Some Further Observations on the Sex Ratio Among Infants Born to Survivors of the Atomic Bombings of Hiroshima and Nagasaki

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SOME YEARS AGO, we presented the evidence then existing pertinent to the association in man of the sex ratio with parental exposure to ionizing radiation (Schull and Neel, 1958). At that time, we tentatively concluded that "the sex of children born to the survivors of the atomic bombings of Hiroshima and Nagasaki reveals significant changes in the sex ratio of these children, changes in the direction to be expected if exposure had resulted in the induction of sex-linked lethal mutations." This conclusion was reached through a somewhat tortuous line of reasoning, for no single study, in Japan or elsewhere, offered unequivocal evidence of a radiation-induced change. In the years which have intervened, there have been two developments which warrant a reinspection of this association and, of course, the earlier conclusion. First, further data are available. Second, we now recognize additional complexities in the problem, in particular that nondisjunction of the sex chromosomes can occur in man and, if increased by ionizing radiation, could complicate the interpretation of any changes in the sex ratio. Specifically, a radiation-induced increase in the frequency of nondisjunction conceivably could either obscure an increase in sex-linked lethal mutants or lead to a spuriously high estimate of their frequency.

The purpose of this paper is to record some 47,624 observations made in Hiroshima and Nagasaki in the years 1956 through 1962 relevant to the functional relationship between the sex ratio and parental exposure to atomic radiation and, in the light of these further observations, to review the evidence presently available on this issue. In terms of the total radiation dose represented, these new data increase the observations previously available by about 70%.

STUDIES OF THE SEX RATIO IN HIROSHIMA AND NAGASAKI

The data from Hiroshima and Nagasaki concerning the effects of radiation on the sex ratio fall into four categories, as follows, three of which have been

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presented previously: (1) the sex ratio in the infants born to *unrelated* parents in the years 1948 through 1953 (Neel and Schull, 1956), (2) the sex ratio in infants born to *related* parents in the years 1948 through 1953 (Schull and Neel, 1958, 1959), (3) the sex ratio in infants born to unrelated parents in the years 1954 through 1955 (Neel and Schull, 1956), and (4) the sex ratio in infants born to parents (related and unrelated) in the years 1956 through 1962. The rationale for analyzing pregnancy terminations of biologically related parents separately from unrelated parents has been presented elsewhere (Schull and Neel, 1959). The principal distinctions between these groups, aside from consanguinity in the parents, are as follows: Categories (1) and (2) differ from (3) and (4) in that pregnancies included in (1) and (2) were ascertained through a system of registration carried out in conjunction with the special ration registration for pregnant women which existed in the postwar period in Japan; whereas (3) and (4) were ascertained at the time that the city office of vital statistics was notified of the birth of a child. The details of these two methods of ascertainment have been given elsewhere (Neel and Schull, 1956; Schull and Neel, 1958). All children comprising categories (1) and (2) were examined by physicians either in the employ of the Atomic Bomb Casualty Commission (ABCC) or the Japanese National Institute of Health; among the functions of these physicians was the verification of the sex of the child as reported by the individual attending the delivery of the child, generally a midwife. In groups (3) and (4), the sex ascribed to a given infant is that reported at the registration of the birth and was not verified by a physician employed by either of the agencies previously mentioned. Categories (1) and (2) differ from one another only insofar as the children are the offspring of unrelated spouses in one instance, (1), and not in the other, (2). Groups (3) and (4) differ in two respects. First, group (3) represents *all* of the births reported to the municipal authorities in the years 1954 through 1955 except those where the parents were related; whereas group (4) represents only those births reported to the municipal authorities in the years 1956 through 1962 where either both parents were included in the so-called Master Sample which forms the basis of the Life Span Study of the Atomic Bomb Casualty Commission (Beebe, Ishida, and Jablon, 1962) or, if the exposure status of one parent was unknown, the other was stated to have been within 2,000 meters of ground zero. In the former instance, the exposure status of both parents was known to ABCC; in the latter, further effort was necessary to complete the exposure histories of the spouses.

In the years 1954 through 1955, whenever the exposure status of an individual was unknown, an effort was made routinely, either by mail or by interview, to ascertain whether the person had been exposed to the atomic bombing of Hiroshima and/or Nagasaki. If the answer was affirmative, a trained field investigator obtained an exposure history which included such items as the distance from ground zero at the time of the bombing (ATB), the occurrence of symptoms indicative of radiation sickness, etc. Since the files of ABCC included all individuals, irrespective of place of residence, who had reported themselves to be exposed either at the time of the national census of

Japan in 1950 or at an earlier *ad hoc* radiation census of these two cities, rarely did an individual whose exposure status was not known prove to have been exposed. Thus, the vast majority of inquiries, undertaken at considerable cost in time and effort, failed to augment the group of children of greatest interest, namely, those born to exposed parents. Accordingly, when the burden of field interviews exceeded the manpower available, as was inevitable since the relative proportion of births to nonexposed parents—those least likely to be included in the Master File—increased with each year, the decision was reached retroactive to 1956 to accept for study only those births where either the exposure status of both parents could be ascertained by a file check or where the exposure of only one parent had to be determined by interview, the other parent having been in the so-called "proximally exposed" group, i.e., within 2,000 meters of the hypocenter ATB. Clearly, this decision, from which the present body of data stems, resulted in the loss to the series of some children one or both of whose parents were exposed, but this number is presumably small, for a loss would occur only if the parents had not been included in one of the aforementioned censuses or if, at the time of these censuses, they had elected to deny their exposure.

As previously stated, the data comprising categories (1), (2), and (3) have been analyzed and the results presented elsewhere (summary in Schull and Neel, 1958). Briefly, the analysis proceeded as follows: Within each of the three categories, the pregnancies were viewed as divisible into three sets, namely, those where the mother was exposed and the father not, where the father was exposed and the mother not, and where both parents were exposed. Within each of these sets, there existed three or more dosage levels. Thus, for each of the categories (1), (2), and (3), it was possible to fit three linear regressions of the frequency of male births on the dose of radiation received by the parent(s). Two of these, corresponding to those cases where only one parent was exposed, were of the form

$$E(p_i) = p_0 + bd_i,$$

where $E(p_i)$ is the expected proportion of males in the i^{th} exposure class; p_0 is the proportion of males expected at zero dose, i.e., in the nonexposed group; d_i is the dose in the i^{th} exposure class; and b is the regression coefficient. The third regression was of the form

$$E(p_{ij}) = p_0 + b_1F_i + b_2M_j$$

where b_1 and b_2 are now partial regression coefficients, F_i and M_j are, respectively, the doses in the i^{th} paternal and j^{th} maternal exposure groups, and p_0 is, again, the proportion of males expected in the nonexposed class. The regressions which were, in fact, fitted were weighted to allow for the differences in the numbers of observations at the various exposure levels. The weights which were used were the reciprocals of the variances of the proportion of males at the different dosage levels; this variation was assumed to be solely binomial in origin, an assumption which is not wholly justified in view of the occurrence of siblings in the data and the effects of the extraneous variables which have been

TABLE 1. MEANS AND REGRESSION COEFFICIENTS OBTAINED BY FITTING A WEIGHTED LINEAR REGRESSION OF THE PROPORTION OF MALE BIRTHS TO AVERAGE GROUP EXPOSURE IN *r* IN THE HIROSHIMA AND NAGASAKI DATA

The values in parentheses are those obtained when unexposed parents are rejected. (Extended from Schull and Neel, 1958)

	Father only exposed		Mother only exposed		Both parents exposed		
	p_0	b*	p_0	b	p_0	Father b	Mother b
1948–1953							
Unrelated parents	0.5202	0.0058 (0.0094)	0.5213	−0.0101† (−0.0111)	0.5102	0.0039	−0.0037
Related parents	0.5307	0.0188 (0.0423)	0.5204	−0.0116 (0.0386)	0.5310	0.0024	−0.0179
1954–1955							
Unrelated parents	0.5211	0.0039 (0.0047)	0.5186	0.0090 (0.0141)	0.5484	0.0137	−0.0269
1956–1962	0.5150	−0.0016 (−0.0036)	0.5141	0.0072 (0.0077)	0.5137	−0.0129	0.0044
All data combined	0.5191	−0.0001	0.5185	0.0027	0.5166	−0.0020	−0.0035

*Increase or decrease per 100 rep.
†Significant at the 5% level.

mentioned. The problems inherent in treating nonbinomial variation and the types of bias it may introduce have been discussed by Cochran (1940). The final weights were obtained by iteration, starting with the observed proportions as trial values. The intercepts and regression coefficients which were obtained for the first three categories of data are given in Table 1.

We present in Tables 2 and 3, along with the earlier data, the 47,624 observations in Hiroshima and Nagasaki which have become available since the analysis summarized in the previous paragraphs. These observations are distributed by maternal and paternal exposure; for a justification of the average exposures assigned to the various groups, the reader is referred to an earlier publication (Neel and Schull, 1956, Chapter 4).* The years and cities have been pooled, but only after a search was made for significant heterogeneity within cities between years and within years between cities. No consistent, significant differences emerged either between cities or years. The results of an analysis of these more recent data, in the manner previously

*Since this paper was submitted, there has appeared a re-estimation of the gamma and neutron distance-dose relationships associated with the nuclear devices exploded over Hiroshima and Nagasaki (see Auxier *et al.*, 1966. Free-field radiation-dose distributions from the Hiroshima and Nagasaki bombings. *Health Physics* 12: 425–429). These new estimates suggest that the values previously assumed to hold for Hiroshima may be in error (upwards) by a factor of two, on the average; there are no substantial changes in the doses in Nagasaki. Clearly, if true, the regression coefficients given in Table 1 are too high; however, there remain many unresolved problems associated with individual exposures in these cities which counsel caution in a too hasty extrapolation from these new curves to the biological situation. Thus, we are still uncertain of the appropriate attenuation factors for various forms of shielding and the integrated fall-out dose, and, moreover, biological dosimeters such as frequency of epilation, etc., are at variance in the middle distances with the purely physical estimates.

TABLE 2. SUMMARY OF THE FINDINGS IN HIROSHIMA AND NAGASAKI WITH REGARD TO THE ASSOCIATION OF THE FREQUENCY OF MALE BIRTHS AND PARENTAL EXPOSURE

Only one parent exposed.

Father only exposed			Estimated mean exposure (rep)	Mother only exposed			Estimated mean exposure (rep)
Total births	Male births	p		Total births	Male births	p	
1948–1953, PARENTS UNRELATED							
31,904	16,613	0.5207	0	31,904	16,613	0.5207	0
3,670	1,892	0.5155	8	14,684	7,681	0.5231	8
839	442	0.5268	75	2,932	1,474	0.5027	75
534	284	0.5318	200	1,676	850	0.5072	200
1954–1955, PARENTS UNRELATED							
11,640	6,067	0.5212	0	11,640	6,067	0.5212	0
1,498	774	0.5167	8	4,926	2,512	0.5099	8
387	211	0.5452	75	1,026	562	0.5478	75
219	113	0.5160	200	592	311	0.5253	200
1948–1953, PARENTS RELATED							
2,622	1,396	0.5324	0	2,622	1,396	0.5324	0
295	152	0.5153	8	963	466	0.4839	8
83	46	0.5542	100	258	134	0.5194	100
1956–1962, ALL PARENTS							
20,382	10,483	0.5143	0	20,382	10,483	0.5143	0
4,841	2,505	0.5175	8	9,284	4,788	0.5157	8
1,730	892	0.5156	75	2,087	1,060	0.5079	75
1,199	612	0.5104	200	1,191	638	0.5357	200

outlined, are also given in Table 1. With the addition of these data, there are now sixteen regression coefficients associated with the four categories of observations. Only one, namely, mothers only exposed, 1948 through 1953, unrelated parents, can be shown to be significantly different from zero. Furthermore, inspection of the array of regression coefficients with respect to the direction and magnitude of the changes with parental exposure fails to suggest an unequivocal pattern; we note six of eight regression coefficients associated with paternal exposure are positive whereas three of eight associated with maternal exposure are positive. Neither of these arrays of signs is particularly unlikely under the hypothesis that plus and minus signs are equally probable. It will be noted that the regression coefficients observed in the new data tend to be opposite in sign from those obtained previously, thereby essentially destroying the consistency in the data upon which so much of the earlier argument for an effect of radiation on the sex ratio was based. Finally, if the differences between the various sets of observations are ignored and the aggregate analyzed, the data fail to disclose a significant association of either maternal or paternal exposure with the sex ratio.

It will be noted from Table 2 that certain observations, those where both parents were unexposed, enter into the estimation of the maternal effect when the father was not exposed as well as the paternal effect when the mother was

TABLE 3. SUMMARY OF THE FINDINGS IN HIROSHIMA AND NAGASAKI WITH REGARD TO THE ASSOCIATION OF THE FREQUENCY OF MALE BIRTHS AND PARENTAL EXPOSURE

Total births	Male births	p	Estimated mean exposure (rep)	
			Mother	Father
		1948–1953, PARENTS UNRELATED		
5994	3053	0.5093	8	8
658	337	0.5122	8	75
422	225	0.5332	8	200
703	354	0.5036	75	8
615	319	0.5187	75	75
192	94	0.4896	75	200
318	165	0.5189	200	8
145	72	0.4966	200	75
145	71	0.4896	200	200
		1954–1955, PARENTS UNRELATED		
1474	806	0.5468	8	8
220	129	0.5864	8	75
174	101	0.5805	8	200
212	111	0.5236	75	8
107	53	0.4953	75	75
66	35	0.5303	75	200
89	48	0.5393	200	8
43	20	0.4651	200	75
33	18	0.5455	200	200
		1948–1953, PARENTS RELATED		
394	208	0.5279	8	8
69	38	0.5507	8	100
54	29	0.5370	100	8
43	21	0.4884	100	100
		1956–1962, ALL PARENTS		
3899	1996	0.5119	8	8
756	374	0.4947	8	75
572	283	0.4948	8	200
608	334	0.5493	75	8
314	160	0.5096	75	75
144	68	0.4722	75	200
374	183	0.4893	200	8
124	70	0.5645	200	75
119	59	0.4958	200	200

unexposed. These regression coefficients are, therefore, not wholly independent of one another, and one might argue that we are not dealing here with 16 independent regression coefficients but some lesser number. To obtain estimates of the effect of maternal and paternal exposure, when only one parent was exposed, which are fully independent, we need merely omit the observations on both parents not exposed. Although this achieves statistical independence, it must be clearly borne in mind that the loss of data which is involved leads also to a loss in the precision of the estimates. The values in parentheses in Table 1 are those obtained when unexposed parents are rejected.

Thus far we have emphasized our efforts to demonstrate a significant association of the sex ratio with parental exposure; however, there is another aspect to the evaluation of radiation induced effects to which these data can contribute, and this is the specification of the upper limits of an effect which may have been induced but was not demonstrated. An approximate solution of this problem adequate for our purposes proceeds somewhat as follows: For convenience, we restrict our attention to the adequacy of these data for demonstrating differences between a single moderate-to-heavily exposed population and a suitable comparison population. More specifically, we seek to determine the probability of rejecting the hypothesis of no difference, given a fixed sample size, when the true situation is one wherein the exposed group differs from the standard by some amount, say d, for varying values of d. The groups of concern to us here are those terminations occurring to parents (1) neither of whom had exposures exceeding 8 rep, on the average, *the comparison group*, and (2) one or both of whom had exposures equaling or exceeding 75 rep, on the average, *the exposed group*. To simplify the calculations further, we shall assume that

1. The proportion of male births in the comparison population is known without error.
2. The normal approximation to the binomial distribution has the requisite accuracy over the critical range; here this includes those values for the exposed group which deviate from the comparison by not more than 5%.
3. The level of confidence with regard to the null hypothesis is 0.05.

We shall, in addition, limit ourselves to the cases of one parent exposed and assume that in these instances the direction of the deviation is specifiable in advance. The one-sided power functions or operating characteristics (see Paulson and Wallis, 1947) which one generates under these restrictions and for sample sizes of 9,762 (mothers) and 4,991 (fathers) are set out in Fig. 1. Before considering this figure, a comment or two on the assumptions enumerated above seems in order. Obviously the first assumption, namely, that the true proportion of male births in the comparison population is known without error, is not strictly satisfied by these data; however, the sample available on which to base the comparison value is sufficiently large, in excess of 75,000 births, that the error associated with the estimate of the true proportion of male births in this group is small under all circumstances and can be disregarded when contrasted with the error associated with an estimate based on the sample sizes available for the irradiated groups. The normal approximation requires no special justification since the sample size is not small and neither the proportion of male births in the comparison or the irradiated group is close to 0 or 1. Finally, the level of confidence is the conventional one.

To utilize Fig. 1, we must first define what constitutes an "adequate test." We shall say that a test is adequate with regard to the alternatives, $p_e - p_c > d$, where p_e and p_c are, respectively, the frequencies of male births in the exposed and comparison populations if the prior probability of detecting de-

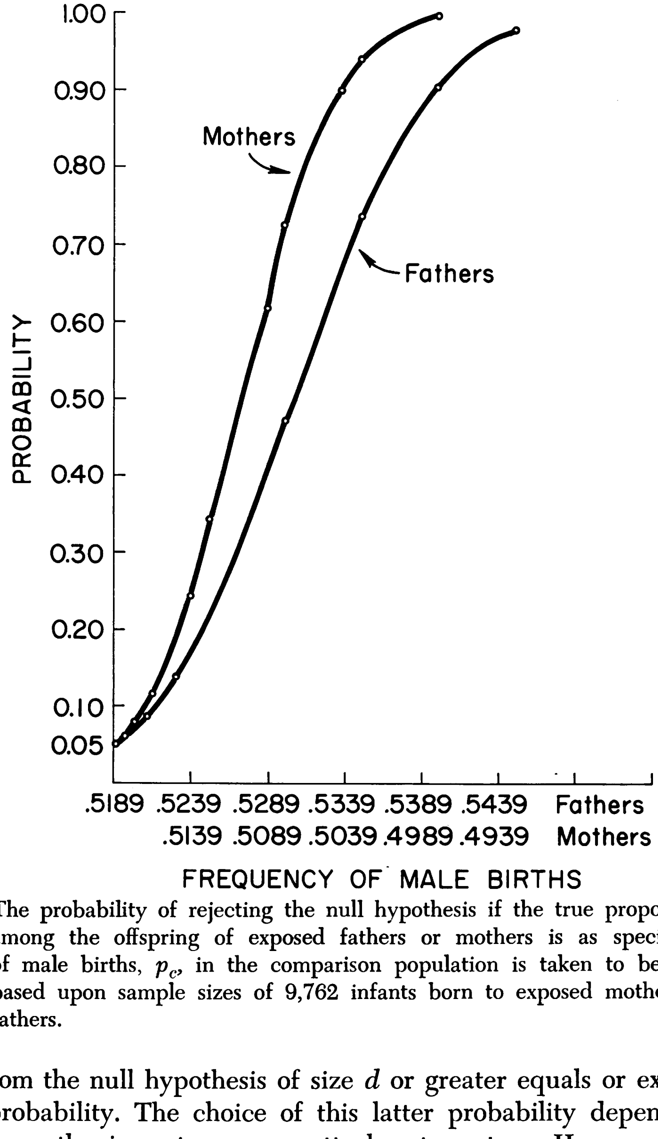

FIG. 1. The probability of rejecting the null hypothesis if the true proportion of male births, p_e, among the offspring of exposed fathers or mothers is as specified and the proportion of male births, p_c, in the comparison population is taken to be 0.5189. The curves are based upon sample sizes of 9,762 infants born to exposed mothers and 4,991 to exposed fathers.

partures from the null hypothesis of size *d* or greater equals or exceeds some specified probability. The choice of this latter probability depends in large measure upon the importance one attaches to a type II error, that is, to accepting the null hypothesis as true when in fact it is false. In the present instance, it would seem to be the more cautious course to minimize such errors. Accordingly, we shall set the frequency of such errors to be 0.10, and this is tantamount to asserting that adequate power is 0.90. This value may well be too high in view of the simplifications we have introduced and the fact that not all of the observations which are germane enter into the specification of the curves in Fig. 1. However, the error is a conservative one insofar as the adequacy of these data is, in fact, greater than that which is here claimed for them. It is apparent from Fig. 1 that these data are adequate to detect a departure of approximately 1.5% (absolute) in the case of exposed mothers, and 2.2% in the case of exposed fathers.

DISCUSSION

Other Studies of the Effect of Radiation on the Sex Ratio in Man

We have elsewhere summarized the results of the various studies through 1962 on the relationship between exposure to radiation and the sex ratio in man (Neel, 1963; Schull, 1963). In four of the six studies involving paternal radiation, the sex ratio was increased; in all three instances involving maternal radiation, the sex ratio was decreased. A study missed in those summaries involved a small series of women exposed in the Joachimstal mines, in whose offspring the sex ratio was lower than in controls (Muller, Kubat, and Marsalek, 1962). A further study by Cox (1964) reports a decrease in the sex ratio in the children of Canadian patients receiving repeated diagnostic radiation because of congenital dislocation of the hip. Thus, in four of six other studies involving paternal radiation, the sex ratio is increased, while in five of five studies involving maternal radiation, the sex ratio is decreased. Although the apparent effect is statistically significant in only one of these studies, the manner in which the findings parallel expectation on the basis of simple sex-linked inheritance has made it tempting to accept their validity.

The circumstances and "information content" of the various studies to date are extremely uneven, rendering precise comparisons difficult. However, although an exact calculation is impossible, it would appear that the radiation dose represented in the children of exposed parents described in this and previous reports on Hiroshima and Nagasaki is greater than the sum total of the radiation doses represented by the children included in all other published studies to date. In addition to the numbers and doses involved, there is the added value in the present study of a system of ascertainment which ensures uniform treatment of all offspring regardless of the exposure status of their parents. On the basis of the operational curves described earlier, the present data are incompatible with effects of the magnitude reported in the papers of Musil (1962), Muller, Kubat, and Marsalek (1962), and Cox (1964). Contrariwise, they are consistent with the results of the remaining investigations.

On an Interpretation of the Present Studies

Ionizing radiation can and undoubtedly does produce lethal mutations associated with the X chromosome, and under the simplest of circumstances these mutations may lead to an altered sex ratio among progeny born subsequent to exposure. There is, we believe, more or less universal acceptance of the truth of this assertion, but this is not the issue as we see it. Rather it is a question of the best possible estimate of the rate of induction of sex-linked lethal mutations and the realization that other forces may be at work which make the simplistic point of view just set forth of dubious value. In particular, two questions concern us. First, what explanation, if any, can be advanced for the apparent reversal of an effect perceived, albeit dimly, in the earlier data from Hiroshima and Nagasaki? Second, what interpretation is to be placed upon the totality of data presently available?

With respect to the first of these questions, one possible explanation, of course, is that there was in fact no effect and that the apparent effect in the earlier data was fortuitous. But, if one assumes that the apparent effect was real, then obviously one is obliged to conclude that the later data, that is, the observations from 1956 to 1962, are not *in pari materia* with the earlier. This could be so because of a confounding of extraneous variation, but we have no evidence to support such a supposition. There is, however, another possibility. Some experimental evidence suggests that in female mice the yield in mutations, following an exposure experience, may diminish with time either as a consequence of the repair of certain mutations, of cell selection, or both (see Russell, 1965). It is conceivable, therefore, that the number of sex-linked lethal mutations potentially recoverable from the populations of Hiroshima and Nagasaki has diminished with time. However, a comparison of the regression coefficients for the three time intervals in which the data have been analyzed fails to reveal clear evidence for a time trend. It is possible, of course, that if a tendency of the kind implied exists, it is obscured by the accumulation of spontaneous sex-linked lethal mutations to be anticipated with time, especially in males (cf. Novitski and Sandler, 1956; Novitski and Kimball, 1958). However, if the difference in age between exposed and nonexposed parents is increasing with the passing years, then one might expect the increased frequency of spontaneous mutations to dampen the reduction in induced mutations. The net effect would be to minimize a trend. If, on the other hand, the difference in parental ages between the comparison groups is diminishing with time, possibly even to the point where the exposed parents are younger on the average, then the trend might be maximized. Although improbable perhaps, the sign of the regression coefficients might even be altered if the exposed parents were actually younger than the nonexposed.

One possible complication in the Japanese data as well as that from elsewhere in the world concerns the occurrence of chromosomal abnormalities involving the X or Y chromosome. While it has not been rigorously demonstrated that such abnormalities in man increase with exposure to ionizing radiation, there is evidence from other organisms which makes a presumption to this effect reasonable. Be this as it may, any effort to assay the impact of chromosomal abnormalities upon the sex ratio ultimately becomes an attempt to ascertain the relative frequencies of gametes lacking a sex chromosome and those having an accessory one among the gametes produced by an exposed father on the one hand and by an exposed mother on the other. Suffice it to state that current information precludes an exact analysis of this problem, but, to the extent that an evaluation is possible, it would seem that chromosomal abnormalities are not likely to alter the direction of change in the sex ratio anticipated on the basis of the segregation of sex-linked lethals but will almost certainly alter the magnitude of the latter change (see Neel, 1963).

We have repeatedly stressed the unsatisfactory nature of the sex ratio as a variable. It is apparently influenced by any number of factors, e.g. maternal age, paternal age, parity, etc. While the effects of these variables are generally small, adequate explanation of their origin has not been advanced despite the existence of bodies of data far larger than those pertinent to the radiation problem. Unfortunately, these unexplained perturbations are often lost sight of, and only the elegance of the genetic argument is seen. As matters stand—

and we sincerely hope this is our last word on the subject—the Hiroshima-Nagasaki data fail to provide unequivocal evidence for an effect of radiation on the sex ratio, although they are consistent with a small effect in the early post-bomb years which has since disappeared. The manner in which these data can be combined with the other findings from Hiroshima and Nagasaki to shed light on the "doubling dose" of radiation for man will be dealt with elsewhere (Kato, Schull, and Neel, 1966).

SUMMARY

Data are presented on the sex ratio of 47,624 children born in Hiroshima and Nagasaki in the years 1956 through 1962. The total number of births in these two cities for which information is available is now 140,542, and of this number in 73,994 instances one or both parents were exposed to the atomic bombings. The suggestion of an effect of exposure on sex ratio in the earlier data is not borne out by the present findings. One can argue either that a small early effect has disappeared or that the original observation had no biological significance.

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