A Cohort-Type Study of Survival in the Children of Parents Exposed to Atomic Bombings

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AMONG THE GENETIC EFFECTS to be expected in the first generation progeny of mammals exposed to radiation is a shortening of the life span due to the action of deleterious mutations. Although in recent years a considerable body of data concerned with such experimental species as mice, rats, and swine has become available, pertinent observations in man remain, for obvious reasons, rare. The purpose of this paper is to describe a continuing study in Hiroshima and Nagasaki, the objective of which is to determine through a cohort approach whether the life span of liveborn children one or both of whose parents were exposed to the mixed radiation spectrum of the atomic bombings differs from that of suitable control children. The data will then be employed to approximate a "minimum doubling dose" for man.

The observations may be regarded as both a follow-up and an extension of the earlier study of Neel and Schull (1956), in which there was no evidence of an increased death rate among the children of survivors during the first six postpartum days, or, in a subsample, during the first nine months of life expectancy. Malformed children were excluded from these calculations, but the frequency of malformations was not elevated. Inasmuch as the interval since birth of the surviving subjects of the present study ranged at the time of investigation between three and 15 years, with a mean of nine, the results to be reported cover the age interval in which maximum prereproductive mortality occurs but still must be regarded as preliminary. A consideration of the pertinent literature on other mammals, including man, will be delayed until the Discussion.

Factors Determining the Design of the Study

Two different albeit related approaches to the question of the effect of parental exposure to ionizing radiation upon the survival of their progeny can

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be envisaged. On the one hand, an effort can be made to determine whether the frequencies of death within some specified period of time differ in the offspring of exposed and control groups. Virtually all of the studies thus far reported are of this nature, and most involve rather short time periods, often only the first year of life. On the other hand, an effort can be made to determine the cumulative mortality experience in cohorts, some from exposed parents and some not, with a view toward defining survivorship curves. Patently, in the latter approach, death rates can be compared and hence this type of study includes the first. We are aware of no studies of mortality among the children of exposed parents of the life-expectancy kind except for the one to be reported here, but the merits of this type of investigation appear to us overwhelming. In the present instance, once it had been determined that a cohort analysis was feasible and the decision had been reached to adopt such an approach, the ultimate shape which the study assumed stemmed largely from certain administrative and scientific considerations to which we briefly turn.

The potential size of the study groups. The largest study group which can be envisaged is that population consisting of all children born alive subsequent to May 1, 1946, one or both of whose parents were present either in Hiroshima or Nagasaki or both cities at the time of the atomic bombings. This population is not now fully definable and will not be so until every person exposed to either or both of the bombs has passed beyond the reproductive age span. This will not occur for possibly another 30 years. Clearly, then, it is not yet possible to attempt to study the maximal population. The population to be dealt with in this presentation consisted of all children born between May 1, 1946, and December 31, 1958, to parents whose residence at the birth of their child was Hiroshima or Nagasaki and whose exposure status was either known to the Atomic Bomb Casualty Commission (ABCC) or could readily be obtained. The former date corresponds to the earliest time at which pregnancies conceived subsequent to the bombing would be expected to terminate normally; the latter date defines the maximal sample size possible when this cohort was established in 1959. Since it can be shown that at least 82% of the children ever to be born to exposed parents residing in Hiroshima and Nagasaki were born prior to January 1, 1959, relatively little appeared to be gained by further delay in initiating the study.

The probable duration of the study. Ideally in a study of life expectancy in a cohort, survivorship is followed until such time as all or virtually all members of the cohort have succumbed. In the present instance, this represents some 80 or 90 years, and it is obviously unlikely that the study will, in fact, continue for that length of time. Accordingly, it seemed important to emphasize the collection of data adequate to define with the requisite precision the earlier portions of the life curve, on the assumption that any change in life expectancy would be reflected in the early as well as the late portions of the survival curve.

The existence of the koseki system. There has existed in Japan since the last quarter of the nineteenth century a system of compulsory family registration. Vital events affecting the composition of a given family or the status of members of that family must be reported to the office having custody of the family's

record. The latter is termed the *koseki.* An indispensable part of the system is the legal or permanent address of the family, known as the *honseki.* Changes in the latter must also be reported to the *koseki* office. Because of the care with which Japanese family records are maintained, knowledge of the last, or any recent, *honseki* of an individual is a virtual guarantee that the survival status of that individual can be determined indefinitely. More complete accounts of the system are to be found in Naruge (1956), Ohkura (1960), and Yanase (1962); see also Schull and Neel (1965).

The availability through previous or current studies of ABCC of ancillary data of great relevance to the interpretation of an apparent effect of radiation. In the years 1948–1953, one facet of the activities of ABCC involved a comprehensive attempt to determine whether the pregnancy terminations occurring to parents, one or both of whom were exposed to the atomic bombs, differed from those occurring to a suitable control. This study, the Genetics Program, has been described in detail elsewhere (Neel and Schull, 1956). In these years the outcome of some 93% of all pregnancies occurring in Hiroshima and Nagasaki and lasting for 21 weeks or more of gestation was investigated. Available on these children, in addition to the results of one and frequently two clinical examinations, are data on a variety of variables of potential interest in the interpretation of an apparent radiation effect or the meaningfulness of the lack of such an effect. These observations range from parental ages at the birth of the children in question and the occurrence of consanguineous marriage to an appraisal of the socioeconomic status of the family at the time of the delivery. For a variety of reasons (see Neel and Schull, 1956), this study terminated early in 1954, but at that time it was decided that further information on the relationship of parental exposure to the sex ratio among children should be collected. This decision gave rise to a second study of interest here, the Sex Ratio Program. The latter involves an attempt to link the sex of children as reported on the birth records filed with the city with the exposure of their parents as known to ABCC. This study began in 1954 and continues. Through these two studies, exposure status can be determined for the parents of the majority of children born in these cities since 1948 without further field investigations, an important administrative consideration.

DESCRIPTION OF STUDY PROCEDURES

Three samples were utilized. The first consists of livebirths occurring between May 1, 1946, and January 31, 1948, i.e., prior to the previously mentioned Genetics Program, and was derived from municipal birth records. The second stems from the livebirths recorded in these cities in the interval from February 1, 1948, through December 31, 1953, under the Genetics Program. The third was drawn from livebirths recorded in the Sex Ratio Program in the years from January 1, 1954, through December 31, 1958. Within each of the three samples, in order to facilitate follow-up and to reduce extraneous sources of variation, the following selection criteria were imposed:

1. Parental residence *at the birth of the child* must have been within Hiroshima or Nagasaki. This restriction stemmed from the knowledge that (a)

infant and childhood mortality varies appreciably from urban to urban-rural areas in Japan and (b) establishing proper controls for exposed persons who had left the two cities prior to childbirth would be extremely difficult.

2. *Honseki* was not restricted to Hiroshima or Nagasaki. Although restriction of *honseki* to these two cities would have materially simplified the follow-up, the loss of data which this step would have entailed seemed prohibitive.

3. Multiple births were excluded on the grounds that the mortality rates are appreciably different from those of single births, and they are too infrequent to warrant the added analytic complication they introduce.

4. The samples were to include *all* infants born to parents one or both of whom were known to the ABCC to have been within 2000 meters of the hypocenter at the time of the bombing. In addition, from among births occurring in the two cities to parents whose exposure status was on file with ABCC, equal numbers of children were to be randomly drawn from among births to parents (a) one or both of whom were exposed in the interval 2500–9999 meters (neither parent was, of course, to be nearer) and (b) neither of whom were in the cities at the time of the atomic bombings. These latter two samples were to be matched with the former group by sex and year of birth. This procedure yields three major or, if joint parental exposure is considered, nine minor exposure groups, as shown in Fig. 1. In view of some findings to be brought out later, it should be emphasized that the matching by sex and year of birth was by major but not by minor exposure group.

Fact of death was established by routine, periodic inspection of the appropriate *koseki*. A home visit by a trained "contactor" was utilized to establish *honseki* in those cases where the *koseki* could not be located by routine methods. The first cycle of *koseki* checking was begun in January, 1961, and completed in January, 1964, and it is the results of this cycle which are here reported. Since this cycle embraced some three years of record checking, we shall restrict our attention to deaths prior to December 31, 1961, and the initiation of the first cycle, to obviate the possibility, remote but nonetheless real, that exposure class may have been correlated with the ease or difficulty of follow-up and hence the number of years at risk of death. We present in Table 1 a summary of the results of this cycle of record reviews. It will be noted that among some 54,243 cases, the predominant reason for failure to determine survival status was non-Japanese parentage (i.e., no *koseki* record); in all except 53 instances where the child was Japanese, the survival status of the child in 1961 could be determined. Failure of follow-up because of lack of *koseki* can scarcely be regarded as a source of bias; the 53 children of Japanese parents whose survival status is unknown are too few to influence the data significantly, even if all the cases involved children no longer alive. In subsequent tables, the 810, largely non-Japanese, children in Hiroshima and Nagasaki for whom koseki records were not available have been excluded, as have 14 births in the Sex Ratio Program for whom the information was incomplete. The resulting distribution of children on the basis of the radiation histories of their parents is shown in Table 2. Where death had occurred, a record of the

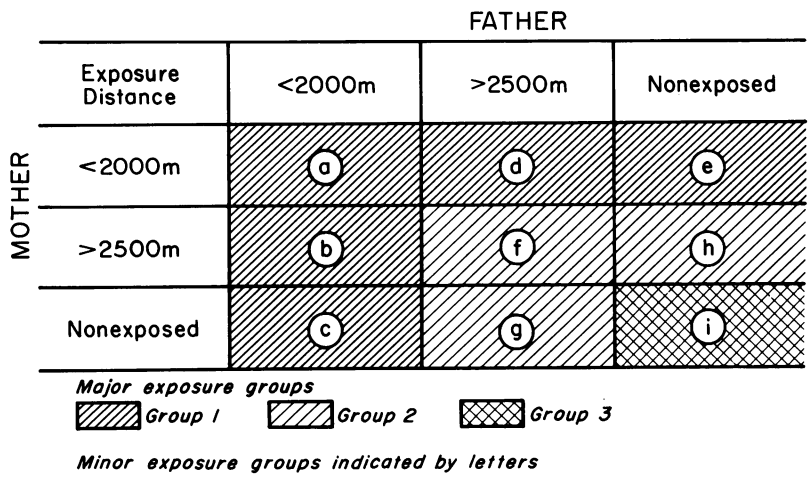

FIG. 1. A diagrammatic representation of the parental exposures, as implied by distance from hypocenter, associated with the three major and nine minor exposure groups.

entry in the "vital statistics" portion of the death certificate was obtained through the co-operation of the Japanese National Institute of Health.

SOURCES OF VARIATION IN MORTALITY OTHER THAN RADIATION

It is common knowledge that fetal, infantile, and childhood mortality are influenced by numerous variables other than radiation. As a consequence, the contribution of this or any other study to the ultimate evaluation of the radiation hazard is directly proportional to the degree to which extraneous sources of variation can be delineated and controlled. Accordingly, we turn now to an account of the possible role of extraneous variables in the mortality data to be presented shortly.

A priori, one recognizes that the survival of a liveborn infant is a function of certain attributes of the infant and, in addition, certain characteristics of the parents and pregnancy. Ample evidence exists attesting to the role in early mortality of parental ages, birth rank, birth weight, duration of pregnancy, and, in a changing society, year of birth. To this list can be added a number of variables commonly termed socioeconomic, such as parental education, parental occupation, the occurrence of consanguineous marriage, social class, and nutrition. Other variables of importance exist, e.g., presence of congenital defect, but of greater importance than an exhaustive enumeration is the recognition that few if any of these concomitant variates are entirely independent of

TABLE 1. RESULTS OF THE FIRST *Koseki* CHECK

	Hiroshima	Nagasaki
Total number in sample	35,289	18,954
Total for whom no *koseki* record is available	744	66
Non-Japanese	710	47
Japanese, *koseki* cannot be located	34	19

TABLE 2. TABULATION OF THE FINAL SAMPLE BY MAJOR AND MINOR EXPOSURE GROUP, PROGRAM COMPONENT, SEX, AND CITY

			Exposure Major Group										
			I						II				III
			Exposure Subgroup										
Sex	Source	Total	Subtotal	*a*	*b*	*c*	*d*	*e*	Subtotal	*f*	*g*	*h*	*i*
								Hiroshima					
Male	Pre-GE-3	3679	1231	288	180	140	185	438	1235	528	123	584	1213
	GE-3	9007	2976	359	258	417	320	1622	3027	665	509	1853	3004
	Sex Ratio	5201	1720	107	194	381	185	853	1732	280	512	940	1749
	Pre-GE-3	3522	1169	280	180	93	167	449	1194	508	141	545	1159
Female	GE-3	8422	2784	360	248	393	276	1507	2812	630	496	1686	2826
	Sex Ratio	4701	1547	108	155	353	163	768	1566	211	455	900	1588
								Nagasaki					
Male	Pre-GE-3	1521	507	58	100	56	87	206	507	235	56	216	507
	GE-3	4544	1513	98	329	229	163	694	1520	439	240	841	1511
	Sex Ratio	3425	1139	55	201	212	129	542	1142	297	211	634	1144
	Pre-GE-3	1502	501	72	137	56	55	181	501	230	56	215	500
Female	GE-3	4514	1508	119	272	236	150	731	1506	406	245	855	1500
	Sex Ratio	3381	1126	53	190	228	137	518	1128	283	226	619	1127
Total		53419	17721	1957	2444	2794	2017	8509	17870	4712	3270	9888	17828

every other. Thus, for example, we recognize that parental ages and birth rank are significantly correlated, and, since both apparently affect mortality rates, it is not immediately obvious whether their effects are attributable to the same basic phenomenon or to a different one. In this particular instance, the latter appears to be true, for there exists an effect of parity upon the frequency of death in the postnatal period not accountable for in terms of variation in parental ages (see Neel and Schull, 1956, Chapter 11). Relationships of this nature considerably complicate efforts to control the effects of extraneous variables on mortality through selection of the comparison groups, since samples matched on multiple variables are often not feasible. We shall return to this issue after a consideration of the relationship to exposure groups of the concomitant variables previously enumerated.

It will be recalled that three samples were selected for study, namely, a sample (1) for the years May 1, 1946, through January 31, 1948, derived from the birth information on file at the city offices of Hiroshima and Nagasaki, (2) for the years February 1, 1948, through December 31, 1953, derived from the so-called Genetics Program of the ABCC, and finally (3) for the years January 1, 1954, through December 31, 1958, derived from the Sex Ratio Program. Through city birth records and the records associated with the two programs previously mentioned, it has been possible to obtain information on virtually all births with respect to maternal age, paternal age, parity, birth weight, duration of pregnancy, and year of birth. The most conspicuous exception to this statement involves birth weight, which was not routinely recorded on the Japanese birth certificate in the years immediately following World War Two (routine recording began in the latter half of 1947). Let us consider, now, the relationship of each of these five concomitants to the *major* exposure groups.

Year of birth. Substantial changes have been effected in infant mortality in Japan in the years since 1945. When one considers that the major portion of the mortality in the first two decades of life expectancy occurs in the first year, patently variation in year of birth among the exposure classes could obscure a radiation effect or produce a spurious one. While the method of sample selection ostensibly precludes significant differences within each of the three samples, the possibility exists that an equal degree of completeness of follow-up is not achieved in all radiation groups, and some variation, perhaps non-negligible, is thereby introduced. In Table 3, we present a summary of the results of comparing the distributions of the six concomitant variables previously enumerated within sex-city-major exposure groups. Reference to this table reveals that year of birth does not differ significantly among exposure groups within either city or within samples within cities.

Maternal age. The significant effect of maternal age upon early mortality in this sample has been well documented by Neel and Schull (1956). The nature of this effect is complex but, in general, one finds that early mortality in age-specific parity distributions or parity-specific age distributions tends to be J or U-shaped (see also Yerushalmy, 1938; Tsunoda, 1956; Newcombe, 1964; Newcombe and Tavendale, 1965). This of course implies an optimal age associated

TABLE 3. SUMMARY OF CONTINGENCY χ^2 COMPARISONS OF THE DISTRIBUTION OF CONCOMITANT VARIABLES IN EXPOSURE MAIN GROUPS

Variables	City	Male				Female			
		Pre-GE-3	GE-3	Sex Ratio	Total	Pre-GE-3	GE-3	Sex Ratio	Total
Year of birth	H	NS	NS	NS	NS	NS	NS	NS	NS
	N	NS	NS	NS	NS	NS	NS	NS	NS
Maternal age	H	**	**	*	**	**	**	NS	**
	N	**	**	**	**	**	**	*	**
Parity	H	**	**	NS	**	**	**	**	**
	N	**	**	**	**	**	NS	**	**
Duration of pregnancy	H	NS	NS	NS	NS	NS	NS	NS	NS
	N	NS	NS	NS	NS	NS	NS	NS	NS
Birth weight	H	NS	NS	NS	NS	NS	NS	NS	NS
	N	NS	NS	NS	NS	NS	*	NS	NS
Paternal age	H	**	**	**	**	**	**	**	**
	N	**	**	**	**	**	**	**	**

*Significant at 5% level.
**Significant at 1% level.
NS = Not significant.

with a given parity, or an optimal parity for a given age. Be this as it may, the effect is sufficiently pronounced that failure to take into account this concomitant could have serious consequences. We note from Table 3 that the exposure groups differ significantly in maternal age within virtually all samples in both cities. In general, the more "heavily" exposed mothers are older than the more "lightly" exposed, and the latter are, in turn, older than the nonexposed mothers.

Paternal age. Parental ages are highly correlated, and in view of the known effect of maternal age upon early mortality, one would anticipate an effect of paternal age when maternal age is ignored. It is not clear, however, whether paternal age exerts an effect not explicable in terms of maternal age. Accordingly, it seemed appropriate to determine whether the exposure groups within the various samples differed in paternal age as was to be expected in view of the differences in maternal age. They do (Table 3). Mean paternal age is greater for "heavily" exposed than for "lightly" exposed or nonexposed fathers.

Parity. Parity and maternal age are closely correlated; one would, therefore, expect the exposure groups to differ in mean parities. This is, in fact, the case; on the average, parity is directly related to exposure, the more "heavily" exposed having had more pregnancies. As noted above, there exists an effect of parity not explicable in terms of the correlation between parity and maternal age (see Neel and Schull, 1956, for further details).

Duration of pregnancy. Mortality rates are strikingly and significantly elevated among pregnancies which terminate prematurely; a much lesser effect is associated with postmaturity. It follows, then, that if duration of pregnancy

was significantly related to exposure groups, differences in mortality among the exposure classes might arise. As Table 3 reveals, exposure groups do not differ significantly with respect to duration of pregnancy.

Birth weight. There is no significant association of birth weight with exposure status, in confirmation of the earlier finding of Neel and Schull (1956) on a partially overlapping sample.

To summarize briefly, among the six sources of extraneous variation for which data exist on virtually all births and which are known to be significantly associated with mortality, three, namely, maternal age, paternal age, and parity, differ significantly among the *major* exposure groups within most samples. These differences are such as to lead to augmented mortality rates within the more heavily exposed groups. Thus, an apparent effect of radiation on mortality could not be accepted before these differences were controlled, but on the other hand, if there is no apparent effect even when these differences are ignored, it seems most unlikely one would appear *after* they were controlled.

There are, of course, other important sources of extraneous variation for which data were not available on the birth certificate or through one of the previously mentioned programs. Thus, data were not available on socioeconomic class, yet we know that infant mortality, for example, is higher in the lower socioeconomic classes of Japan. Moreover, the Child Health Survey (Schull and Neel, 1965) revealed a significant effect of socioeconomic status upon physical and mental growth and development of a magnitude which might lead to serious biases in the analysis of mortality data if the socioeconomic concomitants were dissimilarly distributed between the comparison groups. To ascertain whether the latter might or might not be true, a pilot mail survey was undertaken on a small random sample in 1962. The primary purposes of this preliminary survey were to ascertain probable response rates and the quality of responses in a projected larger study. As a consequence of this preliminary study and the experience of the Child Health Survey of Schull and Neel (1965), a larger study involving a random 10% of the pregnancy terminations included in the total sample was initiated in 1964.

A mail questionnaire was sent to the last address known to the ABCC of the parents of 5,294 children, regardless, of course, of present status. If the initial questionnaire was not returned, a second and if need be a third was sent at intervals of two weeks. When a letter was returned as undeliverable, the *koseki* was checked and the questionnaire sent to the most recent address indicated on the record of residence filed with the *koseki.* For those cases where no response was obtained to any one of the three possible mailings, a field follow-up was conducted if the family lived in Hiroshima or Nagasaki or areas immediately adjacent thereto (see Table 4). It will be noted that data were collected on all save some 4% of the sample; it seems unlikely that the failure to obtain information on so small a group could markedly bias the results to be presented. Information was sought with respect to parental occupation, parental schooling, survival status of the parents, the size of the home (in mats) and the number of persons normally residing therein, food expenditures per

TABLE 4. ACCUMULATED RESPONSE RATE IN THE MAIL SURVEY ON SOCIOECONOMIC STATUS BY CITY

	First mailing		Second mailing		Third mailing		Field investigation	
	H	N	H	N	H	N	H	N
Total number	3416 (100%)	1878 (100%)	3416 (100%)	1878 (100%)	3416 (100%)	1878 (100%)	3416 (100%)	1878 (100%)
Responses	1130 (33.1%)	802 (42.7%)	2129 (62.3%)	1120 (59.6%)	2397 (70.2%)	1247 (66.4%)	3306 (96.8%)	1774 (94.5%)

person per month, and, finally, a brief indication of the child's nutrition in terms of the consumption of certain dietary staples, namely, fish, meat, eggs, and milk.

Table 5 summarizes the tests of significance with regard to the distributions of the aforementioned variables among the exposure groups within samples and cities. We note that number of mats per person, food expenditures, and consumption of dietary staples do not differ among the comparison groups. However, parental industry (and possibly occupation within industry), schooling, and survival status are significantly different. Thus, we observe relatively more children one or both of whose parents are dead in the proximally exposed group than in either of the other two samples. Exposed parents are less well educated than nonexposed, and relatively more farmers and fishermen are to be found in the distally exposed groups than in either of the other two comparison groups. These findings are, in general, in accord with those for the other concomitant variables to which attention has been directed. Thus, for example, we know that the exposed parents are older on the average than nonexposed parents (see Table 3) and that the education received by the average individual in Japan has steadily increased in the post-war era. We would expect, therefore, the exposed to be less well educated than the younger, nonexposed population. *In general, these differences in distribution of extraneous socioeconomic variables, like those associated with the variables discussed earlier, are such as to lead to an inflation of mortality rates in the children of the "heavily" exposed group as contrasted with the other two comparison groups.*

THE RELATIONSHIP OF MORTALITY TO EXPOSURE

The various tabulations, analyses, and comparisons of the data have been quite extensive; only a very condensed account can be presented. Table 6 sets out the data subclassified by city, sex, main exposure group, and year of risk. A profusion of comparisons is possible. Age-specific rates are given only for those years to which all the individuals in a defined cohort have been exposed. However, the figure for total deaths includes not only those occurring during the risk years experienced by the entire group but also those occurring during risk years experienced by only a proportion of the cohort. Accordingly, while the figure may be used in comparisons between groups of the three segments of the study, it has no normative value in the strict sense. Inspection of the

TABLE 5. SUMMARY OF CONTINGENCY χ^2 COMPARISONS OF THE DISTRIBUTION OF SOCIOECONOMIC VARIABLES IN EXPOSURE MAIN GROUPS

Socioeconomic variables	City	Male				Female			
		Pre-GE-3	GE-3	Sex Ratio	Total	Pre-GE-3	GE-3	Sex Ratio	Total
Father's education	H	NS	NS	NS	*	NS	NS	NS	**
	N	NS	NS	NS	NS	NS	NS	NS	NS
Mother's education	H	*	NS	*	**	NS	NS	NS	**
	N	NS	NS	NS	*	NS	NS	NS	NS
Father's occupation	H	NS	NS	NS	*	NS	NS	NS	NS
	N	NS	NS	NS	NS	NS	NS	NS	NS
Father's industry	H	NS	NS	NS	**	NS	NS	NS	NS
	N	NS	NS	**	**	NS	NS	NS	NS
Mats per person	H	NS	NS	NS	NS	NS	NS	NS	NS
	N	NS	NS	NS	NS	NS	NS	NS	NS
Food cost per person	H	NS	NS	NS	NS	NS	NS	NS	NS
	N	NS	NS	NS	NS	*	NS	NS	NS
Survival status of parents	H	NS	**	NS	**	*	NS	NS	NS
	N	NS	NS	NS	NS	NS	*	NS	NS
Eating habit:									
Fish	H	NS	NS	NS	NS	NS	NS	NS	NS
	N	*	NS	NS	NS	NS	NS	NS	NS
Meat	H	NS	NS	NS	NS	NS	NS	NS	NS
	N	NS	NS	NS	NS	**	NS	NS	NS
Eggs	H	NS	NS	NS	NS	NS	NS	NS	NS
	N	NS	NS	NS	NS	NS	NS	NS	NS
Milk	H	*	NS	NS	NS	NS	NS	NS	NS
	N	NS	NS	NS	NS	NS	NS	NS	NS

*Significant at 5% level.
**Significant at 1% level.
NS = Not significant.

table fails to reveal evidence of a systematic change in mortality experience related to parental major exposure group within either sex in either city. None of the χ^2 values derived from 12 3×2 contrasts based on the totals for each city-sex-program component approaches significance. This is in spite of the fact, it will be recalled, that extraneous sources of variation are so distributed as to lead to an inflation of mortality in major exposure group 1. The data on the first year of life expectancy support the earlier report of Neel and Schull (1956) that no significant association was observable between mortality in the first year of life and parental exposure. The data are, of course, not wholly independent of those presented in the aforementioned publication.

In view of these data it seemed unlikely that analysis of cause of death would be particularly revealing. However, such analyses were performed,

TABLE 6. TOTAL AND AGE-SPECIFIC DEATH RATES (ALL CAUSES OF DEATH) BY EXPOSURE MAIN GROUP (PER 1,000)

Source of data	Age at death	Total			Exposure 1			Exposure 2			Exposure 3			χ^2 (df = 2)
		N*	D*	P*	N	D	P	N	D	P	N	D	P	
							Hiroshima male							
	Total	3679	290	78.8	1231	85	69.0	1235	102	82.6	1213	103	84.9	2.49
	0	3679	160	43.5	1231	50	40.6	1235	51	41.3	1213	59	48.6	
	1	3519	48	13.6	1181	12	10.2	1184	18	15.2	1154	18	15.6	
	2	3471	21	6.1	1169	6	5.1	1166	10	8.6	1136	5	4.4	
	3	3450	20	5.8	1163	5	4.3	1156	7	6.1	1131	8	7.1	
	4	3430	14	4.1	1158	4	3.5	1149	6	5.2	1123	4	3.6	
	5	3416	6	1.8	1154	3	2.6	1143	2	1.8	1119	1	0.9	
Pre-GE-3	6	3410	3	0.9	1151	—	—	1141	1	0.9	1118	2	1.8	
	7	3407	3	0.9	1151	1	0.9	1140	2	1.8	1116	—	—	
	8	3404	2	0.6	1150	1	0.9	1138	1	0.9	1116	—	—	
	9	3402	1	0.3	1149	1	0.9	1137	—	—	1116	—	—	
	10	3401	5	1.5	1148	—	—	1137	—	—	1116	5	4.5	
	11	3396	2	0.6	1148	—	—	1137	2	1.8	1111	—	—	
	12	3394	—	—	1148	—	—	1135	—	—	1111	—	—	
	13	3394	5	1.5	1148	**2**	1.7	1135	**2**	1.8	1111	1	0.9	
	14–15		0			**0**			**0**			0		
	Total	9007	610	67.7	2976	185	62.2	3027	232	76.6	3004	193	64.2	5.86
	0	9007	388	43.1	2976	126	42.3	3027	148	48.9	3004	114	38.0	
	1	8619	62	7.2	2850	18	6.3	2879	24	8.3	2890	20	6.9	
	2	8557	43	5.0	2832	11	3.9	2855	15	5.3	2870	17	5.9	
	3	8514	28	3.3	2821	5	1.8	2840	14	4.9	2853	9	3.2	
GE-3	4	8486	22	2.6	2816	5	1.8	2826	7	2.5	2844	10	3.5	
	5	8464	22	2.6	2811	8	2.9	2819	7	2.5	2834	7	2.5	
	6	8442	12	1.4	2803	4	1.4	2812	4	1.4	2827	4	1.4	
	7	8430	9	1.1	2799	1	0.4	2808	4	1.4	2823	4	1.4	
	8	8421	8	1.0	2798	2	0.7	2804	3	1.1	2819	3	1.1	
	9–12		16			**5**			**6**			5		
	Total	5201	197	37.9	1720	70	40.7	1732	67	38.7	1749	60	34.3	1.01
	0	5201	134	25.8	1720	48	27.9	1732	44	25.4	1749	42	24.0	
Sex Ratio	1	5067	23	4.5	1672	6	3.6	1688	9	5.3	1707	8	4.7	
	2	5044	13	2.6	1666	4	2.4	1679	6	3.6	1699	3	1.8	
	3	5031	10	2.0	1662	5	3.0	1673	3	1.8	1696	2	1.2	
	4–7		17			7			5			5		

*N = number of subjects, D = number of deaths, P = death rate per 1,000.

TABLE 6. *(Continued)*

Source of data	Age at death	Total			Exposure 1			Exposure 2			Exposure 3			χ^2 (df = 2)
		N*	D*	P*	N	D	P	N	D	P	N	D	P	
						Hiroshima female								
	Total	3522	262	74.4	1169	85	72.7	1194	98	82.1	1159	79	68.2	1.73
	0	3522	141	40.0	1169	43	36.8	1194	61	51.1	1159	37	31.9	
	1	3381	43	12.7	1126	19	16.9	1133	12	10.6	1122	12	10.7	
	2	3338	29	8.7	1107	7	6.3	1121	9	8.0	1110	13	11.7	
	3	3309	11	3.3	1100	2	1.8	1112	3	2.7	1097	6	5.5	
Pre-GE-3	4	3298	15	4.6	1098	3	2.7	1109	5	4.5	1091	7	6.4	
	5	3283	11	3.4	1095	5	4.6	1104	4	3.6	1084	2	1.9	
	6	3272	2	0.6	1090	1	0.9	1100	1	0.9	1082	—	—	
	7	3270	—	—	1089	—	—	1099	—	—	1082	—	—	
	8	3270	2	0.6	1089	1	0.9	1099	1	0.9	1082	—	—	
	9	3268	2	0.6	1088	2	1.8	1098	—	—	1082	—	—	
	10	3266	2	0.6	1086	—	—	1098	1	0.9	1082	1	0.9	
	11	3264	1	0.3	1086	—	—	1097	1	0.9	1081	—	—	
	12	3263	1	0.3	1086	1	0.9	1096	—	—	1081	—	—	
	13	3262	2	0.6	1085	1	0.9	1096	—	—	1081	1	0.9	
	14–15		0			0			0			79		
	Total	8422	483	57.3	2784	168	60.3	2812	167	59.4	2826	148	52.4	1.97
	0	8422	293	34.8	2784	90	32.3	2812	108	38.4	2826	95	33.6	
	1	8129	64	7.9	2694	20	7.4	2704	23	8.5	2731	21	7.7	
	2	8065	49	6.1	2674	23	8.6	2681	15	5.6	2710	11	4.1	
	3	8016	21	2.6	2651	9	3.4	2666	6	2.3	2699	6	2.2	
GE-3	4	7995	24	3.0	2642	12	4.5	2660	8	3.0	2693	4	1.5	
	5	7971	12	1.5	2630	7	2.7	2652	1	0.4	2689	4	1.5	
	6	7959	3	0.4	2623	2	0.8	2651	1	0.4	2685	—	—	
	7	7956	5	0.6	2621	1	0.4	2650	2	0.8	2685	2	0.7	
	8	7951	2	0.3	2620	1	0.4	2648	—	—	2683	1	0.4	
	9–12		10			3			3			4		
	Total	4701	139	29.6	1547	50	32.3	1566	38	24.3	1588	51	32.1	2.31
	0	4701	106	22.6	1547	39	25.2	1566	28	17.9	1588	39	24.6	
Sex Ratio	1	4595	12	2.6	1508	6	4.0	1538	3	2.0	1549	3	1.9	
	2	4583	8	1.8	1502	2	1.3	1535	3	2.0	1546	3	1.9	
	3	4575	6	1.3	1500	1	0.7	1532	2	1.3	1543	3	1.9	
	4–7		7			2			2			3		

*N = number of subjects, D = number of deaths, P = death rate per 1,000.

TABLE 6. *(Continued)*

Source of data	Age at death	Total			Exposure 1			Exposure 2			Exposure 3			χ^2 (df = 2)
		N*	D*	P*	N	D	P	N	D	P	N	D	P	
						Nagasaki male								
	Total	1521	136	89.4	507	42	82.8	507	46	90.7	507	48	94.7	0.45
	0	1521	73	48.0	507	23	45.4	507	26	51.3	507	24	47.3	
	1	1448	26	18.0	484	7	14.5	481	7	14.6	483	12	24.8	
	2	1422	10	7.0	477	2	4.2	474	5	10.6	471	3	6.4	
	3	1412	11	7.8	475	3	6.3	469	4	8.5	468	4	8.6	
	4	1401	5	3.6	472	4	8.5	465	1	2.2	464	—	—	
Pre-GE-3	5	1396	1	0.7	468	1	2.1	464	—	—	464	—	—	
	6	1395	3	2.2	467	1	2.1	464	2	4.3	464	—	—	
	7	1392	2	1.4	466	—	—	462	1	2.2	464	1	2.2	
	8	1390	1	0.7	466	—	—	461	—	—	463	1	2.2	
	9	1389	1	0.7	466	—	—	461	—	—	462	1	2.2	
	10	1388	—	—	466	—	—	461	—	—	461	—	—	
	11	1388	2	1.4	466	1	2.1	461	—	—	461	1	2.2	
	12	1386	1	0.7	465	—	—	461	—	—	460	1	2.2	
	13	1385	—	—	465	—	—	461	—	—	459	—	—	
	14–15		0			**0**			**0**			0		
	Total	4544	308	67.8	1513	104	68.7	1520	110	72.4	1511	94	62.2	1.27
	0	4544	201	44.2	1513	71	46.9	1520	72	47.4	1511	58	38.4	
	1	4343	29	6.7	1442	8	5.6	1448	12	8.3	1453	9	6.2	
	2	4314	28	6.5	1434	9	6.3	1436	9	6.3	1444	10	6.9	
	3	4286	12	2.8	1425	5	3.5	1427	5	3.5	1434	2	1.4	
GE-3	4	4274	16	3.7	1420	3	2.1	1422	7	4.9	1432	6	4.2	
	5	4258	4	0.9	1417	1	0.7	1415	1	0.7	1426	2	1.4	
	6	4254	4	0.9	1416	3	2.1	1414	1	0.7	1424	—	—	
	7	4250	—	—	1413	—	—	1413	—	—	1424	—	—	
	8	4250	11	2.6	1413	3	2.1	1413	2	1.4	1424	6	4.2	
	9–12		3			**1**			**1**			1		
	Total	3425	149	43.5	1139	51	44.8	1142	56	49.0	1144	42	36.7	2.15
	0	3425	118	34.5	1139	43	37.8	1142	42	36.8	1144	33	28.9	
Sex Ratio	1	3307	10	3.0	1096	4	3.7	1100	4	3.6	1111	2	1.8	
	2	3297	6	1.8	1092	—	—	1096	2	1.8	1109	4	3.6	
	3	3291	8	2.4	1092	2	1.8	1094	4	3.7	1105	2	1.8	
	4–7		7			2			4			1		

*N = number of subjects, D = number of deaths, P = death rate per 1,000.

TABLE 6. *(Continued)*

Source of data	Age at death	Total			Exposure 1			Exposure 2			Exposure 3			χ^2 (df = 2)
		N*	D*	P*	N	D	P	N	D	P	N	D	P	
						Nagasaki female								
	Total	1502	133	88.5	501	47	93.8	501	48	95.8	500	38	76.0	1.48
	0	1502	65	43.3	501	22	43.9	501	25	50.0	500	18	36.0	
	1	1437	30	20.9	479	12	25.1	476	10	21.0	482	8	16.6	
	2	1407	13	9.2	467	3	6.4	466	6	12.9	474	4	8.4	
	3	1394	7	5.0	464	3	6.5	460	2	4.4	470	2	4.3	
	4	1387	9	6.5	461	3	6.5	458	2	4.4	468	4	8.6	
	5	1378	3	2.2	458	1	2.2	456	2	4.4	464	—	—	
Pre-GE-3	6	1375	1	0.7	457	1	2.2	454	—	—	464	—	—	
	7	1374	—	—	456	—	—	454	—	—	464	—	—	
	8	1374	1	0.7	456	—	—	454	—	—	464	1	2.2	
	9	1373	1	0.7	456	—	—	454	1	2.2	463	—	—	
	10	1372	—	—	456	—	—	453	—	—	463	—	—	
	11	1372	—	—	456	—	—	453	—	—	463	—	—	
	12	1372	1	0.7	456	1	2.2	453	—	—	463	—	—	
	13	1371	—	—	455	—	—	453	—	—	463	—	—	
	14–15		2						0			1		
	Total	4514	286	63.4	1508	93	61.7	1506	85	56.4	1500	108	72.0	3.17
	0	4514	174	38.6	1508	59	39.1	1506	49	32.5	1500	66	44.0	
	1	4340	32	7.4	1449	9	6.2	1457	11	7.6	1434	12	8.4	
	2	4308	25	5.8	1440	9	6.3	1446	9	6.2	1422	7	4.9	
GE-3	3	4283	17	4.0	1431	4	2.8	1437	5	3.5	1415	8	5.7	
	4	4266	15	3.5	1427	5	3.5	1432	4	2.8	1407	6	4.3	
	5	4251	9	2.1	1422	3	2.1	1428	4	2.8	1401	2	1.4	
	6	4242	4	0.9	1419	1	0.7	1424	1	0.7	1399	2	1.4	
	7	4238	4	0.9	1418	—	—	1423	2	1.4	1397	2	1.4	
	8	4234	2	0.5	1418	1	0.7	1421	—	—	1395	1	0.7	
	9–12		4						0			2		
	Total	3381	104	30.8	1126	34	30.2	1128	35	31.0	1127	35	31.1	0.01
	0	3381	79	23.4	1126	26	23.1	1128	26	23.1	1127	27	24.0	
Sex Ratio	1	3302	9	2.7	1100	1	0.9	1102	3	2.7	1100	5	4.6	
	2	3293	6	1.8	1099	3	2.7	1099	3	2.7	1095	—	—	
	3	3287	3	0.9	1096	1	0.9	1096	2	1.8	1095	—	—	
	4–7		7			3			1			3		

*N = number of subjects, D = number of deaths, P = death rate per 1,000.

TABLE 7. CAUSE OF DEATH, EXPRESSED AS SPECIFIC DEATH RATES (PER 10,000) BY MAJOR EXPOSURE GROUP

The numbers on which these rates are based are also given; they correspond to the appropriate totals in Table 2.

Cause of death	Male				Female			
	Total	Exp. 1	Exp. 2	Exp. 3	Total	Exp. 1	Exp. 2	Exp. 3
				Hiroshima				
All causes	613.3	573.6	669.0	596.7	531.1	550.9	545.8	498.8
Infectious disease	66.0	47.2	73.4	77.1	91.3	96.4	89.7	87.9
Neoplasm	*4.5	3.4	10.0	0	6.6	5.5	5.4	9.0
Allergy or nutrition	15.1	15.2	15.0	15.1	10.2	10.9	9.0	10.8
Blood disease	0.6	0	1.7	0	0.6	1.8	0	0
Nervous, sense organ	24.0	25.3	23.4	23.5	18.6	20.0	19.7	16.1
Circulatory system	4.5	6.7	5.0	1.7	7.2	3.6	5.4	12.6
Respiratory system	91.1	86.0	91.8	95.5	65.5	65.5	75.4	55.6
Digestive system	78.8	81.0	85.1	70.4	66.1	85.5	57.4	55.6
Genitourinary system	3.9	1.7	1.7	8.4	3.0	1.8	3.6	3.6
Skin	2.2	3.4	3.3	0	1.2	3.6	0	0
Bone	1.1	1.7	0	1.7	0.6	1.8	0	0
Congenital malformation	24.0	16.9	31.7	23.5	*15.0	12.7	25.1	7.2
Newborn disease	114.0	118.1	135.1	88.8	123.2	120.0	125.6	123.8
Ill-defined	110.1	114.7	105.1	110.6	85.9	81.8	91.5	84.3
Accident	67.6	52.3	80.1	70.4	31.2	36.4	34.1	23.3
Total number of subjects	17887	5927	5994	5966	16645	5500	5572	5573
				Nagasaki				
All causes	624.9	623.6	669.0	581.9	556.6	555.0	535.9	578.8
Infectious disease	99.1	79.1	132.5	85.4	92.6	89.3	79.7	108.7
Neoplasm	12.6	12.7	6.3	19.0	6.4	6.4	3.2	9.6
Allergy or nutrition	15.8	19.0	12.6	15.8	13.8	15.9	12.8	12.8
Blood disease	3.2	0	9.5	0	1.1	0	3.2	0
Nervous, sense organ	12.6	22.2	3.2	12.7	17.0	19.1	15.9	16.0
Circulatory system	3.2	3.2	0	6.3	7.4	3.2	9.6	9.6
Respiratory system	104.3	110.8	104.1	98.0	94.7	98.9	92.5	92.7
Digestive system	69.5	72.8	72.6	63.3	61.7	73.4	60.6	51.2
Genitourinary system	8.4	12.7	9.5	3.2	4.3	3.2	9.6	0
Skin	6.3	9.5	6.3	3.2	3.2	0	3.2	6.4
Bone	0	0	0	0	0	0	0	0
Congenital malformation	23.2	22.2	31.6	15.8	18.1	3.2	25.5	25.6
Newborn disease	154.9	148.8	179.9	136.0	118.1	118.0	108.5	127.9
Ill-defined	71.7	76.0	75.7	63.3	88.3	95.7	82.9	86.3
Accident	32.7	31.7	25.2	41.1	22.3	22.3	25.5	19.2
Total number of subjects	9490	3159	3169	3162	9397	3135	3135	3127

*Difference of death rates among the three exposure groups are statistically significant at 5% level.

more with a view toward the completeness befitting a scientific problem of this gravity than because of prior expectations. Table 7 sets forth deaths per 10,000 for the more common categories of causes of death within sexes, cities, and the three major exposure groups. All three components of the data have been combined in this analysis. For each row, the significance of the difference between the observed number of deaths and the number expected on the basis of random distribution by exposure has been tested by χ^2. We observe only two significant associations, both at the five per cent level and both in Hiroshima. Firstly, deaths from congenital defects differ in females, but as a consequence of relatively more malformations in the lightly exposed than in the heavily or nonexposed groups. Secondly, the frequency with which death results from a neoplasm varies in males, but again the difference is one of

relatively more deaths in the lightly exposed group than in either of the other two. This latter effect does not appear in Nagasaki, although with regard to deaths due to congenital defects a trend similar in some respects to the one observed in Hiroshima does obtain.

It will be recalled that the major exposure groups differ in maternal age, paternal age, and parity, in a manner which might be expected to result in "false" radiation effects. In the face of failure to demonstrate any apparent effects despite these known biases, it is improbable that significance would emerge after analyses which took these variables into account. Nevertheless, because we are interested not only in significance but in a best estimate, which might at some time in the future be combined with the results of others, we have also analyzed the data on a maternal age specific basis, a paternal age specific basis, a parity specific basis, and various combinations of paternal and maternal age and parity. Publication of all the voluminous tables is out of the question. However, Tables 8, 9, and 10 present deaths per thousand by sex, city, and major exposure group for specified maternal ages, specified paternal ages, and specified parities. Perusal of these three tables again fails to suggest any consistent, significant effect of parental exposure. Thus, for example, we note from Table 8 that when mothers are 25–29 years of age (the largest maternal age group), death rates in the lightly exposed exceed those in the heavily exposed group in two of four possible instances, the nonexposed rates exceed those of the heavily exposed group in three of four, and the nonexposed exceed the lightly exposed three out of four times. In the two comparisons where there is significance at the 5% level, the death rates in males born to exposure group 1 parents are lower than those observed for one or both of the control groups. In Tables 9 and 10, there are three additional comparisons at the 5% level of significance. Again exposure group 1 males have *lower* mortality rates. These three tables involve 92 comparisons; the fact that 5 comparisons are significant at the 5% level can be explained by chance. We are intrigued by the *better* survival of group 1 male children in all 5 cases but can scarcely interpret this as a radiation effect! Since, had the deviation been in the opposite direction, it would have been tempting to read greater significance into it, this is a reminder of the need for caution in interpreting data of this type.

There exists the remote possibility, because of the correlations which exist between parental ages and parity, that simultaneous control of two or more of these variates might be informative. Control of all three variables through classification of the data so diminishes the numbers of observations as to make any conclusion hazardous. We do present in Tables 11 and 12, however, for both sexes, cities, and exposure groups, parity specific death rates and paternal age specific death rates for a fixed maternal age, namely, 25–29, chosen for presentation because this encompasses the largest body of data for any such comparison. No trends apparently related to radiation exposure group are to be observed; none of the χ^2's for the row comparisons is significant.

As Fig. 1 illustrates, when the exposure status of both parents is considered, children may fall into any one of nine minor exposure categories. The genetic

TABLE 8. THE RELATIONSHIP BETWEEN MATERNAL AGE SPECIFIC DEATH RATES (PER 1000) AND MAJOR EXPOSURE GROUP. (TOTAL SAMPLE)

The numbers in parentheses are the numbers of children in that category. The number of children whose mother's age at birth was unknown is also indicated.

Maternal age	Male				Female			
	Total	Exp. 1	Exp. 2	Exp. 3	Total	Exp. 1	Exp. 2	Exp. 3
				Hiroshima				
15–19	94.1	90.0	70.6	128.6	81.2	107.5	54.8	73.5
	(255)	(100)	(85)	(70)	(234)	(93)	(73)	(68)
20–24	58.0*	57.6	68.4	48.8	53.1	52.7	54.3	52.5
	(4928)	(1494)	(1651)	(1783)	(4554)	(1442)	(1455)	(1657)
25–29	55.0	54.8	52.5	57.6	44.3	44.2	47.6	41.5
	(7085)	(2334)	(2267)	(2484)	(6563)	(2102)	(2145)	(2316)
30–34	71.3*	56.7	80.0	77.7	59.7	58.0	63.3	57.5
	(3662)	(1253)	(1263)	(1146)	(3419)	(1155)	(1185)	(1079)
35–39	68.2	66.4	79.9	54.2	60.7	74.5	51.7	54.7
	(1554)	(572)	(576)	(406)	(1482)	(537)	(561)	(384)
40–44	72.9	37.0	108.8	80.0	92.1	92.6	90.9	93.8
	(384)	(162)	(147)	(75)	(369)	(162)	(143)	(64)
45+	105.3	166.7	0.0	0.0	166.7	222.2	100.0	200.0
	(19)	(12)	(5)	(2)	(24)	(9)	(10)	(5)
Total	61.3	57.4	66.9	59.7	53.1	55.1	54.4	49.9
	(17887)	(5927)	(5994)	(5966)	(16645)	(5500)	(5572)	(5573)
Unknown	0	0	0	0	0	0	0	0
				Nagasaki				
15–19	87.0	63.8	142.9	28.6	62.5	35.1	62.5	102.6
	(138)	(47)	(56)	(35)	(144)	(57)	(48)	(39)
20–24	78.1	86.9	72.8	74.0	59.8	57.5	67.0	55.0
	(2088)	(725)	(701)	(662)	(2125)	(765)	(687)	(673)
25–29	55.2	49.2	57.6	59.0	49.6	53.2	40.8	54.6
	(3572)	(1241)	(1128)	(1203)	(3409)	(1128)	(1127)	(1154)
30–34	57.6	54.3	64.7	54.3	58.2	60.4	54.0	60.1
	(2151)	(645)	(696)	(810)	(2216)	(695)	(722)	(799)
35–39	60.9	77.4	67.6	37.7	57.8	60.0	56.4	57.2
	(1149)	(349)	(429)	(371)	(1125)	(350)	(408)	(367)
40–44	68.1	56.3	81.1	64.9	67.2	38.8	80.9	87.0
	(367)	(142)	(148)	(77)	(357)	(129)	(136)	(92)
45+	80.0	.0	181.8	.0	.0	.0	.0	.0
	(25)	(10)	(11)	(4)	(19)	(9)	(7)	(3)
Total	62.5	62.4	66.9	58.2	55.7	55.5	53.6	57.9
	(9490)	(3159)	(3169)	(3162)	(9395)	(3133)	(3135)	(3127)
Unknown	0	0	0	0	0	0	0	0

*Difference of death rates among the three exposure groups are statistically significant at 5% level.

complement of children both of whose parents were within 2000 meters of the hypocenter at the time of the blast (minor group *a*) received substantially more radiation than that of children only one of whose parents was within 2000 meters but the other unexposed or lightly exposed (minor groups *b*, *c*, *d*, and *e*). (See Discussion for actual estimates.) Although highly unlikely in view of the foregoing, the possibility had to be considered that a radiation effect

TABLE 9. THE RELATIONSHIP BETWEEN PATERNAL AGE SPECIFIC DEATH RATES (PER 1000) AND MAJOR EXPOSURE GROUP. (TOTAL SAMPLE)

The numbers in parentheses are the number of subjects. The number of children whose father's age at birth of child was unknown is also indicated.

Paternal age	Male				Female			
	Total	Exp. 1	Exp. 2	Exp. 3	Total	Exp. 1	Exp. 2	Exp. 3
				Hiroshima				
15–19	125.0	200.0	.0	.0	142.9	166.7	83.3	250.0
	(16)	(10)	(5)	(1)	(28)	(12)	(12)	(4)
20–24	62.3	51.3	71.4	64.0	53.4	56.3	50.4	53.5
	(1140)	(390)	(406)	(344)	(1011)	(355)	(357)	(299)
25–29	55.2	54.6	59.5	51.5	47.2	49.8	41.4	50.5
	(5018)	(1575)	(1715)	(1728)	(4685)	(1446)	(1594)	(1645)
30–34	58.7	58.0	63.2	55.3	48.5	47.0	58.4	41.4
	(5743)	(1776)	(1851)	(2116)	(5315)	(1680)	(1678)	(1957)
35–39	64.4	60.2	67.3	65.5	53.9	55.9	58.7	47.4
	(3403)	(1129)	(1144)	(1130)	(3115)	(1001)	(1039)	(1075)
40–44	72.0*	51.8	82.9	86.6	72.3	64.7	73.9	80.8
	(1666)	(637)	(567)	(462)	(1646)	(618)	(595)	(433)
45–49	71.3	54.4	91.7	73.5	69.8	92.6	37.7	75.0
	(659)	(294)	(229)	(136)	(602)	(270)	(212)	(120)
50–54	107.7	105.3	133.3	75.0	61.1	60.2	58.8	69.0
	(195)	(95)	(60)	(40)	(180)	(83)	(68)	(29)
55+	65.2	95.2	.0	111.1	114.8	121.2	176.5	.0
	(46)	(21)	(16)	(9)	(61)	(33)	(17)	(11)
Total	61.3	57.4	66.9	59.7	53.1	55.1	54.4	49.9
	(17886)	(5927)	(5993)	(5966)	(16643)	(5498)	(5572)	(5573)
Unknown	1	0	1	0	2	2	0	0
				Nagasaki				
15–19	71.4	.0	142.9	.0	.0	.0	.0	.0
	(14)	(6)	(7)	(1)	(5)	(1)	(3)	(1)
20–24	96.1	98.7	82.1	113.6	50.8	40.9	52.6	62.9
	(562)	(223)	(207)	(132)	(591)	(220)	(228)	(143)
25–29	67.3	72.7	66.1	62.6	54.8	50.6	56.2	58.0
	(2407)	(825)	(847)	(735)	(2392)	(849)	(801)	(742)
30–34	54.4	46.5	59.4	56.9	49.7	53.4	44.7	50.8
	(2940)	(924)	(909)	(1107)	(2795)	(880)	(851)	(1064)
35–39	60.1	59.0	67.9	54.4	60.8	66.9	56.8	59.2
	(1865)	(593)	(574)	(698)	(1893)	(583)	(634)	(676)
40–44	50.0	54.8	59.1	35.1	60.6	60.4	53.6	68.0
	(1079)	(365)	(372)	(342)	(1090)	(364)	(373)	(353)
45–49	64.0	80.0	58.5	49.5	66.4	67.1	68.6	61.9
	(422)	(150)	(171)	(101)	(452)	(164)	(175)	(113)
50–54	110.3	83.3	133.3	108.1	66.7	18.9	94.3	103.4
	(145)	(48)	(60)	(37)	(135)	(53)	(53)	(29)
55+	115.4	41.7	210.5	111.1	71.4	100.0	.0	166.7
	(52)	(24)	(19)	(9)	(42)	(20)	(16)	(6)
Total	62.4	62.4	66.6	58.2	55.7	55.5	53.6	57.9
	(9486)	(3158)	(3166)	(3162)	(9395)	(3134)	(3134)	(3127)
Unknown	4	1	3	0	2	1	1	0

*Difference of death rates among the three exposure groups are statistically significant at 5% level.

TABLE 10. THE RELATIONSHIP BETWEEN PARITY SPECIFIC DEATH RATES (PER 1000) AND MAJOR EXPOSURE GROUP. (TOTAL SAMPLE)

The numbers in parentheses are the number of subjects. The number of children whose mother's parity at birth of child was unknown is also indicated.

	Male				Female			
Parity	Total	Exp. 1	Exp. 2	Exp. 3	Total	Exp. 1	Exp. 2	Exp. 3
				Hiroshima				
1	51.5	50.0	58.4	46.8	45.1	44.1	44.5	46.5
	(5675)	(1839)	(1763)	(2073)	(5345)	(1747)	(1706)	(1892)
2	56.7	59.5	58.1	52.7	48.4	44.1	52.9	48.1
	(5151)	(1698)	(1688)	(1765)	(4713)	(1518)	(1512)	(1683)
3	64.9	59.3	72.9	62.4	46.0	56.4	45.8	36.0
	(3114)	(1046)	(1043)	(1025)	(2979)	(975)	(1005)	(999)
4	73.1*	56.6	69.9	94.7	74.9	90.2	56.1	78.4
	(1751)	(565)	(658)	(528)	(1563)	(543)	(535)	(485)
5	72.9	79.5	66.0	73.9	66.6	68.3	84.1	39.6
	(850)	(302)	(318)	(230)	(826)	(278)	(321)	(227)
6	84.8	73.6	100.0	78.7	78.8	62.5	96.4	72.9
	(460)	(163)	(170)	(127)	(406)	(144)	(166)	(96)
7	99.8*	48.9	134.6	123.6	83.7	87.5	65.9	118.4
	(481)	(184)	(208)	(89)	(418)	(160)	(182)	(76)
Total	60.8	57.3	66.5	58.6	52.0	54.1	52.9	49.1
	(17482)	(5797)	(5848)	(5837)	(16250)	(5365)	(5427)	(5458)
Unknown	405	130	146	129	395	135	145	115
				Nagasaki				
1	70.6	72.7	78.3	59.9	52.5	45.7	48.0	64.6
	(2352)	(825)	(792)	(735)	(2360)	(809)	(792)	(759)
2	52.4	46.7	58.8	52.0	53.2	53.8	59.9	46.5
	(2269)	(728)	(714)	(827)	(2256)	(743)	(718)	(795)
3	62.7	68.9	48.4	69.6	49.5	55.8	43.5	49.2
	(1835)	(595)	(579)	(661)	(1839)	(591)	(598)	(650)
4	54.3	57.1	60.7	45.2	58.8	47.4	60.2	68.8
	(1235)	(403)	(412)	(420)	(1157)	(401)	(349)	(407)
5	57.8	39.4	69.1	65.6	53.5	57.7	54.4	47.6
	(744)	(254)	(246)	(244)	(785)	(260)	(294)	(231)
6	61.8	87.0	65.9	25.9	66.2	102.4	42.9	55.6
	(421)	(138)	(167)	(116)	(393)	(127)	(140)	(126)
7	83.7	73.0	103.6	58.8	76.4	57.3	75.4	104.3
	(502)	(178)	(222)	(102)	(471)	(157)	(199)	(115)
Total	61.8	61.8	66.4	57.0	54.7	53.8	53.4	57.1
	(9358)	(3121)	(3132)	(3105)	(9261)	(3088)	(3090)	(3083)
Unknown	132	38	37	57	136	47	45	44

*Difference of death rates among the three exposure groups are statistically significant at 5% level.

might emerge if the analysis was extended to minor category, and this has been done.

However, when the nine minor exposure groups are compared with respect to the six concomitants for which the three major exposure groups were contrasted (Table 3), not only is there again significant heterogeneity with respect to paternal and maternal ages and parity, but now there is also very significant

TABLE 11. DEATH RATES FOR A FIXED MATERNAL AGE (25–29) BY PARITY PER 1000). (TOTAL SAMPLE)

The numbers in parentheses are the number of subjects. The number of children whose mother's age at birth was known but the parity was not is indicated.

	Male				Female			
Parity	Total	Exp. 1	Exp. 2	Exp. 3	Total	Exp. 1	Exp. 2	Exp. 3
				Hiroshima				
1	46.0	42.5	51.8	44.5	33.3	25.3	36.1	38.2
	(1828)	(636)	(541)	(651)	(1830)	(592)	(609)	(629)
2	52.5	52.0	52.5	52.9	40.6	42.4	46.8	33.8
	(2706)	(885)	(857)	(964)	(2485)	(778)	(790)	(917)
3	54.1	61.0	40.9	60.1	38.7	49.7	34.3	33.1
	(1571)	(508)	(514)	(549)	(1473)	(463)	(496)	(514)
4+	84.4	78.7	75.9	100.0	84.8	79.5	88.8	86.8
	(794)	(254)	(290)	(250)	(672)	(239)	(214)	(219)
Total	54.8	54.3	52.7	57.2	42.7	43.4	45.0	39.9
	(6899)	(2283)	(2202)	(2414)	(6460)	(2072)	(2109)	(2279)
Unknown	186	51	65	70	103	30	36	37
				Nagasaki				
1	56.8	51.5	66.0	52.6	43.9	32.1	34.7	65.5
	(345)	(291)	(288)	(266)	(843)	(280)	(288)	(275)
2	49.5	30.5	52.3	64.9	50.4	52.2	42.1	57.0
	(1172)	(393)	(363)	(416)	(1130)	(364)	(380)	(386)
3	54.8	61.2	45.1	56.6	39.0	50.2	42.3	25.9
	(949)	(343)	(288)	(318)	(872)	(279)	(284)	(309)
4+	54.1	50.0	72.6	39.8	71.4	82.5	47.3	82.8
	(555)	(200)	(179)	(176)	(532)	(194)	(169)	(169)
Total	53.4	47.3	57.2	56.1	49.2	51.9	41.0	54.4
	(3521)	(1227)	(1118)	(1176)	(3377)	(1117)	(1121)	(1139)
Unknown	51	14	10	27	32	11	6	15

heterogeneity in most of the comparisons with respect to year of birth and birth weight, although to a lesser degree than for the first three concomitants. Fig. 2 illustrates for male births the year-of-birth effect during the 13 years of the program in Hiroshima. It will be noted that the line dividing groups *a*, *b*, *c*, *d*, and *e* collectively (major exposure group 1) from groups *f*, *g*, and *h* (major exposure group 2) and the line dividing *f*, *g*, and *h* (group 2) from *i* (group 3) is relatively straight, thus attesting to the effectiveness of the original matching procedure. The significant year-of-birth effects emerge from the changes with time of the proportions of the minor exposure categories within the respective major exposure groups, for which the data were of course unmatched. At least two reasons for the significant year-of-birth effect are apparent from inspection of Fig. 2. On the one hand, the representation of certain subgroups appears to increase (group *c*) or diminish (groups *a* and *f*) with time. On the other hand, for some exposure groups there appear to be increases followed by decreases (groups *e* and *h*).

The several significant differences (none exceeding the 0.01 level) between minor exposure classes with respect to birth weight are in general due to

TABLE 12. DEATH RATES FOR A FIXED MATERNAL AGE (25–29) BY PATERNAL AGE (PER 1000). (TOTAL SAMPLE)

The numbers in parentheses are the number of subjects. The number of children whose mother's age at birth was known but the parity was not is indicated.

Paternal age	Male				Female			
	Total	Exp. 1	Exp. 2	Exp. 3	Total	Exp. 1	Exp. 2	Exp. 3
				Hiroshima				
–24	59.9	45.5	72.7	65.2	59.3*	20.0	29.4	147.1
	(167)	(66)	(55)	(46)	(118)	(50)	(34)	(34)
25–29	50.2	51.2	48.1	51.4	34.9	36.1	30.9	38.1
	(1971)	(645)	(665)	(661)	(1891)	(581)	(680)	(630)
30–34	55.1	53.6	53.9	57.4	43.5	43.3	53.8	35.1
	(3485)	(1101)	(1095)	(1289)	(3193)	(992)	(1004)	(1197)
35–39	55.6	56.0	46.8	63.4	56.8	57.5	64.3	49.2
	(1206)	(411)	(385)	(410)	(1056)	(348)	(342)	(366)
40+	85.9	90.1	89.6	76.9	62.7	62.0	47.1	78.7
	(256)	(111)	(67)	(78)	(303)	(129)	(85)	(89)
Total	55.0	54.8	52.5	57.6	44.4	44.3	47.6	41.5
	(7085)	(2334)	(2267)	(2484)	(6561)	(2100)	(2145)	(2316)
Unknown	0	0	0	0	2	2	0	0
				Nagasaki				
–24	87.5	0.0	148.1	142.9	62.5	74.1	31.3	95.2
	(80)	(32)	(27)	(21)	(80)	(27)	(32)	(21)
25–29	57.4	55.8	51.8	66.4	44.4	35.8	49.5	47.8
	(1081)	(394)	(386)	(301)	(1082)	(363)	(384)	(335)
30–34	49.9	44.1	46.9	57.8	51.0	60.4	36.6	55.3
	(1762)	(589)	(533)	(640)	(1568)	(497)	(492)	(579)
35–39	54.7	59.1	68.5	40.4	49.6	50.3	39.1	59.1
	(530)	(186)	(146)	(198)	(564)	(199)	(179)	(186)
40+	93.2	51.3	166.7	69.8	69.6	119.0	25.0	60.6
	(118)	(39)	(36)	(43)	(115)	(42)	(40)	(33)
Total	55.2	49.2	57.6	59.0	49.6	53.2	40.8	54.6
	(3571)	(1240)	(1128)	(1203)	(3409)	(1128)	(1127)	(1154)
Unknown	1	1	0	0	0	0	0	0

*Difference of death rates among the three exposure groups are statistically significant at 5% level.

heavier birth weights among the groups where exposure was greatest and are thought to be secondary to the age and parity effects which have already been discussed. A "duration of pregnancy" heterogeneity is observed in a single comparison among twelve and may be disregarded. Because of the declining infant and childhood mortality in Japan during the years of this study, it was felt the data should be adjusted for the year-of-birth effect. Accordingly, we present in Table 13 an analysis wherein by city, sex, and program component the observed number of deaths in each minor exposure category is compared with expectation adjusted for differences in years-at-risk per individual for the exposure subgroups. Table 13 reveals two differences at the 5% level of significance, both (again) resulting from a deficiency of deaths among the children of the more heavily irradiated parents.

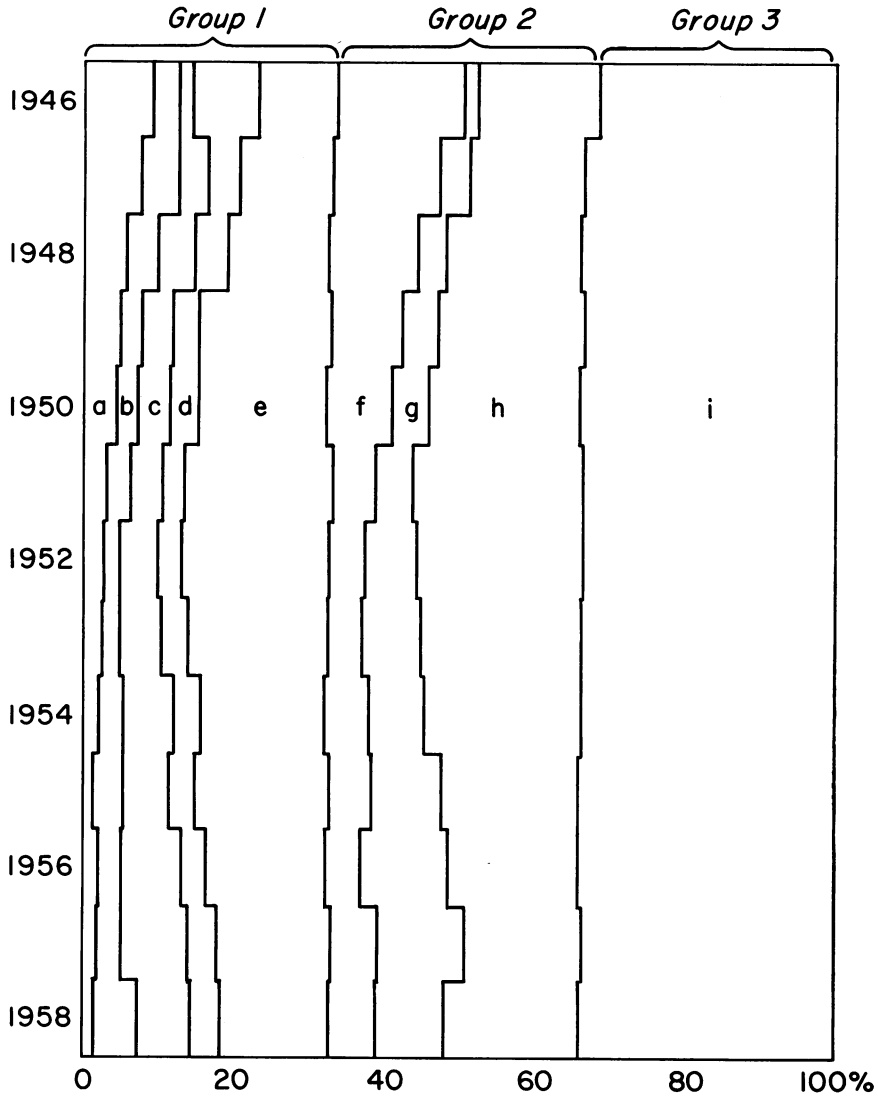

FIG. 2. The contributions of the nine minor exposure groups to the samples available for each year in the interval 1946–1958. The different minor exposure groups are indicated by the same letters as those given in Fig. 1.

Before we enlarge further on these findings, it seems appropriate to inquire into the magnitude of the differences between cohorts which should be detectable with samples of this size. It is conceivable that our failure to find significant differences reflects samples too small to afford a reasonable test of whether the groups under discussion are or are not different. What constitutes a reasonable test involves an intuitive appraisal of the risks to be associated with the two types of judgmental errors which can be made, namely, to assert that there is an effect of radiation when, in fact, there is none, the so-called Type I error, or to assert that there is no effect when, in fact, there is one, the Type II error. The frequency of the former is specified by the level of con-

TABLE 13. A COMPARISON OF OBSERVED AND EXPECTED DEATHS BY MINOR EXPOSURE GROUPS, EXPECTATION BEING AGE-ADJUSTED BECAUSE OF HAVING MEAN PERIODS OF RISK OF DEATH IN THE EXPOSURE GROUPS

		Exposure subgroup									χ^2 (df = 8)
		a	*b*	*c*	*d*	*e*	*f*	*g*	*h*	*i*	
						Hiroshima					
Male											
	Observed death	18	13	19	13	22	38	10	54	103	18.11*
Pre-GE-3	Person-year	3945.0	2423.0	1744.0	2548.5	6034.5	7169.0	1647.5	7765.0	16208.5	
	Expected death	22.9	14.1	10.1	14.8	35.0	41.6	9.6	45.0	94.0	
	Death rate	4.6	5.4	10.9	5.1	6.1	3.6	5.3	7.0	6.4	
	Observed death	27	20	31	16	91	55	43	134	193	13.76
GE-3	Person-year	3867.5	2719.0	4307.5	3439.0	17021.0	7200.5	5126.5	19184.5	31695.0	
	Expected death	24.8	17.4	27.6	22.0	108.9	46.1	32.8	122.8	202.8	
	Death rate	7.0	7.4	7.2	4.7	5.3	7.6	8.4	7.0	6.1	
	Observed death	7	8	12	10	33	16	20	31	60	8.98
Sex Ratio	Person-year	603.5	1048.0	2099.5	1014.5	4862.5	1540.0	2794.0	5397.0	9837.5	
	Expected death	4.0	7.0	14.1	6.8	32.6	10.3	18.7	36.2	65.9	
	Death rate	11.6	7.6	5.7	9.9	6.8	10.4	7.2	5.7	6.1	
Female											
	Observed death	25	16	8	11	25	41	13	44	79	7.05
Pre-GE-3	Person-year	3735.0	2403.0	1230.5	2308.5	6170.5	6837.0	1861.5	7298.5	15737.5	
	Expected death	20.5	13.2	6.8	12.7	33.9	37.6	10.2	40.1	86.6	
	Death rate	6.7	6.7	6.5	4.8	4.1	6.0	7.0	6.0	5.0	
	Observed death	23	14	32	17	82	42	33	92	148	9.35
GE-3	Person-year	3901.0	2670.0	4033.5	2966.0	15954.5	6813.0	5127.0	17856.0	30197.0	
	Expected death	20.7	14.2	21.4	15.7	84.6	36.1	27.2	94.6	160.0	
	Death rate	5.9	5.2	7.9	5.7	5.1	6.2	6.4	5.2	4.9	
	Observed death	4	4	7	3	32	1	16	21	51	13.39
Sex Ratio	Person-year	630.0	847.5	1924.5	940.5	4362.0	1207.5	2449.5	5212.0	8929.0	
	Expected death	3.3	4.4	10.0	4.9	22.7	6.3	12.7	27.1	46.4	
	Death rate	6.3	4.7	3.6	3.2	7.3	0.8	6.5	4.0	5.7	

*Difference of death rates among the nine exposure groups are statistically significant at 5% level.

TABLE 13. *(Continued)*

		Exposure subgroup									χ^2 (df = 8)
		a	*b*	*c*	*d*	*e*	*f*	*g*	*h*	*i*	
						Nagasaki					
Male											
	Observed death	3	10	—	7	22	16	10	20	48	17.69*
Pre-GE-3	Person-year	797.0	1308.0	788.0	1153.5	2646.0	3145.5	676.0	2812.0	6632.5	
	Expected death	5.4	8.9	5.4	7.8	18.0	21.4	4.6	19.1	45.1	
	Death rate	3.8	7.6	0.0	6.1	8.3	5.1	14.8	7.1	7.2	
	Observed death	8	22	17	6	51	31	12	67	94	8.20
GE-3	Person-year	1005.0	3372.5	2304.5	1684.5	6926.0	4542.5	2451.0	8293.5	15401.5	
	Expected death	6.6	22.3	15.2	11.1	45.7	30.0	16.2	54.7	101.6	
	Death rate	8.0	6.5	7.4	3.6	7.4	6.8	4.9	8.1	6.1	
	Observed death	3	13	4	8	23	13	12	31	42	9.98
Sex Ratio	Person-year	303.5	1088.5	1112.0	663.5	3106.0	1605.5	1146.5	3513.0	6358.0	
	Expected death	2.4	8.5	8.7	5.2	24.2	12.5	8.9	27.4	49.6	
	Death rate	9.9	11.9	3.6	12.1	7.4	8.1	10.5	8.8	6.6	
Female											
	Observed death	5	14	5	6	17	24	5	19	38	3.26
Pre-GE-3	Person-year	966.0	1783.5	738.0	711.5	2361.5	2990.0	739.0	2808.5	6660.0	
	Expected death	6.5	11.9	4.9	4.8	15.8	20.0	5.0	18.8	44.6	
	Death rate	5.2	7.8	6.8	8.4	7.2	8.0	6.8	6.8	5.7	
	Observed death	6	18	9	12	48	24	14	47	108	7.77
GE-3	Person-year	1270.5	2763.0	2452.0	1517.0	7354.5	4206.0	2457.5	8742.5	15154.0	
	Expected death	7.9	17.1	15.2	9.4	45.6	26.1	15.2	54.2	94.0	
	Death rate	4.7	6.5	3.7	7.9	6.5	5.7	5.7	5.4	7.1	
	Observed death	3	3	11	4	13	9	4	22	35	7.82
Sex Ratio	Person-year	281.5	1007.0	1213.0	754.5	2882.0	1493.5	1195.0	3452.5	6122.5	
	Expected death	1.6	5.6	6.8	4.2	16.1	8.4	6.7	19.3	34.3	
	Death rate	10.7	3.0	9.1	5.3	4.5	6.0	3.3	6.4	5.7	

*Difference of death rates among the nine exposure groups are statistically significant at 5% level.

fidence which characterizes the test of significance upon which one bases his judgment of whether there is or is not a difference. Conventionally, this is taken to be 0.05. In a fixed sample, when one compares two percentages, the frequency of the Type II error depends upon the size of the samples and the difference between the frequency of the event of interest in a "standard" population and a population to be compared with the standard. Presumably we should like this type of error to be as small as practicable, certainly not greater than one chance in ten, and possibly as small as one in twenty.

To determine whether the cohorts are adequate in the sense that the frequency of Type II errors is small for a variety of reasonable alternatives to the null hypothesis, we have made the following simplifying assumptions: We have assumed that the test of significance to be used to ascertain whether an irradiation effect has or has not occurred involves *either* a comparison of the frequency of death in Exposure Group 1 with that in Exposure Group 2, *or* a comparison of Exposure Group 1 with Exposure Group 3, *or,* finally, a comparison of Group 2 with Group 3. Clearly, the frequency of death in the comparison group, the standard, will depend upon the total number of years at risk of death for the cohort and this will vary with the passage of time. Rather, therefore, than arbitrarily specify some one mortality rate, we have concerned ourselves with the difference between the two groups which we believe it is important to detect whatever may be the frequency of the standard. To avoid the theoretical as well as the computational complications introduced by the fact that the variance of a proportion varies with the proportion, we have elected to replace the frequencies of death by their angular (arcsin) equivalents and thus to concern ourselves with the angular difference (as expressed in degrees) between two percentages which it would be desirable to detect.

Under the conditions set out above, it is possible to show (see Eisenhart, Hastay, and Wallis, 1947) that

$$\xi_D^2 = (1641.6/N)\ (K_a + K_b)^2$$

where ξ_D^2 is the angular difference expressed in degrees, N is the number of observations upon which each of the two estimates of the frequency of death is based, K_a is the normal deviate associated with a confidence level of 0.05 when one is interested in deviation in only one direction from the standard (hence $K_a = 1.645$), and K_b is the frequency of the second type of error previously discussed.

Figure 3 discloses the frequency of Type II errors, say β, expected for various angular differences when the two sample sizes are presumed to be 17,721, the size of the Exposure Group 1 cohort. We note from this figure that if we presume β to be 0.05, then the sample is large enough to detect an angular difference of 1.0. What this means in terms of percentages depends, of course, upon the frequency of deaths in the standard. If the frequency of death in the standard is 0.050, then from a table of the angular transformation (see, for example, Fisher and Yates, 1938, Table XII), we find that these samples are adequate to detect an increase to about 0.058; if the frequency is 0.100, then we could detect a shift wherein the frequency of deaths in the

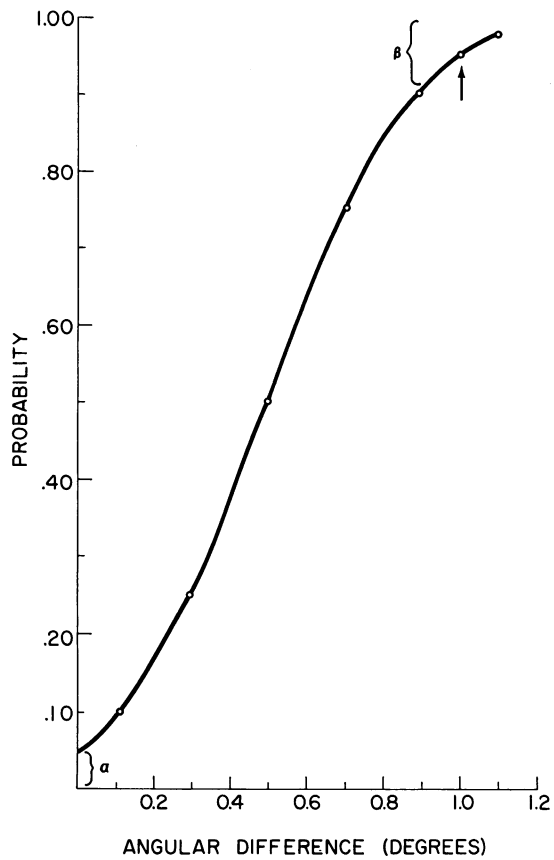

FIG. 3. The operating characteristic of a test comparing two percentages derived from samples of equal size, where the samples consist of 17,721 observations. The ordinate is the power of the test, that is, $1 - \beta$, where β is the frequency of a type II error. The abscissa is the angular difference in degrees between the per cent mortality in the exposed group and in the comparisons group.

exposed cohort equaled or exceeded 0.110. To a close approximation, then, and within the range of interest to us, we are in a position to detect a 10% deviation from the standard, that is, the death rate in the comparison cohort.

DISCUSSION

There emerges from this study no indication that the exposure of parents to the atomic bombs has altered the life expectancy of their children. This failure to demonstrate significant changes in F_1 mortality as a function of parental exposure of course can not be construed as evidence that no genetic effects resulted from exposure to these nuclear devices. Unless one is willing to argue that man differs from all other forms of life thus far studied, lethal and semilethal mutations of a type which might manifest themselves as mortality in the first decade or so of life were induced. But the present study provides no evidence for their existence.

The exact importance to be attached to the present observations depends, of

course, on the estimated mean exposure to radiation experienced by the various exposure groups. The problem of estimating the amount of radiation received by persons exposed to the atomic bombs in Hiroshima and Nagasaki is still troublesome today, after 20 years of study of the question (see, for example, Neel and Schull, 1956; Ritchie and Hurst, 1959; Arakawa, 1960). At present the ABCC employs the so-called T57 Dose Scale, developed on the basis of the reports of Ritchie and Hurst (1959) and Arakawa (1960) and based on distance from the hypocenter and shielding. The estimates of individual dosage so obtained are considered to be accurate, for each city, only to a factor of 2, i.e. the true dose may be as low as 50% of the T57 estimate or it may be 100% greater than the T57 estimate (Jablon, Ishida, and Beebe, 1963). One of the uncertainties in the estimate stems from the fact that for neither of the atomic bombs detonated is the yield accurately known. Efforts to refine all of the factors entering into dose estimates are continuing, but for the present we must be content with this range of uncertainty. This T57 dose is for whole body radiation and fails to take all aspects of shielding into consideration; the gonad dose will presumably be less, although, because of the high energy of the radiation, the attenuation factor should be minor.

A dose estimate is not available for all parents of the subjects for this study. However, the majority of the parents exposed under 2000 m (exposure group 1) are also included (with additional persons of similar radiation background) in a life span study of the survivors being conducted by ABCC. In connection with this study, an average T57 dose has been derived for each 100 m zone, and, as a simple approximation, survivors in each 100 m zone have been assigned the average T57 dose for that zone. This procedure is less than ideal but it seemed likely that the inaccuracies would prove to be of minor importance compared to the 150-fold variations in dose as between 700 and 2000 m. The average dose received by both parents of children in major exposure group 1 thus estimated was 191 and 220 rad in Hiroshima and Nagasaki respectively. These averages are perhaps unduly influenced by a relatively few persons to whom the T57 scale assigns doses presumably incompatible with survival. The median doses, which might be more appropriate under these circumstances, are 65 rad for Hiroshima and 96 rad for Nagasaki. Since the distance-dose curve reveals that radiation is approximately 5 rad and diminishing steadily at 2500 meters, the average dose for exposure group 2 can be considered negligibly close to the background dose. It must be again emphasized, however, that in view of the various problems regarding dosimetry mentioned above, it would be unwise to regard the particular numbers used for dose as more than rough approximations. Using the T57 data, the mean joint exposures to be attributed to parents falling into the various minor categories of major group 1 may be estimated as: for Hiroshima, 270, 184, 187, 130, and 187 rad for groups *a, b, c, d,* and *e* respectively; for Nagasaki, 285, 212, 202, 210 and 223 rad for these same groups. These estimates, incidentally, do not differ to a significant degree from those derived by Neel and Schull in their earlier treatment of this problem.

Assuming the approximate correctness of these dose estimates, is the present

lack of findings consistent with the corpus of experimental data, as well as the other observations on human material? Much of the recent experimental work has been concerned with the effects of chronic radiation repeated over many generations. Both because of the higher genetic yield of x units of radiation given in a single rather than divided doses (Russell, Russell and Kelley, 1958) and the opportunities for selection under these conditions, direct comparisons with these investigations seem unwise. With respect to acute radiation whose effects were evaluated in the first generation following parental exposure, there is still no abundance of data for completely relevant comparisons with the findings of this investigation. In fact, because of differences in the length of life cycle and the "medical care" received by the "indisposed," the "litter size effect" (see below), and differing intervals between radiation and conception, there is room for equivocation regarding any comparison of data from other mammals with man. Perhaps the most germane comparison possible with the present material would be three-week or pre-weaning mortality or a reasonable approximation thereto in experimental mammals with deaths under one year of age in man. Since the present data are so predominantly concerned with offspring resulting from germ cells which in the male were in the spermatogonial stage at the time of radiation and in the female dictyate-stage oöcytes, and because of the relationship between stage of maturation at time of irradiation and genetic yield, comparisons should be restricted to the "post-sterile period" offspring of experimental mammals.

For mice, Russell (Russell, 1955; Russell and Russell, 1959), in extensive experiments, has reported a significant reduction in mean number of offspring at weaning (age 3 weeks) following acute paternal X irradiation. In the largest series, a paternal exposure of 300 r, with mating in the post-sterile period, resulted in a reduction in litter size at weaning of 3.8%. Mean number of liveborn offspring is not given. Kohn (1960) has reported a statistically non-significant decrease in liveborn litter size and pre-weaning survival in the offspring of male mice receiving 525 r in either a single or a divided dose and mated during the post-sterile period. Sugahara (1964) has reported significantly *larger* litter sizes and pre-weaning mortality among the offspring of male mice receiving an acute dose of 600 r and mated during both the pre- and post-sterile period. Finally Frölen (1965) found no significant differences in life span between 161 F_1 males whose fathers had received 500 r of X rays and a control group.

In rats, Chapman, Hansen, Havenstein, and Morton (1964) failed to observe a significant effect on survival up to 69 days in the offspring of males who received 450 r in three divided doses and for whom, because of the experimental design, it was assumed that the sperm responsible for fertilization were from irradiated spermatogonia. Litter size was affected differently by irradiation of the male and female parents; in the rat, unlike the mouse, probability of death appears to decrease with increasing litter size (McGregor, James, and Newcombe, 1960).

In studies utilizing swine, Cox and Willham (1962) reported that following an acute dose of 300 r of X rays to males mated during the post-sterile period,

mortality in their liveborn offspring during the first three weeks of life was significantly increased. However, a later report (D. F. Cox, 1964) found that this apparent effect was confounded by differences in litter size between irradiated and control animals; no statistically significant effect remained when this fact was taken into consideration. This report raises the question of a nonspecific litter size effect in other experimental work with mammals.

The studies on this problem which utilized human material have all been negative. Aside from our own previous reports, the only studies on the effect of acute radiation on survival of offspring involve very small series concerned with the progeny of seemingly infertile women whose infertility was treated with 60 to 65 r of ovarian X radiation (Kaplan, 1957) or of women who in the course of multiple diagnostic X rays received a dose between 7.5 and 20 rads (D. W. Cox, 1964). Not surprisingly, no effects were observed. Neither Crow (1955) nor Macht and Lawrence (1955) noted increased infantile mortality among the children of American radiologists. The gonad doses of chronic irradiation are quite uncertain. Finally, Tanaka and Ohkura (1958) report an insignificant increase in first year mortality among the children of Japanese X-ray technicians as contrasted with the children of pharmacy technicians, from 1.9% to 2.6%, the mean gonad dose in the former being estimated at between 230 and 575 r of X radiation delivered in small pulses over an average of 11.5 years.

In summary, for few of the observations on experimental mammals and none on man are the effects of irradiation on survival in the F_1 significant. However, for the experimental material the trend is in the direction suggested by genetic hypothesis, i.e. reduced survival. Unfortunately, until the confounding effect of litter size has been removed from the experimental data as well as certain other possible biases summarized by Roderick (1964), a direct comparison with the studies on man is not advisable. Although litter size is usually decreased following paternal irradiation, it is sometimes increased. Inspection of the published data suggests that the variance in litter size may also be increased after radiation, making simple corrections difficult. Litter-size specific mortality figures are an obvious step towards accurate comparisons. Whether, because of the possibility of a degree of prenatal selection due to intrauterine competition in litter bearing mammals, even these data can be directly compared with human data is a moot point. However, most investigators would probably agree that there is no conflict between the results of the present studies and those with experimental mammals, even with allowance for the inclusion in the radiation spectrum of the atomic bombs of a neutron component with a higher relative biological effectiveness than gamma radiation.

Russell (1965) has recently reported that the yield in mutations diminishes as the interval between irradiation and conception increases. Since this study reaches back to include the first post-exposure conceptions, it therefore includes the interval most appropriate to the demonstration of atomic-bomb induced mutations.

One wonders whether further study of this group of children is warranted. Certainly we recognize that some 85% of mortality prior to the age of maturity

(say, 20 years) has occurred before the age of 10, and that, therefore, the mortality to be experienced by these groups in the immediate future is minor compared to what has already been experienced. It seems doubtful indeed that further study is likely to be rewarding within the next decade. However, the issues are such that, in the face of any uncertainty, continued study is desirable and uncertainties do exist. In particular it may be argued that the level of medical care in man delays "genetic deaths" until relatively late in the life span. The present study with its orientation toward cohorts and *koseki* determination of fact of death does not require annual nor biennial ascertainment of survivorship status to maintain the necessary currency of address, etc., so that follow-up can continue. It is thus possible to permit a lapse of time such as to increase meaningfully the numbers of deaths before a further cycle of *koseki* checking is initiated.

EPILOGUE

The probability of the increasing exposure of the human species to ionizing radiation has led to much concern among geneticists and others concerning "permissible" levels of exposure. A guide figure in this discussion has been the doubling dose, i.e., the amount of radiation producing the same rate of mutation as that occurring spontaneously each generation. The estimates employed in the most authoritative pronouncements to date are 30–80 r (National Academy of Sciences, 1956) and 10–100 r (United Nations, 1958). The present data, when coupled with several other recent advances in our knowledge of mammalian radiation genetics, would appear to permit a refinement of that estimate. As noted earlier, this study excludes, at the 10% probability level, an increase in the death rate in the children of Group 1 parents in excess of 1%. In this material, some 7% of liveborn children succumb prior to age 8. In order to utilize these data to derive an estimate of the doubling dose, we need to know what proportion of these deaths is due to mutation in the preceding generation, i.e., due to newly arisen dominant mutations lethal prior to age 8. There is no figure presently available based on a detailed study of this mortality experience and, indeed, our present procedures are probably inadequate to the challenge. However, an indirect approach can help us set an approximate figure. Muller (1950) has suggested that a conservative estimate of the total mutation rate per gamete in man is of the order of 0.1. We have suggested that the true value may be several times this (Neel and Schull, 1954) but will work with the more conservative figure for the present. From this value, it follows that about 20% of the population carries a new mutation each generation. From the accumulated literature on the phenotypic effects of spontaneous mutation in *Drosophila,* mice, and man, it seems reasonable to assume that at present in man at least 1 in 40 of these "new" mutations results in an early death, i.e., that in civilized countries with high standards of living, such as Japan, 0.5% of liveborn children die prior to age 8 because of mutation (chromosomal and point) in the preceding generation. This is equivalent to saying that currently approximately 1 in 14 children in Japan dying before age 8 does so because of dominant mutation in the preceding generation. If this assump-

tion is accepted, and it is obviously a key assumption, and if we assign a total parental radiation dose of 100 rad units to Group 1 parents (again conservative),* then the minimal doubling dose for radiation of the Hiroshima-Nagasaki type, for mutations causing postnatal death, is simply

$$\frac{(\text{mean parental dose}) \times \begin{pmatrix}\text{mortality due to spontaneous} \\ \text{mutation in preceding generation}\end{pmatrix}}{(\text{increase in mortality excluded by present data})} = \frac{100 \times 0.5}{1.0} = 50\,\text{r}$$

The propriety of using the present data for this type of calculation is in our opinion reinforced by the fact that of the four other indicators of possible genetic damage studied in Hiroshima and Nagasaki (sex ratio, malformation rate, birth weight, frequency of stillbirth), only one (sex ratio) has shown even a suggestion of a change (Neel and Schull, 1956; Schull and Neel, 1959; Neel, 1963; Schull, Neel, and Hashizume, 1966). It should be pointed out that this calculation makes no assumptions concerning genetic equilibrium, requiring only that the proportion of newly arisen mutations manifesting themselves through death in the next generation is the same for spontaneous and induced mutations.

Two apparently well established facts from mammalian radiation genetics would seem to necessitate a revision of this estimate before it can be applied to a variety of human problems. Firstly, Russell, Russell, and Kelley (1958) and Russell, Russell, and Cupp (1959) have shown that for both male and female mice, the greater the dose rate the higher the yield of mutations for a given dose. The radiation received by the survivors of Hiroshima and Nagasaki was delivered at a relatively high dose rate. Secondly, Russell (1965) has demonstrated a marked decrease in the yield of mutations in the later litters as contrasted with the earlier litters of radiated female mice. Now, the chief sources of human exposure to ionizing radiation—medical and fall-out—involve substantially lower dose rates than in Hiroshima and Nagasaki and, in addition, the average interval between exposure and reproduction will be somewhat longer than the interval in this study. Although a direct and literal extrapolation from mouse to man seems unwise, the aforementioned results in our opinion would lead to a revision of the derived minimal estimate of 50 r to something of the order of 100 r.

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*Since this manuscript was submitted, Auxier *et al.* (Free-field radiation-dose distributions from the Hiroshima and Nagasaki bombings. *Health Physics* 12: 425–429, 1966) have published revised distance-dose curves for Nagasaki and Hiroshima. That for the former city is essentially unchanged. For the latter, there is a significant revision downwards from former estimates, doses being approximately halved at most distances compatible with survival for subjects in the open. The precise effect of this revision on the estimates used in this paper cannot be determined until detailed calculations which include allowance for shielding have been completed. However, the purposely conservative figure of 100 rad for Group 1 parents used in this calculation is now almost certainly more appropriate for Hiroshima than the mean total parental dose of 191 rad given earlier.

SUMMARY

A cohort-type study of children born subsequent to the atomic bombings of Hiroshima and Nagasaki and divisible into three groups on the basis of parental exposure (a heavily exposed group, a lightly exposed one, and a nonexposed set) has failed to disclose significant variation in mortality ascribable to differences in radiation. The average number of years at risk is nine but varies from three to 15 years. Though the comparison groups differ significantly with respect to certain extraneous sources of variation in mortality, notably, parental ages and birth rank, the failure to observe significant mortality differences among the exposure groups is not attributable to the existence of this concomitant variation. In view of the number of years of death at risk on the average and the knowledge that the bulk of mortality prior to the twenty-first birthday is, in fact, prior to the tenth, it seems improbable that mortality prior to maturity can be shown to be a function of parental exposure in either Hiroshima or Nagasaki. Our failure to demonstrate significant differences among the exposure groups does not necessarily imply that there are no differences. It merely means that within these years and numbers of observations no effect is to be seen.

These data, considered in conjunction with the other data from Hiroshima and Nagasaki, may be utilized to approximate the minimal doubling dose for man, i.e., the amount of radiation necessary to produce the same number of mutations as occur spontaneously each generation. It is suggested that the present findings render it unlikely that the figure is less than 50 r for radiation of the type emitted by an atomic bomb and for mutations of the type resulting in early death in the first post-bomb generation. It is further suggested that under the more usual conditions of human exposure to radiation, the doubling dose for mutations of this type is of the order of 100 r.

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