Subjects exposed in utero to the atomic bombs at Hiroshima and Nagasaki, as well as controls, are examined annually at the Atomic Bomb Casualty Commission. The two papers presented below offer findings on the growth and development of children in the study sample, and on those with gross mental retardation.

THE GROWTH AND DEVELOPMENT OF CHILDREN EXPOSED IN UTERO TO THE ATOMIC BOMBS IN HIROSHIMA AND NAGASAKI

James W. Wood, M.D.; Robert J. Keehn, M.S., F.A.P.H.A.; Sadahisa Kawamoto, M.D.; and Kenneth G. Johnson, M.D.

Introduction

MANY effects of fetal irradiation have been demonstrated in experimental animals[1] and reported in children born after maternal pelvic irradiation.[2-4] Effects of whole body irradiation on the growth of children have also been reported,[5-7] but little has been written about the growth of children who have received irradiation while in utero.

Both exposed and suitable control subjects 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), since 1950. The purpose of the present study is to evaluate growth attainment at the 17-year level for the 1,259 examined subjects in this group. Since that age there has been a dispersion of the sample; many have left Hiroshima and Nagasaki for universities or employment elsewhere. Seventeen years of age is near the time of maturation and the most information that may ever be available concerning effects of in utero exposure to the atomic bombs on growth is probably that which was obtained at this age.

Previous reports on subsamples of these children (190-292 subjects) have indicated decreased head size[8-12] and body size[9,11] associated with proximal exposure to the atomic bombs.

Method

The study sample of 1,613 Hiroshima and Nagasaki children is composed of three major comparison groups, based on the distance of the mothers from the hypocenter ATB, and defined as follows: 0-1,999 meter group, 3,000-4,999 meter group, and not-in-city group. Included are children who were at all stages of gestation ATB. The two distal groups were matched for gestational age and sex to the 0-1,999 meter group. Radiation dose estimates (T57D)[13] based on air dose curves and shielding information have been completed for most of the mothers of children in the 0-1,999 meter group.

Subjects are examined annually at ABCC near each birthday. A history is taken and a physical examination, leucocyte count, differential cell count, hematocrit, urinalysis, stool examination, chest and left wrist x-rays, and any other tests clinically indicated are done. Various anthropometric measurements, and at some examinations, vital capacity, visual acuity, and psychometrics are re-

corded. All data are collected and processed without the staff knowing the exposure status of the subjects.

The sample distribution and the percentage of subjects who were examined at age 17, and are included in this analysis of anthropometric data, are shown in Table 1. About 80 per cent of the total sample were examined at that age. The not examined subjects appear to be randomly distributed throughout the different exposure groups. Means for all measurements were calculated separately for each sex and distance group within each city. The group within 2,000 meters was further classified by distance of the mother from the hypocenter, estimated rad dose, and the presence or absence of acute radiation syndrome to produce three high dose-low dose contrasts as follows:

Radiation Dose Classification Subgroups for <2,000 M Group

	High dose category	Low dose category
1 Distance	<1,500 m	1,500–1,999 m
2 Dose	50+ rad	<50 rad
3 Radiation syndrome	Positive	Negative

The group within 2,000 meters was also analyzed by trimester of gestation ATB.

Results

Comparison of Mean Measurements—Age 17

Except for Nagasaki females, mean head circumferences were smaller for those within 2,000 meters as compared to the more distal groups. The greatest differences were observed between "high dose" and "low dose" subgroups and in every comparison the high dose subgroups had the smaller mean head circumferences (Table 2). Except for Nagasaki males, comparisons by distance, 0-1,499 meters vs. 1,500-1,999 meters, were statistically significant ($P \leq 0.01$). The least significance was found in comparisons by presence or absence of the acute radiation syndrome in the mother. However, few mothers gave a history of acute radiation symptoms.

Mean standing height and weight were less for Hiroshima males and females and Nagasaki males who were within 2,000 meters as compared to the more distal groups. For each sex in both cities the means were smallest for the subgroups within 1,500 meters (Table 2) and, except for Nagasaki males, the differences were statistically significant ($P \leq 0.05$). The least significant comparisons were by symptoms of the mother.

Nagasaki females within 2,000 meters had smaller mean intercristic diameters than the distal subjects but analysis by high dose and low dose subgroups revealed no consistent patterns in either city. Mean chest circumferences were smaller for subjects within 2,000 meters as compared to distal subjects and for the high dose as compared to the low

Table 1—Total in utero sample, number and per cent examined at age 17 years

Sex	<2,000 m			3,000–4,999 m			Not-in-city		
	Total	Examined	%	Total	Examined	%	Total	Examined	%
				Hiroshima					
Male	224	168	75.0	221	177	80.1	201	164	81.6
Female	211	160	75.8	211	176	83.4	197	142	72.1
				Nagasaki					
Male	54	43	79.6	71	56	78.9	60	45	75.0
Female	48	36	75.0	61	48	78.7	54	44	81.5

dose subgroups, but few of the differences were statistically significant. No consistent patterns by exposure groups and few significant differences were observed for arm span, vital capacity, maximal and minimal chest circumferences, sitting height, systolic and diastolic blood pressures, and pulse count.

For each sex within each city the mean measurements were compared for the within 1,500 meter and 1,500-1,999 meter subgroups and the 3,000-4,999 meter and not-in-city groups (Table 3). The consistency of smaller means for the most proximal subjects is striking; however, to some extent this reflects the multiple positively correlated measurements on the same individuals. Generally, the means were similar for all groups beyond 1,500 meters.

Height and weight means for individuals at 17 years of age in Hiroshima and Nagasaki Prefectures, as published by the Ministry of Welfare, are shown with those for the present study in Table 4. The ministry's data are for children who were born at about the same time as those in this study sample. In every case their means are larger than those of the subgroups within 1,500 meters and similar to those beyond 1,500 meters.

Mean Measurements by Trimester of Gestation—Age 17

For the group within 2,000 meters, mean measurements by trimester of gestation were compared and no consistent patterns of effect were evident. Similarly, for the subgroups within 1,500 meters no pattern of effect by trimester of gestation was detected. The corresponding trimesters for the within 1,500 meters and 1,500-1,999 meter subgroups were compared and proximal subjects had the smaller means, with the exception of third trimester Hiroshima females and Nagasaki males. Within 1,500 meters there was only one third trimester subject in Nagasaki.

Table 2—Mean measurements, "high dose" and "low dose" subgroups within 2,000 m

Measurement	City	Sex	Distance		T57D rad		Radiation syndrome+	
			<1,500	1,500–1,999	50+	<50	Yes	No
Head circumference (cm)	Hiroshima	Male	53.9 ***	55.1	54.0 ***	55.1	54.3 NS	54.6
		Female	53.1 **	54.0	53.3 *	53.9	52.7 NS	53.7
	Nagasaki	Male	53.8 NS	54.9	54.4 NS	54.6	52.9 **	55.0
		Female	53.7 **	54.8	53.7 **	55.0	53.7 Sugg.	54.5
Standing height (cm)	Hiroshima	Male	163.4 *	165.4	163.7 Sugg.	165.5	165.1 NS	164.6
		Female	151.3 **	153.9	151.8 *	154.1	149.2 *	153.3
	Nagasaki	Male	161.0 NS	162.3	161.9 NS	161.2	159.1 NS	162.5
		Female	161.5 *	155.1	152.4 NS	153.9	151.0 NS	154.1
Body weight (kg)	Hiroshima	Male	51.25 **	54.20	51.95 *	54.59	54.04 NS	52.99
		Female	46.06 *	48.41	46.87 NS	47.75	44.04 *	47.87
	Nagasaki	Male	50.48 NS	52.77	51.81 NS	51.77	4793 Sugg.	53.03
		Female	45.58 **	50.75	44.79 **	50.04	44.74 NS	49.33

+ Acute radiation symptoms in mother. NS = P>0.10; Sugg. 0.10≥P>0.05, * 0.05≥P>0.01, ** 0.01≥P>0.001, *** P≤0.001.

Cumulative Measurement Frequencies—Age 17

The foregoing data demonstrate that there are significant differences between mean growth attainment for children who were exposed in utero within 1,500 meters as compared with the more distally or not exposed children. In an effort to describe more precisely the nature of these differences, cumulative percentage frequencies have been plotted on normal probability paper for all measurements at age 17 years.

When measurements are normally distributed and the number of subjects is

Table 3—Mean measurements, by distance from the hypocenter

Measurement	City	Sex	<1,500 m		1,500–1,999 m		3,000–4,999 m		Not-in-city	
			Mean	Rank+	Mean	Rank	Mean	Rank	Mean	Rank
Head circumference (cm)	Hiroshima	Male	53.9	1	55.1	3	55.0	2	55.1	4
		Female	53.1	1	54.0	2	54.1	3	54.2	4
	Nagasaki	Male	53.8	1	54.9	3	54.9	2	55.4	4
		Female	53.7	1	54.8	4	54.3	2	54.5	3
Standing height (cm)	Hiroshima	Male	163.4	1	165.4	3	165.3	2	165.5	4
		Female	151.3	1	153.9	3.5	153.9	3.5	153.8	2
	Nagasaki	Male	161.0	1	162.3	2	163.0	3	166.7	4
		Female	151.5	1	155.1	4	153.5	3	152.9	2
Body weight (kg)	Hiroshima	Male	51.25	1	54.20	4	53.93	2	54.19	3
		Female	46.06	1	48.41	2	48.61	3	48.95	4
	Nagasaki	Male	50.48	1	52.77	3	52.42	2	54.94	4
		Female	45.58	1	50.75	4	48.46	3	48.29	2
Chest circumference (cm)	Hiroshima	Male	77.2	1	78.3	4	78.1	3	78.0	2
		Female	71.9	1	73.4	4	73.2	3	73.1	2
	Nagasaki	Male	78.7	1	81.0	3	80.8	2	82.0	4
		Female	77.6	1	79.9	4	79.7	2	79.7	3
Intercristic diameter (cm)	Hiroshima	Female	26.8	1	26.9	4	26.8	2	26.9	3
	Nagasaki	Female	26.0	1	27.3	4	27.0	3	26.8	2

+ Rank of mean measurements prior to rounding, smallest to largest (1-4).

Table 4—Mean measurements, ABCC subjects and school health survey

Measurement	City	Sex	ABCC Subjects		School health survey*
			<1,500 m	1,500+ m	
Standing height (cm)	Hiroshima	Male	163.4	165.4	165.7
		Female	151.3	153.9	154.0
	Nagasaki	Male	161.0	164.1	165.6
		Female	151.5	153.5	153.8
Body weight (kg)	Hiroshima	Male	51.2	54.1	56.4
		Female	46.1	48.7	51.0
	Nagasaki	Male	50.5	53.4	56.3
		Female	45.6	48.8	50.2

* Statistical yearbooks, Hiroshima and Nagasaki Prefectures, 1963. (Data for Prefecture.)

large, cumulative frequency curves approximate straight lines. When the number of subjects is small, deviations from a straight line at the tails of the curves may be due to a difference of two or three subjects from the expected.

For most of the measurements the subgroups within 1,500 meters tend to have the lower values throughout the entire range. However, there is considerable variation and, as with mean comparisons, the differences are not impressive except for head circumference, height, and weight. Even for these measurements there are some erratic variations in the Nagasaki data, more for males than females, but this is most probably the result of the small number of subjects in the subgroups within 1,500 meters in Nagasaki (13 males, 17 females). The Nagasaki cumulative frequencies for head circumference, height, and weight do, in a general way, parallel the curves for Hiroshima.

Head circumference data for Hiroshima males and females produce cumulative frequency curves indicating a slightly smaller head size (4-14 mm) for the subgroups within 1,500 meters as compared to the more distal subjects (Figure 1). Standing height for Hiroshima subjects shows a general trend for shorter stature; about 1 cm for males and 1-2 cm for females (Figure 1). The trends for weight are the same as for stature, and they are lighter than their more distally located contemporaries by 1-3 kg.

Discussion

The present study indicates that exposure of the human fetus to the irradiation of the atomic bombs has resulted in limitation of head and body size. The agreement with previous observations[8-12] and the much larger sample size permit little doubt regarding the validity of the findings. The evaluation having been made at age 17 years, when most meaningful growth had been completed, adds strength to the conclusions and suggests that the effects are likely to persist throughout life.

The major effects on growth attainment are those of decreased head circumference, height, and weight with several other measurements showing suggestive differences. Most detectable effects on growth of children who were in utero ATB occur within 1,500 meters from the hypocenter. This is demonstrated by the mean comparisons (Tables 2-4), and the cumulative frequency distributions (Figure 1) which indicate that the observed differences are not caused simply by a reduction in size of a limited number of subjects but rather by a general reduction in growth attainment for all subjects within 1,500 meters. Thus, even for those who would be considered within "normal limits" there has been a failure to achieve optimal growth when compared to distal or nonexposed subjects. Additional assurance that the inferences are applicable to the entire sample was established by comparing the means of subjects not examined at age 17 years with those of the examined group at other ages.

Previous reports from Japan and the Marshall Islands have shown that exposure of young children to ionizing radiation has a limiting effect on growth.[5-7] It is reasonable to expect that similar effects would occur in subjects irradiated while in utero and that the fetus may be susceptible throughout the gestational period, thus making the identification of quantitative differences by gestational age difficult. The search for a trimester-specific effect is further complicated by the additional subdivision of the sample and the resulting small numbers in each age group. In this study, growth limitation was detectable in all trimesters. Those who were within 1,500 meters had smaller mean measurements than the more distal subjects for any trimester, indicating that proximity to the

hypocenter is operative regardless of trimester. A gestational time of maximal or minimal risk in terms of ultimate growth achievement was not detected. This contrasts with observations on mental retardation where prevalence was increased within 1,500 meters and those between 6 and 15 weeks of gestational age ATB were particularly susceptible.[14]

Childhood exposure to whole body irradiation has been shown to result in more growth limitation in boys than girls.[5,6] No sex specific response on growth attainment for the proximal ex-

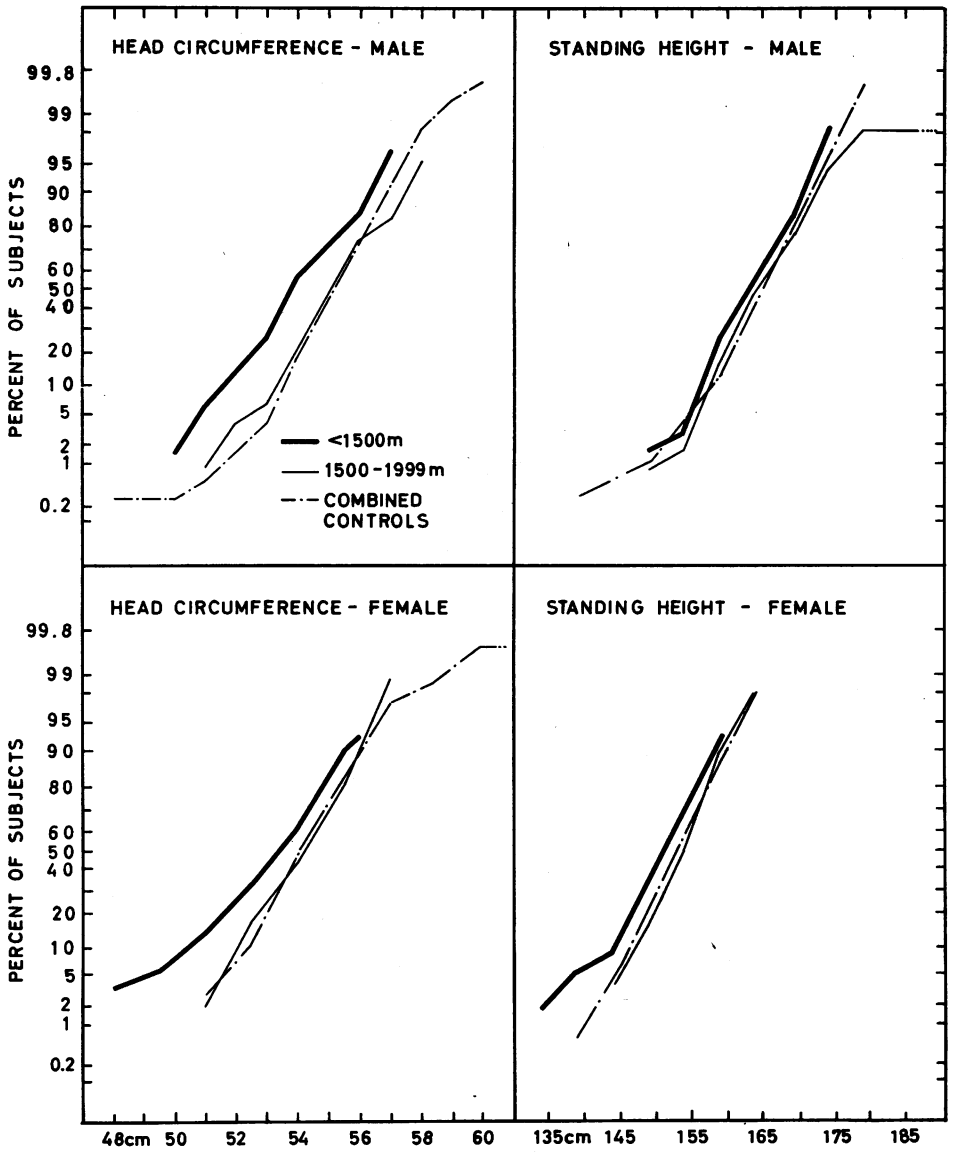

Figure 1—Accumulative per cent frequency, head circumference and standing height, Hiroshima

posed in utero subjects was found, but a dose response (those within 1,500 meters affected) was demonstrated. The radiation dose dropped precipitously at 1,500 meters while the effects of blast, fire, trauma, and disease subsequent to the bombs, extended considerably beyond that limit.[13,15] It is impossible to separate all these various factors, but growth limitation observed within 1,500 meters suggests irradiation as the major cause. Supporting this is the Marshall Islands experience where the source of irradiation was fallout without blast effects, and retardation of growth of exposed children occurred thus, suggesting irradiation of the fetus rather than secondary maternal influences as the cause.

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. At age 17 years, 1,259 of the 1,613 subjects in the study sample were examined and a tendency was observed for the proximal exposed to be least advanced in growth. The major effects are found most frequently in those who had been within 1,500 meters from the hypocenters of the bombs and include decreased head circumference, height, and weight. The levels of these effects do not vary by trimester of gestation.

ACKNOWLEDGMENT—We thank Mr. G. Day for the preparation of the tables and figures and Mr. K. B. Noble for his assistance in the preparation of this report.

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Dr. Wood is affiliated with the Department of Medicine, Yale University School of Medicine (333 Cedar Ave.), New Haven, Conn. He was formerly surgeon, US Public Health Service, Research Branch, Division of Radiological Health and was assigned to the Atomic Bomb Casualty Commission. Mr. Keehn is with the Department of Statistics. Dr. Kawamoto and Dr. Johnson are associated with the Department of Medicine, Atomic Bomb Casualty Commission.

The Atomic Bomb Casualty Commission is a cooperative research agency of the National Academy of Sciences—National Research Council (2101 Constitution Ave., N.W.), Washington, D. C. 20418, and the Japanese National Institute of Health of the Ministry of Health and Welfare. Commission funds have been provided by the US Atomic Energy Commission, the Japanese National Institute of Health, and the US Public Health Service.

This paper was read in part before the Eleventh International Congress of Pediatrics in Tokyo, Japan. It was submitted for publication in June, 1966.