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STUDY OF ADOLESCENTS EXPOSED *IN UTERO* TO THE ATOMIC BOMB, NAGASAKI, JAPAN

I. General Aspects: Clinical and Laboratory Data

With the increasing use of atomic energy in our society, the effects of ionizing radiation, particularly those that are delayed, have become a matter of great concern. Since 1947 the Atomic Bomb Casualty Commission (ABCC) has conducted continuing medical studies among survivors of the atomic bombing in Hiroshima and Nagasaki, including since 1951 a group of children who were irradiated *in utero*.[1] Fetal tissues being particularly sensitive to ionizing radiation,[2,3] this latter group is of special interest.

Information on the effects of ionizing radiation during prenatal development has been gathered mainly from animal experiments.[3-19] These studies have shown that irradiation early in gestation results in increased prenatal deaths, and later irradiation in gross abnormalities or delayed effects.

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An increased frequency of microcephaly occurs in humans irradiated *in utero*. Goldstein and Murphy[13] studied the offspring of 106 women who had received therapeutic doses of radiation during pregnancy and found 16 cases of microcephaly explainable only by radiation. In most of these cases the mother was irradiated before the fifth month of pregnancy. In addition to gross defects, leukemia and malignancy may occur more frequently in children who were irradiated *in utero*[14,15] but this has not always been substantiated.[16,17]

Previous ABCC studies of the children who were exposed *in utero* have also shown greater frequency of microcephaly.[18-20] In 1951, the outcome of pregnancy was studied in women exposed to the atomic bomb in various stages of gestation.[19] In the exposed children, mortality was increased during the fetal period and first year of life, and there was a higher prevalence of microcephaly and mental retardation as compared with controls. Most of the children with mental retardation and microcephaly were found to be offspring of mothers who had suffered the acute radiation syndrome, defined as purpura, epilation, and oropharyngeal lesions occurring after the bombing.[21] A review of findings in the Hiroshima *in utero* group for the first nine years after the bombing revealed an increased prevalence of microcephaly, sometimes associated with mental deficiency.[20] This was most common when the child was between the seventh and fifteenth weeks of gestation and had received a significant dose of radiation, as judged by proximity to the hypocenter or by the occurrence of the acute radiation syndrome in the mother. In subsequent studies, no other consistent differences associated with irradiation *in utero* have been found.[22,23]

During adolescence, a number of biologic changes occur.[24] Concomitant with large increases in height and weight in a relatively short time, there are alterations in the activities of various endocrine glands.[25-28] An intensive study of the *in utero* children during this period of rapid change might reveal clinical and biochemical differences in growth and development, possibly attributable to irradiation from the atomic bomb, between exposed and control children. For this purpose, 286 adolescent children, all of whom were *in utero* at the time of the atomic bombing, were studied in detail during the years 1958-1959 in Nagasaki; this program was part of a long range investigation of *in utero* children begun in Hiroshima in 1954 and Nagasaki in 1956.

The study will be reported in several parts. Thyroid function as measured by serum butanol extractable iodine values has been reported

for a subsample of this group.[20] The present report includes the prevalence of certain diseases associated with radiation, measurements of the pulse, blood pressure, visual acuity, and the routine laboratory studies for the examinations done from age 13 to age 14. Subsequent reports, now in preparation by the authors, will cover other aspects of the study.

TABLE 1. NUMBER OF CHILDREN IN ADOLESCENT STUDY BY DISTANCE FROM HYPOCENTER, MONTH OF GESTATION, AND SEX

*Distance group**	*Gestation month at time of bomb*									*Total*
	Trimester I			*Trimester II*			*Trimester III*			
					Male					
I	7	4	11	4	11	2	4	6	4	53
II	7	4	11	4	11	2	4	6	4	53
III	7	3	5	4	11	2	3	4	4	43
Combined	21	11	27	12	33	6	11	16	12	149
					Female					
I	4	5	5	3	8	4	10	3	5	47
II	4	5	5	2	8	3	11	3	5	46
III	4	6	3	2	8	2	11	3	5	44
Combined	12	16	13	7	24	9	32	9	15	137
					Sexes combined					
I	11	9	16	7	19	6	14	9	9	100
II	11	9	16	6	19	5	15	9	9	99
III	11	9	8	6	19	4	14	7	9	87
Combined	33	27	40	19	57	15	43	25	27	286

* I = 0-1,999 meters from hypocenter.
II = 3,000-4,999 meters from hypocenter.
III = Not in city at time of bomb.

MATERIALS AND METHODS

Subjects

All the children in this study were born between 11:02 A.M., August 9, 1945 and 12:00 P.M., May 31, 1946. This requirement, supplemented by intensive interviewing of the mothers, defined the children as being *in utero* at the time of the atomic bombing (ATB) in Nagasaki.

The study sample totalling 286 children was based on 100 available children, designated Group I, whose mothers were 0-1,999 meters from the hypocenter ATB. For each child in Group I an attempt was made to include a child of the same sex, month of birth, and socio-economic status whose mother was located 3,000-4,999 meters from the hypocenter ATB—the 99 children in this group are designated as Group II. Socio-economic status was ascertained by observations of the home environment and from biographical information. The same procedure was used in

matching a comparison group of children, designated Group III, whose mothers were *not in the city ATB*. However, exact matching for all variables was not possible, and the latter group contains 87 subjects. The composition of this matched sample by comparison group, month of gestation ATB, and sex is shown in Table 1.

Radiation

When the sample was constructed, radiation dose in physical units was not available for all mothers. Therefore, distance from the hypocenter was used as a measure of radiation exposure. Since then, tentative dosage in rads has become available which

TABLE 2. PERCENTAGE DISTRIBUTION AND MEAN OF THE MOTHER'S ESTIMATED RADIATION DOSE* (T57D) BY SEX OF THE OFFSPRING

Radiation dose in rads	*Male*		*Female*		*Combined***	
	Number	*Per cent*	*Number*	*Per cent*	*Number*	*Per cent*
0-19	15	31.2	7	18.4	22	25.6
20-39	12	25.0	9	23.7	21	24.4
40-59	7	14.6	6	15.8	13	15.1
60-79	2	4.2	3	7.9	5	5.8
80-99	1	2.1	1	2.6	2	2.3
100-149	3	6.2	6	15.8	9	10.5
150-459	8	16.7	6	15.8	14	16.3
Total	48	100.0	38	100.0	86	100.0
Mean dose	73.3		85.0		78.5	

* Gamma plus neutrons added at a 1 : 1 ratio.
** Dosage estimates were not made for 14 mothers who were heavily shielded at time of bomb.

takes into account air dose by distance as attenuated by various shielding factors. The procedures used in estimating the doses are described by Arakawa.[80] The log of the dose has a high linear correlation with distance. The tentative dose estimates were computed for 86 of the 100 mothers located 0-1,999 meters from the hypocenter and range from 0-459 rads. All but six of these mothers had dose estimates of 10 rads or greater. Dose estimates could not be calculated for 14 heavily shielded mothers. The frequency distribution of radiation doses is given in Table 2.

Allowances have been made for shielding ATB, but these are tentative dose estimates for the mothers, not for the children, and no allowance has been made for the shielding of the fetus by the mother. The doses must also be regarded as relative because the exact amount of radiation released ATB has not been accurately determined for specific distances. The air dose may have been as much as double or half the currently estimated value, and this uncertainty will affect all the dose estimates proportionately. In compiling tentative dose estimates, neutrons and gamma rays were considered to have the same relative biological effectiveness and were added at a 1 : 1 ratio.[80]

The calculated air dose for mothers located 3,000-4,999 meters from the hypocenter is less than 1.0 rad,[31] and it is thought that there was relatively little contribution from fallout or residual radiation. Their radiation exposure therefore is considered negligible but they experienced traumatic effects of the bombing, as did Group I. Children of mothers located between 3,000-4,999 meters from the hypocenter, and those whose mothers entered the city after the bombing were both utilized as comparison groups in an attempt to separate the traumatic effects of the bombing from possible radiation effects.

Procedure

The children were examined at ages 13 and 14. The examination included a medical history, physical examination, and laboratory tests. Visual acuity was measured by a Snellen chart. At age 13½ a physical examination was performed and an abbreviated history obtained, but no blood samples were taken.

Each child was seen by two physicians who later reviewed the records. Final diagnoses were coded according to the International Statistical Classification.[32] If more than five diseases were present, the physicians coded the five considered most significant.

Laboratory work included complete blood count, urinalysis, and stool examination. A venous blood sample was obtained for determination of total erythrocyte count, hematocrit, hemoglobin concentration,[33] erythrocyte sedimentation rate,[34] total and differential leukocyte counts. From these values red blood cell indices were calculated. At one examination, ABO blood groups were determined. Urinalysis included specific gravity, pH, protein, sugar, and microscopic examination. Nitrazine paper was used to test for pH, the sulfosalicylic acid and nitric acid ring tests for protein, and Benedict's qualitative test for sugar. Stool examination included a test for occult blood and a search for parasites.[35, 36]

Intelligence was evaluated by correlating clinical impression with school records and with the findings of intelligence tests, such as the Koga and Tanaka-B, which had been administered to most subjects prior to the beginning of the present study. The results of the tests, reviewed by one of the present authors (F.M.), were found to be consistent with the clinical impression. Also, those who were considered mentally retarded on the basis of the earlier tests were retested with the Suzuki-Binet, giving results substantially in agreement with the former tests. Though it it recognized that the level of intelligence is difficult to define critically since there are no absolute criteria for establishing mental retardation, it is thought that the intelligence of the subjects in this study has been reasonably well characterized and that all definitely retarded children within the study group have been detected. As outlined above, the three comparison groups have been carefully matched and there are no substantial grounds for suspecting bias in this evaluation.

All data were coded and machine tabulated. The tabulations were screened for statistically significant group differences or for differences among Group I children whose mothers had received varying radiation doses. Trimester of gestation, sex, and age were similarly screened. For many of the clinical observations and laboratory procedures no significant differences were found between comparison groups, trimesters, or children of mothers with different radiation doses estimated either directly or indirectly. Therefore, some of the results of these significance tests have not been presented. In interpreting statistical analyses, frequency of significant results was

considered in relation to the level of significance, and the consistency and direction of the differences.

RESULTS

The prevalence of certain disorders is of interest, particularly those associated with the central nervous system. Of 9 children considered to be mentally retarded, 6 were male and 3 were female. Among the males, 5 were in Group I, and 1 was in Group II, a statistically significant difference ($0.05>P>0.01$); 1 female was in each of the three comparison groups. Four of the 5 males in Group I had been exposed between the 7th and 17th week, and 1 in the 27th week of gestation ATB.

Minor congenital malformations, such as bifid uvula and slight defects of the lumbar spine noted by radiography, were diagnosed in 14 males and 3 females. Among the males, 9 were in Group I, 4 were in Group II and 1 was in Group III. The difference between Group I and Group III is statistically significant ($0.05>P>0.01$). Of the 9 Group I males, 4 were in the first trimester ATB.

The 52 cases of eye disorders were largely accounted for by refractive errors, mainly myopia. In the frequency of eye disorders, the differences between comparison groups were not statistically significant.

The mean radial pulse tended to be slower in Group I, and the differences were statistically significant for both sexes combined at the 13- and 14-year examinations. At the 13-year examination Group I had a mean pulse of 80, compared to 84.3 in Group II ($P\leq0.05$) and 84.4 in Group III ($P\leq0.05$). Group I at the 14-year examination had a mean radial pulse of 78.5 compared to 82.4 in Group II ($P\leq0.05$). A similar difference was not seen at the 13½-year examination, nor was there a significant difference when the sexes were analyzed separately. The mean radial pulse consistently tended to be faster among the females.

No significant differences were noted among comparison groups for mean systolic or diastolic blood pressures. However, in Group I subjects who were in the first trimester ATB, the mean diastolic blood pressure at the 13-year examination for 36 children (sexes combined) was 62 mm. Hg. compared to 66 mm. Hg. for 61 children in the second and third trimesters ($P<0.01$).

For mean visual acuity as recorded for the least effective eye, no statistically significant differences were noted among comparison groups nor among the Group I first trimester children when compared to children who were in other trimesters ATB. Similarly, no statistically significant

differences in acuity were noted among Group I *first trimester* males when analyzed by mother's estimated radiation dose, distance from the hypocenter, or presence versus absence of the acute radiation syndrone.

However, differences were found when Group I females in the *first trimester* ATB were analyzed according to whether the mothers had received an estimated radiation dose of more or less than fifty rads; had experienced the acute radiation syndrome; or had been within 1,500 meters

TABLE 3. MEAN VISUAL ACUITY FOR FIRST TRIMESTER GROUP I FEMALES BY AGE AT EXAMINATION AND RADIATION DOSE, RADIATION SYNDROME, AND MOTHERS' DISTANCE FROM HYPOCENTER

	Trimester of gestation		*First trimester of gestation*					
			Radiation dose		*Radiation syndrome*		*Distance from hypocenter*	
	First	*Second and Third*	*≧50 Rads*	*<50 Rads*	*With*	*Without*	*≦1500M*	*>1500M*
			13-Year examination					
Number	14	31	4	9	2	12	2	12
Mean acuity	20/40.4	20/21.8	20/68.8	20/30.6	20/122.5	20/26.7	20/52.5	20/38.3
Significance	N.S.		N.S.		*		N.S.	
			14-Year examination					
Number	13	25	3	9	2	11	2	11
Mean acuity	20/36.5	20/25.0	20/86.7	20/22.2	20/122.5	20/20.9	20/85.0	20/27.7
Significance	N.S.		*		*		N.S.	

N.S. = Not significant ($0.10<P$).
* = Significant ($0.01<P\leq 0.05$).

of the hypocenter. These comparisons and the significance tests are shown in Table 3. Combinatorial tests were used here because of the extremely skewed distribution of the acuity measurements.

No statistically significant differences in ABO blood groups were found in comparing the three groups. When all groups were combined, blood group A, occurring in 38.8 per cent of the subjects, was most common, followed by 0 (26.0%), B (23.1%), and AB (12.0%).

The mean erythrocyte count and mean hematocrit showed no significant differences for Group I versus Groups II and III, nor between sexes for either examination. The mean erythrocyte count and mean hematocrit tended to be higher at the 14 than at the 13-year examination but the differences between examinations were not significant. Similarly, no sig-

nificant differences in the mean corpuscular volume were noted among the comparison groups or between sexes.

The mean hemoglobin concentration value for the Group I females at the 14-year examination was 12.8 gm/100 ml. compared to 12.2 gm/100 ml. for Group II females and 12.4 gm/100 ml. for females in Group III. This value in Group I was significantly higher than in the two comparison groups, $P<0.01$ and $P<0.05$ respectively. A similar comparison between Group I and Group II females at the 13-year examination was suggestive but not significant. No significant differences were found when Group I females were analyzed by trimester or by the amount of radiation received, nor was a statistically significant difference noted among the males. Mean hemoglobin concentration values showed a tendency to rise with age and males tended to have higher values than females, particularly at the 14-year examination.

No significant differences were noted among comparison groups nor between 13- and 14-year examinations for the mean erythrocyte sedimentation rate. The marked difference between males (9.0 mm/hr.) and females (18.8 mm/hr.) for all groups combined was significant ($P<0.001$).

No comparison group, age, or sex differences were found on analysis of the mean total and differential leukocyte counts.

White blood cells were reported in the urine of 57.8 per cent of the children examined and hematuria in 43.6 per cent. These findings indicate primarily that the presence of a single white or red blood cell was sufficient for a positive report. Disease of the genitourinary system, on the other hand, was coded as a final diagnosis in only 1.7 per cent of all groups for all examinations. No consistent, statistically significant differences were seen in urinary red blood cells, white blood cells, proteinuria, or mean specific gravity between the three comparison groups, nor were differences with age and sex noted.

No significant differences were noted among comparison groups or between sexes in the prevalence of occult blood in the stools. Stool examination for ova and parasites showed *Ancylostoma, Ascaris, Trichocephalus, Enterobius, Hymenolepis nana, Giardia lamblia* and *Entameba coli.* Differences between the three groups are shown graphically in Figure 1. A higher frequency of parasitic infestations was seen more often in Group I than in the other groups. Infestations decreased from the 13- to 14-year examination in all groups and both sexes, excepting Group III females. The most common parasite in Group I was *Trichocephalus,* followed by *Ascaris*; these two parasites occurred somewhat less frequently

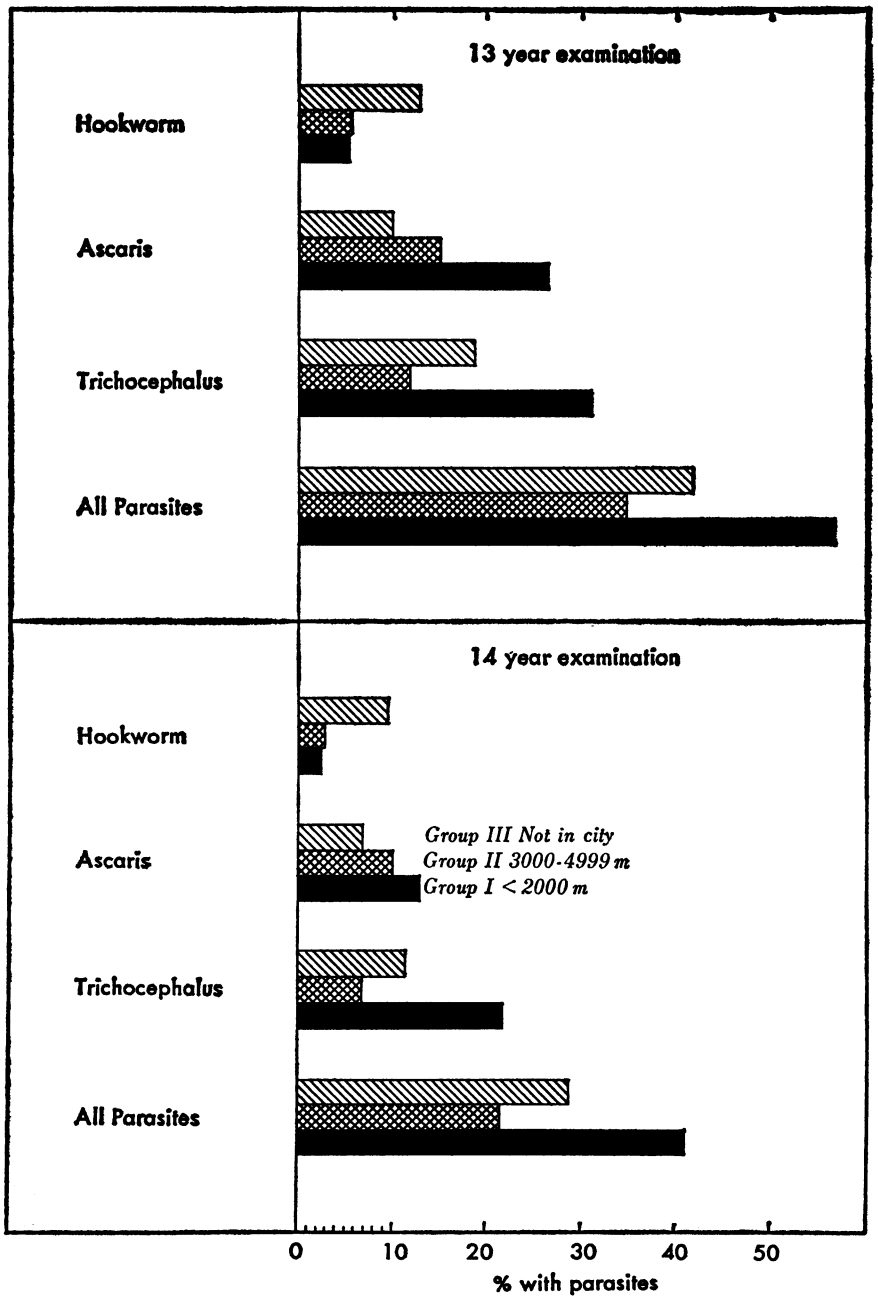

FIG. 1. Distribution of ova and parasites by distance group, age at examination, and sex.

in Groups II and III. Hookworm, on the other hand, though generally lower in frequency than *Trichocephalus* or *Ascaris* in all groups, was found more frequently in Group III than in the other comparison groups. Other parasites found in the stool showed no significant differences among comparison groups.

DISCUSSION

Over 50 per cent of the mothers of the proximal children had estimated radiation doses of 40-459 rads (Table 2). This is probably a biologically significant dose, since other studies have shown that exposure *in utero* to doses as small as 40 rads can damage the fetus;[3] it therefore seems reasonable to search for possible radiation effects among these children.

Mental retardation was found more frequently in Group I, corroborating previous ABCC reports of an increased prevalence of mental retardation among children closest to the hypocenter.[18-20] There were twice as many retarded males as females in the entire sample, and whereas five of the six males were in Group I, there was one retarded female in each of the three comparison groups. The explanation for these differences is not known. Females in Group I received on the average a somewhat higher dose than the males (Table 2), so it is unlikely that radiation dosage is the explanation. Tables 1 and 2 show a slight imbalance, in the sample, of the sex ratio in favor of males, which in Group I amounts to a difference of over 10 per cent, suggesting that the apparent sex difference in mental retardation may be the consequence of this imbalance. In view of the small number of individuals involved, such a conclusion is conjectural.

Minor congenital malformations were also significantly more numerous among males in Group I than in the other two groups. Though it is possible that this is a radiation effect, Group I has been examined more frequently than the other two groups, affording more opportunity for detecting such defects.

In addition to a greater number of malformations among Group I males over females, there was an excess of males with such defects in the total sample, a situation similar to that for mental retardation. This apparent sex difference may be an artifact attributable to the imbalance of the sex ratio in the sample, alluded to above.

It has been suggested that leukemia and malignancy occur more frequently among children who are irradiated *in utero*.[14, 15, 27] However, no leukemia or malignancy were found in the present study. The chance of

one leukemia case occurring in this group of 100 children is less than 0.05, assuming the incidence for this age group to be that in the general population, which is estimated at 30 per million per year.[38] Even at the advanced rate suggested by the data of Brill, *et al.*[39] for those within 2,000 meters of the hypocenter, one would not expect to find a single case of leukemia among 100 children observed up to age 14. Similar considerations apply to malignancy, so it is apparent that the present sample is too small to yield information about the frequency of these two relatively uncommon diseases.

The radial pulse was slower in Group I children but they were examined more frequently, and were less apprehensive about the examination procedure. The differences were not highly significant and tended to occur in the earlier examination.

A significantly lower mean diastolic pressure was found in the first trimester Group I children at the 13-year examination. For all subsequent examinations the mean diastolic pressure of first trimester proximal males and females was also lower, though not significantly so. The consistent differences make it unlikely that this is an isolated sampling variation, but there is no satisfactory explanation to account for the observations.

Visual acuity was of special interest in light of an earlier report documenting significant loss of vision among exposed children aged 7-10 years ATB who were examined nine years later.[20] Although no differences were found among comparison groups in the current study, the first trimester Group I females whose mothers experienced the acute radiation syndrome had significantly poorer visual acuity than did children of asymptomatic mothers.

Similarly, at the 14-year examination, first trimester females whose mothers received an estimated dose of 50 rads or more had significantly poorer visual acuity than those females whose mothers received less than 50 rads. While the differences were significant, only two or three children were involved, so interpretation should be made with caution.

Distribution of the ABO blood groups was similar to that found in the Japanese population as a whole, and these traits had no discernible connection with other findings of the study.

In the hematological examination the only differences among comparison groups were noted in mean hemoglobin values. For females at the 14-year examination the mean hemoglobin value was significantly higher in Group I than in the other two groups. The reasons for this difference are not clear. If menarche in the Group I females were delayed,

menstrual blood loss would not occur, and the mean hemoglobin level would tend to be higher than in the menstruating comparison groups, but no difference appeared in the age at menarche among the comparison groups. Fewer infestations of hookworm in Group I also might cause higher mean hemoglobin values, but the frequency of hookworm infestation is similar to Groups II and III. During adolescence hemoglobin values rise to adult levels, with a more pronounced rise in males than in females.[40, 41] Mean hemoglobin values in the present study conformed to the expected pattern. A similar rise in the hematocrit and red-cell count was also noted.

No significant differences between comparison groups were noted in an earlier hematological study of children who were *in utero* in Hiroshima ATB, although total leukocyte counts progressively decreased with age for all groups.[28] In the Nagasaki children, no fall in the mean leukocyte count was noted and it is possible that this phenomenon may have occurred before the present study began.

A previous ABCC study of children born before the atomic bombing reported a significantly higher prevalence of all urinary abnormalities among females within 2,500 meters of the hypocenter ATB.[42] In the current study these abnormalities showed no consistent pattern in either sex.

Parasite infestation was coded as a diagnosis in 32.2 per cent of cases, and was significantly more frequent in Group I than in Group II. However, when Group I was divided according to rads received, presence of the acute radiation syndrome, or distance from the hypocenter, no differences were found.

The pattern of a higher prevalence of *Trichocephalus* and *Ascaris,* and less Hookworm in Group I (Figure I) is difficult to explain. The difference is consistent, and it seems unlikely that it is due to sampling error. Group III children are in large part offspring of individuals who were repatriated after the war. These individuals might be expected to have a different pattern of parasitic infestation although they probably have been in Nagasaki long enough to change this pattern. Even if this assumption is valid, it does not explain the difference between Groups I and II. Although an attempt had been made to match the comparison groups according to socio-economic status, the varying frequency and pattern of parasitic infestation can probably best be explained by differences in dietary and living habits among these groups.

A consistent and marked decrease in parasitic infestations was seen between the 13- and 14-year examinations because treatment was administered both in the schools and at ABCC.

Between Groups II and III, no consistent differences were found that might suggest traumatic or nonradiation effects of the bomb in the former. Any differences noted in comparing Groups I and II with Group III are much more likely attributable to inherent socio-economic differences distinguishing the latter.

SUMMARY

1. An intensive two-year study of 286 Nagasaki adolescents, ages 13 to 14, was conducted as part of a long-term program to determine possible differences in growth and development which might be attributed to *in utero* exposure to the atomic bomb. Three comparison groups were studied: Group I, whose mothers were within 2,000 meters of the hypocenter; Group II, whose mothers were located between 3,000-4,999 meters from the hypocenter; Group III, whose mothers were not in the city at the time of the bomb.

2. A significantly higher frequency of mental retardation and minor congenital malformations was found in Group I males, but not in the females.

3. Although Group I females who were in the first trimester of gestation at the time of the bomb and whose mothers experienced the acute radiation syndrome had poorer visual acuity than comparable children of asymptomatic mothers, the small number of observations requires caution in interpretation of this finding.

4. Parasitic infestation occurred in about one-third of the subjects, and Group I had significantly greater infestation than did the other comparison groups. *Trichocephalus* and *Ascaris* infestation accounted for the higher prevalence. Hookworm occurred less frequently. It is suggested that these findings are probably associated with different dietary and living habits.

5. No cases of leukemia or malignancy were found, but the sample was not large enough to detect even a tenfold increase in incidence.

6. No consistent significant differences attributable to a radiation effect were noted among the comparison groups in regard to radial pulse, blood pressure, hematologic, or urine examinations.

REFERENCES

1. Hollingsworth, J. W.: Delayed radiation effects in survivors of the atomic bombings. *New Engl. J. Med.*, 1960, *263*, 481-487.
2. Rugh, Roberts: X-irradiation effects on the human fetus. *J. Pediat.*, 1958, *52*, 531-538.
3. Russell, L. B. and Russell, W. L.: Radiation hazards to the embryo and fetus. *Radiology*, 1952, *58*, 369-377.

4. Bagg, H. J.: Disturbances in mammalian development produced by radium emanation. *Amer. J. Anat.*, 1922, *30*, 133-161.
5. Ellinger, F. P.: *Medical Radiation Biology*. Springfield, Ill., Charles C. Thomas, 1957, pp. 433-445.
6. Hanson, F. B.: The effects of X-rays on the albino rat. *Anat. Record*, 1923, *24*, 415 (Abst.).
7. Hicks, S. P.: Developmental malformations produced by radiations. *Amer. J. Roentgenol.*, 1953, *69*, 272-293.
8. Job, T. T., Leibold, G. J., Jr., and Fitzmaurice, H. A.: Biological effects of roentgen rays. The determination of critical periods in mammalian development with X-rays. *Amer. J. Anat.*, 1935, *56*, 97-117.
9. Parkes, A. S.: On the occurrence of the oestrus cycle after X-ray sterilisation. Part II. Irradiation at or before birth. *Proc. roy. Soc. B.*, 1927, *101*, 71-95.
10. Rugh, Roberts: Vertebrate Radiobiology: Embryology. *Ann. Rev. nuclear Sci.*, 1953, *3*, 271-302.
11. Rugh, Roberts and Grupp, Erika: Fractionated X-irradiation of the mammalian embryo and congenital anomalies. *Amer. J. Roentgenol.*, 1960, *84*, 125-144.
12. Russell, L. B.: The effects of radiation on mammalian prenatal development. In *Radiation Biology*, Hollaender, A. (Ed.). New York, McGraw-Hill, 1954, vol. I, part 2, pp. 861-911.
13. Goldstein, Leopold and Murphy, D. P.: Etiology of the ill-health in children born after maternal pelvic irradiation. Part II. Defective children born after post-conception pelvic irradiation. *Amer. J. Roentgenol.*, 1929, *22*, 322-331.
14. Stewart, Alice, Webb, Josefine, and Hewitt, David: A survey of childhood malignancies. *Brit. med. J.*, 1958, *1*, 1495-1508.
15. Ford, D. D., Paterson, J. C. S., and Treuting, W. L.: Fetal exposure to diagnostic X-rays, and leukemia and other malignant diseases in childhood. *J. nat. Cancer Inst.*, 1959, *22*, 1093-1104.
16. Kaplan, H. S.: An evaluation of the somatic and genetic hazards of the medical uses of radiation. *Amer. J. Roentgenol.*, 1958, *80*, 696-706.
17. Court Brown, W. M., Doll, R., and Hill, A. B.: Incidence of leukaemia after exposure to diagnostic radiation *in utero*. *Brit. med. J.*, 1960, *2*, 1539-1545.
18. Plummer, George: Anomalies occurring in children exposed *in utero* to the atomic bomb in Hiroshima. *Pediatrics*, 1952, *10*, 687-693.
19. Yamazaki, J. N., Wright, S. W., and Wright, P. M.: Outcome of pregnancy in women exposed to the atomic bomb in Nagasaki. *Amer. J. Dis. Child.*, 1954, *87*, 448-463.
20. Miller, R. W.: Delayed effects occurring within the first decade after exposure of young individuals to the Hiroshima atomic bomb. *Pediatrics*, 1956, *18*, 1-18.
21. Neel, J. V. and Schull, W. J.: *The Effect of Exposure to the Atomic Bombs on Pregnancy Termination in Hiroshima and Nagasaki*. National Academy of Sciences-National Research Council, Publication No. 461. Washington, D. C., Government Printing Office, 1956, p. 241.
22. Sutow, W. W. and West, Emory: Studies on Nagasaki (Japan) children exposed *in utero* to the atomic bomb: A roentgenographic survey of the skeletal system. *Amer. J. Roentgenol.*, 1955, *74*, 493-499.
23. Takamura, Tsugiso and Ueda, Shoichi: Hematologic findings in children exposed to A-bomb radiation *in utero* in Hiroshima. *Blood*, 1961, *17*, 728-737.
24. Stuart, H. C.: Normal growth and development during adolescence. *New Engl. J. Med.*, 1946, *234*, 666-672, 693-700, 732-738.
25. Nathanson, I. T., Towne, L. E., and Aub, J. C.: Normal excretion of sex hormones in childhood. *Endocrinology*, 1941, *28*, 851-865.
26. Talbot, N. B., Butler, A. M., Berman, R. A., Rodriguez, P. M., and MacLachlan, E. A.: Excretion of 17-ketosteroids by normal and by abnormal children. *Amer. J. Dis. Child.*, 1943, *65*, 364-375.

27. Hamburger, Christian: Normal urinary excretion of neutral 17-ketosteroids with special reference to age and sex variations. *Acta endocr. (Kbh.),* 1948, *1,* 19-37.
28. King, N. B. and Mason, H. L.: Urinary corticosteroid values of children as determined chemically. *J. clin. Endocr.,* 1950, *10,* 479-491.
29. Burrow, G. N., Hamilton, H. B., and Man, E. B.: Serum butanol extractable iodine values of adolescents exposed *in utero* to the atomic bomb in Nagasaki, Japan. *Amer. J. med. Sci.,* 1962, *243,* 751-757.
30. Arakawa, E. T.: Radiation dosimetry in Hiroshima and Nagasaki atomic-bomb survivors. *New Engl. J. Med.,* 1960, *263,* 488-493.
31. Ritchie, R. H. and Hurst, G. S.: Penetration of weapons radiation: Application to the Hiroshima-Nagasaki studies. *Hlth Phys.,* 1959, *1,* 390-404.
32. *Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death,* Vols. 1 & 2. Geneva, World Health Organization, 1949.
33. Crosby, W. H., Munn, J. I., and Furth, F. W.: Standardizing a method for clinical hemoglobinometry. *U.S. armed Forces med. J.,* 1954, *5,* 693-703.
34. Wintrobe, M. M. and Landsberg, J. W.: A standardized technique for the blood sedimentation test. *Amer. J. med. Sci.,* 1935, *189,* 102-115.
35. Ritchie, L. S.: An ether sedimentation technique for routine stool examinations. *Bull. U.S. Army med. Dep.,* 1948, *8,* 326.
36. Pihl, H.: Useful parasitological methods for the clinical and hospital laboratories. *Amer. J. med. Technol.,* 1956, *22,* 18-24.
37. (Editorial.) Harmful effects of diagnostic irradiation. *Lancet,* 1963, *1,* 255-256.
38. Mortality Statistics of Malignant Neoplasms. *Vital Statistics Special Report.* Tokyo, Japan, Japanese Ministry of Health and Welfare, 1960 (in Japanese).
39. Brill, A. B., Tomonaga, Masanobu, and Heyssel, R. M.: Leukemia in man following exposure to ionizing radiation. A summary of the findings in Hiroshima and Nagasaki, and a comparison with other human experience. *Ann. intern. Med.,* 1962, *56,* 590-609.
40. Hawkins, W. W., Speck, Eirlys, and Leonard, V. G.: Variation of the hemoglobin level with age and sex. *Blood,* 1954, *9,* 999-1007.
41. Leichsenring, J. M., Norris, L. M., Lamison, S. A., and Halbert, M. L.: Blood cell values for healthy adolescents. *Amer. J. Dis. Child.,* 1955, *90,* 159-163.
42. Sullivan, M. P. and Takahashi, Yasushi: Incidence of abnormal urinary findings in children exposed to the atomic bomb in Hiroshima. *Pediatrics,* 1957, *19,* 607-613.