

October 15, 1996

**RADIATION EFFECTS RESEARCH FOUNDATION**  
**THE 23RD RERF SCIENTIFIC COUNCIL MEETING**

**November 13 - 15, 1996**  
**Beckman Center, Irvine, California**

**Tentative Agenda**

**Day 1: November 13, Wednesday**

|   |   |                             |
|---|---|-----------------------------|
| 9:00 - 9:30                                 | Executive session   | Drs. Matsunaga/<br>Motulsky |
| 9:30 - 9:35                                 | Greetings by RERF Chairman  | Dr. Shigematsu              |
| 9:35 - 9:45                                 | Briefing on Recent Developments   | Dr. Schull                  |
| 9:45 - 10:15                                | Report from Chief of Research   | Dr. Schull                  |
| 10:15 - 10:30                               | Coffee break  |                             |
| 10:30 - 12:15                               | Discussion of general responses to<br>Blue Ribbon Panel recommendations |                             |
| 12:15                                       | Photograph  |                             |
| 12:30 - 13:30                               | Lunch at Beckman Center   |                             |
| <del>16:30</del> - <del>17:30</del>         |   |                             |
| 13:30 - 15:10                               | Discussion of F1 feasibility study                                      |                             |
| 15:10 - 15:30                               | Coffee break  |                             |
| 15:30 - 16:30                               | Continuation of discussion of F1 study                                  |                             |
| <del>16:30</del> - <del>17:30</del>         |   |                             |
| <sup>3</sup> 16:30 - <sup>15:10</sup> 17:30 | Discussion of restructuring of the<br>Scientific Council                |                             |
| 18:00                                       | Reception and dinner at Beckman Center                                  |                             |

**Day 2: November 14, Thursday**

|               |  |  |
|---------------|--|--|
| 9:00 - 10:30  | Discussion of Strategic Research Plan and Program<br>Management Document |  |
| 10:30 - 10:50 | Coffee break   |  |

10:50 - 12:00 Continuation of discussion of strategic research plan  
12:00 - 13:00 Lunch at Beckman Center  
13:00 - 15:00 Continuation of discussion of strategic research plan  
15:00 - 15:15 Coffee break  
15:15 - 17:30 Continuation of discussion of strategic research plan  
18:00 Dinner for members of the Scientific Council

**Day 3: November 15, Friday**

9:00 - 11:30 Executive session (Closed)  
Preparation of recommendations

11:30 - 12:00 Recommendations Drs. Matsunaga/  
Motulsky

12:00 - 12:05 Closing remarks by RERF Vice Chairman Dr. Schull

12:05 - 13:30 Lunch at Beckman Center

as of 18 October 1996

**TWENTY THIRD SCIENCE COUNCIL MEETING  
THE RADIATION EFFECTS RESEARCH FOUNDATION**

Time and Date: November 13, Wednesday - 15, Friday, 1996

Place: Arnold and Mabel Beckman Center,  
The National Academies of Sciences and Engineering  
100 Academy Drive, Irvine, California 92715, U.S.A.  
Phone:(714)721-2200 FAX:(714)721-2288

List of Expected Participants

SCIENCE COUNCILORS

*Dr. Tomio Hirohata*, Professor Emeritus, Kyushu University

*Dr. Eisei Ishikawa*, Professor Emeritus, Jikeikai University School of Medicine

*Dr. Hiromichi Matsudaira*, Consultant, Japan Science and Technology Corporation

*Dr. Ei Matsunaga*, Professor Emeritus, National Institute of Genetics

*Dr. Shigefumi Okada*, Professor Emeritus, University of Tokyo

*Dr. Curtis C. Harris*, Chief, Laboratory of Human Carcinogenesis National Cancer Institute

*Dr. Clark W. Heath, Jr.*, Vice President for Epidemiology and Statistics, American Cancer Society

*Dr. John B. Little*, James Stevens Simmons Professor of Radiobiology, Harvard University School of Public Health

*Dr. Arno G. Motulsky*, Professor of Medicine and Genetics, School of Medicine, University of Washington

*Dr. Susan Preston-Martin*, Professor, Department of Preventive Medicine, University of Southern California/Norris Comprehensive Cancer Center

OBSERVERS

*Mr. Masayuki Kimura*, Director, Planning Division, Health Service Bureau, Ministry of Health and Welfare

*Dr. Hiroshi Maruyama*, Assistant Director, Planning Division, Health Service Bureau, Ministry of Health and Welfare

*Dr. Takashi Kitaba*, Unit Chief, Planning Division, Health Service Bureau, Ministry of Health and Welfare

*Dr. Paul Seligman*, Deputy Assistant Secretary for Health, US Department of Energy

*Mr. Frank C. Hawkins*, Director, Office of International Health Studies, US Department of Energy

*Dr. Joseph Weiss*, Program Manager, DoE Postdoctoral Fellowship Program, and Japan Project Team Administrator

*Ms. Elizabeth L. White*, Japan Project Team, Office of International Health Studies, US Department of Energy

*Dr. Paul Gilman*, Executive Director, Commission on Life Sciences, National Research Council, National Academy of Sciences

*Dr. John D. Zimbrick*, Director, Board on Radiation Effects Research, Commission on Life Sciences, National Research Council, National Academy of Sciences

*Mrs. Catherine Berkley*, Administrative Associate, National Research Council, National Academy of Sciences

*Ms. Doris E. Taylor*, Administrative Assistant, National Research Council, National Academy of Sciences

*Dr. Seymour Abrahamson*, Professor of Zoology, University of Wisconsin

*Dr. Mortimer L. Mendelsohn*, Associate director for Biomedical and Environmental Research, Lawrence Livermore National Laboratory

*Dr. Sheldon Wolff*, Professor of Cytogenetics, University of California, San Francisco

#### SUPERVISOR

*Mr. David Williams*, Senior Financial Advisor, National Academy of Sciences

#### RERF DIRECTORS

Dr. Itsuzo Shigematsu, Chairman

Dr. William J. Schull, Vice Chairman and Chief of Research

Dr. Yutaka Hasegawa, Permanent Director

#### RERF OPERATING COMMITTEE MEMBERS

Mr. Yasukiyo Hirano, Chief of Secretariat

Mr. Richard D. Sperry, Administrative Adviser

#### RERF DEPARTMENT CHIEFS/ASSISTANT CHIEF

Dr. Kazunori Kodama, Department Chief, Clinical Studies

Dr. Kiyohiko Mabuchi, Department Chief, Epidemiology

Dr. Chiyoko Sato, Department Chief, Genetics

Dr. Nori Nakamura, Assistant Chief, Department of Genetics

Dr. Dale L. Preston, Department Chief, Statistics

Dr. Toshio Seyama, Assistant Chief, Department of Radiobiology

Ms. Jill L. Ohara, Chief, Department of Information and Technology

#### INTERPRETERS

Mrs. Eiko Ishizaki

Ms. Naomi Umehara

## 第 23 回放射線影響研究所専門評議員会

日 時：平成 8 年 11 月 13 日（水）～15 日（金）  
場 所：米国学士院・米国技術院所属 アーノルト・メーベル・ヘックマンセンター  
100 Academy Drive, Irvine, California 92715  
TEL:(714)721-2200 FAX:(714)721-2288

出席予定者

1996 年 10 月 16 日現在

### 専門評議員

廣畑 富雄；九州大学名誉教授  
石川 栄世；東京慈恵会医科大学名誉教授  
松平 寛通；科学技術振興事業団顧問  
松永 英；国立遺伝学研究所名誉教授  
岡田 重文；東京大学名誉教授  
Curtis C. Harris；米国がん研究所人体発癌研究室長  
Clark W. Heath, Jr.；米国がん学会疫学統計学担当副会長  
John B. Little；米国 Harvard 大学放射線生物学 James Stevens Simmons  
記念講座教授  
Arno G. Motulsky；米国 Washington 大学医学部内科学及び遺伝学教授  
Susan Preston-Martin；米国南カリフォルニア大学 Norris 総合がんセンター予防医学教室  
教授

### オブザーバー

木村 政之；厚生省 保健医療局 企画課 課長  
丸山 浩；厚生省 保健医療局 企画課 課長補佐  
北波 孝；厚生省 保健医療局 企画課 係長  
Paul Seligman；米国エネルギー省 保健局副次官補  
Frank Hawkins；米国エネルギー省 国際保健調査部長  
Joseph Weiss；米国エネルギー省 学位取得後フェロシッププログラム管理官・日本  
プロジェクトチーム主事  
Elizabeth L. White；米国エネルギー省 国際保健調査部 日本プロジェクトチーム  
Paul Gilman；米国学士院 学術会議 生命科学部会 常任理事  
John D. Zimbrick；米国学士院 学術会議 生命科学部会 放射線影響研究委員会  
常任理事  
Catherine Berkley；米国学士院 学術会議 生命科学部会 放射線影響研究委員会  
課長補佐

Doris E. Taylor ; 米国学士院 学術会議 生命科学部会 放射線影響研究委員会  
秘書

Seymour Abrahamson ; 米国 Wisconsin 大学 動物学教授

Mortimer L. Mendelsohn ; 元米国ローレンスリバモア研究所副所長 生物医学  
及び環境研究担当

Sheldon Wolff ; 米国 California 大学 San Francisco 校 細胞遺伝学教授

## 監 事

David Williams ; 米国学士院 上級財政顧問

## 放影研理事

重松 逸造 ; 理事長

William J. Schull ; 副理事長・研究担当理事

長谷川 豊 ; 常務理事

## 放影研運営委員

平野 康清 ; 事務局長

Richard D. Sperry ; 事務局参与

## 放影研部長・副部長

児玉 和紀 ; 臨床研究部長

馬淵 清彦 ; 疫学部長

佐藤 千代子 ; 遺伝学部長

中村 典 ; 遺伝学副部長

Dale L. Preston ; 統計部長

瀬山 敏雄 ; 放射線生物学部副部長

Jill L. Ohara ; 情報技術部長

## 通訳

石寄英子

梅原直美



1 26 August 1996

2  
3 **RESPONSES TO RECOMMENDATIONS OF THE BLUE RIBBON PANEL**  
4 **DRAFT FOR COMMENTS AND DISCUSSION ONLY**  
5

6  
7 Introduction:

8 At the urging of the Science Council of the Radiation Effects Research  
9 Foundation (RERF) and with the concurrence and financial support of the  
10 governments of Japan and the United States, an international Blue Ribbon Panel  
11 was established in the autumn of 1995 to review the content and quality of the  
12 current research program at the Foundation, to evaluate the importance and  
13 merit of this research, and to suggest future studies that should be  
14 conducted. In addition, this Panel was requested to assess the scientific  
15 peer review process in use at the Foundation and to identify areas of research  
16 that could be conducted together with other institutions both in Japan and  
17 worldwide. The Panel, which was under the chairmanship of Professor Roger H.  
18 Clarke, Director of the United Kingdom's National Radiological Protection  
19 Board, met on two occasions once in Japan at the Foundation's two laboratories  
20 and once at the National Radiological Protection Board in Great Britain. On  
21 July 2, 1996, the Panel presented its final report to the two governments and  
22 to the management and staff of the Radiation Effects Research Foundation.  
23 Their report details some 21 recommendations. The Foundation has moved as  
24 expeditiously as practical in the drafting of its responses to these since the  
25 recommendations and our proposed actions impinge on the planning of future  
26 research activities and the funds needed to support them. The various  
27 recommendations are set forth in the paragraphs to follow along with the steps  
28 to be taken by the Foundation to implement the Panel's advice. These steps  
29 are the outgrowth of extensive discussions within the Foundation involving all  
30 of the professional staff and the resident Directors.

31 Before we turn to the individual recommendations and our responses, we  
32 would like to express our sincere appreciation to the Panel for its timely and  
33 cogent recommendations, and the thoroughness and objectivity with which it  
34 approached its charges. We are confident that with the continued financial  
35 support of the two governments, and the endorsement of the steps we propose  
36 by the survivors and their children as well as the scientific community at  
37 large, the Foundation will emerge from this review stronger and more dedicated  
38 in its efforts to understand the health effects of exposure to ionizing  
39 radiation and thereby to serve the survivors and their children better.

40  
41 The recommendations and the Foundation's responses:  
42

43 Recommendation 1.

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

51

52 Response:

53 The Foundation welcomes this affirmation of the importance of its  
54 Departments of Epidemiology and the need to continue the collection of  
55 mortality and cancer incidence data. These data are central to the mission  
56 of the Foundation and deserving of the highest research priority. But we  
57 note too that research on radiation-related non-cancer mortality is  
58 potentially one of the most significant issues in the years ahead for the  
59 Foundation. In addition, we recognize that the wealth of information  
60 collected over the years is potentially valuable to studies of lifestyle and  
61 other non-radiation risk factors. We will place more emphasis on analysis of  
62 such information which will provide better understanding of how radiation  
63 exposures are involved in the pathogenesis of disease in the presence of other  
64 factors. Such an approach will be particularly useful for studying the nature  
65 of radiation-related non-cancer risks, but should be equally relevant for  
66 cancer studies. This is an area in which collaboration with outside  
67 institutions may be particularly fruitful.

68 As the Blue Ribbon Panel aptly recognized, the Departments of  
69 Epidemiology are woefully understaffed. Attempts to rectify this situation  
70 have thus far met with limited success. Renewed, creative efforts are being  
71 undertaken to deal with this serious problem. While the Foundation should be  
72 able to solve our immediate needs, it is not feasible to deal with these  
73 staffing problems on an individual replacement basis, and a program of  
74 continuing recruitment activities must be put in place. In view of the  
75 problems in the recruiting of qualified epidemiologists and their central role  
76 in all RERF research, it is essential to have the ability to hire qualified  
77 epidemiologists when they are identified. In order to facilitate recruitment  
78 and to strengthen collaborative work, the Foundation hopes to develop formal  
79 ties to strong US epidemiology programs along the lines of the planned RERF-  
80 University of Southern California-NAS collaboration that was abandoned as a  
81 result of uncertainties about the Academy's role in the management of the  
82 Foundation.

83 It is vital to the future of the Foundation that it take advantage of  
84 the Academy's role in recruitment of non-Japanese staff. This is one of the

85 most consequential activities that the Academy performs, and it is important  
86 that adequate funding and personnel resources are available to support this  
87 effort. In the past, contracts were awarded to groups to assist the Academy  
88 in promoting interest in employment opportunities at the Foundation. There  
89 is potentially great return on such investment in terms of attracting  
90 qualified personnel and the progress in research that results. The Foundation  
91 also intends to work closely with the Academy in areas other than recruiting  
92 to take advantage of the Academy's broad contacts throughout the scientific  
93 community to increase awareness of the Foundation's research and to identify  
94 new investigative initiatives. As a first step we are particularly interested  
95 in working with the Academy on a proposal to organize a workshop on radiation  
96 and non-cancer mortality that would bring together a broad spectrum of  
97 scientists who would be presented with a detailed summary of the emerging  
98 evidence for an association between radiation and non-cancer endpoints  
99 (including mortality and clinical findings). We believe that such a workshop  
100 could directly benefit our program by helping us to develop ideas for future  
101 work on non-cancer effects and serve to stimulate outside groups to undertake  
102 studies that might suggest possible mechanisms for such late effects.

103 In addition to the recruitment of experienced epidemiologists we propose  
104 the establishment of a number of two year Foundation-supported post-doctoral  
105 positions. Such a program can help us deal with immediate personnel needs,  
106 serve as a source for recruitment of permanent staff, strengthen ties to other  
107 institutions, and increase awareness of the research opportunities at the  
108 Foundation. This approach will be especially useful in the recruitment and  
109 training of Japanese epidemiologists for work at RERF.

110 It would also be of benefit to Epidemiology and all other departments  
111 to encourage a more effective use of the established program of sabbaticals  
112 at RERF to enable long-term staff to obtain additional training and experience  
113 related to the Foundation's needs. As with the post-doctoral program, better  
114 use of the sabbatical system would directly benefit the Foundation through the  
115 acquisition of new skills and strengthen ties with university groups.

116  
117 *Recommendation 2.*

118 *We recommend that the Department of Statistics should continue to*  
119 *produce analyses of the risks of radiation exposure in collaboration with the*  
120 *Epidemiology Departments and that the high quality of the research in the*  
121 *Statistics Department be maintained.*

122  
123 *Response:*

124 The Foundation recognizes the need to maintain a staff in the Department  
125 of Statistics of the highest achievable caliber and to encourage that staff  
126 to continue its research in collaboration with the Departments of

127 Epidemiology. The statistical staff has a well-deserved worldwide reputation  
128 which, since their activities impinge on every department at the Foundation,  
129 needs careful, continued nurturing. To this end, a vigorous effort will be  
130 made to increase the staff of this department. As with the Departments of  
131 Epidemiology, we have begun to recruit statisticians through advertisements  
132 in suitable professional journals and direct contacts with statistical groups  
133 in the United States. In order to deal with immediate needs regarding  
134 analyses of longitudinal clinical data, arrangements are being made by the  
135 Foundation for an experienced statistician familiar with these data to work  
136 with the staff on a part-time contract basis. However, in view of the short-  
137 term status of much of the staff and the difficulties in hiring experienced  
138 statisticians, an on-going recruitment effort must be maintained. The  
139 Department of Statistics will also seek to recruit Foundation-funded post-  
140 doctoral fellows to work on specific projects such as the mechanistic modeling  
141 of radiation-induced cancer or pattern recognition problems involved in the  
142 search for evidence of mutation in the  $F_1$ .

143  
144 *Recommendation 3.*

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

149  
150 *Response:*

151 The Foundation welcomes the Blue Ribbon Panel's endorsement of its past  
152 practices and will continue to strive to make its data as widely and easily  
153 accessible to others as is consistent with established practices regarding  
154 privacy and confidentiality of the information. While RERF plans to continue  
155 to distribute data on floppy disks, the Information Technology Department is  
156 currently developing an online data access facility that will allow people  
157 outside the Foundation to obtain publicly available data files using the  
158 Internet.

159 Since the establishment of the fixed surveillance samples in 1958-1959,  
160 the Foundation and its predecessor, the Atomic Bomb Casualty Commission  
161 (ABCC), has followed a policy of sharing its information with other  
162 investigators as widely as circumstances permitted. During the period 1960-85  
163 extensive appendix tabulations were provided with the primary reports on  
164 mortality, which came as close as was then technically feasible to presenting  
165 the data in the form from which the calculations in these reports were made  
166 (see, e.g., Beebe, Land and Kato, ABCC TR 1-77). As statistical methods were  
167 developed in the 1980's which used the data in more detail, a decision was  
168 made to provide on electronic media the far more detailed cross-tabulations

169 upon which the calculations were based. This is exceptional among medical  
170 research institutions and the response has been extremely gratifying for RERF  
171 investigators due to the importance and richness of the data, and possible  
172 controversies regarding their interpretation.

173 Where some significant data are yet to be made available, this is  
174 primarily due to the difficulties in organizing the data, much of which was  
175 gathered many years ago and used infrequently in recent years. For example,  
176 it has required a major effort over the past two years to organize the data  
177 in a unified way regarding cancer mortality among those exposed in utero.  
178 Similar efforts need to be made for other data, such as those on mental  
179 testing done on the in utero cohort, but as has been noted the staffing in  
180 Epidemiology and Statistics is not at ideal levels, and there are priorities  
181 for the work to be done. Despite difficulties we believe it will be possible  
182 to make progress in these areas. It should be noted that there are  
183 significant difficulties as well due to the dynamic nature of the data sets,  
184 involving corrections and updates. Attention will be given to a more  
185 elaborate version control system to deal with this difficulty than presently  
186 exists.

187  
188 *Recommendation 4.*

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

193  
194 *Response:*

195 Management of RERF recognizes that data sets as large and complex as  
196 those at the Foundation can only be properly managed, stored and documented  
197 if the computing technology to support management of the data and their  
198 analysis is adequate to the task. An effort to improve computing capabilities  
199 began several years ago with the shift from a mainframe to a work station  
200 oriented network. This has already had enormous impact on the computing  
201 environment at the Foundation. It has made analyses of the data more  
202 convenient, has stimulated the development of new software, and has created  
203 the basis for easier communication among staff within the Foundation as well  
204 as outside of it. Yet much remains to be done both in the area of database  
205 design, development and maintenance to facilitate use of the data for  
206 research. Much more data must still be organized and loaded into the  
207 database. Staff turnover and the freeze on recruitment during the past two  
208 years has adversely affected the rate of progress being made. With the new  
209 policy for selective recruitment now in effect, we will recruit sufficient  
210 staff with appropriate levels of expertise to fill the gap. Recruitment

211 efforts are already underway to replace the loss of systems administrators,  
212 who maintain and support the overall computing system infrastructure upon  
213 which data management activities are carried out. Qualified system  
214 specialists are most likely to be found in the United States, and this will  
215 require a coordinated and continuing recruitment effort in association with  
216 the National Academy of Sciences. But there is also an urgent, pressing need  
217 to recruit staff for the Department who can help manage the continued  
218 development of the RERF research database since without further development  
219 research will be slowed and possibly compromised to some degree through the  
220 inability to utilize fully the richness of the data available at the  
221 Foundation.

222 Approaches are being made to a number of computer sciences departments  
223 at universities in Japan to seek their help in recruitment. The goal is to  
224 establish relationships that will provide a source of staff in the future, and  
225 dissertation opportunities for advanced students in the computer sciences who  
226 may find their experiences at RERF so rewarding that they elect to remain at  
227 the Foundation or if they go elsewhere, would be aware of the Foundation's  
228 needs and might encourage their own students and colleagues to participate in  
229 the Foundation's activities.

230 There is a need too to continually upgrade the computing hardware.  
231 Although the initial investment may be large in some instances and require  
232 additional funds, this continued upgrading is cost-effective in the long run.  
233 However such changes are contingent upon the availability of staff members who  
234 are conversant with advances in hardware and database management tools. To  
235 maintain this technological expertise management will encourage wider use of  
236 the program of sabbatical leaves that currently exists at the Foundation.

237  
238 *Recommendation 5.*

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

244  
245 Response:

246 Elsewhere (Recommendation 17) the Blue Ribbon Panel has urged the  
247 Foundation to institute a program of quinquennial peer reviews of each of the  
248 six major departments. The reviewers are to be multinational in origin, and  
249 the review committee chaired by a different member of the Science Council.  
250 Management proposes to begin this transition to the new method of peer review  
251 of departmental research activities with an in-depth review of the Department  
252 of Clinical Studies. This review will be held at the earliest moment

253 feasible, once suitable reviewers have been identified. The aims of the  
254 review will be to strengthen those projects which appear most fruitful, and  
255 to identify and discontinue those that seem scientifically unpromising and do  
256 not contribute directly to the well-being of the survivors. In addition, this  
257 review will explore ways in which the biennial examinations can best serve the  
258 health needs of the survivors, and the provisions of the Atomic Bomb Survivors  
259 Relief Law. However, if this review is to be held expeditiously, as we sense  
260 the Panel would encourage, the chairman may have to be drawn from outside the  
261 Science Council if the proposed restructuring of the Council itself is  
262 delayed. Once this review is underway, plans will be formulated for the next  
263 review, probably of the Department of Radiobiology since some reorientation  
264 of its activities is contemplated.

265

266 *Recommendation 6.*

267

268 *We recognise that the AHS is vital to the wellbeing of the survivors and*  
269 *we recommend that this important service continue, since we believe it has led*  
270 *to their high level of cooperation with RERF. As the population ages and*  
271 *health problems become more complex, consideration needs to be given to*  
272 *ensuring that the voluntary participation remains high.*

272

273 *Response:*

274

275 We acknowledge that maintaining a high participation rate is essential  
276 if the findings stemming from the biennial physical examinations of the  
277 survivors are to be representative of the cohort under surveillance. To  
278 maintain this high level of participation two steps need to be continued and  
279 possibly expanded. First, we must continue to provide expenses for  
280 transporting the survivors to the Foundation's clinical facilities. Second,  
281 as the cohorts age, many more of the survivors are bed-ridden, hospitalized  
282 or institutionalized. It becomes increasingly important, therefore, to  
283 maintain and strengthen our program of home visits by Foundation physicians,  
284 and in the instance of Hiroshima to extend these visits, as has been done in  
285 Nagasaki, to include the local hospitals and institutions that care for the  
286 chronically ill. The health surveillance system introduced in 1995, using  
287 periodic mailed questionnaires followed by telephone contact, will also be  
288 continued and strengthened in order to minimize the loss of information due  
289 to non-participation at the biennial examination. These are all essential  
290 activities since it is anticipated that participation in the biennial  
291 examinations will drop significantly due to the aging nature of the AHS  
292 population in the near future. No less important than the steps identified  
293 in maintaining a high level of cooperation, is the need to continue to inform  
294 the survivors of our findings on them promptly, thoroughly, and in  
comprehensible language.

295 *Recommendation 7.*

296 *We recommend that the studies on the health of the offspring (F<sub>1</sub>*  
297 *generation) of the survivors continue, since they may elucidate data on*  
298 *multifactorial disease while also providing direct benefit to the survivors*  
299 *and their offspring.*

300

301 Response:

302 As the Panel's report notes, there has been no systematic study of the  
303 health status of the offspring of the survivors since the termination of the  
304 early clinical genetics program conducted in the late 1940's through the early  
305 1950's. Those examinations that have been conducted since have been largely  
306 voluntary, stimulated by the concerns of individuals who participated in the  
307 cytogenetic and biochemical studies conducted in the mid-70's to the mid-80's  
308 under the aegis of the Department of Genetics. These examinations although  
309 undoubtedly informative for the individuals concerned provide a weak basis for  
310 the estimation of the health effects on the children of the survivors. We  
311 will return to this recommendation and the steps proposed to address it when  
312 Recommendation 13 is considered.

313

314 *Recommendation 8.*

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

319

320 Response:

321 Plans are being developed to examine samples from the two cities  
322 simultaneously in Hiroshima to eliminate any inter-laboratory biases and to  
323 establish whether or not a city difference actually obtains. Without the  
324 simultaneous scrutiny of samples from Hiroshima and Nagasaki we will not be  
325 able to rule out inter-laboratory biases. These plans include not only  
326 comparison of FISH analysis but ESR results where possible. Collaborative  
327 work will be sought regarding ESR and chromosome studies for Nagasaki  
328 survivors where we can assist the investigators at Nagasaki University by  
329 providing chromosome data on the tooth donors. However, if these comparisons  
330 of biologically and physics based dose estimates are to be rigorous we must  
331 be confident of the physics assessments, and here some uncertainties remain.  
332 Resolution of these uncertainties hinge heavily on guidance from the Dosimetry  
333 Committee.

334

335 *Recommendation 9.*

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

338  
339 Response:

340           The Foundation recognizes that its collection of biological materials  
341 is virtually unique, and intends to continue to support the personnel and the  
342 facilities needed to maintain the present cell-lines and other stored  
343 material. Proper storage and documentation of these materials are essential  
344 if they are to serve the needs of the Foundation's investigators, and to be  
345 useful to research workers elsewhere. Adequate safeguards must also be  
346 established and maintained to ensure that this material is not inadvertently  
347 lost through accidents, such as power failures, or cataclysmic natural events,  
348 viz., typhoons, or human errors. While some safeguards are in place, they  
349 warrant periodic review as techniques for storage change, the size of the  
350 collection grows, and new sorts of specimens are added which may require  
351 different storage methods. The Foundation has established a Committee on  
352 Biological Samples which will be encouraged to take an active, leadership role  
353 in ensuring that the requisite safeguards are in place and periodically  
354 reviewed.

355           Continued collection and management of tissue samples will be essential  
356 for the conduct of molecular epidemiological research. It should be  
357 recognized that the majority of tissue samples must be obtained from outside  
358 sources and that such tissues are being sought both by the Foundation and  
359 outside investigators. For more than two decades, RERF has collaborated with  
360 the local medical associations in the maintenance of the Hiroshima and  
361 Nagasaki tissue registries, which register histologically-diagnosed tumor  
362 cases together with tissues. The Foundation will provide the leadership,  
363 working with the local medical and research community, to establish a "tissue  
364 bank" for sharing tumor tissues to be used for molecular biological research  
365 both outside and at RERF. Using the tissue registries as the basis, a  
366 database management system will be developed to catalogue useful tissues in  
367 the community, and their location and condition. An appropriate review  
368 process will be established for research uses of these tissues. It is  
369 expected that the establishment and maintenance of such a program will require  
370 a considerable amount of manpower that RERF will have to provide.

371  
372 *Recommendation 10.*

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

375  
376 Response:

377           The Foundation recognizes the importance of a strong program in

378 cytogenetics both for its application to unresolved issues relating to  
379 dosimetry, and its value as a direct marker of radiation damage. It is  
380 management's intent to see that the cytogenetics section in the Department of  
381 Genetics continues to be adequately staffed and equipped to meet the  
382 challenges ahead.

383 Current cytogenetic projects include techniques using conventional G-  
384 banding and FISH (fluorescence in situ hybridization), all of which have  
385 served to establish calibration curves for biodosimetric uses in support of  
386 ESR measurements on tooth enamel from A-bomb survivors, and have obvious  
387 advantages in the identification of bias in the physical dose estimates.  
388 These projects are also in line with the detection of clonal expansion of stem  
389 cells with certain types of chromosomal aberrations in the lymphoid and other  
390 somatic tissues of the survivors, and provide the basis for collaboration with  
391 the Department of Radiobiology. Such clonal expansion of cells may be an  
392 indicator of a predisposition to cancer. Finally, it warrants noting that  
393 these techniques in conjunction with genetic linkage studies can be helpful  
394 in the physical localization of specific mutant genes within the human genome  
395 that may be seen among the children of the survivors.

396  
397 *Recommendation 11.*

398 *We recommend that the Department of Radiobiology should focus on*  
399 *molecular epidemiology and immunology and that strong links should be forged*  
400 *between RERF and the relevant groups around the world involved in modelling*  
401 *the carcinogenic process.*

402  
403 *Response:*

404 As the Blue Ribbon Panel has recognized, the somatic mutation studies,  
405 which have represented a major investment on the part of the Department of  
406 Radiobiology and have been fruitful in the past, seem to have reached a  
407 logical end. Many of the assays which have been developed and used are  
408 valuable as dosimeters only if exposure to ionizing radiation has been recent,  
409 a situation which does not obtain with regard to the survivors. The  
410 department itself has recognized the limitations of these assays and, in  
411 recent years, has initiated various new studies that address the issue of  
412 radiation carcinogenesis from an immunological and molecular biological  
413 standpoint. It is important, we believe, to examine the role of immune  
414 function in the etiology of disease, especially cancer. The Department has  
415 professionals trained in immunology as well as the molecular biology of cancer  
416 who are interested in such studies. Management of the Foundation intends to  
417 begin immediately to reorient the department's activities by stressing greater  
418 investment into these projects as recommended by the Panel.

419 Very little is known about the clonal expansions that originate from

420 individual normal and mutant stem cells and recent progress in hematology and  
421 immunology make it possible to directly analyze and detect alterations in  
422 specific gene markers of stem cells. However, since many scientists elsewhere  
423 still request RERF to measure mutation frequencies in exposed people,  
424 maintenance of the mutation assays, albeit at a much reduced level, is  
425 necessary for the furtherance of international collaborations and these assays  
426 remain useful in the assessment of some aspects of aging and cancer risk.

427 Initial efforts to further the development of a program in molecular  
428 epidemiology at the Foundation will involve the identification of a few  
429 specific areas of research which can be uniquely undertaken at the Foundation  
430 and to explore aspects of research that can be effectively pursued with  
431 outside groups. An active but focussed research program in molecular biology  
432 at the Foundation is essential if others are to be aware of the RERF resources  
433 and to ensure that we are viewed as an attractive partner for collaboration.  
434 Legal and other issues related to the use of tissue and other biological  
435 samples also need to be resolved. A workshop will be held involving  
436 international and local investigators to discuss these issues since  
437 uncontrolled use of tissues and other biological materials without a central  
438 research agenda could lead to a wasteful depletion of valuable material.

439  
440 *Recommendation 12.*

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

447  
448 *Response:*

449 As the Panel has stated, the follow-up of the atomic bomb survivors is  
450 the largest and longest study of individuals exposed to acute doses of  
451 ionizing radiation extant. As a consequence it is recognized as the most  
452 important single source of information for the establishment of risks  
453 worldwide, but these risks will be incomplete until such time as the full life  
454 experience of these individuals is available. Therefore, we welcome the  
455 Panel's recommendations that the studies continue until such time as the last  
456 of the cohort members is dead, but this ideal may be impractical and some  
457 limit may have to be set to the duration of follow-up based on the potential  
458 biological importance of the data that might still be obtained. Nonetheless  
459 it is important to note that most of those survivors exposed as children are  
460 still alive and that important information on them will not come until late  
461 in their lives. Similarly, as the cohort diminishes in size the accumulated

462 data grow correspondingly, and the late part of the study will be especially  
463 important in these respects.

464 We recognize too that the Adult Health Study represents one of the few  
465 programs at the Foundation that has immediate and direct medical and social  
466 benefits to the survivors. All possible effort will be made to provide  
467 information to the AHS cohort members for health promotion as well as to  
468 ensure primary and secondary prevention of diseases which are known to be  
469 radiation-related and are common among aged populations. Moreover, as  
470 indicated in the response to recommendation 9, one of the important activities  
471 of the AHS examination is to obtain, with appropriate consent, biological  
472 samples from individual survivors for future projects.

473  
474 *Recommendation 13.*

475 *We recommend consideration be given to further investigation into the*  
476 *health of the offspring (F<sub>1</sub> cohort) since it may well yield valuable*  
477 *information on genetic effects, especially when conducted together with*  
478 *research using the new molecular genetics techniques.*

479  
480 Response:

481 The Foundation has begun plans to support this recommendation. We are  
482 currently exploring the design of a preliminary study which should provide the  
483 information needed to assess the feasibility of a larger effort and to design  
484 a meaningful study, if one proves possible (see Annex A). This design must,  
485 of course, not only offer clinical examinations but incorporate the newer  
486 molecular technologies that have developed so rapidly over the past decade.  
487 This will necessarily entail the collection of further specimens and decisions  
488 regarding the most appropriate molecular techniques for use in the immediate  
489 future. The Department of Genetics has been a significant player in the  
490 development of rapid and inexpensive means to assess mutational damage, and  
491 some of these developments, such as 2-dimensional electrophoresis of DNA are  
492 sufficiently far advanced as to be applicable soon to widespread use. The  
493 advantages of this approach, as opposed to the sequencing of the entire human  
494 genome, are many. The methods are inexpensive, they can be applied to large  
495 numbers of samples, and they focus on DNA fragments generally associated with  
496 genes known to be functional and thus avoid much, if not all of the problem  
497 posed by the redundancy in the human genome. It warrants noting that in  
498 addition to the information such a study would provide on radiation-related  
499 mutational damage, it would yield an enormous amount of basic data on DNA  
500 diversity among human beings since at least 15% of the genes recognized by 2-  
501 dimensional electrophoresis are known to be variable. However, image analysis  
502 is an essential part of any 2-dimensional electrophoretic study of DNA  
503 fragments, and this will require support of the Information Technology

504 Department in the rewriting of the 2-DE software that was developed at the  
505 University of Michigan and is currently in use in the Department of Genetics.  
506 This software was developed for older computers and cannot be readily used  
507 with the up-grades that have occurred and are contemplated in the computer  
508 system at RERF. There is also a need for increased support for statistical  
509 analysis and management of the large amount of data generated by these  
510 studies.

511

512 *Recommendation 14.*

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

516

517 Response:

'8

519 Molecular epidemiological studies will be one of the research areas of  
520 highest priority in relation to the elucidation of radiation-induced  
521 carcinogenesis. Here the tissue banks referred to in our response to  
522 Recommendation 9 will play an important role. Most of the advances in DNA  
523 technology are available in the Department of Radiobiology to meet this  
524 recommendation. But management and staff at the Foundation appreciate the  
525 need to maintain well equipped and staffed facilities in this area. Without  
526 such, efforts to determine the shape of the dose-response curve for health  
527 effects at low doses of radiation will be seriously compromised. Progress in  
528 this sphere is apt to be heavily dependent upon the development of automated  
529 methods of analyses since the sample sizes required at the lower doses to  
530 demonstrate significant health effects will be large.

531

531 *Recommendation 15.*

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

536

537 Response:

538 The Foundation was arguably the first research institution in Japan to  
539 organize an institutional review board (IRB) charged with the development of  
540 policies governing access to its information and specimens, and assurance of  
541 the privacy of the individual and confidentiality of the data. When it was  
542 established in 1976 the Human Investigation Committee, the Foundation's IRB,  
543 was modeled on the guidelines set forth in the Declaration of Helsinki (1964)  
544 and revisions (1973) and by the National Institutes of Health of the United  
545 States in several issues of the Federal Register, the most recent being the

546 US Federal Register, Volume 56, Number 117, June 18, 1991, pp. 28002-28032.  
547 These policies have been reviewed on several occasions in the past, the most  
548 recent one in 1995. However, these guidelines were established primarily with  
549 a view toward studies occurring at the Foundation and may not adequately  
550 account for the work of investigators elsewhere. These policies will be  
551 reviewed anew by the Human Investigation Committee to ensure that they do so.  
552 If they do not, there are numerous paradigms that could be used at the  
553 international level such as the policies established by the Human Genome  
554 Project or the Human Genome Diversity Project both of which are international  
555 in scope. However, it is important to note in the context of this  
556 recommendation that since the establishment of the Human Investigation  
557 Committee all of the samples obtained from participants in the Adult Health  
558 Study as well as the other cohorts under surveillance by the Foundation have  
559 been collected only after oral or written informed consent was secured. Since  
560 1994 either a written consent form has been inserted into the medical record,  
561 or if consent was only verbal, the fact that the subject had been informed and  
562 agreement obtained has been noted in the medical or study record. One change  
563 that seems likely in this process is explicitly informing the subject that any  
564 specimen he or she may contribute for storage at the Foundation might be  
565 analyzed elsewhere, since most of the subjects undoubtedly tacitly assume that  
566 specimen analysis will occur at the Foundation and that the findings of such  
567 analyses will be used to evaluate their health status and to support RERF  
568 studies. Indeed, this was explicitly stated to those trios (father-mother-  
569 child) participating in the Department of Genetics efforts to establish cell-  
570 lines for future genetic analyses. We do not, therefore, propose to request  
571 additional blood samples from the survivors and their children to provide to  
572 investigators elsewhere since such requests are apt to have an inhibiting  
573 effect upon participation rates. However, we do propose to share with them  
574 our Epstein-Barr virus transformed cell lines.

575 To obtain access to these materials the investigator will be expected  
576 to submit a research protocol for review by the Foundation's Research Protocol  
577 Committee and its Human Investigation Committee. This protocol should  
578 identify the nature of the project, the rationale for the use of the  
579 Foundation's material, and document the collaborative aspects of the proposal.

580  
581 *Recommendation 16.*  
582 *In the context of the current organisational structure, we recommend*  
583 *that successive five-year Strategic Plans, with annual updates, be developed*  
584 *and offered through the Executive Committee for approval by the Board of*  
585 *Directors.*

586  
587 Response:

588           The management of RERF will begin to implement this recommendation  
589 immediately. Although five year plans have been developed in the past, they  
590 have not been systematically updated nor have they been used as effectively  
591 as would be desired. To begin this task all of the departments at RERF will  
592 be asked to submit their personnel and financial needs and plans for the five  
593 years immediately ahead, including the priority they would assign to  
594 individual research activities they propose and the time line for completion  
595 of specific activities. These will then be collated and coordinated by the  
596 Foundation's Research Committee and brought before the Executive and Operating  
597 Committees for approval and implementation after concurrence has been obtained  
598 from the Science Council and the Board of Directors. This process will be  
599 repeated annually.

600

601 *Recommendation 17.*

602

603           *We also recommend a new peer review process be established with*  
604 *multinational teams reviewing each Department every five years, each team*  
605 *being chaired, for example, by a different member of the Science Council.*

606

607 *Response:*

608

609           Management of the Foundation acknowledges that it has not used the peer  
610 review process as effectively as it might, and heartily endorses this  
611 recommendation for a change. We have long had a roster of consultants, expert  
612 advisers, and visiting research scientists whose skills have not been used to  
613 maximum advantage. Most of these individuals reside in Japan. There would  
614 seem value to expanding this roster to include international representatives  
615 from a wider array of disciplines so that the roster could serve as a pool  
616 from whence to draw reviewers in the recommended periodic evaluations of the  
617 activities of the major research departments at the Foundation.

618

619           This new peer review process is seen as replacing the reviews that have  
620 been conducted by the Science Council in the past; however, it is assumed the  
621 Science Council will take cognizance of these reviews in its evaluation of the  
622 overall scientific program of the Foundation. This change should permit the  
623 Council to focus more attention on issues of scientific policy and the  
624 development of new directions of research.

625

626 *Recommendation 18.*

627

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

630 Response:

631 While the Foundation is sympathetic to this recommendation, its  
632 implementation will require a change in the Act of Endowment where Article 31  
633 states that appointments of Scientific Councilors will be for four years and  
634 sets no limits on the number of terms they may serve although only two are  
635 recommended. Changes in the Act of Endowment require an affirmative vote of  
636 not less than three-fourths (3/4) of the Board Members at the meeting of the  
637 Board of Directors and approval by the competent Minister(s) but do not become  
638 effective retroactively. The Executive Committee appreciates the intent of  
639 this recommendation and will urge that at the next meeting of the Board of  
640 Directors, or a mail ballot if such is approved, changes be made in the Act  
641 of Endowment to accord with this recommendation (see Annex B). If the Board  
642 approves, the current councilors will be requested to resign and we will  
643 develop a plan for staggered times of appointment so that it will be possible  
644 to replace two councilors each year. Simultaneously we will reexamine the  
645 distribution of disciplines represented by the Councilors to ensure that all  
646 of the major ones of importance to the Foundation's research are represented.

647

648 *Recommendation 19.*

649 *We recommend that consideration be given to formal links being*  
650 *established, or strengthened, to universities or other research institutions*  
651 *in Japan and especially to the universities in Hiroshima and Nagasaki, with*  
652 *RERF Department Chiefs having visiting or part-time Professorships and*  
653 *undertaking teaching commitments together with Ph.D. students being involved*  
654 *on projects at RERF.*

655

656 Response:

657 This is a suggestion that the Foundation welcomes, and will do what it  
658 can to implement. While informal links have existed in the past and continue  
659 to do so in the present, formal links which might result in part-time teaching  
660 responsibilities for the Foundation staff will undoubtedly require the  
661 administrative approval of the Ministries of Health and Welfare and Education.  
662 These approvals would have to be negotiated by others, but the Panel's  
663 suggestion may provide the needed impetus to effect such relationships.  
664 Parenthetically it should be noted that many of RERF's staff are already  
665 serving as part-time lecturers at various universities including those in  
666 Hiroshima and Nagasaki. To further the intent of this recommendation,  
667 affiliations with regional universities similar in kind to those associated  
668 with some of the national laboratories in the United States, such as Argonne  
669 or Oak Ridge, could be developed. Clearly there would be much merit to a more  
670 intimate involvement of the Foundation's professional staff in educational  
671 enterprises. An immediate step that could be taken in conjunction with

672 Geniken (Research Institute of Radiation Biology and Medicine, Hiroshima  
673 University), Genken (Atomic Disease Institute, Nagasaki University) and Hoiken  
674 (the National Institute of Radiological Sciences at Chiba) would be the  
675 development of a short, intensive course in radiation biology. Such a course  
676 could relieve the aforementioned institutions of some of the burden of short-  
677 term trainees if a time for the course was specified sufficiently far in  
678 advance to permit potential participants to plan their visits to Japan.

679

680 *Recommendation 20.*

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

685

36  
686 Response:

687 Two avenues to the implementation of this recommendation will be  
688 immediately explored. First, management will enter into negotiations with the  
689 European Union to explore the feasibility of the Union establishing a series  
690 of research fellowships with work to be pursued in Japan at the Foundation.  
691 Second, the US Department of Energy seeks to create one or more centers of  
692 excellence for the training of research workers in radiation biology. These  
693 centers are to be affiliated with universities in the United States.  
694 Applications for such centers are currently under review, and once decisions  
695 have been made with regard to their location(s), the Foundation will enter  
696 into negotiations with the designated universities to establish an exchange  
697 of research fellows and trainees. It is assumed, of course that the  
698 Foundation will play a role in the selection of fellows for training at its  
699 facilities in all instances. It is further assumed that the fellows will  
700 carry their own stipend from either the European Union or the as yet unnamed  
701 centers of excellence in the United States, and a modest ancillary budget that  
702 will cover the costs to the Foundation of supporting the fellow's research.  
703 Management of this program of training will be distinct from the internally  
704 developed program of post-doctoral fellows referred to previously.

705

706 *Recommendation 21.*

707 *We recommend that, in view of the accumulated knowledge at RERF, it be*  
708 *developed as an Information Centre to promote informed public understanding*  
709 *of the risks of radiation.*

710

711 Response:

712 Several steps have been taken to enhance the Foundation's role as an  
713 information center. First, as one of the activities to promote public

714 understanding of RERF's achievements, the Foundations' statement on the  
715 Worldwide Web has been considerably expanded to detail the history of the  
716 Foundation, its research program and the findings, address commonly asked  
717 questions by the survivors as well as other individuals exposed to ionizing  
718 radiation, indicate how the Foundation can be contacted, provide a simple  
719 explanation of ionizing radiation, and a glossary of terms commonly  
720 encountered in radiation biology. It is management's aim to continue to  
721 expand this material and to see that it is updated as frequently as  
722 circumstances warrant. Other forms of public relations activities include  
723 publication of news letters, RERF Update and Japanese news letters,  
724 contribution of articles to local medical journals, and the continuation of  
725 annual open houses that began in 1995. But it is clear that a more consistent  
726 effort to inform the public of the risks associated with exposure to ionizing  
727 radiation is needed than has occurred in the past.

728 A broader role for the Foundation as an information center must take  
729 cognizance of the aspirations of the citizens of Hiroshima and Nagasaki and  
730 the Ministry of Health and Welfare to establish an archival and information  
731 center in each of these two cities as a continuing memorial to the A-bomb  
732 deceased. The Foundation's scientific expertise has been sought in the  
733 furtherance of this objective, and we continue to be supportive of these  
734 aspirations.  
735

1996年8月26日

## ブルーリボン委員会勧告への対応 コメントおよび討議用対応案

### 緒言

放射線影響研究所（放影研）専門評議員会による勧告が出され、その勧告に日米両国政府が同意し資金を提供したことを受けて、放影研で現在行われている調査プログラムの内容と質を検討し、調査の重要性と利点を評価し、また今後どのような調査を行うべきかを提言するために国際ブルーリボン委員会が1995年秋に設立された。更に同委員会は、放影研の科学的研究評価（ピアレビュー）過程を検討すること、また日本内外の他機関と共同で実施できる調査分野を審議することも依頼された。英国放射線防護庁 Roger H. Clarke 総裁を委員長とする同委員会は、広島・長崎の放影研で第一回目の会議を、そして英国放射線防護庁で第2回目の会議を持った。1996年7月2日、委員会は、両国政府と放影研の理事および職員に最終報告書を提出した。報告書には21項目の勧告が列挙されている。放影研は、当勧告および放影研が提案する措置が将来の調査活動の計画またその計画遂行に必要な資金に影響を与えることから、出来るだけ迅速に対応案を用意した。以下に勧告と委員会の提案を実行するために放影研が取るべき措置を示す。これらの措置は、放影研全研究員および常務理事による広範にわたる討議の所産である。

個々の勧告および対応策に触れる前に、時宜を得た説得力に富む勧告を出して頂いたこと、また周到かつ客観的に任務を遂行して下さいことに対して、委員会に感謝したい。日米両国政府から引き続き経済的支援が得られ、ブルーリボン委員会の勧告に答えて我々が打ち出す方策に対して被爆者とその子供達ならびに学界全体の支持が得られれば、放影研はこの勧告を基盤としてより強力な研究所になり、電離放射線被曝の健康影響について更に理解を深めると共に被爆者とその子供達により良く奉仕することができる。

### 勧告および放影研対応

#### 勧告1

疫学部は死亡およびがん罹患に関するデータを引き続き収集すべきであり、この作業は強化されるべきであると勧告する。データの量と範囲からみて、放影研の管理者はこれらの調査を最優先すべきである。更に、既に収集済みの将来的に価値があると思われる情報を解析するために国内、海外の他の研究所の疫学者と共同して調査を遂行すべきである。

#### 対応：

放影研は、疫学部の重要性と死亡およびがん罹患に関するデータを引き続き収集する必要性に対する委員会の支持を歓迎する。これらのデータは放影研の使命の中核となるものであり、最優先順位が与えられるべきである。しかし、放射線に関連したがん以外の死亡が、放影研にとってこれから最も重要な問題の一つになる可能性があることにも留意すべきである。加えて、長年かけて収集された豊富な資料が生活様式、またその他の放射線以外のリスク因子について調査するための貴重な資料となりうる。他の因子が存在する場合に放射

線被曝が如何に疾患発生に係わるかを理解する役に立つこのような情報の解析に一層重きをおく。このような取り組みかたは、放射線に関連したがん以外の疾患リスクを調べるために特に有益であるが、がん調査に関しても同様に意味がある。外部機関との共同研究が特に成果をあげる分野がこれであろう。

ブルーリボン委員会が指摘するように、疫学部の人員不足は深刻である。この状況を改善する試みがこれまでなされたが、十分な成果を見ることはできなかった。この重大な問題に対処するためにこれまでにない新しい試みがなされている。放影研が直面するニーズを満たせるようにすべきではあるが、この人員問題を個別補充体制により解決することは実行不可能であり、継続的な雇用プログラムを確立すべきである。優秀な疫学者の採用問題また彼らが放影研の研究プログラム全般で果たす中心的な役割を考えると、優秀な疫学者が見つかり次第採用できるようにすることが必要である。採用を速やかに行い、共同研究を強化するために、放影研は、放影研—南カリフォルニア大学—学士院の協力体制計画のような米国の有力な疫学部と正式な提携を結びたいと考える。この計画は、放影研運営に関する学士院の役割が不明確であったために中止されている。

外国人職員を採用するために学士院の能力を活用することは放影研の将来にとって重要である。これは学士院の活動のうち最も重要な役割の一つである。またこの試みを支援するための十分な資金および人的資源が得られることが重要である。過去において、放影研における雇用機会への興味を高めるために学士院を補助していたグループと契約を結んでいた。優秀な人材の関心を引き、その結果見られる調査の進展を考えるとこのような投資からの見返りは大きいと考える。放影研は、職員採用以外でも学士院と密に協力し、放影研の調査への意識を高め、新しく研究指導者を見つけるために科学界全体に及ぶ学士院の広い交流関係を活用したい。その第一歩として、学士院と協力しつつ、広範な専門分野からの科学者が一堂に集まり放射線とがん以外の疾患による死亡について検討するワークショップを開催するための提案を纏めたい。放射線とがん以外の疾患（死亡率と臨床所見を含む）の関連について明らかにされつつある証拠の詳細な要約をそこでは発表する。このようなワークショップを開催することは、がん以外の影響に関する将来の調査活動計画を立てる助けとなり当所に直接的な恩恵をもたらし、また外部機関が刺激を受け、このような後影響の機序を探求する調査に着手するのではないかと考える。

経験ある疫学者の採用に加え、放影研支援による2年間の博士課程終了者を数名受け入れるプログラムを設立することを提案する。このようなプログラムにより、放影研は直面する人員上のニーズを満たすことができ、正職員採用の際の候補者となり、他機関との関係を強化し、放影研における調査の機会についての意識を高めることができる。この方法は、日本人疫学者を放影研で採用したり、また研修させる際に特に有益である。

長期在職者が、放影研のニーズに合った研修を受け、また経験を更に積むことができるようにするために、既存の放影研特別研究制度をより有効に活用するよう奨励することは疫学部を始め他の部にとっても有益である。博士課程終了者のためのプログラム同様、特別研究制度を有効に活用することは新しい技術の取得や大学との関係の強化につながり放影研に直接利益をもたらす。

## 勧告 2

統計部は疫学部と協力して放射線被曝リスクの解析を引き続き行うこと、また統計部門における質の高い調査研究を維持すべきことを勧告する。

対応：

放影研管理者は統計部に可能な限り優秀な人材を揃え、同部が疫学部と協力して調査を継続することを奨励する必要があると考える。統計部研究職員の評判は広く世界に轟いている。同部の活動は研究所の全ての部に影響を及ぼすので、慎重で継続的な質の維持・向上が必要である。そのため、同部の人員増員には積極的に努力する。疫学部同様、学術雑誌に採用広告を掲載、また米国の統計グループに直接連絡を取るなどして統計学者の採用を進めている。経時的臨床データの解析という当面のニーズに対処するために、当該データに精通した経験のある統計学者が非常勤の任期雇用という形で職員と共同で解析ができるように調整中である。しかし、職員の多くが短期間しか在職しない、また経験ある統計学者を雇用することが困難である現状を考慮すると現行の採用も引き続き行わなければならない。また、統計学部は放射線誘発癌のメカニスティックモデルの作成やF<sub>1</sub>における突然変異の証拠を探るためのパターン認知の問題など、特定のプロジェクトに係わる博士課程終了者を放影研資金を使って採用する努力をしている。

## 勧告 3

統計部は、引き続き他の研究グループが死亡率および罹患率に関する基礎データセットを解析に使用できるようにすることを勧告する。同様に、精神遅滞、IQ、その他胎内被曝に関連した調査結果などに関するデータセットも利用可能にしていくべきである。

対応：

放影研は、ブルーリボン委員会が当研究所の過去の実践を支持したことを歓迎し、情報のプライバシーと機密性に関する慣行は現状通り維持しつつ外部研究者がより広範にまたより簡便にデータにアクセスできるよう引き続き努力していく。放影研は引き続きデータをフロッピーディスクを用いて提供していく一方で、情報技術部では放影研以外の人々がインターネットを介して一般使用が可能なデータにアクセスできるようなオンライン・データ・アクセス・システムを現在開発中である。

1958 - 1959年に固定監視集団を設定して以来、放影研およびその前身である原爆傷害調査委員会(ABCC)は、状況が許す限り広範に他の研究者と情報を共有するという方針を取ってきた。1960年から1985年まで死亡率に関する報告書には多数の表が付録として掲載されており、当時の技術で可能な限りこれらの報告書の計算に用いたものと同じ形式のデータを提示した(参照例: ABCC TR 1-77, Beebe, Land, 加藤)。1980年代になりデータを詳細に使用する統計技術が開発され、計算の基本となる更に詳しい交差表を電子媒介を使い提供することを決定した。これは、医学調査機関では異例なケースであり、データの重要性和豊富さ、またデータ解釈上起こるかもしれない論議を考えると、放影研研究員にとって極めて満足のいく反応が得られている。

重要なデータが未だ提供できていない分野があるが、これは主として、これらデータの多くがかなり前に収集されたデータであり、最近ではあまり使用されていないためにデータを系統的に整理することが困難なためである。例えば、胎内被爆者におけるがん死亡率データを統一した形式で編成するために過去2年間多大な努力が払われた。胎内被爆者を対象に行った知能検査データを始めとして、他のデータについても同様の作業を行う必要がある。しかし、先に述べたように疫学・統計部の職員数は理想的なレベルが維持されておらず、また行うべき仕事には優先順位が付いている。困難ではあるが、これらの分野で進歩を見ることは可能であると考えられる。また、訂正および更新というデータセットの変遷が理由で、かなりの困難が生ずることにも留意すべきである。このような難点に対処するために、既存のバージョン管理体系よりも入念な体系を作る努力をする。

#### **勧告 4**

数十年にわたり収集された大量のデータが正しく保存、記録され、放影研の研究者がアクセスできるようにすることは大変重要であるので、情報技術部に引き続きゆるぎない支援を与えることを勧告する。

対応：

放影研管理者は、当研究所のデータほど大量で複雑なデータセットを正しく管理、保存、記録するには、データ管理および解析を支援するのに十分なコンピュータ技術が不可欠であることを認識している。コンピュータ能力改善の試みは、大型汎用コンピュータからワークステーションを使ったネットワーク環境へ移行した数年前に始まった。この移行は、研究所のコンピュータ環境に大きな影響を及ぼした。これにより、データ解析が容易になり、新しいソフトウェアの開発が活発になり、研究所内の職員間の連絡および研究所外部への連絡を簡便にする基盤ができた。しかし、調査データの使用を容易にするためにデータベースのデザイン、開発、保全の部分ではまだすべきことが多く残されている。まだ多くのデータを整理し、データベースに組み入れなければならない。過去2年間の人事移動や職員採用の凍結はその進展に悪影響を与えてきた。部門によっては採用も行うという新しい方針が取られるようになったので、欠員を補充するために十分な人数の熟練職員を採用する。データ管理を行うコンピュータシステム構造全体を維持・支援するシステム管理者の後任募集が既に始まっている。適任のシステムスペシャリストは米国で見つかる可能性の方が高く、そのためには学士院と協力・調整して募集を継続することが必要である。しかし、それと同時に、もしデータベース構築作業が進まなければ、放影研で使用可能な豊富なデータを完全に使用できなくなり、そのせいで調査の進展に遅延をもたらしたり、また調査の信頼性を幾分傷つけることにもなりかねないので、放影研調査用データベースの構築作業を運営管理できる職員も緊急に同部で採用しなければならない。

日本の大学のコンピュータ科学部に採用の支援を求めるために、接触中である。将来の新規採用の際に紹介を受け、またコンピュータ科学の修士、博士過程を修める学生が論文を作成できる機会を与えるような関係を築いていくことが目標である。それらの学生は放影研での経験を有益だと考え、当研究所に就職することを選択するかもしれないし、たとえ他機関

に就職したとしても、放影研の必要性を理解し学生または同僚に放影研の活動に参加するよう奨励してくれるかもしれない。

コンピュータのハードウェアを頻繁にアップグレード（更新）する必要もある。初期投資額が大きい場合もあり、また追加予算が必要な場合もあるが、長い目で見た場合、この継続的なアップグレードは費用効率が高い。しかし、このような変更は、ハードウェアおよびデータベース管理ツールの進歩に精通している職員がいるか否かに係わってくる。専門技術知識を維持することを目的とし、放影研管理者は既存の放影研特別研究制度を広く活用することを推奨する。

## **勸告 5**

臨床調査プロジェクトの多くは今後も続行すべきであるが、調査プログラムを厳密に検討し、成果が得られないと思われるものは中止することを勧告する。1945 年には子供で、現在成人に達している者については、放射線感受性が若い時に最も高いと思われるので、調査を継続すべきである。

対応：

他の箇所（勸告 17）で、ブルーリボン委員会は、5 年毎に放影研の主要 6 部門の各々を科学的研究評価（ピアレビュー）する制度を設けるべきであると勧告している。審査委員は多国籍から成り、専門評議員会の異なる委員が各審査委員会の委員長を務める。放影研管理者は、部門別調査活動のピアレビューという新しい方針への移行を、臨床研究部を詳細に審査することから始めることを提案する。適任の審査委員が選択され次第、出来るだけ早い時期にこの審査を行う。この審査の目的は、大きな成功が期待されるプロジェクトを強化し、科学的に成果が得られない、また原爆被爆者の福祉に直接貢献しないと思われるプロジェクトを見極め中止することである。更に、この審査により被爆者援護法の条項を満たし、原爆被爆者の健康に関するニーズに最も良く貢献できる 2 年に一度の健康調査の方法を探求して行く。しかし、もし提案されている専門評議員会の再構成が遅れば、この審査を迅速に行うためには（ブルーリボン委員会はそれを推奨していると思われるので）、委員長を専門評議員以外から選ばなければならないかもしれない。この審査が動きだせば、次の審査に関する計画も立てることができる。次の審査としては、放射線生物学部の活動に関する方針の変更が予期されるので、同部の審査が考えられる。

## **勸告 6**

AHS は被爆者の福祉のために極めて重要であり、放影研に対する被爆者の非常な協力を可能にしたと考えられるので、この観点から重要なサービスの継続を勧告する。被爆者の高齢化が進んで、健康問題は更に複雑となっており、高い受診率を維持するための配慮が必要である。

対応：

被爆者の 2 年に一度の健康診断から得られる所見が、現在監視中の集団を的確に表すようにするには、高い受診率を維持することは必須であることを認識している。この高受診率を

維持するためには、次の2点を引き続き実行し、また拡大することが必要である。まず、被爆者が放影研臨床研究施設に来院するための交通費を放影研が引き続き負担する。次に、集団は高齢化しており、被爆者の多くが寝たきりであったり、病院または施設に収容されている。ゆえに、放影研医師が各家庭を訪問する制度を続行し、また強化していくことが一層重要になっており、広島の場合は、長崎ですでに実行されているように慢性病患者を治療している地区の病院や施設まで範囲を広げて訪問することが重要である。定期的な質問票郵送およびそれに続く電話連絡によって1995年から導入された健康監視システムも続行・強化し、2年に一度の健康診断を受けないことによる情報の損失を最小限に抑える。AHS 集団の老化により受診率の急激な減少が近い将来に予想されるのでこれらは全て重要な活動である。高受診率維持のために言及した手段と同じ位重要であるのが、引き続き被爆者に所見結果を迅速、徹底的に、また分かり易い言葉で知らせることである。

### **勸告 7**

被爆者の子供 (F<sub>1</sub>) の健康に関する調査は、多因子性疾患についてのデータを提供するかもしれないし、また被爆者とその子供に直接恩恵を与えると考えられるので、今後も継続するよう勧告する。

対応：

委員会の報告書で指摘されているように、1940年代終わりから1950年初めまで行われた臨床遺伝プログラムの終了以降には被爆者の子供について系統的な健康調査は行われていない。それ以降に行われた検査は、遺伝学部が1970年代半ばから1980年代半ばまで実施した細胞遺伝学および生化学調査の対象者が関心を示した時に実施したもので、そのほとんどが自発的検査であった。これらの検査から得られた情報は、当該対象者にとっては疑いもなく有益ではあるが、被爆者の子供の健康影響推定の根拠としては弱い。勸告13を考える時にこの勧告および提案措置についてもう一度触れる。

### **勸告 8**

FISH 分析および ESR のための生物試料の保存ならびに生物試料に基づく線量推定値と物理学的線量推定値との比較に必要なこれら試料についての記録作成を勧告する。

対応：

広島・長崎の研究所間の偏りを除去し、両市間に実際差があるか否かを調べるために両市で収集した試料を広島で同時に検査する計画を立案中である。広島・長崎の試料を同時に精査しなければ、研究所間の差を除外することはできないであろう。計画には FISH 解析の比較だけではなく、可能な部分では ESR の結果の比較も含める。歯試料提供者の染色体データを提供することにより長崎大学研究者に協力することが可能であるので長崎被爆者の ESR および染色体調査の共同研究の可能性を探る。しかし、生物学的線量推定と物理学的線量推定の比較を正確に行うには、物理学的測定に確信を持たねばならず、不確定要素が依然として存在している。これら不確定要素の解明については、線量委員会の指導に拠る部分が多い。

## **勸告 9**

生物試料の保存と将来の分子遺伝学研究のための保存試料についての記録作成の続行を勧告する。

対応：

放影研は、当所の生物試料収集は実際他に類を見ないものであると認識しており、既存の細胞株を始め他の保存試料を維持するために必要な人員および施設を引き続き支援する。放影研研究員のニーズを満たし、また外部研究者が有益に利用できるようにするには、試料を正しく保管また記録することは重要である。また、試料が停電、台風のような天災などの事故または人的ミスが原因で不注意により失われることがないように、十分な安全措置を確立し、維持しなければならない。このような安全措置を整える一方で、保存技術が変化し、収集試料が増大し、また異なる保存技術が必要な新しい種類の試料が加わった時など、定期的に当該措置を再検討する必要がある。放影研は、生物学的試料委員会を設立した。同委員会は、必要な安全措置が整い、定期的に再検討されていることを積極的に率先して確認する役割を担っている。

組織試料を引き続き収集し保存することは分子疫学調査を行うためには絶対必要である。大部分の組織試料は外部から入手しなければならず、また放影研および外部研究者がこのような組織を入手しようとしていることに留意しなければならない。過去 20 年以上にわたり、放影研は広島および長崎の医師会と協力し、組織学的に診断された腫瘍と組織を登録する組織登録の維持管理を行ってきた。放影研は、地域の医療および調査団体と協力し率先して放影研また放影研以外の研究者達が分子生物学的調査のために腫瘍組織を共用できるようにするために「組織バンク」を設立する。組織登録を基盤とし、地域社会で有益であると思われる組織とその保存場所および状態の目録を作成するためにデータベース管理システムを開発する。調査を目的とした当該組織の使用については審査手順を設ける。このようなプログラムの確立・維持には放影研がかなりの労力を提供しなければならない。

## **勸告 10**

細胞遺伝学における最も進んだ方法および専門知識・技術を今後も放影研に導入することを勧告する。

対応：

当研究所は、細胞遺伝学調査が線量評価に関連した未解決の問題の解明を可能にし、また、放射線傷害の直接的なマーカーと成り得るので、この調査プログラムを強化することが重要であると認識している。従って、放影研管理者は、遺伝学部の細胞遺伝学研究室に今後も将来の課題に対応できるように適正な人員を配置し、必要な設備を導入する所存である。

現在の細胞遺伝学調査においては、従来の G 分染法や FISH 法（蛍光 in situ ハイブリダイゼーション）を用いた技術が利用されており、これらはすべて、原爆被爆者から提供された抜去歯のエナメル質について行われた ESR 測定と共に生物学的線量評価のための校正曲線の確立に役立っており、物理学的線量推定値の偏りの発見にも明らかに有益である。このよ

うな技法に基づく調査はまた、被爆者のリンパ球およびその他の体細胞組織に見られる特定の染色体異常を有する幹細胞のクローンの拡大の究明とも関連しており、放射線生物学部との協力の基盤を提供している。このような細胞のクローンの拡大は、がん罹患者しやすい体質の指標となるかもしれない。最後に、これらの技法を用いた調査は、遺伝的連鎖に関する調査と共に被爆者の子供達に見られるかもしれないヒトゲノム内の特定の突然変異遺伝子の位置を決定するのに有益であるかもしれないことを付言したい。

## **勸告 11**

放射線生物学部は分子疫学と免疫学に重点を置き、発がん過程のモデル作成に参与している世界中の研究グループと放影研とが強力に連携することを勧告する。

対応：

ブルーリボン委員会が認めている通り、放射線生物学部が多大な努力を傾注し、過去においては成果を挙げた体細胞突然変異調査は必然的に終局を迎えたようである。開発され、利用された検出方法の多くは、最近の電離放射線被曝にのみ適用できる線量計として重要であるが、被爆者調査には不適當である。同部自身もこれらの測定法の限界を認めており、最近では免疫学的・分子生物学的観点から放射線発がん問題と取り組む種々の調査を新たに開始している。特にがんの病因における免疫機能が果たす役割について検討することが重要と考える。同部には、免疫学およびがんに関する分子生物学の分野の教育を受け、このような調査に関心を持つ研究員がいる。放影研管理者は、委員会が勧告したプロジェクトに更に努力を傾注することにより放射線生物学部の活動方針を速やかに修正する予定である。

各々の正常幹細胞また突然変異幹細胞から生ずるクローンの拡大についてはほとんど知られておらず、また近年の血液学と免疫学における進展により幹細胞の特定の遺伝子マーカーに発生した変異を探知し、直接的に解析できるようになった。しかし、外部研究者から放影研に対して被曝者の突然変異頻度測定の実験が依然として多くあるので、かなり縮小したレベルであってもこれらの突然変異測定法を維持することは、国際協力推進には必要であり、また、これらの測定法は老化およびがんリスクの幾つかの側面について調べるには依然として有益である。

放影研における分子疫学プログラムを遂行するために、まず放影研でのみ遂行可能な調査を幾つか探し出し、外部グループと効果的に行うことができる調査分野について探る。外部研究者に放影研の試料について知らせ、共同研究の相手機関として価値がある研究所であると認められるようにするには、放影研で活発ではあるが焦点を絞った分子生物学調査プログラムを行うことが重要である。組織およびその他の生物学的試料の使用に関する法律上の問題なども解決しなければならない。中枢をなす研究計画もなく組織およびその他の生物学試料を無制御に使用することは、これら貴重な試料の無駄な枯渇にもつながるので、これらの問題について検討するために国内外の研究者が参加するワークショップを開催する。

## **勸告 12**

新生物および非新生物に対する放射線の影響について信頼すべき完全な評価ができる

ように被爆者集団が消滅するまで LSS 調査プログラムを継続することを勧告する。また、AHS 調査プログラムは医学的、社会的の両面において、原爆被爆者およびその子孫の健康増進に直接利益となる事業と考える。

対応：

委員会が主張する通り、原爆被爆者の追跡調査は、現存する電離放射線急性被曝集団についての最大かつ最長の調査である。この調査は、世界中の放射線リスク推定のための最も重要な唯一の情報源であるが、被爆者についての生涯にわたる情報が得られる時期までは、リスク推定値は不完全である。従って、被爆者集団の最後の一人が死亡するまで追跡調査を継続することを求めた委員会の勧告を歓迎する。しかし、この理想は、実際には不可能かもしれない。今なお入手可能なデータの生物学的重要性を基に追跡期間に期限を付ける必要があるかもしれない。しかしながら、小児期に被爆したこれらの被爆者のほとんどが現在でも生存しており、重要な情報が得られるのは彼らが晩年に達してからであることに留意すべきである。同様に、集団が小さくなるにつれて、蓄積データ量は増大するので、後期の調査が持つ意味は大きくなる。

また、AHS 調査プログラムは、被爆者に対して医学的、社会的に直接利益になる、当所の数少ない事業の一つであることを我々も認識している。既知の放射線関連疾患および高齢化集団に頻発する疾患の一次的また二次的な予防と健康増進を目的として AHS 対象者に情報を提供するためあらゆる努力を払う。更に、勧告 9 に対する対応の中で示唆したように、AHS の重要な活動の一つは、被爆者から、その同意を得た上で、将来の調査のために生物学的試料を入手することである。

### **勧告 13**

被爆者の子供 (F<sub>1</sub> 集団) の健康についての更なる調査は、特に新しい分子遺伝学的技法を用いた研究と併せて実施すると、遺伝的影響に関する価値ある情報を提供するかもしれないので、これについて検討することを勧告する。

対応：

当研究所は、この勧告を実行に移すための計画に着手した。現在、予備調査を計画中であるが、これにより、大規模調査の実施可能性を検討し、可能であるとわかれば有意義な調査を計画するために必要な情報が得られると思われる (付属書類 A)。この調査計画には、臨床検査だけではなく過去 10 年間に急速に発展してきた最新の分子学的技法も当然含まれる。従って、更に多くの試料を収集し、近い将来利用する最も適切な分子学的技法を選択しなければならない。遺伝学部は突然変異性障害を速やかに検出するための安価な方法の開発において重要な役割を果たしてきた。2 次元電気泳動法を利用した DNA 分析を始めとするこのような技法の幾つかは極めて高度なレベルに達しており、まもなく広範な分野で利用可能になる。ヒトゲノム全体の配列決定と比較して、上記の方法には多くの利点がある。これらは安価で、大量の試料に利用でき、また、機能的な遺伝子と通常関係のある DNA 断片を対象とするので、ヒトゲノムを使用した場合の冗長性の問題のうち、全てではないとしても多くを回避できる。このような調査により放射線関連の突然変異性障害に関する情報が得られるだ

けでなく、2次元電気泳動法により識別される遺伝子の少なくとも15%に変異が生じ易いことがわかっているため、ヒトにおけるDNAの多様性に関する膨大な基礎的データが得られると考えられる。しかし、画像解析はDNA断片の2次元電気泳動法調査にとって欠くことのできない部分であり、ミシガン大学で開発され、現在遺伝学部で使用している2-DEソフトウェアを書き直すために情報技術部の支援が必要である。このソフトウェアは旧式のコンピュータ用に開発されており、既にアップグレードされたり、また将来アップグレードを考えている放影研コンピュータシステムでは、そのまますぐには使用できない。また、これらの調査から生成された大量のデータの統計解析および管理を支援する必要性が増大している。

#### **勧告 14**

**発がんの分子学的機序に関して最近開始された研究は、放射線の低線量域における線量反応曲線の形状の究明に重点を置くべきである。**

対応：

- 分子疫学調査は、放射線による発がんメカニズムの究明のための最優先課題の一つである。勧告9の対応策で言及した組織バンクがここでは重要な役割を果たすことになる。放射線生物学部では、この勧告に従うために必要な高度のDNA技法のほとんどが利用可能である。しかし、この分野の調査を実施するためには、設備と人員の充実した施設を維持する必要がある。これが実行されなければ、低線量放射線による健康影響の線量反応の形状を正確に決定することは極めて困難であろう。低線量で有意な健康影響を示すには数多くの対象者が必要なので、この分野での進捗は自動解析法の開発に大いに左右される。

#### **勧告 15**

**放影研には、重要な外科・剖検試料のほか、血清、血漿、リンパ球試料が保存されている。特に、外部での研究のために提供する生物試料の管理と提供に際しての倫理について、明瞭な方針を確立することを勧告する。**

対応：

- 放影研は、その保有する情報および試料へのアクセスならびに調査対象者のプライバシー保護とデータの機密性の保証に関する方針決定を目的とする所内検討委員会（IRB）を日本で最初に設けた研究機関であると思われる。放影研のIRBである人権擁護調査委員会は、ヘルシンキ宣言（1964年）およびその改訂版（1973年）と米国衛生研究所が一連の官報に挙げた指針に基づいて1976年に設立された。最近に出された官報の指針は、1991年6月18日発刊の56巻117号28002-28032頁である。上記の方針は過去に幾度か再検討され、最近では1995年に再検討が行われた。しかし、当該方針は主に放影研の調査を念頭に策定されており、他の研究所での調査には不適當かもしれない。この点を改善するために人権擁護調査委員会による方針の再検討を行う。放影研の方針が他の研究所での調査に不適當であるとしても、ヒトゲノム調査プロジェクトやヒトゲノム多様性調査プロジェクトなどの国際的なプロジェクトにより設定された方針など、国際的なレベルで利用できるものが数多くある。ここで、この勧告の趣旨を考慮し、人権擁護調査委員会の設立以来、口頭または文書による同意が得ら

れた場合にのみ成人健康調査その他の放影研の調査集団から試料を入手していることを付言することは重要であると思われる。1994年以降、同意書を医療記録に挿入するか、同意が口頭で得られたものであれば、調査対象者に説明が行われた上で同意が得られたことを医療記録か調査記録に記入している。従来の手順に変更を加え、調査対象者が放影研で保存用に提供する試料が他の研究所で使用される可能性があることを本人に明瞭に知らせるのも適当であろう。これは、対象者の大多数が試料の分析は放影研で行われ、提供者の健康状態を調べるため、また放影研調査のために解析結果を使用すると暗黙のうちに了解していることが明らかでないためである。実際、将来遺伝学的解析を行うために細胞株を樹立するという遺伝学部の試みに協力しているトリオ（父-母-子）にもこの点を明らかに説明している。ゆえに、外部研究者に提供することを目的に被爆者とその子供達に更に多くの血液の提供を求めることを提案しない。それは、そのような要求が受診率を低下させる恐れがあるからである。しかし、Epstein-Barr ウイルスで形質転換した細胞株を外部研究者と共用することを提案する。

これらの試料へのアクセス権を取得するためには、研究者は研究計画書を提出し、放影研研究計画書審査委員会および人権擁護調査委員会の審査を受けることになる。計画書には、研究計画の性質、放影研試料を使用する理由を明記し、共同研究である旨を文書で記さなければならない。

### **勸告 16**

**現在の組織構成において 5 年総合計画を立て、それを毎年更新し、役員会を通して理事会の承認を得ることを勧告する。**

対応：

放影研管理者はこの勧告を速やかに実行する予定である。過去に 5 年計画は作成されたことはあるが、それらが系統的に更新されたり、有効に利用されたことはない。5 年計画作成に当たり、放影研のすべての部門には、今後 5 年間の各部の必要人員と予算および計画を提出するよう要請する。その中には、提案する個々の調査活動に割り当てた優先順位や特定の活動の完了までの時間的スケジュールも含む。各部の計画は放影研の研究調査委員会により調整され、役員会および運営委員会の承認を受け、専門評議員会および理事会の同意を得た後実施される。この過程は毎年くり返し行われる。

### **勸告 17**

**また、各部を 5 年毎に検討する国際的専門家グループによる新しい審査手順を確立し、例えば各グループの委員長を専門評議員会の異なる委員が務めることを勧告する。**

対応：

放影研管理者は、専門家による審査手順を有効に活用してこなかったことを認め、この勧告を歓迎する。長年の間、多くの研究者を顧問、専門委員および非常勤研究員として任命してきたが、彼らの能力を最大限に活用してこなかった。彼らの多くは日本在住の研究者である。今後諸外国の広範な分野の研究者を顧問等に委嘱することにより、その中から今回勧告されている放影研の重要な調査部門の活動に関する定期的評価を行う審査者を選任できるよ

うにしたい。

この新しい専門家による審査手順は、これまで専門評議員会が行ってきた審査に取って代わるものと見られているが、専門評議員会はこれらの審査結果を受理し放影研の科学プログラム全般を審理すると思われる。この変更により、専門評議員会は学術的方針上の問題および調査の方向付けに集中することができる。

### **勧告 18**

専門評議員会が放影研の評価および指導においてより積極的な関与をし、より活発な役割を担うことを勧告する。その構成は、放影研の研究に関係するすべての主要分野を反映すべきである。さらに、評議員の任期は5年として再選は一回のみとし、毎年2人が交代するような方式を勧告する。

対応：

当研究所は、この勧告に同意するものの、その実施には寄附行為の変更が必要と考える。寄附行為の31条においては、専門評議員の任期は4年とされ、再選については、2期が推奨されているが、寄附行為では特に限度は設けられていない。寄附行為を変更するためには、理事会で理事の3/4以上による賛成を得た上、主務大臣の承認を得なければならないが、遡及的に効力を生ずるものではない。役員会はこの勧告の趣旨に賛同し、次回理事会において、（あるいは、もし承認されれば郵便投票によって、）この勧告に沿って寄附行為を変更するよう提案する（付属書類B）。理事会の承認が得られれば、現在の評議員に辞任を求め、毎年2名の評議員が交代できるようにまず種々の時期における任命計画を立てる。同時に、評議員の専門分野を再検討し、放影研調査にとって重要な分野がすべて反映されるようにする。

### **勧告 19**

日本の大学または他の研究機関、特に広島・長崎の大学との正式な連携関係を確立または強化し、放影研の部長が客員教授を務め、教鞭を取ると共に、大学院の学生が放影研プロジェクトに関わることを考慮するよう勧告する。

対応：

放影研はこの勧告を歓迎し、その実施のために可能な措置を講ずる。非公式の連携関係は過去に存在し、現在も依然として存在するが、放影研の研究員が教鞭を取るような正式な連携関係を確立するためには、厚生省および文部省の承認が明らかに必要である。これらの承認を得るためにはその他の機関による交渉が必要と思われるが、委員会の提案は、このような連携関係確立を促進すると考えられる。ちなみに放影研研究員の多くは既に広島・長崎の大学を始め諸大学で非常勤講師を務めている。本勧告の趣旨を推進するために、Argonne 研究所や Oak Ridge 研究所など、米国における幾つかの国立研究所との連携関係と同様の関係を地域の大学との間に確立することができるであろう。放影研の研究員が教育機関とこれまで以上に密接な関係を持つことは明らかに有益である。原医研（広島大学原爆放射能医学研究所）、原研（長崎大学原爆後障害医療研究施設）および放医研（放射線医学総合研究所（千葉））との間に短期間で実現し得る連携関係としては、放射線生物学に関する短期集中講座

の開設が挙げられる。講座の開設時期を早い時期に公表して受講者がそれに合わせて来日計画を立てられるようにすれば、上述した各研究所における短期研修者に関わる負担が幾分軽減できる。

#### **勸告 20**

放影研が、日米二国間の研究者交流に加えて、他国および地域的または国際的機関との研究者交流のための正式プログラムを確立することを検討するよう勧告する。

対応：

この勧告を実施するために、当面二つの方法を取ることができる。第一に、放影研管理者は、放影研で研究に携わる研究者のための奨学金制度を欧州連合が設けることができるかどうか、同連合と交渉に入る予定である。第二に、米国エネルギー省は、放射線生物学分野における研究者の研修のために、一つないし複数の研修センターを開設することを検討している。このような研修センターには米国の諸大学との間に連携をもたせる予定である。このようなセンターの候補機関の選考が現在行われており、それが終了した段階で、放影研は指名を受けた大学と研修者交換プログラムを開始するための交渉を行う。無論、放影研施設で受け入れる研修者は常に放影研が選考するものとする。更に、研修者には欧州連合またはこれから決定される米国の研修センターから奨学金が支払われ、研修者受け入れに要する経費を賄うための幾分か補助資金が放影研に支給されるものとする。前述の放影研内で策定される博士課程終了者用プログラムとこの研修プログラムとは明らかに異なるものとして運営される。

#### **勸告 21**

放影研に蓄積されている知識からみて、放射線リスクに関する一般の理解を深めるための情報センターとして放影研を発展させることを勧告する。

対応：

情報センターとしての放影研の役割を強化するために幾つかの措置が取られてきた。第一に、放影研の成果を一般大衆に理解してもらう活動の一環として、放影研は WWW 上の記述を大幅に拡大し、放影研の歴史、調査プログラムおよび調査結果の詳細；被爆者およびその他の電離放射線被曝者により頻繁に尋ねられる質問；放影研への連絡方法；電離放射線についての概略；および放射線生物学で良く使用される用語について説明を掲載している。管理者は引き続き内容を充実させ、必要に応じて頻繁に更新していくつもりである。その他の渉外活動としては、RERF Update および日本語のニュースレターといった会報、地元医学雑誌への投稿、また 1995 年より行っているオープンハウスを引き続き年に一度開催するなどがある。しかし、電離放射線被曝に関連したリスクについて、これまで以上に一貫して一般大衆に情報を提供する必要があることは明らかである。

情報センターとしての放影研の役割を拡大する際には、原爆死没者のための記念館として原爆資料保存・情報センターを広島と長崎に設立したいという両市の市民および厚生省の意向を考慮すべきである。このような目的の遂行のために放影研の専門的支援が求められており、我々は今後もそれに応じる所存である。

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42

ANNEX A

ASCERTAINMENT OF DISEASE AND DISABILITY AMONG F<sub>1</sub> ADULTS

A Feasibility Study

Since the inception of the genetic studies of the survivors of the atomic bombing of Hiroshima and Nagasaki and their children in 1947, a variety of different strategies have been used to estimate the extent of the mutational damage arising from parental exposure to atomic radiation. These strategies have included the physical examination of some 77,000 infants born in these cities in the years 1947-1953, a continuing mortality surveillance of a cohort of 75,581 F<sub>1</sub> individuals of whom 71,077 are still alive but we intend to extend this cohort to include the 11,670 individuals known through the Biochemical Genetics Study who are not presently in the mortality surveillance, cytogenetic studies, as well as biochemical studies involving some 30 odd genetic loci at which the occurrence of structural and "null" or deficiency mutations was assessed by gel electrophoresis (structural) or an analysis of enzyme kinetics (null). Although as yet there has been no discernible increase in genetic damage among the children, the issue of whether a significant increase does or does not obtain remains a pressing one and there is considerable apprehension among the F<sub>1</sub> themselves. 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<sub>1</sub> after the first year of life which might detect an increase in these diseases and disorders.

The Blue Ribbon Panel convened to assess the research program of the Radiation Effects Research Foundation and to recommend future directions of research has urged that consideration be given to the feasibility of studying diseases and disabilities of late onset among the F<sub>1</sub>. This proposal is an effort to respond to this recommendation.

**Aims:**

The aims of this preliminary study are several-fold, but the principal

43 one is to establish the feasibility of a comprehensive study of the occurrence  
44 among the children of the survivors of diseases of late onset with a major  
45 genetic contribution with a view toward estimating the radiation-related risk  
46 of such diseases. The immediate objectives are to (1) identify a surveillance  
47 cohort of  $F_1$  individuals that can be followed for some as yet uncertain period  
48 of time, (2) determine the stability of the  $F_1$  population, that is, determine  
49 the proportion that may be lost to follow-up as a consequence of migration  
50 outside the Foundation's conventional contact areas, (3) estimate the probable  
51 participation rate in a more comprehensive study, if the latter seems  
52 feasible, and (4) determine the logistical or design problems that might arise  
53 in a full scale study.

54  
55 **Study design:** While a variety of study designs can be envisaged for  
56 ascertaining the frequency of disease and disability among the  $F_1$ , the only  
57 one which seems likely to meet the health concerns of these individuals and  
58 be scientifically rigorous is a program of physical examinations conducted by  
59 the Foundation staff in a manner analogous to the examinations associated with  
60 the Adult Health Study. A program of routine clinical examinations of a  
61 cohort of  $F_1$  individuals managed by the Foundation has many advantages. It  
62 would enable us to capture subclinical precursor changes for some diseases,  
63 such as hyperlipidemia or subclinical diabetes, and to characterize disease  
64 more precisely. It would also ensure uniformity in the examination process,  
65 and better quality control of the information. Moreover, it would make easily  
66 possible the collection of sample specimens for molecular genetic analysis.  
67 This approach would be costly, and might require a study population much  
68 larger than that of the Adult Health Study when both the children and their  
69 parents (or other siblings) are taken into account. But even a single  
70 examination of a fraction of the  $F_1$  could provide useful information on multi-  
71 factorial disease prevalence and serve as a source of biological specimens  
72 that might be used in future studies even if an ongoing clinical follow-up was  
73 deemed impractical. Moreover, there is much to be gained from the conduct of  
74 a mail survey through which data could be obtained on current health status  
75 and concomitants of disease (occupation, smoking and drinking habits) that  
76 will be useful in the continuing mortality surveillance of the  $F_1$  as well as  
77 for possible clinical studies.

78  
79 **Some general problems:** A number of potential problems can be identified a  
80 priori that must be suitably addressed if a full scale study is to be  
81 undertaken and prove successful. As previously stated, among the aims of the  
82 feasibility study would be to determine the kind and magnitude of these  
83 problems, and to devise ways that their effects could be mitigated or  
84 eliminated. Among these problems are the following:

85           1) *Name changes*: It can be assumed that most, if not all of the female  
86 children identified in earlier studies from which presumably a study cohort  
87 would be drawn, will have married, and thus the last name known to the  
88 Foundation is unlikely to be the current one. Current name could, however,  
89 be obtained through a search of the koseki in which the child was originally  
90 enrolled and the joseki-bo, the "struck off the record" book, which contains  
91 changes in a given koseki, and current address can be found in the koseki  
92 fuhyou. To do this would require approval of the Ministry of Justice obtained  
93 through the koseki-ka in various cities. Since the Foundation presently uses  
94 the good offices of the Ministry in the Life Span Study, presumably this  
95 approval would be granted and the koseki checked on a fee-for-service basis.  
96

97           2) *Migration*: Japan's population in the postwar era has been  
98 substantially more mobile than it previously was. This increased mobility is  
99 generally age and gender dependent, younger individuals being much more likely  
100 to have migrated from their family homes to other areas of Japan than was true  
101 of their parents and males more likely to migrate than females. The only  
102 systematic attempt to determine migration and possible refusal rates among the  
103 F<sub>1</sub> occurred in the course of the biochemical genetics study. The target  
104 population in this instance was some 41,587 members of the F<sub>1</sub> Mortality  
105 Surveillance Study. Through 1981, this study revealed that 27% had migrated  
106 out of either Hiroshima or Nagasaki. Migration rates were higher among the  
107 children of non-exposed parents than exposed parents (29 vs 24%) but there was  
108 little difference between cities in the migration rates for children of  
109 exposed parents. However, refusal to participate among individuals within  
110 contactable areas was different between cities with cooperation being poorer  
111 in Hiroshima than Nagasaki (24 vs 16%). An additional 4-7% of individuals  
112 ostensibly residing in the contactable areas were "unavailable," and  
113 presumably these individuals are covert refusals. Clearly a major effort  
114 would have to be made to encourage a higher participation rate.  
115

116           3) *Establishment of newly arisen mutations as distinct from transmitted*  
117 *ones previously existing in the family of the subject*: Estimation of  
118 mutational damage requires distinguishing between newly arisen mutations and  
119 those that have arisen in the past and were transmitted to the individual.  
120 Customarily this is done by examining the parents of the individual in  
121 question. Thus information on more than one individual is needed. For the  
122 older members of the F<sub>1</sub> cohort, this information may be difficult to obtain  
123 since their parents may be dead and their siblings, if any, dispersed.  
124 However, it should be noted that some information on health status would be  
125 available on those parents who are enrolled in the Adult Health Study and the  
126 Life Span Study, and this would embrace most, if not all of the parents who

127 received significant doses. Moreover, for those parents who are or, if dead,  
128 were in the Adult Health Study biological specimens for molecular genetic  
129 studies may already be available.

130  
131 4) *Identification of study endpoints:* Any study of disease and  
132 disability among the adult  $F_1$  will require defining the endpoints to be  
133 identified. Several alternatives exist. Ascertainment could focus on the  
134 occurrence of all common diseases or defects of probable multifactorial  
135 origin, or on some subset of the latter.

136  
137 For many of these common chronic conditions, such as diabetes,  
138 hypertension, and hypercholesterolemia, "candidate" genes are known, that is,  
139 genes which are thought to be functionally involved in the processes that give  
140 rise to these conditions. Many of these genes have been sequenced and the  
141 common allele as well as less common ones, including newly arisen mutants, can  
142 be characterized with the appropriate molecular techniques. Moreover, for  
143 some, estimates already exist of their importance as reflected in the  
144 proportion of inter-individual variability ascribable to allelic variation at  
145 particular loci. Although this area of research is still in its infancy,  
146 developments are moving rapidly and the number of potentially informative  
147 genes will surely increase.

148  
149 **Sample size requirements:** Obviously the sample size(s) needed will depend upon  
150 the design and the objectives of the study. At the feasibility level, where  
151 presumably the intent is to identify and estimate the magnitude of problems  
152 that might arise in a full scale study, the requisite sample size will be  
153 determined more by the precision sought in identifying and estimating the  
154 magnitude of these problems than by the magnitude of the health effect one  
155 seeks to detect. But, sooner or later, the issue will arise as to the sample  
156 requirements for a full scale study, and information obtained in the  
157 feasibility study would be crucial to assessing these requirements. The  
158 average age of the  $F_1$  individuals known to the Foundation is about 38 years  
159 which is relatively young when diseases such as atherosclerosis, diabetes, and  
160 even cancer are considered. However, early onset of these diseases often  
161 connotes a higher likelihood of a major genetic contribution. Thus, for  
162 example, the occurrence of early myocardial infarction, before the age of 50,  
163 aggregates more strongly in families than infarctions at a later age in life.  
164 Similarly individuals with the *Brc1* and *Brc2* genes associated with breast  
165 cancer usually exhibit their cancer earlier than occurs among women without  
166 these genes. Finally, studies of precocious onset of hypertension in  
167 conjunction with abnormalities in electrolyte handling have revealed at least  
168 four rare mendelian syndromes, namely, glucocorticoid-remediable aldosteronism

169 (GRA), Liddle syndrome (or pseudoaldosteronism), pseudoaldosteronism type II  
170 (Gordon syndrome) and the syndrome of apparent mineralocorticosteroid excess  
171 (AME). Given the prevalence of hypertensive disorders in Japan, these  
172 syndromes and the renin-angiotensin system itself, which plays a vital role  
173 in kidney function and renal homeostasis and hence in blood pressure  
174 regulation, would seem worthy objects of study. Again, in the case of the  
175 rennin-angiotensin system, four candidate loci are known, specifically, REN  
176 (rennin), ACE (angiotensin converting enzyme), AGT (which encodes rennin  
177 substrate angiotensinogen), and AT1, and others suspected. Appendix Table 1  
178 lists some of the candidate genes for hypertension and non-insulin dependent  
179 diabetes mellitus that might be considered. Still another possible candidate  
180 disease is hereditary nonpolyposis colorectal cancer. The frequency of  
181 colorectal cancer has been increasing in Japan and mismatch repair genes  
182 (hMLH1, hMSH2, hPMS1, and hPMS2) are known to be related to this malignancy.  
183 Abnormality in these genes can be detected by examining microsatellites.

184  
185 Unfortunately, the data from which to estimate the prevalence or  
186 incidence of common chronic diseases in the absence of exposure to ionizing  
187 radiation in Japan are limited. Two sources of information are available, but  
188 neither are faultless. At the time of the last national census information  
189 was obtained on the prevalence of a number of chronic disease; these data are  
190 based on self reports and almost certainly underestimate the true prevalence.  
191 The prevalences per 1000 individuals of hypertension, coronary heart disease  
192 and diabetes among males ages 35-44, and 45-54 were 16.4 and 57 for  
193 hypertension, 2.4, and 8.5 for coronary heart disease, and 6.2 and 20 for  
194 diabetes, respectively. The corresponding figures for females in the same age  
195 categories were 14.4 and 65.4 for hypertension, 1.3 and 5.6 for coronary heart  
196 disease, and 3.7 and 11.7 for diabetes. More useful numbers come from the  
197 Adult Health Study itself, and in particular the findings on survivors 0-19  
198 years of age at the time of the bombing in the tenth examination cycle (when  
199 these individuals would have been 34-53 years old, approximating the age  
200 distribution in the F<sub>1</sub> now). At that time the prevalence per 1000 individuals  
201 of hypertensive heart disease (specifically, essential hypertension and  
202 hypertensive heart and renal disease) was 27 (sexes combined), of  
203 arteriosclerotic and degenerative heart disease (acute myocardial infarction,  
204 other acute and subacute forms of ischaemic heart disease, old myocardial  
205 infarction, angina pectoris, and other forms of chronic ischaemic heart  
206 disease) was 8, and for diabetes mellitus the prevalence was 44. Note that  
207 if other forms of hypertensive heart disease (specifically, hypertensive heart  
208 disease, hypertensive renal disease, and secondary hypertension) are included  
209 in the rubric hypertensive heart disease alluded to above, the overall  
210 prevalence is 45 (sexes combined). Clearly, these diseases are not yet common

211 among individuals in the  $F_1$  age range. Collectively, one would expect about  
212 1 in 10 individuals to exhibit one or more of these three diseases. This  
213 number would be larger if behavioral and psychiatric disorders were also  
214 included.

215  
216 To the extent that data from other countries are a reasonable surrogate,  
217 these data suggest that approximately 65% of the population will develop one  
218 or more of these diseases in the course of a lifetime, but given the age  
219 distribution of the  $F_1$  and a single clinical examination perhaps no more than  
220 10% of the  $F_1$  population would exhibit a chronic disease of possible  
221 multifactorial origin. Information on the magnitude of the radiation-related  
222 increase in the genetic component of these diseases is even more limited.  
223 What little information is available has been derived largely from models  
224 whose applicability is open to question and involve assumptions regarding  
225 parameter values that may not be realistic; however, these models suggest that  
226 at 1 Sv the increased risk may be in the range of 1-2%, and since the mean  
227 conjoint parental dose in the  $F_1$  is estimated to be about 0.40 Sv, this  
228 implies a change of about 0.5% to 1%.

229  
230 **Locale for feasibility study:** A feasibility study might be conducted only in  
231 Hiroshima, only in Nagasaki, or in both cities simultaneously. Again, each  
232 of these choices has advantages and disadvantages. For example, at the time  
233 of the cytogenetic and biochemical studies mentioned earlier, the  
234 participation rate among the  $F_1$  in Nagasaki was significantly higher than that  
235 in Hiroshima and the strong relationship that exists between the Foundation  
236 and the University Medical School and Hospital could make access to relevant  
237 health findings easier. But the limited size of the staff of the Foundation  
238 in Nagasaki would pose a problem, and the probable higher participation rate  
239 could be misleading in assessing the overall feasibility of a full scale study  
240 since the number of exposed survivors is much larger in Hiroshima although the  
241 number of  $F_1$  children is about the same because of the larger mean family size  
242 in Nagasaki.

243  
244 **Feasibility study sample:** The easiest starting point for identifying a  
245 feasibility study sample would be the current sample of  $F_1$  individuals in the  
246 mortality surveillance which numbers about 75,000 individuals, as previously  
247 indicated, but could be easily and inexpensively extended to include those  
248 individuals known through the Biochemical Genetics Study. This sample  
249 includes births in the two cities after May 1946 through December 1985 when  
250 it was presumed that most of the survivors, irrespective of their age at  
251 exposure, would have completed their reproductive careers. A fuller  
252 description of this sample will be found in the section on **Alternative**

253 **sampling strategies** to follow. The only limitations on enrollment in the  
254 sample were the infant had to be liveborn and a singleton (multiple births  
255 were deliberately excluded because their survival experience is much different  
256 from that of single births and their number too small to provide reasonably  
257 precise estimates of survival). Since this sample is under continuing  
258 surveillance, addresses of its members should be reasonably current, and for  
259 those females who are now married, their married name should be known.  
260

261 The initial step would involve mailing a questionnaire to all of those  
262 individuals found to be alive at the last cycle of mortality surveillance  
263 seeking their current address (if different from the last one known to the  
264 Foundation), what health care program is available to them (National Health  
265 Insurance, Company program, and the like), their impression of the current  
266 state of their health (this would include a listing of common diseases and  
267 disorders which they might circle if pertinent), information on occupation,  
268 smoking, alcohol consumption, and reproductive history, and an expression of  
269 their willingness to participate in a study of their health status which might  
270 entail a physical examination at the clinical facilities of the Foundation.  
271 This questionnaire would presumably provide information on the proportion of  
272 individuals residing within the usual contact areas employed by the  
273 Foundation, a crude estimate of the prevalence of chronic disease among the  
274  $F_1$ , and an expression of the probable participation rate in a full scale  
275 study. It should be noted that the questionnaire findings would also have  
276 important relevance to the continuing mortality surveillance of the  $F_1$  through  
277 providing information on health problems and concomitants of disease before  
278 death.  
279

280 The next step would be the selection of a stratified subsample of 400-  
281 500 individuals chosen approximately equally from Hiroshima and Nagasaki and  
282 from those individuals reporting chronic illness and those not doing so to be  
283 invited to the Foundation for clinical examinations and specimen collection.  
284 The physical examination envisaged would be the same as that currently used  
285 in the Adult Health Study. This subsample would provide information on the  
286 occurrence of disease, and a better indication of the participation to be  
287 expected if the full scale study should emphasize clinical examinations under  
288 the Foundation's aegis.  
289

290 Collectively, these steps should provide the bases for assessing the  
291 feasibility of a full scale study, and designing a study that will be  
292 responsive to the concerns of the  $F_1$  and provide information of scientific  
293 value.  
294

295 Finally, the specimens obtained could be used to supplement the current  
296 study of the two dimensional electrophoretic methods for analyzing DNA that  
297 have been developed by the Department of Genetics. This system relies on the  
298 use of the *NotI* cutter and two enzymes and can detect about 1500 DNA fragments  
299 with the aid of a computer. Of these 1500, about 700 are usable in the sense  
300 that they can be studied both qualitatively and quantitatively. Since three  
301 separate enzyme systems are now available, this implies somewhat more than  
302 2000 fragments can be studied. Here the principal purposes of the feasibility  
303 study would be the development of better estimates of the cost of analysis per  
304 specimen or per locus studied and the identification of technical problems  
305 that might arise in a full scale study.

306  
307 It is our intention to present the results of the feasibility study to  
308 a panel of epidemiologists, geneticists and statisticians to solicit their  
309 recommendations for the full scale study if such seems warranted and  
310 practical.

311  
312 **Alternative sampling strategies:** An alternative sampling strategy would be  
313 to focus on the 800 families where permanent lymphocytic cell lines have been  
314 established. Altogether these 800 families represent about 2,700 individuals.  
315 At the time blood was collected on these individuals complete hematologic and  
316 clinical biochemical studies occurred, and this information is machine  
317 retrievable. However physical examinations were not done although at least  
318 one parent is generally a member of the Adult Health Study and health status  
319 should be available on these individuals. This then would represent a  
320 potential sampling frame of about 800 unexamined parents and 1120 children.  
321 Not all, of course, need to be examined in the feasibility phase. The  
322 advantage of this strategy is that permanent lymphocytic cell lines are  
323 already available for molecular genetic studies on the children and the  
324 parents. The disadvantage is that these families will be, on the average,  
325 younger than the overall  $F_1$  cohort and the prevalence of chronic disease  
326 correspondingly smaller.

327  
328 Still another alternative would be to focus on or add to the  $F_1$   
329 Mortality Sample the so-called BGS Extension Sample-1 (5,491) that includes  
330 children born between May 1946 and December 1958 who were not included in the  
331 original Mortality Sample, and BGS Extension Sample-2 (6,120) children born  
332 after 1959. Among these two extension samples, 3467 children were examined  
333 in the Biochemical Genetics Study at the protein level. Since these children  
334 have cooperated in the past, it can be assumed that a high participation rate  
335 would occur in any new health study.

337 **Estimated time required to conduct a feasibility study:**  
338       Approximately two years would be required to complete the survey, the  
339 4-500 examinations envisaged, given that these must be superimposed on the  
340 program of biennial examinations of the Adult Health Study sample, and the  
341 genotyping.  
342

343 **Tentative budget estimate:**  
344

345       (a) *Design and distribution of the questionnaire to all of the*  
346 *surviving F<sub>1</sub> currently being followed by the Foundation:*

347

|     |   |                |
|-----|---|----------------|
| 348 | Approximately 300 yen per person (82,000 persons) | 24,600,000 yen |
| 349 |   |                |

350       (b) *Cost of clinical examination, including contacting,*  
351 *laboratory studies, and administrative costs :*

|     |  |               |
|-----|--|---------------|
| 352 |  |               |
| 353 | Estimated cost 16,360 yen per person (500 persons) | 8,180,000 yen |
| 354 |  |               |

355       (c) *Cost of laboratory procedures:*

|     |  |               |
|-----|--|---------------|
| 356 |  |               |
| 357 | Estimated cost for genotyping 50 persons | 1,100,000 yen |
| 358 |  |               |

|     |                 |                |
|-----|-----------------|----------------|
| 359 | TOTAL COST:     | 33,880,000 yen |
| 360 |                 |                |
| 361 | COST PER ANNUM: | 16,940,000 yen |

Table 1. Some candidate genes for hypertension and non-insulin-dependent diabetes mellitus under the column headed association or linkage  
 a ○ implies a positive study and an × a negative one

Hypertension

| Gene   | Association or linkage |
|--|------------------------|
| Glycogen synthase                            | ○                      |
| Endothelin-1                                 | ○                      |
| Endothelin (A) receptor <sup>a)</sup>        | ×<br>×                 |
| Natriuretic peptide                          | ○                      |
| Glycophorin A (MN blood type)                | ○                      |
| HLA class II (DRB, DPB1)                     | ×                      |
| Endothelial cell nitric oxide synthase       | ×                      |
| Angiotensinogen <sup>b)</sup>                | ×××○××○<br>○○<br>○○×   |
| SA gene                                      | ○×                     |
| α-2 Adrenergic receptor                      | ○×                     |
| Prorenin                                     | ×                      |
| Angiotensin II type 1 receptor <sup>a)</sup> | ○○<br>××               |
| Haptoglobin                                  | ○○                     |
| Angiotensin I converting enzyme (ACE)        | ×××××○××○              |
| Insulin receptor (INSR) <sup>b)</sup>        | ×××<br>○○×<br>○        |
| Low-density-lipoprotein receptor (LDLR)      | ×                      |
| Apolipoprotein CIII <sup>a)</sup>            | ○<br>×                 |
| Renal kallikrein (KLK1)                      | ×                      |

<sup>a)</sup> Two different types of markers on each gene were examined.

<sup>b)</sup> Three different types of markers on each gene were examined.

## Non-Insulin-Dependent Diabetes Mellitus (NI DDM)

| Gene   | Association or linkage | Gene   | Association or linkage |
|--|------------------------|--|------------------------|
| Apolipoprotein E   | ○○○×                   | Interferon-gamma (IFN- $\gamma$ )                              | ×                      |
| Ras associated with diabetes (RAD1)                                  | ×                      | N-acetyltransferase (NAT)                                      | ×                      |
| Angiotensin I converting enzyme (ACE)                                | ××××○○                 | Cholesteryl ester transfer protein (CETP)                      | ○                      |
| Glycogen synthase  | ○○××○                  | Glucagon-like peptide-1 (GLP-1)                                | ×                      |
| Plasminogen activator inhibitor-1 (PAI-1)                            | ○○×                    | Liver/pancreatic $\beta$ cell type glucose transporter (GLUT2) | ○×××                   |
| Insulin receptor substrate-1   | ×××○×                  | Apolipoprotein A-IV  | ○×                     |
| $\beta$ -3 adrenergic receptor                                       | ○                      | Insulin <sup>a)</sup>  | ×                      |
| Muscle glycogen synthase   | ○                      | Adenosine deaminase (ADA)                                      | ×××                    |
| Aldose reductase   | ○                      | Islet-1  | ×                      |
| Glucagon receptor  | ○                      | Apolipoprotein CIII  | ○                      |
| Glucokinase <sup>a)</sup>  | ○○○<br>×○×××○<br>○××   | Insulin-responsive glucose transporter (GLUT4)                 | ××                     |
| Low density lipoprotein receptor                                     | ×                      | Fatty acid-binding protein 2 (FABP)                            | ×                      |
| Hexokinase II  | ×××                    | Glucagon-like peptide-1 receptor                               | ×                      |
| Insulin-stimulating protein kinase ( $\alpha$ , $\beta$ , $\gamma$ ) | ×                      | Apolipoprotein B   | ○                      |
| Protein phosphatase 1 ( $\alpha$ , $\beta$ , $\gamma$ )              | ×                      | Insulin receptor <sup>a)</sup>                                 | ×                      |
| Apolipoprotein D   | ○                      | Hep G2/erythrocyto glucose transporter (GLUT1)                 | ×                      |

<sup>a)</sup> Two different types of markers on each gene were examined.

**付録 A**  
**成人 F<sub>1</sub> における疾患および障害の発見**  
**試験調査**

広島・長崎の被爆者とその子供に関する遺伝学的調査が1947年に開始されて以来、親の原爆放射線被曝による突然変異性障害の程度を推定するために様々な戦略が用いられてきた。例えば、1947年から1953年までに両市で生まれた約77,000人の幼児についての理学的検査、被爆者の子供（F<sub>1</sub>）75,581人から成る集団についての継続中の死亡率調査（この集団のうち71,077人はまだ生存しているが、現在調査対象者ではない、遺伝生化学調査により確認された11,670人を含めることにより、この集団を拡大しようと考えている）、細胞遺伝学調査、ならびに構造突然変異および「ヌル」すなわち欠損突然変異をゲル電気泳動法（構造突然変異）または酵素反応速度解析（ヌル突然変異）により評価した30余りの遺伝子座位についての生化学調査などが実施されてきた。これまでのところ、被爆者の子供における遺伝的障害に増加は認められていないが、有意な増加が認められるか否かは早急に究明すべき課題であり、F<sub>1</sub>自身にとっても大きな懸念材料となっている。これまで用いられた突然変異リスク評価方法のいずれも、遺伝的障害全体を対象とはしていなかった。例えば、新生児の臨床調査プログラムは、出生直後に現れる先天性異常の発見を企図したものであったが、後年にならなければ容易に探知できない異常や、思春期以降までは発生しない単純な、あるいは複雑な遺伝性障害を発見することはできなかった。後者は、すべての遺伝性障害の中で断然多いが、このような疾患や障害の増加を探知するために、生後1年以降のF<sub>1</sub>について系統的な健康診断プログラムがこれまで実施されたことはない。

放射線影響研究所の調査プログラムの評価と調査の将来方向についての勧告作成のために組織されたブルーリボン委員会は、F<sub>1</sub>における遅発性の疾患および障害調査の実施可能性について検討するよう強く求めた。今回提案する調査はこの勧告に対応するためのものである。  
**目的：**この予備調査の目的は幾つかあるが、主なものは、被爆者の子供における遺伝が大きく関与する遅発性疾患について、その放射線関連リスク推定を目的とした包括的調査の実施可能性を検討することである。当面の目的は、（1）期間は限定できないが、しばらくの間追跡調査が可能なF<sub>1</sub>の調査対象集団の設定；（2）F<sub>1</sub>集団の安定性の決定、すなわち、放影研の従来連絡地域以外への転出による追跡中止例の割合の決定；（3）より包括的な調査が可能と思われれば、その受診率の推定；ならびに（4）本格的調査で生ずると思われる、資源または企画上の問題の列挙、などである。

**調査計画：**F<sub>1</sub>における疾患および障害の頻度の決定のためには様々な調査計画が考えられるが、対象者の健康上の関心を満足させ、学術的にも成果が期待できる調査は、成人健康調査に関連して行われた調査と同様の方法で行われる理学的調査プログラムである。放影研によりF<sub>1</sub>集団について通常業務として実施される臨床調査プログラムには多くの利点がある。このような調査により、高脂血症や無症候性糖尿病などの特定疾患の無症候性前駆変化を捉えたり、疾患の特徴をより正確に把握することが可能であろう。また、調査過程の統一性とこれまで以上に優れた情報の精度管理を保証することも可能であろう。更に、分子遺伝学的解

析のための試料収集も容易になるであろう。このような方法には経費がかかり、子供とその両親（または同胞）を対象とすれば、成人健康調査よりも大規模な調査集団が必要かも知れない。しかし、F<sub>1</sub> 集団の一部について一度調査するだけでも、多因子性疾患有病率について有益な情報が得られ、進行中の臨床追跡調査が実施不可能になっても、将来利用可能な生物学的試料が入手できる。更に、現在の健康状態および疾患の交絡因子（職業、喫煙および飲酒）についてのデータが入手できる郵便調査の実施は極めて有益であり、進行中の F<sub>1</sub> 集団の死亡率調査と共に将来の臨床調査にも有益であろう。

**一般的問題：**成功の可能性の高い本格的調査を実施するためには適切な方法で取り組まなければならない、幾つかの問題をあらかじめ指摘することができる。前述した通り、この試験調査の目的の中には、このような問題の種類と大きさの決定と、その影響の軽減または除去のための方法の発見が含まれている。このような問題とは次のようなものである。

1) 姓の変更：おそらく調査集団の基盤となるであろう初期の調査で同定された女兒のすべてではないにしてもほとんどは結婚しており、当所が入手している姓は現在の姓とは異なると考えられる。しかし、現在の姓は、子供が当初登録された戸籍と戸籍上の修正を含む除籍簿を調べれば入手できるし、現住所は戸籍付表からわかる。このためには、市の戸籍課を通じて法務省の認可が必要である。放影研は現在寿命調査の実施にあたり同省の協力を得ているが、今回の件についてもおそらく承認が得られ、一件あたり一定の料金で戸籍の閲覧が可能と思われる。

2) 転出：戦後日本人の転居は戦前と比較してはるかに激しくなっている。この転居の増加は全般的に年齢と性に依存しており、若年層ほどその親の世代よりも自分の出生地から国内の他の地域へと転出する割合が高く、また、女性よりも男性の方が転出する割合が高い。F<sub>1</sub> における転出率と受診拒否率を決定しようとする唯一の系統的試みが遺伝生化学調査の過程で行われた。その対象となった集団は F<sub>1</sub> 死亡率調査が行われている 41,587 人であった。この調査では、1981 年までに 27% が広島または長崎から転出したことを示した。転出率は非被爆者の子供の方が被爆者の子供よりも高かったが（29% 対 24%）、被爆者の子供の転出率に都市間差はほとんどなかった。しかし、連絡地域内での受診拒否率は両市間で異なり、広島の方が長崎よりも高かった（24% 対 16%）。連絡地域に居住していると思われる更に 4-7% の人が「来所不可能」であり、隠れた受診拒否者と考えられる。受診率の向上のために多大な努力を傾注すべきことは明瞭である。

3) 調査対象者の家族に以前認められた遺伝性突然変異とは異なる新しく発生した突然変異の確認：突然変異性障害の推定には、以前発生し、対象者に遺伝した突然変異と新しく発生した突然変異とを区別することが必要である。従来は、当該対象者の両親を調べることによりこの区別を行っている。従って、複数の人物についての情報が必要である。F<sub>1</sub> 集団のうち年齢の高い者については、両親が死亡し、同胞が離散しているかも知れないので、このような情報を入手するのが困難と思われる。しかし、成人健康調査および寿命調査の対象者である親の健康状態については何らかの情報が得られるであろうし、このような調査対象者には、有意な線量に被曝した親のすべてではないにしてもほとんどが含まれると考えられる。更に、現在成人健康調査の対象者であるか、死亡していれば、以前に対象者であった親については、

分子遺伝調査のための生物学的試料がすでに入手されているかも知れない。

4) 調査指標の同定：成人  $F_1$  における疾患および障害の調査には、同定すべき指標の決定が必要である。これには幾つかの方法がある。すなわち、おそらく多因子性と思われるすべての通常の疾患または異常の発生に重点を置くか、または、その一部に重点を置くか、である。

糖尿病、高血圧および高コレステロール血症などの通常良く認められる慢性疾患の多くには、その発生に関与する遺伝子、すなわち、これらの疾患を招来する過程に機能的に関与すると考えられる遺伝子が知られている。これらの遺伝子の多くはその遺伝子配列が決定され、頻繁に認められる対立遺伝子ならびに新しく発生した突然変異を含む余り頻繁でない対立遺伝子を適切な分子技法を用いて調べることができる。更に、幾つかの遺伝子については、特定の遺伝子座における対立遺伝子の多様性に起因する個体間の変動の割合に反映されているように、その重要性についてすでに推定がなされている。この研究領域はまだ緒に就いたばかりであるが、進歩は著しく、多くの情報を提供する可能性のある遺伝子の数が増大することは確かである。

**集団の規模についての条件：**必要な調査集団の規模が調査の計画と目的に依存することは明瞭である。試験調査の段階では、本格的調査で生ずると考えられる問題の程度を確認し、推定することが目的となると考えられるので、必要な調査集団の規模は、探知したいと考えている健康影響の程度よりも、上記のような確認・推定の過程における精確さにより決定されるであろう。しかし、本格的調査のための集団の条件についての問題は遅かれ早かれ浮上してくると考えられ、今回の試験調査で得られる情報はこれらの条件の評価に不可欠であろう。放影研が確認した  $F_1$  調査対象者の平均年齢は約 38 歳であり、アテローム性動脈硬化症、糖尿病および癌などの疾患を検討するには比較的若い。しかし、これらの疾患の早期発生には、重要な遺伝的影響が関与している可能性が高い。例えば、50 歳以前の心筋梗塞発生は、それ以後の同疾患発生よりも、家族内集積性が高い。同様に、乳癌に関連した *Brc1* および *Brc2* 遺伝子を有する女性には、これらの遺伝子を持たない女性よりも早期に癌が発生しやすい。最後に、電解質処理異常に関連した高血圧の早期発生に関する調査では、少なくとも四つの希なメンデル症候群、すなわち、グルココルチコイド治療性アルドステロン症 (GRA)、Liddle 症候群 (または偽アルドステロン症)、偽アルドステロン症 II 型 (Gordon 症候群) および顕性ミネラルコルチコステロイド過剰 (AME) 症候群が認められた。日本における高血圧性疾患の罹患率を考慮すれば、これらの症候群ならびに腎臓の機能と恒常性および血圧の調整に重要な役割を果たすレニン-アンギオテンシン系は適切な調査の対象と考えられる。レニン-アンギオテンシン系の場合はまた、四つの遺伝子座すなわち、REN (レニン)、ACE (アンギオテンシン変換酵素)、AGT (レニン基質アンギオテンシノーゲンをコード化する) および AT1 の関与が知られており、また、その他にも関与が疑われる遺伝子が知られている。高血圧および非インシュリン依存性糖尿病に関与していると考えられ、検討に値する遺伝子の幾つかを付表 1 に示した。もう一つの検討対象となり得る疾患は遺伝性非ポリープ性大腸癌である。日本では大腸癌の頻度が増加しており、ミスマッチ修復遺伝子 (*hMLH1*、*hMSH2*、*hPMS1* および *hPMS2*) がこの悪性疾患と関連していることが知られている。これらの遺伝子

における異常はマイクロサテライトを調べることにより検出できる。

残念ながら、電離放射線被曝がない場合の日本における通常の慢性疾患の有病率・罹患率を推定できるデータは限られている。情報源は二つあるが、いずれにも欠点がある。前回の国勢調査の際に幾つかの慢性疾患の有病率についての情報が得られた。このデータは自己申告したものであり、実際の有病率を下回っていることはほぼ確実である。35-44歳および45-54歳の男性における高血圧、冠状動脈性心臓疾患および糖尿病の1000人当たりの有病率は、それぞれ、高血圧が16.4および57、冠状動脈性心臓疾患が2.4および8.5、糖尿病が6.2および20であった。同じ年齢区分の女性の有病率は、高血圧が14.4および65.4、冠状動脈性心臓疾患が1.3および5.6、糖尿病が3.7および11.7であった。成人健康調査、特に被爆時年齢が0-19歳の被爆者について第10検診周期（同じ被爆者が34-53歳で、F<sub>1</sub>の現在の年齢分布に近い時期）に得られた所見から、より有用な数値が得られている。この時点では、高血圧性心臓疾患（特に、本態性高血圧および高血圧性心臓・腎臓疾患）の1000人当たりの有病率は27（男女合計）であり、動脈硬化および退行性心臓疾患（急性心筋梗塞、その他の急性および亜急性虚血性心臓疾患、陳旧性心筋梗塞、狭心症、およびその他の慢性虚血性心臓疾患）の場合は8、糖尿病の場合は44であった。その他の高血圧性心臓疾患（特に高血圧性心臓疾患、高血圧性腎臓疾患および二次性高血圧）を上記の主要な高血圧性心臓疾患に含めると、全体の有病率は45（男女合計）となる。これらの疾患がF<sub>1</sub>の年齢層ではまだ通常発生しないことは明瞭である。全体的に見て、10人中約1人がこれら三つの疾患の一つあるいはそれ以上に罹患すると予想される。行動性および精神性異常も含めると、この数値は更に大きくなるであろう。

諸外国のデータがF<sub>1</sub>にもかなり当てはまるとすれば、上記のデータは、F<sub>1</sub>集団の約65%が生涯のうちにこれらの疾患の一つあるいは複数に罹患することを示唆するが、F<sub>1</sub>の年齢分布を考えると、臨床検査を一回のみ実施するならば、多因子性慢性疾患が観察されるのはF<sub>1</sub>集団の10%未満であると考えられる。このような疾患のうちの遺伝性疾患の放射線による増加の程度に関する情報は更に限られている。この限られた情報は、応用性に問題があり、現実的でないかもしれないパラメータ値についての推論を含むモデルから主に得られたものである。しかし、これらのモデルによれば、1 Svにおけるリスクの増加は1-2%の範囲であり、F<sub>1</sub>における親の平均合計線量は約0.40 Svなので、約0.5%から1%までの変化が示唆される。

**試験調査の場所：**試験調査は広島のみまたは長崎のみで実施するか、あるいは両市同時に実施することもできる。いずれを選択した場合でも長所と短所がある。例えば、前述した細胞遺伝学および生化学的調査の際に、長崎のF<sub>1</sub>における受診率は広島の場合よりも有意に高かったし、放影研と大学の医学部および付属病院との強い連携により、適切な健康関連データを容易に利用できるかもしれない。しかし、長崎放影研の職員数が少ないことから問題が生じるであろうし、また、長崎の方が家族の平均人数が多いので、F<sub>1</sub>の数は両市ほぼ同じであるにも拘らず、被爆者数は広島の方がはるかに多いため、長崎で受診率がおそらく高いことが、本格的な調査の全体的な実施可能性の評価を誤らせる可能性がある。

**試験調査対象集団：**試験調査対象集団を設定する最も簡単な方法は、前述したように、約75,000人から成る現在のF<sub>1</sub>死亡率調査集団を利用することであるが、遺伝生化学調査で確認

された者をこの集団に含めることにより、調査集団を容易かつ安価に拡大できる。この集団には、1946年5月から、被爆時年齢に拘らず、ほとんどの被爆者が生殖可能な時期を終えたと考えられる1985年12月までに両市で生まれた者が含まれる。この調査集団についての詳細な記述は、後に**その他の調査対象者選択方法**の項に示す。対象者選択の唯一の制約は、対象となる子供が生産児で、単生児でなければならないことであった（多生児は、その生存状況が単生児の場合と著しく異なり、その数が少なすぎて生存状況についての正確な推定が不可能であるので、故意に調査対象から除外した）。この集団の調査は継続中なので、対象者の住所は比較的新しく、現在結婚している女性については、結婚後の姓がわかるはずである。

調査の第一段階では、前回の死亡率調査の時点で生存していた者全員に質問票を郵送し、現在の住所（放影研が入手しているものと異なる場合）、利用している健康管理プログラム（国民健康保険、会社でのプログラムなど）、現在の健康状態についての印象（よく発生する疾患および異常のリストを示し、該当すれば丸を付けてもらう）、職業、喫煙、飲酒および妊娠歴についての情報、放影研の臨床施設での理学的検査を含む健康状態に関する調査への協力の意志などについての質問を行う。この質問票によって、放影研の通常連絡地域内に居住する対象者の割合、F<sub>1</sub>における慢性疾患有病率の粗推定値ならびに本格的な調査への推定協力率についての情報が得られるであろう。また、この質問票により、健康上の問題や死亡以前の疾患についての情報が得られるので、F<sub>1</sub>集団について進行中の死亡率調査にも有益であると考えられる。

次の段階では、臨床検査および試料提供のために来所する400-500人の層化副次集団を設定する。その対象者としては、慢性疾患を報告した、あるいはしなかった者で、広島・長崎の居住者からほぼ同数ずつを選ぶ。実施する理学的検査は、現在成人健康調査で行われているものと同じとする。この副次集団により、疾患の発生状況がわかり、また、本格的調査が放影研での臨床検査を主体としたものである場合にどの程度の人に参加するかについてより詳しい情報が得られるであろう。

全体として、上記の各段階によって、本格的調査の実施可能性を評価し、F<sub>1</sub>集団の懸念に対応でき学術的価値のある情報を提供する調査を計画するための基盤が得られるであろう。

最後に、得られた試料は、遺伝学部が開発したDNA解析のための2次元電気泳動法についての現在の研究を補完するのに用いることができる。このシステムでは、NotIカッターと二つの酵素が使用され、コンピュータによって約1500個のDNA断片を検出できる。この1500個のうち、量的および定性的研究が可能という意味から、約700個が利用可能である。三つの異なる酵素システムが現在利用可能なので、2000強の断片を調べることができる。ここでは、試験調査の主要な目的は、検討する試料および遺伝子座1個当たりの解析費用をより詳細に推定し、本格的調査で生ずると考えられる技術的問題を発見することである。

この試験調査の結果を疫学者、遺伝学者および統計学者から成る委員会に提出し、本格的調査が可能であるとすれば、それに対するご意見を伺いたい。

**その他の調査対象者選択方法：**上記に代わる調査対象者の選択方法は、リンパ球永久細胞株が樹立された800家族を用いる方法であろう。これら800家族の合計人数は約2700人である。これらの対象者について採血を行った時に、完全な血液学的・臨床生化学的調査が行わ

れており、この情報を機械検索できる。しかし、一般的に少なくとも片親は成人健康調査の対象者であり、その健康状態についての情報は利用可能であるが、それ以外の者については理学的検査は実施されていない。このため、この対象者選定の基盤となり得る集団には、約800人の未検査の親と1120人の子供が含まれることになる。当然、試験調査段階で全員に検査を行う必要はない。この方法の長所は、子供と親についての分子遺伝学調査のためにリンパ球永久細胞株がすでに得られていることである。短所は、これらの家族は平均してF<sub>1</sub>集団全体よりも若く、従って慢性疾患の有病率が低いことである。

もう一つの方法は、元の死亡率調査集団に含まれていない1946年5月から1958年12月までに生まれた子供を含む、いわゆるBGS拡大調査集団-1(5491人)および1959年以降に生まれたBGS拡大調査集団-2(6120人)を用いるか、これらの集団をF<sub>1</sub>死亡率調査集団に加える方法である。これら二つの拡大集団のうち、3467人は遺伝生化学調査で蛋白質レベルの調査を受けている。これらの対象者は過去に調査に協力しているので、いかなる新しい健康調査にも多数の協力が得られると思われる。

**試験調査実施に必要な推定時間：**400件から500件の検査(成人健康調査の2年毎の検診と並行して行わなければならない)と遺伝子型決定を含め、本調査の完了に約2年必要と考えられる。

**暫定的予算推定：**

(a) 放影研で現在追跡調査中のF<sub>1</sub>全員に送付する質問票の作成と配布：

1人当たり約300円(82,000人)：24,600,000円

(b) 臨床検査費用(連絡、検査室での調査、事務処理用費用を含む)

1人当たり16,360円(500人)：8,180,000円

(c) 検査室での作業用経費

50人の遺伝子型決定に要する推定経費：1,100,000円

合計：33,880,000円

年間経費：16,940,000円

表1. 高血圧および非インシュリン依存性糖尿病との関連性が検討された遺伝子  
 関連性の欄の○は陽性、Xは陰性結果を出した調査を示す。

高血圧

| 遺伝子                                 | 関連性                           |
|-------------------------------------|-------------------------------|
| グリコーゲンシンターゼ                         | ○                             |
| Endothelin-1                        | ○                             |
| Endothelin (A) レセプター <sup>a)</sup>  | X<br>X                        |
| ナトリウム利尿性ペプチド                        | ○                             |
| グリコフォリン A (MN 血液型)                  | ○                             |
| HLA クラス II (DRB, DPB1)              | X                             |
| 内皮細胞酸化窒素シンターゼ                       | X                             |
| アンギオテンシノーゲン <sup>b)</sup>           | X X X ○ X X ○<br>○ ○<br>○ ○ X |
| SA 遺伝子                              | ○ X                           |
| α-2 アドレナリン性レセプター                    | ○ X                           |
| プロレニン                               | X                             |
| アンギオテンシン II 型 I レセプター <sup>a)</sup> | ○ ○<br>X X                    |
| ハプトグロビン                             | ○ ○                           |
| アンギオテンシン I 変換酵素 (ACE)               | X X X X X ○ X X ○             |
| インシュリンレセプター (INSR) <sup>b)</sup>    | X X X<br>○ ○ X<br>○           |
| 低密度リポ蛋白質レセプター (LDLR)                | X                             |
| アポリポ蛋白質 CIII <sup>a)</sup>          | ○<br>X                        |
| 腎臓カリクレイン (KLK1)                     | X                             |

<sup>a)</sup>各遺伝子上の2種類のマーカーを調べた。

<sup>b)</sup>各遺伝子上の3種類のマーカーを調べた。

非インシュリン依存性糖尿病 (NIDDM)

| 遺伝子   | 関連性                           | 遺伝子                               | 関連性     |
|---|-------------------------------|-----------------------------------|---------|
| アポリポ蛋白質 E   | ○ ○ ○ X                       | インターフェロン-ガンマ (IFN- $\gamma$ )     | X       |
| 糖尿病関連 ras (RAD1)                                    | X                             | N-アセチルトランスフェラーゼ (NAT)             | X       |
| アンジオテンシン I 変換酵素 (ACE)                               | X X X X ○ ○                   | コレステリルエステル転移蛋白質 (CETP)            | ○       |
| グリコーゲンシンターゼ   | ○ ○ X X ○                     | グルカゴン様ペプチド-1 (GLP-1)              | X       |
| プラスミノーゲン活性化因子抑制因子-1 (PAI-1)                         | ○ ○ X                         | 肝臓/膵臓 $\beta$ 細胞型グルコース輸送体 (GLUT2) | ○ X X X |
| インシュリンレセプター-基質-1                                    | X X X ○ X                     | アポリポ蛋白質 A-IV                      | ○ X     |
| $\beta$ -3 アドレナリン性レセプター                             | ○                             | インシュリン <sup>a)</sup>              | X<br>X  |
| 筋肉グリコーゲンシンターゼ                                       | ○                             | アデノシンデアミナーゼ (ADA)                 | X X X   |
| アルドース還元酵素   | ○                             | Islet-1                           | X       |
| グルカゴンレセプター  | ○                             | アポリポ蛋白質 CIII                      | ○       |
| グルコキナーゼ <sup>a)</sup>                               | ○ ○ ○<br>X ○ X X X ○<br>○ X X | インシュリン反応性グルコース輸送体 (GLUT4)         | X X     |
| 低密度リポ蛋白質レセプター                                       | X                             | 脂肪酸結合蛋白質 2 (FABP)                 | X       |
| ヘキソキナーゼ II  | X X X                         | グルカゴン様ペプチド-1 レセプター                | X       |
| インシュリン刺激プロテインキナーゼ ( $\alpha$ 、 $\beta$ 、 $\gamma$ ) | X                             | アポリポ蛋白質 B                         | ○       |
| プロテインフォスファターゼ 1 ( $\alpha$ 、 $\beta$ 、 $\gamma$ )   | X                             | インシュリンレセプター <sup>a)</sup>         | X<br>X  |
| アポリポ蛋白質 D   | ○                             | Hep G2/赤血球グルコース輸送体 (GLUT1)        | X       |

<sup>a)</sup>各遺伝子上の 2 種類のマーカーを調べた。

**ANNEX B**

**MEMORANDUM**

**TO:** Members of the Radiation Effects Research Foundation Board of Directors

**FROM:** Itsuzo Shigematsu, MD, Chairman

**SUBJECT:** Restructuring the Foundation's Science Council

**DATE:**

As you are undoubtedly aware, the Blue Ribbon Panel charged with assessing the Foundation's research program and making recommendations for the future has recommended a change in the structure of the Science Council and the terms of appointment of the Councillors. Specifically, they have recommended

*Recommendation 18.*

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

The Foundation's Executive Committee strongly endorses this recommendation and proposes to effect the changes indicated as expeditiously as possible. However, to achieve this end a revision of the Act of Endowment will be needed. At the present time, insofar as the Science Council is concerned, the Act states

Article 30 - This juristic person (meaning the Foundation) shall have not more than ten (10) Scientific Councillors

2. The Scientific Councillors shall be selected and appointed by the Board of Directors, from among those who are possessed of expert knowledge and experience useful for carrying out the activities of the juristic person. The Scientific Councillors to be appointed shall consist of the same numbers of citizens of Japan and the United States of America respectively.

3. The Scientific Councillors shall constitute the Scientific Council which reviews the scientific research programs of the juristic person, and makes recommendations to the Board of Directors with respect to the adoption of a new research program, and/or continuation or alteration of programs under progress.

Article 31 - The term of office of the Scientific Councillors shall be four (4) years.

2. The Scientific Councillors may be re-appointed to their posts.

3. The provisions of paragraphs 5 and 6 of Article 16 shall apply to the Scientific Councillors. [Paragraph 5 states that "in the event an officer's post becomes vacant, his successor shall be promptly elected to serve for the remainder of the term of office of his predecessor" and Paragraph 6 reads "The officers shall continue to perform their duties after the expiration of their terms of office or their resignation, until the time of their successor's assumption of office."]

It is important to note that to effect a change in the Act of Endowment, there must be an affirmative vote of three-fourths or more of the members of the Board of Directors. Changes are not retroactive, and take place at the beginning of the next fiscal year, that is on April 1, in the year following their adoption.

The Executive Committee recommends no change in Article 30 but does

recommend the following changes in Article 31.

*The term of office of the Scientific Councillors shall be five (5) years.*

*2. The Scientific Councillors may be re-appointed but shall not serve for more than two terms.*

*3. Appointment terms will be on a staggered basis so that two Councillors, one Japanese and one American, retire each year subject to the reappointment provision indicated in 2 above.*

Since the next Board of Directors meeting is not to occur until June 1997 and since action at that time would defer implementation of these changes until April 1, 1998, the Executive Committee seeks a mail ballot on this issue so that if approval is forthcoming, the changes can be effected April 1, 1997.

wjs:s

放射線影響研究所理事会メンバー各位

理事長 重松逸造

### 放影研専門評議員会の再編について

ご承知の通り、放影研の調査研究プログラムの評価とその将来に関する勧告を行うことを委任されたブルーリボン委員会は、専門評議員会の構成と評議員の任期の変更を勧告しました。同委員会は特に以下のような勧告を行っています。

#### 勧告 18

専門評議員会が放影研の評価および指導においてより積極的な関与をし、より活発な役割を担うことを勧告する。その構成は、放影研の研究に関係するすべての主要分野を反映すべきである。さらに、評議員の任期は5年として再選は一回のみとし、毎年2人が交代するような方式を勧告する。

放影研役員会はこの勧告を強く支持し、指摘された変更を可能な限り迅速に行うことを提案します。しかし、これを実現するためには、寄附行為の改正が必要です。現在専門評議員会については寄附行為で以下のように規定されています。

第30条 この法人（放影研を指す）に、専門評議員10名以内を置く。

2. 専門評議員は、この法人の事業の遂行に有益な学識を有する者の中から理事会において選任する。この場合においては、日本国の市民である専門評議員とアメリカ合衆国の市民である専門評議員が同数となるよう選任するものとする。

3. 専門評議員は、専門評議員会を構成し、この法人の科学的研究計画を検討し、新しい研究計画の認定又は実施中の研究計画の継続若しくは変更に関して理事会に勧告を行う。

第31条 専門評議員の任期は、4年とする。

2. 専門評議員は、再任されることができる。

3. 第16条第5項及び第6項の規定は、専門評議員について準用する。[第5項では、「役員が欠けた場合において選任される補欠の役員の任期は、前任者の残任期間とする」と規定され、第6項では、「役員は、任期満了後又は辞任後においても、後任者が就任するまでは、その職務を行うものとする」と規定されています。]

寄附行為の修正には、理事会メンバーの3/4以上の賛成が必要です。修正は過去に遡って行うのではなく、承認が得られた次の年度の始めの4月1日に実施されます。

役員会は、第30条については修正を加えず、第31条を次のように修正することを提案します。

専門評議員の任期は5年とする。

2. 専門評議員は再任されることができるが、2期を越えて務めてはならない。

3. 任期はずらし、日米1名ずつ、2名の評議員が毎年交代し、2.の再任規定に従うものとする。

次回理事会は1997年6月に開催されますが、その時点で寄附行為を修正するのであれば、その実施は1998年4月1日まで延期されることになるので、役員会としてはこの問題について郵便による採決を行い、承認が得られれば、1997年4月1日に修正が実施されるようにしたいと考えます。

ご承知の通り、7月2日にブルーリボン委員会の最終報告書を受け取り、それ以後同委員会の勧告に対する我々の対応についての検討に忙殺されております。貴殿も既にこの委員会の報告書を受け取っておられ、その勧告が放影研職員や調査研究の問題のみでなく、運営上の問題をも扱っていることをご承知のことと存じます。我々は、放影研の調査プログラムについてブルーリボン委員会が好意的な評価をされたことに対する感謝の念を表したいと考えていると同時に、建設的なこの勧告に対して誠実に対応したいと考えております。お気付きのことと思いますが、勧告のうち少なくとも一つは専門評議員会の再編について言及しております。このような再編により、放影研調査の今後の変化に対応するために必要な柔軟性が得られると思われるので、我々はこの勧告を支持します。専門評議員会の再編によって短期的には若干の混乱が生じるでしょうが、長期的には放影研に最も有益な結果をもたらすと信じております。この件につきまして貴殿のご協力とご理解を頂きたいと存じます。

ブルーリボン委員会勧告とそれに対する我々の対応が11月の専門評議員会の主な議題となると考えられますので、勧告に対する我々の対応についての文書を早急に貴殿にお送りし、その利点と意義について十分時間をかけてご検討頂きたいと思っております。9月1日までには我々の対応についての文書を貴殿にお送りし、貴殿のご検討、ご意見を頂き、最終的にはご承認を頂きたいと思っております。

理事長  
重松逸造

,

,

Draft: 25 October 1996

**RADIATION EFFECTS RESEARCH FOUNDATION**

**FIVE YEAR**

**STRATEGIC RESEARCH PLAN**

**AND**

**PROGRAM MANAGEMENT, 1997-2001**

**SUBMITTED BY THE RERF EXECUTIVE COMMITTEE**

## TABLE OF CONTENTS

|   |           |
|---|-----------|
| <b>FOREWORD</b> .....   | <b>1</b>  |
| <b>Organization of this Strategic Research Plan and Program Management Document</b> ..... | <b>1</b>  |
| Assumptions used in developing this planning document .....                               | <b>2</b>  |
| <b>THE FOUNDATION</b> .....   | <b>3</b>  |
| <b>RESEARCH GOALS AND OBJECTIVES</b> .....  | <b>4</b>  |
| <b>RESEARCH PROGRAM STRATEGY</b> .....  | <b>5</b>  |
| <b>CURRENT STATUS OF THE RERF COHORTS</b> .....   | <b>7</b>  |
| The Life Span Study cohort .....  | <b>7</b>  |
| The Adult Health Study (AHS) cohort: .....  | <b>8</b>  |
| In Utero Sample .....   | <b>8</b>  |
| The F <sub>1</sub> cohort: .....  | <b>9</b>  |
| <b>THE STRUCTURE OF RESEARCH AT THE FOUNDATION</b> .....                                  | <b>9</b>  |
| Cancer Studies .....  | <b>9</b>  |
| Noncancer Studies .....   | <b>13</b> |
| Heritable Mutations .....   | <b>16</b> |
| Dosimetry .....   | <b>18</b> |
| Database Development .....  | <b>20</b> |
| Current Status and Future Plans for RERF Follow-up Programs .....                         | <b>21</b> |
| <b>RESEARCH PLANS BY DEPARTMENT</b> .....   | <b>23</b> |
| Departments of Clinical Studies .....   | <b>24</b> |
| Program objectives .....  | <b>24</b> |
| Major research activities in the next five years .....                                    | <b>25</b> |
| A. Core activities (Hiroshima and Nagasaki) .....   | <b>25</b> |
| B. Special research activities (Hiroshima) .....  | <b>26</b> |
| C. New research initiatives (Hiroshima) .....   | <b>33</b> |
| D. Special research activities (Nagasaki) .....   | <b>36</b> |
| Departments of Epidemiology .....   | <b>37</b> |
| Program objectives .....  | <b>37</b> |
| A. Core activities .....  | <b>38</b> |
| B. Special research activities .....  | <b>40</b> |
| Site-specific cancer studies .....  | <b>40</b> |
| Case-control studies in progress .....  | <b>43</b> |
| C. New research activities anticipated in the next 5 years .....                          | <b>45</b> |
| Cancer .....  | <b>45</b> |
| Noncancer diseases .....  | <b>46</b> |
| Department of Genetics .....  | <b>52</b> |

|  |           |
|--|-----------|
| The Cytogenetics Program .....                             | 53        |
| Cytogenetic studies of the survivors .....                 | 53        |
| Major research activities in the next five years .....     | 54        |
| A. Core activities .....                                   | 54        |
| B. Special research activities .....                       | 55        |
| Cytogenetic studies of the children of the survivors ..... | 57        |
| Major research activities in the next five years .....     | 57        |
| Biochemical Genetics Program .....                         | 58        |
| Past and recent accomplishments .....                      | 58        |
| Major research activities in the next five years .....     | 59        |
| A. Core activities .....                                   | 59        |
| B. Special research activities .....                       | 61        |
| Department of Radiobiology .....                           | 64        |
| Recent achievements .....                                  | 64        |
| Program objectives .....                                   | 65        |
| Major projects in the next five years .....                | 65        |
| A. Molecular epidemiology .....                            | 66        |
| Core activities (Molecular epidemiology) .....             | 67        |
| Special research activities (Molecular epidemiology) ...   | 69        |
| B. Molecular Oncology .....                                | 70        |
| Core activities (Molecular oncology) .....                 | 70        |
| Special research activities (Molecular oncology) .....     | 71        |
| C. Immunology .....  | 73        |
| Core activities (Immunology) .....                         | 73        |
| Special research activities (Immunology) .....             | 74        |
| Department of Statistics .....                             | 78        |
| Program objectives .....                                   | 78        |
| Major research activities in the next five years .....     | 78        |
| A. Core activities .....                                   | 78        |
| B. Special research activities .....                       | 81        |
| <b>SUPPORTING SERVICES .....</b>                           | <b>84</b> |
| Department of Information Technology .....                 | 84        |
| Program objectives .....                                   | 84        |
| A. Core activities .....                                   | 85        |
| Publication and Documentation Center .....                 | 91        |
| Specific roles .....                                       | 91        |
| Radioisotope Facility .....                                | 91        |
| Management of the RI facility .....                        | 92        |
| Maintenance of a safe working environment .....            | 92        |
| Future of RI facility .....                                | 92        |
| Secretariat .....  | 94        |
| Organization and personnel strength .....                  | 94        |
| Duties .....   | 94        |
| Hiroshima Laboratory .....                                 | 94        |
| Nagasaki Laboratory .....                                  | 95        |

|  |            |
|--|------------|
| <b>MAINTENANCE OF AN ADEQUATE INFRASTRUCTURE</b> ..... | <b>98</b>  |
| <b>Personnel</b> .....                                 | <b>98</b>  |
| <b>Equipment</b> .....                                 | <b>99</b>  |
| <b>Space</b> .....                                     | <b>100</b> |
| <b>SUMMARY</b> .....                                   | <b>103</b> |

## 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 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 both 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 two decades has opened avenues of research of potentially great relevance to RERF and the understanding of the biological bases of radiation-related damage.
- The last few 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 carried out between 1988 and 1993 (see Annex B). The recommendations from these workshops have affected RERF's current research and are influencing plans

48 for future research initiatives.

49  
50 **Assumptions used in developing this planning document**

51  
52 In this assessment of the Foundation's needs to support its scientific program, the  
53 Executive Committee felt it necessary to adopt certain self-imposed restrictions:

- 54  
55 • It was assumed that budgetary limitations will prevent a significant expansion of  
56 the Foundation as a whole, i.e., the level of support provided by its two funding  
57 agencies for research will remain more or less constant (with inflationary  
58 increases only).  
59  
60 • It was further assumed that it was critically important to maintain the appropriate  
61 array of professional, technical, and clerical skills needed to implement the  
62 research.

63  
64 Within these limitations, the Committee believes that its research activities can still  
65 expand through increasing efficiency, through savings created by retirements, and, where  
66 possible, through transfer of general personnel positions to research-oriented ones.

67  
68 The Executive Committee has carefully considered which of all potentially desirable  
69 research activities *could only be carried out* by the Foundation, which *could best be carried out*  
70 by the Foundation, and which *could be carried out elsewhere*, possibly on a collaborative basis.  
71 Prioritization along these lines will avoid the inclusion of research that is not specific to the  
72 Foundation's needs and potential, and will therefore reduce needed resources to only those that  
73 are most appropriate to RERF.  
74

## THE FOUNDATION

75  
76  
77 In the summer of 1945, the residents of Hiroshima and Nagasaki were in all probability,  
78 representative of a typical, heterogeneous wartime population of individuals in Japan. In August  
79 of that year, atomic bombs were detonated over these two cities. Soon thereafter a group of  
80 Japanese and American scientists, known as the Joint Commission for the Investigation of the  
81 Effects of the Atomic Bomb, began the task of assessing the physical damage wrought by the  
82 bombings and of identifying the early health effects of exposure to atomic radiation. This  
83 Commission, in its final report, strongly recommended the establishment, under civilian  
84 auspices, of a program of research to evaluate the long-term health consequences of exposure  
85 to ionizing radiation. In November 1946, President Truman approved a directive to the U.S.  
86 National Academy of Sciences-National Research Council (NAS-NRC) to initiate the long-term  
87 investigation recommended by the Joint Commission. With funding provided by the Atomic  
88 Energy Commission (AEC), now the Department of Energy (DOE), the NAS-NRC established  
89 the Atomic Bomb Casualty Commission (ABCC) in March 1947, and research began shortly  
90 thereafter. The Government of Japan, through the Japanese National Institute of Health, became  
91 a partner in this endeavor.

92  
93 In 1975, the Radiation Effects Research Foundation (RERF) was established and  
94 assumed the responsibilities of the ABCC. This private, nonprofit Foundation, a *zaidan hôjin*,  
95 is incorporated under Japanese law and its research is equally funded by the Governments of  
96 Japan and the United States, through the Ministry of Health and Welfare (MHW) and through  
97 the Department of Energy and the National Academy of Sciences, respectively.  
98 Administratively, the Foundation is governed by a Board of Directors consisting of 12  
99 individuals, six of whom are Japanese citizens and six of whom are United States citizens. The  
100 day-to-day operations are managed by an Executive Committee consisting of four permanent  
101 members of the Board of Directors, two from Japan and two from the U.S., each of whom  
102 resides in Japan. The Permanent Directors consist of a Chairman, a Vice Chairman, a Chief of  
103 Research, and one other Director, who functions as the head of the Foundation's Nagasaki  
104 laboratory. The responsibilities of these individuals, their terms of office, and the like are  
105 specified in the Foundation's charter, known as the Act of Endowment.

106  
107 Functionally, the Foundation consists of five major research departments, namely, the  
108 Departments of Clinical Studies, Epidemiology, Genetics, Radiobiology, and Statistics, supported  
109 by the Information Technology Department (ITD), the Publication and Documentation  
110 Center (PDC), a Radioisotope Facility, and a Secretariat. The ITD is responsible for the  
111 maintenance of the computational capabilities of the Foundation; whereas the Publication and  
112 Documentation Center and Secretariat are responsible for the publications (print and online)  
113 emanating from the Foundation and the administrative details relating to budgeting, personnel,  
114 purchasing, and public affairs, respectively. The Radioisotope Facility serves as a resource for  
115 those departments, such as Genetics and Radiobiology, requiring the use of radioisotopic  
116 materials.

117  
118 The clinical, epidemiological, statistical, and other investigations are conducted in two  
119 laboratories, one in Hiroshima and the other in Nagasaki. The management of both laboratories  
120 is the responsibility of the Executive Committee, and the research activities conducted in the two  
121 laboratories are coordinated by the Chief of Research. To help conduct RERF's research  
122 activities properly there is a series of standing committees such as the Research Protocol and

123 Human Investigation committees. Review of the research program and recommendations on the  
124 relevance and scientific quality of ongoing investigations, as well as future research directions,  
125 are provided to the Board of Directors on an annual basis by a Scientific Council. This Council  
126 is composed of ten experts in areas of research relevant to RERF, five of whom are from Japan  
127 and five of whom are from the United States. As in the instance of the Board of Directors, the  
128 responsibilities of these individuals, their terms of office, and the like are specified in the Act  
129 of Endowment. In addition, over the last eight years, the Council has been instrumental in the  
130 organization of a series of workshops in specific areas of research to provide guidance on  
131 promising approaches for possible implementation in the research programs and many of their  
132 recommendations have been implemented. (See Annex B for a listing of the recent workshops.)  
133

134 As of 1 April 1996, the Foundation had 335 employees, 258 in Hiroshima and 77 in  
135 Nagasaki. Of these 47 represented the professional research staff, 43 in Hiroshima and 4 in  
136 Nagasaki.  
137

138 The Foundation is housed in Hiroshima in a complex of nine interconnected two-story  
139 structures with a gross area of 9,681 square meters (about 105,400 square feet); whereas in  
140 Nagasaki, the Foundation occupies a four story building with a gross area of 2,643 square meters  
141 (28,780 square feet). The facility in Nagasaki is relatively new, but the bulk of the one in  
142 Hiroshima was built in 1950 and is now barely adequate for the Foundation's research needs.  
143

144 To conduct a broadly based research program involving the collection, processing, and  
145 analysis of extensive data on mortality and morbidity in a population as large as that of the  
146 survivors and their children, RERF has developed an organization plan (see Figure 1) for the  
147 coordination of epidemiological, clinical, and laboratory research conducted in two widely  
148 separated laboratories. This plan is periodically reviewed by the Board of Directors and revised  
149 as circumstances warrant.  
150

151 It is important to note that the investigations conducted by the Foundation are the only  
152 opportunity in existence for determining the late biological effects resulting from exposure of  
153 a large number of human beings to single doses of ionizing radiation ranging from very low to  
154 high doses. The results obtained in these investigations provide information that will lead to  
155 improved health care for the survivors as well as individuals who may be exposed to ionizing  
156 radiation elsewhere. Furthermore, the results of these investigations are of fundamental  
157 importance to an understanding of the effects of ionizing radiation on human beings and are,  
158 therefore, essential for estimating radiation risk and setting safe standards for occupational,  
159 medical, and general population exposures. Indeed, the data accumulated by the Foundation is  
160 the major source of information on which the standards established by national and international  
161 radiation protection bodies rest.  
162

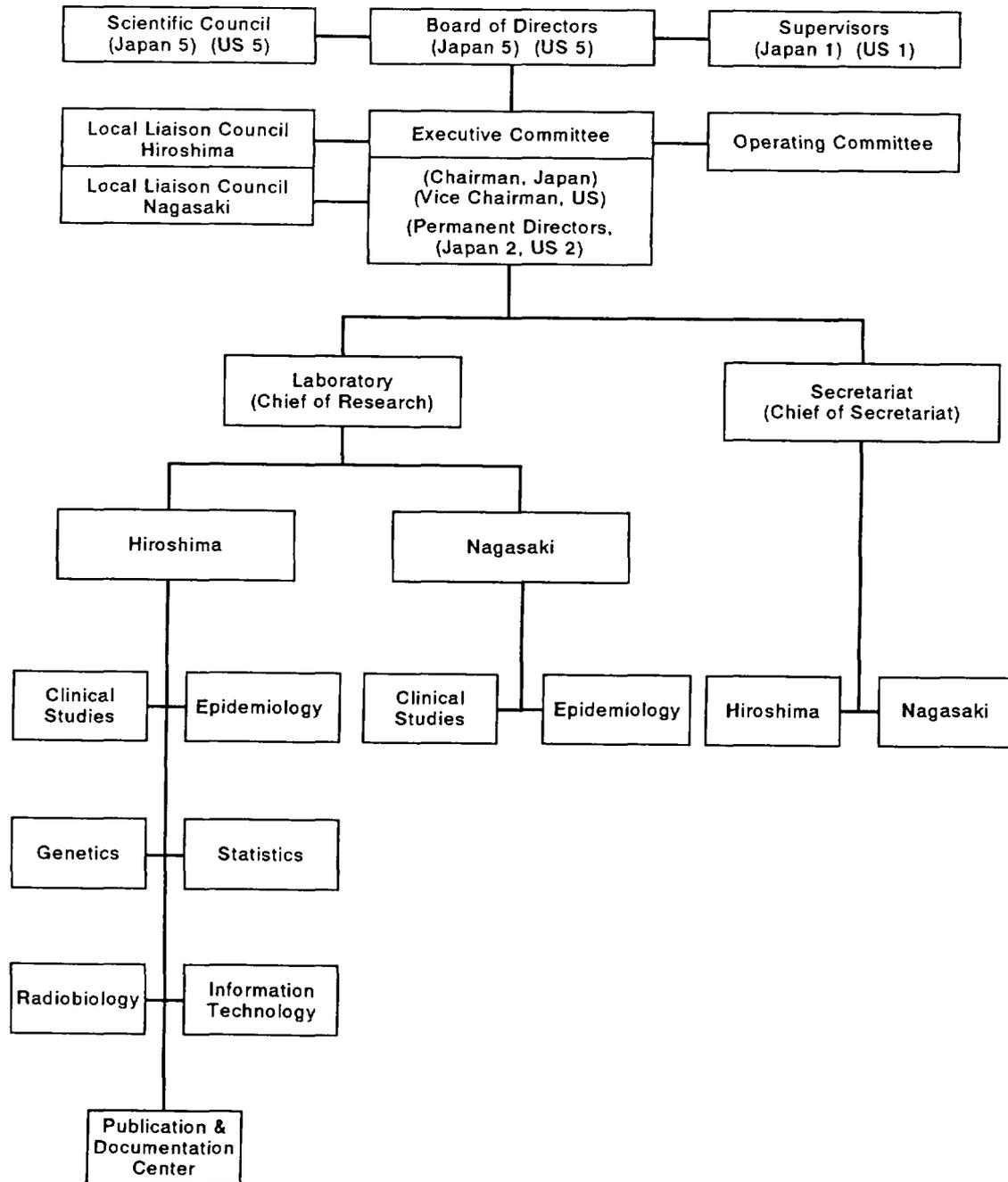
## 163 RESEARCH GOALS AND OBJECTIVES

164

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

Figure 1.

## Organization



171 or revised as need arises, and research priorities established. This strategic research plan has  
172 been developed to achieve these ends.

173  
174 To carry out its responsibilities in an orderly and scientifically sound manner and to be  
175 responsive to its charter, the broad goals of the Foundation are:

- 176  
177 • To determine the late health effects, both somatic and genetic, produced in  
178 human beings from exposure to ionizing radiation.
- 179  
180 • To obtain information on the temporal pattern of cancer expression and other  
181 radiation-related effects and on the role of biological and environmental factors  
182 which may modify the effects resulting from exposure to ionizing radiation.

183  
184 The strategy for addressing these goals is implicit in the following general research  
185 objectives:

- 186  
187 • To conduct long-term epidemiological studies of a fixed sample of exposed and  
188 unexposed individuals to determine the frequency-dose relationships of morbidity  
189 and mortality resulting from radiation exposure and to obtain information on the  
190 differential sensitivity of various tissues.
- 191  
192 • To conduct case-control and other special investigations on cancer induced in  
193 specific tissues or organs to determine the cell types affected and the effects of  
194 modifying factors.
- 195  
196 • To conduct research in molecular and cellular biology to detect somatic mutation,  
197 cell transformation, changes in immunological competence and other biological  
198 events for use in understanding and estimating radiation risk.
- 199  
200 • To utilize all available sensitive and cost-effective approaches for measuring  
201 heritable mutation in the children of exposed and unexposed individuals, and for  
202 assessing the public health impact of these mutations.

203  
204 All research at the Foundation aimed at these goals takes place under published research  
205 protocols that must obtain the approval of the Chief of Research, the Research Protocol  
206 Committee, the Human Investigation Committee, and the Chairman of the Foundation before  
207 they are activated. These protocols are of two kinds, the so-called platform protocols that guide  
208 the major or core research activities of the Foundation, and special research protocols. The core  
209 activities commonly involve more than one department and are collaborative; whereas the  
210 specific research activities may or may not be collaborative. A listing of the currently active  
211 protocols will be found in Annex I. Of primary importance to the Foundation are, of course, the  
212 core activities since ultimately they are the *raison d'être* of the institution.

## 213 214 **RESEARCH PROGRAM STRATEGY**

215  
216 To conduct a successful long-term epidemiological investigation which addresses the  
217 goals of RERF, data must be collected on a continuing, prospective basis using specified samples  
218 of exposed individuals and a matched group of unexposed individuals when a need for a

219 comparison with the latter arises. These data must be collected in a systematic and  
220 epidemiologically acceptable manner to reduce the chance of bias or ambiguity affecting  
221 interpretation of the results observed.  
222

223 The first major program to be initiated by ABCC was the Genetics Program, which  
224 included observations on the occurrence of major congenital abnormalities, sex, birth weight,  
225 viability at birth, and survival during the neonatal period of all newborn infants in Hiroshima and  
226 Nagasaki. The study, which began in 1947 and continued until 1954, encompassed some 76,626  
227 infants, with reexamination of a subsample of approximately 20,000 of these infants at age 8-10  
228 months. Although this major clinical program was terminated in 1954, the cohort thus  
229 established, with subsequent additions, has been followed for survival since that time, as the F<sub>1</sub>  
230 Mortality Study.  
231

232 Most of the early studies on the survivors themselves were essentially ad hoc, each  
233 investigator usually establishing his own study population. In 1955 the Francis Committee  
234 reviewed the research on exposed (and unexposed) persons at ABCC and urged the adoption of  
235 a Unified Study Program as a permanent research guide. The committee's recommendations  
236 were approved and have since provided the basis for much of the current epidemiological and  
237 clinical follow-up of the survivors in Hiroshima and Nagasaki. In 1975, prior to the  
238 establishment of RERF, a second committee, known as the Crow Committee, reviewed the  
239 program and recommended continued investigation of this unique population.  
240

241 Implementation of the Francis Committee recommendations resulted in the establishment  
242 of four major fixed cohorts:  
243

- 244 • the Life Span Study (LSS) cohort of survivors and an unexposed comparison  
245 group who were alive at the time of the bombings;  
246
- 247 • the Adult Health Study (AHS) cohort (a subset of the LSS cohort), whose  
248 members are encouraged to participate in a program of standardized biennial  
249 clinical examinations carried out at RERF;  
250
- 251 • the in-utero (IU) cohort of individuals who were exposed in-utero and matched  
252 controls; and  
253
- 254 • the F<sub>1</sub> cohort of children born between June 1946 and December 1984 to exposed  
255 or unexposed parents.  
256

257 Follow-up of these cohorts is central to the work of the Foundation. The primary follow-  
258 up programs are:  
259

- 260 • mortality ascertainment for most members of all of the cohorts through the  
261 Japanese family registration (*koseki*) system;  
262
- 263 • ascertainment of cancer morbidity through linkage of the cohorts with the  
264 Hiroshima and Nagasaki tumor and tissue registries, which are managed by  
265 RERF;  
266

- 267 • a special registry (the Leukemia Registry) of cases of leukemia and malignant  
268 diseases of the hematopoietic system;
- 269
- 270 • the offering of standardized biennial clinical examinations for members of the  
271 AHS cohort and a (fixed) subset of the IU cohort;
- 272
- 273 • a mail- and telephone-based morbidity surveillance system for AHS cohort  
274 members;
- 275
- 276 • occasional mail surveys carried out within the LSS cohort; and
- 277
- 278 • an autopsy program (active from about 1960 through the early 1980's but  
279 currently inactive).
- 280

281 Analyses of data from the RERF cohorts make use of individual dose estimates. The  
282 basic methods used to compute these estimates were originally developed by researchers at Oak  
283 Ridge and other national laboratories. The current dosimetry system, DS86, was the result of  
284 a binational effort to reassess the physical data and refine the theoretical models that formed the  
285 basis for the dosimetry system (T65D) that had been in use at ABCC and RERF since the late  
286 1960's. Japanese and US scientists are currently working to deal with discrepancies between  
287 DS86 Hiroshima neutron dose estimates and neutron doses inferred from physical measurements  
288 and some biases suggested by RERF biodosimetric data. It is likely that this effort will lead to  
289 revised dosimetry within the next five years. As in the past, RERF researchers will be  
290 responsible for adapting and applying the new dosimetry for use with the survivors.

## 291 **CURRENT STATUS OF THE RERF COHORTS**

292

293

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

### 297 **The Life Span Study cohort:**

298

299

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

315 additions, there are now 120,321 individuals in the LSS cohort, including 93,473 who were in  
316 the city at the time of the bombing.

317  
318 As of the fall of 1996, the mortality follow-up records indicate that 49% of the cohort  
319 members have died and less than 200 individuals have been lost to follow-up (primarily due to  
320 emigration out of Japan). The average age of the surviving members of the cohort is 65.4 years.  
321 When broken down by age at exposure, it is seen that lifetime follow-up is essentially complete  
322 for cohort members who were at least 50 years old at the time of exposure, while more than 90%  
323 of those who were under the age of 20 ATB are still alive. (See Annex A.)

### 324 325 **The Adult Health Study (AHS) cohort:**

326  
327 The AHS cohort is a subset of the LSS cohort. This subset was so defined as to include  
328 all members (4,990 individuals) in the original LSS cohort who were within 2000 m of the  
329 hypocenter and who reported one or more of the cardinal symptoms associated with acute  
330 radiation sickness, that is, epilation, oropharyngeal lesions, and purpura. Three age and sex  
331 matched control groups were chosen from among (1) the survivors within 2,000 meters who  
332 reported no acute radiation symptoms, (2) survivors who were at distances of 2,500 to 10,000  
333 m from the hypocenter ATB, and (3) unexposed LSS cohort members. With the introduction  
334 of individual dose estimates the AHS cohort was supplemented with all remaining members  
335 (2,436 persons) of the LSS whose T65D shielded kerma dose estimate was greater than 1 Gy.  
336 The examination schedule was set so that in any one month a more or less representative cross  
337 section of the entire population would visit the clinic. These examinations are now in the 19th  
338 cycle; however, over time, attrition has reduced the population to about 50% of the original  
339 sample.

340  
341 As of the fall of 1996 more than 9,200 of the 17,397 exposed members of the AHS are  
342 still alive and about 8,000 of these individuals are living in the clinical contacting catchment  
343 area. Among this later group almost 80% participated in the most recent cycle of AHS  
344 examinations.

### 345 346 **In Utero Sample**

347  
348 The in-utero cohort was assembled from a roster of more than 10,000 individuals whose  
349 date of birth was between the date of the bombings and May 1946. This roster was developed  
350 from Hiroshima and Nagasaki birth records, records of early ABCC studies, and data from a  
351 special survey conducted in conjunction with the 1960 Japanese national census. As currently  
352 defined, the cohort includes data from two overlapping samples: a clinical sample defined in the  
353 late 1950's and a mortality cohort defined in the early 1960's. As with the other cohorts these  
354 two groups were defined in terms of a core set of individuals whose mothers were close (within  
355 1,500 m for the clinical and 2,000 m for the mortality samples) together with age and sex  
356 matched groups of more distal or unexposed people. The cohort includes 3,654 individuals of  
357 whom 1,192 were exposed at distances of less than 2,000 m of the hypocenter while 1,356 were  
358 exposed at distances of 2,000 to 10,000 m. Complete mortality follow-up is available for all  
359 members of the IU cohort other than the 59 individuals who were lost to follow-up due to  
360 emigration from Japan or a failure to locate the *koseki* records. There are 755 in-utero survivors  
361 who have been included in analyses of IQ and school performance but are not in the main IU  
362 cohort. Consideration is being given to initiating routine mortality follow-up for these people.

363 A total of 1,021 members of the IU cohort are invited to participate in the AHS examinations.  
364 (This group overlaps but is not the same as the IU clinical cohort whose members were asked  
365 to come to ABCC for annual examinations during their late childhood and adolescence.)  
366

367 Because of the age of members of this cohort (51 or 52 years in the fall of 1996), there  
368 have been few deaths (434) at this time. More than one-third of these occurred during the first  
369 few months of life.  
370

### 371 **The F<sub>1</sub> cohort:**

372  
373 The original F<sub>1</sub> cohort included 53,518 children born to survivors between 1 June 1946  
374 and 31 December 1958 selected from among the 76,626 children identified in the course of the  
375 Genetics Program that ran from 1947 through 1953 or from other sources, generally the birth  
376 records. The F<sub>1</sub> cohort was subsequently extended to include the children of virtually all  
377 proximally exposed members of the Life Span Study cohort and the children of some distally  
378 exposed members of this cohort. At this time the cohort includes 88,484 persons. However,  
379 mortality follow-up is not being carried out for 11,760 cohort members who were selected for  
380 some special clinical studies. Follow-up of these individuals should begin within the next year.  
381 As of the fall of 1996, 5,316 members of the F<sub>1</sub> cohort are known to have died and 1,434 cohort  
382 members have been lost to follow-up. Most of the deaths were infant deaths. The average age  
383 of the surviving cohort members is currently about 38 years. As is discussed below, a mail  
384 survey of the full F<sub>1</sub> cohort and a small study of the feasibility of an F<sub>1</sub> clinical examination  
385 program are being planned.  
386

## 387 **THE STRUCTURE OF RESEARCH AT THE FOUNDATION**

388  
389 Research at the Foundation can be seen as a matrix with one dimension, the spectrum of  
390 health effects resulting from exposure to ionizing radiation, and the other, the disciplinary skills,  
391 represented by the research departments, needed to identify and understand the biological events  
392 that subtend these effects. This duality of aims is implicit in the Unified Program of research  
393 recommended by the Francis Committee and the need to focus most, if not all of the research  
394 effort on the fixed samples described above. This focus implies in turn that much of the research  
395 is integrative and necessarily collaborative. Indeed, no one of the major research departments  
396 at the Foundation stands fully alone; each requires the help of the others either in data collection  
397 and management, their analysis, or their biological interpretation. The collaboration can, of  
398 course, vary in form. It is instructive, therefore, in describing the Foundation's program of  
399 research to view it from both the programmatic perspective and the individual departmental  
400 contributions since one illustrates the inherently collaborative nature and broad sweep of much  
401 of the research and the other illuminates the individual departmental contributions.  
402

### 403 **Cancer Studies**

404  
405 Cancer is the best established, and most important late effect of exposure to ionizing  
406 radiation among the atomic bomb survivors and other exposed populations. There are, however,  
407 several important issues remaining unclear regarding the nature of cancer risk.  
408

### 409 *Major LSS reports*

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

424  
425 During the next five years we will produce a new comprehensive cancer mortality report  
426 (LSS Report 13) covering the period from 1950 through 1995 as well as an updated report on  
427 solid cancer incidence covering the period from 1987 through at least the end of 1992. While  
428 there will undoubtedly continue to be a need for both mortality- and incidence-based risk  
429 assessments, efforts will be made to present a more integrated, comprehensive picture of the  
430 incidence and mortality data. As these analyses are completed we will continue to make the  
431 detailed datasets available to other researchers.

#### 432 *Site-specific incidence studies*

433  
434  
435 The general LSS Reports provide useful summaries of cancer risks in the LSS. However,  
436 they cannot provide an in-depth look at the nature of cancer risks for specific tumor types or  
437 subtypes. To address this problem, RERF researchers in collaboration with the local medical  
438 community and some support from the US National Cancer Institute (NCI) have carried out a  
439 number of studies of cancer incidence at specific sites. These studies involve the identification  
440 of potential LSS cases from a variety of sources (including tumor and tissue registry records,  
441 death certificates, and autopsy reports) using broadly defined selection criteria. The medical  
442 records and, where possible, pathologic material for candidate cases are screened by a panel of  
443 pathologists in order to arrive at a consensus diagnosis. Cases identified in this way are then  
444 analyzed to assess cancer risks.

445  
446 The results of site-specific studies on cancers of the breast and salivary glands have been  
447 published. Reports on skin, CNS tumors, and liver cancer will be completed soon. Over the  
448 next several years studies of thyroid cancer, lung cancer, lymphoid malignancies, and an update  
449 of the breast cancer series will be completed.

450  
451 In contrast to the general LSS Reports, which appear in radiation-related journals, we are  
452 seeking to publish the results of the site-specific incidence studies in the more general medical  
453 literature to increase awareness of the RERF findings in the broader scientific community.

#### 454 *Patterns of excess cancer incidence among those exposed in childhood*

455  
456  
457 As noted above, the excess relative risks associated with radiation exposure among the  
458 youngest survivors are higher than those for other age groups and the data suggest that these

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

#### 469 *Issues in modeling excess cancer risks in the LSS*

470  
471  
472 The analysis of the LSS cancer mortality data continues to raise a variety of interesting  
473 and challenging statistical problems. A number of innovative methods have been developed to  
474 analyze the LSS data. These include extensions of classical regression models for survival  
475 analysis to allow for efficient estimation in large cohorts using general relative and absolute risk  
476 models, procedures to adjust for biases resulting from random errors in individual dose estimates  
477 and to allow for the impact of migration in the analysis of the tumor registry data, and methods  
478 for the joint analysis of data on multiple causes.

479  
480 There is an increasing interest in the application of biologically-motivated models to the  
481 data on radiation and cancer risks. Over the next year or so we expect to complete work on a  
482 generalization of the Armitage-Doll multistage model that provides some useful insights into the  
483 age and time patterns of the excess risk seen in exposed survivors. We are working on the  
484 application of the Moolgavkar-Venzon-Knudson two-stage model to the LSS cancer data.

485  
486 Because of the strong interest in the nature of the dose response at low doses, there is a  
487 need to consider more flexible alternatives to linearity than the simple quadratic and threshold  
488 models generally used. This will involve the development of regression-adjusted nonparametric  
489 smoothers.

490  
491 Over the next two years studies of inter-site variability in radiation-associated excess  
492 cancer incidence and of the comparison of relative risk and absolute rate models in the  
493 description of excess cancer risks will be completed.

#### 494 *Effect modification by nonradiation factors*

495  
496  
497 Use of data from the mail surveys conducted by ABCC-RERF over the past 30 years has  
498 largely been limited to assessments of smoking and lung cancer risks. However, these surveys  
499 also include information on alcohol consumption, nutrition, reproductive history, and  
500 socioeconomic factors. Additional cross-sectional and longitudinal data on non-radiation factors  
501 has been obtained directly from participants in the AHS examinations. The serum samples from  
502 AHS participants that have been collected and stored are also a valuable resource for the study  
503 of nonradiation risk factors and for molecular epidemiological studies.

504  
505 Use of these mail survey and clinical data has been limited in part by the problems in  
506 collating data from the various sources. This problem is being addressed as a part of efforts

507 (discussed further below) to modernize the RERF research database. Thus over the next few  
508 years we plan to undertake a number of projects that will make more extensive use of the mail  
509 survey data. These studies include updated analyses of smoking and the incidence of lung or  
510 other cancers in the LSS, new analyses of alcohol consumption and liver cancer incidence, and  
511 analyses of the impact of socioeconomic factors on comparisons of the exposed and unexposed  
512 (not-in-city) groups.  
513

514 Over the next five years we will conduct a series of case control studies nested in the  
515 AHS to investigate the impact of nonradiation factors on some common but generally nonfatal  
516 cancers (breast, thyroid, and skin). The mail survey and clinical data will be useful either  
517 directly (as a source of data on risk factors) or indirectly (by providing information enabling  
518 more efficient matching of cases and controls) in the design and analysis of such nested case-  
519 control studies.  
520

#### 521 *Radiation and benign tumor incidence*

522

523 Recent AHS data have suggested that there may be radiation-related increases in the risk  
524 of various benign tumors including myoma uteri and parathyroid adenoma among AHS  
525 participants. A study of the prevalence of uterine myoma based on ultrasonographic  
526 examination will be published within a year and reports on the prevalence of several other  
527 benign tumors (liver hemangioma, and ovarian tumor) observed using ultrasound will be  
528 completed within the next two to three years. Consideration is also being given to the conduct  
529 of a study of benign thyroid tumors and other thyroid disorders among Hiroshima AHS  
530 participants. If it is deemed feasible, this study would serve to complement the Nagasaki thyroid  
531 study, which indicated radiation-related increases in risks for these conditions. Within the next  
532 year a 10-year incidence study on hyperparathyroidism among AHS participants will be  
533 completed. It is hoped that this study will provide some hints as to the reason for the elevated  
534 serum calcium and parathyroid hormone levels in heavily exposed survivors.  
535

#### 536 *Cancer incidence and mortality in the in-utero and F<sub>1</sub> cohorts*

537

538 A major comprehensive report on cancer mortality in the in-utero cohort for the period  
539 from 1950 through 1992 is now in press. This report will be supplemented within the next year  
540 by reports on cancer incidence and general mortality patterns in this cohort. In view of the age  
541 of the in-utero population, the number of cancer cases can be expected to increase dramatically  
542 with five additional years of follow-up. Thus it would be appropriate to produce an updated  
543 report on cancer mortality and incidence in the cohort in about five years.  
544

545 Mortality follow-up for the F<sub>1</sub> cohort will be extended to include all people who have  
546 been selected for the BGS study. Once this is done a new comprehensive report on cancer  
547 incidence and mortality in the cohort will be prepared. This report should be completed within  
548 about three years.  
549

#### 550 *Pooling of RERF data with data from other cohorts*

551

552 While the atomic bomb studies are a major source of information on risk assessment,  
553 they cannot address all of the important issues on radiation risks. Comparison of the data on the  
554 A-bomb survivors with that from other exposed populations enables us to examine some of these

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

564  
565 Work being carried out at RERF on a multi-population comparison of breast cancer risks  
566 following radiation exposure in six cohorts, including the LSS, should be completed within the  
567 next year.

#### 568 569 *Trends in Hiroshima and Nagasaki cancer incidence*

570  
571 As noted earlier, RERF operates tumor registries in cooperation with the medical  
572 associations in Hiroshima city and Nagasaki city and prefecture. The linkage between these  
573 general population registries, which are generally regarded as among the best in Japan, and the  
574 LSS, in-utero, and F<sub>1</sub> cohort data is important to the conduct of RERF research. The registries  
575 also provide useful information on cancer risks in the Hiroshima and Nagasaki populations.  
576 While the Hiroshima and Nagasaki registry data are routinely published in IARC's *Cancer*  
577 *Incidence in Five Continents* volumes, the effort devoted to analysis and publication of these  
578 data has been limited (especially in Hiroshima). Over the next five years we will produce a  
579 series of short bilingual reports on trends in cancer incidence in these cities and develop  
580 procedures for the routine production of summary reports on the status of the registries and the  
581 nature of the accumulating data.

#### 582 583 **Noncancer Studies**

##### 584 585 *Noncancer mortality dose response*

586  
587 The evidence for a significant association between radiation and noncancer mortality is  
588 becoming stronger as the follow-up of the LSS cohort continues. Excess risks are seen not only  
589 for cardiovascular disease mortality but also for other broad categories of noncancer disease  
590 mortality. LSS Report 12 Part 2, which will be completed within the next year, will describe  
591 the basic nature of this effect while addressing the uncertainties and limitations of the mortality  
592 data. Over the next five years it will be important to extend the mortality follow-up through at  
593 least 1995 and to carry out further investigations aimed at clarifying, to the extent possible,  
594 issues related to the shape of the dose response and patterns of the excess risk with regard to sex,  
595 age and time. Additional follow-up may also help to determine if there are cause-specific  
596 differences in risk. Because of the lack of known biological mechanisms for a radiation effect  
597 on noncancer disease we must continue to look for factors that might lead to a spurious  
598 association between radiation exposure and noncancer disease mortality in the LSS.

599  
600 There is a highly significant excess risk for noncancer diseases of the blood, with the  
601 excess relative risk per Sv being larger than for any of the solid tumors. A review of these cases  
602 is being undertaken in collaboration with the hematologists associated with the Leukemia

603 Registry. Results of this review should be available in one to two years.

604

605 *Cardiovascular disease*

606

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

616

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

624

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

629

630 *Noncancer effects hypothesis generation*

631

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

641

642 *Liver disease*

643

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

648

649 We plan to investigate the feasibility and power of a nested case-control study using  
650 stored sera to compare HCV infection rates and subtypes prior to the diagnosis of liver cancer

651 or cirrhosis and to look for interactions between radiation dose and HCV infection. Of particular  
652 interest is the recent report that HCV infection can mask the concurrent presence of HBV  
653 infection, leading to an underestimation of the prevalence of the latter infection. Similar studies  
654 on HBV infection have been reported, but in the light of the finding just cited may have to be  
655 redone.

#### 656 657 *Longitudinal analysis of clinical and laboratory measurement data*

658  
659 The recent report of an association between radiation and age-related changes in  
660 cholesterol levels illustrates the usefulness of modern analytical methods in the study of  
661 longitudinal clinical data. These methods will be developed further and applied to other blood  
662 chemistry and hematology data as well as to blood pressure and other clinical measurements.  
663 We will also consider how these methods might be applied in analyses of longitudinal data from  
664 electrocardiograms.

#### 665 666 *Menopause*

667  
668 Analyses of the Nagasaki menopause incidence study indicate that a decrease in age at  
669 menopause is associated with increased radiation dose. A report on these results will be  
670 completed in the coming year. The Nagasaki findings have led to the initiation of a longitudinal  
671 study of FSH and estradiol levels in peri-menopausal women to better characterize the  
672 relationship between self-reported menopause and underlying hormonal changes. Data  
673 collection for this study will continue through 1997 with analyses to be conducted in the  
674 following two or three years. In Nagasaki, longitudinal observations on peri-menopausal  
675 changes in relationship to serum cholesterol and estradiol will continue for the next five years.

#### 676 677 *Aging*

678  
679 A study of the relationship between age-related changes in cognitive function and  
680 radiation dose has been underway since 1992. This study also includes comparison of data on  
681 AHS participants with that for Japanese-Americans in Honolulu and Seattle (NI-HON-SEA  
682 study). Data collection will continue for about one more year with analyses taking place over  
683 the subsequent three years.

684  
685 Osteoporosis is a common age-related disorder influenced by menopause and parathyroid  
686 hormone levels which have been shown to be associated with radiation exposure in the AHS.  
687 Dual photon absorptiometric measurements of spinal bone density of AHS participants, made  
688 since 1989, suggest that bone density increases as radiation dose increases. In order to provide  
689 a more definitive result, measurements of spine and hip bone mineral density using dual X-ray  
690 absorptiometry supplemented with data on total body composition are being obtained for  
691 selected AHS participants. An analysis of the baseline data is being carried out at this time. As  
692 data on these subjects are obtained in future AHS examinations longitudinal analyses of age-  
693 related changes in bone mineral density will be made. Data from this study will also be used in  
694 the NI-HON-SAN collaboration.

695  
696 Estimates of physiological age were computed for AHS participants on the basis of grip  
697 strength, skin elasticity and other factors measured in the 1970-72 AHS exam cycle. These  
698 estimates are being used as covariates in an analysis of rates of mortality and morbidity during

699 the following 20 year period. This analysis should be completed within a year. A new  
700 assessment of physiologic age based on a broader battery of measurements is being planned.

701

### 702 *Molecular epidemiology*

703

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

712

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

721

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

729

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

734

### 735 *Immunology*

736

737 We plan to continue our studies of the features and mechanisms of radiation-induced  
738 disorders in the hemolymphoid system at the cellular and molecular levels. These studies  
739 include radiation effects on the distribution of T-cell subsets in the survivors and of radiation  
740 effects on endocrine and hematopoietic growth factor levels.

741

### 742 **Heritable Mutations**

743

#### 744 *Permanent lymphocyte cell line cultures*

745

746 The 1984 Genetic Study Conference endorsed an RERF plan to establish immortalized

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

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

757  
758  
759 Methods for genome-level (DNA) analyses are developing rapidly. It is likely that the  
760 next five years will see the development of new markers and increasingly powerful methods that  
761 can be used in the search for evidence of mutation in the children of the survivors. At this time,  
762 we are examining several promising approaches. In each approach, mutations are detected by  
763 comparison of a child's gel with that of his or her parents. Indications of a mutation include the  
764 absence or dislocation of bands or spots as well as changes in intensity. As we learn of (or  
765 develop) additional methods it may be necessary to initiate additional pilot studies, in  
766 conjunction with researchers outside of RERF when necessary.

#### 767 Mutations at minisatellite loci

768  
769  
770 An initial study of 100 families will be extended by the addition of 100 families in order  
771 to provide information for enhanced comparisons of the RERF data with the results of a Belarus-  
772 UK comparison (Dubrova et al 1996, Satoh et al 1996) that has been interpreted as providing  
773 evidence of an excess of such mutations among Chernobyl victims.

#### 774 Chemiluminescent bands on Southern filters

775  
776  
777 Employing a quantitative analysis of chemiluminescent bands on Southern filters,  
778 material from the 200 families used in the minisatellite pilot studies will also be screened for  
779 evidence of mutation using DNA probes that correspond to the human counterparts of the seven  
780 mouse-specific loci and other loci including genes that are suspected to be related to several  
781 common chronic diseases, such as hypertension, diabetes mellitus, and hereditary nonpolyposis  
782 colorectal cancer.

#### 783 Two-dimensional electrophoresis (2-DE) methods

784  
785  
786 The Biochemical Genetics Laboratory has developed a 2-DE technique based on <sup>32</sup>P-  
787 labeled DNA digests created with three sets of restriction enzymes. This method produces three  
788 gels per individual having a total number of roughly 2000 spots (fragments) that are suitable for  
789 D/I/R mutation detection. A study using DNA samples from 200 BALB/c mice derived from  
790 irradiated spermatogonia, conducted primarily to prove that the 2-DE technique is capable of  
791 detecting mutations, will be completed within a year. This study will be followed by an  
792 investigation of DNA from the 200 pilot study families. It is expected that this pilot study will  
793 take at least five years to complete. If the spontaneous mutation rate is  $1 \times 10^{-5}$  / fragment /  
794 generation, we would expect to detect five mutations in the 120 children of the 100 control

795 families.

796

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

804

#### 805 *Genetic markers of hypertension*

806

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

812

#### 813 *F<sub>1</sub> mail survey and health study feasibility*

814

815 In response to the recommendations of the Blue Ribbon Panel, we are preparing detailed  
816 plans to carry out a mail survey of all surviving members of the F<sub>1</sub> cohort and to conduct a small  
817 scale study of the feasibility of an ongoing program for ascertainment of disease and disability  
818 in the cohort. The mail survey will provide data that can be used to obtain baseline (self-  
819 reported) information on health status and serve as a source of risk factor data that can be used  
820 in future analyses of the mortality and cancer incidence data in this cohort. The small clinical  
821 study (500 people) will include biochemical genetic studies of several genes related to common  
822 diseases (e.g., hypertension and diabetes). The mail survey and clinical feasibility study will last  
823 about two years and be followed by a workshop to determine what additional studies, if any,  
824 should be carried out by RERF.

825

#### 826 *Genetic epidemiology (family studies)*

827

828

829 Efforts are currently underway to define a database of family relationships within the  
830 LSS, in-utero, and F<sub>1</sub> cohorts. The initial focus is on the families of breast cancer patients in  
831 order to look for evidence of genetic predisposition among women who were diagnosed with  
832 breast cancer before the age of 35. Data on family relationships in the RERF cohorts and the  
833 extensive epidemiological and clinical follow-up data for the cohort members will be a unique  
834 and valuable resource in the study of the impact of genetic factors on disease. Continued  
835 development and use of this resource requires support and collaboration with groups outside of  
836 RERF who are active in this area. Progress will be highly dependent on the availability of  
837 personnel and special financial support.

837

#### 838 **Dosimetry**

839

#### 840 *Biodosimetric studies*

841

842 Over the past thirty years, RERF has played a central role in the development and

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

867  
868 Over the next few years effort will be directed toward a variety of comprehensive  
869 analyses and comparisons of existing biodosimetric data. These analyses will include: an analysis  
870 of all available data from the conventional chromosome aberration studies including assessments  
871 of more detailed data (e.g. interchromosomal:intrachromosomal aberration ratios); continued  
872 comparison of ESR, chromosome aberration data and GPA data as well as comparison of the  
873 correlation between these biological markers and the physical (DS86) dose estimates.

874  
875 While further analyses of the nature of the dose response for the various assays are  
876 important, recent comparisons of the ESR and cytogenetic data demonstrate that the data are also  
877 useful for the detection of errors in individual dose estimates. More importantly, the  
878 biodosimetric data will become increasingly important for the identification of potential  
879 systematic biases and the characterization of uncertainties in the physical dose estimates. For  
880 example, the chromosome aberration data suggest that DS86 dose estimates for Nagasaki factory  
881 workers may be too high by a factor of two or more.

#### 882 *Revision of the DS86 dosimetry system*

883  
884  
885 Ten years after its introduction, there is increasing evidence of systematic errors in DS86  
886 dose estimates. Much attention has been focused on a distance-dependent discrepancy between  
887 measured and calculated values for neutrons in Hiroshima. While estimates based on the best  
888 available information suggest that these changes will have little impact on cancer risk estimates  
889 derived from the survivor data, the fact that these discrepancies exist has led to some serious  
890 questions about the validity of RERF risk estimates. There is also, as noted above, biodosimetric

891 data suggesting that doses may be over-estimated for Nagasaki factory workers (who account  
892 for 30-40% of Nagasaki survivors with DS86 doses in excess of 0.5 Gy). It is expected that  
893 within the next two to three years the US and Japan senior atomic bomb survivor dosimetry  
894 committees will accept a revised dosimetry that will modify the Hiroshima neutrons and,  
895 hopefully, address the factory worker problem. Once a consensus has been reached the current  
896 RERF dosimetry programs will have to be revised and doses recomputed for all survivors. This  
897 will involve a considerable effort on the part of members of the Department of Statistics and ITD  
898 over a period of six months to a year followed by reassessments of the major findings regarding  
899 cancer and other risks.

900  
901 To prepare for the revised DS86 system, to make the basic dosimetry data more easily  
902 available (including shielding histories and acute effects), and to resolve several basic questions  
903 about exposure status for some in-utero mothers and F<sub>1</sub> parents, we have been working to  
904 reorganize and better document the dosimetry data. This effort, which has also included moving  
905 the DS86 system to the new RERF computer system, was begun several years ago and will  
906 continue for another year. This project should lead to the incorporation of all of the basic  
907 dosimetry data into the RERF research database and to a report that thoroughly describes and  
908 documents these data.

## 909 **Database Development**

### 910 *Continued development and documentation of core research database*

911  
912  
913  
914 The introduction of distributed computing has led to great progress in the development  
915 of a modern, unified research database. The new database is built around a newly created master  
916 list of over 700,000 individuals including all members of the major and minor RERF study  
917 cohorts as well as people registered in the tumor and tissue registries. The new system has  
918 simplified data handling for the mortality and cancer incidence follow-up and led to  
919 improvements in data quality through the elimination of redundant copies of data items. Using  
920 the new system researchers have quick direct access to current RERF data and can easily link  
921 their data to other items in the system to obtain data needed for analysis using standard analysis  
922 programs. At this time the database includes demographic, cohort membership, mortality  
923 follow-up, basic dosimetry, and tumor and tissue registry data. However, much additional work  
924 is needed to ensure that the database fully serves RERF's research needs. These activities  
925 include the development of improved documentation (on paper and online) and the  
926 implementation of additional consistency checks to ensure data quality along with an effort to  
927 make researchers more aware of the capability and accessibility of the new system. In addition  
928 to these activities, much of the work on database development over the next several years will  
929 focus on the areas mentioned in the following subsections.

### 930 *Clinical follow-up data*

931  
932  
933 These complex and voluminous data include longitudinal information on clinical  
934 contacting, routine measurement and laboratory test results, the results of special tests, diagnostic  
935 information, and more. Work has progressed on the development of the basic design of the  
936 clinical follow-up data tables to be added to the core database. This database will include data  
937 on the AHS examinations but also data from other special examinations of the in-utero and F<sub>1</sub>  
938 cohorts. It is hoped that the design and implementation of the major tables (focusing on the

939 AHS data) will be completed in a year or two but the effort to incorporate all of the clinical  
940 follow-up data can be expected to take several additional years. In addition to incorporating  
941 these data to the RERF research database, a modernized version of the AHS patient tracking and  
942 clinical management system that will serve as the front-end for continued updating of the clinical  
943 data.

944  
945 *Laboratory data*

946  
947 The data collected in the course of RERF's cytogenetic, biochemical genetic, and  
948 radiobiological studies are stored in computer files, laboratory notebooks and other formats. It  
949 is not practical to add all of these data into the new database at once. However, as new analyses  
950 of archival data are undertaken or new programs are introduced we will incorporate these data  
951 into the main research database. At the present time the conventional chromosome aberration  
952 data are being cleaned and linked to the core database. Over the next year data on other  
953 biodosimetric studies will be added to the system.

954  
955 The DNA studies being carried out in the Biochemical Genetics Laboratory will generate  
956 large amounts of data and analyses will be highly computer-intensive. Thus, there is a need to  
957 develop methods for the storage and management of these data. An interdepartmental effort will  
958 be undertaken to develop effective methods for handling these data.

959  
960 *Detailed dosimetry data*

961  
962 As noted earlier, efforts are currently underway to add all of the basic dosimetric data  
963 (survivor location, shielding history, and acute effects data) into the research database. This  
964 work has involved developing consistency checks and procedures for resolving differences in  
965 data from different sources. The basic work on this project has been completed and the new  
966 dosimetry data tables should be ready for formal addition to the main database within a few  
967 months. Work on documentation of these data will continue for about a year.

968  
969 *Unified inventory of stored samples*

970  
971 Over the last 30+ years more than 120,000 sera and other biological specimens have been  
972 collected and stored for use in future studies. Advances in molecular biology are increasing the  
973 value of this unique resource. At present there is no single inventory of these samples. Over the  
974 next two to three years we will develop a unified inventory of stored samples. This inventory  
975 will be a part of the research database in order to facilitate the planning and conduct of case-  
976 control and family studies that make use of stored samples and to allow this resource to be  
977 managed more effectively.

978  
979 **Current Status and Future Plans for RERF Follow-up Programs**

980  
981 *Mortality ascertainment (koseki check)*

982  
983 RERF carries out a program of active mortality ascertainment for all members of the LSS and  
984 most members of the in-utero and F<sub>1</sub> cohorts. As noted earlier, plans are now being developed  
985 to extend the mortality follow-up to include the 11,760 F<sub>1</sub> cohort members who are not currently  
986 included in the routine follow-up. Death certificate information for survivors whose *honseki*

987 (place of family registration) is in Hiroshima or Nagasaki is routinely received by RERF. For  
988 cohort members whose honseki is not in either of the cities, requests for information are sent  
989 to the appropriate office once every three years. Because of the decreasing number of surviving  
990 members of the LSS cohort and more efficient procedures for handling the data, it should be  
991 possible to obtain information on vital status and cause of death every two years, especially for  
992 members of the LSS cohort.

993

994 *Hiroshima and Nagasaki tumor and tissue registries*

995

996 RERF manages the population-based Hiroshima city and Nagasaki city and prefectural  
997 tumor registries. These registries are recognized as being among the best in Japan. The  
998 Foundation's role in the management of these registries has allowed us to create and maintain  
999 a direct link between the cancer registry data and the RERF cohorts. Without this connection  
1000 the increasingly important analyses of cancer incidence among survivors and their children  
1001 would be difficult, if not impossible. The development of the RERF research database has  
1002 strengthened the linkage between the tumor registries and the LSS cohorts and further  
1003 development of the database will make this linkage even more useful. Over the next five years  
1004 we hope to develop increasingly efficient and effective means for obtaining data on cancer  
1005 incidence among residents of Hiroshima and Nagasaki.

1006

1007 While it is essential for RERF to continue to take a central role in the management of the  
1008 tumor and tissue registries, we are working closely with the Hiroshima prefectural government  
1009 and Hiroshima Medical Association on plans for the development of a new Hiroshima  
1010 prefectural tumor registry and on the inclusion of the Hiroshima tumor and tissue registry  
1011 database as an integral part of the proposed new Hiroshima cancer center. It is hoped that in  
1012 conjunction with these efforts RERF can take a leading role in the creation of a regional tissue  
1013 bank that would serve as a resource for molecular epidemiological studies carried out at RERF  
1014 or other institutions, such as Hiroshima University and the Hiroshima Red Cross Hospital. As  
1015 these plans develop, it should be possible to begin discussions with Nagasaki University and  
1016 other related groups about the establishment of a similar system in Nagasaki.

1017

1018 The tumor registries are community resources and it is essential that more effort be  
1019 devoted to the presentation and analysis of the accumulated data in ways that benefit the  
1020 communities. Steps are being taken to analyze trends for selected cancer types and to publish  
1021 regular, standardized summaries of the tumor registry data in a format that will be useful to  
1022 physicians and others.

1023

1024 *Leukemia registry*

1025

1026 Special efforts to collect data on cases of leukemia and other hematopoietic malignancies  
1027 occurring among the survivors were begun by local physicians and ABCC in the late 1940's.  
1028 Over time these efforts evolved into the Leukemia registry. In recent years virtually all  
1029 ascertainment of leukemia and related disorders is being done through the tumor registry. It is  
1030 now felt that the tumor registries are adequate for the identification of new cases of leukemia and  
1031 related malignant conditions. Hematologists and others associated with the leukemia registry  
1032 are currently involved in a review of survivor deaths attributed to blood diseases other than  
1033 leukemia as well as an effort to reclassify all potential LSS lymphoma and myeloma cases using  
1034 modern diagnostic criteria. Over the next five years we plan to incorporate all of the historical

1035 leukemia registry data into the research database.

1036

1037 *Standardized biennial clinical examinations*

1038

1039 Since 1958 RERF has been giving standardized medical examinations to all participating  
1040 members of the AHS survivor and in-utero cohorts. This examination currently consists of a  
1041 complete physical examination that includes systolic and diastolic blood pressures,  
1042 electrocardiography, radiography, abdominal and thyroid ultrasonography as well as special tests  
1043 of bone mineral density and cognitive function. Data are also collected on smoking and drinking  
1044 habits, diet, and other factors. Overall participation remains high (almost 80% of those who  
1045 were still living in the clinical contacting area participated in the most recent examination cycle).  
1046 Home visits and hospital examinations are conducted for those survivors too infirm or  
1047 incapacitated to participate in examinations at the Foundation's clinic. Participation rates do  
1048 tend to decline sharply among the oldest groups of survivors, and as a consequence of this,  
1049 thought is being given to plans to increase the examination frequency for some of the older  
1050 individuals as well as to the development of cost-effective methods of special morbidity  
1051 surveillance (see next item).

1052

1053 Special one-time examinations have been carried out for selected subsets of the RERF  
1054 cohorts. The major examination programs, included annual examinations during 1956-63 of in-  
1055 utero cohort members during adolescence; special examinations of almost 25,000 F<sub>1</sub> cohort  
1056 members for the biochemical and cytogenetics studies; and most recently the ongoing  
1057 examinations of the F<sub>1</sub> cohort members and parents in conjunction with the establishment of  
1058 permanent lymphocyte cell cultures for future genetic studies. As discussed later, plans are  
1059 being developed to conduct clinical examinations on a limited number of F<sub>1</sub> cohort members in  
1060 order to assess the feasibility of an ongoing clinical examination program for a subset of the F<sub>1</sub>  
1061 cohort members.

1062

1063 *AHS mail- and telephone-based morbidity surveillance*

1064

1065 In response to the recommendations of the 1993 Health Monitoring Workshop, a new  
1066 AHS morbidity surveillance system was introduced in 1995. This system involves a short mail  
1067 survey with subsequent telephone contact at six month intervals. Thus far, response rates have  
1068 exceeded 90%. To validate the information obtained from this survey a system of periodic  
1069 hospital and home visits by physicians or public health nurses within the regular two year  
1070 examination cycle should be introduced.

1071

1072 *Mail surveys*

1073

1074 Since 1965 a number of mail surveys have been carried out on the LSS or AHS cohorts.  
1075 These surveys provide important data on risk factors that cannot be determined by means of the  
1076 routine mortality surveillance program. As described elsewhere, in response to the  
1077 recommendations of the Blue Ribbon Panel, a new mail survey of F<sub>1</sub> cohort members will be  
1078 carried out within the next few years.

1079

1080

## RESEARCH PLANS BY DEPARTMENT

1081

1082 Research at the Foundation centers on two broad fronts, namely, those programs that will

1083 presumably continue well into the future, such as the periodic reports on mortality and cancer  
1084 incidence in the LSS sample, and are commonly designated as the “core activities,” and those  
1085 programs, the “specific research activities,” that are initiated within a single department and are  
1086 generally time-limited. As previously noted, the core activities are set forth in the so-called  
1087 “platform protocols” whereas the specific research activities are described in individual research  
1088 protocols. Largely for convenience, we describe departmental research activities on an  
1089 individual departmental basis.

1090

### 1091 **Departments of Clinical Studies**

1092

1093 The AHS biennial examinations initiated in 1958 continue. The primary purposes of  
1094 these examinations have been to determine the types of diseases and abnormalities in  
1095 physiologically or biochemically determined values that may have occurred as a consequence  
1096 of previous exposure to ionizing radiation and to collate this information with other life  
1097 experiences and death. The AHS clinical examination is the only point of direct contact with  
1098 the survivors and functions as a source of biological materials for various special studies.

1099

1100 The AHS has greatly increased in importance in recent years as a result of the  
1101 accumulation of an enormous body of data on serial medical examinations, with and without the  
1102 superimposed radiation aspects. Particularly noteworthy is the accumulating evidence that  
1103 cardiovascular mortality may have a positive radiation-dose response. This potentially important  
1104 and largely unexpected relationship could never be properly studied using death certificate data  
1105 alone. Similarly intriguing and potentially important relationships arise from the clinical studies  
1106 on hyperparathyroidism and serum levels of parathormone, calcium, and alkaline phosphatase.  
1107 These results suggest that significant deviation in calcium metabolism may be a direct radiation  
1108 effect and raise further questions about bone density and osteoporosis among the survivors. Still  
1109 another unexpected finding is the retrospective evidence that radiation is associated with  
1110 premature menopause and this, in turn, may result in earlier onset of other physiologic conditions  
1111 such as an increase in cholesterol levels and cardiovascular disease. However, given the age of  
1112 the survivors, the window of time for such studies is growing shorter, and it is imperative that  
1113 these opportunities be exploited soon.

1114

1115 The major research elements in the Department's investigations of the AHS sample can  
1116 be categorized as follows: (1) characterization of cancer types in relation to various confounders  
1117 of radiation effects, (2) radiation-related noncancer diseases (benign tumors, cardiovascular  
1118 diseases, and other chronic diseases), (3) aging associated with exposure, (4) radiation-related  
1119 changes in physiological, biochemical, and hematological measurements, (5) medical dosimetry,  
1120 (6) psychosocial changes associated with exposure, and (7) health status of the in-utero exposed.

1121

### 1122 **Program objectives**

1123

1124 1. To provide biennial comprehensive medical examinations to the AHS cohort subjects  
1125 to determine disease occurrence and longitudinal changes in physiological or biochemical  
1126 parameters in relation to exposure to ionizing radiation and to relate this information to effects  
1127 on life span.

1128

1129 2. To conduct special in-depth studies to determine the association between ionizing  
1130 radiation and various health outcomes taking into account the possible effects of other health

1131 determinants (for example, life-style factors, physiological and biochemical determinants, prior  
1132 health history, and menstrual and reproductive history for women).

1133  
1134 3. To collect and store biological materials for basic science uses.

1135  
1136 4. To utilize the accumulated data for epidemiological purposes in general.

1137  
1138 **Major research activities in the next five years**

1139  
1140 **A. Core activities (Hiroshima and Nagasaki):**

1141  
1142 **Priority 1**

1143  
1144 *A-1. Basic AHS examination (RP 2-75):*

1145  
1146 The AHS clinical examinations will be continued in their usual format, but to optimize  
47 the quality and quantity of the clinical information considering the aging of the  
1148 population, a new method of morbidity surveillance was introduced in Hiroshima and  
1149 Nagasaki in 1995 based on the recommendations given by the Health Monitoring  
1150 Workshop in 1993. This method, with modifications if warranted, will be continued.  
1151 The new morbidity surveillance consists of a mail survey followed by telephone contact  
1152 every six months. Since its introduction, the response rate has been more than 90%. To  
1153 validate the information obtained through this new surveillance program, a system of  
1154 periodic hospital and home visits by either physicians or clinical personnel (public health  
1155 nurses) within the examination cycles should be introduced as soon as possible. The  
1156 utility of introducing an annual health examination for older AHS members, such as  
1157 those who are 70 years old or older, will also be carefully assessed both from the  
1158 standpoint of the health of the study participants and research needs.

1159  
1160 *A-2. Application of new methods of longitudinal data analysis:*

1161  
1162 A new method of analysis of longitudinal epidemiological data (which takes fuller  
1163 advantage of the 38 years of accumulated serial measurements than is possible with cross  
1164 sectional analyses) is being developed with support from staff members of the  
1165 Departments of Statistics and Epidemiology. The creation of a new AHS database  
1166 (diseases and measurements) for this type of analysis is currently underway.

1167  
1168 *A-3. Collection and storage of biological materials:*

1169  
1170 Collection and storage of biological materials such as serum, plasma, and lymphocytes  
1171 will be continued with some modification of the method of storage, if necessary. The  
1172 collection of teeth extracted for health reasons will be continued to provide materials for  
1173 ESR measurements through the new AHS surveillance system.

1174  
1175 *A-4. Improvement of clinical examination procedures:*

1176  
1177 In addition to the above, improvement of clinical examination procedures of recognized  
1178 benefit to the study participants, such as early cancer detection or health guidance, to

1179 provide more services to the AHS participants as recommended by the Blue Ribbon  
1180 Panel, will be updated and broadened to maintain a high level of AHS subject  
1181 participation. However, it is unrealistic to obtain such expensive modern equipment as  
1182 a CT scanner or MRI. This kind of test should be performed through collaboration with  
1183 local medical institutions.

1184

1185 Research plan for the next one year (A1-A4):

1186 The plan to produce *AHS Report 8* will be developed. In this report, the study period  
1187 will be extended to 1994 and analytic methods will place greater emphasis on  
1188 confounding and bias due to long-term follow-up, migration and nonparticipation. The  
1189 creation of the new AHS database will be completed. A plan to improve services to  
1190 AHS participants will be developed.

1191

1192 Research plan for the next three years (A1-A4):

1193 The *AHS report 8* will be completed and the results published. The new information  
1194 obtained through the AHS surveillance program should become available for use in AHS  
1195 Report 9. Comprehensive clinical examination procedures of recognized benefit to the  
1196 study participants will be introduced in an effort to provide more services to the  
1197 participants.

1198

1199 **B. Special research activities (Hiroshima):**

1200

1201 Priority 1

1202

1203 B-1. Benign tumors:

1204

1205 a) *Hyperparathyroidism (RP 11-86, 2-89):*

1206

1207 Screening for hyperparathyroidism has been conducted since 1986 by measuring serum  
1208 calcium level. Continued screening will provide not only incidence data on  
1209 hyperparathyroidism but also a clue to the cause of the slightly elevated levels of serum  
1210 calcium and parathyroid hormone seen among survivors exposed to higher radiation  
1211 doses.

1212

1213 Research plan for the next one year:

1214 Data collection for a 10-year incidence study will be completed.

1215

1216 Research plan for the next three years:

1217 The incidence of hyperparathyroidism will be analyzed for radiation effect, using the  
1218 data accumulated in the 10 years from 1988 to 1997.

1219

1220 In collaboration with the Department of Radiobiology, a protocol for a molecular  
1221 biological study (PRAD gene analysis) will be developed to elucidate the etiological  
1222 mechanism underlying parathyroid adenoma and elevated levels of serum calcium and  
1223 parathyroid hormone among individuals exposed to radiation.

1224

1225 b) *Other benign tumor study (RP 6-86):*

1226

1227 Systematic detection of various benign tumors such as myoma uteri, ovarian tumor, and  
1228 liver hemangioma are being undertaken using abdominal ultrasonographic techniques.  
1229

1230 Research plan for the next one year:

1231 Results of the prevalence study of uterine myoma will be published.  
1232

1233 Analysis of the prevalence of liver hemangioma and ovarian tumor determined by  
1234 ultrasonography will be completed.  
1235

1236 *c) Benign thyroid tumors:*

1237  
1238 In Nagasaki, thyroid tumors and disorders were screened for by means of physical  
1239 examination, ultrasonography, and thyroid function tests from 1984 to 1987.  
1240

1241 Research plan for the next one year:

1242 The feasibility of studying benign thyroid tumors or thyroid disorders in Hiroshima will  
1243 be considered.  
1244

1245 Research plan for the next three years:

1246 If the decision is made to initiate a thyroid study in Hiroshima, a research plan will be  
1247 developed and data collection begun.  
1248

1249 *B-2. Cardiovascular disease study (RP 4-85):*

1250  
1251 A longitudinal cardiovascular study has been underway since 1965, and the results of this  
1252 study, covering the period of 1958-1990, suggest a positive radiation effect on the  
1253 incidence of myocardial infarction (MI). The estimated relative risk (RR) at 1 Gy is 1.17  
1254 ( $p=0.02$ , 95% confidence interval: 1.01-1.36). In a Cox regression analysis including  
1255 various factors, such as age, sex, blood pressure, and cholesterol, it was found that  
1256 exposure dose still remained a significant factor, though the association was less than that  
1257 with age, sex, or blood pressure, suggesting that atomic bomb radiation may be involved  
1258 in the occurrence of MI. In addition, the different endpoints of atherosclerosis available  
1259 in the AHS database, such as the prevalence of aortic arch calcification, calcification of  
1260 the abdominal aorta, blood coagulability, the prevalence of isolated systolic  
1261 hypertension, and the prevalence of retinal arteriosclerosis were analyzed, and all of  
1262 these endpoints suggested the presence of radiation effects. Studies in progress include  
1263 those on sudden death and detection of peripheral vascular disease using pulse wave  
1264 velocity (PWV) measurement and ankle-arm blood pressure ratio using Doppler  
1265 equipment. The analysis of radiation effects on conventional risk factors, such as blood  
1266 pressure and cholesterol levels, has been underway for some time. An analysis of plasma  
1267 fibrinogen is also underway as a part of the NI-HON-SAN Study, which will be  
1268 described in more detail later. Studies on new risk factors, such as *H. influenzae* infection  
1269 and homocysteine will be undertaken in the near future either in cross-sectional fashion  
1270 or by a nested case-control study using stored sera. The feasibility of ultrasonographic  
1271 measurement of the wall thickness of the carotid artery to detect latent atherosclerosis  
1272 will be explored. The incidence studies on myocardial infarction and stroke will  
1273 continue beyond the next five-year period because the necessary information can be  
1274 obtained through routine AHS data collection and it is worthwhile to continue to try to

1275 understand the underlying mechanisms. The other studies are conducted over shorter  
1276 periods, such as two years.

1277

1278 Research plan for the next one year:

1279 Manuscripts on myocardial infarction, isolated systolic hypertension, calcification of the  
1280 aortic arch, and pulse wave velocity will be prepared and submitted for journal  
1281 publication. The analysis of plasma fibrinogen will be completed. Data collection on  
1282 ankle-arm blood pressure will be completed. The feasibility of studies of new risk  
1283 factors will be carefully assessed.

1284

1285 Research plan for the next three years:

1286 Data collection on the incidence of myocardial infarction and stroke will continue.  
1287 Results on plasma fibrinogen will be published. If new proposed studies turn out to be  
1288 feasible, data collection will be initiated.

1289

1290 *B-3. Studies of liver disease (RP 9-92):*

1291

1292 Previous studies have shown a higher prevalence of hepatitis B surface (HBs) antigen in  
1293 highly exposed subjects, but no difference in the prevalence of anti-HBs antibody was  
1294 observed between the two groups.

1295

1296 With the availability of the serum assay for hepatitis-Be antigen (HBe) and hepatitis-C  
1297 virus antibody (HCV), a study of liver diseases, such as chronic hepatitis or liver  
1298 cirrhosis, was initiated in 1993 to determine the relationship between radiation dose and  
1299 prevalence of infection by B and C hepatitis virus in the AHS sample.

1300

1301 Research plan for the next one year:

1302 Measurements and analysis of the data on HCV antibody, HB antigen, and antibodies  
1303 will be completed.

1304

1305 Research plan for the next three years:

1306 The design of a nested case-control study using stored serum will be developed. Using  
1307 stored serum collected before onset of hepatoma or liver cirrhosis, the prevalence of  
1308 HCV or subtypes of HCV in cases and controls will be compared.

1309

1310 Priority 2

1311

1312 *B-4. Cancer study (RP 2-75):*

1313

1314 Cancers continue to be one of the most prevalent diseases among AHS subjects. For  
1315 example, from 1969 through 1991, approximately 800 gastric cancers, 280 lung cancers,  
1316 and 200 breast cancers were found among the AHS subjects in Hiroshima.

1317

1318 Cancer screening will continue to be one of the objectives of the AHS, and special  
1319 emphasis will be placed on screening for cancers which are often not fatal, such as skin,  
1320 breast, and thyroid. A new analysis including potential confounders and risk modifiers  
1321 using the information obtained by various questionnaires and clinical measurements at  
1322 the time of the routine AHS examinations, such as dietary factors and medications, will

1323 be conducted. A case-control study will be conducted on various cancers related to  
1324 nutrients, hormones and potential carcinogens such as viral infections using stored  
1325 serum. This study will continue beyond the next five years because all of the necessary  
1326 information is obtained through routine AHS operations.  
1327

1328 Research plan for the next one year:

1329 An attempt will be made to create a new data set for longitudinal analysis using currently  
1330 available information on confounders and/or risk modifiers. An inventory will be  
1331 initiated of stored sera for each cancer case for use in future case-control studies.  
1332

1333 Research plan for the next three years:

1334 If a new data set is constructed, longitudinal analysis will be initiated to identify  
1335 confounders or risk modifiers of radiation in cancers among atomic bomb survivors.  
1336 Once the inventory of stored sera on cancer cases is completed, similar steps will be  
1337 taken for controls. Then, a comprehensive study method will be developed including  
1338 noncancer diseases for nested case-control studies.  
1339

1340 B-5. Aging and radiation:

1341  
1342 Priority 1

1343  
1344 a) *Osteoporosis study (RP 3-91):*  
1345

1346 Osteoporosis is a common aging-related disorder among Japanese, and bone density is  
1347 influenced by premature menopause and parathyroid hormone levels which are known  
1348 to be radiation-related. Measurement of spinal bone density using dual photon  
1349 absorptiometry has been underway since 1989, and the results of this study suggest a  
1350 significant positive relationship between radiation exposure and spinal bone mineral  
1351 density. However, the apparent increase in bone mass measurements may have been a  
1352 confounding effect caused by calcification of the abdominal aorta which is positively  
1353 associated with radiation dose. To solve this problem, bone mineral density in the spine  
1354 and hip using dual X-ray absorptiometry was begun in 1994. Total body composition  
1355 (fat, lean body mass, bone) among the selected AHS samples has been measured using  
1356 the same equipment.  
1357

1358 Research plan for the next one year:

1359 Radiation effects on bone mineral density and body composition including various  
1360 potential risk factors will be analyzed.  
1361

1362 Research plan for the next three years:

1363 A longitudinal analysis will be undertaken to look at the radiation effects on changes in  
1364 bone density with aging.  
1365

1366 b) *Senile dementia (RP 5-92):*  
1367

1368 A dementia study has been underway since 1992 to assess the association between  
1369 radiation exposure and a decline in cognitive function and to determine whether the  
1370 prevalence of senile dementia increases as radiation dose increases. The epidemiological

1371 survey method being used was developed through international collaboration under a  
1372 program known as the NI-HON-SEA study, which will be described later. This study  
1373 may make it possible for the first time to examine the effects of ionizing radiation on the  
1374 mature central nervous system.

1375  
1376 Research plan for the next one year:

1377 Cognitive function tests have been conducted on about 70% of AHS participants at this  
1378 time; the remainder will be tested next year.

1379  
1380 Research plan for the next three years:

1381 Case ascertainment of senile dementia by a neurologist will be complete, and the results  
1382 of an analysis of the data will be written up for publication.

1383  
1384 *c) Menopause study (RP 5-93):*

1385  
1386 Menopause is a general biological marker of aging in women. Information on age at  
1387 menopause has been obtained in past epidemiological surveys in Hiroshima and  
1388 Nagasaki. In Nagasaki, self-reported date of last menstruation period has been routinely  
1389 obtained at the time of the biennial chest X-ray examinations. Incidence of menopause  
1390 among Nagasaki participants was analyzed in 1993 using this self-reported information.  
1391 The results suggest that the higher exposed group experienced an earlier onset of  
1392 menopause. A longitudinal study using hormone measurements as an indicator of  
1393 menopause was initiated in 1994 and is expected to take four years to complete. The  
1394 subjects of this prospective study are premenopausal women who were younger than 10  
1395 years old or were in-utero when exposed to A-bomb radiation..

1396  
1397 Research plan for the next one year:

1398 Two important perimenopausal hormones (FSH and estradiol) level will be measured  
1399 every six months until 1997.

1400  
1401 Research plan for the next three years:

1402 The relationship between radiation exposure and perimenopausal hormones will be  
1403 analyzed.

1404  
1405 Priority 2

1406  
1407 *d) Physiologic aging study (RP 4-86):*

1408  
1409 Accelerated aging resulting from irradiation has been a scientific concern for several  
1410 decades. Earlier studies of the AHS participants have failed to reveal evidence of such  
1411 an effect; however, these studies were conducted almost twenty years ago. It is  
1412 important, therefore, to repeat this study using a broader battery of physiological  
1413 measures and utilizing several endpoints that reflect aging. The endpoints to be used for  
1414 analysis are the incidence of myocardial infarction and stroke, cardiovascular mortality,  
1415 and the prevalence of aortic arch calcification. The physiological measurements to be  
1416 used are hand grip strength and skin elasticity which are being measured as a part of the  
1417 routine AHS examinations in Hiroshima.

1418

1419 Research plan for the next one year:  
1420 Data analysis will be carried out using new endpoints, and a manuscript will be prepared.

1421  
1422 Research plan for the next three years:  
1423 A new research plan including the use of new statistical methods will be developed.

1424  
1425 *B-6. Medical dosimetry (RP 7-86, 8-86):*

1426  
1427 Information on exposure to X-irradiation (radiological examinations at ABCC/RERF,  
1428 radiological examinations elsewhere, and radiation therapy) has been obtained in the  
1429 course of the AHS examinations. The examination of ionizing radiation exposure for  
1430 medical reasons may facilitate assessment of the role of medical X-ray exposures in the  
1431 follow-up studies of A-bomb survivors. However, this is an issue which requires careful  
1432 consideration since it will be patently difficult to incorporate these data into the various  
1433 analyses conducted at RERF.

1434  
1435 Research plan for the next one year:  
1436 Data collection will continue.

1437  
1438 *B-7. Psychosocial studies and others (RP 2-75):*

1439  
1440 Few studies have been done on the psychosocial effects of exposure to the atomic  
1441 bombing, although it is well recognized that they vary greatly in association with  
1442 socioeconomic factors. It is possible that psychosocial factors may have influenced  
1443 disease occurrence as a consequence of previous exposure to ionizing radiation.

1444  
1445 Research plan for the next one year:  
1446 A study will be designed to assess the frequency and nature of the social and  
1447 psychological problems experienced by the survivors with the cooperation of  
1448 psychological specialists. The possibility of international collaboration with scientists  
1449 at the State University of New York will be explored.

1450  
1451 *B-8. Measurements:*

1452  
1453 *Priority 1*

1454  
1455 *a) AHS Clinical measurements (RP 2-75)*

1456  
1457 In the AHS, an enormous amount of information has been obtained on laboratory  
1458 measurements, and it has now become possible to analyze the changes in these  
1459 measurements over time. In collaboration with the Department of Statistics, growth  
1460 curve analyses of the information on total serum cholesterol and blood pressure showed  
1461 that heavily exposed individuals had higher levels of total serum cholesterol. This  
1462 elevated cholesterol level associated with radiation exposure may have been one of the  
1463 confounding factors in the increased cardiovascular morbidity and mortality seen among  
1464 atomic bomb survivors.

1465  
1466 Research plan for the next one year:

1467 Results of the longitudinal analyses of cholesterol and blood pressure will be published.  
1468 The other longitudinal data, including height, weight, and hematological information,  
1469 accumulated since 1958 will be analyzed.

1470

1471 Research plan for the next three years:

1472 Autoanalyzers for biochemical measurements were introduced into the Hiroshima  
1473 Clinical Laboratory in 1986 and into Nagasaki in 1987. Longitudinal analyses will be  
1474 performed on twenty different biochemical measurements accumulated from 1987 to  
1475 1996.

1476

1477 Priority 2

1478

1479 *b) Benign monoclonal gammopathy (RP 6-85):*

1480

1481 Benign monoclonal gammopathy was shown to be suggestively related to radiation dose  
1482 and has the possibility of transforming into multiple myeloma. Screening with protein  
1483 electrophoresis will be continued for detection of cases with monoclonal spike. Cases  
1484 will be further tested for confirmation.

1485

1486 Research plan for the next one year:

1487 Screening by protein electrophoresis will continue as before.

1488

1489 Research plan for the next three years:

1490 The study of the incidence of this condition will be summarized and the results  
1491 published.

1492

1493 *B-9. National and international collaboration (RP 4-85, 5-92, 3-91):*

1494

1495 There have been three major international collaborations underway in Hiroshima. These  
1496 are the NI-HON-SAN Study, the NI-HON-SEA Study, and the Japan-Hawaii  
1497 Osteoporosis Study. All of these studies have been beneficial to RERF because the  
1498 epidemiological methods developed through collaboration have been applied to other  
1499 radiation research, and they have been producing important study results in elucidating  
1500 effects of radiation on noncancer diseases.

1501

1502 At its outset, the NI-HON-SAN Study was a study of cardiovascular diseases among  
1503 Japanese men and men of Japanese descent living in Honolulu and San Francisco. It was  
1504 initiated in 1965. Although follow-up of the San Francisco cohort ceased in the mid-  
1505 1970s, the Japanese and Hawaiian cohorts are still being studied. A symposium to  
1506 commemorate the study's 30th anniversary was held on 2 September 1996 in Hiroshima.

1507

1508 The NI-HON-SEA Study is a study of senile dementia among Japanese men living in  
1509 Japan and men of Japanese descent living in Honolulu and Seattle. It was initiated in  
1510 1992.

1511

1512 The Japan-Hawaii Osteoporosis Study was initiated in 1991.

1513

1514 We have been involved in several national collaborative studies sponsored by the

1515 Ministry of Health and Welfare. Through these national collaborations, it has been possible for  
1516 us to develop epidemiological methods to study radiation effects on noncancer diseases and to  
1517 provide diagnostic services to AHS participants that otherwise could not have been possible. For  
1518 example, free use of a modern bone mineral densitometer to conduct studies of osteoporosis as  
1519 part of a national collaborative study.

1520

1521 Research plan for the next one year:

1522 NI-HON-SAN Study: Results of comparisons of mortality, glucose intolerance, and  
1523 fibrinogen levels will be summarized and published.

1524

1525 NI-HON-SEA Study: Data sets will be created to compare the prevalence of senile  
1526 dementia in the different study cohorts.

1527

1528 Japan-Hawaii Osteoporosis Study: In collaboration with the Hawaii Osteoporosis Center,  
1529 a comparative study of bone mass, bone loss, and potential risk factors of osteoporosis  
1530 among Japanese and Japanese-Americans will be analyzed.

1531

1532 Research plan for the next three years:

1533 NI-HON-SAN Study: Results of comparisons of ankle-arm blood pressure index, EKG  
1534 changes, and pulmonary function will be summarized and published.

1535

1536 NI-HON-SEA Study: Results will be summarized and published.

1537

1538 Japan-Hawaii Osteoporosis Study: Results will be summarized and published.

1539

### 1540 **C. New research initiatives (Hiroshima):**

1541

#### 1542 **Priority 1**

1543

##### 1544 *C-1. Molecular epidemiological study:*

1545

1546 There are many studies describing the importance of oncogenes and tumor suppressors  
1547 in the development of malignant disorders, but the role of ionizing radiation in the  
1548 activation or suppression of these genes is still unclear. In addition, recent studies  
1549 suggest that some of these genes may be involved in the development of atherosclerosis.  
1550 A molecular epidemiological study on the AHS population will be initiated with inter-  
1551 departmental collaboration to examine these issues. For this study, collection of fresh  
1552 biological materials from surgery, such as tissues of cancers, benign tumors, blood  
1553 vessels and skin, is desirable through a more intensive morbidity surveillance, in addition  
1554 to the preservation of lymphocytes of the AHS subjects.

1555

1556 Research plan for the next one year:

1557 A study plan will be developed.

1558

1559 Research plan for the next three years:

1560 If a study is thought to be beneficial for RERF, collection of biological materials will be  
1561 initiated and appropriate techniques for their use will be developed.

1562

1563 C-2. *Feasibility of an F<sub>1</sub> clinical study*

1564  
1565 In response to the recommendations of the Blue Ribbon Panel, the feasibility of a full-  
1566 scale study of chronic disease among the F<sub>1</sub> will begin with a mail survey involving all  
1567 members of the F<sub>1</sub> mortality cohort, to be followed by the clinical examination of a small  
1568 set of these individuals, about 500 persons, and biochemical genetic studies of several  
1569 genes known to be related to common chronic diseases.

1570  
1571 Research plan for the next one year:

1572 The feasibility study will last for two years.

1573  
1574 Research plan for the next three years:

1575 A workshop will be convened to determine whether a full-scale study should be  
1576 conducted.

1577  
1578 Priority 2

1579  
1580 C-3. *Lenticular opacities:*

1581  
1582 A new system of grading the degree of lenticular opacification, developed by the  
1583 research group at NASA, will be introduced and grading will be done using illustrations  
1584 from the cases of cataracts detected in previous ophthalmological surveys. This will be  
1585 part of an international collaboration with NASA that aims to test hypotheses regarding  
1586 the relationship between degree of opacification and radiation dose. For those survivors  
1587 who were young at the time of the bombing and have not been included in previous  
1588 surveys, we will consider use of stereolaminographic images of the lens to provide a  
1589 more objective and permanent basis for the evaluation of changes that may occur in the  
1590 future.

1591  
1592 Research plan for the next one year:

1593 A study plan will be developed.

1594  
1595 Research plan for the next three years:

1596 If the study plan is thought to be beneficial, data collection will be initiated.

1597  
1598 **Project time lines (Hiroshima)**

|                                   | 1996 | 1997 | 1998 | 1999 | 2000 | 2001 |
|-----------------------------------|------|------|------|------|------|------|
| 1600 Core program:                |      |      |      |      |      |      |
| 1601 AHS (RP 2-75):               | ⇒    | ⇒    | ⇒    | ⇒    | ⇒    | ⇒    |
| 1602 Special studies              |      |      |      |      |      |      |
| 1603 Cancer study (RP 2-75)       | ⇒    | ⇒    | ⇒    | ⇒    | ⇒    | ⇒    |
| 1604 Parathyroid (RP 11-86)       | ⇒    | ⇒    | ⇒    | ⇒    | ⇒    | ⇒    |
| 1605 Other benign tumor (RP 6-86) | ⇒    | ⇒    | ⇒    | ⇒    |      |      |
| 1606 Cardiovascular (RP 4-85)     | ⇒    | ⇒    | ⇒    | ⇒    | ⇒    | ⇒    |
| 1607 Liver disease (RP 9-92)      | ⇒    | ⇒    |      |      |      |      |
| 1608 Aging and radiation          |      |      |      |      |      |      |
| 1609 Osteoporosis (RP 3-89)       | ⇒    | ⇒    | ⇒    | ⇒    | ⇒    |      |
| 1610                              |      |      |      |      |      |      |

|      |  |   |   |   |   |   |   |
|------|--|---|---|---|---|---|---|
| 1611 | Dementia (RP 5-92)                       | ⇒ | ⇒ | ⇒ | ⇒ |   |   |
| 1612 | Physiologic aging (RP 4-86)              | ⇒ | ⇒ | ⇒ | ⇒ |   |   |
| 1613 | Menopause (RP 5-93)                      | ⇒ | ⇒ | ⇒ |   |   |   |
| 1614 | Medical dosimetry (RP7-86, 8-86)         | ⇒ | ⇒ | ⇒ | ⇒ | ⇒ | ⇒ |
| 1615 | Psychosocial (RP 2-75)                   | ⇒ | ⇒ | ⇒ | ⇒ |   |   |
| 1616 | Monoclonal gammopathy (RP 6-85)          | ⇒ | ⇒ | ⇒ | ⇒ |   |   |
| 1617 | National and international collaboration |   |   |   |   |   |   |
| 1618 | NI-HON-SAN (RP 4-85)                     | ⇒ | ⇒ | ⇒ | ⇒ | ⇒ | ⇒ |
| 1619 | NI-HON-SEA (RP 5-92)                     | ⇒ | ⇒ | ⇒ | ⇒ |   |   |
| 1620 | Osteoporosis (RP 3-91)                   | ⇒ | ⇒ | ⇒ | ⇒ |   |   |
| 1621 | Molecular epidemiology                   |   | ⇒ | ⇒ | ⇒ | ⇒ | ⇒ |
| 1622 | Cataract                                 |   |   | ⇒ | ⇒ | ⇒ | ⇒ |

### Personnel requirements (Hiroshima)

| Year                 | 1996            | 1997      | 1998      | 1999      | 2000      | 2001      |
|----------------------|-----------------|-----------|-----------|-----------|-----------|-----------|
| Research Scientists* | 6<br>(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        |
| <b>Total</b>         | <b>49.5</b>     | <b>49</b> | <b>49</b> | <b>49</b> | <b>49</b> | <b>49</b> |

\*: If clinical examination of the F<sub>1</sub> 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<sup>2</sup>) (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          |      |       |      |      |                 |
| <b>Total</b>    | <b>1,150.20</b> |      |       |      |      | <b>1,190.20</b> |

\* : Room for hematology currently in use needs expansion for smooth daily operation.

\*\* : Additional space for storage of serum and plasma is needed.

1660 **Equipment budget (Hiroshima) (x ¥ 1,000)**

1661

| 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 |

1665

1666 **D. Special research activities (Nagasaki)**

1667

1668 **Priority 1**

1669

1670

*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).*

1671

1672

1673

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 i.e., radiation may cause earlier deterioration of the atherogenic cholesterol profiles.

1674

1675

1676

1677

1678

1679

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.

1680

1681

1682

*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.*

1683

1684

1685

1686

1687 **Project time lines (Nagasaki)**

1688

1689

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

1690

1691

1692

1693 **Personnel requirements (Nagasaki)**

1694

1695

1696

1697

1698

1699

1700

1701

1702

1703

1704

| Fiscal Year             | 1997 | 1998 | 1999 | 2000 | 2001 |
|-------------------------|------|------|------|------|------|
| Physicians <sup>1</sup> | 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    |

1705  
1706  
1707  
1708  
1709  
1710  
1711  
1712  
1713  
1714  
1715  
1716  
1717  
1718  
1719  
1720  
1721  
1722  
1723  
1724  
1725  
1726  
1727  
1728  
1729  
1730  
1731  
1732  
1733  
1734  
1735  
1736  
1737  
1738  
1739  
1740  
1741  
1742  
1743  
1744  
1745  
1746  
1747  
1748  
1749  
1750  
1751  
1752  
1753  
1754

|                |   |   |   |   |   |
|----------------|---|---|---|---|---|
| Administration | 9 | 9 | 9 | 9 | 9 |
|----------------|---|---|---|---|---|

<sup>1</sup> Dr. Midori Soda is included as 0.5 in the tally of physicians at the Nagasaki Department of Clinical Studies.

### Space requirements (m<sup>2</sup>) (Nagasaki)<sup>1</sup>

| 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  |

<sup>1</sup> Personnel strength and floor space must be expanded if a full-scale study of chronic disease among the F<sub>1</sub> is initiated.

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

| Fiscal Year     | 1997   | 1998  | 1999  | 2000 | 2001 |
|-----------------|--------|-------|-------|------|------|
| Laboratory      | 22,045 | 0     | 0     | 0    | 0    |
| Computer equip. | 1,072  | 1,052 | 2,252 | 452  | 852  |

(x ¥1,000)

<sup>1</sup>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, was 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<sub>1</sub>. The follow-up of these cohorts has long relied on mortality surveillance through the use of the nationwide family registration system, the

1755 *koseki*. Recently, cancer incidence data from improved tumor registries in Hiroshima and  
1756 Nagasaki have become available on these cohorts, adding new dimensions to our studies of  
1757 radiation cancer risks. Continued follow-up of these cohorts is essential in clarifying the  
1758 temporal patterns of cancer risk as young subjects reach ages when background cancer risk is  
1759 increased. In addition, the emerging excess noncancer mortality risk is of particular concern as  
1760 the nature of the risk is still unclear. Although the numerous mail surveys conducted in the LSS  
1761 provide potentially valuable data on the role of nonradiation risk factors, little effort has been  
1762 made to incorporate these data into RERF analyses. We must place increased emphasis on the  
1763 studies of nonradiation risk factors in relation to cancer and noncancer disease risks.  
1764

1765 Because of the nature of the RERF research, the Departments of Epidemiology should  
1766 and will play a key role in the design and conduct of various interdepartmental research  
1767 activities. As indicated in the Blue Ribbon Panel report, one of the most important  
1768 multidisciplinary programs at the present time is the molecular epidemiology of cancer, which  
1769 will require close interdepartmental and interdisciplinary communication. In addition, the  
1770 Departments of Epidemiology must also play a more active role in generating new ideas for  
1771 studies to answer questions arising from the ongoing epidemiological studies, which are being  
1772 conducted in collaboration with other RERF departments or outside research groups.  
1773

1774 The epidemiological research activities in Hiroshima and Nagasaki are carried out  
1775 following common research protocols and procedures. The professional staff in the Department  
1776 of Epidemiology in Hiroshima currently consists of three epidemiologists supplemented by one  
1777 pathology consultant and one visiting pathology investigator. The professional staff in the  
1778 Nagasaki Department of Epidemiology consists of one epidemiologist and one physician. The  
1779 epidemiology staff work closely with the staff in the Department of Statistics in study design,  
1780 data analysis, and preparation of major reports; they also work with the Departments of Statistics  
1781 and Information Technology in database design and development.  
1782

1783 **A. Core activities**  
1784

1785 The core activities of the Epidemiology research program are as follows:  
1786

1787 *A-1. Publication of periodic general reports*  
1788

1789 The Departments of Epidemiology working together with the Department of Statistics  
1790 will continue to produce periodic and specific reports on cancer and noncancer  
1791 mortality as well as cancer incidence resulting from continued follow-up of the LSS,  
1792 in-utero and F<sub>1</sub> cohorts. In view of the uncertainty regarding the cancer risk for the  
1793 young survivors, continued follow-up of the LSS and in-utero cohorts in the next  
1794 decade and beyond is considered critical. Principal periodic reports that are expected  
1795 within the next 5 years include LSS Report 13 on updated cancer and noncancer  
1796 mortality (through 1995), an updated LSS cancer incidence report (through 1992 or  
1797 later), an in-utero cancer incidence report, and F<sub>1</sub> mortality and cancer incidence  
1798 reports.  
1799

1800 Investigations of the noncancer mortality data will be particularly challenging because  
1801 of the multiplicity of factors that must be considered and the paucity of relevant  
1802 biological models. As the survivors age, further follow-up of the cohort will provide

1803 increasingly useful information on this important question. At the same time, it will  
1804 be equally important to define working hypotheses to account for the excess noncancer  
1805 disease risks and to develop and carry out research programs in collaboration with other  
1806 RERF departments and outside research groups.

1807  
1808 *A-2. Conduct of site-specific cancer studies*

1809  
1810 Several site-specific cancer studies are currently active. These studies are designed to  
1811 provide detailed data on pathological features of tumors associated with radiation  
1812 exposure accompanied by in-depth risk analysis, providing insights into the biological  
1813 bases of radiation-induced tumorigenesis. A number of reports from this series of site-  
1814 specific cancer studies will be forthcoming in the next several years.

1815  
1816 *A-3. Continued management of the Hiroshima and Nagasaki tumor and tissue registries,*  
1817 *and development of a tissue bank*

1818  
1819 The Foundation continues to manage the Hiroshima and Nagasaki tumor and tissue  
1820 registries. The Hiroshima and Nagasaki tumor registries provide high-quality cancer  
1821 incidence data. They are among the few registries in Japan whose incidence data have  
1822 been included in several volumes of *Cancer Incidence in Five Continents* (by  
1823 IARC/IACR), a worldwide compilation of cancer incidence data. The LSS cancer  
1824 incidence data published in 1993 and 1994 and the current series of site-specific cancer  
1825 incidence studies would not have been possible without RERF's direct involvement in  
1826 the registry operations. While we will continue to publish the Hiroshima and Nagasaki  
1827 incidence data in future volumes of the above IARC/IACR monograph series, it is  
1828 important that we also produce our own comprehensive and more detailed analyses of  
1829 population-based cancer incidence data.

1830  
1831 RERF, together with the local medical societies, also continues to manage the tissue  
1832 registries. These registries have the potential to be developed into a tissue bank linked  
1833 to the LSS, which will be a tremendously valuable source for molecular oncology  
1834 studies. Therefore, the Departments of Epidemiology must continue to be involved in  
1835 the management and further development of the tumor and tissue registries.

36  
1837 *A-4. Design and conduct of case-control and other special studies to address specific*  
1838 *questions*

1839  
1840 The Epidemiology department also conducts ad hoc case-control or other studies to  
1841 investigate specific hypotheses prompted by regular analyses of the A-bomb survivor  
1842 data or other research developments. Such studies involve personal interviews to elicit  
1843 specific information, make use of existing information, or require biological samples  
1844 such as tissues and frozen sera. Case-control studies nested in the cohort are  
1845 particularly useful for providing answers to the questions of current interest. Illustrative  
1846 examples include studies of liver cancer and viral hepatitis infection (ongoing), breast  
1847 cancer and detailed reproductive history (completed), and stomach cancer and serum  
1848 ferritin (completed). The Department will continue to generate new studies of this kind  
1849 to gain insights into the nature of cancer and noncancer diseases.

1850

1851 A-5. *Studies of radiation and nonradiation factors using mail survey data*

1852  
1853 During the course of the LSS follow-up several mail surveys have been conducted to  
1854 obtain epidemiological information on lifestyle factors such as smoking, alcohol intake,  
1855 diet, and occupation. To date use of this information has been limited to the smoking  
1856 data as related to cancer. Studies of conventional risk factors are also critically  
1857 important in elucidating the nature of the excess noncancer vascular, digestive, and  
1858 respiratory diseases. While some work has been done in the last few years, further  
1859 effort should be devoted to the study of nonradiation risk factors.

1860  
1861 These studies are covered by the following platform research protocols:

1862  
1863 Priority 1

1864  
1865 *RP 1-75: Research plan for RERF studies of the life span of A-bomb survivors,*  
1866 *Hiroshima and Nagasaki*

1867  
1868 *RP 4-75: Research plan for RERF studies of the potential genetic effects of atomic*  
1869 *radiation: Hiroshima and Nagasaki, Part 1. Mortality study of children born to atomic*  
1870 *bomb survivors*

1871  
1872 *RP 18-61: Tumor registry study in Hiroshima and Nagasaki*

1873  
1874 *RP 29-60: Detection of leukemia and related disorders*

1875  
1876 *RP 5-89: Pathology studies in Hiroshima and Nagasaki, revised research plan*  
1877 *(Formerly RP 3-75)*

1878  
1879 *RP 9-88: Guidelines for the conduct of site-specific cancer incidence studies among A-*  
1880 *bomb survivors, Hiroshima and Nagasaki*

1881  
1882 **B. Special research activities**

1883  
1884 **B-1: Site-specific cancer studies**

1885  
1886 Under the platform protocols regarding tumor and leukemia registries (RP 18-61, RP  
1887 29-60) and pathology studies (RP 5-89, RP 9-88), various site-specific cancer studies are now  
1888 under way. Standardized pathology reviews are conducted by panels of pathologists (from  
1889 Hiroshima and Nagasaki) using contemporary classification schemes, and special effort is made  
1890 to ascertain cases beyond those routinely reported to the tumor and tissue registries. Pathology  
1891 slides and tissue blocks obtained for these studies facilitate the conduct of molecular  
1892 epidemiological studies. These site-specific studies in various stages of completion are  
1893 summarized in the table below, followed by a description of the objectives for each study.

1894  
1895 **Current and Planned Site-specific Cancer Studies**

1896  
1897  
1898

| Site | Year | Specific objectives | Current status/Plan |
|------|------|---------------------|---------------------|
|------|------|---------------------|---------------------|

|      |                         |       |  |  |
|------|-------------------------|-------|--|--|
| 1899 |                         | study |  |  |
| 1900 |                         | began |  |  |
| 1901 |                         |       |  |  |
| 1902 |                         |       | <u>Currently active</u>  |  |
| 1903 | 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             |
| 1904 |                         |       |  |  |
| 1905 |                         |       |  |  |
| 1906 |                         |       |  |  |
| 1907 |                         |       |  |  |
| 1908 |                         |       |  |  |
| 1909 | Salivary gland          | 1991  | Benign & malignant tumors; major & minor glands                  | Results presented at Jpn. Soc. Path. Mtg., '95; One paper published; another paper submitted; To be completed within a year                      |
| 1910 |                         |       |  |  |
| 1911 |                         |       |  |  |
| 1912 |                         |       |  |  |
| 1913 |                         |       |  |  |
| 1914 | 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 |
| 1915 |                         |       |  |  |
| 1916 |                         |       |  |  |
| 1917 |                         |       |  |  |
| 1918 |                         |       |  |  |
| 1919 |                         |       |  |  |
| 1920 | Thyroid                 | 1991  | Benign & malignant tumors; microcarcinomas                       | Ready for analysis; Papers to be prepared in the next 2-3 years  |
| 1921 |                         |       |  |  |
| 1922 | Ovary                   | 1992  | Benign & malignant tumors  | Preliminary results presented at Jpn. Soc. Path. Mtg., '96; Analysis in progress; To be completed in 2-3 years                                   |
| 1923 |                         |       |  |  |
| 1924 |                         |       |  |  |
| 1925 |                         |       |  |  |
| 1926 | 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   |
| 1927 |                         |       |  |  |
| 1928 |                         |       |  |  |
| 1929 |                         |       |  |  |
| 1930 | Breast                  | 1993  | Update of the continuing series; risk for young women            | Paper in preparation; To be completed within a year  |
| 1931 |                         |       |  |  |
| 1932 | Lung                    | 1994  | Topographic distribution, cell types and smoking; time trend     | Pathology review in progress; Expected to be completed in 4-5 years  |
| 1933 |                         |       |  |  |
| 1934 |                         |       |  |  |
| 1935 | Lymphoid                | 1994  | Lymphoma, multiple myeloma; T-cell and B-cell origin             | Pathology review started; Expected to be completed in 4-5 years  |
| 1936 |                         |       |  |  |
| 1938 |                         |       |  |  |
| 1939 |                         |       | <u>Planned</u>   |  |
| 1940 | Colon                   |       | Different sub-sites; parallel molecular study                    | To be started  |
| 1941 |                         |       |  |  |
| 1942 | Stomach                 |       | Histological subtypes; EB virus infection                        | To be started  |
| 1943 |                         |       |  |  |
| 1944 | Bone/connective tissues |       | Bone tumors  | To be started  |
| 1945 |                         |       |  |  |
| 1946 |                         |       |  |  |
| 1947 | Priority 1              |       |  |  |
| 1948 |                         |       |  |  |
| 1949 |                         |       |  |  |
| 1950 |                         |       |  |  |

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

1951 This study is designed to provide more definitive data on the rather inconsistent  
1952 evidence thus far available on the risk of lymphoid malignancies in the LSS. The  
1953 objective is to investigate all lymphopietic tumors (lymphomas, multiple myeloma,  
1954 lymphocytic leukemias) between 1950 and 1990 in the LSS. Emphasis is on the  
1955 confirmation and classification of cases using modern techniques. The study involves  
1956 both hematologists and pathologists engaged in lymphoid tumor research. Non-  
1957 Hodgkin's lymphomas are classified by immuno-histochemical studies into T- or B-cell  
1958 lymphomas, and the diagnosis of adult T-cell leukemia is based on detection of proviral  
1959 DNA of HTLV-I using archived tissues.

1960  
1961 *RP 1-94: Studies of lung cancer incidence among the atomic bomb survivors, 1950-90*

1962  
1963 Lung cancer is a late effect of radiation exposure, but several specific issues and  
1964 questions remain to be addressed. These include the specificity of various cell types  
1965 involved in radiation- versus smoking-related cancers, confounding and joint effects of  
1966 smoking in relation to radiation exposure, delineation of the temporal trend with  
1967 allowance given to the age-at-exposure and attained-age effects. ICRP also has recently  
1968 published a new report on lung cancer risk from inhaled radionuclides modeled on an  
1969 anatomical basis in terms of lung "compartments." New information on anatomical  
1970 distribution of lung cancers resulting from uniformly distributed radiation may be  
1971 useful for evaluating the ICRP model. This RP was developed to address these  
1972 questions and issues.

1973  
1974 *RP 6-93: Breast cancer incidence study among atomic bomb survivors, 1950-90*

1975  
1976 This is the latest (started in 1993) of a series of breast cancer incidence surveys,  
1977 extending the follow-up through 1990. Data collection for this series has been  
1978 completed, adding 261 newly accessed cases (250 for the period of 1986-1990 and 11  
1979 prior to 1986). Of these, 58 cases were exposed at <10 years of age, and this should  
1980 strengthen risk estimates for this age-at-exposure group.

1981  
1982 *RP 4-92: Incidence of tumors of the central nervous system among A-bomb survivors*

1983  
1984 In the recent solid cancer incidence report, a suggestive dose response was found  
1985 among those exposed at ages <20 years old for tumors of the nervous system except for  
1986 the brain. These findings prompted the present study. The objective is to ascertain  
1987 malignant and benign tumors of the central nervous system in the LSS from 1950 to  
1988 1987.

1989  
1990 *RP 2-92: Studies of ovarian tumor incidence among the RERF extended Life Span*  
1991 *Study cohort, 1950-87*

1992  
1993 The present study extends the previous ovarian cancer series by 7 years (through 1987)  
1994 and also includes a systematic ascertainment of benign tumors.

1995  
1996 *RP 6-91: Studies of thyroid tumor incidence among the RERF extended Life Span Study*  
1997 *cohort, Hiroshima and Nagasaki, 1950-87*

1998

1999  
2000  
2001  
2002  
2003  
2004  
2005  
2006  
2007  
2008  
2009  
2010  
2011  
2012  
2013  
2014  
2015  
2016  
2017  
2018  
2019  
2020  
2021  
2022  
2023  
2024  
2025  
2026  
2027  
2028  
2029  
2030  
2031  
2032  
2033  
2034  
2035  
2036  
2037  
2038  
2039  
2040  
2041  
2042  
2043  
2044  
2045  
2046

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. An increased number of cases over an extended study period should allow more detailed risk analyses than available previously.

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

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.

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

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.

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

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 also used to characterize the HB and HC viruses.

**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,

2047 reproductive factors, and other suspected cancer risk factors.

2048

2049 Priority 1

2050

2051 *RP 14-79: Interaction between radiation dose and host factors. An epidemiological*  
2052 *case-control study of female breast cancer in atomic bomb survivors*

2053

2054 This study, started in 1979, continues to investigate reproductive and other known risk  
2055 factors in association with radiation. In a study of 196 breast cancer cases and 566  
2056 controls, the risk was found to be positively associated with age at first full-term  
2057 pregnancy, in agreement with the literature; whereas negative, and partially  
2058 independent, associations were observed with number of births and total cumulative  
2059 period of breast feeding. Significant positive associations were also found with history  
2060 of treatment for dysmenorrhea and uterine or ovarian surgery. Neither age at menarche  
2061 nor age at menopause was significantly associated with breast cancer. Multiplicative  
2062 relationships were found between radiation exposure and age at first full-term  
2063 pregnancy, number of children, and cumulative total period of lactation.

2064

2065 A plan is underway to revise this case-control study by adding reproductive and family  
2066 information from various Master-File documents kept at RERF (an example of a  
2067 record-based case-control study).

2068

2069 Priority 2

2070

2071 *RP 12-85: Thyroid cancer*

2072

2073 The study includes 365 cases with histologically diagnosed thyroid cancer and their  
2074 matched controls. Personal interviews have been completed to obtain retrospective  
2075 information on major risk factors such as diet and nutrition, reproductive experiences  
2076 and previous medical history. Factors that have been found to be associated with  
2077 thyroid cancer are: history of cancer in sisters, previous histories of goiter,  
2078 tonsillectomy, ovariectomy, and breast disease, and increased body mass index.  
2079 Analysis is almost completed, and a paper is being prepared for publication. Data from  
2080 this study are included in an NCI pooled analysis of thyroid case-control data from  
2081 various countries.

2082

2083 Priority 3

2084

2085 *RP 10-85: Nutrients and cancer; RP 11-85: hormones and cancer*

2086

2087 These two studies utilize stored sera for nutritional and hormonal assays. Preliminary  
2088 analysis shows a relationship between total estradiol and breast cancer risk. Following  
2089 the first paper on serum ferritin and stomach cancer risk (TR 14-89), the second paper  
2090 on serum selenium and zinc in association with the subsequent development of lung and  
2091 stomach cancer was published (*Cancer Epidemiology, Biomarkers & Prevention*). In  
2092 this study of 208 cases with stomach cancer, and 77 cases with lung cancer and matched  
2093 controls, a slightly increased risk of lung cancer was found to be associated with low  
2094 serum levels of selenium but little association was found with either lung or stomach

2095 cancer across normal selenium or zinc ranges. A paper on breast and other cancers in  
2096 relation to hormone assays is under preparation and is expected to be completed shortly.

2097

### 2098 **C. New research activities anticipated in the next 5 years**

2099

2100 As mentioned above, a number of important specific issues have been identified through  
2101 the follow-up of the major cohorts. These are summarized below:

2102

#### 2103 **Cancer**

2104

2105 Increased cancer risks have been clearly substantiated as a late effect of radiation  
2106 exposure among the survivors. However, several important issues regarding cancer risk remain  
2107 to be clarified.

2108

2109 • Cancer risk among the young: The temporal pattern of cancer risk among the  
2110 survivors exposed as children, as they reach ages at which background cancer  
11 risk is increased.

2112

2113 • Confounding and modifying effects of nonradiation factors: Because smoking  
2114 and other life-style factors are important determinants of cancer,  
2115 cardiovascular and other diseases, more research is needed to study the  
2116 possible confounding and modifying of effects of nonradiation factors. This  
2117 is an area which has received little attention in the past and will require  
2118 collaboration with RERF researchers in other departments and with scientists  
2119 outside RERF.

2120

2121 • Mechanistic models for radiation-induced cancer: Initial attempts by Donald  
2122 Pierce and Mortimer Mendelsohn to develop a mechanistic model for  
2123 radiation-induced cancer using the LSS data have provided some interesting  
2124 and useful insights into how to interpret the age and time dependence of the  
2125 solid cancer risks. There is also increasing interest in other biologically  
2126 motivated models for radiation carcinogenesis. These models may provide  
2127 useful insights into temporal patterns, sex differences and other aspects of the  
2128 radiation-induced excess risk. While most of the developmental work will  
2129 rely on the Statistics staff, RERF provides an environment for close interaction  
2130 with radiation biologists. More effort at RERF along these lines of research  
2131 seems warranted.

2132

2133 • Organ-specific cancer risks: Observed differences in site-specific cancer risks  
2134 are difficult to interpret because of statistical variability and the relatively  
2135 small excess number of cases involved. The joint analysis approach initiated  
2136 by the Department of Statistics on this issue is promising and will be further  
2137 pursued working with members of the Departments of Epidemiology.

2138

2139 • Incidence vs mortality: While mortality follow-up will continue to be the  
2140 primary basis of risk assessment, cancer incidence patterns will play an  
2141 increasingly important role, especially for breast, thyroid, and other less fatal  
2142 cancers. The availability of both cancer mortality and incidence data now

2143 enables us to provide more comprehensive assessment of the radiation risk,  
2144 starting from cancer onset to death. However, it has also become necessary  
2145 to pay attention to how to interpret results from mortality and incidence data.  
2146 It is important to develop methods to provide an integrated presentation of the  
2147 mortality and incidence data. It will also be useful to develop measures of  
2148 detriment using both results. While some work has already been done on  
2149 mortality/incidence comparison and risk of second primary cancers, much  
2150 more work is needed in this area.

## 2151 **Noncancer diseases**

2152  
2153 The evidence of an excess noncancer mortality risk in the LSS data is becoming more  
2154 compelling. Thus, another outstanding issue is further characterization of the noncancer risks  
2155 in the LSS.  
2156

- 2157  
2158 • Working with the Department of Statistics, we will attempt to clarify essential  
59 characteristics of the noncancer excess including such issues as the shape of  
2160 the dose response, patterns of risk by age, sex, and time, etc. Since the excess  
2161 risk appears to be continuing, we can expect that further follow-up will make  
2162 possible more detailed analyses and improve characterization of these risks.  
2163
- 2164 • The AHS is the source of clinical data on diseases and laboratory  
2165 measurements that are immensely useful for characterizing noncancer events.  
2166 Therefore, it will be essential that we work with the Departments of Clinical  
2167 Studies and Statistics to develop studies that integrate the LSS and AHS data  
2168 on radiation effects on noncancer endpoints.  
2169

2170 Some other important questions to be examined are as follows:

- 2171  
2172 • **Misclassification:** We have already shown that the misclassification of cancer  
2173 to noncancer on death certificates contributes only a fraction of the observed  
2174 excess noncancer mortality and that a noncancer excess exists even after the  
2175 correction for such misclassification. More work is needed to learn how best  
2176 to deal with misclassification between different noncancer diseases and how  
2177 this misclassification affects the risk estimates.  
2178
- 2179 • **Confounding, biases and indirect effects:** Whether the observed noncancer  
2180 excess mortality results from confounding or indirect effects of other factors,  
2181 selective or other biases remains a central question. While all available data  
2182 should be used to examine these issues, new ideas are also needed to initiate  
2183 new research and analyses.  
2184
- 2185 • **Plausible disease mechanisms:** A serious problem with the noncancer risk is  
2186 the paucity of biological models for radiation induction of noncancer diseases  
2187 at low dose levels. This is an area in which the development of new  
2188 innovative research ideas requires close interaction with biologists and clinical  
2189 investigators. Such collaborations should help us generate and test hypotheses  
2190 regarding plausible mechanisms for the effects.

2191  
2192  
2193  
2194  
2195  
2196  
2197  
2198  
2199  
2200  
2201  
2202  
2203  
2204  
2205  
2206  
2207  
2208  
2209  
2210  
2211  
2212  
2213  
2214  
2215  
2216  
2217  
2218  
2219  
2220  
2221  
2222  
2223  
2224  
2225  
2226  
2227  
2228  
2229  
2230  
2231  
2232  
2233  
2234  
2235  
2236  
2237  
2238

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.

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 department's involvement in the tumor and tissue registries and its long-standing relationship with the local medical community, 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<sub>1</sub> mail survey*

As part of the planned clinical examination of the F<sub>1</sub> 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 analysis of mortality and morbidity data on the F<sub>1</sub> 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. Some preliminary work has been undertaken in collaboration with the Departments of Statistics, Clinical Studies and Information

2239 Technology to set up a family pedigree database. In view of the evidence relating  
 2240 genetic predisposition for breast cancer, a pilot study is now underway to construct  
 2241 family pedigrees for young breast cancer patients and older breast cancer patients (as  
 2242 a comparison group). To obtain useful results, more formal research protocols should  
 2243 be developed involving geneticists and epidemiologists.  
 2244

2245 **Personnel requirements (Hiroshima)**

2246  
 2247 In the last few years, the size of the Epidemiology professional staff in Hiroshima has  
 2248 decreased from 6 (4 Japanese and 2 US) to 3 (Japanese only), while that in Nagasaki remained  
 2249 2 (both Japanese). In view of the ongoing and anticipated research activities, the current size is  
 2250 grossly inadequate. The minimum requirement for Hiroshima is 6 professionals as it was in  
 2251 1994. Because of the generally high level of epidemiologists trained in the US and some  
 2252 European countries, efforts are underway to recruit two epidemiologists through NAS. We also  
 2253 plan to recruit one Japanese epidemiologist. Finally, in anticipation of the retirement of the  
 2254 current Department Chief in 5 years, we should begin to consider the recruitment of another  
 2255 Japanese M.D. or Ph.D. level epidemiologist.  
 2256

2257 The Epidemiology support staff for Hiroshima has also decreased in size and currently  
 2258 consists of 35 full-time and 4 part-time employees. The support staff provides research  
 2259 assistance (data preparation, tabulation and analyses), technical assistance (the Master-File and  
 2260 tumor registry database management, medical record abstraction for the tumor registry  
 2261 operation, histo-pathology work for cancer studies), clerical work (Master-File and tumor  
 2262 registry) and secretarial and administrative assistance. The current total size of 39 is adequate.  
 2263

2264 **Hiroshima**

| Area                | Fiscal Year         |      |      |      |      |      |
|---------------------|---------------------|------|------|------|------|------|
|                     | Current             | 1997 | 1998 | 1999 | 2000 | 2001 |
| 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) <sup>1</sup> | 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   |

2281 <sup>1</sup> Part-time employees shown in parentheses.  
 2282

2283 **Space requirements (m<sup>2</sup>) (Hiroshima)**

| Area                | Fiscal Year |      |      |      |      |      |
|---------------------|-------------|------|------|------|------|------|
|                     | Current     | 1997 | 1998 | 1999 | 2000 | 2001 |
| Research scientists | 73          | 105  | 105  | 105  | 105  | 105  |
| Administration      | 18          | 20   | 20   | 20   | 20   | 20   |

|      |                            |     |     |     |     |     |     |
|------|----------------------------|-----|-----|-----|-----|-----|-----|
| 2289 | Research assistants        | 20  | 20  | 20  | 20  | 20  | 20  |
| 2290 | Master File                | 307 | 210 | 210 | 210 | 210 | 210 |
| 2291 | Tumor registry             | 112 | 210 | 210 | 210 | 210 | 210 |
| 2292 | Pathology                  | 181 | 180 | 180 | 180 | 180 | 180 |
| 2293 | Other Support <sup>1</sup> | 57  | 40  | 40  | 40  | 40  | 40  |
| 2294 | -----<br>Total             | 768 | 785 | 785 | 785 | 785 | 785 |

<sup>1</sup> 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 <sup>1</sup> | 6,060       | 6,000 | 6,200 | 6,140 | 6,140 |
| New computer hardware and software <sup>2</sup>    | 660         | 780   | 640   | 760   | 760   |
| Pathology lab                                      | 970+        | 150   | 150   | 150   | 150   |
| -----<br>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 <sup>1</sup> | 4,292       | 4,200 | 4,390 | 4,298 | 4,348 |
| New computer hardware and software <sup>2</sup>    | 549         | 617   | 536   | 608   | 608   |

2336

|      | Pathology lab <sup>3</sup> | 970+  | 150   | 150   | 150   | 150   |
|------|----------------------------|-------|-------|-------|-------|-------|
| 2337 | Total                      | 5,811 | 4,967 | 5,076 | 5,056 | 5,106 |

2338

1. 75% use for research assumed.

2339

2. 75% use for research assumed.

2340

3. 100% use for research assumed.

2341

2342 **Personnel requirements (Nagasaki)**

2343

2344

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.

2346

2347

2348

2349

2350

2351

2352

2353

2354

2355

2356

2357

The epidemiology support staff for Nagasaki has decreased in size and currently consists of 20 full-time employees. The support staff provides technical assistance (maintenance of the computer system, the master-File and tumor registry database management, medical record abstraction for the tumor registry operation, 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 by the employment of one research assistant mentioned above.

## Nagasaki

2358

2359

2360

2361

2362

2363

2364

2365

2366

2367

2368

2369

2370

2371

2372

2373

2374

| Area                 | Fiscal Year |      |      |      |      |      |
|----------------------|-------------|------|------|------|------|------|
|                      | 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   |

2373 **Space requirements (m<sup>2</sup>) (Nagasaki)**

2374

2375

| Area | Fiscal Year |  |  |  |  |  |
|------|-------------|--|--|--|--|--|
|      |             |  |  |  |  |  |
|      |             |  |  |  |  |  |

|      | Current                    | 1997       | 1998       | 1999       | 2000       | 2001       |
|------|----------------------------|------------|------------|------------|------------|------------|
| 2376 | Research scientists        | 28*        | 50         | 50         | 50         | 50         |
| 2377 | Research assistant         | 0          | 10         | 10         | 10         | 10         |
| 2378 | Master File                | 146        | 146        | 146        | 146        | 146        |
| 2379 | Tumor registry             | 61         | 70         | 70         | 70         | 70         |
| 2380 | Pathology                  | 82         | 82         | 82         | 82         | 82         |
| 2381 | Computer technicians       | 18         | 22         | 22         | 22         | 22         |
| 2382 | Other Support <sup>1</sup> | 96         | 96         | 96         | 96         | 96         |
| 2383 | <b>Total</b>               | <b>431</b> | <b>476</b> | <b>476</b> | <b>476</b> | <b>476</b> |

2384 <sup>1</sup> Includes space for data and document storage (52m<sup>2</sup>), network communication servers and equipment  
 2385 (18m<sup>2</sup>) and underground storage of pathology samples (26m<sup>2</sup>).  
 2386

### 2387 **Equipment budget (Nagasaki) (x ¥ 1,000)**

| 2388 | Budget category     | Fiscal Year  |              |              |            |              |
|------|---------------------|--------------|--------------|--------------|------------|--------------|
|      |                     | 1997         | 1998         | 1999         | 2000       | 2001         |
| 2390 | Computer hardware   | 2,570        | 2,500        | 1,000        | 0          | 3,000        |
| 2391 | replacement/upgrade |              |              |              |            |              |
| 2392 | additional          | 570          |              |              |            |              |
| 2393 | Printer             | 1,900        | 700          | 1,500        | 700        | 1,900        |
| 2394 | replacement/upgrade |              |              |              |            |              |
| 2395 | Software upgrade    | 968          | 144          | 1,044        | 144        | 1,044        |
| 2396 | additional          | 190          |              |              |            |              |
| 2397 | Pathology lab       | 1,618        | 30           | 30           | 30         | 30           |
| 2398 | <b>Total</b>        | <b>7,816</b> | <b>3,374</b> | <b>3,574</b> | <b>874</b> | <b>5,974</b> |

2399  
 2400  
 2401 **Survey Expenses (x ¥ 1,000)**

| 2402 |              | Projection    |               |               |               |               |               |               |               |               |
|------|--------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|
|      |              | 1993          | 1994          | 1995          | 1996          | 1997          | 1998          | 1999          | 2000          | 2001          |
| 2403 |              |               |               |               |               |               |               |               |               |               |
| 2404 |              |               |               |               |               |               |               |               |               |               |
| 2405 | Mortality    |               |               |               |               |               |               |               |               |               |
| 2406 | surveillance |               |               |               |               |               |               |               |               |               |
| 2407 | Hiroshima    | 13,509        | 13,524        | 13,450        | 17,082        | 17,000        | 17,850        | 17,850        | 18,740        | 18,740        |
| 2408 | Nagasaki     | 7,489         | 7,337         | 7,423         | 11,294        | 11,000        | 11,550        | 11,550        | 12,130        | 12,130        |
| 2409 | <b>Total</b> | <b>20,998</b> | <b>20,861</b> | <b>20,873</b> | <b>28,376</b> | <b>28,000</b> | <b>29,400</b> | <b>29,400</b> | <b>30,870</b> | <b>30,870</b> |

|      |           |        |        |        |        |        |        |        |        |        |
|------|-----------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| 2410 | Tissue    |        |        |        |        |        |        |        |        |        |
| 2411 | registry  |        |        |        |        |        |        |        |        |        |
| 2412 | Hiroshima | 12,000 | 12,000 | 12,000 | 12,000 | 12,000 | 12,000 | 12,000 | 12,000 | 12,000 |
| 2413 | Nagasaki  | 12,000 | 12,000 | 12,000 | 12,000 | 12,000 | 12,000 | 12,000 | 12,000 | 12,000 |
| 2414 | Total     | 24,000 | 24,000 | 24,000 | 24,000 | 24,000 | 24,000 | 24,000 | 24,000 | 24,000 |
| 2415 | F1 mail   |        |        |        |        | 13,300 | 13,300 | 13,300 | 13,000 |        |
| 2416 | survey    |        |        |        |        |        |        |        |        |        |
| 2417 | Hiroshima |        |        |        |        |        |        |        |        |        |
| 2418 | &         |        |        |        |        |        |        |        |        |        |
| 2419 | Nagasaki  |        |        |        |        |        |        |        |        |        |

|      |             |   |  |        |        |        |        |        |        |  |
|------|-------------|---|--|--------|--------|--------|--------|--------|--------|--|
| 2420 | Grand Total |   |  | 52,376 | 65,300 | 66,700 | 66,700 | 68,170 | 54,870 |  |
| 2421 | 1)          | Mortality surveillance: Projections based on a 5% biennial increase in fees for koseki request plus postage.  |  |        |        |        |        |        |        |  |
| 2422 |             |   |  |        |        |        |        |        |        |  |
| 2423 | 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. |  |        |        |        |        |        |        |  |
| 2424 |             |   |  |        |        |        |        |        |        |  |
| 2425 |             |   |  |        |        |        |        |        |        |  |
| 2426 |             |   |  |        |        |        |        |        |        |  |
| 2427 |             |   |  |        |        |        |        |        |        |  |

#### Construction of LSS-based Family Pedigree Database

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

|      | Current  | 1997   | 1998   | 1999   | 2000   | 2001   |
|------|----------|--------|--------|--------|--------|--------|
| 2432 |          |        |        |        |        |        |
| 2433 | Koseki   | 19,450 | 19,450 | 19,400 | 19,400 | 19,400 |
| 2434 | check    |        |        |        |        |        |
| 2435 | Supplies | 150    | 150    | 140    | 140    | 140    |
| 2436 | 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 that had occurred in germ cells were carried out in the two laboratories by examining the children of the survivors selected from the same F<sub>1</sub> cohort. However, in the last 10 years, the cytogenetics program has been focused on screening for somatic chromosome abnormalities in the survivors in order to establish biological dosimetry as an alternative to physical dose estimation through

2455 the application of electron spin resonance (ESR) of tooth enamel obtained from the survivors.  
2456 The efforts of the biochemical genetics program have been concentrated on developing  
2457 technologies for the detection of germ cell DNA mutations in the children of the survivors and  
2458 establishing cell lines from 1000 parent-child trios, with half of the trios including at least one  
2459 proximally exposed parent.

2460  
2461 In the next five years, in each program, on-going projects will be continued. In addition,  
2462 the FISH (fluorescence in situ hybridization) technique will be utilized for the physical  
2463 localization of unreported genes or new mutations in specific genes detected in the biochemical  
2464 genetics program by using single probes of DNA fragments and, vice versa, a subsample of the  
2465 1000 trios whose lymphocytes and cell lines have been stored in our cell bank for the  
2466 biochemical genetics program will be examined for the detection of chromosomal germline  
2467 mutations.

2468  
2469 **The Cytogenetics Program**

2470  
2471 The research objectives of the Cytogenetics Laboratory are two fold. First, to collect  
2472 cytogenetic information on the survivors and to use this information to strengthen the DS86 dose  
2473 estimates, either by validating them or by indicating possible biases in them. Second, to  
2474 determine by means of the F<sub>1</sub> cytogenetic studies whether parental exposure to A-bomb radiation  
2475 caused an increased frequency of chromosomal abnormalities in their progeny. Since these aims  
2476 entail different studies, we describe them separately.

2477  
2478 **Cytogenetic studies of the survivors**

2479  
2480 Past experience has confirmed that the conventional Giemsa staining method can detect  
2481 nearly two-thirds of all reciprocal translocations. However, even with the best techniques and  
2482 highly qualified investigators, the chromosome aberration data on each survivor scatter quite  
2483 widely when regressed on the individual DS86 doses. This statistical "overdispersion" could be  
2484 attributable to two possible sources of error, one physical and the other biological. The former  
2485 includes errors in the physical estimation of the DS86 dose itself and in the interview  
2486 information regarding location and shielding conditions ATB. The latter includes possible  
2487 differences in radioresponse among individuals due to genetic factors, age ATB, sex, and life-  
2488 style, including smoking habits, for example. To estimate the relative contributions of these  
2489 possible confounding factors, it has long been considered desirable to estimate dose using  
2490 another biodosimetric marker independent of the cytogenetic results.

2491  
2492 The frequency of mutations in somatic cells was once considered a good candidate, and  
2493 several assays were investigated by the Department of Radiobiology to see if these could serve  
2494 as alternative biodosimetric tools. However, among some five different assays, only the  
2495 glycophorin A (GPA) assay in erythrocytes could detect exposures to radiation that occurred  
2496 several decades earlier. Furthermore, the overdispersion of mutant frequency was even greater  
2497 than that seen in the chromosome data, most likely due to a "jackpot-type" event (an occasional  
2498 large "payoff-type" event) stemming from the relatively small number of bone marrow stem  
2499 cells (the target cells for mutation by radiation exposure revealed by the GPA assay) which are  
2500 actively producing mature red blood cells. Thus, the erythrocyte-based GPA mutation assay  
2501 does not seem capable of serving as an alternative tool for biodosimetry on individuals.

2502

2503 Electron spin resonance (ESR) to detect radicals in tooth enamel has been used by a  
2504 number of laboratories as another indicator of past radiation exposure. Since installation of ESR  
2505 equipment in the cytogenetics laboratory (January 1995), 100 teeth selected from over 300  
2506 samples donated during the past nearly 10 years have been examined. The results show a close  
2507 association with the cytogenetic data from the tooth donors, and the ESR method appears to be  
2508 a promising alternative means to estimate individual doses, which in turn supports the  
2509 cytogenetic data on the survivors. Since ESR can be applied only to extracted teeth whereas  
2510 chromosome tests require only 1 to 2 ml of blood which can be readily obtained from most of  
2511 the survivors, ESR cannot supplant cytogenetic tests but serves to reemphasize the value of the  
2512 latter.

## 2513 2514 **Major research activities in the next five years**

### 2515 2516 **A. Core activities**

#### 2517 2518 **Priority 1**

##### 2519 2520 *A-1. RP 8-93 FISH examination of Hiroshima and Nagasaki survivors*

2521  
2522 A recent summary of the cytogenetic data on over 2000 survivors revealed two important  
2523 issues with respect to the accuracy of the dose estimates based on physical grounds.

2524  
2525 First, the dose-response relationship for Nagasaki survivors exposed in factories was  
2526 unusually shallow, only one-half as steep as that for the survivors exposed in Japanese  
2527 houses. This implies that the DS86 system overestimated the doses of these factory  
2528 workers. Second, among the survivors exposed in Japanese houses, the dose responses  
2529 were similar in both cities, but the Hiroshima curve is consistently above the Nagasaki  
2530 one, suggesting the possibility of a small systematic error in the calculation of the DS86  
2531 doses. However, because the conventional staining method used in cytogenetic studies  
2532 is known to be affected by observer bias (the Hiroshima and Nagasaki survivors were  
2533 examined separately in the two laboratories by different investigators), we need to  
2534 confirm these findings using FISH, the most objective method of scoring stable-type  
2535 chromosome aberrations. This will be undertaken in the Hiroshima laboratory  
2536 exclusively.

2537  
2538 In 1994, collection of blood samples began with the aim of applying the FISH technique  
2539 about 200 survivors a year for five years. In 1995, the sampling scheme was extended  
2540 to include an additional 200 survivors of specific interest (for example, tooth donors for  
2541 ESR, carriers of clonal chromosomal aberrations, mothers of the in utero exposed, etc.).  
2542 Further extension is planned in the near future to maximize sampling of those who were  
2543 below 20 years of age ATB and have DS86 doses of about 0.5 Gy or more. (The total  
2544 number subjects will be about 1,500.)

2545  
2546 The motivation for this large scale survey comes from our recent finding, based on tooth  
2547 enamel ESR and the cytogenetic data on the tooth donors, that the cytogenetic data are  
2548 closely related to the real radiation dose. In terms of the highest radiosensitivity of the  
2549 youngest cohort for development of excess cancers, evaluation of biases in DS86 dose  
2550 estimates is critical and only cytogenetic data can provide the necessary information. For

2551 this purpose, information on middle to high dose survivors is more important not only  
2552 because they have the higher risks for cancer but also the fraction of LSS cohort  
2553 members with such doses included in the AHS is larger (the fraction is 85% for those  
2554 with DS86 doses of above 1 Gy).

2555

## 2556 **B. Special research activities**

2557

### 2558 Priority 1

2559

#### 2560 *B-1. RP 1-92 Characterization of the ESR assay*

2561

2562 Because the ESR assay is rather new, laboratory techniques differ in the various steps of  
2563 the assay procedure. Creation of international guidelines for standardization of the assay  
2564 is in progress, and we are eager to compare our technique with that of others to reduce  
2565 possible laboratory-specific errors in estimating the dose. The major advantage of the  
2566 ESR assay is that the measurement itself is not destructive and the same specimen can  
2567 be repeatedly measured. ESR results for the first 100 tooth samples along with the  
2568 cytogenetic data on the tooth donors will be published in 1997.

2569

2570 We propose to examine an additional 100 teeth in the future and to couple this  
2571 examination with the FISH technique using lymphocytes from the tooth donors to  
2572 strengthen the current results. At the same time, tooth collection will continue.

2573

#### 2574 *B-2. RP 8-93 Clonal chromosome aberrations*

2575

2576 During the past studies using conventional staining methods, some 20 survivors were  
2577 identified who carry identical chromosome changes in 3 or more lymphocytes, defined  
2578 as clonal aberrations. A priori, clonal expansion can occur in two ways. Either stem  
2579 cells proliferated extensively and produced a large number of progeny or mature  
2580 lymphocytes proliferated after being stimulated by certain antigen(s). In the former case,  
2581 clonal aberrations are expected to be seen mainly in naive T cells (CD45RA<sup>+</sup>), whereas  
2582 in the latter case, mainly in memory T cells (CD45RO<sup>+</sup>). Studies using separated  
2583 lymphocytes (CD45RA<sup>+</sup> or CD45RO<sup>+</sup>) are in progress and results will be obtained within  
2584 2 years.

2585

2586 Depending upon the findings, further detailed examinations (for example, CD4<sup>+</sup> vs CD8<sup>+</sup>  
2587 lymphocytes) may be necessary. This research will be performed in collaboration with  
2588 the Department of Radiobiology.

2589

#### 2590 *B-3. RP 8-93 FISH examination of exposed parent(s) in the F<sub>1</sub> molecular genetics study sample*

2591

2592 We now know that the DS86 dose estimates contain potentially systematic errors.  
2593 Because the molecular genetics study sample is a small subsample of the AHS cohort,  
2594 and a considerable fraction of the high dose survivors in Nagasaki consists of factory  
2595 workers whose DS86 doses seem to be overestimated, it would be prudent to examine  
2596 the exposed parent(s) with assigned DS86 doses above a certain level (say, 1 Gy) for the  
2597 chromosome aberration frequency of lymphocytes to validate their gonadal doses.  
2598

2599 Because most of the exposed parents are in the AHS, they will be included in the routine  
2600 FISH examination and the total number of parents examined will be nearly 200. The  
2601 study requires at least one AHS examination cycle (two years) or possibly two (four  
2602 years). This study will require the participation of the Departments of Clinical Studies.  
2603

2604 *B-4. RP 1-92 Detailed comparison of ESR dose with DS86 dose*  
2605  
2606 The 100 tooth samples that have been examined by ESR were derived from 69 survivors.  
2607 The ESR estimated tooth dose and DS86 kerma dose show a positive correlation, but  
2608 considerable variation does exist. In some cases, the chromosome data and the ESR data  
2609 fit one another closely but deviate substantially from the DS86 estimates. As previously  
2610 said, these discrepancies are likely to be due to errors in the information on survivor  
2611 location ATB and are most likely unrelated to errors in the program designed to compute  
2612 the DS86 dose. It would be useful to scrutinize the relationships among ESR dose,  
2613 cytogenetic information, and DS86 dose in the remaining cases so that consistent  
2614 deviations related to shielding conditions and other factors can be detected.

2615 . .5  
2616 Priority 2

2617  
2618 *B-5. RP 1-92 Scrutiny of ESR and DS86 doses for tooth donors*  
2619  
2620 As mentioned in the previous section, ESR data are the first physical measurements of  
2621 gamma dose on individual survivors, and they should be carefully compared with the  
2622 DS86 estimates. In 1995, Dean C. Kaul (SAIC) expressed an interest in the DS86 dose  
2623 information on the tooth donors. A collaborative program with SAIC would be valuable  
2624 if the necessary internal administrative agreements can be reached.  
2625

2626 *B-6. RP 8-93 Domain structure of chromosomes in interphase nuclei*  
2627  
2628 Brenner's hypothesis states that the ratio of interchromosomal versus intrachromosomal  
2629 aberrations, termed the F-value, decreases from over 10 to nearly 5 as the LET of  
2630 radiation increases. Current data, both in vivo and in vitro, obtained in the Cytogenetics  
2631 Laboratory at RERF do not seem compatible with this hypothesis. There is no evidence  
2632 that "the majority of the effective dose received by individuals in Hiroshima ... came  
2633 from neutrons" as described by Brenner (1996), but the most recent tooth enamel ESR  
2634 versus translocation data show that the majority of the cytogenetic effects are caused by  
2635 gamma-ray exposure.

2636  
2637 Because the hypothesis is derived from the domain structure of chromosomes in  
2638 interphase nuclei, several approaches from independent angles should be helpful to  
2639 understand the issue. For example, do reciprocal translocations occur randomly among  
2640 chromosomes? Do inactive X chromosomes in females undergo translocation less  
2641 frequently? Are translocation breakpoints distributed homogeneously throughout a  
2642 chromosome arm? Most of these questions can be answered by careful analysis of data  
2643 presently available (both by G-band and FISH), and no extensive new experiments are  
2644 required.

2645  
2646 *B-7. Research on genetic instability*

2647 Recent studies, both in vivo and in vitro, suggest that radiation exposure causes genetic  
2648 instability in cells. We plan two approaches. One is to carefully examine previously  
2649 collected G-band data to see if cells which have undergone a chromosomal change have  
2650 an increased chance of having a second change. Second, if radiation exposure can cause  
2651 instability which lasts for the lifetime of the individual, the frequency of unstable  
2652 aberrations (dicentrics) would be expected to increase with dose. Scrutiny of the  
2653 previously collected large set of cytogenetic data based on conventional staining  
2654 procedures should provide an answer to this.

2655  
2656 *B-8. Assessment of errors in the DS86 system*

2657  
2658 As previously stated, recent ESR results on tooth enamel revealed that the ESR estimated  
2659 dose more closely correlates with chromosome aberration data on the tooth donors than  
2660 DS86 estimates. This finding along with in vitro studies indicate that chromosome data  
2661 are good measures of the true dose. The extensive body of cytogenetic data collected in  
2662 the past should be reviewed to estimate the distribution of true dose at different levels  
2663 of DS86 dose.

2664  
2665 **Cytogenetic studies of the children of the survivors**

2666  
2667 Using conventional staining methods, an extensive cytogenetic survey was conducted in  
2668 the past involving nearly 16,000 F<sub>1</sub> persons (8,000 born to exposed parent(s) and 8,000 to the  
2669 unexposed). The results showed only one de novo autosomal mutation in each group, although  
2670 not all of the parents of aberration-carrying individuals could be cytogenetically examined.  
2671 Thus, no evidence of a radiation effect on the germ cells has been observed so far.

2672  
2673 **Major research activities in the next five years**

2674  
2675 **Priority 1**

2676  
2677 *C-1. Examination of EBV-transformed B-cell lines by the G-banding method*

2678  
2679 Because the previously used conventional staining method can detect only gross  
2680 structural changes and is not suitable for detecting small deletions, it will be necessary  
2681 to apply the G-banding method which is suited for detecting small changes.

2682  
2683 EBV-transformed B-cell lines established from trios of families for molecular genetic  
2684 studies in the Laboratory of Biochemical Genetics would be an appropriate source of  
2685 materials, both in terms of sample size, estimated gonadal dose, and availability of cells  
2686 from the parents. The work will require 3 to 4 years.

2687  
2688 **Priority 2**

2689  
2690 *C-2. Development of FISH using a single probe*

2691  
2692 One application of the FISH technique is mapping using a single gene probe or a probe  
2693 for a specific DNA segment. In the future, in the Laboratory of Biochemical Genetics,  
2694 we anticipate that mutant genes will be detected using molecular analysis of the children

2695 born to the survivors. FISH mapping of the mutated gene would be useful in  
2696 characterizing the mutation.

2697

### 2698 **Project time lines (Cytogenetics)**

2699

| 2700 Fiscal Year                      | 1997 | 1998 | 1999 | 2000 | 2001 |
|---------------------------------------|------|------|------|------|------|
| 2701 1. FISH examination of survivors | ⇒    | ⇒    | ⇒    | ⇒    | ⇒    |
| 2702 2. FISH by a single probe        | ⇒    | ⇒    |      |      |      |
| 2703 3. Chromosome domain structure   | ⇒    | ⇒    |      |      |      |
| 2704 4. Genetic instability           | ⇒    | ⇒    |      |      |      |
| 2705 5. Assessment of DS86 errors     | ⇒    | ⇒    |      |      |      |

2706

2707

### 2708 **Biochemical Genetics Program**

2709

2710 The primary objective of the biochemical genetics program is to determine whether an  
2711 increase in mutations measurable at the molecular level has occurred in the children born to A-  
2712 bomb exposed parents in Hiroshima and Nagasaki.

2713

### 2714 **Past and recent accomplishments**

2715

2716 Extensive studies of the children of the survivors of the atomic bombings of Hiroshima  
2717 and Nagasaki, using various endpoints such as untoward pregnancy outcomes, mortality,  
2718 chromosome aberrations, and gene mutations screened at the protein level, have thus far yielded  
2719 no statistically significant increases in genetic effects compared to a control population.

2720

2721 Because it is important to determine the mutation rate induced by radiation in this  
2722 unique population, detecting mutations at the DNA level has been explored in a feasibility study.  
2723 Establishment of cell lines from parent-child trios was recommended by the Genetic Study  
2724 Conference held in 1984. It is anticipated that immortalized B-lymphocyte cell lines from 1000  
2725 families, one-half of them from a proximally exposed parent(s), will be maintained at RERF.  
2726 Cell lines from 800 families composed of 1600 parents having DS86 estimates and 1200  
2727 children are now in the cell bank. This is the largest properly selected population in the world  
2728 for the detection of radiation effects on human germline mutations. The Human Germline  
2729 Mutagenesis Workshop held in 1991 recommended starting a pilot study using 100 families (50  
2730 exposed and 50 control families), a subsample of the 800 families, to compare various types of  
2731 DNA as potential targets for the detection of germinal mutations with various techniques,  
2732 because there was no information about the genes sensitive to radiation-induced mutagenesis.  
2733 In keeping with this recommendation, microsatellites, minisatellites and various functional  
2734 single-copy sequences in 124 children and both parents of the 100 families have been examined  
2735 to determine whether deletion/insertion/rearrangement (D/I/R) type mutations or mutations  
2736 causing other types of quantitative changes, all commonly produced by radiation, as well as  
2737 nucleotide substitutions, exist at higher frequency in the children of the exposed parents.

2738

2739 Preliminary studies have failed to reveal a significant difference between the children  
2740 of the exposed and the control parents in the mutation rates at the microsatellite and the  
2741 minisatellite loci, both of which are repetitive sequences dispersed through the human genome.

2742 We have developed two techniques to screen for D/I/R type mutations in single-copy  
2743 sequences. One is the quantitative measurement of intensities of chemiluminescent bands on  
2744 Southern filters and the other is the two-dimensional electrophoresis (2-DE) of DNA digests  
2745 followed by a quantitative image analysis of <sup>32</sup>P-labeled spots. Each technique can detect a 50%  
2746 decrease or increase in band intensity or spot intensity that is derived from the D/I/R events on  
2747 the totality of a single allele. Thus, these techniques are suitable to detect a fresh D/I/R type  
2748 mutation because a fresh mutation would usually be detected in a heterozygote for a normal and  
2749 a variant allele.

## 2750 **Major research activities in the next five years**

### 2751 **A. Core activities**

#### 2752 **Priority 1**

##### 2753 *A-1. Pilot studies for the detection of D/I/R type mutations*

2754 In addition to the original 100 families, a new set of 100 families (50 exposed and 50  
2755 control families) will be selected and screened for mutations at the minisatellite loci  
2756 during the first two years. It is important to use a larger body of data to confirm our  
2757 preliminary results, which showed no effect of A-bomb radiation on genetic instability  
2758 at the minisatellite loci in human germ cells obtained from the original 100 families,  
2759 including children derived from 65 exposed gametes with a mean dose of 1.9 Sv. We  
2760 have assumed that the 65 gametes received, on average, the doubling dose estimated  
2761 by Neel et al. (1990)), namely, 1.7-2.2 Sv. For a locus with a spontaneous mutation  
2762 rate of 0.02 per gamete, which is the mean mutation rate of the six minisatellite loci  
2763 examined in the previous study, using standard power function statistics (a Type I error  
2764 of 0.05 and a Type II error of 0.2), we calculate that we would need to survey two  
2765 samples (exposed and unexposed) of 1,188 germ cells each to observe a significant  
2766 difference at the 0.05 level.

2767 By examining 60 children from an additional 50 exposed families, each one of them  
2768 having one exposed parent and the mean gonadal dose of the parent being 1.9 Sv, it is  
2769 anticipated that we can examine the required number of alleles for each sample.  
2770 Dubrova et al. reported that mutation rates at minisatellite loci in 79 children of parents  
2771 who lived in heavily polluted areas of Belarus after the Chernobyl accident were twice  
2772 that of 105 control children from the United Kingdom although the estimated individual  
2773 dose from external and internal chronic exposure to <sup>137</sup>Cs of inhabitants of those areas  
2774 was less than 5 mSv per year. By comparing their data with our new data based on the  
2775 projected additional sampling, it may be possible to determine whether there is a  
2776 difference in biological effects of radiation between acute external exposure and  
2777 chronic internal exposure.

2778 The pilot study for the screening of D/I/R mutations will be carried out with the  
2779 quantitative measurement of intensities of chemiluminescent bands on Southern filters  
2780 on two hundred families (the original 100 families and the new 100 families). Probes  
2781 to be used are DNA fragments from the human counterparts of the seven mouse  
2782 specific loci, other genes located nearby, and genes supposedly related to common  
2783

2790 chronic diseases such as hypertension, diabetes mellitus and hereditary nonpolyposis  
2791 colorectal cancer (HNPCC).

2792  
2793 The 2-DE technique will be used in the pilot study. DNA samples from the 200  
2794 families will be examined using this technique after digestion with three sets of  
2795 restriction enzymes, i.e., NotI/EcoRV-HinfI (NotI/EcoRV and HinfI being used before  
2796 and after the first dimensional electrophoresis, respectively), NotI/EcoRV-PvuII and  
2797 NotI/EcoRV/PvuII-HinfI, products of each set of enzymes being different from those  
2798 produced with the other two sets of enzymes. These three kinds of DNA digests  
2799 labeled with  $^{32}\text{P}$  from one individual will be electrophoresed separately, and the  
2800 resulting three gels will be quantitatively analyzed. A total of 2000 spots (fragments)  
2801 will be suitable for the detection of the D/I/R type mutations among 6000 spots  
2802 (fragments) visualized on the three autoradiograms from the three gels. With the  
2803 current research design (2000 diploid fragments scored per three gels per individual),  
2804 5 mutations would be detected in 120 children from 100 control families, if we assume  
2805 that the spontaneous mutation rate is  $1 \times 10^{-5}$ /fragment/generation.

2806  
2807 Image analysis is an essential part of any 2-DE study of DNA fragments, and this will  
2808 require support of the Information Technology Department (ITD) in the rewriting of  
2809 the 2-DE software developed at the University of Michigan and currently in use in the  
2810 Department of Genetics. This software was developed for older computer operating  
2811 systems and cannot be readily used with the system upgrades that already have occurred  
2812 and that are contemplated in future computer system upgrades at RERF. In addition,  
2813 to organize data from the various DNA examinations and perform analyses, support  
2814 from the ITD and the Department of Statistics will be required.

2815  
2816 Physical localization of mutant genes and their normal counterparts will be carried out  
2817 using the FISH technique in collaboration with the Cytogenetics Laboratory. To  
2818 understand the characteristics (physical nature and functional effects) of new mutations,  
2819 not only molecular biological data but also physical data are essential.

2820  
2821 In each of the 100 exposed families, at least one parent belongs to the most heavily  
2822 exposed group among the approximately 400 exposed parents on whom permanent cell  
2823 lines have been established. Therefore, if the mutation rate detected in the children of  
2824 the exposed group is significantly higher than that in the children of the control group,  
2825 and the efficiency of the technique we propose is sufficiently high to warrant screening  
2826 a larger number of samples, the study will be expanded to determine the dose response  
2827 relationship. However, if there is no significant difference in the mutation rates  
2828 between the two groups or the efficiency of the technique is too low, the study will not  
2829 be continued and new methods will be introduced or developed.

2830  
2831 *A-2. Culture of permanent lymphocyte cell lines as sources of biological samples for*  
2832 *the study of germ cell mutations*

2833  
2834 Initially, families for this program were selected on the basis of T65DR doses since the  
2835 DS86 system did not exist when the original selections were made. Some of the cell  
2836 lines already established are from families including parents whose DS86 doses are  
2837 unavailable. New families for which parental DS86 doses are available will be selected

2838 and cell lines will be established keeping the original goal of 1000 families in mind.  
2839 This means we shall try to add 200 families in Hiroshima and Nagasaki over the next  
2840 two years.

2841  
2842 In the beginning of the pilot study for the detection of mutations, DNA extracted from  
2843 cell lines established from members of the 100 families, a subsample of the 1000  
2844 families of the cell-line project, was used. However, recently, in order not to exhaust  
2845 the cell lines, portions of the cell lines have been proliferated and the resulting "re-  
2846 cultured cell lines" have been used for routine purposes. For the additional new 100  
2847 families to be examined in the pilot study, the "re-cultured cell lines" will be produced  
2848 and they will be used as sources of DNA.

2849  
2850 **B. Special research activities**

2851  
2852 **Priority 1**

2853  
2854 *B-1. A feasibility study on the ascertainment of disease and disability among offspring*  
2855 *of the survivors (Feasibility of F<sub>1</sub> health study)*

2856  
2857 The Blue Ribbon Panel urged that consideration be given to the feasibility of studying  
2858 diseases and disabilities of late onset among the offspring (F<sub>1</sub> generation) of the  
2859 survivors. A protocol for the feasibility study has been written. It includes a mail  
2860 questionnaire survey for a total of 82,000 F<sub>1</sub> (F<sub>1</sub> Mortality Sample and the so-called  
2861 BGS Extension Samples), physical examination of approximately 500 F<sub>1</sub> (F<sub>1</sub> reporting  
2862 chronic illness and those not doing so) in the Departments of Clinical Studies, and  
2863 analyses of genes related to common diseases such as hypertension and diabetes  
2864 mellitus in approximately 50 F<sub>1</sub>. It is anticipated that it will take two years to complete  
2865 the study. As soon as results of the feasibility study are obtained, a workshop will be  
2866 held to determine whether a full-scale study is practical and warranted. Thus, the  
2867 feasibility study will be carried out as a collaborative undertaking involving the  
2868 Departments of Clinical Studies, Epidemiology, Statistics and Genetics.

2869  
70 *B-2. Assessment of detectability of germ cell mutations by the 2-DE technique*  
2871 *(Detectability of mutations by 2-DE: Approved by Chief of Research Donald Harkness*  
2872 *on 14 March 1995)*

2873  
2874 A pilot study, which was begun in 1996 for the assessment of detectability of the 2-DE  
2875 technique of radiation-induced germ cell mutations in mammals, will be continued for  
2876 one more year. DNA samples from 100 control mice (BALB/c) and from two groups  
2877 of 100 F<sub>1</sub> mice, one derived from spermatogonia irradiated with 3 Gy and the other  
2878 from spermatogonia irradiated with 5 Gy, are being examined with the 2-DE technique  
2879 after digestion with two sets (NotI/EcoRV-HinfI and NotI/EcoRV-PvuII) of restriction  
2880 enzymes. The search for D/I/R type mutations that result in spots with 50% decreased  
2881 intensity at the normal positions among 1000 spots on a gel are being carried out using  
2882 the quantitative image analysis. Among DNA samples from 43 F<sub>1</sub> mice of 5 Gy  
2883 irradiated male parents, examined in 1996, one mutation was detected. Results of the  
2884 study will provide basic information for the estimation of the number of children of A-  
2885 bomb survivors that should be examined in order to obtain statistically significant

2886 results.

2887  
2888 *B-3. Pilot study to evaluate various markers in potential candidate genes associated*  
2889 *with hypertension. (Pilot study for the hypertension markers)*  
2890

2891 Suggestive radiation-related increases in cardiovascular disease incidence and the  
2892 prevalence of aortic arch calcification and systolic hypertension have been reported.  
2893 The Blue Ribbon Panel states that further studies are required to confirm a real  
2894 association between radiation exposure and atherosclerosis. This indicates the  
2895 importance of studying at the molecular level the hypertension observed in the AHS  
2896 population. A protocol is being prepared for a pilot study to evaluate several markers  
2897 in potential candidate genes associated with hypertension. Some 100 individuals each  
2898 from the normal group and the hypertension group, defined by the 1993 WHO/ISH  
2899 classification among the participants of the AHS, will be examined for their  
2900 polymorphic markers in several candidate genes. DNA will be extracted from  
2901 lymphocytes in the blood samples obtained in the biennial physical examination  
2902 conducted at the Departments of Clinical Studies. Because some AHS participants with  
2903 hypertension are parents of the cell line project for the germinal mutation study, family  
2904 studies for the potential markers associated with hypertension will be able to be carried  
2905 out.  
2906

2907 **Project time lines (Biochemical Genetics)**

| 2909 | Project                                      | 1996 | 1997 | 1998 | 1999 | 2000 | 2001 |
|------|--|------|------|------|------|------|------|
| 2910 | Feasibility for F <sub>1</sub> -health study |      | ⇒    | ⇒    |      |      |      |
| 2911 | Detectability of mutations by 2-DE           | ⇒    | ⇒    |      |      |      |      |
| 2912 | Pilot study for the hypertension markers     |      | ⇒    | ⇒    |      |      |      |

2913  
2914 **Personnel Requirements (Department of Genetics)**  
2915

| 2916 | Fiscal Year         | 1996               | 1997 | 1998 | 1999 | 2000 | 2001 |
|------|---------------------|--------------------|------|------|------|------|------|
| 2917 | Research Scientists |                    |      |      |      |      |      |
| 2918 | Cytogenetics        | 5                  | 5    | 5    | 5    | 5    | 5    |
| 2919 | Biochem. Genet.     | 4+0.5 <sup>1</sup> | 5    | 5    | 5    | 5    | 5    |
| 2920 | Technicians         |                    |      |      |      |      |      |
| 2921 | Cytogenetics        | 5                  | 6    | 6    | 6    | 6    | 6    |
| 2922 | Biochem. Genet.     | 11 <sup>2</sup>    | 12   | 12   | 12   | 12   | 12   |
| 2923 | Clerks              |                    |      |      |      |      |      |
| 2924 | Cytogenetics        | 1                  | 1    | 2    | 2    | 2    | 2    |
| 2925 | Biochem. Genet.     | 2.2 <sup>3</sup>   | 3    | 3    | 3    | 3    | 3    |

2927 <sup>1</sup> One visiting scientist (Dr. Murakami) is concurrently assigned to the Departments of Genetics (50%) and Clinical  
 2928 Studies (50%). Her employment as a permanent research scientist is required.

2929 <sup>2</sup> One young technician retired at the end of FY95 and no replacement has been made.

2930 <sup>3</sup> One clerk is concurrently assigned to the Department of Genetics (20%) and the Publication & Documentation  
 2931 Center (80%).

2932

2933

### Space requirements (m<sup>2</sup>) (Department of Genetics)

2934

| 2935 | Fiscal Year                     | 1996             | 1997              | 1998  | 1999  | 2000  | 2001  |
|------|---------------------------------|------------------|-------------------|-------|-------|-------|-------|
| 2936 | Bench Research                  |                  |                   |       |       |       |       |
| 2937 | Cytogenetics                    | 146.2            | 146.2             | 146.2 | 146.2 | 146.2 | 146.2 |
| 2938 | Biochem. Genet.                 | 402 <sup>1</sup> | 442               | 442   | 442   | 442   | 442   |
| 2939 | Support Space                   |                  |                   |       |       |       |       |
| 2940 | Offices cytogenetics            | 73.2             | 83.2 <sup>2</sup> | 83.2  | 83.2  | 83.2  | 83.2  |
| 2941 | Biochem. Genet. <sup>3</sup>    | 100              | 100               | 100   | 100   | 100   | 100   |
| 2942 | Slide Storage(Cytogenetics)     | 7.3              | 17.3 <sup>4</sup> | 17.3  | 17.3  | 17.3  | 17.3  |
| 2943 | Storage Space(Biochem Genet.).. | 23               | 23                | 23    | 23    | 23    | 23    |
| 2944 | Total                           |                  |                   |       |       |       |       |
| 2945 | Cytogenetics                    | 226.7            | 246.7             | 246   | 246.7 | 246.7 | 246.7 |
| 2946 | Biochem. Genetics.              | 525              | 565               | 565   | 565   | 565   | 565   |
| 2947 |                                 |                  |                   |       |       |       |       |
| 2948 | Grand Total                     | 751.7            | 811.7             | 811.7 | 811.7 | 811.7 | 811.7 |

2949

2950 <sup>1</sup> Some corridor space where various research equipment, refrigerators and incubators are installed for  
 2951 daily use is included.

2952 <sup>2</sup> Computer space (+10 m<sup>2</sup>).

2953 <sup>3</sup> Space used for image analysis of the 2-DE gels and other types of gel analyses is included.

2954 <sup>4</sup> Nagasaki slide storage (+10 m<sup>2</sup>).

2955 <sup>5</sup> Space for liquid nitrogen tanks, deep freezers and glassware for experiments.

2956

2957

### Equipment Budget (× ¥ 1,000)

2958

| 2959 | Fiscal Year             | 1997  | 1998  | 1999  | 2000  | 2001  |
|------|-------------------------|-------|-------|-------|-------|-------|
| 2960 | Equipment               |       |       |       |       |       |
| 2961 | Routine Replacement     |       |       |       |       |       |
| 2962 | Laboratory              | 2,149 | 3,695 | 4,789 | 0     | 0     |
| 2963 | Computer <sup>2</sup>   | 2,641 | 326   | 1,127 | 1,116 | 2,929 |
| 2964 | Routine New             |       |       |       |       |       |
| 2965 | Computer <sup>1</sup>   | 2,200 | 850   | 890   | 930   | 490   |
|      | Computer <sup>2,3</sup> | 600   | 150   | 155   | 160   | 50    |

|      |  |                        |                     |                      |        |        |
|------|--|------------------------|---------------------|----------------------|--------|--------|
| 2966 | Major New  |                        |                     |                      |        |        |
| 2967 | Acquisitions/Rep   | 13,000 <sup>4,5)</sup> | 5,000 <sup>6)</sup> | 22,880 <sup>7)</sup> | 0      | 0      |
| 2968 | I.   |                        |                     |                      |        |        |
| 2969 | Total  | 21,011                 | 10,347              | 30,381               | 2,794  | 4,002  |
| 2970 |  |                        |                     |                      |        |        |
| 2971 | Lab Supplies/Reagents <sup>8)</sup>  | 24,000                 | 26,400              | 28,800               | 31,200 | 33,600 |
| 2972 | <sup>1)</sup> Laboratory and computer equipment for research purpose. For computer, 80% of cost for hardware and 50% of that for software are included into this category.   |                        |                     |                      |        |        |
| 2973 | <sup>2)</sup> Equipment for administrative/service-related. For computer, 20% of cost for hardware and 50% of that for software are included into this category.   |                        |                     |                      |        |        |
| 2974 | <sup>3)</sup> All new hard disks are for research purpose.   |                        |                     |                      |        |        |
| 2975 | <sup>4)</sup> Software for 2-DE Analysis (¥10,000,000): For 2-DE analysis, a 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 we ask a computer scientist outside of the RERF to rewrite it, estimated cost is about ¥10,000,000.  |                        |                     |                      |        |        |
| 2976 | <sup>5)</sup> 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 two apparatuses which we have been using for these 8 years was broken and its parts are unavailable. A new apparatus is essentially necessary to continue our research.   |                        |                     |                      |        |        |
| 2977 | <sup>6)</sup> 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. A camera has been used for 5 years at the end of 1997 and its sensitivity for photons is decreasing. The old camera should be replaced by new one.   |                        |                     |                      |        |        |
| 2978 | <sup>7)</sup> Bio-Imaging Analyzer with Imaging Plates and Cassettes (¥22,880,000): In the 2-DE analysis, spot pattern on a gel is visualized by making autoradiogram for which at least two weeks or more is necessary. This will be a big problem in the screening for mutations by using the 2-DE technique. By using this image analyzer, the problem will be solved and accuracy of the spot intensity will be much improved because it has high sensitivity for radioactivity. |                        |                     |                      |        |        |
| 2979 | <sup>8)</sup> A 10% yearly increase is included.   |                        |                     |                      |        |        |
| 2980 |  |                        |                     |                      |        |        |
| 2981 |  |                        |                     |                      |        |        |
| 2982 |  |                        |                     |                      |        |        |
| 2983 |  |                        |                     |                      |        |        |
| 2984 |  |                        |                     |                      |        |        |
| 2985 |  |                        |                     |                      |        |        |
| 2986 |  |                        |                     |                      |        |        |
| 2987 |  |                        |                     |                      |        |        |
| 2988 |  |                        |                     |                      |        |        |
| 2989 |  |                        |                     |                      |        |        |
| 2990 |  |                        |                     |                      |        |        |
| 2991 |  |                        |                     |                      |        |        |
| 2992 |  |                        |                     |                      |        |        |
| 2993 |  |                        |                     |                      |        |        |
| 2994 |  |                        |                     |                      |        |        |
| 2995 |  |                        |                     |                      |        |        |

## 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, histopathological, 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:

- (1) The immunologic studies have revealed that among atomic-bomb survivors immune

3012 function, such as mitogen and alloantigen responsiveness of T-cells, lymphocyte subpopulation  
3013 numbers, and anti-Epstein-Barr virus immunity, is still compromised fifty years after the atomic  
3014 bombings.

3015  
3016 (2) The department has established various mutation assays, namely, the HPRT, HLA,  
3017 Fcγ RIII, TCR, and GPA assays, and applied these to ascertain radiation doses among atomic  
3018 bomb survivors and to estimate the risk of cancer development. These studies have shown that  
3019 the somatic mutation frequency at the glycophorin A locus increases with increasing dose of A-  
3020 bomb radiation, suggesting that various diseases among the A-bomb survivors, including cancer,  
3021 develop in part from genetic alterations induced by radiation.

3022  
3023 (3) The molecular oncology/epidemiology study was initiated six years ago to elucidate  
3024 possible unique molecular finger prints in cancers among A-bomb survivors. Technical  
3025 problems in using formalin-fixed paraffin-embedded samples from the A-bomb survivors have  
3026 been resolved. The molecular analyses of liver cancer and skin cancer are on going.

3027  
3028 In addition to the above mentioned studies, new research areas have been opened up to  
3029 understand the precise mechanisms of radiation-induced damage, which might be important in  
3030 cancer development. It is now evident that alterations of cancer-specific genes, such as RET  
3031 oncogene activation and BCR-ABL translocation, can be induced by radiation.

3032  
3033 **Program objectives**

3034  
3035 The survivors of the atomic bombings represent a population of individuals who have  
3036 been exposed to a wide range of doses of ionizing radiation; therefore, the primary objective of  
3037 RERF has been to ascertain the effects that might have been produced in the exposed individuals  
3038 and their children as a result of exposure to A-bomb radiation, and to relate these changes to  
3039 dose and to the subsequent health effects which may have occurred. Consequently, until  
3040 recently, research at RERF has focused primarily on the long-term epidemiological studies of  
3041 A-bomb survivors to ascertain morbidity and mortality of the exposed population, specific  
3042 investigations on health-related effects that might be related to radiation exposure, and genetic  
3043 studies to ascertain the mutation rate resulting from radiation exposure in the children of the  
3044 survivors but clearly there is an important need for molecular and cellular studies aimed at  
3045 revealing the underlying bases of this morbidity and mortality. It is thus important to bear in  
3046 mind that if the Foundation is to achieve its goals it must necessarily maintain a balance between  
3047 mechanistic studies aimed at understanding the biological bases of radiation-induced changes  
3048 and the statistical description of risk. It behooves the Foundation, therefore, to establish a  
3049 credible and strong program in molecular and cellular research if the biological origin of  
3050 radiation-related damage is to be understood.

3051  
3052 Accordingly, the mission of the Department of Radiobiology is to study the molecular  
3053 mechanisms of radiation-induced carcinogenesis in A-bomb survivors. We also believe that it  
3054 is our mission to clarify what the biological effects of radiation are on human health and why  
3055 and how disease is induced as a consequent process.

3056  
3057 **Major projects in the next five years.**

3058

3059 In the coming 5 years, as we explain in the next several pages, some current studies will  
3060 be phased out, others will be continued, and new ones will be introduced. The determination of  
3061 the fate of these studies will be based on their relevance to several factors. Simultaneously the  
3062 department will concentrate its energy on three major core activities, namely, molecular  
3063 epidemiology, molecular oncology, and immunology.  
3064

3065 The studies will be prioritized by the direct impact they are projected to have on these  
3066 three core fields. That is, the highest priority studies will be the ones that can potentially  
3067 produce supportive evidence for the radiogenic etiology of diseases occurring in the A-bomb  
3068 survivors via damage of key molecules and their pathways.  
3069

### 3070 **A. Molecular epidemiology**

3071  
3072 A major objective of the molecular epidemiological study is to identify radiation-induced  
3073 gene alterations in cancer and normal tissues of A-bomb survivors, and thereby to provide  
3074 significant insights into the molecular mechanisms of human radiation carcinogenesis and  
3075 disease development. To accomplish this goal, we will analyze cancer-associated genes such as  
3076 oncogenes and tumor suppressor genes in archival and surgical specimens of normal and tumor  
3077 tissues obtained from A-bomb survivors.  
3078

3079 Molecular epidemiology at RERF combines powerful data analysis methods for  
3080 elucidating trends in disease development among the A-bomb survivors with state-of-the-art  
3081 techniques in molecular biology. Such a partnership of disciplines can produce the first line of  
3082 attack for understanding the mechanisms behind the observed human diseases following  
3083 exposure to the A-bomb radiation. There are now many epidemiological studies demonstrating  
3084 an effect of the A-bomb on the survivors; and with these results are hypotheses that try to  
3085 explain them. For example one belief is that cancer incidence is heightened among the exposed  
3086 because the radiation inflicted damage to the DNA of cells led to the loss of function of some  
3087 crucial genes that controlled growth. But what are these genes? In which tissues are they most  
3088 affected? Why does sex, age ATB, dose of exposure make a difference? There are no clear  
3089 answers to these and many other questions. Generation of some of these answers may help in  
3090 the treatment and prevention of diseases in numerous groups such as other radiation exposed  
3091 people, chemically exposed people, and cancer patients, as well as in the A-bomb population.  
3092 But study of the A-bomb survivor population, because of its size and because it and its tissues  
3093 have been so well catalogued and followed up for nearly a lifetime, will provide the best  
3094 opportunities for such analyses.  
3095

3096 The large repository of archival tissues makes possible extensive retrospective molecular  
3097 epidemiological studies. As indicated in the following table, high priority studies will include  
3098 those cases showing the highest relative risk with sufficient number of high dose, histologically  
3099 verified samples such as the female breast, thyroid, and skin. Because analysis of these cancers,  
3100 given that 33 of 43, 12 of 17, and 15 of 22 breast, thyroid, and skin cancers, respectively, are due  
3101 to radiation, have the highest probability of producing the most statistically significant difference  
3102 between the exposed and control groups.  
3103

3104 Estimation of the cancer cases due to radiation  
3105

| Cancer site   | ERR<br>1 Sv | 0.01 - 0.99 Sv |                 |  | 1.0 Sv       |                 |  | HV (%) |
|---------------|-------------|----------------|-----------------|--|--------------|-----------------|--|--------|
|               |             | mean<br>dose   | No. of<br>cases | Fraction of<br>cases due to<br>radiation | mean<br>dose | No. of<br>cases | Fraction of<br>cases due to<br>radiation |        |
| 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. RP 7-92, 3-93, 7-93, 2-94 Oncogenes and tumor suppressor genes in A-bomb survivors with cancer*

Cancer development is believed to be a multi-step process. The steps are not known but major roles appear to be played are 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 p53 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*

3164 The usefulness of preserved tissue specimens from A-bomb survivors has been  
3165 demonstrated by means of the PCR method. PCR is a revolutionary method for the  
3166 amplification of DNA by over a million fold. Thus PCR makes it possible to study  
3167 the genes of A-bomb survivor using microscopic quantities of archival tissues from  
3168 as far back as 1950.

3169  
3170 *A-3-1. Skin cancer (RP3-93)*

3171  
3172 We have already prepared DNA from 60 tissue samples of skin cancer and are  
3173 currently analyzing the ras and p53 genes. We will continue this analysis and start  
3174 an analysis of the patched gene, which has been recently cloned and found to be  
3175 frequently mutated in skin cancer.

3176  
3177 *A-3-2. Liver cancer (RP2-94)*

3178  
3179 In addition to skin cancer, molecular analyses of liver cancer (total sample number  
3180 is 800) are on going. Currently studies of mutation in the p53 tumor suppressor  
3181 gene and genomic integration of the hepatitis B and C viruses are being carried out.  
3182 It may take two more years to complete these analyses.

3183  
3184 *A-3-3. Thyroid cancer (RP7-93)*

3185  
3186 Thyroid cancer should also be analyzed at the molecular level since it is among the  
3187 cancers with the highest risk seen in the A-bomb survivors, implying that this cancer  
3188 may be one of the best candidates for the identification of an A-bomb radiation-  
3189 induced unique fingerprint, if such exists. Thyroid samples will be analyzed for  
3190 aberrations in RET by immunohistochemistry using monoclonal antibodies against  
3191 the RET proteins, which is not expressed in normal thyroid tissues.

3192  
3193 *A-3-4. Female breast cancer (RP7-92)*

3194  
3195 Breast cancer has one of the highest increased risks in the survivors. The risk is  
3196 even higher for those survivors exposed at a young age with an ERR at 1 Sv of 3.21  
3197 and 2.61 for age ATB of 0 - 9 years and 10 - 19 years, respectively. Moreover,  
3198 breast cancer is a potential familial cancer that may predispose some women to  
3199 radiogenic breast malignancies. These studies will be complemented by research on  
3200 the genetic background of cancer patients among the A-bomb survivors (see special  
3201 research activity B). BRCA1 and 2 have so far shown the best prospects as genes  
3202 in the cause of the disease.

3203  
3204 Breast samples will be screened for BRCA1 mutations by immunohistochemistry  
3205 since antibodies to detect mutations are commercially available.

3206  
3207 *A-5-5. Others*

3208  
3209 Salivary cancer is another important candidate for analysis at the molecular level,  
3210 since it has been revealed recently that the ERR is 3.47 at 1 Sv which makes it the  
3211 highest risk cancer among the survivors. Specific salivary gland cancer related

3212  
3213  
3214  
3215  
3216  
3217  
3218  
3219  
3220  
3221  
3222  
3223  
3224  
3225  
3226  
3227  
... 28  
3229  
3230  
3231  
3232  
3233  
3234  
3235  
3236  
3237  
3238  
3239  
3240  
3241  
3242  
3243  
... 14  
3245  
3246  
3247  
3248  
3249  
3250  
3251  
3252  
3253  
3254  
3255  
3256  
3257  
3258  
3259

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 elucidate 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 surveys 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 elucidate 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*

3260 In atherosclerosis one possibility is the ras oncogene. Screening will be conducted  
3261 by immunohistochemistry. This study will be in collaboration with the Department  
3262 of Clinical Studies.

3263

## 3264 **B. Molecular Oncology**

3265

3266 Molecular oncology is closely related to molecular epidemiology. Whereas the latter  
3267 produces trends of molecular changes in radiogenic cancers, the former provides the explanation  
3268 or mechanism for how these changes work to cause cancer. Such results will supply the direct  
3269 evidence for the carcinogenic effect of A-bomb exposure on the survivors. Knowledge of the  
3270 mechanism will allow improved management of exposure to ionizing radiation as well as  
3271 provide information in the treatment and prevention of related diseases.

3272

3273 As stated earlier, molecular epidemiology will provide much of the basis for other  
3274 molecular studies. To delve deeper into the mechanisms, further, more manipulative  
3275 experiments will be necessary. Manipulations will include working with live human cells from  
3276 the A-bomb survivors, other human populations, and with human tissues in animal models, in  
3277 that order of priority. Live cells are necessary in order to recreate as accurately as possible the  
3278 events and responses of the cells in the survivors after A-bomb exposure. In the light of recent  
3279 advances and the relatively large radiation effects for breast and thyroid cancer, studies of tissues  
3280 from breast and thyroid cancer cases among the high dose survivors have the potential to yield  
3281 important results. It may also be useful to supplement the search for characteristic gene  
3282 alterations in cancer cells with a search for evidence of specific mutations associated with cancer  
3283 development in the blood of cancer-free survivors.

3284

3285 The Blue Ribbon panel emphasized the necessity to determine the shape of the dose-  
3286 response curve for radiation carcinogenesis at low doses of radiation. The recommendation  
3287 suggested initiation of a molecular oncological study to clarify the molecular mechanisms in  
3288 human radiation carcinogenesis.

3289

### 3290 **Core activities (Molecular oncology)**

3291

3292

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

3293

3294 It was observed in the recent somatic mutation study that the GPA mutation  
3295 frequencies increased with increasing A-bomb radiation doses, and the dose-  
3296 response curve is very similar to that for solid tumor incidence among the A-bomb  
3297 survivors. We can expect that since radiation may cause DNA damage randomly in  
3298 the cell, cancer-related gene alteration could have been induced and remained in the  
3299 cells of the A-bomb survivors. Based on the multi-step carcinogenesis theory, it  
3300 may be suspected that cells carrying cancer-related gene alterations and proteins  
3301 exist in blood cells among the A-bomb survivors.

3302

#### *A-1. Detection of the cells carrying mutations*

3303

3304 Recent advances in flow cytometry make it possible to analyze translocation of  
3305 cancer-associated genes by in-cell PCR methods using fluorescent primers. BCR-  
3306 ABL and Bcl2 translocations are both associated with blood malignancies and can  
3307

3308 be detected in peripheral blood lymphocytes by this method.

3309  
3310 Newly developed antibodies against oncogenes and tumor suppressor gene products  
3311 will be used to detect cells carrying cancer-associated gene alterations in the blood  
3312 among A-bomb survivors. This technique can demonstrate the existence of mutant  
3313 gene products or changes in levels of normal gene products which may be especially  
3314 pertinent in cases of deletion of tumor suppressor genes like p53 and possibly the  
3315 ataxia telangiectasia mutated (ATM) gene. The projected number of samples to be  
3316 studied is a 300 (control and high risk group). These approaches could provide  
3317 meaningful information for understanding the molecular mechanisms of human  
3318 radiation carcinogenesis and cancer risk estimation.

3319  
3320 **Special research activities (Molecular oncology)**

3321  
3322 Priority 1

3323  
3324 *B. RP 18-81 Human radiation carcinogenesis*

3325  
3326 Strategically, not only are studies directly looking at tissues from the A-bomb  
3327 survivors important, but studies taking advantage of experimental models should be  
3328 very helpful in interpreting effects on the survivors. In the experimental system we  
3329 have developed, we can examine the first and consequent events occurring in the cell  
3330 at the cellular and molecular levels which may have crucial roles in human  
3331 carcinogenesis.

3332  
3333 *B-1. Models*

3334  
3335 The severe combined immunodeficient (SCID) mouse-human chimera makes it  
3336 possible to study radiation effects on humans in vivo, and thereby provide more  
3337 relevant and meaningful information than those obtained in vitro or from other non-  
3338 human animal models. We have already established a transplantation system of  
3339 normal human tissues (skin, intestine, thyroid and bone marrow) to SCID mice  
3340 which preserves in situ histology, structure and function. These models will be  
3341 improved so that they are as close to the human situation as possible and will be  
3342 applied to the studies on radiation response (see B-2) and radiation carcinogenesis  
3343 (see B-3) described below.

3344  
3345 *B-2. Radiation Response*

3346  
3347 We will analyze cellular and molecular changes in human tissue/cell after radiation  
3348 exposure, especially at low doses. This system will enable us to follow the various  
3349 molecular changes in vivo in human tissues following irradiation. For example, this  
3350 model demonstrated the dose-response and cellular mechanism of human radiation-  
3351 induced epilation, which were not clear from the survivor study. Preliminary  
3352 findings using the SCID-hu intestine model suggest that human crypt stem cells in  
3353 the intestine are extremely resistant to radiation-induced apoptosis in comparison to  
3354 mouse stem cells.

3355

3356  
3357  
3358  
3359  
3360  
3361  
3362  
3363  
3364  
3365  
3366  
3367  
3368  
3369  
3370  
3371  
3372  
3373  
3374  
3375  
3376  
3377  
3378  
3379  
3380  
3381  
3382  
3383  
3384  
3385  
3386  
3387  
3388  
3389  
3390  
3391  
3392  
3393  
3394  
3395  
3396  
3397  
3398  
3399  
3400  
3401  
3402  
3403

*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. RP 7-87 Radiation-susceptibility of somatic cells in radiation carcinogenesis*

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.

3404 **C. Immunology**

3405  
3406  
3407  
3408  
3409  
3410  
3411  
3412  
3413  
3414  
3415  
3416  
3417  
3418  
3419  
3420  
3421  
3422  
3423  
3424  
3425  
3426  
3427  
3428  
3429  
3430  
3431  
3432  
3433  
3434  
3435  
36  
3437  
3438  
3439  
3440  
3441  
3442  
3443  
3444  
3445  
3446  
3447  
3448  
3449  
3450  
3451

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

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. RP 3-87, 1-93 T-cell*

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. RP 3-87, 7-89 B-cell and stem cell*

As previously reported, white-blood cell production including B-lymphopoiesis is

3452 significantly increased with radiation dose, especially in female survivors. We have  
3453 also observed a dose-dependent increase in hematopoietic stem cell functions in  
3454 female A-bomb survivors. Based on these findings, we should focus on the analysis  
3455 of the molecular mechanism of radiation-associated hyperfunctions of hematopoietic  
3456 stem cells. We will measure some hematopoietic factors such as stem cell growth  
3457 factor and IL-6, both associated with white-blood cell production and B-  
3458 lymphopoiesis. It has been suggested by previous mouse studies that the endocrine  
3459 system such as sex hormones (estrogen) is involved in the control mechanism of  
3460 hematopoiesis. It was proposed that the decreased level of estrogen after menopause  
3461 enhances the production of interleukin 6 and osteoclasts and thereby causes  
3462 osteoporosis in female. Based on these findings, we will compare the onsets of  
3463 menopause and these hematopoietic growth factors for about 500 female survivors.  
3464 This will take about 2 years. This study will be in collaboration with the  
3465 Department of Clinical Studies.

3466  
3467 *A-3. RP 2-90 Blood cell preservation*

3468  
3469 To ensure that appropriate materials will be available for future studies of the late  
3470 effects of exposure to A-bomb radiation, and to allow the exploitation of potential  
3471 future technological advances and scientific discoveries, we are cryopreserving live  
3472 blood cells from AHS participants in Hiroshima and Nagasaki. From 1990 to 1996,  
3473 (3 AHS cycles), lymphocytes and granulocytes from 4,420 Hiroshima and 3,766  
3474 Nagasaki survivors were cryopreserved. We will continue this effort to complete  
3475 all AHS participants. In the near future, retrospective study of immunological  
3476 functions using these cryopreserved materials will be possible for the survivors who  
3477 eventually develop cancer or other disease.

3478  
3479 **Special research activities (Immunology)**

3480  
3481 **Priority 1**

3482  
3483 *B. RP 3-87, 7-89, 1-93 Clonal expansion*

3484  
3485 *B-1. Mutant stem cells*

3486  
3487 After the atomic bombing, the number of hematopoietic stem cells decreased by cell  
3488 killing and bone marrow death occurred in many survivors. Several months after  
3489 the bombing the number of these cells should have returned to the normal level.  
3490 Clonal expansion of stem cells should have been involved in this recovery process  
3491 in many survivors. We will focus our efforts on clonal expansion of hematopoietic  
3492 stem cells carrying mutations and chromosome aberrations. So far two such cases  
3493 have been documented by mutation and cytogenetic markers; further study is needed  
3494 to illustrate that clonal expansion occurs as a result of A-bomb exposure. We will  
3495 survey such cases using somatic mutations in blood cells (T-cells and granulocytes)  
3496 as a marker. Stem cell expansion will also be analyzed at the molecular level for  
3497 CD34<sup>+</sup> cells isolated from survivors' peripheral blood by a cell sorter. This work will  
3498 be in collaboration with the Cytogenetics Laboratory.

3500  
3501  
3502  
3503  
3504  
3505  
3506  
3507  
3508  
3509  
3510  
3511  
3512  
3513  
3514  
3515  
3516  
3517  
3518  
3519  
3520  
3521  
3522  
3523  
3524  
3525  
3526  
3527  
3528  
3529  
3530  
3531  
3532  
3533  
3534  
3535  
3536  
3537  
3538  
3539  
3540  
3541  
3542  
3543  
3544  
3545  
3546  
3547

*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

3548  
3549  
3550  
3551  
3552  
3553  
3554  
3555  
3556  
3557  
3558  
3559  
3560  
3561  
3562  
3563  
3564  
3565  
3566  
3567  
3568  
3569  
3570  
3571  
3572  
3573  
3574  
3575  
3576  
3577  
3578  
3579  
3580  
3581  
3582  
3583  
3584  
3585  
3586  
3587  
3588  
3589  
3590  
3591  
3592  
3593  
3594  
3595

*D. RP 7-88 Somatic mutations*

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. RP 7-88 Follow up study*

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. It can be expected that 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.

3596 Differential display is a potentially powerful technique that may reveal differences in  
 3597 transcription of various genes between tumor and normal cells. The tumor and normal parts of  
 3598 archival tissue sections can be separated and compared for changes that may have occurred in  
 3599 cancer related genes as a result of A-bomb exposure. A similar comparison technique is  
 3600 comparative genomic hybridization (CGH) which can scan the entire genome for possible  
 3601 changes, such as relatively large ( $10^7$  bp) deletions, in cancer DNA versus normal DNA.  
 3602

3603 The introduction of new technologies is also important as new problems arise. After  
 3604 arrival of the new confocal microscope system, we will be able to study various new facets of  
 3605 radiation effects on cellular function and cellular structure. New studies that can be initiated are  
 3606 alterations of signal transduction in radiation induced tumors or molecular analysis of a single  
 3607 or a few cells from surgical and paraffin embedded archival tissues of the survivors. Such  
 3608 abilities will help to increase sensitivity and resolution for detection of changes in tissue samples.  
 3609

3610 Finally, it should be noted that most of the studies in the Department of Radiobiology  
 3611 cannot be performed without collaboration with the Departments of Clinical Studies, Genetics,  
 3612 Epidemiology, and Statistics. In view of RERF's limited resources it is important for us to  
 3613 develop a general research plan that defines specific projects that can be done at RERF and  
 3614 projects on which collaboration is important and establishes mechanisms for seeking this  
 3615 collaboration and, where necessary, support.  
 3616

3617 **Project time lines**

|                                       | 1997 | 1998 | 1999 | 2000 | 2001 |
|---------------------------------------|------|------|------|------|------|
| 3620 a) Genetic background            | ⇒    | ⇒    | ⇒    | ⇒    | ⇒    |
| 3621 b) Non-cancer diseases           |      |      | ⇒    | ⇒    | ⇒    |
| 3622 c) Human carcinogenesis          | ⇒    | ⇒    | ⇒    | ⇒    | ⇒    |
| 3623 d) Susceptibility to radiation   | ⇒    | ⇒    | ⇒    | ⇒    | ⇒    |
| 3624 e) Clonal expansion              | ⇒    | ⇒    | ⇒    |      |      |
| 3625 f) Viral immunity                | ⇒    | ⇒    | ⇒    | ⇒    |      |
| 3626 g) Somatic mutations             | ⇒    | ⇒    | ⇒    | ⇒    | ⇒    |
| 3627 h) Immunity to oncogene products |      | ⇒    | ⇒    | ⇒    | ⇒    |
| 3628 i) Somatic mutation in-utero     | ⇒    | ⇒    | ⇒    | ⇒    |      |

3629  
 3630 **Personnel requirements**

3631  
 3632 The present staff is barely adequate to conduct the studies in radiobiology outlined above.  
 3633 In order to perform the studies, the following are needed;

- 3634 1. a permanent researcher who can conduct molecular and pathological analysis of cancer  
 3635 is essential for molecular epidemiology because identification of tumors is the *sine qua*  
 3636 *non* of the study.
- 3637 2. allocation of the proper support staff to the molecular epidemiology program for tissue  
 3638 collection.  
 3639

| Fiscal Year              | Present | 1997 | 1998 | 1999 | 2000 | 2001 |
|--------------------------|---------|------|------|------|------|------|
| 3641 Research Associates |         |      |      |      |      |      |
| 3642 Immunology          | 5       | 5    | 4    | 4    | 4    | 4    |

|      |                        |    |    |    |    |    |    |
|------|------------------------|----|----|----|----|----|----|
| 3644 | Molecular epidemiology | 5  | 6  | 7  | 7  | 8  | 8  |
| 3645 | and oncology           |    |    |    |    |    |    |
| 3646 |                        |    |    |    |    |    |    |
| 3647 | Technicians            |    |    |    |    |    |    |
| 3648 | Immunology             | 10 | 7  | 7  | 5  | 5  | 5  |
| 3649 | Molecular epidemiology | 3  | 7  | 8  | 10 | 10 | 10 |
| 3650 | and oncology           |    |    |    |    |    |    |
| 3651 |                        |    |    |    |    |    |    |
| 3652 | Technician helpers     | 2  | 2  | 2  | 2  | 1  | 1  |
| 3653 |                        |    |    |    |    |    |    |
| 3654 | Clerks                 | 5  | 5  | 4  | 4  | 4  | 4  |
| 3655 |                        |    |    |    |    |    |    |
| 3656 | Total                  | 30 | 32 | 32 | 32 | 32 | 32 |

**Space requirements (m<sup>2</sup>)**

| Fiscal Year | (1996)                 | 1997 | 1998 | 1999 | 2000 | 2001 |
|-------------|------------------------|------|------|------|------|------|
| 3660        | Bench Research         |      |      |      |      |      |
| 3661        | Immunology             | 292  | 292  | 292  | 292  | 292  |
| 3662        | Molecular epidemiology | 91   | 200  | 200  | 200  | 200  |
| 3663        | and oncology           |      |      |      |      |      |
| 3664        | Support Space and      | 97   | 157  | 157  | 157  | 157  |
| 3665        | Offices                |      |      |      |      |      |
| 3666        |                        |      |      |      |      |      |

Room G105 (temporarily used by the department of radiobiology; 53m<sup>2</sup>) 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**

3694 The core research and analysis activities carried out by the Department of Statistics focus  
3695 largely on the need for continued analysis and improved presentation of the RERF  
3696 epidemiological, clinical, and laboratory data. In addition to direct collaborations with other  
3697 RERF researchers, RERF statisticians are actively involved in research that leads to the  
3698 development and implementation of statistical methods applicable to the RERF data.  
3699

3700 Preparation of the RERF reports on the epidemiologic follow-up of the survivors and  
3701 their children require significant contributions from both the Departments of Epidemiology and  
3702 Statistics. As a consequence of the need for more sophisticated statistical analyses and a shortage  
3703 of epidemiologists, statisticians have taken increasingly central roles in work on LSS reports and  
3704 other epidemiological studies at RERF. Because of staff reductions in the Department of  
3705 Statistics we have had to devote an increased proportion of our resources to the epidemiological  
3706 studies, which has made it increasingly difficult for us to address the statistical needs of RERF's  
3707 clinical and laboratory programs. Over the next few years it will be necessary to maintain (or  
3708 even slightly increase) our current level of support for the epidemiologic studies, but it is  
3709 especially important for us to provide a greater level of support for the statistical needs of  
3710 RERF's clinical and laboratory research programs.  
3711

3712 It should be stressed that the work of the department is largely determined by the nature  
3713 of statistical issues that arise in the course of RERF research. Thus, other than stating that RERF  
3714 research will continue to be a source of interesting and challenging statistical problems it is  
3715 difficult to make specific predictions about future statistical research at RERF.  
3716

3717 Priority 1

3718  
3719 A-1 *Assessment of mortality and cancer morbidity for the LSS, in-utero, and F<sub>1</sub> cohorts*  
3720

3721 A significant portion of the work of RERF statisticians is concerned with ongoing  
3722 analyses of the LSS follow-up data. This work is carried out in close collaboration with  
3723 members of the Departments of Epidemiology. Over the next year we plan to complete  
3724 the final part of LSS Report 12 dealing with noncancer mortality for the period from  
3725 1950 through 1990. Within the next three years we intend to produce general summary  
3726 reports extending mortality data through 1995 and tumor registry-based cancer  
3727 incidence data through at least 1992. In preparing these updated reports we hope to  
3728 develop methods for merging the mortality and incidence reports. Members of the in-  
3729 utero and F<sub>1</sub> cohorts are now reaching ages at which mortality and cancer incidence  
3730 rates increase markedly. A series of reports on mortality and cancer morbidity among  
3731 the in-utero exposed will be completed in the coming year. Work on similar reports for  
3732 the F<sub>1</sub> cohort is underway. It is likely that the in-utero findings will be updated during  
3733 the coming five years since the number of deaths and cancer cases can be expected to  
3734 increase rapidly with the lengthening follow-up.  
3735

3736 RERF statisticians are also taking a leading role in the analysis and preparation of the  
3737 reports on cancer risks based on the results of detailed site-specific pathology reviews,  
3738 including those of the central nervous system (CNS tumors), liver cancer, and thyroid  
3739 cancer. An important part of the department's work on these studies concerns the  
3740 development of standards for the management of data arising from these site-specific  
3741 studies in order to ensure that the findings are reflected in the tumor registry and are

3742 available for use in future analyses.

3743  
3744 While RERF statisticians, together with members of the Departments of Epidemiology,  
3745 plan, carry out and report the results of the analyses of these data, the statisticians' most  
3746 important contributions concern the development and application of analytical methods  
3747 and software needed to analyze and summarize these data and the development of  
3748 procedures to address specific problems which arise in the course of work with the  
3749 RERF data. These problems include: the development of a general class of statistical  
3750 models that can be used for the description of and inference about patterns in the excess  
3751 relative risks and excess absolute rates associated with radiation exposure; methods for  
3752 the joint analysis of site-specific risk data; the development of procedures to adjust for  
3753 biases in risk estimates caused by random errors in individual dose estimates;  
3754 development of methods to determine the impact of death certificate misclassification  
3755 on cancer and noncancer risk estimates; the development of methods to adjust for the  
3756 impact of migration in analyses of the LSS cancer incidence data; statistical issues  
3757 related to RBE estimation from the LSS data; and the development and application of  
3758 "mechanistic" models for radiation carcinogenesis.

3759  
3760 As noted below, an effort is now underway to incorporate the data obtained from the  
3761 various mail surveys into the RERF research database. As this effort progresses it will  
3762 become possible to make more effective use of these data in analyses of confounding  
3763 and effect modification in RERF's epidemiological studies.

3764  
3765 *A-2 Analysis of Clinical Studies Data*

3766  
3767 The clinical data are an important and underutilized RERF resource. The Department  
3768 of Statistics role in making more effective use of these data includes the application of  
3769 recent developments in the analysis of complex longitudinal data sets to the RERF data  
3770 and the development of more effective ways to store and access these data. While some  
3771 progress on analysis of these data has been made in recent years, there is a need to  
3772 devote more of the departmental resources to the issues related to the clinical data. An  
3773 area of particular importance over the next few years concerns studies that integrate the  
3774 epidemiological and clinical data related to the finding of an association between  
3775 radiation exposure and noncancer mortality. These analyses will undoubtedly lead to  
3776 challenging statistical problems.

3777  
3778 *A-3 Analyses of Laboratory Data*

3779  
3780 The investigations carried out by the staff of the Departments of Genetics and  
3781 Radiobiology often require statistical collaboration for planning and analysis. At the  
3782 present time statisticians are actively involved in comprehensive final analyses of the  
3783 conventional chromosome aberration data, assessment of the data on various somatic  
3784 mutation assays, and the provision of advice and support for a broad range of fairly  
3785 routine statistical analyses carried out by the researchers in the laboratories. Analyses  
3786 of the laboratory data present a number of challenging statistical problems including  
3787 issues related to over-dispersion (due to dosimetry error or unmeasured covariates) and  
3788 correlated data. Over the next few years there will be a need for significant additional  
3789 statistical support for the analyses of the 2-DE DNA study data (pattern recognition),

3790 for the planning and analysis of molecular epidemiological studies, and for work on the  
3791 comparison of various potential biodosimeters.

#### 3792 3793 *A-4 Database development*

3794  
3795 The Department of Statistics has taken a leading role in the design and documentation  
3796 of the new RERF research database. While the ITD is responsible for the actual  
3797 implementation of the database, much of the design work involves issues of direct  
3798 concern to the Department of Statistics. These issues include clarification of study  
3799 population definitions, specification of contents of and relationships between individual  
3800 database tables, and the identification of appropriate data sources, and, in some cases,  
3801 the development of new coding schemes for specific items. At the present time the  
3802 RERF research database includes most of the epidemiological follow-up data and basic  
3803 dosimetry data for the major cohorts. Current efforts are focused primarily on the  
3804 integration of the mail survey, clinical follow-up data, laboratory data and detailed  
3805 dosimetric data (including shielding history and acute effects data), into the RERF  
3806 research database.

#### 3807 3808 *A-5 Dosimetry*

3809  
3810 The Department of Statistics is responsible for management of the basic dosimetry data  
3811 and for the computation of dose estimates for individual survivors. Current work  
3812 includes the development of an expanded roster of persons whose exposure status is of  
3813 interest to RERF (in addition to LSS cohort members, this roster includes mothers of  
3814 in-utero cohort members and parents of F<sub>1</sub> cohort members) and the restructuring of the  
3815 shielding history and acute effects data. As a part of this effort we are also working on  
3816 an updated description of cohort definitions and dose estimation procedures. In the  
3817 decade since the introduction of DS86 a number of questions have been raised about  
3818 certain aspects of current survivor dose estimates (including errors in Hiroshima  
3819 neutron estimates, problems with gamma doses levels in both cities, and possible biases  
3820 in estimated doses for Nagasaki factory workers). RERF has been asked to develop and  
3821 maintain a database related to physical measurements as a part of the ongoing  
3822 reassessment of DS86. It now appears likely that this reassessment will lead to the  
3823 introduction of a new dosimetry system within the next five years. Even though current  
3824 efforts to reorganize RERF's basic dosimetric data will make it easier to implement a  
3825 new dosimetry system, the introduction of the new system will still require significant  
3826 effort on the part of staff from the Department of Statistics and the ITD. (Work on  
3827 dosimetry is covered by RP 18-59, *Shielding Survey and Dosimetry Study*.)

### 3828 3829 **B. Special research activities**

3830  
3831 Most of the work of the Department of Statistics arises from projects undertaken in  
3832 relationship to our core activities which revolve around collaborations with researchers from  
3833 other departments. At this time there are only five time-limited special research projects and one  
3834 outside contract for which the department has primary responsibility. While the department will  
3835 continue to deal with new statistical problems that arise in the course of work related to our core  
3836 activities, there is little likelihood that department members will initiate new research protocol-  
3837 based projects in the coming years.

3838 Priority 2

3839  
3840 B-1 *Blood groups in Adult Health Study and in-utero ATB subjects, Hiroshima and*  
3841 *Nagasaki (RP 63-63, Izumi S, Ohara J, Preston DL, Hamilton HB).*

3842  
3843 The study is intended to examine blood group frequencies in the LSS and to investigate  
3844 the relationship between serological type and mortality or morbidity for selected  
3845 diseases. Following a long period of inactivity, a manuscript describing blood group  
3846 frequencies for members of the AHS and F<sub>1</sub> cohorts has been prepared. Over the next  
3847 two years we hope to work with members of the Departments of Clinical Studies to  
3848 plan and conduct analyses of the relationship between blood group and cause-specific  
3849 mortality.

3850  
3851 B-2 *Cancer studies of occupational and environmental radiation exposure in the*  
3852 *Mayak Nuclear Facility and the surrounding areas in the South Urals, Russia (NIH*  
3853 *Contract N01-CP-51025, Principal Investigators: Preston DL, Mabuchi K,*  
3854 *Koshurnkova NA, Kossenko MM).*

3855  
3856 When the extent of radioactive contamination at the Mayak Nuclear Facility and the  
3857 surrounding area became clear, the Foundation was approached to assist in the design  
3858 and implementation of studies to determine the health consequences of exposure to this  
3859 contamination. This contract supports joint work with the US National Cancer Institute  
3860 and scientists at the Branch Laboratory 1 (Ozersk) and the Urals Research Center for  
3861 Radiation Medicine (Chelyabinsk) in the Russian Federation on improvements to the  
3862 epidemiological follow-up data risk estimation procedures for the Russian studies. It  
3863 is hoped that by the end of this three year contract in September 1998 we will be able  
3864 to complete some solid cancer and leukemia risk assessments for the Mayak worker and  
3865 Techa River populations. During the first year of the contract, significant progress has  
3866 been made on improvements in the quality of the follow-up data for these cohorts. A  
3867 paper describing the nature of the Techa River cohort just prior to the beginning of the  
3868 NCI-RERF collaboration including comparison of the demographics of the LSS and  
3869 Techa River cohorts has been completed.

3870  
3871 Priority 3

3872  
3873 B-3 *Radiation effects on the brain and central nervous system (RP 5-87 and RP 8-89).*

3874  
3875 One of these studies is intended to search for physical evidence of radiation-related  
3876 damage to the brain among in-utero survivors (RP 5-87) based on special examinations  
3877 of a small number of in-utero survivors. The second (RP 8-89) was to make use of  
3878 autopsy material to investigate the late effects of A-bomb exposure on aging of the  
3879 CNS and to obtain basic data which would improve understanding of brain changes that  
3880 may have resulted from A-bomb exposure. There has been no significant activity on  
3881 either of these projects for several years. Without the active involvement of physicians,  
3882 pathologists and others responsible for obtaining the cooperation of the in-utero  
3883 survivors for the first study or the specimens required for the second, these studies  
3884 cannot continue. With the retirement of Masanori Otake earlier this year, no one at  
3885 RERF is actively involved in either of these projects. It is unlikely that there will be

3886 any progress on either of these projects in the next five years. In view of the current  
 3887 level of support for these projects and the needs of other projects, it would probably be  
 3888 best to terminate them.  
 3889

3890 **Personnel requirements**

3891  
 3892 The number of research scientist positions has decreased from 10 to 7 as a result of  
 3893 retirements and the general cutbacks that have taken place over the past few years without any  
 3894 decrease in the workload. It is likely that we will lose another statistician within the next few  
 3895 months. These losses have seriously reduced our ability to meet RERF's needs for statistical  
 3896 support in all areas, but particularly with regard to work on the clinical and laboratory data.  
 3897 Recently we have been able to take some steps to deal with the impact of these losses. These  
 3898 steps include recruiting (through NAS) one or two additional statisticians, seeking approval of  
 3899 the Executive Committee to hire an experienced statistician to work part time under contract on  
 3900 problems related to analysis of the AHS data, and contacting statisticians at various Japanese  
 3901 institutions to solicit support (and candidates) for post-doctoral training in the Department of  
 3902 Statistics. Prior efforts to recruit qualified Japanese statisticians have been only modestly  
 3903 productive and as a consequence the Department has had and continues to have a need for a high  
 3904 proportion of non-Japanese statisticians, who tend to turnover frequently. This turnover gives  
 3905 us the flexibility to seek statisticians who can meet current needs, but it also means that we need  
 3906 to have the ability to hire qualified statisticians in anticipation of upcoming losses.  
 3907

3908 In view of the nature of the department's work the table below is designed to reflect  
 3909 personnel needs associated with each of the core activities.  
 3910

| Area                       | Fiscal Year |      |      |      |      |      |
|----------------------------|-------------|------|------|------|------|------|
|                            | Current     | 1997 | 1998 | 1999 | 2000 | 2001 |
| <i>Research Associates</i> |             |      |      |      |      |      |
| 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  |
| <i>Total</i>               | 7           | 9    | 10   | 10   | 10   | 10   |
| <i>Research Assistants</i> |             |      |      |      |      |      |
| 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 |
| <i>Total</i>               | 3           | 3    | 3    | 3    | 3    | 3    |
| Clerical                   | 2           | 2    | 2    | 2    | 2    | 2    |

3931 **Space requirements (m<sup>2</sup>)**

3932  
 3933 The space requirements for the Department of Statistics are summarized in the following  
 3934 table. The totals do not include hallways.  
 3935

| Area             | Fiscal Year      |            |            |            |            |            |
|------------------|------------------|------------|------------|------------|------------|------------|
|                  | Current          | 1997       | 1998       | 1999       | 2000       | 2001       |
| Office           | 125 <sup>†</sup> | 142        | 142        | 142        | 142        | 142        |
| Clerical Support | 18               | 18         | 18         | 18         | 18         | 18         |
| Other Support ‡  | 57               | 40         | 40         | 40         | 40         | 40         |
| <i>Total</i>     | <i>200</i>       | <i>200</i> | <i>200</i> | <i>200</i> | <i>200</i> | <i>200</i> |

† 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 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 regular basis. It should be noted that, as in recent years, Department of Statistics computers that are replaced can usually be used by other departments for additional years. The following table presents estimates of the total costs for computer equipment for the Department for the next five years.

| Budget Category                   | Fiscal Year  |              |              |              |              |
|-----------------------------------|--------------|--------------|--------------|--------------|--------------|
|                                   | 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        |
| <i>Total</i>                      | <i>5,075</i> | <i>5,275</i> | <i>5,410</i> | <i>5,590</i> | <i>5,675</i> |

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.

| Budget Category                   | Fiscal Year  |              |              |              |              |
|-----------------------------------|--------------|--------------|--------------|--------------|--------------|
|                                   | 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        |
| <i>Total</i>                      | <i>3,650</i> | <i>3,700</i> | <i>3,890</i> | <i>3,940</i> | <i>4,080</i> |

## SUPPORTING SERVICES

### Department of Information Technology

#### Program objectives

3980 The Information Technology Department (ITD) provides the necessary computing and  
3981 data tools to all RERF departments to support the Foundation's research and administrative  
3982 activities. Responsibilities are to maintain computer systems and software, manage the RERF  
3983 research database, provide user support, and introduce new technology as appropriate to meet  
3984 evolving needs. Although located in Hiroshima, planning, development, and support work extends  
3985 to the Nagasaki Laboratory, and ITD coordinates activities with the two Nagasaki computer staff  
3986 in the Department of Epidemiology. ITD also is responsible for operation of the library in  
3987 Hiroshima, another information service at RERF. The Hiroshima library provides support to the  
3988 library in Nagasaki as well.

3989  
3990 To ensure that computing resources remain relevant and to play a leading role in  
3991 ascertaining technology and user support needs, a key aspect of ITD activities is to maintain  
3992 effective liaison with all RERF departments. ITD also must seek collaboration to utilize the  
3993 technical skills of staff in other departments and that outside RERF to complement and  
3994 supplement technical capabilities within the department. These are extremely important for making  
3995 effective progress on multidisciplinary projects such as those involving database design, systems  
3996 development, and support of laboratory research projects.

3997  
3998 Because many of the activities undertaken by ITD reflect its technical support role in  
3999 research activities, ITD project content within some of the core activity categories will change as  
4000 research program emphasis evolves and changes. Project content listed below represents known  
4001 major foci within the upcoming five-year period.

#### 4002 **A. Core activities**

- 4003 • *Maintain and keep current the RERF computing environment*

4004  
4005  
4006  
4007 ITD is responsible for the management and maintenance of all personal computers, Unix  
4008 workstations, disk and tape data storage, printers, scanners, and other peripheral equipment.  
4009 Network design and support responsibilities include the TCP/IP Ethernet network that links  
4010 all computing resources within the Hiroshima and Nagasaki laboratories, the communications  
4011 line linking the two laboratories, and the communications line linking RERF to the Internet.  
4012 ITD provides maintenance and support of all operating systems, application software, and  
4013 Internet services for these computer systems. With an increased awareness of the role that  
4014 computers can play in the workplace, demand for resources and support continues to rise in  
4015 all departments as they seek ways to automate work activities and increase staff productivity,  
4016 partially in response to coping with personnel downsizing that has occurred (and continues)  
4017 at the Foundation. It also is anticipated that the research demand for these resources and  
4018 services will continue to increase as new research techniques increasingly rely on interfacing  
4019 computers with laboratory equipment to process data.

4020  
4021 ITD staff play an active role in assessing new technology and its relevance to RERF  
4022 activities. The introduction of new tools to users ensures that the most recent and appropriate  
4023 technologies are available to enable researchers to work competitively in their research fields  
4024 and ensures that the RERF computing environment will remain compatible with future  
4025 computer technology.

4026

4027 The RERF computing system has expanded greatly over the past few years, both within the  
4028 two laboratories and in terms of outside linkage via connection to the Internet and dial-in  
4029 lines to RERF. Because all RERF departments now rely quite heavily on computing  
4030 resources to carry out their work, it is important that efforts be undertaken to review and  
4031 strengthen system security. This includes additional measures to guard against unauthorized  
4032 access to the RERF system by outsiders, to maintain confidentiality both within and outside  
4033 RERF of personal identification data on study participants, and to ensure that appropriate  
4034 disaster prevention/recovery plans and procedures are in place. These are necessary to  
4035 protect the unique repository of data accumulated during the existence of ABCC/RERF,  
4036 minimize system down time, and minimize user productivity loss resulting from damage to  
4037 equipment, software, and data.

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

4040  
4041 As indicated in the Database Development section within The Structure of Research at the  
4042 Foundation, the installed hardware and software that now comprises the RERF distributed  
4043 computing system has resulted in great progress in building a new research database using  
4044 modern relational database technology. This technology has made it much easier for  
4045 researchers to access data, link information from different sources, and extract the desired  
4046 items for analysis. The new system has simplified data flow procedures for much of the  
4047 mortality and incidence data follow-up activities. This, together with the elimination of  
4048 redundant data storage, has contributed to improved data quality. The database system also  
4049 supports direct links with certain analysis software packages, eliminating the need to create  
4050 interim work files for analysis. However, much work remains to ensure that the database will  
4051 serve the wide array of research needs at RERF.

4052  
4053 Of utmost importance over the next several years is continued development of a  
4054 comprehensive picture of study participants by clarifying study populations and incorporating  
4055 more information into the database. As described earlier, more detailed data related to the  
4056 major cohorts, such as clinical data, mail surveys, and dosimetry will be added. Biological  
4057 materials collected over the years are a valuable resource for current and future studies. It  
4058 is important to create a centralized registry of these materials and link it to other study  
4059 participant data so that these samples are efficiently and effectively shared and used by the  
4060 different RERF research programs. It also will be important to address both the volume of  
4061 data and special data management issues that are expected to arise from data generated from  
4062 the Department of Genetics DNA studies. All database work is being undertaken as a joint  
4063 effort of the ITD and the departments responsible for collecting and using the data. These  
4064 efforts involve major input on design issues from the Departments of Statistics and  
4065 Epidemiology.

4066  
4067 Together with developmental activities, it is important to provide information and training  
4068 that will ensure that researchers are aware of the capability of the system and how to use it.  
4069 In addition, researchers must have adequate information about the data in order to use it  
4070 properly. Thus, it also is important to make suitable documentation available on paper and  
4071 on-line to meet that need. Together with the Departments of Statistics and Epidemiology,  
4072 ITD will be working toward that end.

4073

- 4074 • *Develop and maintain application systems*

4075

4076 Application systems are developed, as necessary, to meet specific needs at RERF, but, as

4077 much as possible, they are developed using commercial software packages to minimize time-

4078 and labor-intensive custom programming and maintenance efforts.

4079

4080 ITD has developed and supported the Adult Health Study (AHS) patient tracking and clinical

4081 management system. The hardware and software for this system is over ten years old, and

4082 efforts already are underway to develop a replacement system that will be compatible with

4083 the new network and software used for all other RERF activities.

4084

4085 ITD developed and currently maintains a name matching system used by the Departments of

4086 Epidemiology for its follow-up activities. With this system, individual follow-up information

4087 received from outside sources is matched with RERF database records so that mortality and

4088 incidence data can be updated accordingly.

4089

4090 ITD provides support to Department of Statistics efforts of managing and maintaining

4091 dosimetry-related data and the system used for computation of dose estimates for individual

4092 survivors. Increased support for this activity is anticipated because of the likelihood that

4093 dosimetry reassessment activities will result in implementation of a new dosimetry system.

4094

4095 A significant increase in programming and data management support will be needed for the

4096 Department of Genetics' two-dimensional electrophoresis image analysis of DNA fragments.

4097 This work will involve a joint effort among the Departments of Genetics, and Statistics, and

4098 ITD.

4099

4100 The development of a new business system has enabled most day-to-day business computing

4101 activities to be carried out by staff in the Secretariat. ITD staff continue to play an integral

4102 role in troubleshooting, maintenance, and, as necessary, providing some of the more

4103 complex enhancements that users are not able to implement on their own.

4104

4105 • *Expand training and information outreach for users*

4106

4107 The distributed computing environment has provided users with direct access to many

4108 powerful hardware and software tools. An effective program of training and information

4109 dissemination is essential to enable users to make optimal use of these tools. While important

4110 initial progress has been made, many important subject areas still need to be covered or

4111 further supplemented. Thus, additional emphasis is being placed on organizing additional

4112 training courses and information seminars. Planning, preparation of materials, and actual

4113 instruction must involve those most familiar with software to ensure training and content is

4114 effective and relevant for RERF users. ITD has adopted a multi-departmental approach to

4115 this activity and has received collaborative support of departments who have staff expertise

4116 in pertinent areas. This has been a very effective way to meet educational needs. The user

4117 response to training courses conducted thus far has been overwhelming. Training could be

4118 conducted more efficiently and timely if room space and equipment could be expanded to

4119 better accommodate participant demand.

4120

4121 ITD also disseminates information to users outside a class or seminar setting. With the recent  
4122 elimination of RERF's in-house publishing capabilities, ITD uses email and plans to expand  
4123 its use of the Intranet as a means to providing a greater amount of reference information and  
4124 announcements in a timely manner.

- 4126 • *Support expansion of RERF information dissemination to outside communities*

4127  
4128 ITD is providing technical support to the Publication and Documentation Center in its use  
4129 of the Internet World Wide Web to widen accessibility and visibility of RERF's research  
4130 activities to the outside. The RERF Web pages recently were reorganized and expanded, and  
4131 information on those pages addresses issues of interest to both the scientific community and  
4132 the general public. To widen accessibility and to provide a faster and less expensive method  
4133 of distribution, ITD is working on enhancements that will allow Web users to download  
4134 RERF public data and documentation files already available on floppy disk, such as those  
4135 used in analyses conducted for Life Span Study Report 12.

- 4136  
4137 • *Maintain the RERF library and archive*

4138  
4139 Much of the institutional memory regarding ABCC and RERF has been and continues to be  
4140 lost due to the many retirements occurring. Although efforts to establish a centralized archive  
4141 have been initiated by various groups in the past, currently there exists no institutional  
4142 archive documenting historical decisions, procedures, and materials that bear significance to  
4143 the unique activities of the institution and that provide important background perspectives  
4144 to current research efforts. If RERF is to retain its history, it is important to renew efforts  
4145 in establishing the archive. The first step would require that RERF obtain outside expertise  
4146 to obtain guidance in the planning, database cataloging, and management of archives for  
4147 research institutions. As information services, the library and archive activities ideally should  
4148 be coordinated and integrated with each other.

4149  
4150 Due to staff losses, it has become difficult for the library to keep pace with the work needed  
4151 to provide journals and books to researchers in a timely fashion. Together with the need to  
4152 investigate and introduce new services that will give researchers wider access to research  
4153 information, this provides a strong basis for reassessing library activities. The aim should be  
4154 to identify the services that researchers find essential to their work and to determine how the  
4155 library can provide those services effectively. With this information, the Foundation can  
4156 ascertain what the appropriate resources are in terms of equipment, services, and personnel  
4157 to meet those needs. This process should include streamlining and modernizing in-house  
4158 library activities and establishing additional links to outside services for more effective and  
4159 efficient operation. It will be extremely important to supplement or replace current on-line  
4160 services with those that provide continuous update of publication and other research  
4161 reference materials. It would be helpful to seek outside expertise in recent library technology  
4162 to guide the efforts of library staff. Collaborative support from ITD computing staff will be  
4163 needed for library and archive efforts.

#### 4164 4165 **Personnel requirements**

4166  
4167 Approximately over the last two years, ITD has lost a total of 5 computer

4168 professional/technical staff. This represents a 40% and 60% loss, respectively, among the two  
 4169 fastest growing areas of demand, database management and systems administration. During this  
 4170 period, ITD workload has increased dramatically. With the transition from a mainframe to a  
 4171 distributed computing environment, computing resources have become an integral part of the  
 4172 Foundation infrastructure upon which research, support, and business activities depend. The  
 4173 amount of equipment and software that must be maintained and the demand for support and  
 4174 services continues to grow out of the need to remain competitive on the research front and to  
 4175 automate activities to cope with personnel downsizing occurring throughout the Foundation. The  
 4176 introduction of modern database technology has renewed efforts by both computer and scientific  
 4177 staff to re-examine and reorganize data, and to expand and document the new research database  
 4178 to increase accessibility and usability of data, much of which has never been fully utilized. All  
 4179 these efforts to support research have been hindered because of staff shortages. In other cases,  
 4180 such as providing support for 2-DE image analysis, ITD currently has no personnel resources to  
 4181 undertake application development requirements. Without further action, the situation will worsen  
 4182 rapidly, and many of the core activity needs will go unmet. The department chief will depart at  
 4183 the beginning of 1997, and another two staff will leave within the coming 12 months. Anticipated  
 4184 attrition by 1999 without replacements will leave only one-third the original computing staff from  
 4185 two years ago.

4187 To deal with the situation, recruitment is underway through NAS for a department chief  
 4188 and systems administrators. To seek additional sources of personnel and expertise, initial steps  
 4189 have been taken to explore the possibility of collaborative and post-graduate research/training  
 4190 relationships with regional Japanese universities. Additional recruitment of experienced database  
 4191 management personnel and qualified Japanese computer technical staff is essential.

4193 Although reassessment of the library has not yet been undertaken, it is evident that  
 4194 establishment of the archive and proper operation and maintenance of the library will require one  
 4195 additional staff for the combined library/archive. During full-scale development and cataloging  
 4196 phases for the archive, additional staff will be required, most likely on a temporary basis (either  
 4197 on concurrent assignment from other departments or hired on contract).

| Area                    | Fiscal Year |           |           |           |           |           |
|-------------------------|-------------|-----------|-----------|-----------|-----------|-----------|
|                         | 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         |
| <b>Total</b>            | <b>18</b>   | <b>21</b> | <b>23</b> | <b>24</b> | <b>24</b> | <b>24</b> |

**Space requirements (m<sup>2</sup>)**

4210 Estimates reflect office space needed for new staff and space for the assortment of  
 4211 computers and peripheral equipment that staff must have in their immediate work area for

4212 development, testing, and troubleshooting activities. A small increase in support space is needed  
 4213 to guarantee that all computer servers are installed in a temperature-controlled, restricted access  
 4214 area for security purposes, and to permit use of a projection panel in the training room to provide  
 4215 effective instruction on methods and procedures. Initial archives work most likely can be  
 4216 accommodated in the existing library space. The increase indicated in future years assumes that  
 4217 methods and resources can be introduced that would enable the library to reorganize and  
 4218 economize how it uses its current space, so that once the archive is in the full implementation  
 4219 phase, additional space required to house those materials is minimized.  
 4220

| 4221 | Area                       | Fiscal Year |            |            |            |            |            |
|------|----------------------------|-------------|------------|------------|------------|------------|------------|
|      |                            | Current     | 1997       | 1998       | 1999       | 2000       | 2001       |
| 4222 | Office                     | 180         | 228        | 228        | 228        | 228        | 228        |
| 4223 | Clerical Administrative    | 31          | 31         | 31         | 31         | 31         | 31         |
| 4224 | Library/Archives           | 337         | 337        | 337        | 357        | 357        | 357        |
| 4225 | Other Support <sup>1</sup> | 166         | 183        | 183        | 183        | 183        | 183        |
| 4226 | <b>Total</b>               | <b>714</b>  | <b>779</b> | <b>779</b> | <b>799</b> | <b>799</b> | <b>799</b> |

4227 <sup>1</sup> includes server, user training, diagnostic workbench, and conference rooms  
 4228  
 4229  
 4230

4231 **Equipment budget (x ¥ 1,000)**  
 4232

4233 In the table below, computer hardware and software used by ITD staff to carry out development  
 4234 and support work are distinguished from resources used to provide RERF-wide services to users.  
 4235 In order to perform development, testing, and technical support, it is necessary for ITD to have  
 4236 within the department a variety of equipment and software used in other departments. Estimates  
 4237 are based on a three year schedule for replacement of computers. A faster turnaround is built in  
 4238 for systems administrators, who must troubleshoot problems on new systems installed in other  
 4239 departments. Functional equipment rotated out of service will be used to help keep the training  
 4240 room current, moved to meet needs in other departments, and serve as emergency replacements  
 4241 to minimize down time on critical work activities. Also accounted for is the ongoing need to  
 4242 expand network storage capacity. In the area of RERF-wide services and resources, the regular  
 4243 upgrading and replacement of hardware and software are an essential aspect of maintaining a  
 4244 modern computer environment, ensuring that it keeps pace with future technology developments  
 4245 and provides state-of-the-art tools for research.

| 4246 | Budget category           | Fiscal Year |             |              |              |              |
|------|---------------------------|-------------|-------------|--------------|--------------|--------------|
|      |                           | 1997        | 1998        | 1999         | 2000         | 2001         |
| 4247 | <i>ITD staff</i>          |             |             |              |              |              |
| 4248 | Replacement hardware      | 7800        | 8520        | 9095         | 9095         | 9550         |
| 4249 | and software              |             |             |              |              |              |
| 4250 | New hardware and          | 1100        | 900         | 1155         | 945          | 1210         |
| 4251 | software                  |             |             |              |              |              |
| 4252 | <i>ITD staff total</i>    | <i>8900</i> | <i>9420</i> | <i>10250</i> | <i>10040</i> | <i>10760</i> |
| 4253 | <i>RERF-wide services</i> |             |             |              |              |              |
| 4254 |                           |             |             |              |              |              |

|      |   |        |        |        |        |        |
|------|---|--------|--------|--------|--------|--------|
| 4255 | Computer and networking   | 36000  | 36000  | 37800  | 37800  | 39700  |
| 4256 | hardware/software   |        |        |        |        |        |
| 4257 | replacement   |        |        |        |        |        |
| 4258 | -----<br>Grand Total  | 44,900 | 45,420 | 48,050 | 47,840 | 50,460 |
| 4259 | + Support fees that cover Unix workstation hardware maintenance contracts,                |        |        |        |        |        |
| 4260 | annual software license fees, and network line lease fees are included in the Secretariat |        |        |        |        |        |
| 4261 | operations budget.  |        |        |        |        |        |

4262  
4263 **Publication and Documentation Center**

4264  
4265           Dissemination of the findings of the Foundation's research to the scientific and lay  
4266 communities, nationally and internationally, is centered in the Publication and Documentation  
4267 Center. Broadly stated, the duties of the Center are the following: editing, production,  
4268 preservation and management of publications; translation and interpretation services.

4269  
4270 **Specific roles**

- 4271  
4272       a). Preparation of technical reports on the results of RERF research and studies, and  
4273 distribution of them to interested organizations as well as to researchers worldwide.  
4274  
4275       b). Administrative procedures for the review of research manuscripts up to publication  
4276 thereof in journals; administrative support for research scientists by documentation  
4277 of research results and by preserving and making available to them research  
4278 protocols, abstracts for scientific meeting presentation, and reprints.  
4279  
4280       c). Publication of English and Japanese Newsletters, annual reports, and bibliographies  
4281 of publications; management of RERF's World Wide Web site.  
4282  
4283       d). Proofreading and editing of English manuscripts; translation and interpreting  
4284 services requested by departments; preparation of figures, diagrams, and slides  
4285 using computers; photographic activities  
4286

4287  
4288 **Organization**

4289 **Personnel strength at PDC for the past six years and projection of changes**

|                | Fiscal Years |      |      |      |      |      |
|----------------|--------------|------|------|------|------|------|
|                | 1990         | 1991 | 1992 | 1993 | 1994 | 1995 |
| 4293 Research  | 1            | 2    | 4    | 2    | 2    | 1    |
| 4294 Clerical  | 30           | 25   | 26   | 28   | 27   | 25   |
| 4295 Technical | 1            | 0    | 0    | 0    | 0    | 0    |

4296  
4297           PDC's operational requirements cannot be fulfilled if replacements for retiring  
4298 employees are not employed. Continued operation at current level requires at least maintenance  
4299 of the current personnel strength.

4300  
4301 **Radioisotope Facility**

4302  
4303           The duties of the RI Facility are 1) management of the facility in accordance with

4304 Japanese laws, 2) maintenance of a safe working environment, and 3) summarization and  
4305 realization of requests from facility users. It should be noted that until recently the Foundation  
4306 maintained two radioisotope facilities, one in Hiroshima and one in Nagasaki. With the closure  
4307 of the radiobiology program in Nagasaki, the facility there was no longer needed and was placed  
4308 on inactive status. It has not, however, been formally closed. Whether it should be closed or  
4309 merely maintained in an inactive status hinges on two considerations, namely, future use and  
4310 cost. If this facility should be needed in the future for RERF research purposes, it would be  
4311 cheaper in the long run to continue to maintain it. At present, the annual maintenance costs are  
4312 between ¥ 700,000-800,000 but this will diminish in the future. If the facility is formally closed,  
4313 the space and equipment must be decontaminated in accordance with Japanese regulations. This  
4314 has been estimated to cost ¥ 8,000,000. Formal closure would, of course, free the space for other  
4315 uses, and this is an important consideration given the size of the Nagasaki Laboratory. As yet  
4316 no decision has been made about the fate of this facility.

4317  
4318 The remarks to follow pertain only to the Hiroshima facility.  
4319

4320 **Management of the RI facility**

4321  
4322 The RI Facility is being operated in accordance with various national laws. Detailed  
4323 record-keeping on many aspects of the RI facility operation (e.g., measurements on air dose rate,  
4324 concentration of RI in drainage, and the radiation dose to which the user is exposed) is mandated  
4325 by law for safe operation of the facility. It is obligatory to submit summary reports of these data  
4326 to the Science and Technology Agency. Preparation of these documents has been completely  
4327 computerized. However, the equipment being used to record and manage these data has  
4328 exceeded its service life and should be replaced.

4329  
4330 **Maintenance of a safe working environment**

4331  
4332 The RI facility supports the activities of the Departments of Clinical Studies, Genetics,  
4333 and Radiobiology. At present, 31 users are sharing a laboratory space of 75 m<sup>2</sup>. Space per user  
4334 at our laboratory is less than that at laboratories of other institutions. Furthermore, the  
4335 equipment being used in our laboratory, such as the 2D-DNA electrophoretic apparatus, is larger  
4336 than usual and occupies more space. In addition, studies being conducted at RERF are mainly  
4337 conducted on a large scale, and many samples are simultaneously examined. Therefore, lots of  
4338 different pieces of equipment are used simultaneously. It is dangerous to perform many  
4339 experiments in such a small place. Expansion of the facility has been requested, but no action  
4340 has been taken due to a shortage of funds.

4341  
4342 **Future of RI facility**

4343  
4344 The RI facility will be used for many aspects of the molecular studies newly proposed  
4345 by the Blue Ribbon Panel. With future technical developments, it is likely that some of these  
4346 studies will depend less on the RI facility than at present (e.g., DNA sequencing, Southern  
4347 method, etc.). However, it can be easily imagined that more experiments will be performed at  
4348 the RI facility, offsetting the number of experiments that will cease due to using the above-  
4349 mentioned new techniques. Expansion of laboratory space is essential.

4350  
4351 Replacement of equipment is also needed. The current automatic developing machine  
4352 for X-ray film and the  $\gamma$ -well counter may break down at any time. Repair is impossible because  
4353 no spare parts are available for these old models. One possible option to replacement purchase

4354 is to relocate the  $\gamma$ -well counter from the Nagasaki Laboratory to Hiroshima. If this is feasible,  
 4355 measuring contamination on the surface of the equipment and transportation of the equipment  
 4356 to Hiroshima are the only two expenses that must be borne.  
 4357

4358 Renovation of the facility is necessary to satisfy the need to change the type and amount  
 4359 of radioisotopes being used. Installation of a larger drainage tank is especially necessary.  
 4360

4361 **Personnel requirements**

| 4363 Fiscal Year         | 1996             | 1997 | 1998 | 1999 | 2000 | 2001 |
|--------------------------|------------------|------|------|------|------|------|
| 4364 Research Scientists | 0.1 <sup>1</sup> | 0.1  | 0.1  | 0.1  | 0.1  | 0.1  |
| 4365 Technicians         | 0.7 <sup>2</sup> | 1    | 1    | 1    | 1    | 1    |

4366  
 4367 <sup>1</sup> One scientist is concurrently assigned to the Department of Genetics (90%) and the RI Facility (10%).  
 4368 <sup>2</sup> One technician is concurrently assigned in the RI Facility (70%) and the Department of Clinical Studies  
 4369 (30%).  
 4370

4371 **Space requirements (m<sup>2</sup>)**

| 4373 Fiscal Year                   | 1996 | 1997 | 1998 | 1999 | 2000 | 2001 |
|------------------------------------|------|------|------|------|------|------|
| 4374 Bench Research                | 75   | 120* | 120  | 120  | 120  | 120  |
| 4375 Support Space                 |      |      |      |      |      |      |
| 4376 Darkroom                      | 12.5 | 12.5 | 12.5 | 12.5 | 12.5 | 12.5 |
| 4377 Contamination inspection room | 7.7  | 7.7  | 7.7  | 7.7  | 7.7  | 7.7  |
| 4378 RI depository                 | 5.5  | 5.5  | 5.5  | 5.5  | 5.5  | 5.5  |
| 4379 Storage disposal room         | 9.1  | 9.1  | 9.1  | 9.1  | 9.1  | 9.1  |
| 4380 Waste disposal room           | 6.8  | 6.8  | 6.8  | 6.8  | 6.8  | 6.8  |
| 4381 Exhaust facility              | 9.9  | 9.9  | 9.9  | 9.9  | 9.9  | 9.9  |
| 4382 Stock room                    | 6.0  | 6.0  | 6.0  | 6.0  | 6.0  | 6.0  |
| 4383 Office                        | 12.5 | 12.5 | 12.5 | 12.5 | 12.5 | 12.5 |
| 4384 Total                         | 145  | 190  | 190  | 190  | 190  | 190  |

4385  
 4386 \*: Space for stairs and corridor is included.  
 4387

4388 **Equipment budget (× ¥ 1,000)**

| 4391 Fiscal Year | 4392 New/<br>Repl | Item                | Q'ty | Unit Cost<br>(×¥1000) | Total<br>(×¥1000) |
|------------------|-------------------|---------------------|------|-----------------------|-------------------|
| 4393 1997        | N                 | PC                  | 1    | 570                   | 570               |
| 4394             | R                 | Printer             | 1    | 220                   | 220               |
| 4395             | R                 | Software version up | 1    | 50                    | 50                |
| 4396             |                   |                     |      |                       |                   |
| 4397 1998        | R                 | PC                  | 1    | 500                   | 500               |
| 4398             |                   |                     |      |                       |                   |
| 4399 1999        | R                 | Software version up | 2    | 50                    | 100               |
| 4400             |                   |                     |      |                       |                   |
| 4401 2001        | R                 | PC                  | 1    | 500                   | 500               |

|      |   |                     |   |     |     |
|------|---|---------------------|---|-----|-----|
| 4402 | R | Printer             | 1 | 220 | 220 |
| 4403 | R | Software version up | 2 | 50  | 100 |

4404

4406

4407

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

4408

4409

**Secretariat**

4410

4411

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).

4412

4413

4414

4415

4416

4417

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

4418

4419

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

4420

4421

4422

[Hiroshima]

4423

Assistant Chiefs and others (3)

4424

Director's Office (5) +2

4425

General Affairs Sec. (18)

General Affairs Unit (7)

4426

4427

4428

Document and Archive Unit (2)

4429

4430

4431

Personnel Sec. (6)

Personnel Unit (3) +1

4432

4433

4434

Payroll Unit (2)

4435

4436

Accounting Sec. (7)

Accounting Unit (3) +1

Secretariat (65)

Receipts & Disbursement Unit (3)

4437

4438

4439

Supply & Property Sec. (14)

Supply Unit (4) +1

4440

4441

4442

Physical Plant Unit (5)

4443

4444

Welfare Unit (4)

4445

4446

4447

[Nagasaki]

Assistant Chief (1)

Public Relations Office (2) +2

4448

4449

General Affairs Sec. (11)

General Affairs Unit (4)

4450

4451

4452

Accounting Sec. (5)

Accounting Unit (2) +1

4453

Supply Unit (2)

**Duties**

4454

**Hiroshima Laboratory**

4455

4456

**1. General Affairs Section**



4503  
 4504  
 4505  
 4506  
 4507  
 4508  
 4509  
 4510  
 4511  
 4512  
 4513  
 4514  
 4515  
 4516  
 4517  
 18  
 4519  
 4520  
 4521  
 4522  
 4523

|                             |           |    |    |    |    |    |    |    |
|-----------------------------|-----------|----|----|----|----|----|----|----|
|                             | Technical | 15 | 18 | 10 | 10 | 10 | 6  | 5  |
|                             | Total     | 29 | 32 | 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     | Clerical  | 13 | 14 | 15 | 14 | 12 | 12 | 10 |
|                             | Technical | 1  | 1  | 1  | 1  | 1  | 1  | 1  |
|                             | Total     | 14 | 15 | 16 | 15 | 13 | 13 | 11 |
| Accounting Section          | Clerical  | 5  | 4  | 5  | 5  | 6  | 6  | 5  |
|                             | Technical | 3  | 3  | 3  | 3  | 1  | 1  | 0  |
|                             | 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 no. | 1996   |      | 1997   |      | 1998   |      | 1999   |      | 2000   |      | 2001   |      | 02 |   |   |    |   |   |    |
|-----------------------------|-------------------------|--------|------|--------|------|--------|------|--------|------|--------|------|--------|------|----|---|---|----|---|---|----|
|                             |                         | Apr. I | Ret. |    |   |   |    |   |   |    |
| 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.        | 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.      | 9                       | 9      |      |        | 9    |        |      | 9      |      |        | 9    |        |      | 9  | 2 |   | 7  | 1 |   | 6  |
| Clerical                    | 5                       | 5      |      |        | 5    |        |      | 5      | 1    |        | 4    |        |      | 4  |   |   | 4  |   |   | 4  |
| Technical                   | 14                      | 14     | 0    | 0      | 14   | 0      | 0    | 14     | 1    | 0      | 13   | 0      | 0    | 13 | 2 | 0 | 11 | 1 | 0 | 10 |
| Total                       | 14                      | 17     | 3    | 0      | 14   | 1      | 0    | 13     | 2    | 0      | 11   | 0      | 0    | 11 | 0 | 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.        | 7                       | 10     | 3    |        | 7    | 1      |      | 6      |      |        | 6    |        |      | 6  |   |   | 6  | 1 |   | 5  |
| Clerical                    | 1                       | 1      |      |        | 1    |        |      | 1      |      |        | 1    |        |      | 1  |   |   | 1  |   |   | 1  |
| Technical                   | 8                       | 11     | 3    | 0      | 8    | 1      | 0    | 7      | 0    | 0      | 7    | 0      | 0    | 7  | 0 | 0 | 7  | 1 | 0 | 6  |
| 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

4548  
 4549 c) Relationship with duties of the Publication and Documentation Center  
 4550  
 4551 Despite the research support aspects of PDC, better results can be expected by removing the  
 4552 division between the duties of the Secretariat and those of PDC. Therefore, in the future, translation  
 4553 which is done at PDC at present and the public relations activities will be put under the charge of  
 4554 the Secretariat together with the Document and Archive Unit and the External Affairs Unit for  
 4555 better utilization of talent. The duties relating to research protocols and technical reports will be  
 4556 placed under the direct charge of the Chief of Research for better coordination of activities. These  
 4557 arrangements should be further discussed. However, they are not considered in the estimation of  
 4558 personnel strength required.

4559  
 4560 Changes in personnel strength

4561  
 4562 1. Actual changes (1990 - 1996)  
 4563

| Personnel no.<br>as of April 1 | Total | Directors | Chief of<br>Secretariat | Research<br>Scientists | General<br>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                  |

4564  
 4565  
 4566  
 4567  
 4568  
 4569  
 4570  
 4571  
 4572  
 4573  
 4574 **MAINTENANCE OF AN ADEQUATE INFRASTRUCTURE**

4575 Three needs are paramount if the Foundation is to fulfill its mission as set out in the  
 4576 preceding pages. First, there must be adequate staff and these individuals must have the appropriate  
 4577 skills to meet an evolving research program. Second, there must be the requisite equipment to  
 4578 support the research activities of that staff. Finally, there must be sufficient, suitable space in which  
 4579 to house the staff and equipment. Given the recent pace of technological developments it is difficult  
 4580 to project these needs over the next five years with the assurance that is desirable. Nonetheless,  
 4581 some projection is obviously necessary and to make that projection assumptions must be made. We  
 4582 now set out the assumptions that underlie the projections to follow.

4583 **Personnel**

4584 First, some further reduction in staff from that presently obtaining is possible. However,  
 4585 this assertion tacitly assumes that the future, through increasing use of computer technology,  
 4586 automated laboratory equipment, and better, faster means of communication, will make some  
 4587 current positions that are labor intensive redundant and others less time-consuming. But, it is our  
 4588 view that this reduction should be an orderly one and not so precipitous as to jeopardize the  
 4589 Foundation's research and capacity to fulfill its charge. Accordingly, we have projected staff needs  
 4590 on the assumption that to maintain a viable staff size it will be necessary to replace two out of every  
 4591 three retirements over the next five years. This will amount to a further reduction in staff of about  
 4592 10% over this period of time; however, the impact of this further loss in personnel must be seen in  
 4593 the context of the 25% reduction that has occurred in the past five years and to which we are still

4594 adjusting.

4595           These replacements will be recruited on the basis of demonstrated need and will not be  
4596 automatically made to the department or unit from which the retiree(s) came. Emphasis will be  
4597 placed upon technical staff, such X-ray technicians, clinical and research laboratory personnel, and  
4598 clinical and public health nurses with due allowance for changing workloads with time. However,  
4599 it is clear that an adequate cadre of support staff is also essential and replacements will be made in  
4600 the Secretariat, the Information Technology Department, and the Publication and Documentation  
4601 Center to ensure this end.

4602           Second, there are staff inequities between Hiroshima and Nagasaki that need to be resolved.  
4603 For example, with the closure of the Radiobiology Department in Nagasaki, all of the technicians  
4604 employed in this laboratory were transferred to the Clinical Laboratory there. This has resulted in  
4605 a staff that is actually larger than the one in the Clinical Laboratory in Hiroshima despite the much  
4606 heavier workload of the latter. These technicians should be offered transfer to Hiroshima or to other  
4607 positions as retirements occur in lieu of a replacement. Other instances of inequity can be cited.

4608           Third, particularly detrimental to the Foundation's research activities has been the loss of  
4609 professional employees. Over the past five years, when no replacements of any sort occurred, their  
4610 number has fallen from 60 to 47. Since it is precisely these employees that are essential to the  
4611 Foundation's mission we propose increasing this number to 50.

4612           Projected yearly staff changes by broad work categories are given in the tables at the end  
4613 of this section. These tables should be seen as guides, and not as firm commitments which will, as  
4614 previously said, be determined by need.

## 4615 **Equipment**

4616           Contemporary science rests on increasingly complex and sophisticated equipment both in  
4617 the laboratory and as a means of communication, data management and analysis. Much of this  
4618 equipment has, unfortunately, a relatively short useful life, arguably three to five years in most  
4619 instances. This implies, in turn, that replacements will be necessary periodically. Again, it is our  
4620 intent to make these replacements on the basis of need and relevance to the current research  
4621 program. Wherever equipment is outdated for use in one department, if circumstances permit, it  
4622 will be transferred to another department with less demanding needs.

4623           Clearly high on the list of priorities will be the maintenance of a strong computing capability  
4624 including the continued cost of transition from a mainframe environment to a distributed system.  
4625 This is essential not only to research but to the proper administration of that research. As the body  
4626 of information available at the Foundation grows, which is inevitable, the need for efficient data  
4627 management grows too. Moreover, significant staff reduction appears possible only if some of the  
4628 current routine work can be automated, and delegated to computers.

4629           Budget projections for the next quinquennium will be found at the end of this section. These  
4630 projections set forth personnel and operating costs as well as equipment needs. However, in  
4631 departure from previous budget projections, equipment expenditures have been divided into those  
4632 supporting research and those supporting administrative needs. In the past, administrative  
4633 equipment needs, primarily computing capability, have generally been funded out of operating costs  
4634 and therefore, not reflected in the overall equipment forecasts. This accounts for much of the  
4635 seemingly larger equipment projections seen in these tables. It should also be noted that the bulk

4636 of the equipment expenditures predicted are for the replacement of outdated apparatus and not new  
4637 devices, new in the sense of not previously in use at the Foundation.

4638 **Space**

4639 Although planning for the relocation of the Foundation's facilities in Hiroshima continues,  
4640 there is as yet no firm date for this to occur. Accordingly, for the purposes of this document, we  
4641 have assumed that the relocation will not occur in the next five years. However, if this should prove  
4642 to be incorrect, clearly additional costs over those here projected would occur. It is important to  
4643 note that the Hiroshima facilities are old, and barely adequate; however, we continue to review  
4644 space allocations and strive for the most efficient use of the space that is available. This process  
4645 of review will continue.

4646

4647

4648

## Changes of personnel strength

4649

(2/3 replacement of retirements)

4650

4651

4652

4653

4654

4655

4656

4657

4658

4659

4660

4661

4662

4663

4664

4665

4666

4667

4668

4669

4670

4671

4672

4673

4674

4675

4676

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

4677

**Comparison of personnel strength between actual and requested (Total)**

4678

**2/3 replacement of retirements)**

4679

4680

4681

4682

4683

4684

4685

4686

4687

4688

4689

4690

4691

4692

4693

4694

4695

4696

4697

4698

4699

4700

4701

4702

4703

4704

4705

4706

|        |              | 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    | <b>331</b>   | <b>5</b> | <b>46.5</b> | <b>279.5</b> | <b>188</b> | <b>11</b> | <b>60.5</b> | <b>20</b> |
| 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    | <b>342.5</b> | <b>5</b> | <b>50.5</b> | <b>287</b>   | <b>195</b> | <b>11</b> | <b>62</b>   | <b>19</b> |
| 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          |          | 50          | 254          | 170        | 13        | 53          | 18        |
|        | Requested    | <b>346.5</b> | <b>5</b> | <b>51.5</b> | <b>290</b>   | <b>198</b> | <b>11</b> | <b>63</b>   | <b>18</b> |
| 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    | <b>348.5</b> | <b>5</b> | <b>52.5</b> | <b>291</b>   | <b>199</b> | <b>11</b> | <b>63</b>   | <b>18</b> |
| 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    | <b>347.5</b> | <b>5</b> | <b>52.5</b> | <b>290</b>   | <b>199</b> | <b>10</b> | <b>63</b>   | <b>18</b> |
|        | Replacement  | 9            |          |             | 9            | 8          |           |             | 1         |
|        | as of Apr. 1 | 312          | 5        | 50          | 257          | 172        | 13        | 54          | 18        |

|      |        |              |       |   |      |     |     |    |    |    |
|------|--------|--------------|-------|---|------|-----|-----|----|----|----|
| 4707 | FY2001 | Retirement   | 10    |   | 2    | 8   | 7   | 0  | 0  | 1  |
| 4708 |        | Sub-total    | 302   | 5 | 48   | 249 | 165 | 13 | 54 | 17 |
| 4709 |        | Requested    | 347.5 | 5 | 52.5 | 290 | 199 | 10 | 63 | 18 |
| 4710 | FY2002 | Replacement  | 8     |   | 2    | 6   | 5   |    |    | 1  |
| 4711 |        | as of Apr. 1 | 310   | 5 | 50   | 255 | 170 | 13 | 54 | 18 |
| 4712 |        |              |       |   |      |     |     |    |    |    |

## SUMMARY

4714            Investigations have been in progress for 50 years to ascertain the effects produced by  
4715 radiation in the survivors of the atomic bombings of Hiroshima and Nagasaki. It is appropriate to  
4716 ask (1) what the results of these studies have been, (2) what more is to be done, and (3) what  
4717 changes, if any, are anticipated in the future for RERF. One purpose of this document is to address  
4718 these issues.

4719            The long-term follow-up of this unique population has provided results of considerable value  
4720 to the medical as well as the radiobiological community. Significant associations between radiation  
4721 dose and cancer have been seen among the survivors for most types of cancer, including leukemia,  
4722 multiple myeloma and cancers of the thyroid, lung, breast, stomach, skin, colon, esophagus, liver,  
4723 urinary tract, and ovaries. The RERF data provide unique, quantitative information on how these  
4724 risks are affected by sex, age-at-exposure, and time. The excess relative risks for most solid cancers  
4725 are found to be higher for men than women and to increase with decreasing age at exposure. There  
4726 is weak evidence that the high relative risks seen for those exposed as children have decreased with  
4727 time while the relative risks for those exposed as adults have remained constant. Recent analyses  
4728 of the LSS data indicate that excess rates increase throughout life and that these rates do not vary  
4729 much with sex and age-at-exposure. The RERF data also provide evidence of a positive association  
4730 between radiation dose and noncancer disease mortality. While this effect is small, it does not  
4731 appear to be an artifact of misclassification of cause of death on death certificates. Clinical studies  
4732 of cardiovascular disease morbidity and related endpoints have been carried out using the RERF  
4733 clinical data. The results of these studies also support the notion of a radiation effect on some  
4734 noncancer diseases. Over the next few years we must develop a more unified approach for  
4735 combining the epidemiological and clinical data on radiation and noncancer disease morbidity. The  
4736 presence of dose-dependent developmental effects on survivors who were exposed in-utero is well-  
4737 documented and it is now becoming clear that radiation exposure is associated with elevated risks  
4738 of cancer later in life for this group of survivors. If, as seems likely, these risks continue throughout  
4739 life the coming decades will provide further information on the extent and nature of these risks. It  
4740 is also important to follow-up earlier findings that the developing human brain is extremely  
4741 sensitive to teratogenic effects of relatively low doses of ionizing radiation since this vulnerability  
4742 might manifest itself in earlier onset of cognitive disorders and an increased frequency of senile  
4743 dementia.

4744            Evidence is still lacking that radiation induces heritable genetic damage in humans.  
4745 Research with experimental animals, however, has clearly demonstrated that heritable changes are  
4746 positively associated with radiation exposure. In general, RERF's findings in various genetic  
4747 studies are as expected if the atomic-bomb radiation exposure has produced mutations. But, to date,

研究部門備品要求表 (1996年～2001年)  
Equipment Requests by Research Departments

| 部・局   | DEPARTMENT       | FY1996 | FY1997 | FY1998  | FY1999 | FY2000 | FY2001 | 合計      |
|-------|------------------|--------|--------|---------|--------|--------|--------|---------|
| 疫学部   | EPIDEMIOLOGY     | 0      | 6,020  | 4,900   | 5,540  | 5,225  | 6,030  | 27,715  |
| 臨床研究部 | CLINICAL STUDIES | 0      | 5,800  | 2,533   | 13,528 | 0      | 7,283  | 29,144  |
| 遺伝学部  | GENETICS         | 0      | 18,349 | 32,075  | 5,269  | 0      | 0      | 55,693  |
| 放射線部  | RADIOBIOLOGY     | 25,000 | 23,400 | 83,200  | 20,000 | 13,300 | 6,200  | 171,100 |
| 統計部   | STATISTICS       | 0      | 5,075  | 5,275   | 5,410  | 5,590  | 5,675  | 27,025  |
| 広島合計  | HIROSHIMA TOTAL  | 25,000 | 58,644 | 127,983 | 49,747 | 24,115 | 25,188 | 310,677 |
| 臨床研究部 | CLINICAL STUDIES | 0      | 19,045 | 0       | 0      | 3,000  | 0      | 22,045  |
| 疫学部   | EPIDEMIOLOGY     | 0      | 6,334  | 4,810   | 3,310  | 3,310  | 3,310  | 21,074  |
| 長崎合計  | NAGASAKI TOTAL   | 0      | 25,379 | 4,810   | 3,310  | 6,310  | 3,310  | 43,119  |
| 両市合計  | BOTH TOTAL       | 25,000 | 84,023 | 132,793 | 53,057 | 30,425 | 28,498 | 353,796 |

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① | ITD (1)         | 0      | 44,900 | 45,420 | 48,050 | 47,840 | 50,460 | 236,670 |
| "②         | ITD (2)         | 0      | 13,434 | 4,996  | 300    | 2,500  | 7,800  | 29,030  |
| 放射線同位体RI   | RI FACILITIES   | 0      | 3,100  | 0      | 450    | 960    | 1,100  | 5,610   |
| 事務局        | SECRETARIAT     | 1,770  | 6,440  | 8,320  | 4,690  | 2,950  | 1,420  | 25,590  |
| 広島合計       | HIROSHIMA TOTAL | 1,770  | 76,734 | 62,376 | 58,450 | 56,790 | 63,980 | 320,100 |
| 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   |
| 両市合計       | BOTH TOTAL      | 4,490  | 79,354 | 62,816 | 60,670 | 57,830 | 63,980 | 329,140 |

|    |  |        |         |         |         |        |        |         |
|----|--|--------|---------|---------|---------|--------|--------|---------|
| 合計 |  | 29,490 | 163,377 | 195,609 | 113,727 | 88,255 | 92,478 | 682,936 |
|----|--|--------|---------|---------|---------|--------|--------|---------|

| 現金購入 | PURCHASE COST | リース支払い  | LEASE CHARGE | 従来のリース支払 | CHARGE  | 合計      | TOTAL   |
|------|---------------|---------|--------------|----------|---------|---------|---------|
|      | 4,490         | 116,037 | 86,696       | 76,789   | 72,855  | 82,695  | 439,562 |
|      | 5,790         | 16,754  | 41,978       | 50,533   | 54,099  | 50,575  | 219,729 |
|      | 17,095        | 5,082   | 5,082        | 5,082    | 4,598   | 2,177   | 39,116  |
| 合計   | 27,375        | 137,873 | 133,756      | 132,404  | 131,552 | 135,447 | 698,407 |

研究情報センター① ITD ITDのみ購入分  
研究情報センター② ITD 他部署購入分 (AHS分)

ITD (1) shows purchase requests for ITD's use  
ITD (2) shows purchase requests for other departments' use for AHS

コンピューター関係分 For Computer 2,850 96,555 75,051 71,745 77,645 394,251

4748 the differences between the children of proximally and distally exposed survivors are far from  
4749 significant. However, none of the strategies to assess mutation risk used thus far has addressed the  
4750 full gamut of possible genetic damage. For example, the program of clinical examinations of the  
4751 newborn was designed to identify congenital abnormalities demonstrable soon after birth but could  
4752 not identify those abnormalities that are not readily detectable until later in life, nor those simply  
4753 or complexly inherited disabilities that do not manifest themselves until adolescence or later. The  
4754 latter represent by far the largest proportion of all inherited handicaps, and there has been no  
4755 systematic program of health examinations of the F<sub>1</sub> after the first year of life which might detect  
4756 an increase in these diseases and disorders.

4757 Developments in molecular biology have identified a number of new approaches that will  
4758 permit mutations at the level of nucleotide bases in DNA to be detected in human populations in  
4759 the foreseeable future. Although these techniques are not available for use at the present time to  
4760 monitor human mutation rates, cells from exposed and unexposed parents and their children are  
4761 being collected now. Some of these cells are being immortalized using the Epstein-Barr virus,  
4762 cultured, and stored for use when the new molecular approaches to mutation detection can be used  
4763 cost-effectively.

4764 These investigations at RERF will (1) strengthen evidence about the cancer dose-response,  
4765 (2) clarify the impact of exposure on cancer risks for the survivors exposed as children in-utero, (3)  
4766 provide additional information on the nature of radiation effects on cardiovascular and other  
4767 noncancer diseases, and (4) offer new insights into the role of biological and environmental factors  
4768 on radiation risks.

4769 Initial efforts to develop a database that contains information on family relationships among  
4770 members of the LSS and other RERF cohorts suggest that these data can be useful for studies of the  
4771 interaction between hereditary factors and radiation- or nonradiation-related cancer risks. This work  
4772 will continue during the next five years provided that adequate computing and personnel resources  
4773 are available.

4774 Public concern over the potential risks of exposure to ionizing radiation shows no sign of  
4775 abating; indeed it is possibly even greater now than in the past largely due to a series of accidents  
4776 at nuclear power generating facilities, and increased medical usage. To allay this concern will  
4777 require greater knowledge of how radiation affects somatic and genetic diseases in human beings.  
4778 While there are experts in most disciplines related to understanding radiation effects on humans at  
4779 many institutions all over the world, the Foundation is the only one with many of these experts in  
4780 one place, and with access to the largest, well-defined and studied population of radiation-exposed  
4781 individuals. To not maintain this "critical mass" of interested scientists focused on this important  
4782 human problem would create a serious setback. In addition, with the increasing concern of the  
4783 effects of environmental chemicals on human health, RERF scientists have the potential to use the  
4784 information from this unique population to determine how chemical and radiation effects might  
4785 interact.

4786 With the decrease in the numbers of the A-bomb survivors occurring, and the current lack  
4787 of sensitive and fully validated techniques to measure mutational effects in both somatic and germ  
4788 cells, emphasis has been and should continue to be placed on the long-term storage of biological  
4789 material until appropriate techniques to measure important parameters can be developed. In  
4790 addition, research should be directed towards the incorporation of new molecular biological

4791 approaches in the study of the F<sub>1</sub> generation and the incorporation of new concepts and techniques  
4792 from molecular and cell biology to study the non-mutagenic mechanisms that may modify radiation  
4793 effects, aspects that are not, at present, part of the Foundation's current research base.

4794           The development of such new molecular biological techniques; of new conceptual  
4795 understanding of chronic diseases, including cancer; of the deeper insights into the role of  
4796 oncogenes and tumor suppressor genes; and an understanding of chemicals which enhance or  
4797 suppress tumor growth can be expected to stimulate new laboratory approaches and new  
4798 epidemiological studies.

## 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

### SELECTED REFERENCES

- Pierce, D. A., Shimizu, Y., Preston, D. L., Vaeth, M., and Mabuchi, K.: Studies of the Mortality of Atomic Bomb Survivors. Report 12, Part I. Cancer: 1950-1990. Radiat. Res. 146: 1-27, 1996.
- Preston, D. L., Kusumi, S., Tomonaga, M., Izumi, S., Ron, E., Kuramoto, A., Kamada, N., Dohy, H., Matsuo, T., Nonaka, H., Thompson, D. E., Soda, M. and Mabuchi, K.: Cancer incidence in atomic bomb survivors. Part III. Leukemia, lymphoma and multiple myeloma, 1950-1987. Radiat. Res. 137: S68-S97, 1994.
- Schull, W. J.: Effects of Atomic Radiation: A Half Century of Studies from Hiroshima and Nagasaki. New York: John Wiley and Sons, Inc., 1995.
- Shigematsu, I., Ito, C., Kamada, N., Akiyama, M., and Sasaki, H. (Eds.): Effects of A-Bomb Radiation on the Human Body. Tokyo: Bunkodo Co., Ltd., 1995.
- Thompson, D. E., Mabuchi, K., Ron, E., Soda, M., Tokunaga, M., Ochikubo, S., Sugimoto, S., Ikeda, T., Terasaki, M., Izumi, S. and Preston, D. L.: Cancer incidence in atomic bomb survivors. Part II. Solid tumors, 1958-1987. Radiat. Res. 1327: S17-S67, 1994.

## ANNEX D

### MASTER SAMPLE, PROPER AND RESERVE BY EXPOSURE CATEGORY AND CITY

| Exposure<br>Group (M) | Proper<br>Part | Reserve<br>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<br>(LSS) | Extended<br>(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<br>(only) | Birth records | 1,104     | 247      | 1,351 |
|                              | ABCC records  | 183       | 34       | 217   |
|                              | 1960 Census   | 416       | 62       | 478   |
| In utero clinical<br>(only)  | Birth records | 0         | 0        | 0     |
|                              | 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<sub>1</sub> MORTALITY SAMPLE, ORIGINAL AND EXTENDED

| Sample   | City      |          | Total  |
|----------|-----------|----------|--------|
|          | Hiroshima | Nagasaki |        |
| 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 erythrocyte 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 I. 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/<br>Repl | Item                     | Q'ty | Unit Cost<br>(x¥1000) | Total<br>(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       |              |                          |      |                       | <u>27,104</u>     |

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 1977 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 equipments 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/<br>Repl | Item                        | Q'ty | Unit Cost<br>(x¥1000) | Total<br>(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                 | <u>22,045</u>     |

### Department of Genetics

| Fiscal year | New/<br>Repl | Item   | Q'ty | Unit Cost<br>(x¥1000) | Total<br>(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       |              |  |      |                       | <u>51,493</u>     |

### Department of Radiobiology

| Fiscal year | New/<br>Repl | Item                           | Q'ty | Unit Cost<br>(x¥1000) | Total<br>(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 <sup>(1)</sup> | 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          |
| 1999 | R | Cell Sorter (FACSVantage) <sup>(2)</sup> | 1 | 75,000 | 75,000         |
|      | R | Deep Freezer                             | 1 | 2,200  | 2,200          |
|      | R | Thermal Cycler                           | 2 | 850    | 1,700          |
|      | R | Power Supply                             | 2 | 550    | 1,100          |
|      | R | FACScan <sup>(2)</sup>                   | 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  | <u>164,600</u> |

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 reduce 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\_°C)**

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/<br>Repl | Item                                 | Q'ty  | Unit Cost<br>(x¥1000) | Total<br>(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 |                       | <u>4,010</u>      |

### Publications and Documentation Center

| Fiscal Year | New/<br>Repl | Item                      | Q'ty  | Unit Cost<br>(x¥1000) | Total<br>(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 |                       | <u>23,200</u>     |

**Secretariat, Hiroshima**

| Fiscal Year               | New/<br>Repl | Item     | Q'ty | Unit Cost<br>(x¥1000) | Total<br>(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               |
| <b>Total</b>              |              |          |      |                       | <b>25,390</b>     |

## Secretariat, Nagasaki

| Fiscal Year             | New/<br>Repl | Item     | Q'ty | Unit Cost<br>(x¥1000) | Total<br>(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                 | <u>9,040</u>      |

**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                 | -                           |
|      | <b>Total</b>                |     |           | <b>2,301</b>       | <b>2,311</b>                |
| 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                 | -                           |
|      | <b>Total</b>                |     |           | <b>52</b>          | <b>1,900</b>                |
| 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                 | -                           |
|      | <b>Total</b>                |     |           | <b>657</b>         | <b>2,025</b>                |
| 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                 | -                           |
|      | <b>Total</b>                |     |           | <b>102</b>         | <b>610</b>                  |
| 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           | -            |
|  | <b>Total</b>                |   |    | <b>1,857</b> | <b>2,425</b> |
|  | <b>Grand Total</b>          |   |    | <b>4,969</b> | <b>9,271</b> |

**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                 | -                           |
|      | <b>Total</b>               |     |           | <b>127</b>         | <b>945</b>                  |
| 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                 | -                           |
|      | <b>Total</b>               |     |           | <b>452</b>         | <b>600</b>                  |
| 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                 | -                           |
|      | <b>Total</b>               |     |           | <b>527</b>         | <b>1,725</b>                |
| 2000 | Laser printer (Replace)    | 1   | 400       | -                  | 400                         |
|      | Exceed Software version up | 2   | 6         | 12                 | -                           |
|      | Origin Software version up | 2   | 20        | 40                 | -                           |
|      | <b>Total</b>               |     |           | <b>52</b>          | <b>400</b>                  |
| 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                 | -                           |
|      | <b>Total</b>               |     |           | <b>527</b>         | <b>325</b>                  |
|      | <b>Grand Total</b>         |     |           | <b>1,685</b>       | <b>3,995</b>                |

**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                | -                           |
|      | <b>Total</b>               |     |           | <b>5,811</b>       | <b>1,879</b>                |
| 1998 | PC replacement             | 8   | 500       | 2,800              | 1,200                       |
|      | Printer Replacement        | 1   | 500       | 350                | 150                         |
|      | New Hardware               | 1   | 500       | 421                | 79                          |
|      | Software upgrades          | 25  | 60        | 1,050              | 450                         |
|      | New software               | 7   | 40        | 196                | 84                          |
|      | Path equipment replacement | 1   | 150       | 150                | -                           |
|      | <b>Total</b>               |     |           | <b>4,967</b>       | <b>1,963</b>                |
| 1999 | PC replacement             | 8   | 525       | 2,940              | 1,260                       |
|      | Printer Replacement        | 1   | 500       | 400                | 100                         |
|      | New Hardware               | 1   | 520       | 440                | 80                          |
|      | Software upgrades          | 25  | 60        | 1,050              | 450                         |
|      | New software               | 3   | 40        | 96                 | 24                          |
|      | Path equipment replacement | 1   | 150       | 150                | -                           |
|      | <b>Total</b>               |     |           | <b>5,076</b>       | <b>1,914</b>                |
| 2000 | PC replacement             | 8   | 525       | 2,940              | 1,260                       |
|      | Printer Replacement        | 1   | 500       | 350                | 150                         |
|      | New Hardware               | 1   | 520       | 440                | 80                          |
|      | Software upgrades          | 16  | 90        | 1,008              | 432                         |
|      | New software               | 6   | 40        | 168                | 72                          |
|      | Path equipment replacement | 1   | 150       | 150                | -                           |
|      | <b>Total</b>               |     |           | <b>5,056</b>       | <b>1,994</b>                |
| 2001 | PC replacement             | 8   | 525       | 2,940              | 1,260                       |
|      | Printer Replacement        | 1   | 500       | 400                | 100                         |
|      | New Hardware               | 1   | 520       | 416                | 104                         |
|      | Software upgrades          | 16  | 90        | 1,008              | 432                         |
|      | New software               | 6   | 40        | 192                | 48                          |

|  |                            |   |     |               |              |
|--|----------------------------|---|-----|---------------|--------------|
|  | Path equipment replacement | 1 | 150 | 150           | -            |
|  | <b>Total</b>               |   |     | <b>5,106</b>  | <b>1,944</b> |
|  | <b>Grand Total</b>         |   |     | <b>26,016</b> | <b>9,694</b> |

**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                          |
|      | <b>Total</b>                            |     |           | <b>4,917</b>       | <b>1,281</b>                |
| 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                 | -                           |
|      | <b>Total</b>                            |     |           | <b>2,381</b>       | <b>963</b>                  |
| 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            | -            |
|      | <b>Total</b>                 |    |     | <b>2,791</b>  | <b>753</b>   |
| 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            | -            |
|      | <b>Total</b>                 |    |     | <b>681</b>    | <b>163</b>   |
| 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            | -            |
|      | <b>Total</b>                 |    |     | <b>4,711</b>  | <b>1,233</b> |
|      | <b>Grand Total</b>           |    |     | <b>15,482</b> | <b>4,392</b> |

**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                         |
|      | <b>Total</b>          |     |           | <b>4,841</b>       | <b>1,021</b>                |
| 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                          |
|      | <b>Total</b>          |     |           | <b>1,176</b>       | <b>476</b>                  |
| 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           |
|      | <b>Total</b>          |    |       | <b>2,017</b>  | <b>715</b>   |
| 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           |
|      | <b>Total</b>          |    |       | <b>2,046</b>  | <b>748</b>   |
| 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           |
|      | <b>Total</b>          |    |       | <b>3,419</b>  | <b>583</b>   |
|      | <b>Grand Total</b>    |    |       | <b>13,499</b> | <b>3,543</b> |

**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                 | -                           |
|      | <b>Total</b>            |     |           | <b>2,006</b>       | <b>2,506</b>                |
| 1998 | PCP5-90(Replace)        | 2   | 500       | -                  | 1,000                       |
|      | Laserprinter(Replace)   | 1   | 400       | -                  | 400                         |
|      | ExceedSoftwareversionup | 2   | 6         | 12                 | -                           |
|      | OriginSoftwareversionup | 2   | 20        | 40                 | -                           |
|      | <b>Total</b>            |     |           | <b>52</b>          | <b>1,400</b>                |
| 1999 | BasicSoftwareversionup  | 6   | 50        | 150                | 150                         |
|      | BasicSoftwareversionup  | 5   | 50        | -                  | 250                         |
|      | ExceedSoftwareversionup | 2   | 6         | 12                 | -                           |

|      |                         |   |     |              |              |
|------|-------------------------|---|-----|--------------|--------------|
|      | OriginSoftwareversionup | 2 | 20  | 40           | -            |
|      | CorelDrawSoft.versionup | 2 | 40  | 80           | -            |
|      | <b>Total</b>            |   |     | <b>282</b>   | <b>400</b>   |
| 2000 | Softwareversionup(OS)   | 6 | 20  | 60           | 60           |
|      | Softwareversionup(OS)   | 5 | 20  | -            | 100          |
|      | ExceedSoftwareversionup | 2 | 6   | 12           | -            |
|      | OriginSoftwareversionup | 2 | 20  | 40           | -            |
|      | <b>Total</b>            |   |     | <b>112</b>   | <b>160</b>   |
| 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           | -            |
|      | <b>Total</b>            |   |     | <b>1,882</b> | <b>800</b>   |
|      | <b>GrandTotal</b>       |   |     | <b>4,334</b> | <b>5,266</b> |

**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                          |
|      | Software upgrades    | 12  | 83        | 700                | 300                         |
|      | New software         | 6   | 50        | 250                | 50                          |
|      | <b>Total</b>         |     |           | <b>3,650</b>       | <b>1,425</b>                |
| 1998 | PC replacement       | 6   | 500       | 2,000              | 1,000                       |
|      | Printer Replacement  | 1   | 500       | 350                | 150                         |
|      | New Hardware         | 1   | 475       | 400                | 75                          |
|      | Software upgrades    | 12  | 83        | 700                | 300                         |
|      | New software         | 6   | 50        | 250                | 50                          |
|      | <b>Total</b>         |     |           | <b>3,700</b>       | <b>1,575</b>                |
| 1999 | PC replacement       | 6   | 525       | 2,100              | 1,050                       |
|      | Network Disk Storage | 1   | 320       | 320                | -                           |
|      | New Hardware         | 1   | 520       | 440                | 80                          |
|      | Software 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           |
|      | Software 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           |
|      | Software upgrades    | 12 | 92  | 770           | 330          |
|      | New software         | 6  | 63  | 300           | 80           |
|      | Total                |    |     | 4,080         | 1,595        |
|      | <b>Grand Total</b>   |    |     | <b>19,260</b> | <b>7,765</b> |

**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                       |
|      | <i>RERF-wide services:<br/>computer and network<br/>hardware/software<br/>replacement</i> | 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                       |

|      |  |    |        |   |                |
|------|--|----|--------|---|----------------|
|      | <i>RERF-wide services:</i><br>computer and network<br>hardware/software<br>replacement | 1  | 36,000 | - | 36,000         |
|      | Grand Total  |    |        | - | <b>45,420</b>  |
| 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  |    |        | - | <b>10,250</b>  |
|      | <i>RERF-wide services:</i><br>computer and network<br>hardware/software<br>replacement | 1  | 37,800 | - | 37,800         |
|      | Grand Total  |    |        | - | <b>48,050</b>  |
| 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  |    |        | - | <b>10,040</b>  |
|      | <i>RERF-wide services:</i><br>computer and network<br>hardware/software<br>replacement | 1  | 37,800 | - | 37,800         |
|      | Grand Total  |    |        | - | <b>47,840</b>  |
| 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  |    |        | - | <b>10,760</b>  |
|      | <i>RERF-wide services:</i><br>computer and network<br>hardware/software<br>replacement | 1  | 39,700 | - | 39,700         |
|      | Grand Total  |    |        | - | <b>50,460</b>  |
|      | <b>Five-Year Total</b>   |    |        | - | <b>236,670</b> |

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 | 3,227,676 | 3,304,603 | 3,742,938 | 3,635,153 | 3,559,650 | 3,881,353 | 2,781,100 | 3,692,476 | 3,296,604 | 3,170,297 | 3,301,463 | 3,252,828 |
| (m. allowance)  | (208,852) | (163,105) | (391,230) | (274,021) | (405,884) | (947,102) | (27,137)  | (789,902) | (446,993) | (314,997) | (427,976) | (335,835) |
| Operating costs | 802,336   | 858,687   | 871,424   | 851,988   | 799,292   | 851,549   | 725,385   | 825,395   | 825,905   | 842,691   | 849,616   | 871,914   |
| Total           | 4,030,012 | 4,163,290 | 4,614,362 | 4,487,141 | 4,358,942 | 4,732,902 | 3,506,485 | 4,571,871 | 4,122,509 | 4,012,988 | 4,151,079 | 4,123,942 |

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 | 138,467 | 128,673 | 135,000 | 131,310 | 142,033 |
| 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  |

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.