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REFLECTIONS ON THE WORK OF THE ATOMIC BOMB CASUALTY COMMISSION IN JAPAN

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The atomic bombs dropped on Hiroshima and Nagasaki in 1945 led to the organization of the Atomic Bomb Casualty Commission (ABCC), whose history contains important lessons for epidemiologists concerned with large-scale investigations of problems requiring long-term, prospective study. The history is perhaps all the more meaningful because it is not a linear process starting from a definitive protocol and moving through well-planned stages of development to a fulfillment clearly visualized at the outset. Rather, it is an adaptive process, the record of a struggle against difficulties of many different kinds, its continuation dependent on the vision of relatively few people, on the growing social need for information about the health hazards created by a burgeoning nuclear technology, and on a belated infusion of epidemiologic concepts and methods without which the studies of somatic effects seemed doomed to failure. But it is also a bifurcated history, in that the genetic studies do not fit this general pattern. They stand apart as superbly planned and efficiently conducted and yet with little evident influence on the somatic studies which have come to dominate the program.

The lessons to be learned from the history of the ABCC concern research strategy, specific methodologic issues, and how to maintain an effective research organization dedicated to a major long-term, prospective study. Just as its problems of strategy and method are not specific to the investigation of the effects of ionizing radiation, so its problems of survival and management are not confined to the operation of a research enterprise far from its institutional base or in a foreign country.

For epidemiologists it is important to understand that the ABCC studies were set in motion without substantial epidemiologic input, that epidemiologic concepts and principles rescued the effort after it had reached low ebb in 1955, and that its entire history underscores the value of the epidemiologic approach. Some illustrious names in epidemiology and statistics aided in the introduction of epidemiologic thinking that so greatly contributed to its success: William G. Cochran, Harold F. Dorn, Thomas Francis, Jr., John E. Gordon, Alexander D. Langmuir, and Thomas Parran.

CHRONOLOGY

The atomic bombs dropped on August 6 and 9, 1945, were followed by the Japanese surrender on August 14. US Army, Navy, and Manhattan District investigating teams began arriving in September, and on October 12 a "Joint Commission for the Investigation of the Effects of the Atomic Bomb in Japan" was formed by authority of the Supreme Commander of the Allied Powers to perform a coordinated study in cooperation with Japanese groups already on the scene. From that study of acute effects (1) arose the proposal for a continuing study under

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Abbreviations: ABCC, Atomic Bomb Casualty Commission; AEC, Atomic Energy Commission; AHS, Adult Health Study; ATB, at the time of the bomb; BEIR, biological effects of ionizing radiation; BGS, Biochemical Genetics Study; F_1, conceived after the bomb; LET, linear energy transfer; LSS, Life Span Study; JNIH, Japanese National Institute of Health; NAS, National Academy of Sciences; NRC, National Research Council; ORNL, Oak Ridge National Laboratory; RBE, relative biological effectiveness; RERF, Radiation Effects Research Foundation; T...D, tentative dose.

civilian, non-governmental auspices. On November 26, 1946, President Truman approved a directive to the National Academy of Sciences-National Research Council (NAS-NRC) "to undertake a long range, continuing study of the biological and medical effects of the atomic bomb on man." In the planning documents specific interest is expressed in cancer, leukemia, shortened life span, reduced vigor, altered development, sterility, modified genetic pattern, changes in vision, "shifted epidemiology," abnormal pigmentation, and epilation.

A team was sent to Japan to explore the situation, establish an interim organization, and make recommendations for a long-term program. An NAS-NRC Committee on Atomic Casualties was organized under the chairmanship of Thomas M. Rivers. (Other members were George W. Beadle, Detlev W. Bronk, Austin M. Brues, George M. Lyon, C. P. Rhoads, Shields Warren, Stafford L. Warren, George H. Whipple, and Raymond E. Zirkle.) At its first meeting on March 25, 1947, the Committee heard an encouraging report from Brues and Paul S. Henshaw on their investigative mission to Japan and on the steps being taken there to establish an interim organization that soon became the Atomic Bomb Casualty Commission. The newly formed Atomic Energy Commission (AEC) was to provide the necessary funds under a contract with the NAS. The findings of the studies were expected to be useful in industrial, medical, and military uses of atomic energy.

1947–1950. At the outset the Commission, with the help of US occupation authorities, was very much involved in building an organization, providing for its logistic support in impoverished Japan, responding to the interests of US investigators with specific interests, e.g., in hematology, growth and development, and cataracts, and laying the groundwork for a systematic medical examination program. Of greatest importance, in retrospect, were Neel and Schull's genetic study (2), presented to the Committee on Atomic Casualties at its second meeting on May 1, 1947, and an agreement with Japanese authorities to supplement the October, 1950, population census with an inquiry about exposure to the atomic bombs. The records of the Joint Commission had proved to have little value because of inadequate personal identification, and the need for a firm sampling base for screening studies had become evident. Partly because of concern over the unknown importance of fallout and residual radiation, Kure was chosen as a control city for Hiroshima, and mention was made of Sasebo as a control for Nagasaki. By the end of the period, ABCC had functioning departments of genetics, cytogenetics, obstetrics and gynecology, pediatrics, internal medicine, surgery, ophthalmology, radiology, pathology, biochemistry, microbiology, and biometrics. The newly formed Japanese National Institute of Health (JNIH) was asked to provide an interface between ABCC and the Japanese community, and arrangements were made for pathological specimens to be sent to the then (US) Army Institute of Pathology.

1950–1955. During the next few years Neel and Schull's genetic study (2) was brought to a successful conclusion, definite evidence of the leukemogenic effect was obtained (3), and studies of the *in utero* exposed revealed the existence of small heads and mental retardation in the most proximally exposed (4). Ophthalmologic surveys were continued, as were the growth and development studies. Shielding surveys were begun in an effort to get closer to a physical measure of radiation exposure. A medical examination program for adults, begun in 1950, faltered progressively in the face of negative findings and declining participation. Under fiscal pressure, and with AEC assurances that fallout and residual radiation were unimportant, efforts to employ Kure and Sasebo as control cities were

abandoned. Continuity of leadership could not be maintained. As the war in Korea progressed, and inflation in Japan worsened, a fiscal crisis loomed and late in 1954 there was even talk of closing the operation entirely. By 1955 there were serious doubts about prospects for the future, examination programs were failing, little that was new was being seen, and staff was discouraged. The validity of the preliminary findings of a study of mortality was seriously questioned at an *ad hoc* NRC conference. (Conferees included Langmuir, Chairman, Dorn, Gordon, A. E. Brandt, Felix E. Moore, H. M. Luykx, and Seymour Jablon.)

Late in 1955, Francis, together with Moore and Jablon, made a site visit to ABCC at the request of R. Keith Cannan, Chairman of the NRC Division of Medical Sciences. Their mission was to make an objective scientific appraisal of the institution and its program, and to make recommendations for the future. In their report they provided not only a thorough assessment of the situation, but also an over-all strategy for the future with emphasis on the integration of different screening and observational modalities through the mechanism of a fixed cohort of exposed and non-exposed subjects (5). The specific components of the recommended program, soon adopted as the Unified Study Program, were: a fixed sample; epidemiologic detection or continuing morbidity survey; clinical detection; post-mortem detection; and death certificate study.

1955–1961. Adoption of the recommendations of the Francis Committee was the turning-point for ABCC. Although the staff voiced numerous objections, except for the epidemiologic detection plan (weekly reporting of illness or death by lay monitors each responsible for 15–20 survivors in his neighborhood), the Unified Study Program was put into effect, first by Cannan, who served as acting director in Japan for five months in 1957, and then by George B. Darling of the Yale University School of Medicine, who served as director from 1957 until 1972. Ties were formed with the Yale University School of Medicine, the University of California at Los Angeles (UCLA) School of Medicine, and the Follow-up Agency of the National Research Council to provide leadership and staff for the ABCC departments of medicine, pathology, and statistics, respectively. In 1958 these groups began sending personnel of their own, including department heads. The clinical program was reorganized first, as the Adult Health Study (AHS) (6), and put into operation in 1957–1958, in large part through the efforts of Arthur J. McDowell, who later organized and directed the Health Examination Survey of the US National Center for Health Statistics, and James W. Hollingsworth of the Yale University School of Medicine. The AHS sample of 20,000 became the first segment of the mortality sample for what the Francis Committee called the death certificate study, later named the Life Span Study (LSS); the sample of 100,000 LSS subjects was completed in 1961 (7) and then extended to 109,000 in 1967 (8). A second mortality study of about 2800 *in utero* exposed and controls was designed in 1960 (9), and a third (F_1, conceived after the bomb) mortality study of 54,000 children of survivors and of non-exposed parents was designed in that same year to detect any genetic damage sufficient to influence mortality (10).

In lieu of the Francis plan for lay observers to report illness among small panels of survivors, consideration was given to health surveys of industrial populations containing significant numbers of A-bomb survivors and to home visits. These techniques were not found to be cost-effective, however, and were soon abandoned in favor of routine history-taking at the biennial AHS examination.

The pathology program was the most difficult to integrate with the new clinical and mortality studies, as both post-

mortem and surgical specimen examinations had for many years been performed as a free service to the medical community with little regard for their research value. In 1961 such examinations were restricted to the several fixed cohorts under study (LSS and AHS, F_1, and *in utero*), and by 1963 the autopsy rate in the LSS sample had risen from 7 to 44 per cent regardless of place of death (11).

The Adult Health Study was designed to detect changes in the incidence or natural history of disease, physiologic or biochemical changes or "markers" (short of actual disease), new disease entities, and nonspecific changes in vigor or acceleration of aging (6). Three levels of observation were defined: 1) a standard history, physical, and laboratory examination repeated periodically; 2) supplementary observations serving *ad hoc* inquiries into particular diseases or organ-systems; and 3) supplementary observations testing specific ideas about possible effects.

With the completion of the design for the LSS study (12), Darling inaugurated a series of bilingual protocols in technical report format that became institutional imperatives and ensured continuity of effort in the face of turnover of personnel. With notable exceptions, US personnel served two-year terms. Although there was far more stability among the Japanese staff, especially JNIH personnel, many of these also served tours of one to two years. The protocols for major programs (LSS, AHS, F_1, *in utero*, pathology) included agreements with the JNIH for joint sponsorship and conduct. Protocols for substudies were less formal but were also published in bilingual format. In 1959 also the Director began the bilingual Technical Report series into which all ABCC work, whether intended for publication or not, was entered prior to publication.

Shortly after the Francis Report, the Oak Ridge National Laboratory (ORNL) began a determined effort to develop a physical dosimetry program by means of which survivors might be classified by absorbed dose rather than by distance from the hypocenter and acute radiation symptoms (13). By 1958, this program *(Ichiban)* of the Health Physics Division, ORNL, combined with ABCC documentation of each survivor's location and shielding configuration at the time of the bomb (ATB), had produced a first tentative dosimetry plan (T57D) that was used to screen for effects and to begin the investigation of dose-response relationships.

Tumor registries were established by the city medical association in Hiroshima in 1957 and in Nagasaki in 1958 (14), and the leukemia detection program begun in 1947 became a registry operation about 1959. Initially the numerator data were combined with estimates of the survivor populations resident in the two cities, distributed by distance from each hypocenter.

1961–1975. Reorientation of the pathology program within the framework of the Unified Study Program made it possible to develop much-needed information on the reliability of the Japanese death certificate (15), which was customarily filled out before any autopsy could be done at ABCC, on ascertainment bias, and on the influence of radiation on tumors not well diagnosed on the death certificate. Pathologists also investigated the hypothesis of radiation-accelerated aging (16–18) and contributed importantly to the studies of cardiovascular and cerebrovascular diseases, especially the *Ni-Hon-San* study (19).

Further experimental work on shielding and the discovery that the yield of the Hiroshima weapon had been grossly exaggerated led to calculation of the second-generation (T65D) dose estimates in 1966–1967 (20). Absorbed organ doses based on the T65D values have recently been provided by Kerr (21). Hashizume and Maruyama (22) of the National Institute of Radiological Sciences in Japan

have also developed parallel air-dose curves for each city, and factors for converting kerma estimates to absorbed organ- or tissue-dose estimates.

Early in the 1960s it became clear that estimates of the survivor population resident in the two cities had become unreliable because information on migration was inadequate. Accordingly, only cases falling within the fixed cohorts (LSS, AHS, F_1, *in utero)* were henceforth used in analyses of the effect of radiation (23). Although the Nagasaki Tumor Registry remained strong and reasonably complete, the Hiroshima University material generally did not find its way into the Registry, and in 1973 the Hiroshima Prefectural Medical Association established a "tissue registry" with similar goals to which the University medical departments do contribute. In 1974 the Nagasaki City Medical Association commenced the operation of its tissue registry (24). A combination of the two registries in each city guarantees virtually complete ascertainment of malignant tumors for investigative purposes.

In the mid-1960s the three-day peripheral leukocyte culture technique of Moorhead et al. (25) became established under Bloom et al. (26), and a major cytogenetic program was begun to investigate the effect of radiation on the leukocytes of A-bomb survivors (27). In recent years cytogenetic techniques have also been used by Awa (28) and his associates in the investigation of F_1 subjects for somatic-cell changes that would reflect radiation-induced germ-cell changes in their exposed parents.

Throughout the 1960s inflation proceeded at a brisk pace in Japan, with total ABCC costs rising from $1.9 million for a staff of 905 in 1959 to $4.2 million for a staff of 695 in 1970. In 1971 the Japanese yen was revalued, so that dollar costs rose even higher. By FY 74 the total was up to $6.2 million with no increase in staff, and a substantial input from the US National Cancer Institute was required to fend off disaster. In his annual report for 1967–1968, Darling made a plea for a stronger commitment by the government of Japan to the support and direction of the institution, but it was not until 1973 that the two governments began the dialogue that led finally, in November, 1974, to an agreement on a new organization, a Japanese foundation established by the Health and Welfare Ministry, to succeed ABCC. The objectives and program remained unchanged, but management was vested in a binational board of directors for the newly created Radiation Effects Research Foundation (RERF) which replaced ABCC on April 1, 1975. The act of endowment provided that control be shared equally by the two governments through their representatives on the board and on an advisory scientific council, and through their budgetary support. The US support by the Department of Energy continues to be provided through the National Academy of Sciences as before.

In February, 1975, in anticipation of the organizational change, the NAS sent to Japan a Committee for Scientific Review of ABCC under the chairmanship of James E. Crow. (Other members were Henry S. Kaplan, Paul A. Marks, Robert W. Miller, John B. Storer, Arthur C. Upton, and Jablon.) The Committee recommended, *inter alia,* that: 1) the basic elements of the ABCC program continue under the Foundation; 2) the Life Span and F_1 mortality studies be strengthened by linkage to the tumor and tissue registries; 3) the Adult Health Study be modified to give greater emphasis to objective measurements and automated histories, and less emphasis to physical examination; 4) autopsies no longer be actively solicited and pathologists concern themselves with the examination of tissues and participation in study teams investigating specific diseases; 5) the cytogenetic program be continued and strengthened as needed;

6) the *in utero* sample be studied not only via death certificates but also through periodic examination; and 7) the new tissue registries be actively supported and used in research, and initiation of cancer screening programs be considered (29). A major new research proposal by Neel, the Biochemical Genetics Study (BGS), was also recommended for early implementation. Pilot work had shown feasibility and personnel had been trained in the search for protein variants with such techniques as starch gel electrophoresis and high-speed centrifugal analysis.

At the outset the new foundation faced the important programmatic issues defined in the Crow report (29). By early 1979 all the necessary decisions had been made, the decision to discontinue routine autopsy contacting being the most controversial and difficult. With the autopsy rate below 20 per cent, most autopsies being performed elsewhere in medical care facilities, and repeated efforts to stimulate the program having failed, discontinuation of the very expensive autopsy contacting process that had evoked resentment in the community eventually became inevitable.

Research goals and methods

Goals

The scientific goals of ABCC/RERF have evolved and matured over the three decades of its history in response to the growth of knowledge in the field and the social need for specific information to support regulatory policy and procedures. Because of its isolated position in Japan, however, and the absence of any strong radiobiological emphasis in its staffing, the institutional goals have seemed less influenced by specific radiobiological considerations than one might expect.

From the outset the goals have been dominated by a desire to identify the effects of ionizing radiation rather than to measure them or to explain them in terms of fundamental mechanisms. The process of identification has been fueled by interests in specific effects and by the belief that a broad screening program was required to catalogue the late effects of radiation. Interest in the measurement of effects had to wait upon their identification, and upon the development of dosimetry adequate to serve it.

Until the Francis Report, and except for the genetic study, clinical concepts and goals determined program. Conceived as an opportunity to exploit a unique situation, the program quickly focused on specific interests in cataracts, growth and development, hematologic effects, and genetic effects. As the institution took shape, however, its broad purpose was also expressed in non-specific screening of representative samples of heavily exposed survivors and of lightly exposed or non-exposed controls. These were mainly clinical efforts by internists and pediatricians with laboratory support. If ionizing radiation produced unique lesions, perhaps biochemical or pathologic investigation would have proved more fruitful; but in the absence of unique lesions, investigation necessarily depended on statistical comparisons whose power of detection depended, in turn, on relative size of effect, length of latent period, and size of sample.

Adoption of the Francis Report greatly strengthened the program but did little to change the goals: detection of effects remained the dominant theme, and systematic screening the dominant method. An interest in measurement appeared first in the work of Brill et al. (30) on leukemia 10 years after the leukemogenic effect was first demonstrated (3). In the early 1960s an excess of thyroid cancer was shown (31) and later in the decade breast cancer (32) and lung cancer (33) were added to the list without, however, any real attention to the quantitative aspects of these effects. It was in the reports on the Life Span Study (8, 34) that the interest in quantitating effects first became fully established, with the

latter report (34) providing much of the basis for the estimates in the NAS BEIR report of 1972 (35).

The interest in screening is now no longer dominant, although the expectation is that the nearly general carcinogenic effect of ionizing radiation will eventually be illustrated by a wider array of specific sites and cell types than is presently recognized. Also, there remains some interest in the hypothesis of accelerated aging (36), and a great interest in the possibility of demonstrating the presumed genetic effect of ionizing radiation (24). But, in the main, the goals now center on the measurement of effects rather than on their identification, on dose-response estimates, on the functional form of the dose-response relationship, on the quantitative aspects of latency and duration of effect, on the evaluation of the relative biological effectiveness (RBE) for neutrons, and on the influence of both host factors and environmental factors on the dose-response relationship (24). In addition, there is a greater interest in mechanisms, especially in the possibility that immunologic changes may underlie or mediate the carcinogenic effects that are being demonstrated by epidemiologic methods.

Strategies

One must conclude that no explicit research strategy governed the work of ABCC until the recommendations of the Francis Committee were adopted, although in its report to the NAS the Francis Committee made it clear that the recommended Unified Study Program should be regarded as an extension and rationalization of the program to date (5):

> In an effort to provide increased stability, integration of purpose and effort, and cross-stimulation, the Committee presents with recommendation a Unified Study Program. It is believed that the program retains the valuable features of present procedures but should provide greater consistency and increase the sensitivity of detection at every level.

The proposed strategy, of course, was primarily a strategy for screening, which was the task of the time, well before there was serious talk of developing a physical dosimetry. It was by no means inconsistent with the present emphasis on measurement of effects and analysis of their dependence upon host and environmental factors other than radiation, but did not make explicit provision for this reorientation of goals. It stressed 1) multiple observational systems; 2) interlocking of observations through the use of a common cohort of subjects; and 3) continuity of effort through institutionalization of research plans and recruitment of research personnel from an established agency in the US. In its specifics it ignored the continuing need for information on the genetic effects of ionizing radiation and failed to foresee the critical role to be played by physical dosimetry. But the proposed strategy, coupled with Darling's 15-year tenure as Director, and institutional ties with Yale, UCLA, and the NRC Follow-up Agency, made it possible for ABCC to endure beyond the latent period for many of the tumors caused by ionizing radiation, the existence of which now lends so much force to the program.

Although the Unified Study Program is now outmoded, there has been no new synthesis to replace it other than the 1975 report of the Crow Committee that is less a new blueprint for the future than an evaluation of the older strategy with recommendations for changes in emphasis. In many ways the Unified Study Program is now an anachronism, and some of its heavily institutionalized elements deter its progress. This has been particularly true of the clinical detection program, the Adult Health Study, that played such an important role in the initial detection of solid tumors and in narrowing the scope of probable late effects to carcinogenesis. But the AHS sample is too small any longer to carry the burden of the investigations into

carcinogenesis, a burden for which even the LSS sample is none too large, and its ascertainment of tumors is incomplete without the aid of the tumor and tissue registries. Pathologic detection, especially via post-mortem studies, remains a viable concept in the abstract, but in practice is no longer possible; the community will no longer tolerate an aggressive autopsy contacting program. The death certificate study (the LSS) remains central to the effort, and with the T65D dosimetry, supplemented by conversion factors for absorbed doses to individual organs, will undoubtedly remain the centerpiece of RERF strategy. But even the LSS cannot meet the total need with respect to carcinogenesis, because the death certificate is too imprecise in its attribution of death to individual tumors. For a few tumors the sensitivity and specificity ratios are reasonably high, and for all malignant neoplasms as a class, very high (15), but merely to complete the catalogue of tissues vulnerable to the carcinogenic force of radiation more precision is needed than the death certificate can provide. It must be supplemented by information from tumor and tissue registries, or by *ad hoc* surveys (37), for which the LSS sample continues to provide a most valuable sampling frame.

The Adult Health Study was always the most expensive part of the Unified Study Program, in some years requiring more than half the operating budget. Now, although no longer cost-effective, it cannot be dropped, but only attenuated, because it is the only visible direct contribution to the welfare of the A-bomb survivors. Without some such service to the community it is doubtful that RERF could survive. And, as long as the AHS sample is kept under surveillance, it provides a useful sampling frame for special, *ad hoc* studies requiring clinical examination of subjects. There are other elements in the current strategy, elements that involve possible mechanisms by which ionizing radiation produces biologic effects. One is the cytogenetic program, in which it has been shown that somatic cells exhibit dose-dependent chromosomal changes decades after the insult. But whether these changes are now merely a biologic record of the radiation injury, or portend biologic changes, remains unknown. Finally, there is an active program in which immunologic impairment is being sought as a late effect of ionizing radiation (38).

Sampling considerations

The population and sources of information. The population has three distinct parts: those exposed prenatally, those exposed postnatally, and those conceived only after the bomb (the F_1). Each component posed problems for representative sampling. The Joint Commission sample of examined patients was of unknown representativeness and, in any case, the records contained insufficient identifying information. In 1949 ABCC scientists took a Radiation Census in both cities, identifying about 86,000 survivors in Hiroshima, 94,000 in Nagasaki, and drew upon the results in setting up their early screening programs. In connection with the first postwar national population census in 1950, 284,000 survivors were identified throughout Japan, 98,000 in Hiroshima, and 97,000 in Nagasaki, from responses to the question: "Was any member of this household in Hiroshima City or Nagasaki City at the time of the A-bomb?" It was this sample that the Francis Committee recommended as the basis for the fixed cohorts in the Unified Study Program. As it provided no information on the events of 1945–1950, or on the possibly different health status of survivors who were no longer in the bombed cities in 1950, however, use was later made of the 1946 Hiroshima Atomic Bomb Casualty Census to investigate

these problems (39). Supplementary 10 per cent sample censuses were conducted by ABCC in 1950 and 1951 to identify representative non-exposed subjects, and exposure status has generally been a feature of subsequent official censuses in Hiroshima and Nagasaki.

The *in utero* exposed were defined on the basis of local birth records in the nine months after the bombs plus field investigation of the exposure status of their parents. In developing his F_1 sample for the first genetic study, Neel had access to pregnant women registering for supplementary food rations during 1948–1952. Later this sample was augmented from birth registrations in the 1946–1958 period, to create the present F_1 mortality sample (10). The sample for Neel's Biochemical Genetics Study of F_1 subjects draws upon these samples but additional F_1 subjects were obtained from the family registries of the LSS sample.

Contrasts. Of particular interest is the structure of the statistical contrasts established by ABCC to detect and measure effects. After a brief flirtation with Kure and Sasebo as control cities for Hiroshima and Nagasaki, this approach was abandoned in favor of intrinsic controls. Virtually all of the research performed at ABCC has made use of internal controls, much of it in dichotomies of high dose vs. non-exposed, or high dose vs. low dose, comparisons. Increasingly, however, as the dosimetry improved, regression methods have been used both to identify effects and to estimate their size. The regression approach is well served by the stratified sampling plan based on the recommendations of the Francis Committee for the LSS, for example, in which all eligible survivors under 2.0 km from the hypocenter ATB were to be selected and group-matched by age and sex within city to distally exposed (2.5 to 10.0 km) and to non-exposed subjects, with the addition of all eligibles within the 2.0 to 2.5 km zone. Of about 480,000 individuals thought to be in the two cities at the time of the Francis Report in 1955, about 8.5 per cent were survivors exposed <2.0 km; 5.0 per cent between 2.0 and 2.5 km; 29.4 per cent between 2.5 and 10.0 km; and about 57.0 per cent were non-exposed. When it became possible to calculate individual doses for survivors in the LSS sample, there was good coverage of the entire dose range, including 0.

In all analyses, whether regression or not, the non-exposed occupy an ambiguous position because of differences in health history and their more favorable mortality experience in the early 1950s (40), perhaps because of the selective influence of migration. In time, however, as their mortality rates mounted to the level of the zero-dose group, the non-exposed have been used to augment it. The non-exposed include so-called "early entrants," those who entered the city only after the burst to perform rescue work, see relatives, and the like. This subgroup has long been controversial because some Japanese investigators have claimed that the early entrants have experienced an unduly high incidence of leukemia (41). Within the non-exposed group of the LSS sample, they are identifiable and ABCC studies have revealed no suggestion of excess mortality (34); the dosimetry research suggests that their average exposure was probably not biologically significant (42).

Demographic variables. Migration in and out of the city has been somewhat troublesome from the start. The first attempt at a mortality study, in which all deaths among A-bomb survivors in the city were related to estimates of their number in the city population, foundered on uncertainties as to the effects of migration. The integrity of the fixed cohorts recommended by the Francis Committee has removed much of the impact of migration on ABCC studies, but observational methods such as the biennial clinical examination of AHS subjects, and the various registries, can be applied only to those who remain in the area. Fortunately, out-migration has been independent of

dose (43), so that such programs have not been seriously impaired by migration. Migration does not affect the ascertainment of mortality, as Japan has a national system of family registration, one feature of which is a permanent address *(honseki)*. Vital events occurring anywhere in Japan must be reported to the office having custody of the family registry *(koseki)*.

Sample size. Although the fixed cohorts recommended by the Francis Committee were thought by some NAS advisors to be unmanageably large, they proved to be too small for some purposes, especially in Nagasaki. Dependence upon those exposed <2.0 km ATB as the keystone of the LSS sampling plan resulted in a Nagasaki sample much smaller than the Hiroshima sample, the implications of which were not appreciated until it became plain that what was most wanted from these studies was the dose-response behavior of the Nagasaki sample because its exposure was almost entirely to gamma radiation. The strong admixture of neutrons in Hiroshima, and their high correlation with the gamma dose, make it impossible to separate their effects. Even when a two-cities analysis is made and separate estimates derived for gamma and neutron radiation, it is the Nagasaki experience that appears to control the gamma risk estimate. At the time the LSS sample was being put together (12), it was thought that the air-dose curves for the two cities were very similar. In the mid-1960s it was realized that the yield of the Hiroshima weapon was about 12.5 kilotons, not 20 as previously believed (44). In consequence, the 2.0 km cut that was to have been at about 10 rads in each city actually divided the distributions at about 17 rads in Nagasaki and 2 rads in Hiroshima; at 2.5 km the dose was about 3 rads. Now, when the importance of the cut had been made at 2.5 km in Nagasaki, the Nagasaki sample would have been perhaps 70 per cent larger, but still much smaller than the Hiroshima sample and no stronger in the region beyond 3 rads. Now, when the importance of estimates in the low-dose range is so acute, it is clear that the Nagasaki sample is too small, and especially so at the low-dose end.

The Nagasaki leukemia data have been subjected to several analyses to determine an appropriate dose-response curve and contrasted with the Hiroshima data to estimate the RBE of neutrons (45–48). It is of more than passing interest, therefore, that of the 231 Nagasaki Leukemia Registry cases for the 1946–1974 period, only 34 could be used in analyses based on the LSS sample (49). The uncertainty attached to any dose-response analysis of the leukemia cases in the LSS sample for Nagasaki is so great as to reduce it almost to the level of a *tour de force,* but at present there is no reliable substitute for the LSS sample.

Although the number of A-bomb survivors is not small by ordinary standards, some of the risks for which better estimates are needed are probably so small that even upper confidence limits are likely to be quite high. This is especially true of the genetic risk; even with more than 25 different biochemical markers being examined in perhaps 10,000 offspring of irradiated parents and 10,000 controls in Neel's Biochemical Genetics Study, it seems very doubtful that a significant increase in the mutation rate can be shown. But the study should nevertheless provide quantitative information now lacking, and an empirically determined upper limit on the radiation-induced increment in mutation rate would have great value. Somewhat similar considerations pertain to the estimation of the carcinogenic risk of low doses of low-linear energy transfer (LET) radiation, i.e., those in the neighborhood of background and of the present protection standard for the general population. The chance of demonstrating non-zero risks at this level seems quite small, for the signal/noise ratio is likely to be quite low, and the Nagasaki sample does not

have strong representation in the low-dose range. In this instance it seems doubtful that useful estimates of the low-dose carcinogenic risk will be forthcoming from the Nagasaki data in the absence of prior knowledge of the best functional form for the dose-response curve. The mortality data through 1974 were insufficient to provide statistically significant evidence of any relationship between dose and all forms of cancer except leukemia in Nagasaki, even when the entire range of dose was taken into account (49).

A very useful sampling aid in the AHS has been the subdivision of the sample into 24 schedule groups, one for each month of the two-year examination cycle, so that a representative sub-sample of patients would be called in each month. Short-term studies could be undertaken with the assurance that the examinees were representative and covered the full range of exposure.

Observational methods

The observational methods employed in the studies of the A-bomb survivors span many levels of biologic organization and range from the biochemical and subcellular to the gross morphologic and the behavioral. They vary from the routine and commonplace, such as height, weight, and blood pressure determinations, to unusual or new methods such as starch gel electrophoresis and high-speed centrifugal analysis to detect protein variants in red cells and serum. This variety reflects, in the first instance, the breadth and depth of the search for the effects of ionizing radiation on human health and, in the second, the rapidly changing technology of the times, particularly in biochemistry. Some of the change, of course, has been at the expense of comparability from one time to the next, so that even here, where the intent was to examine patients in the same way cycle after cycle, close comparability has proved elusive, especially in the history and physical examination. Even for routine laboratory determinations, e.g., serum cholesterol, it has not been easy to re-calibrate values obtained at different times with different methods to permit the investigation of changing trends accompanying the great dietary changes occurring in Japan.

Dosimetry. Radiation dose being the fundamental independent variable, the history of ABCC has been in no small part a progressive refinement in the approach to its determination, a process that is still going on. The essential elements are 1) determination of the epicenter and hypocenter of the explosion (50); 2) determination of the precise location of the survivor and the configuration of his environmental shielding (51); 3) determination of the shape of the air-dose curves from weapons tests (44); 4) normalization of the air-dose curves to the yield of each weapon (44); 5) estimation of attenuation factors for environmental shielding (52); 6) estimation of attenuation factors for specific body tissues (21); and 7) estimation of fallout and residual radiation (42). For all but the first two elements the distinction between gamma and neutron radiation is fundamental.

The dosimetry system developed by ORNL in conjunction with ABCC has enabled individual dose estimates to be calculated for 97 per cent of the LSS sample. The remainder represent deaths in the early 1950s for whom shielding histories could not be obtained and survivors whose shielding situations have thus far defied quantitative evaluation, e.g., those in streetcars. Estimates of the error of a dose determination have been made (53), but are necessarily rather approximate. Validation studies of the location of survivors ATB have been generally encouraging, but some of the calculated doses are impossibly high and have been arbitrarily reduced to 600 rads (34). The T65 air-dose curves of Auxier (13) have been reasonably well confirmed by Hashizume and Maruyama (22) from the radioactivity and thermoluminescence in-

duced in building materials at various distances from the hypocenter. The attenuation factors for converting rads kerma to critical organ doses (21) have only begun to be used and it is too early to know how stable these factors are. There is fairly good agreement between the factors generated by the ORNL group and the group at the Japanese National Institute of Radiological Sciences.

Mortality. Observations as to mortality have primarily to do with cause of death, but the extensive series of post-mortem examinations (4353 in 1970) (15) has made it possible to do organ surveys and biochemical determinations as well. The principal autopsy diagnosis has been compared with the certified cause of death in order to determine the validity of death certificate information. These comparisons have provided useful perspective on the underlying cause of death obtained from the death certificate and have demonstrated the importance of supplementing that information with tissue diagnoses available through the cancer registries.

Mortality ascertainment is one of the strongest features of the ABCC studies. Initially ABCC copied all death certificates filed in each city for case-finding and for collation with samples under study. With the actualization of the Unified Study Program, however, eligibility for membership in the fixed cohorts generally depended on knowledge of the *honseki,* or permanent family address. Inquiry could then be made at any time at the corresponding city office to determine survival. Knowing the fact of death, and with appropriate approval, the investigator can have access to the vital statistics schedule containing the cause of death, usually at the health center of jurisdiction. Mortality ascertainment has been continually monitored in a variety of ways and is known to be virtually complete.

Morbidity. Morbidity ascertainment is, of course, much more complex, especially if the concept is broadened to include anthropometric measurements and physiologic changes that suggest no illness but nevertheless are of interest in relation to radiation dose. And at ABCC/RERF morbidity has been perhaps the least successful of the observational systems. Many approaches were tried or at least given serious consideration: reporting admissions to hospitals as they occur, funding a medical care plan that would report each hospital admission of members of the fixed cohort, periodic home visits, and interim mail questionnaires. In the end it was necessary to rely on the biennial screening examination for virtually all the historical information on the AHS sample, and to supplement the routine inquiry at the time of the clinic visit with *ad hoc* interviews and questionnaires as required. Mail questionnaires were used, however, to expand base-line demographic and historical information on the remainder of the LSS sample, and with some success, initially in connection with the needs of the *Ni-Hon-San* study.

The search for morbidity, and for physiologic changes or other characteristics not pathognomic of disease, was the driving force for the Adult Health Study. It was expected that a standard diagnostic examination and history, conducted at two-year intervals, and supplemented by epidemiologic field surveys or hospital reporting of interim illness and by an active surgical pathology service, would bring to light the great bulk of the significant illness in the sample (6). It could also be strengthened by periodic examination of all patients suspected of having a particular disease, and by intensive organ-system reviews in support of which special observational procedures would be employed (6). There was, however, a much greater emphasis on the detection and diagnosis of illness than upon the systematic recording of objective observations. Thus, in time, the accumulated data had their chief value as an index

to probable illness, the future study of which then required calling in the patients above a certain level of suspicion with respect to a particular diagnosis so that uniform, standardized studies could be performed.

As initially planned, clinical observations were to be standardized by teaching, by supplementary written instructions, and by standard record forms, and checked to the greatest extent possible by an independent observer. Anything unusual was to be pursued in an appropriate way, so that any existing disease or other condition could be correctly diagnosed, and the patient referred for any needed treatment. Despite considerable success in the early years of the program, after the first few cycles it proved difficult to maintain the high standards set, especially with respect to independent review and recordkeeping.

Although the process of examining patients proved very difficult to standardize and control indefinitely, the AHS subjects responded well to the biennial solicitations, and their continued flow through the clinics, in 24 randomly selected subsets called up in turn throughout each month of the cycle, provided an unusual opportunity for the special surveys that have been the chief output of the AHS program (54). And, although it did not prove possible to improve their interim histories by means of mail questionnaires or home visits, or by systematic tapping into the medical care system, it was possible to collect information on particular diseases, especially individual cancers (37), from the local hospitals with which to supplement the information obtained in ABCC clinics. The cancer registries offer the chief device for supplementing the observations made in the clinic, but it has become clear that the AHS sample is too small and the entire LSS sample is now the preferred sampling frame for cancer incidence as well as mortality.

Although the ABCC program has existed to detect and measure the late effects of ionizing radiation, ABCC investigators have taken an interest in disease whether or not radiation appeared to be involved. Both clinical and laboratory interests have contributed to the study of a wide variety of diseases and potential disease-markers and greatly enriched the observational base (55).

Genetics and cytogenetics. A remarkable aspect of the early genetic work was the ascertainment of pregnancy through the registration of pregnant women for supplementary rice rations after the fifth month of pregnancy, and of deliveries through the reports of attending midwives and, occasionally, physicians. Information on stillbirth, birthweight, sex, and any malformation was obtained from the attending midwife or physician. An ABCC physician then examined the child in the home, at once if there was a report of an abnormal termination, otherwise on a more leisurely schedule. By these methods it was possible to study over 93 per cent of all the pregnancies that went to term in the study period, 1948–1953, over 76,000 in all. In addition, a random 28 per cent of the births were selected for examination at nine months of age to detect malformations that might have been overlooked at birth, and to obtain anthropometric data. Autopsies were also performed, especially in Hiroshima, where 62 per cent of infants stillborn or dying in the first six days of life were examined at necropsy. The indicators of possible radiation damage were sex ratio, birthweight, anthropometric measurements, stillbirth, neonatal death, and gross malformations.

Cytogenetic methods first established by Bloom et al. (26) in 1965 play a large role in the studies of A-bomb survivors (27). The cell preparations of survivors are examined for interchange aberrations and clones of cells with the same aberration in single individuals. The study of the offspring of irradiated parents is

directed at genetic effects, particularly as these may be manifested by cells containing abnormal numbers of sex chromosome and structural chromosomal abnormalities (28).

In the Biochemical Genetics Study, initially 25 biochemical markers were selected for the search for variants among the F_1 rare enough to justify examination of parents to establish the variant as simply a rare, inherited form, or a possible mutant. Additional markers have since been added to give the inquiry more power.

Statistical methods

Of interest here is not the inventory of specific statistical procedures employed by ABCC/RERF investigators, but the way in which they have been applied to the problems of inference and estimation that have arisen in the program. Statistical methods are basic because, with the possible exception of radiation cataracts, the lesions produced by ionizing radiation are not unique, or identifiable as to specific etiology, so that statistical comparison provides the only means of attributing them to radiation.

Screening for effects. This was easy enough in the case of leukemia where the relative risk among those exposed to the highest dose levels was on the order of 50 to one. But for the general class of carcinogenic effects relative risks of 10 or more are uncommon, and the average, on the order of two or three. The risk of missing real, but small, effects is ever present (56). Most of the screening has been done with dichotomies of high- vs. low-dose groups adjusted for any demographic differences that might otherwise bias the comparison. In recent years these have been supplemented by regression analyses in an effort to achieve the utmost power that the dose distributions would permit.

In the screening efforts of ABCC investigators, little attention has been paid to the RBE for neutrons in analyses that combine the experience of the two cities. Most such analyses have been, in fact, city-specific, and the more that is learned about the human effects of ionizing radiation the more necessary seems a city-specific approach to both screening and estimation. Although most dose-response curves for specific forms of cancer appear to be approximately linear for Hiroshima, dose-response curves for Nagasaki are quite uncertain. Further, not only do the Nagasaki data look non-linear in some instances but non-linearity cannot be excluded on statistical grounds even for breast cancer incidence, which appears linear to the eye (37).

Dose-response. The linear hypothesis became rather firmly established in radiation protection work during the mid-1950s on the basis of experimental work on the genetic effects of ionizing radiation. The force of numerous experimental demonstrations of non-linear dose-response functions for low-LET radiation, combined with the possibly curvilinear dose-response function for leukemia among Nagasaki survivors (45), however, has injected a great deal of uncertainty into all discussions of human data, especially as they are employed to estimate low-dose effects. In the NAS 1972 BEIR Committee report ABCC data were extensively relied upon to produce low-dose estimates on the basis of the linear hypothesis (35). Manipulation of the Hiroshima and Nagasaki leukemia data by several investigators (45–48) has underscored the possibly linear-quadratic form of the dose-response relationship for gamma radiation. In none of these analyses, however, has it been possible to show that the non-linear function fit the data significantly better than the linear function. Moreover, the Nagasaki leukemia data in the LSS sample, on which these results primarily depend, are very few, include 0 observations in one or two dose-intervals, depending on the grouping of dose, and exclude 70 per cent of the infor-

mation in the Leukemia Registry of all survivors diagnosed in the area in the 1946–1974 period, whether or not members of the LSS sample. If the entire Registry sample is examined in relation to the dose-distribution of all survivors enumerated in Nagasaki at the time of the 1950 Census, a much less curvilinear dose-response function is obtained (49). It is by no means certain, therefore, that the true relationship for the leukemogenic response to low-LET radiation is not linear.

More recent work (57) has made use of a dose-response function for low-LET radiation suggested by Brown (58) on the basis of experimental and some theoretical considerations:

$$y = (aD + bD^2)exp^{-cD - dD^2} \quad (1)$$

where y denotes the excess above normal incidence, D is dose, and a, b, c and d are fitted constants constrained to be positive. The exponential term imparts downward curvature in the region of cell-killing, but the number of constants to be fitted is usually too large for human series. Hence,

$$y = aD + bD^2 \quad (2)$$

is the more practical form of expression 1. When both Hiroshima and Nagasaki data are to be fitted, separate account is taken of gamma and neutron dose in the expression

$$y = aD_\gamma + bD_\gamma^2 + cD_n \quad (3)$$

where D_γ is the gamma dose, D_n the neutron dose, and a, b, and c fitted constants. Depending on the data, the values of the fitted constants will emphasize one or another of these terms more or less than others, so that the best fitting function may be linear in both gamma and neutron dose, quadratic in gamma but linear in neutron dose, or both linear and quadratic in gamma and linear in neutron dose. These functions have been fitted to the death certificate data for the period, 1950–1974, to breast cancer incidence data, to the Leukemia Registry data, and to head-size of the *in utero* exposed (57, 59). In no case was it possible to discriminate among the competing dose-response models for the effects of gamma radiation. A corollary finding was that RBE estimates had extremely large standard errors. Further, the estimates of a and b obtained in analyses of both cities jointly differed little from those obtained from fitting the Nagasaki total dose, the neutron component of which is only about 2 per cent.

RBE estimation. In their 1974 paper on leukemia among the A-bomb survivors in the LSS sample, Rossi and Kellerer (45) suggested that the RBE for neutrons in the leukemogenic response was about 45 $D_n^{-\frac{1}{2}}$ where D_n is the neutron dose. Although several other investigators have obtained similar results on the same data (46–48), the Nagasaki leukemia cases in the LSS sample are too few to inspire great confidence in the result. The linear-in-gamma, linear-in-neutron model is equally consistent with the data, and implies a constant RBE of about 10 (59).

Latent period, duration of effect. When models are created for radiation protection purposes and the human experience studied for risk coefficients to be employed with them, one must specify, in effect, the natural history of whatever effect is being modeled—how long after exposure it is before the effect becomes apparent, when it peaks, and how long it lasts. For leukemia ABCC investigators have shown that the effect probably began two to four years after the bombing, peaked six to seven years after the bombing, and essentially disappeared about 30 years after the bombing. These results are in accord with those obtained from the experience of the British patients with ankylosing spondylitis treated by x-ray (60, 61). For solid tumors, however, beginnings and endings are much more difficult to establish, although it is fairly certain that none of the effects, except

perhaps bone cancer, is as short-lived as leukemia. The upswing marking the end of the latent period is a gradual process, and a purely empirical approach, without the benefit of an *a priori* model, is relatively unsatisfactory (49). Present indications are that latent periods for solid tumors probably vary, depending on the tumor, and that they are generally 10 years or longer (57).

Patterning longitudinal observations. With a biennial examination cycle, a standard screening examination on about 85 per cent of eligible subjects at each cycle, and 10 cycles completed, ABCC/RERF investigators would seem to have one of the greatest longitudinal databanks in the world. Yet strictly longitudinal analyses, i.e., those in which serial observations on each individual are assembled and patterned in various ways, as might be done with growth data, are notably few. In recent analyses of blood pressures (62) and serum cholesterol (63), ABCC investigators have examined trends in the movement of these values over time or with age, but only on a group basis. To predict hypertension and cardiovascular mortality, individuals were characterized on the basis of a single early blood pressure reading; most readings were not used. In a growth and development study, however, Shohoji and Pasternack (64) were able to derive a function that could be fitted to the serial data of each individual to characterize his growth pattern, the parameters of which could then be studied in relation to radiation dose or any other risk factor.

Competing risks. Although much of the early experimental work on the accelerated aging effect of ionizing radiation did not make use of life-table or other methods to untangle competing risks (65), epidemiologists working with human data are well aware of this problem. At ABCC life-table techniques have been little used, but expectations have typically been based on person-years or the equivalent, i.e., the number of survivors in successive short intervals. At the end of 1974, just 25 per cent of the A-bomb survivors in the LSS sample had died, so that there might be room for distortion if the problem of competing risks were not kept in mind. Groer (66) has recently questioned the validity of ABCC/RERF analyses on the grounds that competing risks may have been ignored, but the record suggests otherwise.

Other risk factors. Analyses of demographic factors have shown an appreciable sex difference in the risk of radiation-induced leukemia (67), and age differences in the risk of most radiation-induced solid tumors (49). The dose-groups are fairly well balanced as to demographic composition within city, but customarily age- and sex-adjustments are made, either by means of the Mantel-Haenszel procedure (68) or indirect standardization by means of age-, sex-, and calendar year-specific death rates for all Japan (34). There is more variation among dose-groups with respect to socioeconomic factors, however, since the dose in air is a function of distance from the hypocenter. The influence of socioeconomic factors has been too little studied by ABCC/RERF investigators. Such studies as have been performed have not uncovered evidence of confounding sufficient to affect dose-response relationships (49, 69, 70). Of greater current interest is the possibility of interaction between radiation and other risk factors for cancer. Epidemiologic studies of leukemia by ABCC investigators have failed to identify other important risk factors in the A-bomb experience (71), but for both breast cancer (69) and lung cancer (70), factors other than radiation have been shown to be important; in neither case has interaction been demonstrated, but the studies are small. Finally, it must always be borne in mind that most of the energy released by the bombs was in the form of heat and blast, and that all three forms of energy-release are highly

correlated. ABCC investigators have relied mainly on the correspondence of their results with experimental and other human findings and have not generally attempted to factor blast and heat into their analyses. An exception is the joint analyses Jablon et al. (7, 72) made of radiation and burns, which suggested that, for fixed distance, mortality was unrelated to a history of burns.

Contributions to knowledge

A full appreciation of the scientific contributions of the ABCC/RERF program is best gained from the reports of the United Nations Scientific Committee on the Effects of Atomic Radiation (73), from the NAS BEIR Committee reports (35, 57), and from the 1975 supplement to the (Japanese) *Journal of Radiation Research* (74). Here there is reason to mention merely the highlights.

Genetic effects. The genetic studies of Neel and co-workers provide the only substantial data on the probable genetic effects of ionizing radiation in man. Their larger significance lies in their usefulness in setting approximate limits on the frequency of radiation-induced mutations in man and in suggesting that human genes are not much more mutable than those of experimental organisms, notably mice (29). The pregnancy termination study had approximately 90 per cent power to detect a doubling of the normal rates of stillbirth, neonatal death, and malformation (2). In their second report on the F_1 mortality study, Neel et al. (75) estimated the minimum genetic doubling dose for mutations resulting in death during the first 17 years of life to be 46 rem for fathers, 125 rem for mothers. The promise of the present BGS is that it may provide a more direct measure of the mutagenic effect of ionizing radiation. The studies of chromosomal aberrations of leukocytes have been particularly useful in quantitating the dose-response relationships for both gamma and neutron radiation and in demonstrating the existence of clones of aberrant cells (76).

Teratogenesis. The teratogenic effect of ionizing radiation was well established before the A-bomb (77), but it has been both better defined and more precisely measured by studies of the A-bomb survivors than by studies of other series. Diminished stature, small head size, and mental retardation have all been shown to be dependent on the size of the dose to the fetus, and probably also depend on the quality of the radiation (4, 78). Neutrons appear to be more effective than gamma radiation, and the dose-response functions may also differ, at least for microcephaly and mental retardation (78). Studies of fetal age ATB showed that the central nervous system was especially sensitive to radiation during the seventh to the 15th weeks of gestation (79).

Cataracts. The cataractogenic effect of ionizing radiation also was shown before 1950, when the first reports on A-bomb survivors began to appear (80). The ABCC/RERF studies have shown that clinically significant cataracts were probably produced by ionizing radiation only at high doses (81) and that the prevalence of incomplete lesions is dose-dependent (82). Although the quality factor for neutrons is probably well above unity, this has not been definitely shown by ABCC investigators (83).

Cancer. It is with respect to the carcinogenic effect of ionizing radiation that the studies on A-bomb survivors have been most fruitful, contributing information on the specific tumors caused by whole-body radiation (57, 73), on dose-response aspects of radiation carcinogenesis (34, 48, 49), on the quality factor for neutrons (48, 59), on the significance of other environmental factors and of host factors on the carcinogenic response, and on latency and duration of effect.

Life-shortening. The life-shortening effect of ionizing radiation has been

repeatedly demonstrated experimentally, and by implication also in man on the basis of the carcinogenic effect. There are, however, few human studies that provide information on the basis for the life-shortening effect. The ABCC/RERF studies suggest that, in man, the life-shortening effect is probably dependent upon the carcinogenic effect alone, that there probably are not other effects that contribute materially to the mortality burden of exposure to ionizing radiation (84). The data on patients with ankylosing spondylitis treated by x-ray suggest the same conclusion (85), but the mortality experience of US radiologists, when contrasted with that of medical specialists less exposed to ionizing radiation, holds open some possibility that the life-shortening effect may not depend entirely upon excess cancer mortality (86).

Fertility. Investigations of fertility at ABCC have been hampered by insufficient control over the influence of contraception and abortion. In failing to demonstrate a lower level of fertility (87) or a higher prevalence of sterility (88) among A-bomb survivors, however, ABCC investigators have provided significant support for the view that human sterility results only when the dose level is high, perhaps in the lethal range for the male, and that any effect of lower doses on fecundity, e.g., through diminished spermatogenesis, is short-lived. Studies of the *in utero* exposed are in a preliminary stage, but have not thus far provided evidence that fetal exposure induced significant sterility in the A-bomb survivors (89).

Non-radiation work. In addition to their contributions to knowledge of the effects of ionizing radiation on man, ABCC investigators have provided valuable information on a number of diseases in Japan, especially cardiovascular disease, diabetes, rheumatoid arthritis, thyroid disorders, gastric cancer, tuberculosis, pulmonary disease, urinary disease, and diseases of the liver. This work has recently been reviewed by Hamilton and Brody (55). Of particular interest to epidemiologists is the *Ni-Hon-San* study, the comparative clinical, pathologic, and epidemiologic study of cardiovascular and cerebrovascular disease in 45–69-year-old Japanese males living in Hiroshima and Nagasaki, Honolulu, and California (19). The first genetic study led naturally to one on the genetic effects of consanguinity, as it enabled Neel to assemble a sample of 5300 children of consanguineous parents. In their 1958–1960 study of these children and controls, Schull and Neel (90) found the effect of inbreeding on mortality and morbidity in the Japanese to be well below estimates reported for most Caucasian populations.

Sociologic perspectives

US-Japanese relations

The Atomic Bomb Casualty Commission was a unique institution, and its history, as well as its transition to a Japanese national foundation under the Welfare Ministry, deserves the critical scrutiny of competent social scientists. Rooted in an act of war, nourished by an occupying military force, and maintained for three decades by funds provided by the US agency most responsible not only for research in radiation biology, but also for the development of nuclear technology, it has nevertheless made major contributions to knowledge of the empirical risks of ionizing radiation on human health. It is a tribute to the tolerance of the Japanese people, and to the understanding attitude of the Japanese government that, despite some local hostility, despite some confusion in the press and local public opinion as to the mission of ABCC, despite the early ABCC decision to engage in research without providing an extensive medical care service, and despite the frequent portrayal of ABCC as a minimizer of radiation effects, the institution was permitted to continue

and to achieve an international reputation for thorough scientific observation in a controversial field.

The transformation of the American ABCC to the Japanese RERF took place 30 years after WW II, and was stimulated more by a fiscal crisis brought on by Japanese inflation and the declining value of the dollar relative to the yen than by considerations of the effectiveness of an American-controlled study in the Japanese community. Darling, as director of ABCC since 1957, had the vision and the courage to call attention, in his 1967–1968 annual report, to the anachronism that was ABCC 23 years after WW II. But it took the subsequent fiscal crisis, which carried the threat of closure, to bring the two governments to the conference table.

Would ABCC have been more successful if the Japanese presence had become dominant earlier in its history? Certainly one can see in the contraction of ABCC in its last decade, in the difficulty of recruiting Japanese scientists for even short-term assignments, and in the increasing difficulty faced by ABCC investigators in getting data from the medical care facilities in Hiroshima and Nagasaki, ample reason to believe that, under Japanese control, the institution would have been even more successful. And yet there is nothing in the four-year history of RERF to support this. All the old difficulties face RERF as they did ABCC. Japanese university investigators are active contributors to the radiation biology journals, but have shown little interest in epidemiologic studies of the human effects of ionizing radiation. Epidemiology, however, is not well developed in Japan and it lacks support from its sister discipline, statistics, which is little applied to medicine in Japan. The formal study of statistics is largely confined to departments of mathematics in Japanese universities, and no great interest has been taken in medical applications. This is in sharp contrast to the statistical techniques involved in quality control, carried to Japan by W. Edwards Deming during the occupation, embraced by Japanese industry, and long taught mainly in industrial seminars. There are no schools of public health in Japan, and the teaching program of the Institute of Public Health of the Welfare Ministry is aimed chiefly at training health officers.

Although for many years the only systematic access to medical care records has been through the registries for leukemia and other forms of cancer, and the arrangements for these activities have at times been threatened with cancellation, under agreements with the national authorities, access has been granted to the family registers containing information on vital status, and to the cause of death information in the hands of the public health centers.

The survivors

In response to an aggressive contacting policy, participation in the biennial examination program of the Adult Health Study has fallen off very little since the examinations began in 1958, despite the ABCC policy of gathering research information without providing medical care and a generally unfavorable local press. Perhaps subjects have recognized that their examinations would be more thorough and competent than those they might easily obtain at the hands of a busy practitioner seeing 50 to 100 patients a day. The press has often employed the "guinea-pig" model in inveighing against the failure to provide medical care. In sharp contrast to the stable participation rate in the clinical program, the autopsy procurement rate rose rapidly after the start of the new program in 1961, peaked in 1963–1964, and then declined to a point where, in 1975, the Crow Committee recommended discontinuation of the effort, a decision finally made in 1979. Although the reasons for the inability of ABCC personnel for pathology contacting to maintain the rate have been

actively debated at ABCC and RERF, factual data are few and no remedial strategy was devised. There was, however, considerable hostility to the program in press accounts of ABCC activities, with ABCC pathologists caricatured as vultures waiting for the A-bomb survivors to die. And, although the autopsy percentage was generally higher if the deceased had been a subject during life, it was discouraging to find that families who had assented to autopsy on a first occasion would more often refuse when a second member died.

To a foreign observer it would appear that there has been very little effort on the part of Japanese authorities or the medical profession to reassure the A-bomb survivors about their health. With so much public misunderstanding of its mission it would have been folly for ABCC to have attempted in any systematic way to alleviate the anxiety of the survivors about their future health. But one would have thought that Japanese public authorities, or local physicians, might have paid more attention to this problem. Reading Lifton's accounts of interviews with survivors (91), for example, one is often struck by the discrepancy between the survivor's account of his fears and his stated distance from the hypocenter ATB. And when a modified Cornell Medical Health Questionnaire administered to subjects of the Adult Health Study was scored for anxiety about health, there seemed to be little relation between this score and radiation dose, the objective indicator of risk. In the 1950–1974 study of mortality among 82,000 survivors it was estimated, on the assumption of linearity of dose-response, that all 285,000 A-bomb survivors registered throughout Japan in 1950 had probably sustained, in addition to 70,000 deaths attributable to other causes in the 1950–1974 interval, 415 deaths (90 per cent confidence interval, 337–492) from radiation-induced cancer, including leukemia (49). For the 214,000 exposed to no more than one rad, the parallel figures would be about 10 deaths from radiation among about 52,500 deaths in all. But no systematic efforts appear to have been made to reassure survivors, especially those exposed to very low doses. For a long time, in fact, every death of an A-bomb survivor was an "A-bomb death" in the press, and it would appear that much of the propaganda about A-bomb survivors was not in their best interest because it blurred the distinction between deaths caused by radiation and those that would have occurred in the normal course of events. Whether the survivors would, in fact, be able to respond to objective facts with a lessening of anxiety remains unknown. The acute experience was emotionally so profound that factual material might have little reassurance value. But the effort seems not to have been made. Instead, the efforts to impress the world with the very real horrors of nuclear war, and the Japanese government with their need for supplemental income and medical assistance, may, in exaggerating the ill-health of the survivors, tend to perpetuate unnecessary fears among many survivors. Although we have learned more about the human effects of ionizing radiation from the experience of the A-bomb survivors than from any other source, this knowledge may have benefited them very little.

Staffing

In the early years of the post-war reconstruction, ABCC employment was undoubtedly attractive to Japanese professional and scientific personnel, but as Japanese medical education advanced, and the economy prospered, much of the appeal was lost. A foreign institution with only minimal ties in Japan through the JNIH, which itself had little strength to share, and lacking local institutional roots such as might have been formed with the local universities, ABCC had difficulty building and maintaining a

strong Japanese professional staff. Its greatest successes have been in response to unusual leadership and the stimulation of new scientific techniques and procedures, as in Neel's genetic studies, in the cytogenetic program developed by Bloom, and in the early epidemiologic leadership of Keizo Nobechi. (Nobechi is best known for his work on cholera.) Although it is difficult for a foreign observer to judge the strength of the various limiting factors, it does appear that the association of ABCC, and RERF, with the Welfare Ministry rather than with the Education Ministry, and, in particular, the absence of formal ties to medical schools under the aegis of the Education Ministry, has also inhibited Japanese participation in the professional and scientific work of the organization. There was, however, reason to fear that local control might make more difficult the task of objective observation and reporting of findings.

For US investigators a tour at ABCC/RERF is generally attractive only in the very early stages of a career, before patterns are set and institutional ties formed, or in the later stages, when ties are loosening and interests changing. The opportunity to live and work in Japan is a great magnetic force for recruiting US personnel, but the best situation is one in which one's career pattern itself takes one to Japan with no disruption of institutional ties. It was for this reason that the Francis Committee recommended that the NAS-NRC try to establish firm links with US institutions capable of providing staff under secure arrangements. None of the three groups linking themselves to ABCC, however, was both sufficiently dedicated to radiation biology, and sufficiently strong, to continue the relation indefinitely. Perhaps a consortium of universities would have proved more effective. As long as the doctor draft was in effect in the US, it was possible to recruit young physicians for two-year, alternative-service tours at ABCC as officers of the Public Health Service. This was a very important source of professional strength, particularly in clinical medicine and in pathology, but it provided men with little or no investigative experience and no training in radiation biology or nuclear medicine. The lack of trained epidemiologists can be partly overcome by developing collaborative working patterns between internists, say, and statisticians, but the lack of training in radiation biology is not so easily overcome.

Any discussion of staffing would be incomplete without some reference to the fact that the ABCC experience has had a major influence on the shaping of research interests and professional careers for a good many, both Japanese and Americans, and not only physicians but also statisticians, geneticists, and other scientists. This has occurred partly, of course, because so many younger men and women were exposed to ABCC opportunities before their career patterns were established, and partly because of the exceptional opportunities offered at ABCC to those able to perceive them.

Research and service

As the binational discussions leading to RERF appeared on the horizon, there was much taking-stock in the Japanese community, especially in medical organizations and among local government officials. Three themes dominated these discussions: 1) Japanese control; 2) local participation in management; and 3) the joining of research with medical care of the survivors. This last theme represented a general reaction against the ABCC policy of not providing treatment which was thought to reflect an attitude of not caring about the welfare of the survivors. A research operation that assumes responsibility for medical care, of course, thereby commits itself to an entirely different level of expenditure and if there was any single source of financial pressure on ABCC over its three decades of operation it was the cost

of the clinical screening operation, even without any assumption of responsibility for the general medical care of the clinical (AHS) sample. Further, there was nothing callous or uncaring about either ABCC policy or practice. Not only were subjects given written reports of their examination findings but also their physicians were informed. Where referral was indicated it was made. For many years the ABCC clinic in Hiroshima maintained a "diagnostic" ward of 12–15 beds where treatment was provided to patients needing specialized care that ABCC physicians seemed best able to provide. Some treatment was routinely provided in ABCC outpatient clinics, e.g., to those with low hemoglobin levels. And a medical social work program assisted the indigent with funds and referrals for needed medical care. Had the clinics not been run in a caring fashion, the subjects would probably not have been willing to participate in the biennial examination program as fully as they actually have for more than two decades, especially in view of the great improvements Japan has made in its medical care system. Nevertheless, the ABCC clinics were merely on the periphery of that system and their importance to the community, while great in the early years of reconstruction, gradually declined as Japanese medical education and medical facilities improved. Since about 85 per cent of the clinical subjects returned for their biennial examinations, and since the late effects of ionizing radiation are largely confined to cancer, it is by no means clear that an integration of research and medical care would have brought results sooner, or that results would have been more definite or better understood. But the work of ABCC/RERF would have had greater acceptance in the community, and its foreign character might not have seemed so blameworthy. Morbidity would have been more fully ascertained and the opportunity might have been created for systematic morbidity reports akin to the mortality reports that have been so well accepted. And more information would have been available for examining the role of ionizing radiation in the presence of other risk factors. But it is hard to see how the general nature of the findings, their cogency, and their sufficiency, could have been very different even if full ascertainment of morbidity had been possible. If the late effects of ionizing radiation were less confined to cancer, of course, a very different evaluation might have been made.

Summary and conclusions

Reflecting on the history of ABCC, and on the early years of RERF, the successor organization, one sees a very imperfect operation that has, nevertheless, achieved a measure of success that warrants its worldwide recognition in an area of increasing social importance. In its origins one discerns a clear vision of goals, but not of research strategy; its early history was characterized by some fumbling and misdirection in the search for somatic effects of ionizing radiation, while its search for genetic effects was marked by excellence of both strategy and execution. Frequent changes in leadership and fiscal crises brought it to the brink of disaster on more than one occasion, but the ABCC has been maintained by the vision and good sense of some few individuals, by the historic importance of its mission, and perhaps by some early positive findings. Had the military occupation been less benign and the Japanese national character less tolerant, ABCC might well have foundered in its difficulties during its first decade.

Of particular significance for epidemiologists is the dynamic push that was given to the program by an epidemiologic review and redirection under an overall research strategy that proved highly effective for the ensuing two decades. If there is any single, most important lesson to be learned from

the ABCC experience, it is the importance of a research strategy in any long-term, prospective, follow-up study. The general nature of the possible effects must be visualized, the observations needed to detect such effects specified, and sampling alternatives carefully assessed. A particular merit of the Francis proposals was that observations of differing biologic depth became mutally re-inforcing through the use of a common fixed cohort of subjects. The strategy worked well not only during the immediate years after the Francis Report, but also throughout the second decade when the goals became more specifically focused on cancer, and the emphasis began to shift from screening to the measurement of effects. Even now it is outmoded only in some of its particulars.

The lessons of ABCC apply rather directly to the investigation of a disaster situation from which long-term health effects are feared, and with only somewhat less force to any long-term, prospective follow-up study. For me the most important lessons are:

1) Devise an adequate overall strategy early;

2) Register or identify the population of interest as soon as possible, taking particular care to include all the identifiers on which follow-up may depend;

3) Determine the parameters of the exposure in fine detail, with emphasis on objective physical measurements;

4) Employ a cohort approach with a clear plan for making statistically powerful comparisons to identify and to measure effects, either in dose-specific fashion or in exposed vs. unexposed comparisons;

5) Evaluate carefully the potential value and cost-effectiveness of alternative end-points, particularly mortality vs. morbidity and defects;

6) Plan staffing patterns to provide not only excellence of leadership and scientific performance, but also continuity;

7) In a foreign operation of long duration, endeavor to sink deep local roots.

Registration of the population and determination of its exposure need to be done at the earliest possible moment, before migration or blurred memories make the task difficult. A complete registration permits flexibility in sampling and provides a source to which one can return if critical samples are too small or need change. For the long term, good identification is essential.

Case-control methods have their place, even within cohort studies, but in a long-term, prospective study the investigator needs a solid grip on the population of interest that only the study of a fixed cohort can provide. The results of ABCC studies based on all survivors in the city, or otherwise lacking a firm sampling base, were always suspect, and it was one of these that triggered the assignment to the Francis Committee. But cohorts can be too small, and it is clear now that a mistake was made in selecting the Nagasaki sample, and that it should have been made as large as possible. It simply was not appreciated, in the early years, that the Nagasaki sample would be more important than the Hiroshima sample because of the mixed gamma-neutron quality of the Hiroshima radiation. Crucial issues relating to the effect of low-dose, low-LET radiation and dose-response relationships perhaps remain more uncertain today than they might have been had the importance of the Nagasaki experience been fully appreciated when sampling plans were made.

An important lesson of the ABCC experience is that serious considerations should always be given to mortality as an end-point, if this is consistent with the expected nature of the effects being sought. If the effects are being expressed in terms of both morbidity and mortality, then the cost-effectiveness of the mortality approach may outweigh that of the morbidity approach by a wide margin. Programs requiring clinical examinations can be prohibitively expensive if the effects being sought will be expressed

in increased mortality. There is a widespread tendency to deprecate the death certificate, but the experience of ABCC shows that this was the single most important document pertaining to end-results. In another context, of course, this might not be the case, and in 1947 it could not have been known that cancer would be the dominant finding. But there are ways of strengthening death certificate information, as has been done at ABCC, especially through the use of autopsy information and disease registries.

The experience of ABCC clearly shows that a rotating staff can contribute to instability and discontinuity of program, especially when top leadership is also unstable. ABCC learned how to minimize this problem in time, but not until there was an overall research strategy to govern the establishment of priorities and the allocation of resources. As director, Darling insisted on research protocols that were binding on the institution and the individual departments, for all too often a man could not finish his project in a two-year tour, and the larger program elements (LSS, AHS, F_1 mortality, pathology, etc.) had to endure, whatever the preferences of individual investigators might be. Having a single, strong director for 15 years greatly facilitated the implementation of this policy and contributed to the stability of the program in other ways. Finally, although its significance might not apply generally, in an overseas operation especially it is important that there be a home base for personnel sent out on a short, e.g., two-year, tour of service. The ABCC effort in this direction was helpful, but provided no ideal solution; the affiliated departments were too small and too little committed to radiation biology. The UCLA Department of Pathology could send men for only one year at a time and quickly ran out of staff to send. The arrangement with Yale provided chiefs of medicine and supporting staff through 1974, and Stuart C. Finch, who served as chief in 1960–1962 while on leave from Yale, is the current Vice-Chairman and chief of research at RERF. In its 18-year period of responsibility for statistics and epidemiology the NRC Medical Follow-up Agency provided from its own staff a department head for 12 years, and other professional staff for an additional eight man-years. But a consortium of universities might have had more power and provided more effective input than these three separate departments.

Neel's continued interest in the genetic effects of the nuclear radiation from the bombs has been very effectively implemented in an entirely different pattern. Without taking a staff position after 1952 or stationing Michigan University staff at ABCC after 1956, Neel has nevertheless managed to inspire and direct the work in genetics (apart from cytogenetics) over a subsequent period of more than two decades. He is now directing the Biochemical Genetics Study on the basis of visits by himself and members of his staff, and is directing the assignment to the project of RERF staff he has trained in Ann Arbor. This pattern is a very effective one, provided that a viable core organization has independent support.

Finally, although conditions will vary from country to country and time to time, the experience of ABCC suggests that survival of a long-term research operation in a foreign country may be difficult unless deep local roots are developed. ABCC and its staff played a large part in the life of the medical community in the early years but, in time, lacking any real responsibility for the ABCC program, and hastening to achieve parity with medical schools in the West, the local teaching institutions surpassed ABCC in all areas except the narrow field of its specific mission. These institutions provided occasional junior staff, and cooperated in various ABCC studies, but did so without committing any of their real strength to the effort. Had the mission of ABCC

been as fascinating in 1965 as was the mission of the Joint Commission in 1945, the situation might have been otherwise, even without shared responsibility. Perhaps seeing little opportunity in the ABCC program for more than descriptive studies, the local teaching institutions went their own way and ABCC found it increasingly difficult to maintain a strong Japanese staff or a vital place in the medical community.

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