year	Item	Qty	Unit Cost	Research Use Total	Admin and Service Use Total
1997	PC withfull set of standard software	1	570	456	114
	PC 486DX/66 (Replace)	2	500	800	200
	PC 486DX/33 (Replace)	2	500	800	200
	PC 386/33 (Replace with full set of	1	570	456	114
	Laser printer (Replace by 4-year lease)	1	700	560	140
	Laser printer (Replace)	3	400	960	240
	Exceed software (New)	1	40	40	-
	Origin software (New)	1	50	50	-
	Basic software version up	2	50	100	-
	Basic software version up	2	50	-	100
	Basic software version up	13	50	520	130
	Exceed software version up	2	6	12	-
	Exceed software version up	2	6	-	12
	Exceed software version up	9	6	43	11
	Origin software version up	2	20	40	-
	Chameleon software (New)	1	100	80	20
	Total			**4,917**	**1,281**
1998	PC P5-130 (Replace)	1	500	500	-
	PC P5-90 (Replace)	1	500	-	500
	PC P5-90 (Replace)	3	500	1,200	300
	Laser printer (4-year lease)	1	700	560	140
	Exceed software version up	3	6	18	-
	Exceed software version up	2	6	-	12
	Exceed software version up	9	6	43	11
	Origin software version up	3	20	60	-
	Total			**2,381**	**963**
1999	PC P5-130 (Replace)	2	500	800	200
	Laser printer (4-year lease)	1	700	560	140
	Laser printer (Replace)	2	400	640	160
	Basic software version up	3	50	150	-
	Basic software version up	2	50	-	100
	Basic software version up	13	50	520	130
	Exceed software version up	3	6	18	-
	Exceed software version up	2	6	-	12

	Exceed software version up	9	6	43	11
	Origin software version up	3	20	60	-
	Total			**2,791**	**753**
2000	Laser printer (4-year lease)	1	700	560	140
	Exceed software version up	3	6	18	-
	Exceed software version up	2	6	-	12
	Exceed software version up	9	6	43	11
	Origin software version up	3	20	60	-
	Total			**681**	**163**
2001	PC P5-166 (Replace)	6	500	2,400	600
	Laser printer (4-year lease)	1	700	560	140
	Laser printer (Replace)	3	400	960	240
	Basic software version up	3	50	150	-
	Basic software version up	2	50	-	100
	Basic software version up	13	50	520	130
	Exceed software version up	3	6	18	-
	Exceed software version up	2	6	-	12
	Exceed software version up	9	6	43	11
	Origin software version up	3	20	60	-
	Total			**4,711**	**1,233**
	Grand Total			**15,482**	**4,392**

Department of Genetics (Hiroshima)
5-Year Computer Equipment Summary

Year	Item	Qty	Unit Cost	Research Use Total	Admin and Service Use Total
1997	PC (Add)	4	500	1,600	400
	PC hontai (Replace)	4	300	960	240
	Workstation (Replace)	1	1,500	1,500	-
	Hard disk (New)	2	200	400	-
	Software version up	18	20	181	181
	Software (New)	4	100	200	200
	Total			**4,841**	**1,021**
1998	PC (Add)	1	500	400	100
	Hard disk (New)	2	200	400	-
	Software version up	19	34	326	326
	Software (New)	1	100	50	50
	Total			**1,176**	**476**
1999	PC (Add)	1	525	420	105
	PC hontai (Replace)	3	315	756	189
	Hard disk (New)	2	210	420	-

	Software version up	20	37	371	371
	Software (New)	1	100	50	50
	Total			**2,017**	**715**
2000	PC (Add)	1	550	440	110
	Printer (Replace)	2	440	704	176
	Hard disk (New)	2	220	440	-
	Software version up	21	39	412	412
	Software (New)	1	100	50	50
	Total			**2,046**	**748**
2001	PC hontai (Replace)	2	330	528	132
	Workstation (Replace)	1	2,000	2,000	-
	Hard disk (New)	2	220	440	-
	Software version up	21	38	401	401
	Software (New)	1	100	50	50
	Total			**3,419**	**583**
	Grand Total			**13,499**	**3,543**

Department of Radiobiology (Hiroshima)
5-Year Computer Equipment Summary

Year	Item	Qty	Unit Cost	Research Use Total	Admin and Service Use Total
1997	PC DX-66 (Replace)	3	500	-	1,500
	PCP5-166(Add)	4	570	1,824	456
	Laserprinter(Replace)	1	400	-	400
	BasicSoftwareversionup	2	50	50	50
	BasicSoftwareversionup	2	50	-	100
	ExceedSoftwareversionup	2	6	12	-
	OriginSoftwareversionup	2	20	40	-
	CorelDrawSoft.versionup	2	40	80	-
	Total			**2,006**	**2,506**
1998	PCP5-90(Replace)	2	500	-	1,000
	Laserprinter(Replace)	1	400	-	400
	ExceedSoftwareversionup	2	6	12	-
	OriginSoftwareversionup	2	20	40	-
	Total			**52**	**1,400**
1999	BasicSoftwareversionup	6	50	150	150
	BasicSoftwareversionup	5	50	-	250
	ExceedSoftwareversionup	2	6	12	-

	OriginSoftwareversionup	2	20	40	-
	CorelDrawSoft.versionup	2	40	80	-
	Total			**282**	**400**
2000	Softwareversionup(OS)	6	20	60	60
	Softwareversionup(OS)	5	20	-	100
	ExceedSoftwareversionup	2	6	12	-
	OriginSoftwareversionup	2	20	40	-
	Total			**112**	**160**
2001	PCP5-90(Replace)	4	500	1,600	400
	BasicSoftwareversionup	6	50	150	150
	BasicSoftwareversionup	5	50	-	250
	ExceedSoftwareversionup	2	6	12	-
	OriginSoftwareversionup	2	20	40	-
	CorelDrawSoft.versionup	2	40	80	-
	Total			**1,882**	**800**
	GrandTotal			**4,334**	**5,266**

Department of Statistics (Hiroshima)
5-Year Computer Equipment Summary

Year	Item	Qty	Unit Cost	Research Use Total	Admin and Service Use Total
1997	PC replacement	6	500	2,000	1,000
	Network Disk Storage	1	300	300	-
	New Hardware	1	475	400	75
	Sofware upgrades	12	83	700	300
	New software	6	50	250	50
	Total			**3,650**	**1,425**
1998	PC replacement	6	500	2,000	1,000
	Printer Replacement	1	500	350	150
	New Hardware	1	475	400	75
	Sofware upgrades	12	83	700	300
	New software	6	50	250	50
	Total			**3,700**	**1,575**
1999	PC replacement	6	525	2,100	1,050
	Network Disk Storage	1	320	320	-
	New Hardware	1	520	440	80
	Sofware upgrades	12	89	750	315
	New software	6	59	280	75

	Total			**3,890**	**1,520**
2000	PC replacement	6	525	2,100	1,050
	Printer Replacement	1	500	370	130
	New Hardware	1	520	440	80
	Sofware upgrades	12	89	750	315
	New software	6	59	280	75
	Total			**3,940**	**1,650**
2001	PC replacement	6	550	2,200	1,100
	Network Disk Storage	1	330	330	-
	New Hardware	1	565	480	85
	Sofware upgrades	12	92	770	330
	New software	6	63	300	80
	Total			**4,080**	**1,595**
	Grand Total			**19,260**	**7,765**

Department of Information Technology (Hiroshima)
5-Year Computer Equipment Summary

Year	Item	Qty	Unit Cost	Research Use Total	Admin and Service Use Total
1997	PC (Add)	3	520	-	1,560
	PC(Replace)	7	520	-	3,640
	Network disk storage	1	200	-	200
	Printer (Replace)	1	500	-	500
	New hardware	1	500	-	500
	Software (New)	21	19	-	400
	Software version up	21	100	-	2,100
	ITD Staff Total			-	*8,900*
	RERF-wide services: computer and network hardware/software replacement	1	36,000	-	36,000
	Grand Total			-	**44,900**
1998	PC (Add)	2	520	-	1,040
	PC(Replace)	9	520	-	4,680
	Printer (Replace)	1	500	-	500
	New hardware	1	500	-	500
	Software (New)	23	17	-	400
	Software version up	23	100	-	2,300
	ITD Staff Total			-	*9,420*

	RERF-wide services: computer and network hardware/software replacement	1	36,000	-	36,000
	Grand Total			-	**45,420**
1999	PC (Add)	1	550	-	550
	PC(Replace)	10	550	-	5,500
	Network disk storage	1	210	-	210
	Printer (Replace)	1	525	-	525
	New hardware	1	525	-	525
	Software (New)	24	18	-	420
	Software version up	24	105	-	2,520
	ITD Staff Total			-	***10,250***
	RERF-wide services: computer and network hardware/software replacement	1	37,800	-	37,800
	Grand Total			-	**48,050**
2000	PC(Replace)	11	550	-	6,050
	Printer (Replace)	1	525	-	525
	New hardware	1	525	-	525
	Software (New)	24	18	-	420
	Software version up	24	105	-	2,520
	ITD Staff Total			-	***10,040***
	RERF-wide services: computer and network hardware/software replacement	1	37,800	-	37,800
	Grand Total			-	**47,840**
2001	PC(Replace)	11	577	-	6,350
	Network disk storage	1	220	-	220
	Printer (Replace)	1	550	-	550
	New hardware	1	550	-	550
	Software (New)	24	18	-	440
	Software version up	24	110	-	2,650
	ITD Staff Total			-	***10,760***
	RERF-wide services: computer and network hardware/software replacement	1	39,700	-	39,700
	Grand Total			-	**50,460**
	Five-Year Total			-	**236,670**

Actual Personnel Strength and Projected Changes

	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001
Grand Total	427	433	437	435	412	373	335	331	323	318	315	312
Director & Other	6	6	5	6	6	5	5	5	5	5	5	5
Professional Staff	57	61	64	62	57	48	47	50	50	50	50	50
General Staff	364	366	368	367	349	320	283	276	268	263	260	257

Actual Personnel and Operating Costs and Budget Estimates (Unit:¥1,000)

	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001
Personnel costs (Term. allowance)	3,227,676 (208,852)	3,304,603 (163,105)	3,742,938 (391,230)	3,635,153 (274,021)	3,559,650 (405,884)	3,881,353 (947,102)	2,781,100 (27,137)	3,692,476 (789,902)	3,296,604 (446,993)	3,170,297 (314,997)	3,301,463 (427,976)	3,252,828 (335,835)
Operating costs	802,336	858,687	871,424	851,988	799,292	851,549	725,385	819,419	825,866	849,327	850,348	875,590
Total	4,030,012	4,163,290	4,614,362	4,487,141	4,358,942	4,732,902	3,506,485	4,511,895	4,122,470	4,019,624	4,151,811	4,128,418

Actual Costs of Equipment and Supplies and Budget Estimates (Unit:¥1,000)

	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001
Equipment	98,262	110,204	81,072	96,180	125,014	95,965	51,808	132,491	128,634	141,636	132,042	146,509
Supplies(Reagent)	67,587	61,305	70,879	70,154	55,953	49,908	49,908	50,656	51,416	52,187	52,970	53,765
Supplies(Lab)	82,770	71,923	77,649	93,165	83,247	58,413	66,129	67,121	68,128	69,150	70,187	71,240

Note:Personnel and operating costs are actual up to FY95, estimate from FY96 and after. For calculation of personnel costs, 1% base up is assumed for FY96, 2% for FY97 and after. Operating costs in FY96 were estimated to be ¥725,385,000 and a 1.5% yearly increase in FY97 and after.
The number of employees as of 1 January 2002 is 310.

FIVE YEAR STRATEGIC RESEARCH PLAN AND PROGRAM MANAGEMENT

ERRATA

line 343: "Among this later group" should read "Among this latter group"

line 717: "facilitate RERF" should read "facilitate this end RERF"

lines 735-740 should be replaced with the following:

One of the major sources of tissues from the A-bomb survivors is from the on-going collection of blood samples. This supply of viable cells from the survivors is a valuable resource for the study of many diseases including those with immune system dysfunction. Reduced immune function can potentially lead to a variety of pathologic consequences including cancer, which is known to show heightened risk among the survivors. RERF has a matchless opportunity to investigate the late effects of radiation exposure on the immune system.

We plan to continue our studies of the features and mechanisms of radiation-induced disorders in the hematolymphoid system at the cellular and molecular levels. These studies include radiation effects on the distribution of T-cell subsets in the survivors and of radiation effects on endocrine and hematopoietic growth factor levels as well as the study of stem cells, the progenitors of cells which constitute the immune system.

line 941: After clinical management system insert "is being developed"

line 1518: After the word example, insert "we have been able to obtain "

line 2701: "FISH examination or survivors" should read "FISH examination of survivors"

line 2942: The superscript after 17.3 should read 4,5

line 4610: read 64 to 47 rather than 60 to 47

line 4693: the row in the table labeled "sub-total" under the column "Directors" should have the number 5 inserted

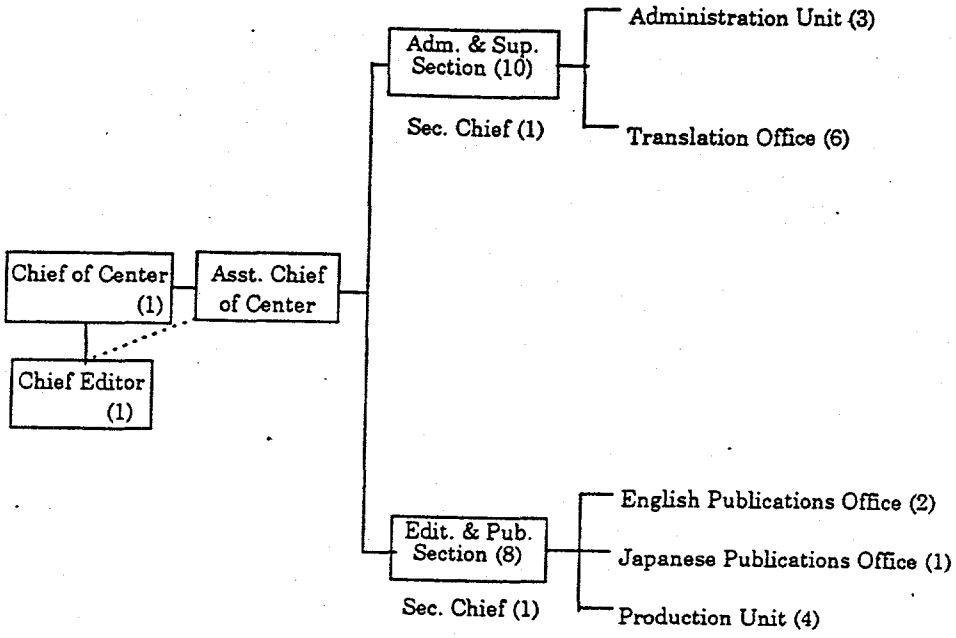
line 4287: After **Organization** please insert the accompanying table of organization that begins with the word Present

Replace the table occurring between page 103 and 104 with the new one attached

Replace the very last table beginning with "Actual Personnel Strength and Project Changes" with the new one with the same heading that is attached

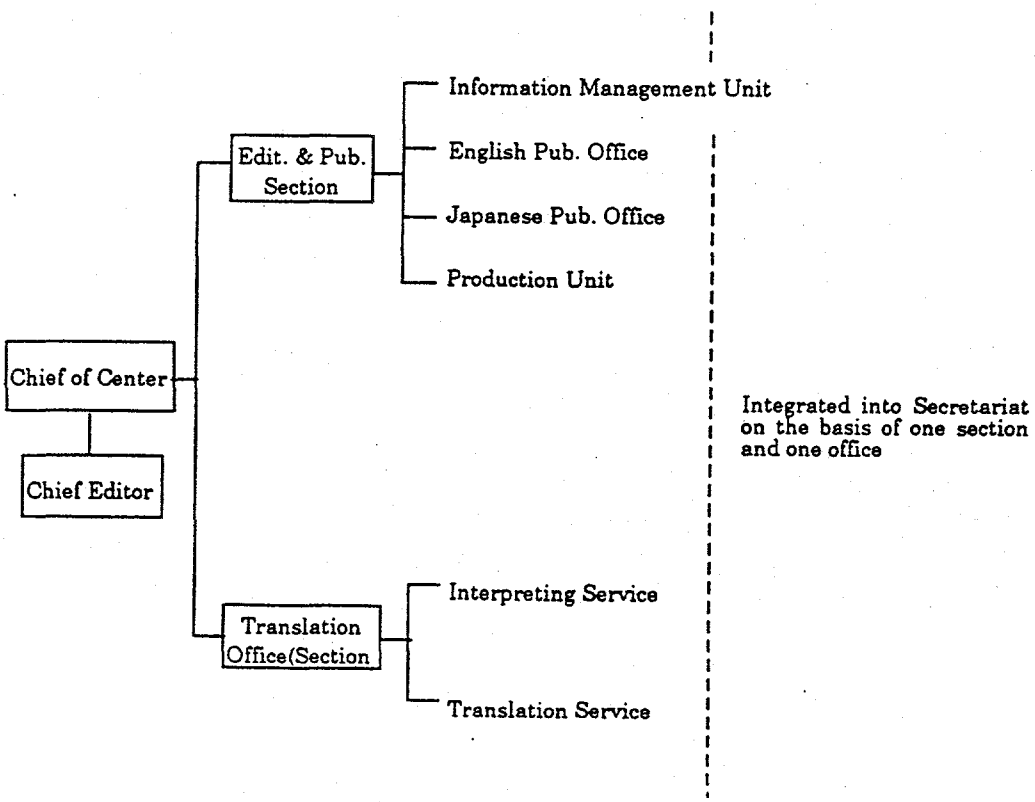
Present

Staff: **Professional** 1
Administrative 20
Total 21



Revised Organizational Structure (draft)

1 January 1998 | 1 January 1999



研究部門備品要求表 (1996年 ~ 2001年)

Equipment Requests by Research Departments

(単位：千円) (UNIT:¥1,000)

	部・局	DEPARTMENT	FY1996	FY1997	FY1998	FY1999	FY2000	FY2001	合計
	疫学部	EPIDEMIOLOGY	0	7,690	6,930	6,990	7,050	7,050	35,710
	臨床研究部	CLINICAL STUDIES	0	8,372	4,485	16,210	712	11,565	41,344
	遺伝学部	GENETICS	0	21,011	10,347	30,381	2,794	4,002	68,535
	放生部	RADIOBIOLOGY	0	49,412	83,652	20,682	13,572	6,882	174,200
	統計部	STATISTICS	0	5,075	5,275	5,410	5,590	5,675	27,025
	広島合計	HIROSHIMA TOTAL	0	91,560	110,689	79,673	29,718	35,174	346,814
	臨床研究部	CLINICAL STUDIES	0	20,117	1,052	2,252	3,452	852	27,725
	疫学部	EPIDEMIOLOGY	0	6,198	3,344	3,544	844	5,944	19,874
	長崎合計	NAGASAKI TOTAL	0	26,315	4,396	5,796	4,296	6,796	47,599
①	両市合計	BOTH TOTAL	0	117,875	115,085	85,469	34,014	41,970	394,413

サポート部門備品要求表 (1996年 ~ 2001年)

Equipment Requests by Supporting Departments

	部・局	DEPARTMENT	FY1996	FY1997	FY1998	FY1999	FY2000	FY2001	合計
	出版資料センター	PDC	0	8,860	3,640	4,960	2,540	3,200	23,200
	研究情報センター	ITD	0	44,900	45,420	48,050	47,840	50,460	236,670
	放射線同位 RI	RI FACILITIES	0	2,500	0	450	360	700	4,010
	事務局	SECRETARIAT	1,770	6,240	8,320	4,690	2,950	1,420	25,390
	広島合計	HIROSHIMA TOTAL	1,770	62,500	57,380	58,150	53,690	55,780	289,270
	事務局	SECRETARIAT	2,720	2,620	440	2,220	1,040	0	9,040
	長崎合計	NAGASAKI TOTAL	2,720	2,620	440	2,220	1,040	0	9,040
②	両市合計	BOTH TOTAL	4,490	65,120	57,820	60,370	54,730	55,780	298,310

①+②	合計		4,490	182,995	172,905	145,839	88,744	97,750	692,723

現金購入	PURCHASE COST	4,490	110,655	86,872	86,021	73,344	87,967	449,349
リース支払い	LEASE CHARGE	0	16,754	36,680	50,533	54,100	56,365	214,431
従来のリース支払	CURRENT LEASE CHARGE	17,095	5,082	5,082	5,082	4,598	2,177	39,116
合計	TOTAL	21,585	132,491	128,634	141,636	132,042	146,509	702,896

コンピューター関係分	For Computer	4,490	94,381	80,017	82,462	73,314	86,797	421,461