REVIEW

The children of atomic bomb survivors: a synopsis

INSTITUTE OF PHYSICS PUBLISHING JOURNAL OF RADIOLOGICAL PROTECTION

J. Radiol. Prot. **23** (2003) 369–384 PII: S0952-4746(03)70534-5

REVIEW

The children of atomic bomb survivors: a synopsis

William J Schull

The Human Genetics Center, School of Public Health, University of Texas Health Science Center, Houston, TX 77225, USA

E-mail: w.schull@att.net

Received 20 April 2003, accepted for publication 25 July 2003
Published 8 December 2003
Online at stacks.iop.org/JRP/23/R369

Abstract

When the atomic bombing of Hiroshima and Nagasaki occurred in the summer of 1945, most members of the public presumed that many of the children conceived by the survivors would be grossly deformed or seriously damaged in other ways as a consequence of radiation-induced mutations. Although the experimental data then available, largely limited to studies of *Drosophila melanogaster*, the common fruit fly, did not support this perception, the limitations of the data and the depth of public concern warranted a careful follow-up of the children born to the survivors. To this end a surveillance was begun in 1947 of all pregnancy outcomes after 20 weeks of gestation in these two cities. Over the half century subsequent to the initiation of this surveillance, some 80-odd thousand pregnancy outcomes have been studied and a variety of potential indicators of mutational damage measured. This report summarises the findings of these studies and offers an estimate of the genetic risk based on these findings.

1. Introduction

In the autumn of 1945, when studies began to evaluate the physical and biological damage from the atomic bombing of Hiroshima and Nagasaki, public concern focused more on the genetic consequences than any other untoward health outcome. A wealth of experimental evidence existed attesting to the mutagenic effects of ionising radiation on such diverse plant and animal species as *Drosophila melanogaster* (the fruit fly), *Zea mays* (corn) and even *Habrobracon juglandis* (the solitary wasp). This evidence suggested that the increase in mutations was linearly related to dose; obviously implying that any dose, however small, would have genetic consequences. While it was assumed that the same must hold true for the human species, it was the nature of these consequences and not the linearity with dose that disturbed the public. Many individuals had visions of an epidemic of births culminating in misshapen monsters or infants condemned to early death for other, less dramatic, genetic reasons. An objective

understanding of the effects was needed and to achieve this it would be necessary to estimate, if possible, the number of newly arisen radiation-induced mutations, and to determine their long-term public health impact.

Two strategies suggested themselves. First, one could undertake a specific locus study, as had been commonly done in the experimental studies cited above, or second, one could pursue a study of the birth characteristics of concern to the public, specifically congenital defects and early death. Each of these alternatives has its advantages and limitations. The specific locus approach has the merit of leading to an estimate of the probability of mutation at one or more definable genetic loci, but to be truly informative, the sampling error of this estimate must be small, and this entails a very large number of locus tests. More precisely put, the product of the number of loci under study times the number of newly born infants tested times the probability of a mutation per locus per unit exposure times the average dose must be sufficiently large to result in a statistically demonstrable increase in the number of mutations over that expected in the absence of exposure. Given the experimental evidence bearing on the probability of a radiation-induced mutation (about 3×10^{-8}/gene/roentgen), the number of specific loci then known in the human (<10), and the number of newly born infants to be anticipated each year in these cities at that time (possibly 6000–7000 births/year/city), 'back of the envelope' calculations were sufficient to demonstrate that this approach was impractical. One could not achieve enough locus tests in a reasonable period of time to provide acceptable 'stability' to the estimated mutation rate. Accordingly, the early genetic study focused on a clinical assessment of the health of the children born in these two cities to the survivors and to unexposed parents. This approach had the merit of addressing the public's apprehensions directly, but it could not yield an estimate of the probability of mutation at specific genetic loci.

The design of an appropriate study of birth outcomes in these cities was not trivial. Both were physically devastated and economically impoverished, and could offer little in the way of supportive resources. Thus, the study had to be logistically self-sufficient, yet flexible enough to accommodate future scientific developments of moment. The design that emerged hinged heavily on three circumstances then obtaining in Japan. First, food rationing, established in the course of the war, continued. However, it was possible for pregnant women, upon registering their pregnancies with the proper local governmental office, to obtain rationed food to sustain themselves and their unborn offspring. Registration could occur at any time after a woman was aware that she had conceived, but the supplemental rice ration was only authorised after the 20th week of pregnancy. As a result, it was the usual practice to register pregnancies after the onset of the 5th lunar month and not before[1]. With the approval of the local Japanese health authorities, a programme was initiated wherein these mothers-to-be enrolled their pregnancies with the Atomic Bomb Casualty Commission (ABCC), the agency charged with the follow-up studies, when they registered with the municipal authorities. To simplify this dual registration, ABCC's clerks were stationed at the city offices, where ration registration occurred. In addition to identifying the mother and father, these clerks obtained data on parental exposure, previous reproductive performance, and the expected date of confinement of the mother for the current pregnancy. The form on which this information was recorded was completed in duplicate; one copy was given to the pregnant woman or her representative and the other retained by the ABCC. The pregnant woman was encouraged to give her copy to the attendant at her delivery who then recorded the infant's life status, birth weight, and some particulars associated with the delivery itself.

[1] This fact made the study of the possible association of early embryonic and foetal loss with dose difficult, and the data that were collected are ambiguous.

Second, at that time, most births occurred at home in the presence of a midwife. Of necessity, the surveillance program would depend heavily upon the involvement of the midwives and home visits. However, a midwife could not be expected to recognise and describe all of the possible congenital malformations that might arise. It was essential, therefore, that each newborn infant be seen by a physician as soon as possible after birth.

Third, the education of physicians had been accelerated during the war to meet the requirements of the country's military. With defeat and the economic stringencies it brought, many of these young physicians were unemployed. They provided a reservoir for the recruitment of physicians to meet the Commission's needs.

Registrations began in the spring of 1947 and in the succeeding 6 years over 76 000 pregnancies were studied, approximately evenly distributed between the two cities. Throughout these years, completeness of registration and the accuracy of the information were constant concerns. To assess completeness, ABCC's data were periodically compared with the birth records of the city, and the midwives were encouraged to report all births, including those to unregistered mothers. Often these unregistered births involved infants born out of wedlock, or occurred to mothers who were registered in other communities or who simply 'forgot' to register. Evaluation of the accuracy of the general information obtained at the time of registration or the home visit was more difficult, and could only be done by comparing successive registrations, where this occurred, or through comparison of the information obtained on the parents with that obtained on these individuals through other studies of the Commission.

Accuracy of the clinical information could be assessed through comparison of the diagnostic findings at the time of the home visit with those made at the follow-up clinic[2]. This was routinely done. But other sources of information existed to assess, albeit indirectly, the accuracy of the diagnoses of congenital defects. For example, the findings on the children born to nonexposed parents could be and were compared with other studies on the occurrence of malformations among Japanese living elsewhere. The largest and most extensive comparison study occurred at the Tokyo Red Cross Maternity Hospital. It involved 49 645 births in the years from 1922 through 1940. The frequency of major birth defects in this series and in our own was surprisingly good when the comparison was restricted to the same diagnoses, 0.88% versus 0.85%.[3]

Inevitably, as the genetics study progressed, other problems arose. One disturbing matter was the changing attitude and policies of the Japanese government toward the growth of its population. Families were encouraged to have fewer children, and as an inducement, in 1948 the government liberalised the legal basis for the artificial termination of a pregnancy. This act allowed a pregnancy to be interrupted if it was deemed likely to lead to a severely handicapped individual (the so-called eugenics clause), posed a serious threat to the mother's health or created an intolerable economic burden on the family. Although use of the provisions of the law was voluntary, to avoid capricious implementation the circumstances under which each of these alternatives could be invoked were defined. To abort a pregnancy for economic reasons, the family had to be receiving governmental assistance. To utilise the eugenics clause, the likelihood of an untoward pregnancy had to be evaluated by a committee of physicians.

[2] Not all congenital defects of import are readily recognisable at or shortly after the birth of an infant. Cognisant of this limitation of newborn examinations a second examination of a randomly selected subset of infants occurred between 8 and 10 months after birth. This examination took place in the clinical facilities of the Commission.

[3] It should be noted that a hospital series in Japan at that time was unlikely to be a random sample, but probably included a disproportionate representation of complications of pregnancy. Moreover, certain of the malformations such as hydrocele, congenital teeth and partial albinism, which were included as major malformations in the Tokyo series, were seen as minor by the Commission. When these diagnoses are included in the 'raw' estimate from the Tokyo series, the correspondence is somewhat poorer, 0.92% versus 0.85%.

However, the threat a pregnancy constituted to the mother's health was a matter of the clinical judgment of her personal physician. Since any pregnancy entails some risk, most of the abortions performed were authorised under this provision, the easiest to satisfy.

Pregnancies were usually terminated between the 4th and 8th week in a doctor's office. Under the law, these terminations were to be reported to the local health offices, but no means of systematic enforcement of this requirement was mandated. It was very difficult, therefore, to obtain a reliable estimate of how many pregnancies were being aborted. The limited data available suggested that almost as many pregnancies were being aborted in Hiroshima each month as came to term, and presumably the same held true in Nagasaki. This had huge implications for the study—a precipitous fall in the birth rate could compromise collecting sufficient data to evaluate the radiation hazard or, if pregnancies were more likely to be aborted when one or both parents had been exposed, could introduce biases that would be difficult to manage. Fortunately, economic considerations, and not the fact of exposure, were the major determiners of a family's decision to abort a pregnancy. Nevertheless, a significant drop in the birth rate did occur. Japan's crude birth rate fell from 30 or so per 1000 individuals in 1950 to about 16 in a period of roughly 5 years.

This clinical surveillance ended in the spring of 1954, after it was clear that those individuals who were adults at the time of their exposure were completing their fertility[4].

2. Pregnancy outcome

The indicators of possible genetic effects that can be drawn from the physical examination of newborns are gender, birth weight and prematurity, presence of compromising or life-threatening malformations, occurrence of death during the neonatal period, i.e. the first month of life following birth, and growth and development. Among the 76 000 pregnancies studied, not all could be used to analyse the relationship of these indicators to radiation. Some 3264 of the pregnancies reported to us were not registered with the municipal authorities in Hiroshima or Nagasaki. These cases were excluded for it was unclear how complete the reporting of unregistered births was. Occasionally the data were incomplete in other ways, such as in recording the age of a parent, or the birth weight of the infant, or the information on the mother, the father, or both was inadequate to determine their exposure status and possible dose. These cases were also excluded.

The findings on the pregnancy outcomes can be summarised under the rubric 'untoward pregnancy outcome'. The latter includes pregnancies that ended in a child with a major congenital defect, that was stillborn, that died during the first week of life or some combination of these events. Among the 70 073 pregnancies available for analysis, parental gonadal doses could not be computed on 14 770 (Otake *et al* 1990). To avoid the loss of information inherent in the pregnancy outcomes where DS86 parental doses were lacking, two analyses were undertaken—one (table 1) based on 69 706 pregnancies, including 14 403 pregnancies where DS86 doses were not available but a tentative dose could be assigned pending completion of efforts to provide DS86 doses (no dose could be assigned, even tentatively, to 367 of the 70 073 cases) and the other (data not shown) based on the 55 303 pregnancies where the parental doses were known. The increase in frequency of untoward pregnancy outcome in the larger sample (as measured by the slope of the dose–response relationship after adjustment for extraneous sources of variation) was 26 cases per 1000 000 pregnancies to parents who

[4] The decision to terminate the study was based on the advice of an *ad hoc* committee; however, the committee recommended that further data be collected on the survival of newly born infants and on the sex ratio—the proportion of pregnancies leading to the birth of a male infant.

Table 1. The change in the frequency of untoward pregnancy outcomes in the original cohort of births per sievert of joint parental gonadal dose equivalent based upon an assumed neutron relative biological effectiveness (RBE) of 20, extended (DS86 + *ad hoc*) cohort (after Otake *et al* (1990)).

Variable	Regression coefficient	Standard error
Regression model: $P_i = \text{constant} + \sum_{j=1}^{6} b_j x_{ij}$ (background) $+ b_{\mathrm{D}}$ dose$_j$		
	Background effects	
Constant	0.038 56	0.005 82
City	0.001 00	0.001 67
Sex	0.002 38	0.001 65
Mean age of father	−0.000 23	0.000 20
Mean age of mother	0.000 34	0.000 28
Birth order of child	0.000 19	0.000 66
Year of birth	0.001 79[a]	0.000 55
	Excess risk	
Joint parental exposure	0.002 64	0.002 77
cov(constant, dose) $= -0.2827 \times 10^{-9}$ corr(constant, dose) $= -0.0175$ background effects		

[a] Significance level: $P < 0.01$.

had received gonadal doses of 0.01 Gy or more[5]. The smaller sample, where the doses were more reliable, suggested a slightly greater increase—42 cases per 1000 000. A large statistical error is associated with both of these estimates, but this fact notwithstanding, the public health burden these additional cases impose must be judged in the context of the number of untoward pregnancy outcomes to be expected had the parents not been exposed, a very much larger number.

An alternative to accepting these values literally is to ask what is the lower limit of the dose that would double the risk? To obtain this value one reasons as follows: the excess relative risk is merely the ratio of the increase in untoward pregnancy outcome per sievert to their naturally occurring frequency in the absence of exposure to radiation. Since the increase expressed per sievert is 0.002 64 and the background rate is 0.038 56 (see table 1), this ratio is 0.0685. The sampling error of this ratio is 0.0726, and hence the plausible upper limit of the ratio (commonly calculated as the value which would be exceeded only one time in 20 by chance alone) is about 0.19 (taking the ratio plus 1.64 times its sampling error). Since the lowest plausible dose that would double the risk of untoward pregnancy outcome is associated with the highest plausible excess risk suggested by the data and since the doubling of the risk is by definition that dose at which the radiation-related contribution is equal to the background, the lower limit to the dose, D, that would double the risk suggested by these data, is about 0.2 Sv (or $0.038\,56 = 0.19D$). Or to return to the original aim—to determine what range of doses would be unlikely to double the risk—we can exclude doses below 20 cSv.

[5] It warrants noting that the results described for untoward pregnancy outcome are not materially altered if malformations, stillbirths or neonatal deaths are analysed separately. No one of these three end points is significantly associated with parental exposure (see table 2). The most common abnormalities, exclusive of congenital heart disease, were anencephaly, harelip with or without cleft palate, cleft palate alone, club foot, polydactyly and syndactyly. These seven abnormalities accounted for 445 of the 594 malformed infants born to parents who were not related to one another. As to stillbirths, Parker *et al* (1999) have reported a statistically significant association of such births with the doses of ionising radiation received by men working at the Sellafield nuclear facility in Cumbria. However, their findings have been challenged on the grounds that they are incompatible with not only the Japanese data but the findings of other investigators as well (see Little (1999) and Abrahamson and Tawn (2001)).

Table 2. The change in the frequencies of congenital malformations, stillbirths, and neonatal deaths in the original cohort of births per sievert of joint parental gonadal equivalent based upon an assumed neutron RBE of 20, extended (DS86 + *ad hoc*) cohort (after Otake *et al* (1990)).

Variable	Regression coefficient	Standard error
Regression model: $P_i = \text{constant} + \sum_{j=1}^{6} b_j x_{ij}$ (background) + b_D dose$_j$		
Malformation		
Joint parental exposure	0.001 01	0.001 54
Birth order of child	0.000 64[a]	0.000 36
Year of birth	0.001 31[b]	0.000 28
Stillbirths		
Joint parental exposure	0.000 92	0.001 63
Birth order of child	−0.000 59	0.000 38
Year of birth	−0.000 28	0.000 32
Neonatal deaths		
Joint parental exposure	0.001 28	0.001 85
Birth order of child	0.000 26	0.000 43
Year of birth	0.000 68[a]	0.000 37

[a] Significance level: $P < 0.10$.
[b] Significance level: $P < 0.01$.

3. Mortality after birth

When originally constructed, the F_1 mortality cohort consisted of 52 621 live, single births where the exposure of both parents was known[6]. To this group has been added 22 984 births in the years from January 1959 to December 1983, of which 11 196 were to parents of known exposure status. Most of these latter parents were too young at the time of their exposure to have had children in the years prior to the selection of the original three groups. Deaths within the study population are identified through examination of the obligatory family register (the *koseki*)[7]. Altogether the original cohort and the extension consists of 76 817 live births, but of these 3589 were excluded because they did not have Japanese citizenship (and could not be followed through the *koseki* system) or because the information available on parental exposure was inadequate to compute a dose. Among the 72 228 remaining individuals, the exposures of both parents can be estimated directly in 67 586 cases, and indirectly in 4642 instances.

Among those 67 586 children whose parents have directly estimated DS86 doses, there were 3852 deaths. When the frequency of noncancer deaths (2766), exclusive of those ascribed to accident or suicide (584) or unknown cause (359), is related to parental dose considered jointly, the deaths increase slightly, but not statistically significantly so, as dose increases[8]. The excess relative risk of death at all ages due to causes other than cancer at 1 Sv is 0.030 (±0.046). If this risk is computed on the basis of only those deaths occurring before age 20 (some 73% of the sample had attained this age in 1985), the excess relative risk is somewhat higher (0.038) (Yoshimoto *et al* 1991).

[6] The original cohort consisted of three equal groups, namely about 18 000 children born to parents (a) one or both of whom were exposed within 2000 m of the hypocentre, another group matched by city, sex and age to the first whose parents were (b) 2500 m or more from the hypocentre, and finally a third group similarly matched by city, sex and age of whom neither parent (c) was present in Hiroshima or Nagasaki at the time of the bombing.

[7] All vital events affecting the composition of a family—such as births, deaths, marriages, adoptions—must be reported to the office having custody of the family's *koseki*.

[8] Of those deaths without known cause, 322 occurred in the first year of life, and could have been due to infantile diarrhoea, respiratory diseases or other infections, but this is not certain.

Given the relationship of mutations (somatic as well as germinal) to cancer, it is interesting to note that of the 2881 deaths attributed to disease (that is excluding deaths from unknown causes, accidents or suicide, or unknown tumours), 115 were ascribed to cancer. The most common of these cancers was leukaemia; 44 of the 115 cancer deaths were due to this malignancy and 30 of these 44 resulted in death before the age of 20. However, no clear trend in the occurrence of either leukaemia or other cancers before the age of 20, or after, with increasing parental dose exists as yet (Yoshimoto *et al* 1990).

As in the case of untoward pregnancy outcomes, doses can be estimated at which the added risk of cancer or of noncancer deaths would be doubled. However, to provide an estimate of the doubling dose for noncancer deaths that is independent of the one for untoward pregnancy outcome, those deaths occurring in the first 14 days of life in the years 1948–1953 must be excluded, since these deaths are already included in the estimate for untoward pregnancy outcomes. When this is done, and account is taken of the fraction of such deaths ascribable to mutation in the previous generation, the lower bounds (90%) for the doses that would double the rate of occurrence of cancer and noncancer deaths are 0.07–0.15 and 0.81–1.32 Sv respectively.

It is important to note that although others (see, for example, Gardner *et al* (1990))[9] have alleged an association of leukaemia with preconception exposure a significant increase in leukaemia with parental exposure has not been seen in Hiroshima and Nagasaki.

4. Chromosomal abnormalities

Exposure to ionising radiation results in an increased frequency of the failure of chromosomes to separate. This event is termed nondisjunction and results in one of the two daughter cells arising from cell division lacking a chromosome, whereas the other cell has one more chromosome than normal. Individuals with one, two or a few chromosomes more or less than the normal number are said to be aneuploids. Aneuploidy may involve the autosomal chromosomes, i.e. 1–22, or the X or Y chromosomes. In general, abnormalities of the X or Y chromosome are less life-threatening than abnormalities of the other chromosomes. In addition to aneuploidy, chromosomal rearrangements, where material from one chromosome is transferred to another, are possible. Rearrangements are either balanced, if the total chromosomal material is unchanged, or unbalanced, if chromosomal material is lost or gained.

Two separate studies of Down syndrome (trisomy 21) and one of the syndromes associated with sex chromosomal aneuploidy have been made. Neither of the studies of Down syndrome found evidence of a relationship between maternal irradiation and this disorder (Schull and Neel 1962, Slavin *et al* 1966). The study of sex chromosomal aneuploidy conducted in Hiroshima was based on a search for sex chromatin abnormalities in cells taken from the lining of the mouth (Omori *et al* 1965). This survey revealed no cases of Turner syndrome—individuals who appear to be females on the basis of their external genitalia but have only one X chromosome—among some 2660 females examined, but three cases of Klinefelter syndrome—individuals who appear to be males but actually have more than one X chromosome—were seen among the 4481 males examined. None of the three, however, were conceived by parents exposed to the bombing of Hiroshima or Nagasaki.

To offset the limitations of the studies just described, a more systematic cytogenetic investigation of the children of exposed parents was begun in 1967, the subjects being drawn from the cohorts established for the F_1 mortality study (Awa *et al* 1988, Awa 2003). Since

[9] The findings of Gardner and his colleagues precipitated an active, occasionally acrimonious debate as to their cause (see Abrahamson (1990) and Little (1990), for examples). The prevailing opinion favours a nonradiation origin.

Table 3. The frequency of sex-chromosome aneuploids among the children of the survivors of the atomic bombing of Hiroshima and Nagasaki as a function of the combined parental doses, based on the DS86 (adapted from table 3 of Neel *et al* (1990)).

Combined parental dose (Sv)	Number of children	Mean dose (Sv)	Number of aneuploids	Per cent
0.0	8 225	0	24	0.29
0.001–0.050	1 346	0.024	0	—
0.051–0.100	951	0.073	2	0.21
0.101–0.500	2 693	0.263	9	0.33
0.501–1.00	1 531	0.719	3	0.20
1.01–1.50	686	1.227	2	0.29
1.51–2.00	295	1.716	1	0.34
2.01–2.50	157	2.228	0	—
2.50+	331	3.674	2	0.60
Unknown	83		0	—
Total	16 298		43	0.26

children younger than 12 were not enrolled in the cytogenetic study (venepuncture was viewed as too traumatic for younger children), the survey does not yield adequate data on the frequency of chromosomal abnormalities such as unbalanced autosomal rearrangements and autosomal trisomies where death commonly occurs before the age of 12. The data on sex chromosomal abnormalities and balanced autosomal rearrangements should, however, be relatively unbiased, since these abnormalities are not associated with early mortality as stated previously. Awa (2003) has reported the frequency of sex chromosome abnormalities and autosomal structural rearrangements among 8322 children of exposed parents and 7976 children of 'controls' (parents exposed beyond 2499 m at the time of the bombings). He notes that 'among the children born to exposed parents, 19 individuals (0.23%) exhibited sex chromosome abnormalities and 23 (0.28%) exhibited autosomal structural rearrangements; whereas among the children of unexposed parents, 24 (0.30%) and 27 (0.34%), respectively, were observed to exhibit these abnormalities'.

These findings would seem to suggest that sex chromosome abnormalities actually decrease with exposure, but a simple comparison of the exposed with the unexposed is misleading. When the frequency of sex chromosome abnormalities is examined in terms of the combined gonadal dose received by the parents, the frequency increases slightly, albeit not statistically significantly so, with combined parental dose (table 3)[10]. The rate of increase in sex chromosome abnormalities expressed as the change in per cent per sievert is 0.044 ($\pm$0.069), and the estimated background rate is 0.252 ($\pm$0.044). Stated somewhat differently, these numbers imply that among 10 000 children whose parents were not exposed one would expect to encounter 25 with a sex chromosomal abnormality, whereas if their parents had been exposed to 1 Sv that number would rise to about 29. No similar analysis is possible for the autosomal structural rearrangements, since so few of these appear to be mutations—most were also present in one or the other of the parents of the child with the chromosomal abnormality.

Among the balanced rearrangements involving different autosomal chromosomes, the majority were either reciprocal translocations, Robertsonian translocations or pericentric inversions. Most of these rearrangements (90%) could not be ascribed to newly arisen

[10] The most commonly encountered sex chromosomal anomalies were males with Klinefelter syndrome (XXY) and females with an additional X chromosome (XXX). Both of these disorders are associated with infertility and a variety of clinical signs that can differ in their severity, ranging from normality or near normality to an obvious physical defect.

chromosomal mutations, as stated above, since the same defect was often found in the lymphocytes of one or the other of the two parents. While family studies were not possible on all of the children with balanced structural changes, because one of the parents had died, lived outside the contact area or refused to participate, they did occur in 27 out of 43 cases, and among these 27 only two appeared to be new mutations, one in the proximal group and one in the distal.

5. Biochemical studies

Electrophoresis created a new means to identify abnormal protein molecules in the assessment of the genetic effects of atomic bomb exposure. Its utility rests on the fact that proteins carry an electrical charge—whether this charge is positive, negative or absent depends upon the specific amino acids that make up the protein. If mutation results in an alteration of the composition of a protein, one reflected in the charge of that protein, electrophoresis might show that the protein has been altered structurally. Such alterations are called electrophoretic variants or structural mutations. If there is no alteration in charge, or if the alteration does not produce a band that can be visualised electrophoretically, electrophoresis will be uninformative. Similarly, if the mutation results in a failure to specify a protein at all, electrophoresis will be uninformative, since there will be no protein to migrate. The latter mutations are described as deficiency variants or 'null' mutations.

These deficiency variants or null mutants are recognised through a diminution in enzyme activity when the latter is measured under standardised conditions. Assessing enzymatic activity manually is tedious and error prone, and was not a promising avenue of investigation until the centrifugal fast analyser was developed. This device can automatically load, mix, and analyse 30–40 specimens at a time, and has made possible the study of not only a large number of specimens but numerous enzymes as well. But, it has some limitations. It can be applied only to those enzymes whose activity is measurable spectrophotometrically. Moreover, if the variability that normally occurs between specimens from different individuals is too large, the diminution in activity associated with a new null mutant may not be separable from the background variability.

This biochemical approach, like the cytogenetic one, is free of many of the ambiguities inherent in the study of population characteristics, and has, as a result, been vigorously pursued[11]. A full-scale investigation employing electrophoretic techniques was begun in Hiroshima and Nagasaki in 1976. The subjects were drawn from the groups of children identified for the mortality study previously described. The same blood sample served the needs of the biochemical and the cytogenetic programmes. Most of the proteins easily studied in blood specimens are enzymes, found either in the red blood cells or in white cells, but some nonenzymic proteins in the serum can also be studied electrophoretically. Accordingly, each child was examined for rare electrophoretic variants of 28 proteins of the blood plasma and red cells, and a subset of these children were also examined for deficiency variants of nine of the red-cell enzymes.

[11] It was recognised at the outset that this approach, although entailing a massive amount of work, would have little discriminatory power if the information at our disposal was correct. This can be illustrated as follows: if one assumes that (a) the induced mutation rate per codon per 0.01 Sv is about 1 in 100 000 000, (b) 200 codons are needed to specify the structure of the average enzyme and (c) 28 enzymes can be tested on (d) 20 000 individuals whose parents received an average exposure of 0.20 Sv, then fewer than 11 new mutations would be expected. Of these only a third or so would be detected electrophoretically. These three or four potentially recognisable variants would be hidden, as it were, in 1120 000 tests. While the numbers cited are merely approximations to the actual observations, they cannot be wrong by much and if the 'true' mutation rate is lower than suggested, the expected number of mutants is smaller still.

A rare electrophoretic variant is defined in this context as one with a frequency of less than 2% in the population and an 'enzyme deficiency' or 'low activity' variant as one resulting in an enzyme activity level three standard deviations below the mean (or less than 66% of normal activity). When either variant is encountered, its occurrence is verified, i.e. the possibility of a technical error is excluded, and then blood samples from both parents are examined for the presence of a similar variant. If the variant is not found in one or other of the parents, and if an error in assigning parentage is improbable, it presumably represents a new mutation. To establish parentage, since *a priori* the probability that the putative parents are not the real parents is several orders of magnitude larger than the probability of a new mutation, some 11 different red cell antigenic systems and the major histocompatibility phenotypes, the HLA system, were used to search for evidence that the putative parents were not the actual parents of the child. While such testing does not prove parentage, it can only exclude falsely identified parents, the battery used was sufficiently large that the *a priori* probability of failing to detect a falsely identified parent was approximately the same as the *a priori* probability of a new mutation.

Neel *et al* (Neel *et al* 1988) have estimated that they have information on the equivalent of 667 404 locus tests on 13 052 children born to parents whose average combined gonadal dose is about 0.47 Sv. Three probable mutations were seen[12]. Three mutants were also seen in the equivalent of 466 881 locus tests on 10 609 children whose parents (one or both) were exposed beyond 2499 m and received less than 10 mSv.[13]

Satoh *et al* (Satoh *et al* 1983) have reported the results of the 122 270 determinations, distributed over nine enzymes, to assess the impact of parental exposure on the frequency of 'deficiency variants.' One probable mutant in 60 529 locus tests on 4989 children whose parents (one or both) received more than 0.01 Sv of radiation was seen, but none among the 61 741 tests on the 5026 children of distally exposed parents. The one apparent mutant involves the enzyme triosephosphate isomerase.

Thus, after more than 1256 000 biochemical tests, when the results of the studies of structural and activity variants are combined, four mutants have been seen among the children of parents receiving more than 0.01 Sv, and three among those whose parents received less than 0.01 Sv. The mutation rates in the two groups of children are almost identical; the values are 0.60×10^{-5} mutations per generation in those who are the offspring of parents receiving more than 0.01 Sv of gonadal exposure, and 0.64×10^{-5} in those whose parents received less than 0.01 Sv. The confidence intervals for these two estimates are $(0.2–1.5) \times 10^{-5}$ and $(0.1–1.9) \times 10^{-5}$ respectively.

6. The growth and development of these children

At the time of the initial clinical studies of these children measurements were obtained to characterise their growth and development in the first 9 months or so of life. Four measurements were made—height, weight and head and chest circumference. Analysis of these in 1956 did not reveal any systematic impairment of growth and development with increasing parental exposure.

Later, when these children were 6–17 years old, their growth and development was reassessed using the measurements of stature, weight, sitting height and chest circumference routinely obtained each year in the public schools in Hiroshima. At this time, T65 doses

[12] These mutations involved a slowly migrating variant of the enzyme glutamate pyruvate transaminase, a slowly migrating variant of phosphoglucomutase-2 and a variant of nucleoside phosphorylase.

[13] These mutants involved the proteins known as haptoglobin, 6-phosphogluconate dehydrogenase, and adenosine deaminase.

were available for most of their parents. Again, no evidence emerged of a radiation-related retardation in their development (Furusho and Otake 1978a, 1978b, 1979, 1980, 1985).

Neither of these sets of data has been reanalysed with the new (DS86) dosimetry, and it is debatable whether such an analysis is worthwhile. The absence of any trend of impairment with dose in the first year of life or later makes it improbable that one would be found now.

7. The sex ratio

When the genetic studies began, it was believed that individuals inheriting an X chromosome from their father and one from their mother were destined to be females; whereas those individuals who inherited a Y chromosome from their father and an X from their mother would be males. These notions suggested, in turn, that when mutations induced in the X chromosome by ionising radiation are lethal, their expression would be manifested differently in the two sexes and would depend, partly, upon whether the X chromosome was inherited from the mother or the father. More specifically, since a father transmits his X chromosome to his daughters exclusively, if a lethal mutation were present on the X chromosome in the father's sperm, it would find expression only in his daughters. Whereas, since mothers transmit their X chromosomes equally to their sons and daughters, a lethal mutation might find expression in either sex. If the mutation was dominant, that is, expressed itself if only one copy was present, the two sexes would be affected equally often; however, if the mutation was recessive (normally requiring two copies for expression), since the male has only one X chromosome, it would manifest itself in males, but in females manifestation of the new mutant would occur only if the second X chromosome fortuitously carried a functionally similar gene. It follows from these thoughts that since the likelihood of a mutation increases as dose increases, if the father was exposed, more female embryos would be lost, and at birth the relative proportion of males would be greater than would be true if the father was not exposed. If, on the other hand, the mother was exposed, more male embryos would be lost, and at birth the relative proportion of males would decrease. If both parents were exposed, the resulting proportion of male births, would be related to the individual parental doses and the frequency of dominant versus recessive lethal mutations. As can be seen, this theory made fairly specific predictions that could be compared with the actual observations that were accumulating.

When the data from the initial study were examined, it appeared that the proportion of male births was, in fact, declining with dose when the mother was exposed, and increasing, albeit modestly, with increasing paternal dose. The rate of change with dose was not, however, statistically significant, although in the direction predicted by theory. It was for this reason that when the clinical phase of the studies ended, data on the sex ratio continued to be collected on the supposition that the rate of change might become statistically significant with further information. To this end, observations on the frequency of male births were continued through 1966. However, when these additional observations were analysed, the results did not support the earlier findings; the modest changes seen were opposite to those predicted by theory (Schull *et al* 1966).

Today, the earlier arguments regarding sex determination are known to have been overly simple. First, they did not take into account the occurrence of X chromosome aneuploids, e.g. the Klinefelter and Turner syndromes, which might confuse the determination of the sex of an individual as revealed by a clinical examination shortly after birth. Individuals with abnormal numbers of X chromosomes are more frequent in most populations than one would expect new sex-linked radiation-induced lethal mutations to be, at least at the dose of the average survivor. Second, it is now known that in females only one of the two X chromosomes within a cell is functionally active. This inactivation of one of the X chromosomes, known

as lyonisation, makes the prediction of the behaviour of a potentially lethal gene on the X chromosome more difficult, since the inactivation appears not to be random. Given these developments, most human geneticists no longer accept the early arguments, and contend that prediction of the effects of lethal mutations on the proportion of male births is not possible. Thus, no effort will be made to estimate the possible doubling dose for X-linked lethal mutations in the paragraphs that follow.

8. An overall estimate of genetic risk

Two parameters have been used to characterise the risk of radiation-related mutation. These are the probability of a mutation at a specific genetic locus per unit of dose to the gonads, and the 'doubling dose'. The latter is that dose at which there would be induced as many radiation-related mutations as would occur spontaneously in a generation, so that the overall rate of mutation is actually doubled. Since so few estimates exist of locus-specific rates of human mutation, either induced or spontaneously occurring, we turn to the estimation of the doubling dose suggested by the various sets of data just described and the uncertainties inherent in this estimate.

The process of estimating a doubling dose can be illustrated using the data on untoward pregnancy outcomes. Recall that the increase in such events is 0.002 64 Sv^{-1}, the background rate is 0.038 56, and the excess relative risk at 1 Sv is 0.0685. We have seen that the lowest plausible dose that would double the risk of an untoward pregnancy outcome derived from the excess relative risk is about 0.20 Sv. But this is not the genetic doubling dose, since not all untoward pregnancy outcomes are genetic in origin; some could arise, for example, from exposure during pregnancy to a variety of drugs or environmental agents that impair the normal growth and development of the embryo or foetus. To derive a genetic doubling dose, it is necessary to postulate what fraction of untoward pregnancy outcomes is attributable to spontaneous mutation in the preceding generation. This value is not known with certainty; however, from a variety of lines of evidence it can be estimated to lie between 0.33 and 0.53%. These values suggest a genetic doubling dose for untoward pregnancy outcomes in the range of 0.63–1.01 Sv. Note that had this calculation been based on the sample excluding those cases where an *ad hoc* dose was used, the doubling dose would lie between 0.50 and 0.80 Sv. The difference between these two ranges is small when the uncertainties in the estimates are taken into account.

Theoretically, an estimate of the doubling dose could be obtained for each of the different measures of mutational damage, i.e. untoward pregnancy outcome, cancer and noncancer mortality, sex chromosome aneuploids, biochemical studies and so on. These would differ for a variety of reasons including chance, the different samples employed, the sensitivity of the specific measurement, the validity of the assumptions inherent in passing from the observations to the estimate, and the fact that the doubling dose may actually differ for these outcomes. The preferred estimate, therefore, would be some combination of the individual estimates that takes into account their differences. But it is not clear how this should be done. Should it be on the basis of their presumed genetic specificity, the sizes of the samples involved or in some other manner?

Neel *et al* (Neel *et al* 1990) have argued that the simplest overall estimate is the one that adds together the individual estimates. They justify this cumulation 'on the grounds that each regression involves the relationship to radiation exposure, in the same cohort, of specific, independently determined events'. This line of reasoning leads to the lower estimate of the doubling dose associated with exposure to acute doses of low-LET radiation derived from these values being 1.69 Sv (0.006 32/0.003 75), and the upper estimate being 2.23 Sv

(0.008 35/0.003 75). It should be noted, however, that these limits reflect only the biological uncertainties. This range, 1.69–2.23 Sv, does not consider the additional errors inherent in the estimation procedure itself, and if this could be adequately done, the range of uncertainty would be even larger. Be this as it may, based on the experiences in Hiroshima and Nagasaki, the doubling dose for acute gonadal radiation appears to be about 2.0 Sv. And for chronic exposure, assuming a reduction in effectiveness with a low dose rate of two (which is consonant with experimental studies of mutagenesis), the doubling dose is about 4.0 Sv.

What is to be made of these numbers? First, it warrants noting that these estimates are higher than the 1 Gy that has been used in the past to guide regulatory action. However, the estimate of 1 Gy was based largely on experimental studies of mutations arising in mice following exposure to x-rays or gamma rays derived from cobalt-60. Little cognisance was taken in this estimate of the human data, limited though they were. Nonetheless, the experimental and human data appeared to conflict. Neel and Lewis (1990) have re-examined the earlier experimental data and those that have accumulated since Russell's studies, focusing on the observations they contend are most appropriate to the human situation. When this is done, a doubling dose is obtained for chronic exposure of the mouse of about 4.0 Gy. They conclude, therefore, that the conflict between the human and the mouse data is much less than has been conjectured.

Second, it must be noted that the human data are based upon instantaneous exposure, and experimental evidence shows that doses accumulated slowly over time, such as occurs in most occupational settings, produce fewer mutations for the same total dose than acute exposure. How much smaller the number may be is debatable. We have assumed chronic exposure to low-LET radiation to be only half as effective as acute exposure—a value consistent with present genetic knowledge—but if in fact chronic exposures are even less effective, the doubling dose would be higher than estimated here. Finally, if these newer estimates are correct, then in the past there has been an overestimation of the risk, but given the many uncertainties to which we have alluded, this error was prudent.

As has been stated before, at the outset of the ABCC's activities, public concern over the possible genetic effects of exposure to atomic radiation was at least as great as that over cancer, and possibly greater. Over time, this emphasis has shifted to cancer. This undoubtedly reflects the failure to find unequivocal evidence of genetic damage on the one hand, and the dramatic findings on cancer, on the other. Understandably, but unfortunately, this has led to a failure to recognise that the absence of demonstrable radiation-related findings is no less noteworthy. Such negative findings must be more guardedly interpreted, however, and have a tentativeness some find disturbing. They cannot be interpreted as implying that *absolutely no effect* has occurred. The latter conclusion could be legitimately drawn only if it were possible to examine, in the necessary detail, every single pertinent event within the population of interest. Epidemiological studies deal, however, with samples not populations, since statistically the population under investigation is viewed as indefinitely or infinitely large. The sample available to an investigator may or may not represent the larger population from which it is drawn, or, irrespective of its size, it could be too small to reveal those changes that occur very infrequently. And in this sense, the genetic findings can be seen as 'inconclusive', since although an effect was not found, it cannot be concluded that none exists. However, one can compute the size of an effect which could have existed but gone unrecognised. But ultimately, of course, the acceptance of these findings should rest on the comprehensiveness of the study design and the care and thoroughness with which that design was implemented.

The Commission's findings can be seen as reassuring in at least two different ways. First, where genetic theory suggested 'no effect' would be demonstrable, 'no effect' was found. The study does not then contradict current theory, and as a result makes more plausible

extrapolations based upon previously accumulated information and understanding. This would not necessarily be true of a single study that did not find an effect, particularly if it were based upon a small sample. However, in the present instance, there is not merely one but many mutually reinforcing 'negative' findings, and all are based upon samples of considerable size. Second, the findings should be seen as reassuring to the public, since they argue forcefully against the fears of a devastating genetic effect. More immediately, they do not support the notion of an epidemic of malformed infants, genetic or otherwise in origin.

9. The future

Death or the occurrence of a congenital malformation has meaning to everyone; the occurrence of a new mutant of glutamate pyruvate transaminase, for example, does not. To the geneticist, however, the latter event has a precision not to be found in changes in those variables where the role of genetic factors is still uncertain. Mortality surveillances are inexpensive; biochemical studies are not. Undoubtedly, with time, technological developments will narrow the cost difference. To meet this contingency, some years ago the Radiation Effects Research Foundation, the successor to ABCC, launched a programme to collect and establish permanent cell lines of peripheral B-lymphocytes on a group consisting of 1000 children of survivors and their parents (500 trios—the child and its two parents—selected because the parents had relatively high radiation exposures, and 500 controls). Even now, the feasibility of two-dimensional gel electrophoresis, DNA sequencing and various uses of restriction fragments, or minisatellites, or denaturing gradient gel electrophoresis to assess the frequency of newly arisen mutations is being explored. These alternatives, more elegant than those used in the past, must still confront the matter of their relevance to the concerns of the public, and these centre on the health and well-being of our children. It would seem important in the public health perspective, therefore, that future studies focus primarily on genes with known functions and not upon the massive amount of DNA that is apparently nonfunctional or involved in regulatory functions that cannot now be discerned. Ultimately, it is information to guide personal conduct that the public seeks and the provision of this information provides the greatest justification for the enormous investment in time and money that has been made in the genetic studies of the survivors and their children.

Note added in proof. Since this manuscript was submitted, an analysis of mortality among the children of the survivors has appeared that extends the data through 1999. The relevant publication is by Izumi S, Suyama A and Koyama K (2003 Radiation-related mortality among offspring of atomic-bomb survivors: a half-century of follow-up *Int. J. Cancer* **107** 292–7). Mortality rates are still no different among the children of exposed parents as compared with unexposed parents, and mortality does not increase with dose.

Résumé

Quand les bombardements atomiques sur Hiroshima et Nagasaki eurent lieu durant l'été 1945, la plus grande partie du public a présumé que beaucoup des enfants engendrés par les survivants seraient énormément contrefaits ou souffriraient de diverses lésions, conséquences de mutations induites par le rayonnement. Les données expérimentales disponibles alors se limitaient à des études sur les mélanomes de la drosophile, la mouche commune des fruits; elles ne corroboraient pas cette perception des choses; cependant, le peu de données, la préoccupation profonde du public, justifiaient un suivi soigneux des enfants engendrés par les survivants. Dans ce but, et ce dans les deux cités, on a commencé en 1947 à surveiller toutes les grossesses se terminant après 20 semaines de gestation. Durant le demi siècle qui a suivi le début de cette surveillance, on a étudié quelques 80 000 fins de grossesse; on a

mesuré toute une série d'indicateurs potentiels de dommages dus à des mutations. Ce rapport synthétise les résultats de ces études; il évalue le risque génétique fondé sur ces résultats.

Zusammenfassung

Als im Sommer 1945 Atombomben über Hiroshima und Nagasaki abgeworfen wurden, gingen die meisten Menschen davon aus, dass viele Kinder, die von den Überlebenden gezeugt wurden, als Folge strahlungsinduzierter Mutationen stark deformiert oder auf andere Weise ernsthaft geschädigt wären. Zwar unterstützten die damals zur Verfügung stehenden experimentellen Daten, die weitgehend auf Studien der Drosophila melanogaster, der gewöhnlichen Fruchtfliege, beschränkt waren, diese Auffassung nicht; dennoch rechtfertigte die Beschränkung der Daten und das Ausmaßder Sorgen, die sich die Öffentlichkeit machte, eine sorgfältige Folgeuntersuchung der Kinder, die den Überlebenden geboren wurden. Aus diesem Grund wurde 1947 eine Studie aller Schwangerschaften begonnen, die 20 Wochen nach der Schwangerschaft in diesen beiden Städten endete. Im Verlaufe des halben Jahrhunderts nach Beginn dieser Untersuchung wurden mehr als 80 000 Schwangerschaftsbeendigungen untersucht und eine Vielzahl potenzieller Indikatoren über mutationsbedingte Schäden gemessen. Dieser Bericht fasst die Erkenntnisse dieser Studien zusammen und bietet eine Abschätzung des genetischen Risikos auf der Grundlage dieser Erkenntnisse.

References

Abrahamson S 1990 Commentary: childhood leukemia at Sellafield *Radiat. Res.* **123** 237–8

Abrahamson S and Tawn E J 2001 Risk of stillbirth in offspring of men exposed to ionising radiation *J. Radiol. Prot.* **21** 133–44

Awa A A 2003 Mutation research at ABCC/RERF: cytogenetic studies of atomic bomb exposed populations *Mutat. Res.* **543** 1–15

Awa A A, Honda T, Neriishi S, Sofuni T, Shimba H, Ohtaki K, Nakano M, Kodama Y, Itoh M and Hamilton H B 1988 Cytogenetic study of the offspring of atomic bomb survivors, Hiroshima and Nagasaki *Radiation Effects Research Foundation Technical Report 21-88*

Furusho T and Otake M 1978a A search for genetic effects of atomic bomb radiation on the growth and development of the F1 generation: 1. Stature of 15 to 17 year-old senior high school students in Hiroshima *ABCC Technical Report 4-78*

Furusho T and Otake M 1978b A search for genetic effects of atomic bomb radiation on the growth and development of the F1 generation: 2. Body weight, sitting height and chest circumference of 15 to 17 year-old senior high school students in Hiroshima *ABCC Technical Report 5-78*

Furusho T and Otake M 1979 A search for genetic effects of atomic bomb radiation on the growth and development of the F1 generation: 3. Stature of 12 to 14 year-old junior high school students in Hiroshima *ABCC Technical Report 14-79*

Furusho T and Otake M 1980 A search for genetic effects of atomic bomb radiation on the growth and development of the F1 generation: 4. Body weight, sitting height and chest circumference of 12 to 14 year-old junior high school students in Hiroshima *ABCC Technical Report 5-80*

Furusho T and Otake M 1985 A search for genetic effects of atomic bomb radiation on the growth and development of the F1 generation: 5. Stature of 6 to 11 year-old elementary school pupils in Hiroshima *ABCC Technical Report 9-85*

Gardner M J, Snee M P, Hall A J, Powell C A, Downes S and Terrell J D 1990 Results of case-control study of leukaemia and lymphoma among young people near Sellafield nuclear plant in West Cumbria *Br. Med. J.* **300** 423–9

Little M P 1990 A comparison between the risks of childhood leukaemia from parental exposure to radiation in the Sellafield workforce and those displayed among the Japanese bomb survivors *J. Radiol. Prot.* **10** 185–98

Little M P 1999 A comparison of the risk of stillbirth associated with paternal pre-conception irradiation in the Sellafield workforce with that of stillbirth and untoward pregnancy outcome among Japanese atomic survivors *J. Radiol. Prot.* **19** 361–73

Neel J V and Lewis S E 1990 The comparative radiation genetics of humans and mice *Annu. Rev. Genet.* **24** 327–62

Neel J V, Satoh C, Goriki K, Asakawa J, Fujita M, Takahashi N, Kageoka T and Hazama R 1988 Search for mutations altering protein charge and/or function in the children of atomic bomb survivors. Final report *Am. J. Hum. Genet.* **42** 663–76

Neel J V and Schull W J 1991 *The Children of Atomic Bomb Survivors: A Genetic Study* (Washington, DC: National Academy Press) pp vi and 591

Neel J V, Schull W J, Awa A A, Satoh C, Kato H, Otake M and Yoshimoto Y 1990 The children of parents exposed to atomic bombs: estimates of the genetic doubling dose of radiation for humans *Am. J. Hum. Genet.* **46** 1053–72

Omori Y, Morrow L B, Ishimaru T, Johnson K G, Maeda T, Shibukawa T and Takaki K 1965 A buccal smear survey for sex chromatin aberration in Hiroshima high school children *ABCC Technical Report 11-65*

Otake M, Schull W J and Neel J V 1990 The effects of exposure to the atomic bombing of Hiroshima and Nagasaki on congenital malformations, stillbirths and early mortality among the children of atomic bomb survivors: a reanalysis *Radiat. Res.* **122** 1–11

Parker L, Pearce M S, Dickinson H O, Aitkin M and Craft A W 1999 Stillbirths among offspring of male radiation workers at Sellafield nuclear reprocessing plant *Lancet* **354** 1407–14

Satoh C, Neel J V, Yamashita A, Goriki K, Fujita M and Hamilton H B 1983 Frequency among Japanese of heterozygotes for deficiency variants of 11 enzymes *Am. J. Hum. Genet.* **35** 656–74

Schull W J 1995 *Effects of Atomic Radiation* (New York: Wiley–Liss Inc.) pp xiii and 397

Schull W J and Neel J V 1962 Maternal radiation and mongolism *Lancet* **i** 537–8

Schull W J, Neel J V and Hashizume A 1966 Some further observations on the sex ratio among infants born to survivors of the atomic bombings of Hiroshima and Nagasaki *Am. J. Hum. Genet.* **18** 328–38

Slavin R F, Kamada N and Hamilton H B 1966 A cytogenetic study of 92 cases of Down's syndrome, Hiroshima and Nagasaki *ABCC Technical Report 2-66*

Yoshimoto Y, Neel J V, Schull W J, Kato H, Mabuchi K, Soda M and Eto R 1990 The frequency of malignant tumors during the first two decades of life in the offspring of atomic bomb survivors *Am. J. Hum. Genet.* **46** 1041–52

Yoshimoto Y, Schull W J, Kato H and Neel J V 1991 Mortality among the offspring (F1) of atomic bomb survivors, 1946–1985 *Japan. J. Radiat. Res.* **32** 327–51