C. Growth and Development Following Prenatal and Childhood Exposure to Atomic Radiation

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Studies of growth and development of Hiroshima and Nagasaki children have shown significant long-range effects associated with exposure to the atomic bombs. Radiation to the fetus during early pregnancy, even at relatively low doses, may result in reduced growth, smaller head size, and mental retardation. Harmful effects of radiation later in pregnancy and in early childhood have not been as clearly demonstrated, however reduction in growth is also found among Hiroshima children.

INTRODUCTION

A causal relationship between exposure to ionizing radiation and subsequent retardation of growth and development in man was suggested nearly 50 years ago. Today there are considerable data associating increased risks for abnormal physiologic and mental development with radiation. Much of this information particularly concerning in utero exposure has come from the Atomic Bomb Casualty Commission (ABCC).

Since cells which are rapidly proliferating and differentiating are the most radiosensitive, the effects of radiation in man might be expected to be most pronounced following prenatal or childhood exposure. The ABCC has conducted epidemiologic studies since 1947 in an attempt to document the extent to which such exposure may impair growth. In this paper we will review those studies of atomic bomb survivors concerned with assessing the risk of both in utero and childhood exposure to atomic radiation.

EFFECTS FOLLOWING IN UTERO EXPOSURE

Reports of microcephaly in infants born of mothers given therapeutic pelvic irradiation during pregnancy began appearing in the early 1920's. In the first relatively large scale study into the question of radiation-induced fetal damage, Goldstein and Murphy reported in 1929 that nearly half of 75 children born of women who had received intensive therapeutic pelvic roentgen or radium irradiation during pregnancy had physical or mental abnormalities. Seventy-five percent of the abnormalities, principally severe disturbances of the central nervous system, could be attributed to no cause other than (high dose) radiation. Most of the exposures were given early in pregnancy; however, the defects were also found when irradiation occurred after the fifth month of gestation.

When the study of survivors exposed to the atomic bombs began, it was thought

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that microcephaly would be seen among those prenatally exposed. Indeed in 1950 Plum-
ger4> examined 205 Hiroshima children of age 4-1/2 years who were exposed during the
first trimester of gestation, and reported an increased prevalence of microcephaly
among those exposed within 1200 m of the hypocenter. Examining Hiroshima children
in 1954, at age 8 years, Miller5> found that the prevalence and severity of microcephaly
increased as distance from the hypocenter decreased, and furthermore that the cases
seemed to be generally limited to those exposed during the 7th to 15th week of ges-
tation.

In 1951 Yamazaki et al6> attempted to reconstruct pregnancy outcome histories for
Nagasaki women who were pregnant in August 1945 when the atomic bomb was deto-
nated. Thirty women who were exposed at close distances to the center of the explo-
sion, and who experienced major radiation symptoms, were identified. Although their
number was small, the pregnancy loss was considerable. Twenty-three percent of the
pregnancies ended in fetal loss. Of the live births, 26% died within the first year of
life. Of the remainder, 29% were microcephalic. The corresponding percentages for
comparison groups of persons lightly exposed were all markedly less (all less than 5%).

From extensive field investigations during the late 1940's and early 1950's, the ABCC
developed an identification file of persons who were in utero at the time of the bomb
and were still residents in Hiroshima and Nagasaki. By the late 1950's the ABCC es-
tablished a fixed sample of approximately 1600 Hiroshima and Nagasaki children in
utero at the time of the bombs. The sample consisted of three sex and gestational age
matched groups of nearly equal size: a group of children exposed within 2000 meters
of the bombs, a group much less exposed and a non-exposed group. The children were
scheduled for physical examinations annually from 1956 through 1965.

Utilizing data from the annual examinations in Nagasaki, Burrow et al7> found
smaller average head circumference and diminished height and weight during adoles-
cence (ages 13-15) in females who were heavily exposed. Wood et al8> noted the same
findings in both sexes in Hiroshima but again only in females in Nagasaki, at age 17,
among those who were heavily exposed in utero.

The early ABCC studies used distance from the center of the explosion as the pri-
mary measure of radiation exposure. By the mid to late 1960's a dosimetry system de-
veloped by the Oak Ridge National Laboratory enabled the calculation of individual es-
timates of the radiation doses (gamma plus neutron) received by the children's mothers
at the time of the bombs. The dose estimates were based on the mother's distance from
the center of the bomb as well as shielding configurations which protected her from
the full radiation impact.

When the Hiroshima and Nagasaki data obtained from the annual examinations were
analyzed with respect to individual dose estimates, a teratogenic effect in Hiroshima
children was seen at doses as low as 10 to 19 rad9> (Table 1, Figure 1). Head circumfer-
ence (less than 2 standard deviations below the age- and sex-specific mean head size
for at least one measurement and less than 1 standard deviation below average for all
other examinations) was significantly decreased at this dose level. Furthermore, there
was a progressive increase in the frequency of small head size with increasing dose.
The effect was virtually limited to persons exposed before the 18th week of pregnancy.
Small head circumference was found in 43% of the children in Hiroshima exposed to
more than 50 rads of radiation in this gestational age period; seventy-five percent of those exposed to 20 or more rads had head size below average. Had persons been included who died prior to age 10, or been measured only prior to this age, the high dose effect likely would have been accentuated.

In Nagasaki an increased prevalence of small head circumference was found, but only among those whose mothers received doses of over 150 rad. In both cities, following maternal doses of 150 rad or more, the occurrence of small head circumference was often accompanied by mental retardation.

Mean height was less among those heavily exposed; however, exceptionally small height (less than 2 standard deviations below the mean) only accompanied small head circumference at high doses (150+ rad), and at such doses nearly all of those with small height were mentally retarded.

Wood et al (10) reported 30 cases of mental retardation as of age 17 among members of the in utero sample. Blot and Miller (11) found the frequency of mental retardation among Hiroshima children exposed at doses of from 50-99 to be significantly increased,
Table 2. Number of cases and relative risk of mental retardation according to dose category

| Dose (rad)       | Hiroshima | Nagasaki |
|------------------|-----------|----------|
|                  | Sample Size | Cases | Relative Risk | Sample Size | Cases | Relative Risk |
| Not in city or distally exposed | 830 | 5(2) | 1.0 (1.0) | 246 | 4(2) | 1.0 (1.0) |
| 0-9              | 145       | 3(1)   | 3.4 (3.8) | 11  | 0    | ...         |
| 10-49            | 189       | 2(1)   | 1.8 (1.5) | 45  | 0    | ...         |
| 50-99            | 47        | 3(1)   | 10.6 (11.8) | 20 | 0    | ...         |
| 100-199          | 29        | 4(1)   | 22.9 (28.6) | 13 | 0    | ...         |
| 200-299          | 8         | 3      | 62.3 (104) | 5   | 1(1) | 12.3        |
| 300+             | 6         | 2      | 55.3 (92.2) | 7 | 3    | 26.4 (52.7) |

1) Numbers in parentheses are numbers of cases (included in the totals) whose mental retardation was apparently due to causes other than intrauterine radiation.
2) Numbers in parentheses are relative risks excluding cases whose mental retardation was apparently due to non-radiation causes.

and found the prevalence to be further increased at higher doses (Table 2). More than 50 times the expected number of cases were found for those exposed to over 200 rad in Hiroshima.

In Nagasaki no effect on head circumference or mental retardation was consistently seen at doses below 150+ rad. The difference in effect between the two cities is considered possibly attributable to the presence of neutrons in Hiroshima, virtually absent in Nagasaki. Neutrons accounted for 20-30% of the total radiation dose at doses below 150 rad in Hiroshima. Similar inter-city differences in radiation effects have also been observed with respect to leukemia and other cancers.

Recently data on bone maturation were analyzed with respect to radiation dose received in utero, and no correlation was found between exposure dose to the mother and time of epiphyseal closure. Overall, however, the ABCC studies on the growth and development of persons in utero at the time of the atomic bomb in 1945 have generally shown a harmful effect of that exposure. The effect is characterized by an overall reduction in physical growth, particularly a reduction in head size, and an impairment in mental development. Estimation of dose to the fetus, rather than maternal whole-body dose, has now been made. A reanalysis of Hiroshima and Nagasaki data with respect to fetal dose is being carried out to further delineate the risk of prenatal exposure to the atomic bombs.

EFFECTS FOLLOWING CHILDHOOD EXPOSURE

Studies within the decade following the atomic bombs on survivors directly exposed in childhood were inconsistent but suggestive of a detrimental effect on growth. During the years 1947-51 school children from Hiroshima and Nagasaki were compared with those in neighboring cities. Lower growth attainment levels were found only among boys in Hiroshima. Reynolds studied more than 2700 school age children in Hiroshima in 1951-53, and reported some height, weight, and other growth differences consistent with a radiation effect. Nehemias analyzed the same data and found a significant correlation between an aggregate of 12 anthropometric measurements and an exposure
index. Because of naturally occurring population differences, and lack of information on non-radiation factors which influence growth, it could not be stated with certainty that radiation was the cause of smaller anthropometric size.

In 1958 the ABCC established a fixed sample of approximately 20,000 Hiroshima and Nagasaki survivors and controls, a portion of whom were exposed in childhood. The cohort members were followed by means of biennial clinical examinations at the ABCC which included routine measurements of height and weight. In the fifth cycle of examinations (1966-68), height and weight measurements were obtained for approximately 3200 individuals who were less than age 18 years at the time of the bomb in 1945. Their ages in 1966 ranged from 21 to 38 years. Classifying these anthropometric measurements by age at the time of the bomb and radiation dose category revealed smaller average height in both sexes in Hiroshima among those exposed to high (100+) doses in early childhood. As seen in Table 3, differences among the dose groups diminished with increasing age. When exposure had occurred before 6 years of age at 100+ rad, the average adult height was reduced (at least 4.4 cm among males and 2.5 cm among females). For those aged 6 to 11 years at the time of the bomb, smallest height was found in the 100+ rad group, though to a lesser degree. No apparent differences in mean height between the dose groups were seen for those aged 12 to 17 at the time of the bomb. In Nagasaki a significant dose effect was not found. Smaller height was seen in Nagasaki females exposed to 100+ rad at ages 0-5 years, but not in Nagasaki males.

In Hiroshima average weight was lowest in both sexes in the highest dose group at all ages. No significant dose effect was seen in Nagasaki.

The difference in effect between Hiroshima and Nagasaki was again thought possibly attributable to the differing quality of radiation released by the atomic bombs in the two cities; however, non-radiation related factors could not be discounted. It is of interest that in the studies of both Burrow et al and Wood et al, the effect of in-

Table 3. Average heights (cm) in 1966-68, for Hiroshima adults who were under age 18 years at the time of the atomic bomb in 1945

| Age in 1945 (years) | Dose (rad) | Not in city in 1945 | 0-9 | 10-99 | 100+ |
|--------------------|------------|---------------------|-----|-------|------|
|                    | Males      |                     |     |       |      |
| 0-5                | mean       | 166.4**             | 166.1** | 165.9** | 161.5 |
|                    | n          | 34                  | 40  | 42    | 30   |
| 6-11               | mean       | 162.3               | 164.2 | 166.3*  | 162.2 |
|                    | n          | 32                  | 38  | 25    | 23   |
| 12-17              | mean       | 164.3               | 163.6 | 164.3   | 163.4 |
|                    | n          | 128                 | 249 | 107   | 89   |
|                    | Females    |                     |     |       |      |
| 0-5                | mean       | 153.3*              | 153.6** | 152.9*  | 150.4 |
|                    | n          | 50                  | 69  | 59    | 34   |
| 6-11               | mean       | 152.5               | 153.6* | 153.5*  | 150.5 |
|                    | n          | 36                  | 65  | 40    | 28   |
| 12-17              | mean       | 152.1               | 152.3 | 152.2   | 151.9 |
|                    | n          | 107                 | 281 | 209   | 117  |

* (P < .05) greater than 100+ average.
** (P < .01) greater than 100+ average.
trauterine exposure upon average growth also was not observed among Nagasaki boys.

CONCLUSION

Studies of growth and development of Hiroshima and Nagasaki children have shown significant long-range harmful effects associated with the atomic bombs, particularly among those who were in utero at the time of exposure. The demonstrated dose-response relationships, and the consistency of ABCC findings with prior studies in man\(^1\) and in animals,\(^{2,21,22}\) strongly implicate radiation as a cause of physical and mental retardation when exposure occurs early in gestation.

Exposure later in pregnancy may also result in somatic retardation, but the effect is far less serious. The findings of smaller size among those in Hiroshima exposed to high doses in early childhood, with a lesser effect following exposure at later ages, suggest that radiation may have a potential for physical retardation well into the growth cycle. Because of the lack of a dose gradient, the unknown influence of non-radiation related factors, and the absence of effect in Nagasaki, the results of the ABCC studies on those exposed in childhood must be interpreted cautiously. Nevertheless some effect seems likely, especially since radiation effects following childhood exposure have been observed elsewhere in man\(^{23,24}\) and in animals,\(^{2,25}\) and in animals a relative biological effectiveness on growth greater for neutrons than for x-irradiation has been demonstrated.\(^{25}\)

REFERENCES

1. Goldstein, L. and Murphy, D. (1929) Etiology of ill-health children born after maternal pelvic irradiation. II. Defective children born after post-conception pelvic irradiation. *Am. J. Roentgenol.* 22: 322-331.
2. Hicks, S. P. and D'Amato, C. (1966) Effects of ionizing radiation. *Adv. Teratol.* 1: 196-250.
3. Murphy, D. P. (1928) Ovarian irradiation, its effect on the health of subsequent children: Review of the literature, experimental and clinical, with a report of 320 human pregnancies. *Surg. Gynecol. Obstet.* 47: 201-215.
4. Plummer, G. W. (1952) Anomalies occurring in children exposed in utero to the atomic bomb in Hiroshima. *Pediatrics* 10: 687-692.
5. Miller, R. W. (1956) Delayed effects occurring within the first decade after exposure of young individuals to the Hiroshima atomic bomb. *Pediatrics* 18: 1-17.
6. Yamazaki, J. N., Wright, S. W. and Wright, P. M. (1954) Outcome of pregnancy in women exposed to the atomic bomb in Nagasaki. *Am. J. Dis. Child.* 87: 448-463.
7. Burrow, G. N., Hamilton, H. B. and Hrubec, Z. (1965) Study of adolescents exposed in utero to the atomic bomb, Nagasaki, Japan. II. Growth and development. *J. Am. Med. Assoc.* 192: 357-364.
8. Wood, J. W., Keesn, R. J., Kawamoto, S. and Johnson, K. G. (1967) The growth and development of children exposed in utero to the atomic bombs in Hiroshima and Nagasaki. *Am. J. Public Health* 57: 1374-1380.
9. Miller, R. W. and Blot, W. J. (1972) Small head size following in utero exposure to atomic radiation. *Lancet* 2: 784-787.
10. Wood, J. W., Johnson, K. G. and Omori, Y. (1967) Mental retardation in children exposed in utero to the atomic bombs in Hiroshima and Nagasaki. *Am. J. Public Health* 57: 1381-1389.
11. Blot, W. J. and Miller, R. W. (1973) Mental retardation following in utero exposure to the atomic bombs of Hiroshima and Nagasaki. *Radiology* 106: 617-619.
12. Milton, R. C. and Shohoji, T. (1968) Tentative 1965 radiation dose estimation for atomic bomb survivors, Hiroshima and Nagasaki. *ABCC Tech. Report* 1-68.
13. Ishimaru, T., Hoshino, T., Ichimaru, M., Okada, H., Tomiyasu, T., Tsuchimoto, T. and Yama-
moto, T. (1971) Leukemia in atomic bomb survivors, Hiroshima and Nagasaki, 1 October 1950-30 September 1966. Radiat. Res. 45: 216-233.
14. Jablon, S., Fujita, S., Fukushima, K., Ishimaru, T. and Auxier, J. (1969) RBE of neutrons in Japanese survivors. Symposium on neutrons in radiobiology. Oak Ridge, Tenn., USAEC CONF-691106.
15. Russell, W. J., Keehn, R. J., Ihno, Y., Hattori, F., Kogure, T. and Imamura, K. (1973) Bone maturation in children exposed to the a-bomb in utero. Radiology 108: 367-374.
16. Hashizume, T., Maruyama, T., Nishizawa, K. and Nishimura, A. (1973) Dose estimation of human fetus exposed in utero to radiations from atomic bombs in Hiroshima and Nagasaki. J. Radiat. Res. 14: 346-362.
17. Gruelich, W. N., Crimson, C. S. and Turner, M. L. (1953) The physical growth and development of children who survived the atomic bombings of Hiroshima and Nagasaki. J. Pediatr. 43: 121-145.
18. Reynolds, E. L. (1959) Growth and development of Hiroshima children exposed to the atomic bomb. ABCC Tech. Report 20-59.
19. Nehemias, J. V. (1962) Multivariate analysis and the IBM 704 computer applied to ABCC data on growth of surviving Hiroshima children. Health Phys. 8: 165-186.
20. Belsky, J. L. and Biot, W. J. (1975) Adult stature in relation to childhood exposure to the atomic bombs of Hiroshima and Nagasaki. Am. J. Public Health. 65: 489-494.
21. Rugh, R. (1958) X-irradiation effects on the human fetus. J. Pediatr. 52: 531-538.
22. Rugh, R. (1971) X-ray induced teratogenesis in the mouse and its possible significance to man. Radiology 99: 433-443.
23. Van Cleve, C. D. (1968) Late somatic effects of ionizing radiation. Division of Technical Information, Oak Ridge, Tennessee. USAEC, TID-24310: 168-171.
24. Sutow, W. W., Conard, R. A. and Griffith, K. M. (1965) Growth status of children exposed to fallout radiation on the Marshall Islands. Pediatrics 36: 721-731.
25. Sikow, M. R. and Mahlum, D. D. (1961) Radiation biology of the fetal and juvenile mammal. Division of Technical Information. Oak Ridge, Tennessee. USAEC, CONF-690501.