

# MENTAL RETARDATION IN CHILDREN EXPOSED IN UTERO TO THE ATOMIC BOMBS IN HIROSHIMA AND NAGASAKI

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IONIZING irradiation to the fetus damages neural tissue in experimental animals<sup>1,2</sup> and mental retardation and microcephaly have been reported in children who were exposed to maternal pelvic irradiation.<sup>3,4</sup> There have also been several reports of an increased occurrence of mental retardation in children who were exposed in utero to the atomic bombs in Hiroshima and Nagasaki in August, 1945.<sup>5-10</sup> An increased susceptibility of the fetus to radiation during the first 15 weeks of gestation<sup>8,10</sup> and an association between mental retardation and small head size has been shown.<sup>6-8,10</sup> These previous studies were made on samples of between 190 and 292 subjects at periods ranging from five to 20 years after exposure.

A group of 1,613 children who were in utero at the time of the atomic bombs (ATB) in Hiroshima and Nagasaki have been studied at the Atomic Bomb Casualty Commission (ABCC) on a long-term basis. This report evaluates all members of that sample for mental retardation and correlates retardation with exposure distance and gestational age ATB. This study includes 99 per cent of all subjects from the previous studies, has the benefit of larger numbers, of additional accumulated data, and the fact that mental retardation is generally more easily and more accurately recognized at later ages. The subjects are now young adults and there is a growing attrition and dispersion of the sample. It is, therefore, unlikely that any significant additional data will ever become available to bear on this problem.

## Method

The study sample and general clinic procedures have been described elsewhere.<sup>11</sup> The sample includes 1,613 children who were at all stages of gestation and at various distances from the hypocenter ATB. In each city the more distal (3,000-4,999 meters) and not-in-city subjects are matched by gestational age and sex to the proximal group (within 2,000 meters). Near each birthday the subjects come to ABCC for a history, physical examination, anthropometric measurements, routine tests on blood, urine and stool, and any additional procedures indicated. At some examinations other specific tests including psychometrics (Koga, Goodenough, Tanaka B) are done.

As a method of screening the population for mental retardation, subjects meeting the following criteria were reviewed:

1. Those examined 1955-1964, with one or more suggestive diagnoses: ICD 300-326 mental, psychoneurotic, and personality disorders, including mental retardation; ICD 752-753 malformations of the nervous system and sense organs including hydrocephalus and microcephaly.
2. Those examined at age 17 years whose head circumference was minus 1.75 standard deviations or more from the mean of the controls, i.e., the 5 per cent of subjects with smallest head circumferences based on "normal distribution" statistical theory.
3. The 72 subjects (all from Hiroshima) who were not examined at ABCC during 1955-1964. Of these, 30 had been examined at some time; 42 had never been examined at ABCC, but had been regularly visited by clinical contactors.

All information including medical charts, contact records, school and work achievement, and psychometric test results were used. Occasionally, additional needed information was obtained by re-examination of the subject and interview of the family. Without knowledge of exposure status, these data were jointly evaluated by three of the authors using criteria employed in a recent study,<sup>10</sup> and a decision was reached regarding the presence or absence of mental retardation. Mental retardation was diagnosed only if a subject were unable to perform simple calculations, to make simple conversation, to care for himself, or if he was completely unmanageable or had been institutionalized.

By one or more methods, all 1,613 subjects were screened for mental retardation with the following results:

the three patients never examined and for whom no record of a home visit was available, subsequent investigation revealed no evidence of retardation. For the not examined cases these alternate indexes have therefore been used, with full confidence, as a means of evaluation.

To determine the statistical significance of observed differences in the prevalence of mental retardation, chi-square tests with 1 degree of freedom were computed, using Yate's correction for small numbers. The resulting probabilities were halved since the assumption being tested is that the closer the subjects were to the hypocenter ATB the higher is the prevalence of retardation.

### Results

A total of 30 mentally retarded subjects were found in the entire in utero

	Hiroshima		Nagasaki	
	Subjects reviewed	Classified retarded	Subjects reviewed	Classified retarded
Suggestive diagnoses, total	40	18	20	8
Small head circumference total	57	7	14	1
Suggestive diagnoses plus small head circumference	13	7	4	1
Not examined 1955-1964	72	4	0	-

The adequacy of the selected diagnoses for identifying retarded subjects is supported by the fact that all eight of the retarded subjects found in the head-size screened subjects (seven Hiroshima and one Nagasaki) had one or more of the selected diagnoses. The screening by diagnosis did not miss a single retarded subject in the small head sample.

For all cases where mental retardation has been established by clinical evaluation, the clinical contactors had also independently noted the condition in their records. At least 18 of the 42 subjects who were not examined at ABCC had entered high schools or universities. For

sample, 22/1265 (1.7 per cent) for Hiroshima and 8/348 (2.3 per cent) for Nagasaki. There were 16 retarded subjects among the 1,259 children examined at 17 years of age, 11/987 (1.1 per cent) for Hiroshima and 5/272 (1.8 per cent) for Nagasaki. The prevalence of retardation by city, sex, and distance from hypocenter ATB is shown in Table 1. In Hiroshima the prevalence of retardation was significantly higher ( $0.01 > P > 0.005$ ) in the group within 2,000 meters (2.4 per cent) than in the combined control (3,000-4,999 meters plus not-in-city) group (0.5 per cent). Subdivision of those within 2,000 meters showed that the group within 1,500

meters had significantly ( $0.05 > P > 0.025$ ) more retardation (5.0 per cent) than did the group between 1,500-1,999 meters (1.0 per cent). The excess of retardation in the 1,500-1,999 meter group over that for the combined control groups was not significant, although the same pattern of differences was seen for each sex.

Of the 278 subjects not examined at age 17 in Hiroshima, 11 (4.0 per cent) were mentally retarded. The pattern of differences between distance categories is the same as that for examined cases, although the percentages of retarded subjects are generally two to three times higher in those not examined (Table 2).

The prevalence of mental retardation in the entire Hiroshima in utero sample (Table 3) was tested in the same manner as the data in Tables 1 and 2 with the following results:

- 0-1,999 m (3.9%) vs. combined controls (0.6%)  $p < 0.005$
- 0-1,499 m (7.7%) vs. 1,500-1,999 m (1.5%)  $p < 0.005$
- 1,500-1,999 m (1.5%) vs. combined controls (0.6%)  $p < 0.15$

In Nagasaki, due to the small numbers of subjects it was difficult to establish statistical significance by distance categories for the prevalence of retardation. The group within 1,500 meters had more retardation than the 1,500-1,999 meter group which in turn had slightly less retardation than the combined control group, but neither comparison was significant.

An interesting aspect of the screening procedure for identifying mentally retarded subjects was the opportunity afforded to search for etiologic factors which might result in retardation. This search also was conducted without knowledge of the retarded subject's exposure category. Distribution of the nine cases, with a condition which might in itself be associated with retardation, is shown in Table 3. In Hiroshima, six of the 22 retarded subjects (27.3 per cent) were considered to have an explanation for their retardation, three of eight cases (37.5 per cent) in Nagasaki. The proportions of such cases were about one-quarter for those within 1,500 meters, and the 1,500-1,999 meter sub-

**Table 1—Prevalence of mental retardation in subjects examined at age 17 years**

Distance		Hiroshima		Nagasaki	
		Male	Female	Male	Female
<1,500 m	Examined	63	58	13	17
	Retarded	3	3	2	1
	%	4.8	5.2	15.4	5.9
1,500-1,999	Examined	105	102	30	19
	Retarded	0	2	0	0
	%	0	2.0	0	0
3,000-4,999	Examined	177	176	56	48
	Retarded	0	1	0	1
	%	0	0.6	0	2.1
Not-in-city	Examined	164	142	45	44
	Retarded	2	0	0	1
	%	1.2	0	0	2.3
Total	Examined	509	478	144	128
	Retarded	5	6	2	3
	%	1.0	1.3	1.4	2.3

**Table 2—Prevalence of mental retardation in subjects not examined at age 17 years**

Distance		Hiroshima		Nagasaki	
		Male	Female	Male	Female
<1,500 m	Examined	26	22	4	3
	Retarded	4	3	0	0
	%	15.4	13.6	0	0
1,500-1,999	Examined	30	29	7	9
	Retarded	2	0	1	0
	%	6.7	0	14.3	0
3,000-4,999	Examined	44	35	15	13
	Retarded	1	0	0	1
	%	2.3	0	0	7.7
<b>Not-in-city</b>	Examined	37	55	15	10
	Retarded	0	1	1	0
	%	0	1.8	6.7	0
<b>Total</b>	Examined	137	141	41	35
	Retarded	7	4	2	1
	%	5.1	2.8	4.9	2.9

groups, but nearly one-half for the combined controls. Possible "explanations" for the observed retardation were:

Hiroshima	Sex	Distance (m)
Neonatal jaundice	F	1,000
Mongolism	F	1,200
Mongolism	F	1,400
Japanese B encephalitis in infancy	F	1,700
Retarded sibling	M	3,100
Mongolism	M	Not-in-city
Nagasaki		
Von Recklinghausen's disease	M	1,100
Congenital syphilis	F	3,000
Foot delivery, prolonged labor, and possible birth trauma	F	4,400

If the nine subjects with possible explanations for retardation are excluded, the remaining 21 cases show the same pattern of differences in prevalence of mental retardation (Tables 1-3). The prevalence of "unexplained" mentally retarded subjects in Hiroshima in the subgroup within 1,500 meters is twice as high for males as for females.

The evidence for an association between distance and the prevalence of retardation is strengthened when the data are examined by month of birth (Table 4 and Figure 1). Of the 13 retarded subjects in the Hiroshima subgroup within 1,500 meters, 10 (76.9 per cent) were born in January or February, 1946, whereas only 59 subjects (34.9 per cent) of the entire subgroup within 1,500 meters were born in those months ( $0.01 > P > 0.001$ ). In the 1,500-1,999 meter subgroup there is a suggestion of a similar, but much less marked, tendency for retarded subjects to be born in these two months, while retarded subjects in the combined control groups have more widely scattered months of birth.

Retarded subjects in the subgroups within 1,500 meters had a median gestation of 12 completed weeks ATB, a mean gestation of 13 weeks and range of 6 to 27 weeks (Figure 2). Fewer retarded subjects are in the 1,500-1,999 meter category but the similarity of the distribution by weeks of gestation to those within 1,500 meters is apparent, median = 13 weeks, mean = 14 weeks, range =

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Table 3—Prevalence of mental retardation in the entire in utero study sample

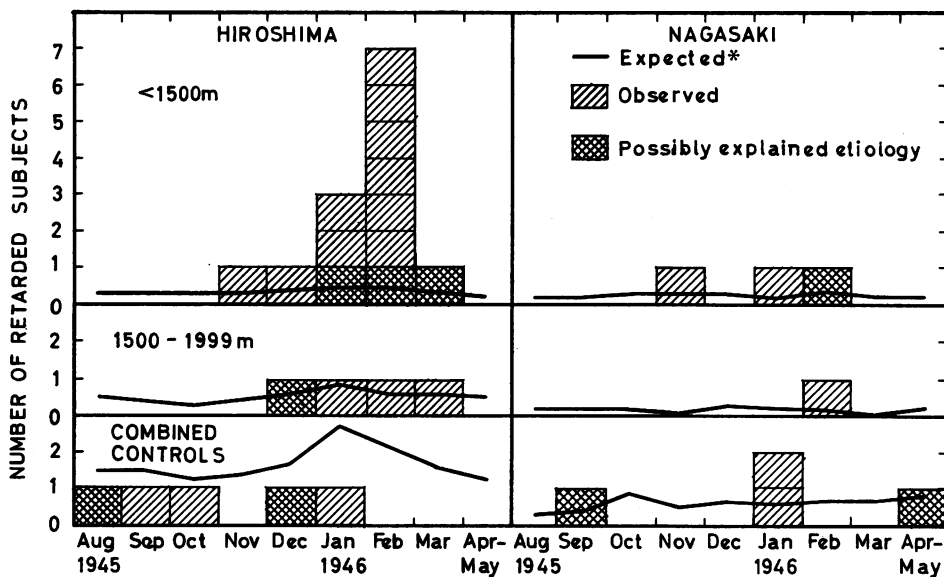
Distance		Hiroshima		Nagasaki	
		Male	Female	Male	Female
<1,500 m	Examined	89	80	17	20
	Retarded	7	6 (3)	2 (1)	1
	%	7.9	7.5	11.8	5.0
1,500-1,999	Examined	135	131	37	28
	Retarded	2	2 (1)	1	0
	%	1.5	1.5	2.7	0
3,000-4,999	Examined	221	211	71	61
	Retarded	1 (1)	1	0	2 (2)
	%	0.5	0.5	0	3.3
Not-in-city	Examined	201	197	60	54
	Retarded	2 (1)	1	1	1
	%	1.0	0.5	1.7	1.9
Total	Examined	646	619	185	163
	Retarded	12 (2)	10 (4)	4 (1)	4 (2)
	%	1.9	1.6	2.2	2.5

Number in parentheses: cases with possibly "explained" etiology included in total.

Table 4—Prevalence of mental retardation by month of birth

Distance		Month of birth								
		1945						1946		Apr. May
		Aug.	Sept.	Oct.	Nov.	Dec.	Jan.	Feb.	Mar.	
Hiroshima										
<1,500 m	Examined	15	19	16	15	21	29	30	17	7
	Retarded	0	0	0	1	1	3	7	1	0
	%	0	0	0	6.7	4.8	10.3	23.3	5.9	0
1,500-1,999	Examined	26	21	19	23	29	50	34	35	29
	Retarded	0	0	0	0	1	1	1	1	0
	%	0	0	0	0	3.4	2.0	2.9	2.9	0
Combined controls	Examined	82	80	68	75	91	158	119	89	68
	Retarded	1	1	1	0	1	1	0	0	0
	%	1.2	1.2	1.5	0	1.1	0.6	0	0	0
Nagasaki										
<1,500 m	Examined	6	3	8	9	7	4	11	8	8
	Retarded	0	0	0	1	0	1	1	0	0
	%	0	0	0	11.1	0	25.0	9.1	0	0
1,500-1,999	Examined	3	3	5	2	8	4	6	2	5
	Retarded	0	0	0	0	0	0	1	0	0
	%	0	0	0	0	0	0	16.7	0	0
Combined controls	Examined	14	19	40	22	31	25	30	31	34
	Retarded	0	1	0	0	0	2	0	0	1
	%	0	5.3	0	0	0	8.0	0	0	2.9

Figure 1—Observed and expected mentally retarded subjects by month of birth



\*Based on percentage distribution of subjects by month of birth

6-22 weeks. For the combined controls, retarded subjects were broadly distributed with regard to weeks of gestation ATB.

Nearly all of the mentally retarded subjects have smaller than average head circumferences (Table 5). These data are based on many different ages at examination and preclude showing the mean and standard deviations of head circumference for all ages and each city-sex category. Of the 30 retarded subjects, 26 had head circumferences of minus 1 cm or more from the mean for their age and sex and half were minus 3 cm or more (1.5 cm is approximately 1 SD). Of the mentally retarded subjects within 1,500 meters, 75 per cent had a head circumference of 3 cm or more below the mean. However, the general reduction in head circumference among the subjects within 1,500 meters described in an earlier report was usually not associated with mental retardation.<sup>10</sup> Of the 71 subjects selected for detailed

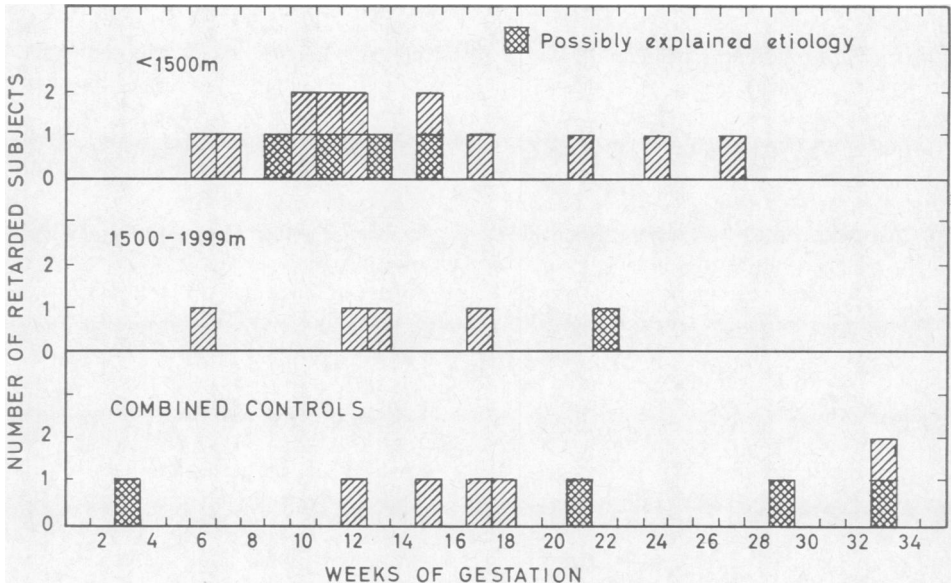
study because of small head size only eight were retarded.

If only those 21 subjects without "explanation" for their retardation are considered, the trends demonstrated by month of birth, weeks of gestation ATB, and head circumference, are the same as those presented for the total group of 30 mentally retarded subjects.

## Discussion

The prevalence of mental retardation in subjects exposed in utero within 1,500 meters is higher by fivefold than in the more distally located subjects. The pattern of differences is the same whether for the entire sample, for subjects examined at age 17 years, or for subjects not examined at age 17 years. One might expect a higher prevalence of mental retardation in subjects not examined at age 17 years. To bring a 17-year-old retarded subject to the clinic often poses real problems for the parents and many

Figure 2—Mentally retarded subjects by weeks of gestation, ATB



of the retarded are by that age confined to institutions. In addition, there is a higher mortality rate among mentally retarded children.<sup>10</sup> The association between exposure and retardation is strengthened by the fact that after exclusion of all subjects with known pos-

sible causes for mental retardation the relationship to proximal exposure to the atomic bombs is still positive.

Mental retardation in a subsample of the Hiroshima children was reported in 1956 and a re-evaluation of those subjects in 1965 has generally supported

Table 5—Deviation of head circumference of mentally retarded individuals from the means for their city, age, and sex

Deviation (cm)	<1,500 m	1,500-1,999 m	Combined controls	Total
Larger	0	0	2 (1)	2
Smaller	16 (4)	5 (1)	7 (4)	28
<0.9	0	0	2	2
1.0-1.9	3 (1)	1	2 (2)	6
2.0-2.9	1	2	0	3
3.0-3.9	2	0	2 (1)	4
4.0-4.9	2	1 (1)	0	3
5.0-5.9	3 (2)	0	0	3
6.0-6.9	1	0	0	1
7.0-7.9	2 (1)	0	1 (1)	3
8.0-8.9	0	0	0	0
9.0-9.9	2	1	0	3
10.0+	0	0	0	0
Mean deviation	-4.9 cm	-3.3 cm	-1.4 cm	-3.6 cm

Number in parentheses: cases with possibly explained etiology included in total.

the earlier findings.<sup>8,10</sup> However, the mental evaluation of 1956 and 1965 differed for several subjects, primarily because a later estimate of mental status is likely to be more accurate. These discrepancies in Hiroshima are discussed in a previous report.<sup>10</sup> A study in Nagasaki in 1958-1960 identified nine mentally retarded children,<sup>9</sup> all of whom are members of the present study sample. Two of the boys previously reported as retarded are currently employed in occupations requiring a normal level of intelligence. A retarded female in the current Nagasaki sample was not in the previous study.

Most of the retarded subjects within 1,500 meters were at 6-15 weeks gestation ATB and were born in January or February, 1946. This correlates closely with the time of brain differentiation and the development of the cerebral cortex, presumably a time of increased neural radiosensitivity.<sup>12</sup> However, mental defects from an insult later in fetal life can occur since highly radiosensitive neuroblasts are present from about four weeks of gestation until after birth.<sup>1,12,13</sup> It is quite possible that other limitations on optimal mental achievement may exist in the study group but were not detected by the criteria for mental retardation.

To define the mechanism by which these children became mentally retarded is impossible. After excluding cases with disease states which might explain the retardation, the significant relationship between mental retardation and proximal exposure to the atomic bombs still remains. There is no assurance, however, that some of the "explanations" might not be related to exposure. It is noteworthy that in the control groups about 50 per cent had possible "explanations" for their mental retardation while only 25 per cent of the proximal cases were so "explained." The correlation between distance from the hypocenter and prevalence of mental retardation indi-

cates exposure to the atomic bombs as the major etiological factor.

The possible contribution of maternal influences secondary to trauma, blast, fire, or disease cannot be disproved, but such devastation was also experienced far beyond 1,500 meters, whereas the range of significantly high levels of radiation was much more restricted.<sup>14,15</sup> It is conceivable that after proximal irradiation some mothers may have had radiation-induced blood dyscrasias resulting in increased susceptibility to infections and subsequent fetal damage. This explanation seems rather unlikely and histories of such instances of infection are lacking. It is most likely that the excess of retarded subjects within 1,500 meters resulted from direct cellular damage by radiation to the neural tissue of the fetus. This concept is supported by previous studies in experimental animals<sup>16,17</sup> and other reports of retarded children following in utero irradiation.<sup>3,4</sup>

The consistency of the increased prevalence of mental retardation in the 1,500-1,999 meter group in Hiroshima compared with the combined control group is of interest. A lower order of effect may in fact exist although tests of significance fail to confirm it. This suspicion is supported by the mentally retarded subjects in the 1,500-1,999 meter group having a similar distribution by month of birth, weeks of gestation ATB, and head circumference, as for the subjects within 1,500 meters, and dissimilar to the distribution for the combined controls. Considering the radiosensitivity of the neuroblast, this excess may well be the result of irradiation but could also represent the effect of other complicating factors such as blast, fire, disease, or poor nutrition.

Of the 30 retarded subjects, 28 had head circumferences below the mean for their age and sex. Mentally retarded subjects in the group within 1,500 meters had the smallest head circumfer-



ences but the general reduction in head size for that group was not usually associated with retardation. Indeed, several subjects with head circumferences minus three standard deviations are mentally normal; one is a university student. The relationship between mental retardation and small head size is not clear, except that retarded subjects generally have smaller than average heads, but mental retardation is not always found in those with small heads. The causative factors involved in the development of small heads and those leading to mental retardation may be, to some degree, independent. General head size limitation is observed for all stages of gestation for those within 1,500 meters,<sup>11</sup> while 6-15 weeks gestation ATB proved to be the most sensitive time for the development of mental retardation, suggesting a differential radiosensitivity for calvarium and brain.

### Summary

Subjects who were exposed in utero to the atomic bombs in Hiroshima and Nagasaki, along with suitable controls, are examined annually at the Atomic Bomb Casualty Commission. Of the 1,613 subjects in the study sample, 30 have gross mental retardation. Within 1,500 meters from the hypocenter the prevalence of mental retardation is five times as high as for the more distal subjects, and six to 15 weeks gestation was the most sensitive period. Even when subjects with possible "explanations" for their retardation are excluded, the pattern of differences remains the same. All but two of the retarded subjects had smaller than average heads and for those who were within 1,500 meters this effect is accentuated.

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who have over the years contributed to the collection of these data is sincerely acknowledged. The efforts of the members of the Department of Medical Sociology, especially Dr. Y. Scott Matsumoto and Mr. M. Komatsu are appreciated. The authors are particularly grateful to Mr. G. Day for the tables and figures and to Mr. K. B. Noble for his help in preparing this report.

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See Page 1390 for Appendix Table

**Appendix Table—Mentally retarded subjects, in utero sample, Hiroshima and Nagasaki**

MF number	Source*	Sex	Distance (meters)	Gestation (weeks)	Remarks
Hiroshima					
226683	2	M	3,100	21	Other retarded sibling
241728	1, 2	F	1,700	17	
245763	2	M	1,200	10	
245977	3	F	1,000	9	Neonatal jaundice
246116	1, 2	M	1,000	10	
312021	3	F	Not-in-city	18	
400133	2	F	3,200	33	
400211	3	F	700	12	
400590	2	M	900	7	
400716	2	M	900	21	
401023	3	F	1,200	13	Mongoloid
401081	1, 2	F	1,100	15	
401141	2	M	1,000	12	
403929	1, 2	M	Not-in-city	29	Mongoloid
404032	1, 2	F	1,400	15	Mongoloid
404259	2	M	1,500	12	
433800	2	F	1,700	22	Japanese B encephalitis in infancy
440056	2	M	Not-in-city	12	
440463	1, 2	M	1,100	24	
444522	1, 2	F	900	6	
471693	2	M	1,200	11	
857279	2	M	1,700	13	
Nagasaki					
050968	2	F	4,400	3	Prolonged labor, possible birth trauma
057021	2	F	3,000	33	Congenital syphilis
078481	2	F	1,100	27	
078487	2	M	1,100	11	Von Recklinghausen's disease
142623	2	M	1,700	6	
143818	1, 2	M	1,000	17	
151845	2	F	Not-in-city	17	
152396	2	M	Not-in-city	15	

\* 1—Small head at time of the fifth cycle examination. 2—Suspicious clinical diagnosis any time 1955-1964. 3—Not seen at ABCC since 1955.

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