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Editorial

Studies of Atomic Bomb Survivors
Understanding Radiation Effects

Public concern about ionizing radiation, particularly radiation produced by nuclear processes, originated at the end of World War II, when atomic bombs were dropped on Hiroshima and Nagasaki, Japan. We owe much to the members of the Joint Commission for the Investigation of the Effects of the Atomic Bombs, who, in 1946, had the vision, in the face of the destruction and turmoil brought about by the bombings, to see that essential knowledge on the health effects of radiation might be gained from that dreadful experience.[1]

See also pp 596,601, and 605.

To this end, the epidemiologic studies of atomic bomb survivors have provided the single most important source of information on the immediate and delayed effects of acute, whole-body exposure to ionizing radiation. These ongoing studies are reviewed in three articles in this issue of THE JOURNAL by Yoshimoto,[2] Yamazaki and Schull,[3] and Shimizu and colleagues.[4] The studies, which are now conducted at the Radiation Effects Research Foundation (RERF) in Hiroshima, have been supported for over 40 years by the US and Japanese governments. Many of the analyses focus on a sample of more than 100 000 survivors who were identified from a 1950 national census. The population includes men, women, and children, followed up prospectively to the present time, who received a range of doses from background to near lethal levels.

The studies of atomic bomb survivors cannot provide information on every effect of radiation. These are studies of a single, relatively high-dose exposure, and not of intermittent or continuous low-dose exposures such as those most of us experience from medical, occupational, or environmental situations. The RERF studies cannot address directly the effects of low doses (<=0.2 Gy), and various assumptions have to be made to extrapolate risks from high doses (>=DGy) to risks from low levels of radiation exposure. Further, only a relatively small number of deaths from cancer among the exposed survivors can be attributed to radiation, which limits the statistical inferences that can be drawn, especially when the data are divided by cancer type, age at exposure, time after exposure, and organ dose.

Other limitations of the RERF data include problems associated with applying radiation risk estimates obtained from a Japanese population to other populations with different underlying rates of cancer (eg, the stomach is the most common cancer site in Japan but stomach cancer occurs infrequently in the United States); the probability of cancer risk among survivors having been influenced by thermal or blast effects, malnutrition, sanitary conditions, infectious diseases, and other health problems; doubts about the accuracy of dose estimates; and the frequent reliance on death certificate diagnoses, rather than measures of cancer incidence.

Despite these shortcomings, these studies have provided the framework for understanding the biologic effects of radiation. It was only about 30 years ago, for example, when the major concerns of radiation exposure centered on possible genetic effects. Ionizing radiation is known to cause heritable mutations in many species of plants and animals, but intense study of nearly 70 000 offspring of atomic bomb survivors has failed to identify an increase in congenital anomalies, cancer, chromosome aberrations in circulating lymphocytes, or mutational blood protein changes. Based on a recent analysis of eight different indicators, humans now appear less sensitive to the genetic effects of radiation than previously thought.[5]

In contrast, a report from the United Kingdom has raised the possibility that paternal occupational exposure before conception might be the cause of a small cluster of leukemia that was found in young people who reside near Sellafield, a large nuclear fuel reprocessing complex.[6] The Sellafield workers received much lower doses than atomic bomb survivors, and over a period of months or years, not seconds. Experimental studies, however, indicate that low doses and prolonged exposures produce many fewer mutations than do high doses and brief exposures. Thus, alternative explanations for the leukemias found near Sellafield, such as exposure to chemical mutagens, ingestion of alpha-particle-emitting radionuclides, and possibly a viral infection, are being pursued.[7]

Continued follow-up of the Japanese survivors has changed the emphasis of concern from genetic to somatic effects.[2] The primary late effects have been cancer, persistent chromosomal aberrations in circulating lymphocytes, and lenticular opacities[8,9] Young children who were exposed to atomic bomb radiation also experienced impaired growth. However, mortality due to diseases other than cancer has not been conclusively linked to radiation, nor has there been any evidence of aging and life-shortening.

Among the children of atomic bomb survivors, exposure in utero to ionizing radiation did cause diminished stature, small head size, mental retardation, and subsequent seizures.[3] According to Yamazaki and Schull,[3] recent analyses suggest that during certain stages of fetal development (8 to 15 weeks' gestation), the central nervous system is especially sensitive to radiation and that a slight lowering of IQ might follow even relatively-low-dose exposures.

Despite numerous studies that correlate childhood leukemia with prenatal diagnostic x-ray exposure, the absence of such an effect among atomic bomb survivors continues to raise questions about the causal nature of this association.[10,11] Further follow-up of the survivors who were exposed in utero, however, suggests that they may be at increased risk of cancer in adult life.[2] Since newborns treated with radiation are known to be at elevated risk of developing cancers in adulthood,[12] it should come as no surprise that exposures just a few months before birth would also carry some risk. However, inferences from studies of the in utero population must be made cautiously because the numbers of individuals with cancer are small, the mix of tumors include some that are not clearly related to radiation exposures, and no leukemias or breast cancers were seen in the high-dose group.

Cancer has been the major late effect of radiation exposure in the atomic bomb survivors.[4] A wavelike pattern of leukemia risk was seen over time, peaking within 10 years of exposure and diminishing to near baseline levels after 30 years. Chronic lymphocytic leukemia has not been seen in excess in any exposed population. Thyroid cancer was the first solid tumor reported to be in excess. Special incidence

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surveys of the atomic bomb survivors also have provided valuable information on radiation-induced breast cancer.[13] The breasts of young women appear especially vulnerable to radiation injury, and even young children are at high risk many years after exposure. Risk decreases with increasing age at exposure and women older than 40 years are at very low risk for radiation-induced breast cancer.

Thus, the tissues most sensitive to the carcinogenic action of radiation are the bone marrow, thyroid, and female breast.[9,14] Other cancers conclusively linked to radiation among atomic bomb survivors include cancers of the lung, stomach, colon, bladder, and esophagus.[4] Cancers possibly increased due to exposure among this cohort include cancers of the kidney, ovary, salivary gland, brain and central nervous system, and multiple myeloma. Hodgkin's disease, non-Hodgkin's lymphoma, and cancers of the liver, gallbladder, rectum, uterine corpus, uterine cervix, bone, connective tissue, pancreas, prostate, and testis have not been correlated with exposures to radiation from the atomic bomb. Thus, while it is often stated that radiation causes all forms of cancer, many sites show no increase among atomic bomb survivors.

There is emerging evidence from other epidemiologic studies that, as in experimental studies,[10,15] cancer risk may be lower when exposures are protracted. For example, women who reside in areas with high levels of natural background radiation in China have the same rates of thyroid modularity as women exposed to normal levels.[16] This similarity is seen despite a difference in cumulative dose of approximately 0.09 Gy, a level previously linked to high rates of thyroid cancer following acute exposures in childhood.[17] Large-scale studies of patients who were given diagnostic doses of radioactive iodine 131 also do not provide evidence of excess cancers of the thyroid or other sites,[18] a suggesting that the prolonged nature of the exposure to iodine 131, with its 8-day radioactive half-life, might allow ample time for cellular repair of radiation damage. In one study, women who were subjected to nearly 100 chest fluoroscopes during lung-collapse therapy for tuberculosis were found to be at increased risk of breast cancer, but not lung cancer, despite lung doses of the order of 0.8 Gy.[19,20] While breast cancer maybe a special case in which even highly fractionated exposures do not appreciably decrease risk, the risk of other tumors maybe reduced when exposures are delivered intermittently over time.

Some studies of pioneering radiologists and medical x-ray workers have reported increased rates of leukemia and skin cancer, but other cancers were not consistently elevated.[21] An analysis of three groups of nuclear radiation workers was unable to identify an increase in leukemia or any cancer, with the exception of multiple myeloma.[22] To date, no pattern of significant increase in cancer has been demonstrated among various populations of exposed nuclear radiation workers.[11]

Data from the atomic bomb survivors provide much of the scientific basis for setting radiation protection standards. For example, the National Academy of Sciences' Committee on the Biological Effects of Ionizing Radiations (BEIR) has estimated radiation risks for low-level exposures based on the RERF data.[9,14] The 1980 BEIR III committee incorporated an implicit "dose rate effectiveness factor" of 2.5 into its modeling procedures (ie, it was assumed that spreading the dose over time would reduce risk by a factor of about 2.5).[14] While asserting the importance of a dose rate factor, the 1990 BEIR V committee did not incorporate one for any cancer, except leukemia.[9] The decision not to use a dose rate factor partially explains the larger lifetime risk projections found in BEIR V compared with BEIR III. Other reasons include the information that was available from further follow-up of the Japanese survivors, the sharp reduction in the magnitude of estimated neutron exposures, and different assumptions about dose-response and time-response models. In a sense, the assumptions used to model risk following low-dose exposures may have had as much influence on the lifetime risk projections as did the actual data. Further follow-up will test the validity of these assumptions.

As much as 3% to 5% of all cancers might be attributable to all sources of radiation, including medical, occupational, and environmental exposures. Large radiation doses cause cancer, but we may never know whether small doses, on the order of natural background radiation, do so. Nonetheless, it is prudent to assume that there is no threshold below which radiation would fail to cause some deleterious effect, and models must be applied to estimate hazards at low doses. In this regard, the study of Japanese atomic bomb survivors has generated an extensive body of data, and continues to provide the framework by which we understand the effects of radiation and judge the potential risks from low-level exposures.

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