# Genetic Effects of the Atomic Bombs: A Reappraisal

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*Summary.* Data are presented on four indicators of genetic effects from studies of children born to survivors of the atomic bombings of Hiroshima and Nagasaki. The indicators are frequency of untoward pregnancy outcomes (stillbirth, major congenital defect, death during first postnatal week); occurrence of death in live-born children, through an average life expectancy of 17 years; frequency of children with sex chromosome aneuploidy; and frequency of children with mutation resulting in an electrophoretic variant. In no instance is there a statistically significant effect of parental exposure; but for all indicators the observed effect is in the direction suggested by the hypothesis that genetic damage resulted from the exposure. On the basis of assumptions concerning the contribution that spontaneous mutation in the preceding generation makes to the indicators in question, it is possible to estimate the genetic doubling dose for radiation for the first three indicators (the data base is still too small for the fourth). The average of these estimates is 156 rems. This is some four times higher than the results from experimental studies on the mouse with comparable radiation sources, which have been the principal guide to the presumed human sensitivities. The relevance of these data in setting permissible limits for human exposures is discussed briefly.

Concern about the effects of ionizing radiation, which peaked during the period of atmospheric testing of nuclear weapons in the 1950's, has become active again as the United States and other nations debate the role of nuclear power in their future and as allegations of late effects of low-level radiation exposures accumulate. With respect to the genetic risks, experimental studies have provided a framework within which to view the problem (*1*). They have also demonstrated the complexities of estimating the impact of an exposure to radiation on populations of organisms (in contrast to a specific locus system), as well as the many ways in which the apparent genetic responses of diverse species to radiation may vary. In consequence, there is a need for properly controlled human data.

Since mid-1946, the birth cohorts of Hiroshima and Nagasaki have served as the basis for studies of the potential genetic effects of the atomic bombs. It is our purpose here to present a coherent picture of the findings to date. We first examine the effect of parental exposure on a number of indicators of genetic damage *in* offspring; then, using estimates of gonadal dose, we develop a preliminary estimate of the amount of ionizing radiation that, under the conditions of these exposures, with these indicators, in this population, will produce a 100 percent increase over the spontaneous mutation rate—in other words, the doubling dose. Inasmuch as the public is currently concerned primarily with the effects of low-level exposures, it is important at the outset to point out that of the persons receiving one or more rads of radiation [also referred to as kerma (*1a*)], some 50 percent are estimated to fall within the dose range of 1 to 9 rads, with roughly half the surface exposure reaching the gonad.

## Historical Review of Genetic Studies

The genetic studies to be described were undertaken initially by the Atomic Bomb Casualty Commission and subsequently (in 1975) by the Radiation Effects Research Foundation (RERF). Beebe (*2*) has reviewed the more recent activities of these organizations. The first steps toward a genetic program were taken in 1946, and a full-scale program was initiated in 1948, primarily, as necessitated by the times and circumstances, morphological in nature.

The Japanese postwar rationing system included a special provision for pregnant women after the fifth lunar month of pregnancy. A preliminary study revealed that the vast majority of pregnant women availed themselves of this provision. It was therefore possible to identify practically all pregnant women in Hiroshima and Nagasaki at about the fifth month of gestation. These women were requested at the time of ration registration to complete a questionnaire concerning previous reproductive history and exposure of themselves and their spouses to the atomic bombs. The consanguinity of the marriage was also determined since an uneven distribution in the frequency of consanguineous marriage in relation to radiation exposure could introduce a significant bias into the study (*3*). When the pregnancy terminated, the attendant at birth (usually a midwife) submitted a brief report on the outcome. As soon as possible thereafter, an effort was made to have a physician examine the infant, regardless of the attendant's report. Where permission could be obtained, autopsies were performed on stillborn infants or those that died during the neonatal period. Finally, on a randomized basis, about half of all infants examined shortly after birth were reexamined at age 8 to 10 months. If no termination had been reported for a registered pregnancy by 1 month after the expected date of confinement, a follow-up was initiated. Limited data on socioeconomic status were collected on a randomized 10 percent subsample, as well as on all untoward pregnancy terminations. Further details of the study are provided in (*4, 5*).

The indicators of possible genetic effects that could be extracted from this program—all, of course, confounded by a variety of extraneous factors—were sex, birth weight, viability at birth, presence of gross malformation, occurrence of death during the neonatal period, and physical development at age 8 to 10 months. Analysis of the data through 1953 suggested that this clinical program—the so-called GE-3 study—had reached its logical conclusion (*4*). Because of borderline findings with respect

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to sex ratio and survival of live-born infants, however, collection of data on these variables in relation to parental radiation history was continued. The study on sex ratio was extended to embrace essentially all births in Hiroshima and Nagasaki through 1962 (*6*). However, the ongoing study of survival, the $F_1$ Mortality Study, was based on a more restricted sample, consisting of (i) all infants live-born in the two cities between May 1946 and December 1958 one or both of whose parents were proximally exposed to the atomic bombs (that is, within 2000 meters of the hypocenter), (ii) an age- and sex-matched cohort randomly drawn from the remaining births during this same period in the two cities, for which one parent was distally exposed (2500 m or more from the hypocenter) and the other either distally exposed or not exposed at all, and (iii) a second age- and sex-matched cohort randomly drawn from the remaining births where neither parent was exposed. Children born to individuals one or both of whom were within 2001 to 2500 m of the hypocenter were excluded from the study because of difficulty in accurately evaluating the very low doses received at this distance. A full description of the study is given in (*7–9*).

As human cytogenetics developed in the late 1950's and early 1960's it became apparent that cytological studies of the survivors and their offspring were desirable. Accordingly, on the basis of a pilot study conducted in 1967, an investigation of the children of exposed parents was initiated in 1968, the subjects being drawn initially from the cohorts established for the $F_1$ Mortality Study. Awa and colleagues have described this study (*10, 11*). Ten metaphase preparations are routinely examined from each child. Since the youngest children in the study are 13 (the age at which a blood sample is first obtained) and the oldest (born in 1946) are now 34, the survey will not yield adequate data on the frequency of cytogenetic abnormalities associated with increased mortality rates, such as unbalanced autosomal structural rearrangements and autosomal trisomies. The data on sex chromosome abnormalities and balanced autosomal structural rearrangements should, however, be relatively unbiased even now.

The advent of convenient and inexpensive electrophoretic techniques for the identification of abnormal protein molecules in the 1950's and 1960's offered an approach to the study of the genetic effects of the atomic bombs that was free of many of the ambiguities of previous techniques. By the early 1970's electrophoretic techniques had been developed for a large number of serum and erythrocytic proteins, and in 1976, after a 3-year pilot study, an investigation employing these techniques—the Biochemical Genetics Study—was undertaken (*12, 13*). The subjects are drawn from the cohorts of children born to proximally and distally exposed parents identified for the $F_1$ Mortality Study. The same blood sample serves both this program and the Cytogenetic Study although, because the latter was initiated first and cannot process as many specimens, there is not complete overlap between the two samples of children thus far studied. To increase the numbers of children available for these studies, the two cohorts are currently being extended to include births from 1959 through 1975.

Each child is examined for rare electrophoretic variants of 28 proteins of the blood plasma and erythrocyte, and for activity variants of a subset of eight erythrocytic enzymes. A rare variant is defined in this context as one with a phenotype frequency of less than 2 percent in the population. When such a variant is encountered, its occurrence is verified, and then blood samples from both parents are examined for the presence of a similar variant. If the variant is not encountered in either parent, there are two possible explanations: mutation, or a discrepancy between legal and biological parentage. The latter possibility is explored with studies of alleles at 11 different loci, which should detect some 80 percent of such discrepancies. In view of the many speculations about a possibly large recessive component in the genetic effects of the atomic bombs, which would be manifested over many generations, we point out that the electrophoretic approach should provide insight into the magnitude of any induced recessive genetic effects.

## Evaluating the Genetically Effective Radiation Exposure

For a variety of reasons, assessment of the amount of gonadal radiation received by the exposed parents of the children under investigation has proved difficult. In our first analysis of the morphological data (*3*), it was not possible to do more than assign the parents to five categories, ranging from those exhibiting symptoms of radiation sickness following the bombings to those not in either city at the time of the bombings. Since the 1950's, a major effort has been devoted to estimating the surface (whole-body) dose for each survivor within 1600 m of the hypocenter in Hiroshima and 2000 m in Nagasaki (*14–16*). At these distances, the sum of the gamma ray and neutron exposures (kerma) is approximately the same in each city, slightly more than 10 rads. These individual exposure estimates, known as the T65D estimates, are based on the distance-dose relations of the two explosions and reconstructions of the position and shielding of each exposed person. Because of the much greater neutron component thought to have been emitted by the Hiroshima bomb, these relations are not the same for the two cities. Separate gamma and neutron doses have been assigned each survivor. The errors inherent in the individual surface doses may amount to as much as ±30 percent (*17*). However, no systematic biases in the assignment of dose have been recognized. The exact position of the hypocenter in Nagasaki was not resolved until late 1978, and thus only recently has the final assignment of dose in that city occurred. These revised estimates (T65DR) are the basis of the present analysis. However, discussions of the amount and types of radiation received by those exposed to the bombs continue (*18*), and there may be further revisions of the dose estimates.

The assignment of individual doses greatly increases the power of the possible statistical analyses of these data. Not unexpectedly, however, there are some residual problems in the assignment that will probably never be resolved. For roughly 3 percent of the persons exposed in Hiroshima or Nagasaki (many now dead), either the history of position at the time of the bombings is incomplete or the shielding data are complex, so that even an approximate dose cannot be computed. In most of the analyses to be described, children born to parents whose dose is unknown were excluded from consideration, but in the Biochemical Genetics Study these parents have been assigned the mean dose of all survivors within the same area.

In assigning a genetically effective (gonadal) dose, two further problems arise: how to evaluate the attenuation of the surface dose by the intervening tissues, and how to estimate the relative biological effectiveness (RBE) of the neutron component in the assigned doses. The first problem is complicated by the differential attenuation of the gamma ray and neutron components of the dose, as determined from models of the human body. In computing gonadal doses, we used tables developed by Kerr (*19*) for the types of radiation emitted by the

atomic bombs, which provide separate attenuation factors for gonadal exposure to adult males and females and for neutron and gamma radiation. Uncertainty about precise posture at the time of the bombings complicates the calculation of organ dose and introduces a further source of error into the estimation of gonadal dose. Use of Kerr's adult-based tables is a conservative practice, since some parents were still children at the time of the bombings (with lesser attenuation of dose). No allowance has been made for the possibility of exposure to small amounts of residual radiation following the bombings (*20*). All analyses to be presented are now based on the estimated gonadal dose of the parents.

With respect to the assignment of an RBE to the neutron component of the dose, under the best of circumstances that assignment would follow from the results of the study. In the absence of statistically significant findings (see below), this is difficult; we must also be guided by experimental data. Studies of the genetic effects of acute neutron doses of 50 to 100 rads on mouse spermatogonia and mature oocytes in a specific locus test system yielded RBE's of about 5 (*21*), and in earlier work we adopted that figure (*9*). Although there are no data at very low neutron doses from this test system, recent work of Grahn *et al.* (*22*) with other, softer genetic end points in the mouse suggests that at acute neutron doses below 5 rads the RBE may be as high as 20. Under certain assumptions, similar or even higher RBE's at low neutron doses can be invoked from the atomic bomb experience for several end points that may be viewed as the result of somatic cell "mutations," such as acute leukemia (*23*) and chromosome aberrations in leukocytes (*24*). The neutron doses in the exposed parents were generally low. For example, among the proximally exposed parents in the $F_1$ Mortality Study who are estimated to have received 1 rad or more of neutron exposure, the estimated neutron doses are: 1 to 4 rads, 8357 persons; 5 to 9 rads, 2463 persons; 10 to 19 rads, 1378 persons; 20 to 49 rads, 1150 persons, 50 to 99 rads, 501 persons; and 100+ rads, 410 persons. Nevertheless, we will assign neutrons an RBE of 5 for genetic effects, a conservative position when we turn to the genetic doubling dose. The assignment of an RBE to the neutron component permits us to express the dose in rems and so facilitates the comparison of these results with experimental studies in which doubling doses have been developed for low LET (linear energy transfer) radiation.

Table 1. Distribution of untoward pregnancy outcomes (UPO) by parental gonadal dose (cities and sexes combined). The T65DR dose estimates were used. An untoward pregnancy outcome is one that terminated in a child who had a major congenital defect, was stillborn, or died in the neonatal period.

| Mother's exposure (rads) | Total | | | Father's gonadal dose (rads) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | NIC* | | | 0 | | | 1–9 | | | 10–99 | | | 100+ | | |
| | Cases | UPO | Percent | Cases | UPO | Percent | Cases | UPO | Percent | Cases | UPO | Percent | Cases | UPO | Percent | Cases | UPO | Percent |
| 100+ | 452 | 20 | 4.42 | 348 | 14 | 4.02 | 44 | 5 | 11.36 | 25 | 1 | 4.00 | 14 | 0 | 0.00 | 21 | 0 | 0.00 |
| 10–99 | 2,776 | 152 | 5.48 | 1,964 | 113 | 5.75 | 324 | 14 | 4.32 | 136 | 9 | 6.62 | 285 | 14 | 4.91 | 67 | 2 | 2.99 |
| 1–9 | 5,309 | 236 | 4.45 | 3,538 | 168 | 4.75 | 770 | 25 | 3.25 | 667 | 21 | 3.15 | 270 | 16 | 5.93 | 64 | 6 | 9.38 |
| 0 | 22,088 | 1,078 | 4.88 | 14,862 | 709 | 4.77 | 5,540 | 284 | 5.13 | 999 | 49 | 4.90 | 467 | 26 | 5.57 | 220 | 10 | 4.55 |
| NIC | 39,457 | 1,846 | 4.68 | 34,117 | 1,580 | 4.63 | 3,389 | 173 | 5.10 | 1,102 | 49 | 4.45 | 596 | 28 | 4.70 | 253 | 16 | 6.32 |
| Total | 70,082 | 3,332 | 4.75 | 54,829 | 2,584 | 4.71 | 10,067 | 501 | 4.98 | 2,929 | 129 | 4.40 | 1,632 | 84 | 5.15 | 625 | 34 | 5.44 |

*Not in city.

The genetically effective dose represented by each child is the sum of the parental doses. That these individual doses are, for the most part, modest has been recognized since the first decision to undertake genetic studies in the two cities (*25*). But even though the dose is small and the number of children born to proximally exposed parents is limited, this exposure is unquestionably the most significant experience of normal (well) humans beings with the genetic effects of radiation on record, especially since the total exposure was instantaneous [the greater genetic effectiveness of a given amount of radiation when delivered in a limited rather than a prolonged period of time has been documented for a variety of organisms, including the mouse (*26–28*)]. Because of the relatively small doses involved, as many objective end points as feasible have been pursued in efforts to evaluate the genetic effects of the bombs.

### Strategy of This Presentation

*Genetic considerations.* We will limit this discussion to the data used to derive a genetic doubling dose of radiation. For this reason we will not further consider data on continuously distributed traits such as height and weight (*3, 29–31*) or data on the sex ratio. We note in passing that at no time was there persuasive evidence of depressed growth of the children of the exposed attributable to the induction of dominant mutations. The simple theory of sex-linked inheritance on which predictions of an effect of parental exposures on the sex ratio rested seems no longer tenable. Recent developments—notably the recognition of X-chromosome inactivation, of the probable preferential inactivation of paternally derived X chromosomes, and of the occurrence of chromosomal abnormalities that can obscure a simple anatomic assessment of sex—make it difficult to predict the effects of parental exposure on the sex ratio. The remaining data will be presented under four headings, in the order of their collection.

1) "Untoward outcomes": These include major congenital defect, stillbirth, or death during the first week of life in the children included in the GE-3 study. Results of autopsy examinations and diagnoses of congenital defect at the 9-month examination were used. These outcomes are expected to occur in proportion to radiation dose in the parents, because of the induction of mutations with deleterious effects.

2) Survival of live-born infants: The

analysis of survival is based on the children comprising the $F_1$ Mortality Study. The expectation is an increase in mortality in the children in proportion to the radiation received by the parents. Deaths were followed through 1971; the mean age of the surviving children at that time was 17 years. The study should thus embrace the bulk of prereproductive mortality.

3) Chromosomal abnormalities: The cytogenetic data to be analyzed have most recently been presented by Awa (*32*). The subjects are drawn from the $F_1$ Mortality Study and its extension. The expectation is an increase in cytogenetic abnormalities in the offspring of the exposed. However, blood samples are not obtained until the children are 13 years old, and most children with autosomal aneuploidy will have died before this age, with the possible exception of those with trisomy 21. The findings are thus valid only with respect to balanced translocations and sex chromosome aneuploids.

4) Alterations of specific proteins: The Biochemical Genetics Study was described earlier. As for the Cytogenetic Study, subjects are drawn from the $F_1$ Mortality Study and its extension. Electrophoretic variants that can be attributed to mutation should be more frequent in the children of the exposed than in the children of controls. The findings of the study at its approximate halfway point have recently been published (*13*).

All four bodies of data that we consider here have been described elsewhere. What is unique to this presentation is the newly gained ability to relate the findings to individually assigned gonadal doses, which greatly facilitates the calculation of the genetic doubling dose of radiation.

*Statistical considerations.* Since our earlier analyses of these data were undertaken at a time when individual exposure estimates were unavailable, we were forced to assign individuals to dose categories based on symptomatology and distance, to treat the attribute data as if multiply classified, and to examine "main effects" and "interactions" through a generalization of the analysis of a $2 \times 2 \times 2$ system of classification due to Roy and Kastenbaum (*33, 34*). The details may be found in Neel and Schull (*4*, chap. 6). Recent advances in the analysis of categorical data (*35–38*) and the availability of individual exposure estimates offer new analytic opportunities. We limit ourselves here to one analysis, treating indicators 1 and 2 described above as binomial variables and regressing the observed values on a series of independent variates—parental exposures and extraneous but nonnegligible factors that influence pregnancy outcome, so-called concomitant variables.

Table 2. Increments or decrements in the frequency of untoward pregnancy outcomes per 100 rems of gonadal exposure, based on an assumed neutron RBE of 5. The standard error of each regression coefficient is indicated in parentheses.

| Variable | Regression coefficient |
|---|---|
| Joint parental exposure | 0.001824 (0.003232) |
| Inbreeding* | 0.009826 (0.039437) |
| Multiple births† | 0.2875 (0.4071) |

*Change per percent inbreeding. †Increased risk to twins as opposed to singleton births.

We assume that mutations follow a "one-hit" radiobiological model and thus that

$$P_{ij} = 1 - \exp\left[\alpha_H(\alpha_N) - \sum_{k=1}^{c} \beta_k X_{ijk} - \sum_{k=c+1}^{v} \beta_k X_{ijk}\right]$$

where $P_{ij}$ is the expected proportion in the $ij$th exposure cell; $\alpha_H(\alpha_N)$ is a constant associated with Hiroshima (Nagasaki); $\beta_k$ is the regression coefficient associated with the $k$th ($k = 1, 2, \ldots, v$) independent variate having mean value $X_{ijk}$ in the $ij$th cell; and $c$ and $(v - c)$ are, respectively, the numbers of concomitant and exposure variables. If one replaces the equation above by the power series of which it is the limit and assumes that the terms involving powers of $\beta$ higher than the first are negligible, as is frequently true, then the following approximation seems justifiable:

$$P_{ij} = \alpha_H(\alpha_N) + \sum_{k=1}^{c} \beta_k X_{ijk} + \sum_{k=c+1}^{v} \beta_k X_{ijk}$$

The frequencies of the variables—untoward outcomes and mortality—were regressed on 25 exposure categories characterizable by the mean maternal and paternal gamma and neutron exposures of individuals within that category and by a number of concomitant variables known to influence pregnancy outcome and early infant survival. Different arrays of concomitant and exposure variables were examined. Among the former, we assessed the effects of (i) year of birth, (ii) multiple births, (iii) inbreeding, (iv) maternal age (and its square), (v) paternal age (and its square), and (vi) birth order. All have been shown to influence pregnancy outcome in other studies and can be shown to do so here as well (*4*). Among exposure variables, we examined the effects of (i) total parental exposure (the sum of the mean gamma and neutron exposures), (ii) parental gamma and neutron exposures (the mean gamma and neutron doses separately summed over the two parents), (iii) total individual parental exposures (the simple sum of the mean maternal or paternal gamma and neutron exposures), (iv) a weighted sum of the mean parental gamma and neutron exposures (neutron exposure given five times the value of 1 rad of gamma exposure, that is, viewed as having an RBE of 5), and (v) weighted total parental exposure. Both kerma and tissue doses were analyzed.

Unless otherwise stated, we present here only the results of the analysis based on weighted total parental tissue dose. We selected this analysis for the following reasons. Gamma and neutron exposures are so highly correlated within individuals that their effects are difficult to disentangle. The only seemingly successful strategy thus far has been to utilize the differences in the radiation spectra in the two cities to estimate the neutron effect and hence RBE. But this approach requires the cities to be analyzed separately, and the numbers available for analysis are sharply different (fewer in Nagasaki). If an RBE is assumed, the cities and gamma and neutron exposures can be pooled and the greatest amount of information can be used for estimation of the doubling dose. Finally, in the determination of the regression coefficients the observed frequencies are weighted by the inverse of the variance of the frequency predicted for that cell by the model.

For indicators 3 and 4, where we are concerned with such low-frequency events that regression analysis is impractical, we employ simple chi-square contrasts. In fact, for 4 the events of interest have thus far been so uncommon that no statistical analysis seems justified.

Indicators 1 and 2 are influenced by socioeconomic status. In an earlier analysis (*8*) we found that the unexposed control parents (who came to Hiroshima and Nagasaki after the bombings) were slightly younger and had a little more education and slightly higher occupational ratings than the exposed. The differences as tested by contingency chi-square were of borderline statistical significance and such as might result in higher mortality in the children of the proximally exposed, but the data do not permit rigorous treatment of this possible bias. However, to the extent that these facts inflate the apparent radiation effects, they bias downward the estimate of doubling dose.

## Description of Findings

We will present the findings in the order in which the data were gathered.

*Untoward outcomes.* In 1948 through 1953, 76,617 pregnancy terminations were studied, of which 6,535 are unsuitable for analysis [see section 6.4 in (*4*) for a fuller basis for their exclusion than the brief one that follows]. Of these, 3,264 involved unregistered pregnancies, which frequently were illegitimate conceptions or terminated before the stage in gestation at which registration was legal. Ascertainment of these events is known to be incomplete, and the cases ascertained are markedly biased in exposure and in the frequency of untoward outcomes. Another 1,825 pregnancies were rejected because the distance of an exposed parent was unknown (397), the exposure information was inadequate in other ways to estimate the amount of radiation received (1,219), or the individuals were exposed in one city but were residing in the other and an appropriate comparison group is unclear (209). Finally, 1,446 terminations were excluded because the termination was induced, presumably prematurely from the infant's birth weight (520), the birth weight was unknown and the gestational age and hence legitimacy of registration was uncertain (713), or the birth record was incomplete in some other manner (213). The 70,082 pregnancies considered for analysis here differ from the 65,431 considered previously in the inclusion of inbred infants and multiple births if they satisfied the other criteria (registration, known parental age, and so forth) for acceptance.

Table 1 shows the distribution of untoward pregnancy outcomes by parental gonadal dose. We pooled sexes and cities for brevity, since the results are not significantly different when these factors are considered separately (*39*). Inspection discloses no persuasive trends with maternal or paternal exposure or both. Table 2 gives the results of an analysis of these data. Although we show the relation of untoward outcomes to only two concomitants—inbreeding and multiple birth—the effects of year of birth and parental ages were also estimated. Note that the weighted total parental gonadal dose is not significantly related to pregnancy outcome. Moreover, the risk that accompanies exposure appears to be substantially less than that associated with multiple births or inbreeding.

*Survival of live-born infants.* This analysis is based on the experience of the cohort that comprises the $F_1$ Mortality Study. These are singletons born alive in Hiroshima or Nagasaki in May 1946 through December 1958. Their survival status is routinely ascertained from the household registers (koseki) of which they are part. Table 3 displays deaths in this group before 1 January 1972; sexes and cities are combined. Since the oldest of these individuals was then only 25 years of age, the force of mortality was still relatively small. As in the case of untoward pregnancy outcomes, there is no compelling evidence of increasing mortality with increasing parental gonadal dose. This impression is reinforced by the analysis of these data (see Table 4). A small but nonsignificant increase in mortality occurs with increasing conjoint exposure. Three concomitants have been included: year of birth and mother's and father's ages. Mortality has declined with time, which is expected because of the falling infant mortality rates in Japan. Data on consanguinity exist for only a portion of the $F_1$ cohort; thus it has not been possible to remove the effects of inbreeding. This could lead to underestimation of the effects of radiation, for consanguineous marriages are relatively more common in the not-in-city group and the 0-rad group.

*Cytogenetic studies.* The cytogenetic studies through 1979 yielded 12 individuals with sex chromosome abnormalities and five with balanced autosomal structural rearrangements in 5,058 children of the distally exposed, and 16 sex chromosome abnormalities and 10 balanced rearrangements in 5,762 children of parents one or both of whom were proximally exposed (*32*) (Table 5). The difference in frequency between the two groups is in the direction of hypothesis (an increase with radiation) but far from significance (exact $P = 0.135$). The average gonadal doses for the parents in the second group can be estimated as follows (*19*): Hiroshima fathers, 26.0 γ and 5.6 n; Hiroshima mothers, 25.4 γ and 2.4 n; Nagasaki fathers, 42.3 γ and 0.5 n; and Nagasaki mothers, 36.7 γ and 0.2 n (here γ is used for gamma ray and n for neutron). The mean joint gonadal exposure to radiation for the parents in the proximally exposed panel whose children were examined is 87 rems at a neutron RBE of 5.

*Studies on protein phenotypes.* Through 1979, 289,868 locus tests were performed on the children of the proximally exposed and 208,196 on the children of the distally exposed. Again using Kerr's attenuation factors (*19*), gonadal doses can be estimated as follows: Hiroshima fathers, 20.0 γ and 4.2 n; Hiroshima mothers, 16.6 γ and 1.6 n; Nagasaki fathers, 29.0 γ and 0.3 n; and Nagasaki

Table 3. Distribution by gonadal dose group of the parents of the individuals who comprise the $F_1$ mortality cohort (cities and sexes combined); 2036 individuals (137 deaths, 6.7 percent) with unknown exposures were excluded. The T65DR dose estimates were used.

| Mother's exposure (rad) | Total | | | Father's gonadal dose (rads) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | NIC* | | | 0 | | 1–9 | | | 10–99 | | 100+ | | |
| | Cases | Deaths | Percent | Cases | Deaths | Percent | Cases | Deaths | Percent | Cases | Deaths | Percent | Cases | Deaths | Percent |
| 100+ | 856 | 61 | 7.1 | 642 | 44 | 6.9 | 101 | 4 | 4.0 | 41 | 5 | 12.2 | 29 | 4 | 13.8 | 43 | 4 | 9.3 |
| 10–99 | 5,111 | 313 | 6.1 | 3,580 | 216 | 6.0 | 642 | 38 | 5.9 | 239 | 19 | 8.0 | 523 | 33 | 6.3 | 127 | 7 | 5.5 |
| 1–9 | 5,769 | 363 | 6.3 | 3,530 | 204 | 5.8 | 831 | 47 | 5.7 | 819 | 63 | 7.7 | 472 | 36 | 7.6 | 117 | 13 | 11.1 |
| 0 | 16,189 | 1,096 | 6.8 | 9,648 | 623 | 6.5 | 4,264 | 319 | 7.5 | 897 | 67 | 7.5 | 932 | 65 | 7.0 | 448 | 22 | 4.9 |
| NIC | 22,764 | 1,398 | 6.1 | 17,112 | 1,060 | 6.2 | 2,952 | 189 | 6.4 | 1,021 | 59 | 5.8 | 1,156 | 60 | 5.2 | 523 | 30 | 5.7 |
| Total | 50,689 | 3,231 | 6.4 | 34,512 | 2,147 | 6.2 | 8,790 | 597 | 6.8 | 3,017 | 213 | 7.1 | 3,112 | 198 | 6.4 | 1,258 | 76 | 6.0 |

*Not in city.

mothers, 23.1 γ and 0.1 n. The mean joint parental gonadal exposure per locus studied in their children becomes 59.9 rems for a neutron RBE of 5. (Higher average gonadal doses were obtained in the cytogenetic studies because, lacking the facilities to process as many samples as the biochemical program, these studies concentrated on children of the more heavily exposed.) Thus, the biochemical experience to date with the children of the exposed corresponds to 17,363,093 locus-rems, given an RBE of 5. One probable mutation has been observed among the children of the proximally exposed, and none among the children of the distally exposed. At this stage, no rigorous statistical test of the difference between the two series is possible.

### Implications for the Genetic Doubling Dose of Radiation in Humans

Extensive experimental evidence attests to the genetic effects of radiation; thus there can be no doubt that some mutations were induced in the survivors of the bombings. The chromosomal damage seen in the survivors (*40*) also suggests that this is the case, as, given the correlation between carcinogenic and mutagenic exposures, do the data on increased incidences of leukemia and other malignant neoplasms in the survivors (*41*). Under these circumstances, since the effect may be presumed to exist, it seems permissible even in the absence of statistically significant results to use these data to generate an estimate of the effect. The most convenient way to phrase this estimate is in terms of the genetic doubling dose of radiation.

Any effort to estimate the doubling dose of radiation for mutation in man involves a series of debatable and sometimes tenuous assumptions. We will attempt to state these assumptions with clarity, so that if their basis changes, we or others will have a clear track to revised calculations. In experimental genetics, estimates of the doubling dose vary with the end point, stage of the germ cell at time of treatment, interval between treatment and observations, and so forth. Here we are denied such precision, but we derive a figure not available from experimental observations on mice, namely, an integrated estimate based on the children born over a 21-year period following the irradiation of a highly heterogeneous population.

*Doubling dose for untoward pregnancy outcomes.* Table 2, where the effects of as many extraneous variables as possible are factored out, suggests an increase of 0.00182 in untoward outcome per 100 gonadal rems. We suggested earlier that for Japan—during the interval covered by this study, characterized by an infant and childhood mortality rate of about 7 percent—we could assume that approximately one in each 200 live-born infants died before reaching maturity because of mutation (point or chromosomal) in the preceding generation (*9*). This estimate was based not only on the established frequency of newborns exhibiting the results of such mutations, but also on the frequency of a variety of still poorly defined, nonfamilial pediatric syndromes characterized by failure to thrive, mental retardation, and/or an unusual physiognomy that appear to be genetic in nature (*42–45*). We still believe that this estimate is valid, but to err on the conservative side we will reduce the figure to one in 400 and apply it not only to the survival data (treated in the next section) but also to the data on untoward pregnancy outcomes. Since 1 rem would increase untoward events by 0.0000182, the zygotic doubling dose is simply 0.0025/0.0000182, or 137 rems. Doubling doses are usually expressed as gametic doses. On the assumption of equal mutational contributions by both sexes, the gametic doubling dose would be 69 rems. The data exclude, at the 5 percent level (one-tailed test), a regression coefficient greater than 0.00712/100, which places a lower limit of 18 rems on the estimate of the gametic doubling dose.

Table 4. Increments or decrements in the frequency of death in the $F_1$ mortality cohort per 100 rems of gonadal exposure, based on an assumed neutron RBE of 5. The standard error of each regression coefficient is indicated in parentheses.

| Variable | Regression coefficient |
|---|---|
| Joint parental exposure | 0.000852 (0.002131) |
| Year of birth* | −0.002170 (0.004617) |
| Mother's age† | 0.009130 (0.008171) |
| Father's age† | −0.005156 (0.005534) |

*Change per year in year of birth. †Change per year of parental age.

*Doubling dose for death during infancy and childhood.* The data (Table 4) indicate an increase of 0.00085 in death during infancy and childhood per 100 rems of parental gonadal exposure. We use the estimate that in Japan, during the period covered by this study, one in 400 live-born children died in infancy or childhood because of spontaneous mutation in the preceding generation. The zygotic doubling dose is then 0.0025/0.0000085, or 294 rems, and the gametic, 147 rems, if we assume equal maternal and paternal contributions. The data exclude, at the 5 percent level (one-tailed test), a regression coefficient greater than 0.00435/100, which places a lower limit of 29 rems on the estimate of the gametic doubling dose.

*Doubling dose for sex chromosome aneuploids.* Although reliable data are available for the frequency of both balanced translocations and sex chromosome aneuploids, family studies on the children concerned are not yet complete, and we will base this estimate of doubling dose on sex chromosome aneuploids alone, since these are rarely inherited (*46*) and so for the great majority can be safely attributed to mutation. The frequency in the children of the distally exposed parents is 12/5,058, or 0.00237. The frequency in the children of the proximally exposed, resulting from an average gonadal dose of 87 rems at an RBE of 5, is 16/5,762, or 0.00278. Then the increase per rem is 0.00041/87 = 0.0000047 and the zygotic doubling dose becomes 0.00237/0.0000047, or 504 rems; the gametic doubling dose would be 252 rems. This calculation, of course, assumes linearity of the dose effect.

The reader familiar with our publications on the potential genetic effects of the atomic bombs will note that there has

Table 5. Occurrence of sex chromosome aneuploids in the children of exposed and control parents in Hiroshima and Nagasaki [after Awa (*32*)].

| Sex | Sex chromosome abnormality | Control | Father | Exposed mother | Both | Total |
|---|---|---|---|---|---|---|
| Males | XYY | 3 | 2 | 1 | | 3 |
| | XXY | 5 | 1 | 4 | 1 | 6 |
| | Other | | | 1 | | 1 |
| Females | XXX | 2 | 2 | 1 | 1 | 4 |
| | Other | 2 | | 1 | 1 | 2 |
| | | *Numbers examined* | | | | |
| Males | | 2,267 | 667 | 1,585 | 410 | 2,662 |
| Females | | 2,791 | 775 | 1,861 | 464 | 3,100 |
| Total | | 5,058 | 1,442 | 3,446 | 874 | 5,762 |

been no mention thus far of changes in the sex ratio as a possible indicator of altered mutation rates. We now feel that this is a more complex indicator than it appeared to be 25 years ago. The possible occurrence of exposure-related sex chromosome aneuploids, discussed in the previous paragraph, can be expected to alter the phenotypic sex ratio, but there is no simple theory that provides a precise expectation of the relative proportions of the sex chromosome phenotypes that would appear in newborn infants following an increase in sex chromosome nondisjunction. Furthermore, the phenomenon of Lyonization of the X chromosome in females tends to suggest that mutations which are expressed as sex-linked dominants in females receiving the mutation from their father are probably rare. One can argue that a study of the effect of maternal radiation should still yield important results. We have examined this aspect of the data in the present reanalysis. The regression of sex ratio on maternal exposure is not significant but positive in sign, that is, not in the direction predicted by the concept of an increase in sex-linked lethal mutations in exposed females. We see no way to "correct" these data for the occurrence of sex chromosome aneuploids and/or a Lyonization effect, and conclude only that these data do not contravene the relatively high doubling dose estimate that is emerging from the other indicators.

*Doubling dose for protein phenotypes.* The observed mutation rate in the children of the distally exposed is zero and in the children of the proximally exposed, on the basis of a single probable mutation, $0.34 \times 10^{-5}$ per locus per generation. This is not as yet the material from which to generate an estimate of doubling dose, but we can examine the data for consistency with the other available information. Elsewhere, we reported our failure to demonstrate any electrophoretic mutations in 105,649 locus tests on a U.S. population and 94,796 such tests on Amerindians (*47*), and Harris *et al.* (*48*) found no mutations in the equivalent of 113,478 locus tests based on an English population. Clearly, however, the mutation rate cannot be zero. The failure to demonstrate any mutations of this type in a total of 522,119 locus tests excludes, at the 95 percent level of probability, a mutation rate greater than $0.6 \times 10^{-5}$ per locus per generation in this combination of populations. If we very arbitrarily set the human rate at $0.2 \times 10^{-5}$, the figure emerging from investigations on *Drosophila* (*49–51*), the baseline expectation for the children of proximally exposed is 0.6 mutation. Thus, while the findings appear to be in the direction of hypothesis, they do not hint at any greater genetic susceptibility to the effects of radiation than that suggested by the other indicators.

*An "average" doubling dose.* These estimators of the effect of the atomic bombs are not independent of one another. For instance, there is some overlap between the mortality component in untoward pregnancy outcomes and the $F_1$ Mortality Study and, possibly, between the frequency of sex chromosome aneuploids and survival during infancy and childhood, but the precise correlation is unknown. Thus, no combination of the results into a single parameter whose statistical significance can be evaluated seems defensible. We may, however, average the results of our three estimates of the doubling dose, if no effort is made to attach an error term to that average. While such averaging may obscure real differences in the various end points, there is ample precedent, in the reports of various committees, for settling on a single index figure.

Two sorts of errors enter into the doubling doses we have generated. One sort derives from the estimator (regression or frequency), which may be in error by a factor of 2. The other derives from our assumptions, which may also be in error by a factor of 2. The simple average of our three estimates of the doubling dose is 156 rems. The fourth set of data, on electrophoretic variants, is still consistent with a wide range of possibilities but does not contravene the above estimate. While an error cannot be attached to this estimate, we surmise that the true value is unlikely to be less than 100 rems.

## Discussion

Four different measures of the potential genetic effects of the atomic bombs have been presented. For these measures, the differences between the children of proximally and distally exposed survivors is in the direction expected if a genetic effect had resulted from the experience, but no one of the findings is statistically significant. Since, however, the hypothesis of the genetic effects of radiation is not at issue but may be regarded as a fact, we used these differences between the two groups of children to calculate the doubling dose for radiation of this type.

The results of these analyses do not differ qualitatively in any important way from those of previous analyses of portions of these data. No statistically significant effects of parental exposure were observed earlier, and none are now. The important difference is that only now is it possible with any precision to relate the findings to gonadal doses in rems.

For certain of the indicators, the design of the analysis permits comparing the magnitude of the radiation effect in the first generation to parameters such as inbreeding and multiple births. For what we have defined as untoward pregnancy outcomes, we find that 100 rems of radiation to either parent or distributed over both parents produces an effect equivalent to about one-fifth of 1 percent inbreeding and a very much smaller risk than being one of twins.

A number of assumptions must be made in calculating the human doubling dose, and we have stated them in considerable detail. However, the errors involved under these assumptions and with these data are apt to be no greater than those involved in the current practice of extrapolating to humans data on the mouse, an animal whose spontaneous and induced mutation rates may both differ from human rates. Our assumptions are generally conservative; that is, they should bias the estimate of the doubling dose downward. Furthermore, the data on untoward pregnancy outcomes are limited to the 6 years from 1948 through 1953. If fewer mutations are found in offspring conceived a considerable time after maternal radiation, as is the case in the mouse (*52, 53*), then our data exaggerate the overall genetic effect of maternal radiation and so bias our estimate of doubling dose downward.

Only three of the four indicators lend themselves, at this stage in the study, to estimates of doubling dose. The average of the three estimates is 156 rems for this complex of indicators. For acute, low-LET radiation, the average doubling dose in the mouse for a variety of end points is 30 to 40 rems (*54*), and for want of estimates on man such a value has been cautiously applied to the human situation by a variety of committees and commissions. Even with all possible allowance for the imprecisions in both estimates, the preliminary estimate presented here seems "significantly" higher. It is perhaps important to bear in mind that whereas the doubling dose estimates for the mouse have been based on carefully contrived tests of mutation at specific loci, our present estimates are based more on the vital statistics of comparison populations, and even for

the mouse, efforts to demonstrate an impact of large amounts of radiation on such characteristics as litter size, survival, and body weight have yielded conflicting results (*55*).

In general, human exposure to radiation will not be acute and of the magnitude experienced by the inhabitants of Hiroshima and Nagasaki, but either interrupted or chronic, and at much lower levels. Under these circumstances, the genetic yield of chronic radiation in mice is approximately one-third that of acute radiation (*26–28*). If mice and people are similar in this respect, the doubling dose for human chronic exposures suggested by these data becomes 468 rems, in contrast to the estimate of 100 rems for low-LET, low-dose, low-dose-rate exposure recently adopted by a committee of the International Commission on Radiological Protection (*43*; see also *27*).

Data continue to be collected on three of the indicators discussed in this presentation, namely, survival of children, frequency of sex chromosome aneuploids, and frequency of electrophoretic (and other forms of biochemical) variants. We presume that in time these additional data, in conjunction with a better understanding of the human genetic baselines, will lead to improved estimates of the doubling dose for the various genetic end points employed in this study. We suggest, however, in view of the public concern about the genetic effects of low-level radiation, that an intensive effort be mounted to determine whether the challenge the data we have reviewed presents to "conventional wisdom" is valid. This effort should involve the development of better techniques for the study of germinal mutation and the identification of other key populations for study.

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1a. A variety of physical and biological measures of ionizing radiation are currently used. We shall employ three here: kerma, rad, and rem. Kerma (kinetic energy released in material) describes the kinetic energy transferred to material, biological tissues in this instance, as radiation particles interact with that tissue. A rad is the unit of absorbed dose, that is, the energy actually imparted to matter at the site of interest by ionizing radiation. Note that kerma and rad are equal if all energy released by a particle as it interacts is locally deposited. Finally, the rem (roentgen equivalent man) is a unit of dose equal to the quantity of radiation of any type that produces in man the same biologic effect as 1 roentgen of gamma rays. Simply put, it is the absorbed dose of a given type of radiation multiplied by its relative biological effectiveness.

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