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● *Future Development of Biological Understanding*

INTRAUTERINE RADIATION EXPOSURES AND MENTAL RETARDATION

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Abstract—**Small head size and mental retardation have been known as effects of intrauterine exposure to ionizing radiation since the 1920s. In the 1950s, studies of Japanese atomic-bomb survivors revealed that at 4–17 wk of gestation, the greater the dose, the smaller the brain (and head size), and that beginning at 0.5 Gy (50 rad) in Hiroshima, mental retardation increased in frequency with increasing dose. No other excess of birth defects was observed. Otake and Schull (1984) pointed out that the period of susceptibility to mental retardation coincided with that for proliferation and migration of neuronal elements from near the cerebral ventricles to the cortex. Mental retardation could be the result of interference with this process. Their analysis indicated that exposures at 8–15 wk to 0.01–0.02 Gy (1–2 rad) doubled the frequency of severe mental retardation. This estimate was based on small numbers of mentally retarded atomic-bomb survivors. Although nuclear accidents have occurred recently, new cases will hopefully be too rare to provide further information about the risk of mental retardation. It may be possible, however, to learn about lesser impairment. New psychometric tests may be helpful in detecting subtle deficits in intelligence or neurodevelopmental function. One such test is PEERAMID, which is being used in schools to identify learning disabilities due, for example, to deficits in attention, short- or long-term memory, or in sequencing information. This and other tests could be applied in evaluating survivors of intrauterine exposure to various doses of ionizing radiation. The results could change our understanding of the safety of low-dose exposures.**

INTRODUCTION

SOON after the discovery of x rays, case reports began to appear concerning small head size and mental retardation in infants born of mothers who had received therapeutic x-ray exposures in early pregnancy. A review of the literature, published in 1928 by Murphy, revealed 14 such reports, to which were added 16 cases ascertained by questionnaires sent to departments of obstetrics (Goldstein and Murphy 1929).

ATOMIC-BOMB SURVIVORS: EARLY STUDIES

Six years after the atomic-bomb exposures in Japan, Plummer (1952) reported the first cases to be recognized among those exposed *in utero*. This cohort of children came to the clinics of the Atomic Bomb Casualty Commission before a population base was defined. In 1956, it was found that among fetuses exposed between 4–17 wk of gestational age, the closer they were to the hypocenter, the greater was the frequency of small head circumference (two or more standard deviations below the mean for the age and sex of unexposed children). (There was some reduction in stature, but head size was disproportionately small.) After dosimetry was estimated in 1965 (T65 doses), severe mental retardation (MR), the inability to perform simple functions and care for oneself, was found to rise in frequency at exposures of 0.50–0.99 Gy (50–99 rad) in Hiroshima (Blot and Miller 1973). In Nagasaki, where one-fifth as many pregnant women were exposed, only two children had MR after exposures of the mothers to 2.45 and 3.50 Gy (245 and 350 rad), respectively, in air. Miller and Blot (1972) suggested that radiation exposure may have interacted with such environmental influences as infection, undernutrition, other deprivation and stress. A typhoon took a heavy toll in Hiroshima, for example, on 17 September 1945, and typhoid fever was known to have occurred in the city. If there was an interaction or additive effect, the doses that produced small head size and MR in survivors exposed *in utero* would overestimate these effects of intrauterine radiation after radiologic procedures.

Small head size, 10 times more frequent than MR, was detected at substantially lower doses than for MR in Hiroshima: exposures of 100–190 mGy (10–19 rad) in air (Miller and Mulvihill 1976). During the susceptible gestational age interval, small head size would have been easy to detect beginning 23 wk after exposure, when the first term-births occurred; i.e., in those who were 17 wk of gestational age at the time of exposure. For the next 13 wk, the remaining fetuses that were most sensitive to radiogenic small head size would have been born. After the Chernobyl reactor accident in the Soviet Union, such infants were born between 6 October 1986 and 6 January 1987. With the simplest of devices—a tape-measure—the frequency of small head circumference can be determined (Fig. 1). If enough fetuses were exposed between 4 and

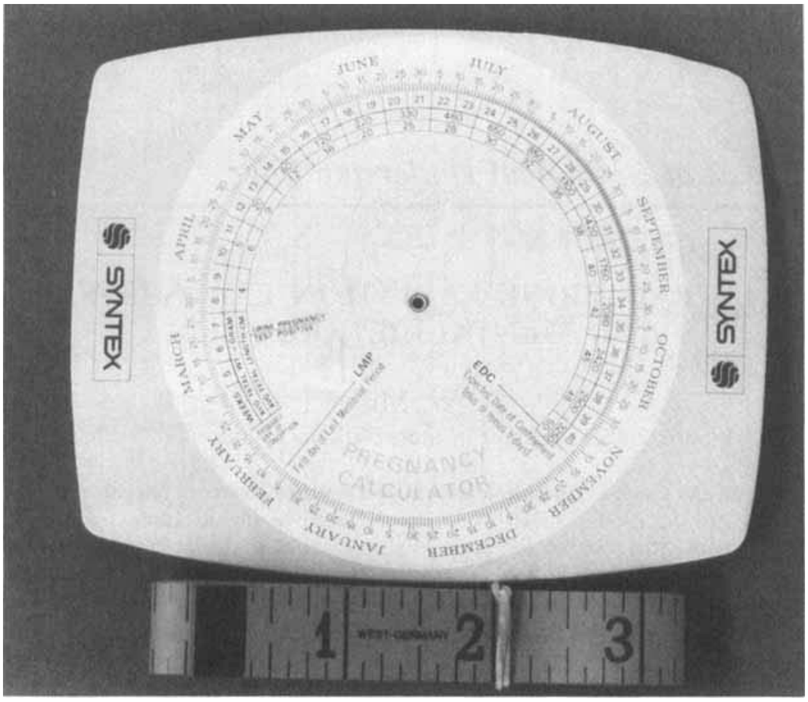

Fig. 1. Implements needed to study small head circumference among those exposed to radiation at 4–17 wk of gestational age: a pregnancy calculator and a tape measure.

17 wk of gestational age to 100 mGy (10 rad) or more, an increase in frequency should be found in proportion to dose (Fig. 2). The frequency in Hiroshima in the group exposed to 100–290 mGy (10–29 rad) was 12 in 78 (15%), compared with two cases expected. An excess, if found in the irradiated Soviet population, would confirm the observations made in Japanese atomic-bomb survivors. If no excess is found, the question of an interaction between radiation and some other environmental influence in Japan would persist. The results have implications for prenatal medical exposures. (A U.S. Nuclear Regulatory Commission delegation which subsequently visited the USSR between 27 February and 6 March 1987 was told that head size had been measured at birth, but apparently no evaluation had yet been made concerning correlation with radiation dose.*)

ATOMIC-BOMB SURVIVORS: RECENT STUDIES

In 1984, Otake and Schull (1984) analyzed the data on *in-utero* exposures again, using a redefined sample, and found that MR occurred primarily when exposure was between 8 and 15 wk of gestational age. Forty percent of these persons did not have small head circumferences (Wood et al. 1967a, 1967b). Otake and Schull noted that the interval from 8–15 wk of gestational age coincides with that for rapid proliferation and migration of neuronal elements from near the cerebral ventricles to the cortex. The brain is unable to replace these lost neurons, and when the loss is sufficient, MR occurs. Normal head size, in some cases, was attributed to filling in by glial (supporting) cells. Small head size without MR is thought to be due to cell depletion, which must involve non-neuronal cells before the eighth week of gestation, because severe MR did not occur in this gestational age-group.

An excess of other congenital malformations has not been observed in the human as it has in experimental animals. One possible explanation, according to Brent, is that the interval of susceptibility in experimental animals consists of 20% of the pregnancy, whereas in human beings it consists of only 5% (from the 20th to the 32nd day of gestation). The exception is for MR, for which the period of susceptibility is 8 wk, amounting to 20% of the pregnancy (Brent 1979).

Schull and Otake (1985) studied intelligence quotient (IQ) scores, as measured by the Koga intelligence test, given in 1955–56 by the Atomic Bomb Casualty Commission. A linear quadratic model for the 8- to 15-wk gestational age-group showed that IQ scores diminished by 21 to 26 points per gray.

Four sources of extraneous variation were identified by Otake and Schull (1984), as described below; none was deemed a confounder of a radiation effect. (1) Genetic variation from inbreeding, greater in Nagasaki than in

* The author was a member of this delegation.

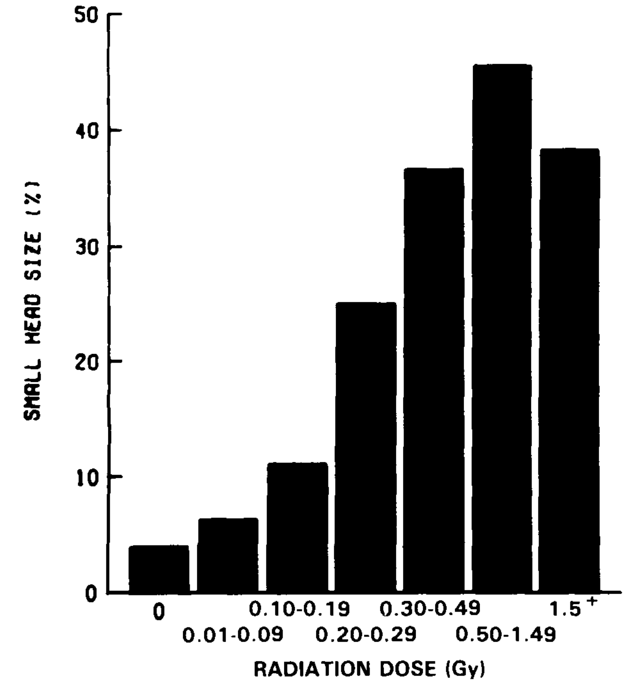

Fig. 2. Relationship of radiation dose to small head circumference after exposure before 18 wk of gestational age in Hiroshima (from Miller and Mulvihill 1976).

Hiroshima, might explain the intercity differences in the frequency of MR but would not explain the shape of the dose-response curve in either city. (2) Malnutrition was discounted as a confounder because no excess of MR was observed after the Dutch famine following World War II, and marasmus has not been reported in Japanese infants after the bombings. (3) Hypoxia from anemia due to acute radiation effects on the marrow of mother and fetuses was thought to have been gradual, occurring later in pregnancy and, contrary to the results observed, should have produced a nonlinear effect; i.e., greatest in the most heavily exposed. (4) Although the question of infection was raised, it was not dealt with. The excess of MR and the lower IQ test scores were considered radiation-induced because: (a) neither tests of skewness nor graphical representation of the data suggested the influence of other variables; (b) the effect was age-specific: it was not found under 8 wk or beyond 26 wk of gestational age; and (c) a dose-response effect was found.

RESEARCH NEEDS

Among research needs are noninvasive tests of the anatomy and function of the cerebral cortex. The possibilities include radiologic imaging of the brain in a search for anatomical abnormalities. In animal experimentation, positron emission tomography scans may show deficits in cerebral function after intrauterine radiation exposure.

It has long been thought that when MR occurs after heavy intrauterine radiation exposure, those with lesser exposures will have more subtle effects; i.e., deficits other than a low IQ score. In the past, there has been no means for measuring such effects, but procedures for doing so have begun to emerge. Levine and his associates, formerly at Boston Children's Hospital and now at the University of North Carolina, have developed a battery of tests for diagnosing specific neurodevelopmental dysfunctions in middle childhood; that is, in children from 9–14 y of age (Levine et al. in press). The parameters measured include neuromaturation, eye-hand coordination, receptive language, language retrieval, expressive language, temporal-sequential organization, visual processing, visual memory and selective attention. Visual processing is measured, for example, by tests of visual vigilance, visual recognition, visual retrieval and form-copying. The administration of these tests, adapted if necessary to those exposed *in utero* to atomic bombs in Japan or to radiation from Chernobyl, should be considered.

Dosimetry for 20 y before 1986 was based on temporary estimates made in 1965 (T65 dosimetry). Evidence has since indicated that the neutron doses in Hiroshima were one-tenth and in Nagasaki were one-half of the T65 estimates (Roesch, 1987). Funding for this research came from a binational collaborative study by U.S. and Japanese physicists, based on the physical effects of atomic radiation in Hiroshima and Nagasaki (DS86 dosimetry). Reevaluation of the dose-response effects after fetal exposure should (and undoubtedly will) be made, comparing the results using the new and the old dosimetry.

CONCLUSIONS

Studies should be undertaken of: (1) neurodevelopmental dysfunction among Japanese exposed *in utero* to the atomic bomb, and (2) the head circumferences of Soviet infants born between 6 October 1986 and 6 January 1987, after exposure *in utero* to radiation from Chernobyl.

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