The Effect of Exposure to the Atomic Bombs on Pregnancy Termination in Hiroshima and Nagasaki: Preliminary Report[1]

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FOR THE PAST SEVEN YEARS a comprehensive program of investigation of the potential delayed effects of exposure to the atomic bombs has been in progress in Hiroshima and Nagasaki, Japan. One facet of this program has been an attempt to provide answers to the following two questions:

1. Can there be observed, during the first year of life, any differences between children conceived subsequent to the atomic bombings of Hiroshima and Nagasaki, one or both of whose parents were exposed to the effects of the bombings, and the children born to suitable control parents?

2. If differences do exist, how are these to be interpreted?

The present communication is based on a preliminary analysis of a portion of these studies. A more complete account will appear at a later date.

The data of this study have been collected as follows. During and ever since World War II there has been in effect in Japan a system of rationing of food and other items. Under this system, any woman reaching the fifth month of pregnancy is, upon certification of the fact by an obstetrician or midwife, granted certain special ration privileges. Because of the economic stringencies of postwar Japan, pregnancy registration approached the 95 per cent level during the period covered by this study. A plan was developed whereby at the time of registration for ration purposes, each pregnant woman or her representative in Hiroshima and Nagasaki completed in duplicate the first two-thirds of a questionnaire which dealt with identifying information, location and symptoms at the time of the atomic bombing, past reproductive performance, and certain details concerning the present pregnancy. The final third of the form, of necessity left blank at the time of registration, included such items as type of termination (stillbirth or livebirth, premature or term), sex, birth weight, and occurrence of malformation. One copy of this form was then given the registrant, the other copy retained by the Commission. At the termination of her pregnancy, each registrant gave her midwife or obstetrician the registration form for completion. In the event of a termination in some way abnormal, the attendant was requested to contact the Commission at once. In the event of an apparently normal termination, on the other hand, the attendant retained the form until collected by a Commission representative, on an approximately weekly schedule. In either event, the newborn child was examined by a physician in the employ of the Commission—as soon as possible if the termination was abnormal, on a more leisurely schedule if reported normal. Autopsies have been performed on as many children who were stillborn or died during the neonatal period as possible. Approximately one-third of the children examined at birth have been reexamined at age nine months.

The duplicate registration forms were used to establish a file based on expected date of confinement. Follow-up studies were instituted if there was no report of the termination of a pregnancy a month after the expected date of confinement. In this way, data were obtained on the outcome of the great majority of registered pregnancies. The chief loss of information involved women who moved out of the two cities subsequent to registration.

For a variety of reasons, in this study the most reliable indices of the amount of irradiation received by a survivor of the bombings were felt to be distance from the hypocenter (the point directly beneath the bomb when it exploded) and the subsequent development of the following symptoms or combination of symptoms: epilation, petechiae, and/or gingivitis. On

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the basis of position at the time of the explosions and the development of symptoms, each parent has been placed in one of the following five radiation categories:

Group 1. Not in Hiroshima or Nagasaki at the time of the bombings. These individuals are either residents of the city who for a variety of reasons were not there at the time of the bombings, or persons who have moved into the city subsequent to the bombings (August of 1945). Approximately two-thirds of the husbands and wives registered in connection with this program fall into this category.

Group 2. In one of the two cities at the time of the bombings, but at distances in excess of 2544 meters from the hypocenter, and not developing any of the cardinal radiation symptoms enumerated above.

Group 3. In one of the two cities and within 1845 to 2544 meters of the hypocenter, but asymptomatic with respect to the cardinal symptoms.

Group 4. In one of the two cities, and less than 1845 meters from the hypocenter, but asymptomatic. Most of these individuals were shielded to a greater or lesser extent from the full effects of the bombs.

Group 5. In one of the two cities, and developing one or more of the cardinal symptoms during the several months following the bombings.

The estimation of the average amount of whole body irradiation, both gamma and neutron, received by the individuals falling into groups 2 to 5 presents a number of problems. Individuals in group 2 probably received on the average only the equivalent of a few roentgen units. On the other hand, group 5 individuals probably received the equivalent of between 200 and 600 r, with the average in the neighborhood of 300 r. Group 3 and group 4 individuals received intermediate dosages, difficult to estimate because of the shielding factor, with group 4 definitely receiving more on the average than group 3.

The possible observable genetic effects of irradiation upon the first generation born after an atomic bombing are many and varied. The indicators utilized in this study were: type of termination (livebirth or stillbirth), sex of child, birth weight, and occurrence of gross congenital malformation. *Each of these possible indicators of genetic damage is also influenced by a number of other factors; there are no unique yardsticks of a genetic effect.* Under these circumstances, the crux of any program of study was the feasibility of establishing a control population which, in so far as possible, differed from the irradiated only with respect to the radiation factor.

Between 1948 and 1952 the outcome of 31,034 pregnancies was determined in Hiroshima, and 31,073 in Nagasaki. A detailed comparison, by city, of the fathers and mothers falling into the five radiation groups has been carried out with respect to age, parity, consanguinity, economic status, incidence of positive serological tests for syphilis, and parental cooperation. Significant differences were found to exist with respect to the first three points of comparison. Although the known relationships of age, parity, and consanguinity to the sex ratio are slight, there exists a considerable literature, substantiated in part in our own data, to indicate significant relationships between age, parity, and consanguineous marriage, on the one hand, and the frequency of stillbirths, birth weight, and the frequency of gross malformations on the other. It is apparent that provision for these differences must be made in the analysis of the data. The further point should be mentioned that, in contrast to the parents falling into radiation categories 2, 3, 4, and 5, more of the individuals in radiation group 1 had previously resided in rural areas or outside the Japanese islands (e.g., Korea, Manchuria).

In addition to the differences between the parents found in radiation groups 1 to 5 described in the preceding paragraph, there exists at least one other important difference between the individuals falling into the various radiation categories. Late somatic effects of irradiation have been established as occurring in a small fraction of relatively heavily irradiated persons. These include cataracts (*1*) and leukemia (*2*). Other more subtle effects may exist. In view of the known relationship between maternal health and certain of the indicators of possible genetic damage, *extreme caution must be exercised in the genetic interpretation of any apparent effect of irradiation mediated solely by the mother.*

The various possible indicators of genetic damage are not independent of one another. Thus, gross malformation and stillbirth are correlated. It was apparent that some allowance had to be made for this fact before the various indicators could be regarded as independent guides to a radiation effect.

With the foregoing considerations in mind, a plan of analysis has been evolved, the first step of which is to subdivide the data as follows:

A—mothers less than 35 years of age and unrelated to their spouses. This amounts to approximately 84 per cent of the Hiroshima and 77 per cent of the Nagasaki registrations.

B—mothers 35 years of age or older and unrelated to their spouses, approximately 10 per cent of the Hiroshima and 15 per cent of the Nagasaki material.

C—mothers related to their spouses, approximately 6 per cent of the Hiroshima and 8 per cent of the Nagasaki material.

Except with reference to the sex ratio, only the *A* data will be considered in the results to be presented. Exclusion of the *C* data from consideration at this time removes the known consanguinity differences, while exclusion of the *B* data very materially reduces the age differential, although significant differences remain. For example, in the Hiroshima data, exclusion of the *B* data reduces the average age difference between radiation group 1,2 and group 4,5 mothers from 3.5 to 1.9 years, whereas in Nagasaki the corresponding reduction is from 1.9 to 0.5 years. Furthermore, inasmuch as significant differences exist between Hiroshima and Nagasaki with respect to age, parity, consanguinity, and anthropological background, and since the proportions falling in the five radiation groups differ for the two cities, the results for the

TABLE 1

Comparison of Certain Characteristics of Children of Parents Falling into Different Radiation Groups

The numbers 1, 2, 4, and 5 as applied to the parents designate the radiation exposure group as defined in the text. Arrows directed upward indicate agreement with genetic hypothesis; the downward-pointing arrows, disagreement. Numbers in parentheses in the columns under the headings Hiroshima and Nagasaki indicate the number of observations.

Indicator	Comparison			Hiroshima	Nagasaki	Significance of difference (normal deviate)	
						Hiroshima	Nagasaki
a. Both parents radiation group (1, 2) vs. both parents (unless otherwise indicated) radiation group (4, 5)							
Proportion of male births (All data)	Both parents (1, 2)	vs.	Mother (4, 5) Father (1, 2)	0.5194 (21737) vs. 0.5102 (3003)	0.5190 (26256) vs. 0.4837 (1445)	0.948 ↑	2.615 ↑
	Both parents (1, 2)	vs.	Mother (1, 2) Father (4, 5)	0.5194 (21737) vs. 0.5166 (962)	0.5190 (26256) vs. 0.5376 (785)	0.170 ↓	1.030 ↑
Proportion of malformed infants (*A* data)	Both parents (1, 2)	vs.	Both parents (4, 5)				
			Male infants	0.0115 (9537) vs. 0.0045 (222)	0.0096 (10409) vs. 0.0145 (69)	1.515 ↓	0.340 ↑
			Female infants	0.0107 (8801) vs. 0.0127 (286)	0.0101 (9694) vs. — (69)	0.271 ↑	—
Proportion of stillbirths (*A* data)	Both parents (1, 2)	vs.	Both parents (4, 5)				
			Male infants	0.0209 (9427) vs. 0.0498 (221)	0.0182 (10309) vs. 0.0147 (68)	1.965 ↑	0.239 ↓
			Female infants	0.0202 (8707) vs. 0.0258 (233)	0.0148 (9596) vs. 0.0145 (69)	0.534 ↑	0.021 ↓
b. Both parents radiation group (1, 2) vs. at least one parent radiation group (5)							
Proportion of male births (All data)	Both parents (1, 2)	vs.	Mother (5) Father (1, 2)	0.5194 (21737) vs. 0.5258 (814)	0.5190 (26256) vs. 0.4801 (477)	0.359 ↓	1.685 ↑
	Both parents (1, 2)	vs.	Mother (1, 2) Father (5)	0.5194 (21737) vs. 0.5187 (347)	0.5190 (26256) vs. 0.5661 (189)	0.026 ↓	1.302 ↑
Proportion of malformed infants (*A* data)	Both parents (1, 2)	vs.	At least one parent (5)				
			Male infants	0.0115 (9537) vs. 0.0081 (618)	0.0096 (10409) vs. 0.0132 (303)	0.903 ↓	0.543 ↑
			Female infants	0.0107 (8801) vs. 0.0139 (577)	0.0101 (9694) vs. 0.0134 (298)	0.641 ↑	0.489 ↑
Proportion of stillbirths (*A* data)	Both parents (1, 2)	vs.	At least one parent (5)				
			Male infants	0.0209 (9427) vs. 0.0294 (613)	0.0182 (10309) vs. 0.0134 (299)	1.218 ↑	0.700 ↓
			Female infants	0.0202 (8707) vs. 0.0246 (569)	0.0148 (9596) vs. 0.0272 (294)	0.660 ↑	1.296 ↑

two cities will be presented and analyzed separately.

In order to render the indicators independent of one another, the first attribute considered in the analysis was the sex ratio, and the second, frequency of malformation. All grossly malformed infants were then excluded from further consideration, and the frequencies of stillbirths in the various radiation groups obtained. Stillborn infants were then excluded from further consideration, and birth weights were examined. Thus the frequencies of stillbirths within the various exposure categories are based only on those infants with no clinically apparent major malformation. Similarly, mean birth weights are based only on those liveborn infants without clinically recognizable gross malformations.

The significance of the observed differences between the children of parents with different radiation histories has been tested by the method of fitting constants to a basically 5×5 table in which the columns correspond to paternal radiation exposure group and the rows to the maternal radiation exposure group. In addition, selected comparisons have been made. In this paper, because of space limitations, when dealing with the attribute data (sex ratio, malformation frequency, stillbirth frequency), only the results of two comparisons will be presented. These are (1) a comparison between the children of parents, both falling in radiation group 1 or 2, and the children of parents, both falling in group 4 or 5, and (2) a comparison of the findings in the children of parents, both falling in radiation group 1 or 2, and the children of parents, at least one of whom falls in radiation group 5. In the first comparison, the amount of radiation which the group 4,5 parents *jointly* received varies from approximately 300 to 1000 r units of radiation, while in the second comparison, where at least one parent is in group 5, the *joint* radiation exposure varies from about 200 to 1000 r units. This presentation involves only a portion of the data; this action is considered justified in a preliminary report because this is *the* most critical comparison in terms of radiation dosage. With respect to the single metrical characteristic (birth weight), the findings are presented as the results of an analysis of variance of the 5 × 5 table mentioned above. In passing, it should be emphasized that the results of other analyses do not differ materially from the comparisons given in Tables 1 and 2. We will consider now the four sets of results shown in the tables.

1. *Sex ratio* (Table 1). Conventional genetic theory suggests that irradiation of the mother should decrease the percentage of males among her offspring, because the males will be affected by induced sex-linked recessive lethals which will not affect females. Radiation of the father, on the other hand, should result in a decrease in the percentage of females among his offspring, due to the action of sex-linked dominant mutations. Any attempt to postulate the magnitude of the differences at a particular radiation level is rendered difficult by many factors, including the present unsatisfactory state of knowledge concerning the homologous segments of the X and Y chromosomes. It is apparent that in Nagasaki the observed differences are as suggested by hypothesis and, when the factor of direction is considered, significant. The differences remain significant when the comparison is limited to the group 2,3 and the group 4,5 parents. However, this finding does not appear in the more numerous Hiroshima data.

2. *Frequency of malformation* (Table 1). It is a reasonable assumption that induced dominant mutations should result in an increase in the frequency of gross malformations among the children of survivors. Several years ago, as reported by Bugher (*3*), there appeared to be some evidence that gross malformations were slightly more frequent among the children of exposed parents than among the children of control parents. The present more extensive data fail to confirm this impression.

3. *Frequency of stillbirths* (Table 1). Induced dominant mutations might also be expected to increase the number of stillbirths. The overall trend is in the direction of hypothesis, but the findings approach the level of significance in only one of the four comparisons of Table 1a, that concerned with male infants born in Hiroshima, and none of the comparisons of Table 1b. A supplementary analysis of all the Hiroshima data arranged in a 5 × 5 table according to the radiation

TABLE 2

ANALYSIS OF BIRTH WEIGHT DATA BY METHOD OF FITTING CONSTANTS

In the two tables on which this analysis is based, the rows are composed of the five maternal exposure groups and the columns of the five paternal exposure groups. The sexes have been analyzed separately.

Source of variation	S.S.	D/F	M.S.	F
a. Hiroshima—analysis of variance				
Test for sex				
Fitting m, b_j, c_k*	259	8		
Difference	3112	1	3112.00	155.99†
Fitting m, a_i, b_j, c_k	3371	9		
Test for mother's exposure				
Fitting m, a_i, c_k	3246	5		
Difference	125	4	31.25	1.57
Fitting m, a_i, b_j, c_k	3371	9		
Test for father's exposure				
Fitting m, a_i, b_j	3220	5		
Difference	151	4	37.75	1.89
Fitting m, a_i, b_j, c_k	3371	9		
Test for interaction				
Fitting m, a_i, b_j, c_k	3371	9		
Difference	1204	40	30.10	1.51‡
Between classes	4575	49		
Between classes	4575	49	93.37	4.68†
Within classes	484126	24269	19.95	
Total	488701	24318		
b. Nagasaki—analysis of variance				
Test for sex				
Fitting m, b_j, c_k*	503	8		
Difference	3413	1	3413.00	167.63†
Fitting m, a_i, b_j, c_k	3916	9		
Test for mother's exposure				
Fitting m, a_i, c_k	3670	5		
Difference	246	4	61.50	3.02‡
Fitting m, a_i, b_j, c_k	3916	9		
Test for father's exposure				
Fitting m, a_i, b_j	3634	5		
Difference	282	4	70.50	3.46†
Fitting m, a_i, b_j, c_k	3916	9		
Test for interaction				
Fitting m, a_i, b_j, c_k	3916	9		
Difference	1161	40	29.03	1.43‡
Between classes	5077	49		
Between classes	5077	49	103.61	5.09†
Within classes	460899	22641	20.36	
Total	465976	22690		

* m = mean.
a_i = constants fitted for sex.
b_j = constants fitted for five categories of maternal exposure.
c_k = constants fitted for five categories of paternal exposure.
† Significant at one per cent level.
‡ Significant at five per cent level.

groups of the father and mother indicates that the effect is a function of mother's exposure, with a significance at the 0.02–0.05 level. The above mentioned stricture regarding maternal somatic effects is especially pertinent in this respect.

4. *Birth weight* (Table 2). Induced mutations might be expected to impair the metabolic processes of the fetus, and so decrease birth weight, i.e., the children of the more heavily irradiated parents might be expected to weigh less at birth. In both cities the interaction terms are significant at the 0.01–0.05 level. Constants are being refitted to these data taking cognizance of this fact. If these interactions are accepted as real, the tests of main effects are only approximate. The latter reveal no differences in Hiroshima but in Nagasaki the effect of both maternal and paternal exposure is at the level of significance. The differences are, however, in a direction contrary to hypothesis. The explanation of this finding is not readily apparent. It is not borne out by a comparison utilizing only radiation categories 2, 3, 4, and 5, nor are there height-weight differences in relation to parental radiation history among the children re-examined at age 9 months. As noted earlier, there are differences in mean parity between the mothers falling into the various radiation exposure groups, such that where both the mother and father had been relatively heavily irradiated there is a tendency for the mother to have borne more children at the time of this study. Inasmuch as parity is significantly related to birth weight (*4*), and since the parity differences have not been entirely eliminated by the truncation of the data which has been described, this may account for at least a portion of the findings with respect to birth weight.

The interpretation of the combined results of independent tests of significance, such as are presented in Tables 1 and 2, poses a number of problems, the solutions of which are not entirely clear at present. Furthermore, although truncation of the data at a maternal age of 35 has reduced the age and parity differential between the various radiation groups, there still remain significant differences. Since certain additional data are yet to become available and certain analytic possibilities remain to be explored, it would appear that an attempt at this time at a definitive interpretation would be premature.

Even in this preliminary note, however, it should be pointed out that these findings, if taken at face value, are entirely consistent with what is known of the radiation genetics of a wide variety of plant and animal material, including Drosophila and mice. It is important to emphasize that the conditions of these observations, as well as the fact that they are confined to the first post-bomb generation, permit the detection of only a small fraction of the total genetic effect of exposure to an atomic bomb. Given our estimates of the radiation dosages involved, it has, by analogy with what is now known of radiation genetics, always been doubtful whether significant findings attributable to the genetic effects of irradiation would be apparent in the first post-bomb generation. It is of interest that of the four indicators herein discussed, the one with respect to which the evidence of a significant effect is strongest—sex ratio—is the one that most biologists would probably feel has the largest genetic component in its etiology. This apparent effect on sex ratio may be related to the relatively high proportion of all known inherited traits which is sex-linked in man in contrast, e.g., to the mouse, cat, or dog. An attempt to extend the sex ratio findings is in progress. There is no indication from this study of any "unusual" sensitivity of human genes to irradiation.

It is apparent from the table that the actual amount of critical material is small. It must be emphasized that this is the total material available during the period covered by this study in the cities of Hiroshima and Nagasaki. The only way that sample size could be increased would be through an attempt to trace the relatively few "heavily" irradiated survivors who have established residence elsewhere, an undertaking that has not appeared feasible nor sufficiently profitable in view of the additional effort and expense such an undertaking would require.

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News and Notes

National Meeting of American Chemical Society

The chemical synthesis of sucrose was among the major advances reported at the American Chemical Society's 124th national meeting, held in Chicago September 6 through 11. A total registration of exactly 10,000 made it the largest ACS meeting ever held outside New York, and the Society set another record when its membership reached 70,000 during the week.

A 33-year-old Canadian chemist, Raymond U. Lemieux, announced the sugar synthesis, which solved a problem that had baffled Emil Fischer and virtually every other carbohydrate chemist for the past half century. Working with George Huber, a 25-year-old Swiss postdoctoral research fellow, in the Prairie Regional Laboratory of the Canadian National Research Council at Saskatoon, Lemieux tackled the project last April despite overwhelming evidence that it could not be done. By June they succeeded in making sucrose