Perinatal Loss and Neurological Abnormalities Among Children of the Atomic Bomb

Nagasaki and Hiroshima Revisited, 1949 to 1989

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Studies of the survivors of the atomic bombing of Hiroshima and Nagasaki who were exposed to ionizing radiation in utero have demonstrated a significant increase in perinatal loss and the vulnerability of the developing fetal brain to injury. These studies have also helped to define the stages in the development of the human brain that are particularly susceptible to radiation-related damage. Exposure at critical junctures in development increases the risk of mental retardation, small head size, subsequent seizures, and poor performance on conventional tests of intelligence and in school. The most critical period, 8 through 15 weeks after fertilization, corresponds to that time in development when neuronal production increases and migration of immature neurons to their cortical sites of function occurs. The epidemiologic data are, however, too sparse to settle unequivocally the nature of the dose-response function and, in particular, whether there is or is not a threshold to damage. If a threshold does exist, it appears to be in the 0.10- to 0.20-Gy fetal-dose range in this vulnerable gestational period.

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AT THE outset of its investigations of the survivors in Hiroshima and Nagasaki, considerable concern was expressed by the Atomic Bomb Casualty Commission over the possible prenatal effects of exposure to the ionizing radiation from the atomic bomb on children. These concerns continued when, in 1975, the Atomic Bomb Casualty Commission was replaced by the Radiation Effects Research Foundation, a private, nonprofit Japanese foundation, supported equally by the government of Japan through the Ministry of Health and Welfare and the government of the United States through the National Academy of Sciences under contract with the US Department of Energy.

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The initial studies of the effects of in utero exposure of the embryo or fetus to ionizing radiation from the atomic bomb in Hiroshima and Nagasaki indicated that excess fetal loss and brain injury that resulted in microcephaly and mental retardation occurred among those children born to mothers who were within 2000 m of the hypocenter at the time of bombing (ATB).[1-3] Subsequent studies identified additional afflicted individuals and confirmed the earlier findings.[4-8] However, estimates of the intrauterine radiation dose were not available until some 35 years after the exposure. Recent reassessment of the earlier findings discloses that severe mental retardation is most likely to occur at a specific gestational period when radiosensitive, critical neurodevelopmental events are taking place.[9]

However, in evaluating the adverse effects of ionizing radiation on the fetus, other factors must also be considered (the blast and thermal effect of the bomb, maternal nutritional status, infections, and stress). For example, the initial reports of the medical effects of the atomic blast describe three broad categories of injury, namely, burns, mechanical injury, and radiation injury.[10-13] All of these could impinge on the outcome of a pregnancy. Singly or in combination with radiation, these various factors could alter the intricate needs of the fetus, affecting its development and viability. It has not been possible, however, to quantify these interactions.

MATERNAL–FETAL CONSIDERATIONS

Malnutrition

The limited food supply in war-torn countries often resulted in malnutrition of varying severity and is a factor to consider in assessing the outcome of pregnancy in Hiroshima and Nagasaki. The already existing shortage of food worsened after the bombing, further impairing maternal nutrition. It is relevant to review briefly the experience reported from Leningrad where more than 1 million persons were said to have perished during the siege of this city, many of them from the cold and starvation.[14,15] The implication of the privation of war during the German occupation on the prenatal and postnatal attrition was documented from Budapest, Amsterdam, and Rotterdam.[16,17] Four hundred eleven infants were born at the Leningrad Pediatric State Institution in the first half of 1942. The birth weight of

Fetal and Infant Mortality and Child Morbidity That Followed Intrauterine Exposure to the Nagasaki Atomic Bomb

Distance From Hypocenter, m	Pregnancies	Abortions	Stillbirths	Neonatal Deaths	Infant Deaths	Total Mortality, No. (%)	Child Morbidity, No. (%)	Unaffected Surviving Children, No. (%)
<2000 With major radiation signs*	30	3	4	3	3	13 (43.3)†	5 (16.7)	12 (40)
<2000 Without major radiation signs	68	1	2	3	0	6 (8.8)	1 (1.5)	61 (89.7)
4000-5000	113	2	1	1	3	7 (6.2)	1 (0.9)	105 (92.9)
Total	**211**	**6**	**7**	**7**	**6**	**26**	**7**	**178**

*Includes one or more of the following: epilation, oropharyngeal lesions, purpura, or petechiae.
†Differs significantly from value for group less than 2000 m without radiation signs. $P<.001$.

half of these infants was less than 2500 g. Forty-two percent (161) of these newborns were considered to be premature. Of this group, 38% (62) survived less than 6 months. In Budapest, in 1944, among 1053 infants younger than 1 year who were admitted to the Children's Clinic of the University of Budapest, 46% (485) died. With the cessation of hostilities and improvement in the supply of food, infant mortality fell rapidly, approaching its prewar level. The effects of maternal malnutrition on newborn infants during a relatively short period of severe food shortages in Holland (1944 to 1945) also has been described. The weights of newborns were significantly lower than those of infants who were born before and after this period. Since a causal relationship between inadequate diet and fetal malformations had been demonstrated by Warkany[18] in an experimental situation, birth defects were expected in these children. However, no significant increase was found.

Infections

No specific viral or bacterial epidemics that could have added to the radiation effect on the fetus are known to have occurred in Hiroshima or Nagasaki in the year that followed the bombing. Recurrent febrile illnesses were, however, reported by many mothers during their pregnancies, especially in those in whom signs of radiation exposure developed. Whether these febrile episodes influenced fetal development is not known.

Radiation Injury

In a comprehensive review, Russell[19] cites the early experimental and clinical findings that followed prenatal irradiation to indicate that the human embryo is subject to radiation injury. These case reports began to appear at a time when the validity of therapeutic abortion, using large doses of x-ray or radium, was being discussed (1911 to 1935). There were instances in which the attempted abortion failed and the fetuses came to term. Some were normal while others were born with abnormalities. Goldstein and Murphy[20] reported microcephaly, sometimes accompanied by mental retardation, in 16 of 28 infants who were born to women who underwent radium therapy for uterine cancer during pregnancy. Skull defects, cleft palate, micromelia, spina bifida, and eye defects were reported by other investigators.

Following the atomic bombing, a resurgence of interest in studies of the effects of prenatal irradiation occurred.[21-25] As a consequence of the demonstration of the vulnerability of the developing human brain to exposure to ionizing radiation in utero, the mechanisms that underlie neural injury continue to receive wide interest, with particular attention focusing on the dose and shape of the dose-response curve relative to age.[26,27] New information on the development of the nervous system and the teratological and biochemical modification by prenatal radiation has increased our understanding of the pathogenesis of radiation injury.[28] We now know that not only are proliferating primitive cells killed, but the cellular and cortical morphology and the normal migration of the surviving cells are altered.[21]

INITIAL STUDIES AND SAMPLES

Nagasaki

One of the first studies of the Atomic Bomb Casuality Commission/Radiation Effects Research Foundation focused on the effects of the atomic explosion on the fetuses of women who were in Nagasaki on August 9, 1945. Two groups of women were identified for this study. One group comprised 1774 women of childbearing age who were exposed within 2000 m of the hypocenter, and the second group comprised another 1774 women of childbearing age who were 4000 to 5000 m from the hypocenter. The women in the latter group were matched by age to those of the group who were exposed within 2000 m. Among these two groups (3458 women), 211 women were pregnant ATB. Of these, 98 mothers were within 2000 m of the hypocenter ATB, and 30 of the 98 women developed signs of radiation sickness (ie, epilation, oropharyngeal lesions, purpura, and petechia) (Table). Sixty-eight of these mothers did not develop major signs of radiation sickness. Serving as controls were the remaining 113 mothers who were 4000 to 5000 m from the hypocenter ATB, a distance considered sufficiently remote from the hypocenter so that minimum effects of the explosion occurred.

Among the 30 pregnant women who were within 2000 m of the hypocenter and who developed signs of radiation sickness, seven (23%) terminated in fetal deaths, and six (20%) experienced neonatal or infant deaths. Of this group, five (17%) children who survived were diagnosed with one or more of the following: mental retardation, eye defects, and urinary incontinence. Twelve (40%) surviving children were unaffected. The overall morbidity and mortality among the 30 individuals is 60%. For the group that was within 2000 m of the hypocenter but did not develop major signs of radiation sickness, the mortality for their fetuses and infants was 8.8%, with 1.5% morbidity for the surviving children. The fetal and infant mortality for the group whose mothers were 4000 to 5000 m from the hypocenter and received little, if any, irradiation was 6.2%, with 0.9% morbidity for the surviving children.

The mean height and head circumference of children born to mothers with "major" signs of radiation sickness were significantly smaller than among children born to mothers in the control group. In the second and third trimester of gestation, fetal and neonatal deaths were significantly elevated in frequency among the offspring of mothers who suffered from radiation sickness. The evaluation of these data was difficult, owing partly to the possible effect of the blast and thermal radiation and partly to the indirect effects of hemorrhage, infection, and malnutrition, as well as the absence of proper dosimetry.

Hiroshima

In the summer and fall of 1950, two hundred five children in Hiroshima who had been exposed to the atomic bombing during the first half of intrauterine life were examined. Seven of 11 children who were exposed within 1200 m in utero had microcephaly with mental re-

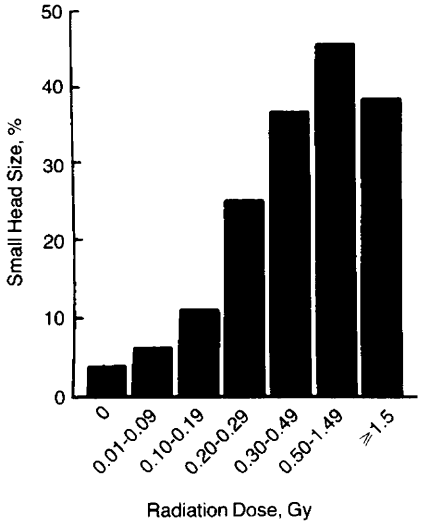

Fig 1.—Small head circumference among children in Hiroshima who were exposed to ionizing radiation in utero before the 18th week of gestation (from Miller and Mulvihill[29]).

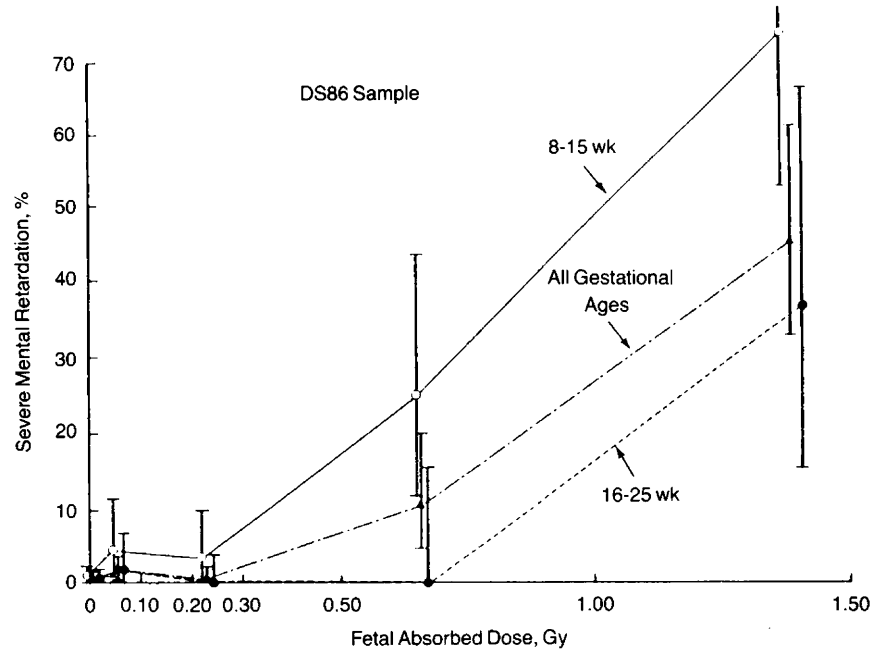

Fig 2.—The frequency of severe mental retardation among those fetuses who were exposed to ionizing radiation in utero by dose and gestational age for Hiroshima and Nagasaki combined. Vertical lines indicate 90% confidence interval (from Otake et al[9]).

tardation.[2] This diagnosis was not made on any of the 194 remaining children who were exposed beyond this distance. By 1956 the addition of other patients with microcephaly and mental retardation to this group in continuing observations at the Atomic Bomb Casualty Commission Pediatric Clinic further defined the contrasting effect at different gestational periods and distances from the hypocenter.[4] Five mentally retarded, microcephalic children were added to the 10 already known, and 16 children with small heads with normal intelligence had been found. Of these 31, thirteen children who were mentally retarded and had head circumferences of more than 3 SDs below normal were between 7 and 15 weeks' gestation ATB. This observation sharply localized the gestational age of greatest susceptibility. It was also observed that the frequency of microcephaly diminished as the distance from the hypocenter increased. Mental retardation was diagnosed on the basis of clinical opinion, history of poor school performance, and unsatisfactory performance on three psychometric tests.

SUBSEQUENT STUDIES AND RADIATION DOSE ESTIMATES

For the first time, in 1972, maternal radiation dose estimates were related to the small head circumference and mental retardation induced by exposure in utero to the effects of the atomic bomb.[7,8,29] The original study samples were enlarged and a cohort of persons in utero at the time of the atomic bombing of Hiroshima and Nagasaki was established. Individual maternal radiation dose estimates were calculated for almost all pregnant women in this study. This was made possible as a result of the continuing effort to obtain a reliable estimate of the radiation dose for the individual survivors by scientists in Japan and the United States.[30-33] The estimates were based on shielding configurations as well as distance from the hypocenter.

In Hiroshima, a progressive increase in the frequency of small head size was found among children whose mothers were exposed before the 18th week of pregnancy (Fig 1). In this context, a small head was one with a circumference of 2 or more SDs below the average circumference (approximately 54 cm at 18 years of age) for the entire sample. The minimum dose at which a clear increase in the frequency of small head size was observed was 0.10 to 0.19 Gy. At 0.19 Gy, 11.1% of the individuals had small head size as contrasted with 4.1% in the nonexposed comparison group. At 0.20 to 0.29 Gy, 25% had small head sizes; at 0.30 to 0.49 Gy, 36.8% had small head sizes; at 0.50 to 1.5 Gy, 45.8% had small head sizes; and at 1.5 Gy or more, 38.5% had small head sizes. At maternal doses of 1.5 Gy or more, small head circumference was often accompanied by mental retardation.

Recent reevaluation of the Japanese atomic bomb survivor data that uses the new dosimetry (DS86)[34] has focused on four types of observations: (1) the frequency of clinically recognized mental retardation,[9] (2) the diminution of intelligence as measured by conventional intelligence tests,[35] (3) scholastic achievement in school,[36] and (4) the occurrence of unprovoked seizures.[37]

Maximum vulnerability to radiation appears to occur from approximately the beginning of the 8th through the 15th week after fertilization (Fig 2).[9] As previously stated, the greatest proliferation of neurons and their migration to the cerebral cortex occur during this time. A period of reduced vulnerability occurs in the following 8 weeks from the 16th through 25th week after fertilization. The latter period accounts for about one quarter of the apparently radiation-related cases of mental retardation. The least vulnerable period is the initial 8 weeks after fertilization. No radiation-related cases of mental retardation have been seen in this developmental stage. This should not be construed as evidence that brain damage does not occur, for it may, but such damage may be of a nature that is incompatible with survival at ages at which mental retardation can be recognized.

Within the period of maximum vulnerability, the simplest statistical model consistent with the data appears to be a linear one without threshold; this mat-

ter will be discussed later. The slope of this relationship corresponds to an increase in frequency of mental retardation of 0.44 per Gy (95% confidence interval [CI], 0.26 to 0.62). The frequency of mental retardation among the general population is about one case per 100 individuals. However, with this linear model, the frequency would rise to approximately 44 cases per 100 individuals at a dose of 1 Gy. Exclusion of those cases of mental retardation with probable non–radiation-related etiology would have little effect on this risk estimate.[9]

The data on intelligence tests and school performance suggest the same two gestational periods of vulnerability to radiation, the first period showing the greatest sensitivity.[35,36] More important, these data suggest a continuum of effects on the developing brain of exposure to ionizing radiation. Indeed, the downward shift seen in the distribution of IQ scores with increasing exposure predicts reasonably well the actual increase in mental retardation observed. This indicates that the impact of exposure to ionizing radiation on cortical function depends on both the dose the individual receives and the developmental level that individual would have reached if he or she had not been exposed. For example, the loss of 5 IQ points in an individual destined to have an IQ of 140 would hardly be a handicap, but a similar loss at an IQ of 75 could result in social impairment.

Seizures are a frequent sequela of impaired brain development and therefore could be expected to affect more children with radiation-related brain damage than children without such damage. Dunn and colleagues[37] have described the incidence and type of seizures among survivors prenatally exposed to the atomic bomb and their association with specific stages of prenatal development at the time of irradiation. Histories of seizures were obtained at biennial, routine clinical examinations that started at 2 years of age. These clinical records were used to classify seizures as febrile or unprovoked without precipitating cause.

Seizures were not recorded among the individuals exposed 0 to 7 weeks after fertilization at doses higher than 0.10 Gy. For irradiation during 8 to 15 weeks after fertilization, the incidence of seizures was highest among individuals with doses that exceeded 0.10 Gy and was linearly related to the level of fetal exposure. This relationship applies to all seizures without regard to the presence of fever or precipitating causes and to unprovoked seizures. The risk ratios for unprovoked seizures that followed exposures within the 8th through 15th week after fertilization are 44 (90% CI, 0.5 to 40.9) after exposure to 0.10 to 0.49 Gy and 24.9 (90% CI, 4.1 to 191.6) after exposure to 0.50 Gy or more when the mentally retarded are included, and 44 (90% CI, 0.5 to 40.9) and 14.5 (90% CI, 0.4 to 199.6), respectively, when they are excluded.

UNCERTAINTIES

Many uncertainties confound these estimates. They include the limited nature of the data, especially concerning mental retardation and convulsions; the appropriateness of the comparison group; errors in the estimation of tissue absorbed doses and the prenatal ages at exposure; and other factors in the postbomb period. Also included are nutrition and disease, which could play a role. But two issues warrant special consideration, namely, the shape of the dose-response function and the existence of a threshold in the dose response.

Dose-Response Function

Within the period of maximum vulnerability, virtually without exception, the data can be satisfactorily approximated by more than one dose-response function, generally by a linear or a linear-quadratic model (Fig 2). Given that neuronal death, errors in neuronal migration, and faulty synaptogenesis could all play a role in the occurrence of cortical dysfunction, and each could have its own different dose-response relationship, there is little or no prior basis for presuming that one or the other of these models better describes the fundamental biologic events involved. The "true" model remains a matter of conjecture, and it is unlikely that epidemiologic studies alone will ever be able to determine what this model may be. The estimation of risk must rest on a series of considerations, not all of which are biologic. Most important, the risk estimate should be a prudent one, and estimates should be based on the lowest level of risk wherever such exists. This argues for the use of a linear dose-response since presumably at lower doses, where the evidence of an effect is weakest, risk would be overestimated if, in fact, a threshold exists.

Is There a Threshold?

Although a linear or a linear-quadratic dose-response relationship describes the observed frequency of mental retardation in the 8th through 15th week of gestation adequately, there could be a threshold. However, the estimation of the value of this presumed threshold is not clear. When all of the cases of mental retardation are included in the analysis, a threshold cannot be shown to exist by statistical means. But if the two cases of mental retardation with Down's syndrome in the 8- through 15-week period are excluded, the 95% lower bound of the threshold ranges from 0.12 to 0.23 Gy. The DS86 dosimetry suggests a threshold in the 16- through 25-week period at 0.21- to 0.70-Gy exposure. The seemingly clear evidence of a threshold in this later stage of development and its uncertainty in the earlier period is consistent with the belief that differential cells are less sensitive to ionizing radiation than immature ones.

BIOLOGIC BASES OF RADIATION-RELATED BRAIN DAMAGE

As yet we know far too little about the cellular and molecular events involved in corticogenesis to do more than speculate on the origin of the effects that are seen. However, the brains of six of the 30 mentally retarded individuals in the study sample, as well as a seventh retarded individual not in the sample, have been examined either at autopsy or through magnetic resonance imaging.[38,39]

The findings are informative and suggest that errors in neuronal migration were common. Such errors were seen or can be inferred in no less than five of the six children exposed in the 8th- through 15th-week "window." For example, at autopsy, coronal sections of the cerebrum of one of the mentally retarded individuals, a male, with a brain weighing 840 g, who died of acute meningitis at 16 years of age, revealed massive ectopic gray matter around the lateral ventricles. Histologically there was an abortive laminar arrangement of nerve cells within the heterotopic gray areas, imitating the normal laminar arrangement of cortical neurons. The cerebellum and hippocampi were normal histologically.

Similarly, in four of five individuals on whom magnetic resonance imaging had occurred there was either direct or indirect evidence of faulty neuronal migration. In two children who were exposed at the 8th or 9th week after fertilization, large areas of periventricular, ectopic gray matter, comparable to those found in the individual who underwent autopsy, were seen. Two individuals, who were exposed in the 12th to 13th week and who did not show readily recognizable ectopic gray areas, did show mild macrogyria, which implies some impairment of the migration of neurons to the cortical zone. Both of these individuals had cerebellar anomalies. Why the immature neuronal cells failed to migrate is not clear, but it could reflect changes in the intracellular adhesiveness that

plays such a large role in the cortical positioning of neuronal cells.[40] Clearly, many questions remain unanswered. There is much still to be learned, but recent advances in the neurosciences suggest that a better understanding will be forthcoming.

RECENT INTERVIEWS WITH SURVIVORS

Recitation of the scientific facts, however, fails to disclose the special lot—the poignancy of life for these survivors and their families. To this end, during a recent return visit to Hiroshima and Nagasaki, interviews were arranged for one of us (J.N.Y.) with mothers of the *Kinoko-kai*, the "Mushroom Cloud Auxiliary." Each mother had in common a retarded child or a child with microcephaly who was prenatally exposed at the time of the bombing.

The mothers retold their ordeal on the fateful days in August 1945 and their tribulations in the 44 years that have followed. At that time, some mothers had been expecting their first children. Some were injured or rendered unconscious as the powerful blast of wind picked them off the ground and threw them several meters away. Many reported a lengthy period of lassitude that followed the bombing, when they experienced high fevers and bloody diarrhea, their hair began to fall out, petechiae peppered their skin, ulcerations developed in their mouth, and sores appeared on their face. Illness often continued to plague them during the remainder of their pregnancies.

Most of these women gave birth to their children in February 1946. The infants were often listless. One had no hair until almost 2 years after birth. Lactation was not affected, and breast milk was ample for the most part. Although food rations were small, many of the mothers believed that a soup made with mashed rice dumplings was the reason an adequate supply of breast milk sustained and provided the necessary nutrients for their infants. Life-threatening illnesses developed in some infants, and febrile episodes accompanied by seizures were not an uncommon occurrence.

When these children were enrolled in school the problems of delayed development became apparent. As they grew older, employment was limited or nonexistent. Some were institutionalized. These individuals are known as "Pika" children, named after the Japanese word, *pika*, which describes the bomb's initial flash. The families of these children fear discrimination. One father, on learning of the prejudice directed toward his child, cautioned his wife to keep silent and not to draw further attention to the family that could jeopardize the marriageability of the other siblings. But new worries beset many of these parents, for they are now 60 to 70 years of age and fear for the future care of their children.

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