LONG-TERM EFFECTS OF IONIZING RADIATION - LESSONS FROM HIROSHIMA AND NAGASAKI

Itsuzo Shigematsu, M. D.[1], Shigenobu Nagataki, M.D [2], Kazunori Kodama, M.D[3].

[1]Consultant Emeritus, [2]Chairman, [3]Chief, Department of Clinical Studies

Radiation Effects Research Foundation, Hiroshima and Nagasaki

Introduction

The United States government established the Atomic Bomb Casualty Commission (ABCC) in Hiroshima and Nagasaki in 1947 and 1948, respectively, under the auspices of the National Academy of Sciences. The purpose was to study late health effects in the people exposed to the atomic bomb radiation To attain this purpose smoothly, branch laboratories of the Japanese National Institute of Health were attached to ABCC in 1948.

This arrangement continued for 28 years until it was replaced in 1975 by the Radiation Effects Research Foundation (RERF) which is equally funded by the two governments of Japan and the United States Thanks to the cooperation of the survivors and the contributions of a multitude of scientists, these studies flourish to this day in what must be the most successful long-term research collaboration between Japan and the United States

Research activities of ABCC and RERF

The first of the major programs to be initiated, in 1947, was a genetic study of the first-generation children of survivors (commonly known as F1) The current research program began as a series of platform protocols based on a fixed cohort of 120,000 survivors who were listed in the Japanese National Census of 1950 The Life Span Study (LSS) follows this entire cohort by means of a national death-certificate retrieval system The Adult Health Study (AHS) follows a subsample of 20,000 survivors using biennial health examinations

Recently, the mortality studies have been enhanced by cancer incidence studies using the RERF-developed tumor registries in Hiroshima and Nagasaki. Finally, a cohort of several thousand individuals who were in utero at the time of the bombings is also being followed

Since the ABCC/RERF fixed cohorts do not include persons who died between the time of the bombings and 1950, the results may reflect a resistant subpopulation of survivors who are not representative of overall human risk. However, study after study has failed to show any difference in the radiation sensitivity of the survivor's cells as a function of the survivor's radiation dose.

The central finding of the mortality and cancer incidence studies is a strikingly linear, nonthreshold increase in cancer risk with radiation dose. (Figure 1) At 1 Sv, the relative risk is approximately 1.6, occurring in essentially all tissues and including benign and malignant diseases. Some evidence points to an even greater risk in the very young, but cumulative mortality of the survivors who were younger than 30 years at the time of the bombings is only 14% at this time We estimate that it will be another 20 years before the question of age sensitivity can be addressed properly, making this one of the primary reasons for continuation of the studies into the future. Beyond cancer risk, a significant, but small and not well-defined excess mortality from heart, vascular, liver, and lung disease is also associated with increased radiation dose (Table 1)

The AHS physical and laboratory examinations provide valuable insight into emerging and nonfatal effects of radiation as well as a source of important biological sample for biodosimetry and related activities. The clinical studies often confirm and even presage the mortality-based studies. Recent examples of clinical findings include the evidences for thyroid, parathyroid, and menstrual malfunction and the subtle and still unexplained changes that occur in calcium metabolism as a function of radiation dose. (Figures 2, 3) The AHS control data have shown a great deal about aging and other changes over time in the Japanese population All of this is made possible by the high, greater than 80%, participation rates in this program.

The RERF genetics investigators have searched vigorously for heritable effects of radiation in the offspring of the survivors To date, not a single one of the many end points has shown a significant effect (Table 2) The data suggest that humans are not unusually sensitive to the genetic effects of radiation and, further, are probably not as sensitive as had been initially extrapolated from experiments in mice. An active effort is under way to verify this conclusion through the use of new technologies, foremost of which is the direct examination of DNA for mutational differences between survivors and their children. In anticipation, DNA from intact families (ie, containing both parents and at least one child) has been collected and stored in liquid nitrogen for future analysis.

Because of the enhanced effects of radiation on the evolving tissues of the embryo, the in utero population is especially vulnerable to health effects. The central nervous system is a major target in early embryogenesis, as evidenced by the reduction of head size and intelligence in those irradiated early in pregnancy. (Figure 4) An extraordinary displacement of patches of cerebral cortex is evident on magnetic resonance images of the most severely affected individuals Cancer mortality is increased in the in utero population, but is indistinguishable from the comparable effect in those who were 9 years of age or younger at the time of exposure

All RERF studies are dependent on radiation dosimetry Currently, we use Dosimetry System 1986 (DS86), as created and monitored by a binational group of experts. Dosimetry related efforts at RERF involve the use of biological end points and the newly evolving and promising method of electron spin resonance of tooth enamel The biodosimetry is of two types: (1) chromosomal aberrations with detection enhanced by fluorescence in situ hybridization, and (2) flow cytometric methods to detect somatic mutation in red blood cell and lymphocytes. These results contribute substantially to development of methods and validation of biological dosimeters, as well as providing insights into mechanisms of radiation effect , To our disappointment, the methods have not clarified the issue of human variability because, without an independent physical dosimeter, we are fundamentally unable to distinguish between biological variability and DS86 error. We hope that this impasse can be broken by physical dosimetry based on tooth enamel.

Although RERF studies are necessarily limited to the effects of acute, whole-body, mixed*f*Á-neutron radiation from the atomic bombs, their comprehensives and duration make them the most definitive descriptions of the late effects of radiation in humans. For this reason, the entire world relies heavily on RERF data to set radiation standards, as demonstrated in the reports of the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), the International Commission on Radiological Protection (ICRP), the International Atomic Energy Agency (IAEA), and the Committee on Biological Effects of Ionizing Radiation (BEIR)

RERF has recently been promoting cooperative studies with the research institutes involved in the Chernobyl and South Urals episodes to exchange information of our experience with that of other exposure experiences The collaborative study subjects are, for example, examinations of chromosomal aberrations and somatic cell mutations (T-cell receptor and glycophorin A) and molecular analysis for the RET oncogene and various cancer suppresser genes

Comments

Epidemiological method for assessing the health risks of radiation exposure is to identify a numerator of those with health abnormalities among a denominator population defined by exposure dose. In Hiroshima and Nagasaki, the identification of the denominator was delayed because of the confusion after the war, but a greater delay has occurred in Chernobyl and, so far, only the numerator has been emphasized. This is regrettable, and every effort should be made to provide an appropriate denominator as soon as possible.

Because of the accelerated aging of atomic bomb survivors, it is becoming more and more difficult to identify the effects of radiation from those of other factors, and health effects that are still unknown may appear with aging phenomena On the other hand, those exposed at younger ages are just now reaching the cancer-prone ages Furthermore, about 50% of the survivors are alive as of the present time. By age at the time of the bombings, 86% of those less than 30 years of age and 92% of those less than 10 years of age are still alive Therefore, it is important to continue careful observations for these survivors.

We should not be satisfied with the results obtained so far about genetic effects, and should pursue the issue with more precise technique such as DNA analysis In the studies of the late health effects of atomic bomb survivors, it is important to clarify not only positive findings showing the presence of abnormalities but also negative findings indicating the absence of abnormalities

Interest in radiation exposure issues has recently reached to a world-wide scale, and ever since the Chernobyl accident, rapidly increasing numbers of people want to learn from the Hiroshima and Nagasaki experience. I believe that it would be accepted by the atomic bomb survivors to make the knowledge on their health effects available for the rest of world. Scientists in Hiroshima and Nagasaki have already promoted many international collaborative works Your support for expanding these collaboration would be appreciated.