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A SURVEY OF CHILDHOOD MALIGNANCIES

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SECTION I. BACKGROUND TO THE SURVEY

The present survey is based on an earlier study of the vital statistics relating to leukaemia (Hewitt, 1955). This had revealed an unusual peak of mortality in the third and fourth years of life which indicated that the subsequent survey should, in the first instance, be restricted to children. The earlier investigation had also led to the suggestion that it might be particularly worth while to study modern innovations, such as radiology.

Method

An attempt was made to trace all children in England and Wales who had died of leukaemia or cancer before their tenth birthday during the years 1953 to 1955 (case group) and to compare their pre-natal and post-natal experiences with those of healthy children (control group). Details of control selection and method of recording data are given later, but the basic idea was to obtain the necessary facts from the mothers by sending a specially appointed " survey doctor " to interview, first, the mother of a dead child, and, secondly, the mother of a live child matched for age, sex, and locality but otherwise picked at random from the local birth register.

Available Cases.—The total number of deaths in the category required was 1,694, of which 792 were ascribed to leukaemia and 902 to other cancers (Registrar-General, 1954–6). By May, 1957, the mothers of 1,416 of these children had been interviewed (677 leukaemia and 739 other cancers). The lost cases represented 16.4% of the total, and included 6.8% who belonged to families that had moved abroad or to an unknown address and 3.1% where the interview could not be arranged in time. The remainder represented refusals to co-operate, 4.5% by parents and 2.0% by doctors.

Appointment of Survey Doctors.—It was a basic principle of the survey that the same doctor should interview both mothers of a given case/control pair, but that pairs in different local authority areas might be seen by different doctors. The 90 pairs belonging to the London County Council area were seen by one of us (J. W.) and the remaining 1,326 pairs by " survey doctors " appointed by the principal medical officer of health to the areas. All local authorities co-operated, so that all parts of the country are represented in the survey. To ensure uniformity in the recording of data and the selection of controls one of us (A. S.) visited each one of the health departments to give detailed instructions about field-work procedures.

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Collecting of Data

Each survey doctor was given a list of the cases in his area. If the mothers or foster-mothers were still living in the area he was to see them and the corresponding control-mothers : if a mother had left the area he was to find and interview a control, but return the case papers to Oxford. These were eventually sent on to the new area, but in this way a central record was kept of all " transfers." No case/control pairs seen by different doctors have been included in the analyses making direct comparison between cases and controls, but they may feature in other analyses—for example, incidence of mongolism. Since the records obtained from foster-mothers contained no information about the pre-natal environment they too have been excluded from the case/control comparisons.

The questionaries for recording the interviews were the same for cases and controls, and were distributed in pairs bearing the same serial number and a so-called final date. This was the date of death of the case, and was a reminder that the medical history of the control child should cease at the so-called onset date—that is, the date when the corresponding child fell ill. The first half of the questionary described the children's medical experiences before the onset date—that is, illnesses, *x*-ray exposures and antibiotics—their feeding habits, and their exposures to non-medical ionizing radiations (television, luminous toys, and pedoscopes) during this period, The second half described the mother and other relatives. The mother's illness and *x*-ray histories ceased at the date of birth of the survey child, but the family histories continued to the date of the interview (this allowed the total number of children in the family, and the number of relatives dying from cancer, to be the number up to the time of the interview). The mother's illness and *x*-ray histories were recorded separately for three periods of her life: (1) the first period, before marriage ; (2) the middle period, between marriage and the relevant conception ; and (3) the final period, during the relevant pregnancy. If the child was illegitimate the first period extended to the relevant conception.

Control Selection

It was clear that some " matching " of the live and dead children was needed, but it was decided to restrict this to three features of cancer deaths which it was not intended to study—namely age, sex, and locality. The distribution of the dead children in respect of these three influences could be readily obtained from official mor-

tality statistics, but as yet nothing was known about, for example, their parity or social class distribution.

Accompanying the papers for each case/control pair was a so-called control selection list. On this was entered the name of the dead child, its sex, when it was born, and the home address at the time of death. Space was provided for half a dozen names of mothers who, in the stated locality, gave birth to a child of the same sex in the same month or half-year. These names were to be obtained from official registers of births. When completed, the list might be passed to a health visitor with instruction to visit the houses in the order in which they were listed. If it proved impossible to arrange an interview with the first mother the reason was to be entered on the list and the second house visited. In this way a record was kept of all first and later choices, also the reasons for not obtaining the control of choice.

Survey Objectives

The survey doctors were told that the purpose of the survey was to compare the medical and social histories of the children before and after birth, and that the promoters were interested both in the nature of all "previous" illnesses and in the investigations and treatments associated with them (the schedules had separate headings for diagnoses, antibiotics, and *x*-ray histories).

Interviewing began in December, 1955, and by the following August 547 case/control records had been completed and returned to Oxford. These formed the basis of a preliminary report, which showed that abdominal *x*-ray films in the relevant pregnancy—that is, direct foetal irradiation—had been reported in 85 cases and 45 controls (Stewart, Webb, Giles, and Hewitt, 1956). For records completed after this date the corresponding numbers were 107 and 58. There is therefore nothing to indicate that awareness of an important finding has affected these records.

Preliminary Findings.—The 1,416 case/control pairs completed by May, 1957, included 89 transfers and 28 adoptions. After removing these 117 pairs the remaining 1,299 (on which most of the findings are based) included 619 leukaemias and 680 other cancers. The controls were represented by 775 first choices and 524 later choices. Only 60% of first choices may seem a low proportion, but the birth registers from which the names were taken had been compiled, on average, six or seven years before the survey began. With the use of a register which is revised annually the Survey of Sickness obtained 84% of their first choices (Logan and Brooke, 1957). A quarter of the children wanted as controls had definitely left the district and a further 5% (marked "no reply") may have done so. Only 6% of the mothers either refused to co-operate or were dead, and 3% were deliberately rejected because the child was dead or had always lived away from its mother. However desirable it may be in theory to include such children in the sample, in practice the records would have been so defective that they would have been of very little use for case/control comparisons.

Failure to obtain 100% of first choices has led to deficits in the control group of three types of children—namely, first-born children, migrants, and twins.

First-born Children and Migrants.—The cases included 510 first-born children and the controls 427. By national standards the first figure is nearer expectation (approximately 500) than the second, it is therefore reasonable to suppose that there is a genuine deficit on the control side and that it is related to the fact that one-child families tend to move house more often than larger families. Because of this deficiency we have, wherever indicated, done separate analyses of the first- and later-born children of primiparae and multiparae, and of migrant and static families.

Twins.—The birth registers from which the controls were taken were, in effect, lists of maternities; hence the control group should contain approximately half the normal proportion of twins. The actual number of control twins was 15 and the "expected" number in the region of 28. By this calculation the number of twins in the case group, 33, is higher, but not significantly higher, than the expected number. Though numerically small, the twins are from the point of view of foetal irradiation important. For this reason they are considered separately in Section II.

In spite of the larger number of first-born children in the case group there was no excess of small families. By the time of the survey most of these children had acquired younger brothers and sisters, and the average family size was the same in both groups (see Section VI).

Demographic Characteristics

The following information about the age, sex, and locality distribution of the cases is based not on the survey findings but on death certificate data.

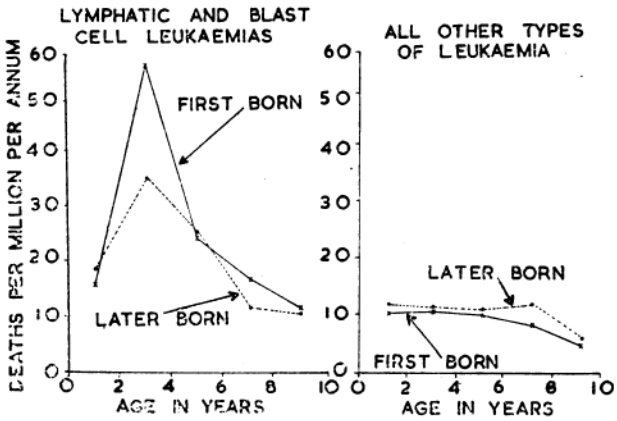
Age and Sex.—The death rates were higher for males than for females and for children under 5 than for children aged 5 to 10. In the leukaemia series the early peak of mortality was shown by a higher death rate for children between 2 and 4 years of age than for younger or older children.

Locality.—Only two regions—Surrey and Manchester—had a suggestive excess of leukaemia deaths, but in general these and the other cancer deaths showed a remarkably even geographical distribution. Classification by size of town revealed greater contrasts, but the highest death rates were in medium-sized towns, not in the largest (see Table I).

TABLE I.—*Comparative Mortality Ratios for Age Group 0–14 in Five Density Aggregates, 1953–5 (England and Wales=100)*

	Leukaemia	Other Malignant Disease
Conurbations	108	100
Towns with over 100,000 inhabitants	98	100
,, 50,000 to 100,000 inhabitants	124	110
,, under 50,000 inhabitants	92	96
Rural areas	86	100
$\chi^2_{(4)}$	12·372	1·451
Value of P	<0·02	>0·80

Birth-rank Distribution.—Since the control group was deficient in first-born children the birth-rank distribution of the cases has been compared with national figures for the years which corresponded to the births of these children—that is, 1943–55 (Registrar-General, 1945–56). According to these statistics, the birth-rank distribution of childhood cancers, other than leukaemia, is typical of the popula-



Approximate leukaemia death rates of first- and later-born children, 1953–5. These rates are based only on 663 leukaemia cases of known parity The inclusion of 14 adopted cases and 115 cases not followed up would give somewhat higher rates per million but would be most unlikely to change the appearance of the graphs.

tion at large, but among leukaemic children there appears to be a 10% excess of first-born children. Division of these children into two groups—(1) lymphatic and blast-cell leukaemias, and (2) other leukaemias—revealed further peculiarities (see Chart). Thus, between the ages of 2 and 4 years the distribution of lymphatic and blast-cell leukaemias indicates a 70% higher risk for first-born children than for other children. Whether this risk is related to the antenatal or post-natal peculiarities of first-born children we do not know. It is, however, deaths in this narrow age group which are largely responsible for the remarkable post-war increase in childhood deaths from leukaemia both in this country and in the U.S.A. (Hewitt, 1955). Our own data on post-natal *x*-ray exposures (see Section IV) also suggest that some of the children who survive to the age of 2, but are dead of leukaemia before the age of 4, belong to a separate aetiological group.

Maternal Age.—The average age of the mothers at the date of birth of the survey children was 28.91 years for the leukaemia series and 28.43 for the other cancer series—that is to say, the group which contained the higher proportion of primiparae was, on average, 25 weeks *older* than the other group. Further examination of the maternal ages showed that this greater average age was determined by a small group of mothers who were over the age of 40 when the leukaemic child was born. These mothers represented 6.9% of the leukaemic series and only 3.5% of the other cancer series. To avoid confusion with the high incidence of mongolism in the leukaemia series (see Section IV) the mothers of mongols were excluded from the next analysis and primiparae were separated from multiparae. In the latter group (which contained the bulk of the women over 40) the average age was 52 weeks higher for the leukaemia than for the other cancer series, a difference which is statistically significant ($P<0.01$). Assuming that age of the mother has not affected the prevalence of other childhood cancers, this suggests that the risk of dying of leukaemia before the age of 10 years is twice as great as usual if the mother is over 40 years of age at the date of birth (this estimate is in no way dependent on the slightly higher incidence of obstetric *x*-ray examinations in elderly women). The independent findings, first, of a large number of mongols in the leukaemia series, and, secondly, of a relatively large number of "old" mothers in the leukaemia series suggest that childhood leukaemia and mongolism are influenced by a common factor, rather than that one disease predisposes to the other (see also Section IV). In a recent American survey the ages of the mothers in a smaller group of children with leukaemia and others cancers also show these contrasts (Manning and Carroll, 1957).

Social-class Distribution.—The basis of the social-class distribution was the father's occupation. A statement of family income was also obtained for 87% of cases and 88% of controls. Since it is common knowledge that professional families move house more often than working-class families, the social and economic distributions have been calculated separately for children who moved house after they were born (migrant series) and children who did not (static series). On this basis there are virtually no social-class or economic distinctions as between cases and controls or between cases of leukaemia and cases of other cancer. (National mortality rates suggest that leukaemia deaths at later ages tend to have an upward social gradient, and other cancer deaths a slight downward gradient.)

SECTION II. MOTHERS' X-RAY HISTORIES

Although the mothers were questioned first about their children and only later about their own health, we shall deal first with the mothers' *x*-ray histories and illnesses. These were recorded separately for (1) the first period, before marriage; (2) the middle period, between marriage and the relevant conception; and (3) the final period, during the relevant pregnancy. Three categories of exposure were distinguished—therapeutic, occupational, and diagnostic. The first two need not detain us. Only 16 mothers (7 cases, 9 controls) reported any radiotherapy and the treatments never coincided with the relevant pregnancy. A further 19 mothers (12 cases, 7 controls) may have been exposed to *x* rays in the course of their work, and for three—all mothers of cases—the work was continued during the final period. The occupations in question were: nurse in radiotherapy department, nurse in a radiological department, and a metal-tester.

Diagnostic X-ray Histories

A summary of the mothers' diagnostic *x*-ray histories is given in Table II. Figures are given for the three periods, separately and jointly, and for two main types of *x*-ray examination (abdominal and other). The figures are numbers of *mothers*, not numbers of films or examinations—that is to say, no woman has been counted more than once in any cell of the Table (consequently the figures for "any period" and "any *x*-ray exposure" are rather lower than the sum of the figures for separate periods and separate types of examination). The figures in italics give the ratios between the numbers of case mothers and the corresponding numbers of control mothers.

TABLE II.—*Number of Mothers Reporting X-ray Examination of Different Sites (Abdomen and Other) in Three Periods (see Text)*

Period	*X*-ray Examinations		
	Abdominal	Other	Any
Before marriage	*44/26=*1·69*	335/275=*1·22*	361/296=*1·22*
Between marriage and relevant conception ..	109/121=*0·90*	213/184=*1·16*	304/285=*1·07*
During relevant pregnancy	178/93=*1·91*	117/100=*1·17*	273/184=*1·48*
Any period	296/215=*1·38*	531/456=*1·16*	692/593=*1·17*

The case/control ratio of 1·91 for abdominal *x*-ray exposures during the relevant pregnancy (1) differs from the "expected" ratio (1·00) at the level of $P< 10^{-4}$; (2) differs from the contemporary ratio for other *x*-ray exposures (1·17) at the level $P\simeq 0{\cdot}011$ and from the ratio for other *x*-ray exposures in any period (1·16) at the level $P<0{\cdot}001$; and (3) differs from the ratio for abdominal *x*-ray exposures in any period (1·38) at the level $P\simeq 0{\cdot}012$.

* 44/26, etc., represent ratio of case mothers to control mothers.

It will be seen that 692 mothers of cases reported at least one diagnostic *x*-ray exposure compared with only 593 mothers of controls, a case/control ratio of 1.17. Though this case excess is significant, it is not very large, and might perhaps be attributed to relative under-reporting of *x*-ray exposures on the control side. If, however, under-reporting by control mothers was the only reason for the case excess one would expect to find similar case/control ratios for each type of examination and for each period of life. In fact the ratio is higher for abdominal (1.38) than for other types of examination (1.16), and higher for all examinations during the relevant pregnancy (1.48) than during earlier periods (1.22 and 1.07). In particular, the ratio for abdominal *x*-ray examinations during the relevant pregnancy is outstandingly high (1.91). The chance probability of obtaining so high a ratio is less than one in ten million. Moreover, as the footnote to Table II shows, this ratio is significantly higher than the ratio for *x*-ray examinations of other sites in this period, and than the ratio for abdominal *x*-ray examinations as a whole. Hence there is prima facie evidence that abdominal *x*-ray examinations during pregnancy—the only type of examination involving direct exposure of the foetus—can contribute to the aetiology of malignant disease in children.

Most of the remainder of this section is devoted to further analysis of the apparent association between foetal irradiation and malignant disease in childhood, but it is necessary first to say something about the figures for the other maternal *x*-ray histories.

One group of maternal *x*-ray histories—those relating to *x*-ray exposures of the abdomen during the middle period—shows a small excess on the *control* side. This was at first thought to be due to the fact that on the control side there were more previous children, and hence more occasions for obstetric *x*-ray exposures in the middle period. However, when the obstetric *x*-ray examinations were separated from

the other abdominal *x*-ray examinations belonging to this period and related to the number of pregnancies at risk (see Table III) there was still a slight excess on the control side. This strengthens the view that the control mothers were as efficient as the mothers of cases in recalling their abdominal *x*-ray examinations.

TABLE III.—*Comparison Between Cases and Controls in Respect of Obstetric X-ray Examinations in the Middle Period (i.e., Between Marriage and the Relevant Conception)*

	Cases	Controls
Total No. of previous pregnancies	1,623	1,742
No. of women reporting obstetric (abdominal) *x*-ray examinations between marriage and relevant conception:		
(*a*) Actual	79	96
(*b*) Expected	84·41	90·59

In the pre-marriage period there was a case excess for abdominal *x*-ray exposures which has to be accepted as technically significant ($P<0.05$). The possibility has therefore to be considered that damage to the maternal gonads may increase the risk of childhood malignancy. But even if this is the correct explanation such damage is of minor interest, for, as judged by the numbers involved, its importance can only be one-quarter of that of direct foetal irradiation.

Unlike the case excess for abdominal *x*-ray examinations, that for other *x*-ray examinations showed no tendency to concentrate in the period of the relevant pregnancy. This seems to dispose of the notion that scatter from *x*-ray exposure of sites other than the abdomen had been harmful to the cases. The meaning of the steady case excess in all periods is not clear. To be on the safe side we will assume (see Table VII) that it is an average measure of the relative under-reporting of *x*-ray exposure by control mothers compared with the case mothers. However, even this group is not completely homogeneous as regards case/control comparisons. On further breakdown it was found that mothers reporting chest *x*-ray examinations were in substantial excess on the case side (ratio of 1.20), but that the numbers reporting skull or limb exposures were virtually identical (133 and 132).

The first step in pursuing the association between foetal irradiation and malignant diseases was to check all reports of abdominal *x*-ray examinations during the relevant pregnancy against hospital records. This revealed a few inaccuracies. Five mothers of cases and five of controls were found to have reported an examination which in fact had been performed during a different pregnancy. In a further 14 instances (9 cases and 5 controls) no hospital record of the alleged examination could be found. The figures shown in Table II do not include any of these faulty records (the effect of removing them was to alter the case/control ratio from 1.86 to 1.91).

Twins.—As already explained there are only 15 twins in the control group compared with an expected number of 28 (see Section I). Since seven of these 15 children had been *x*-rayed *in utero* it is reasonable to suppose that with a full quota of twins there might have been six more control mothers reporting abdominal *x*-ray examinations in the final period.

First-born Children.—Separate analysis of the maternal *x*-ray histories in groups defined by parity (Table IV) showed that the proportion of first-born children who were *x*-rayed *in utero* was approximately 2% higher than the proportion for other children. This slight difference is equivalent to about two "extra" records of direct foetal irradiation on the case side.

TABLE IV.—*Histories of Direct Foetal Irradiation, Distinguishing Three Birth-rank Groups of Cases and Controls*

Position in Family of Child (Birth Rank)	Cases		Controls		Ratio
	No.	%	No.	%	
First	85/510	16·7	36/427	8·4	1·99
Second	47/393	12·0	28/448	6·3	1·90
Later	46/396	11·6	29/424	6·8	1·71
All	178/1,299	13·7	93/1,299	7·2	1·91

Migration (see Table V).—Independent case/control comparisons based on the "migrant" and "static" series (see Section I) showed no significant differences between these two groups.

The last point to be considered is whether the high case/control ratio for abdominal *x*-ray examinations in the relevant pregnancy could be due to the existence in the case group of a condition or conditions which only incidentally caused the child to be *x*-rayed *in utero*. In this connexion it is clearly appropriate to draw a distinction between *x*-rays taken for purely obstetric reasons and other abdominal *x*-rays which happened to coincide with the pregnancy (see Table VI). According to this analysis over

TABLE V.—*Frequency of Direct Foetal Irradiation of Cases Belonging to "Migrant" and "Static" Families and of Corresponding Controls*

Foetal irradiation	Migrant Series		Static Series	
	Cases	Controls	Cases	Controls
Yes	57	23	121	70
No	325	359	796	847
Total	382	382	917	917
χ^2	15·205		14·610	
P	<0·001		<0·001	

90% of the *x*-ray examinations were taken for obstetric reasons, other abdominal *x*-ray examinations representing 9% of cases and 6% of controls. Inasmuch as these other abdominal *x*-ray examinations tended to take place earlier and to involve heavier exposures than the obstetric *x* rays, they might be expected to concentrate on the case side if there were a causal relationship between direct foetal irradiation and childhood malignancies. Hence the slight excess of other abdominal *x*-ray exposures on the case side in no way disturbs this hypothesis.*

TABLE VI.—*Numbers of Mothers Reporting Obstetric and Other Abdominal X-ray Examinations During the Relevant Pregnancy*

X-ray Category and Reasons for *X*-ray Examination	Cases		Controls	
	No.	%	No.	%
Obstetric:				
Position	61	36·3	29	34·5
Size (? twins)	53	31·5	29	34·5
Routine pelvimetry	35	20·8	20	23·8
Diagnosis of pregnancy	4	2·4	1	1·2
Total	153	91·0	79	94·0
Other abdominal:				
Barium meal	6	3·6	1	1·2
Intravenous pyelogram	3	1·8	—	—
Injury	4	2·4	1	1·2
Other	2	1·2	3	3·6
Total	15	9·0	5	6·0
Total of all known indications	168	100·0	84	100·0
Indication for *x*-ray examination unknown	10	—	9	—

We are now in a position to judge the effect of all the factors which might possibly have contributed a spurious element to the case/control ratio for abdominal *x*-ray examinations in the relevant pregnancy. To do this we have made three assumptions which are unfavourable to an explanation in terms of a causal link between foetal irradiation and childhood malignancies. These are: (1) that the excess of twins in the case group is wholly spurious; (2) that ill-health during pregnancy is of such overruling impor-

*Judging by the number of deaths among the children of case and control mothers, the older and the younger children of the case mothers were just as healthy as the older and younger children of the control mothers, nor was there any difference in the stillbirth rates for the case and control groups (see Section VII).

tance that any associated *x*-ray exposure should be ignored; and (3) that the case mothers were 16% more efficient than the control mothers in reporting *x*-ray exposures (on the grounds that the case/control ratio for other *x*-ray examinations was 1.16) (see Table II). These three assumptions have been worked into Table VII, which excludes all twins,

TABLE VII.—*Actual (and Expected) Numbers of Cases and Controls With and Without a History of Direct Foetal Irradiation. Revised Basis of Comparison (see Text)*

	Cases	Controls	Total
Irradiated	141 (118·44)	81 (103·56)	222
Not irradiated	1,125 (1,147·56)	1,204 (1,181·44)	2,328
Total ..	1,266	1,284	2,550

$\chi^2_{(1)}$ with continuity correction is 9·644, equivalent to a normal deviate of 3·10; $P < 0·002$.

counts all abdominal *x*-ray examinations in the final period, other than purely obstetric *x*-ray examinations among the non-irradiated totals, and gives "expected" numbers which are calculated not on the basis of equality but on an "expected" case/control ratio of 1.16 to 1.00. In spite of these drastic modifications there is still an excess of abdominal *x*-ray examinations on the case side which is so large that it would occur by chance in less than one of 500 repeated trials.

In the remainder of this section it is assumed that there is a causal relationship between irradiation *in utero* and childhood malignancies, and four aspects of the risk involved are considered: (1) its relationship to *x*-ray dose, (2) its relationship to the maturity of the foetus at the time of exposure, (3) its relationship to the type of malignant disease, and (4) its absolute size.

Dose-Response Relationship

Court-Brown and Doll (1957) have studied the incidence of leukaemia and aplastic anaemia in adults given deep *x*-ray therapy to the spine. Although they had only 37 cases at their disposal they were able to demonstrate a strong relation between dose and risk of disease. The present series of children includes no fewer than 178 in whom malignant disease had been preceded by antenatal irradiation, and therefore appears to offer ample material for studying dosage effects. There is, however, an important difference which nullifies the advantage of larger numbers. Court-Brown and Doll had an almost "pure" series of radiation-leukaemias, since they gave evidence that over 90% of them would not have occurred but for the preceding *x*-ray exposures. In the present series a high proportion of the cases *x*-rayed *in utero* developed the fatal disease for *other* reasons. The existence of these cases is bound to hinder recognition of a dose-response relationship.

Attempts to collect data for the study of dosage effects met with great difficulties. Over 200 different hospitals had to be asked for records, many of which related to events of more than five years previously. Radiologists supplied all the technical details available, but these were rarely sufficient to support a calculation of dose. Finally, we were reduced to using, as an extremely crude index of dose, the number of films believed to have been taken, though even this was often no more than a reasoned guess on the part of the radiologist and did not include films discarded by the radiographer. Table VIII shows a classification of the cases and controls on this basis. Except in the group with no films the numbers are small and therefore the sampling errors of the case-control ratios are large. The group representing three films breaks the rising sequence of ratios, but at least the lowest and highest ratios (0.93 and 3.20) correspond to the lowest and highest number of films (nil and four or more films). A small group of mothers, not distinguished in the table, who had five or more abdominal *x*-ray examinations during the relevant pregnancy, included 15 cases and only 2 controls. Thus the figures are consistent with, though they do not establish, a relationship between increasing dose and increasing risk.

TABLE VIII.—*Distribution of Cases and Controls Irradiated in Utero According to the Numbers of Abdominal Films Reported Taken During the Relevant Pregnancy*

No. of Films	Cases	Controls	Ratio
0	1,121	1,206	0·93
1	37	27	1·37
2	60	26	2·31
3	23	18	1·28
4 or more	32	10	3·20
(Unknown number)	(26)	(12)	(2·17)
Total:	1,299	1,299	1·00

Timing Effects

The precise date of exposure was ascertained in most cases, and on this basis each mother was classified according to the month of the first exposure (see Table IX). The dated series did not include a single mother examined within 28 days of conception, and only 20 mothers were certainly *x*-rayed in the first half of pregnancy. However, in this small group there were 18 cases and only 2 controls, which represents a much higher case/control ratio than the one for exposures in the second half of pregnancy (148 cases, 83 controls). The variations in the second half of pregnancy all lie within the accepted range of chance variation.

TABLE IX.—*Distribution of Cases and Controls Irradiated in Utero According to Month of Pregnancy*

Gestation Period in Months	Cases	Controls	Case/Control Ratio
1st to 5th	18	2	(9.00)
6th, 7th	15	9	1·67
8th	20	19	1·05
9th	55	30	1·83
10th	58	25	2·32
Total known	166	85	1·95
Unknown	12	8	(1·50)
Total ..	178	93	1·91

A statistical comparison of the cases and controls in the five "known" categories above yields $\chi^2_{(4)} = 9·656$, for which $P < 0·05$.

Tissue Sensitivity

Previous work suggests that, in adults, leukaemia is more likely to be produced by ionizing radiations than other malignant diseases (Court-Brown and Doll, 1957; Faber, 1957). But our own data suggest that in a foetus there may be other tissues which are at least as sensitive to *x* rays as the reticulo-endothelial system (see Table X). In this table the cases have been divided into eight diagnostic groups, and the number of irradiated cases in each of these is compared with the number which would be expected if the *x*-ray exposures were evenly distributed among the cases. In calculating these expected numbers, we have standardized them in ten-yearly age groups, in order to allow for changes in *x*-ray habits during the years in which the survey children

TABLE X.—*Comparative Incidence of Direct Foetal Irradiation in Eight Diagnostic Groups*

Diagnosis	No. of Cases	Irradiated *in utero*		
		%	Actual No.	Expected No.
Lymphatic leukaemia	292	14·4	42	40·31
Myeloblastic ,, ...	124	7·3	9	16·24
Blast-cell and other leukaemias ..	203	13·8	28	27·93
Lymphosarcoma, other reticuloses ..	109	7·3	8	14·24
Malignant tumours of C.N.S. ..	212	12·7	27	28·75
,, ,, kidney	120	15·8	19	16·68
,, ,, suprarenals (incl. *all* neuroblastomas)	87	18·4	16	12·68
Malignant tumours of other sites ..	152	19·1	29	21·16
Total ..	1,299	13·7	178	177·99

In an 8 × 2 table the comparison of actual and expected numbers irradiated and not irradiated yields $\chi^2_{(7)} = 11·832$, compared with 12·017 at the level $P = 0·10$.

were born. On this basis the differences between the actual and expected numbers are of a magnitude which, under chance conditions, would be expected to occur in about one out of ten samples. The group labelled "other sites" had the highest percentage (19.1%). This included three retinoblastomas with three *x*-ray exposures, and 12 teratomas with seven *x*-ray exposures. We hesitate to draw any conclusion about the retinoblastomas, because in an independent series of 39 children who were said to have survived surgical removal of a retinoblastoma we found there had been only seven pre-natal *x*-ray examinations, which is no more than average for all forms of cancer. However, the chance of obtaining as many as seven *x*-ray exposures in 12 cases is only one in a thousand, so it may be that the nests of embryonic tissue contained in teratomas are exceptionally radiosensitive.

Delayed Effects of Foetal Irradiation

The survey was deliberately restricted to children under 10 years of age because it was thought that this was a convenient limit to the time that mothers might be expected to recollect events. But by so doing we may have missed some of the consequences of direct foetal irradiation. If the effects of pre-natal irradiation are exhausted by the age of 10 years one would expect the case/control ratio for foetal irradiation to be higher for children who were under 5 years of age at the onset date than for children who were 5 or over. But, as Table XI shows, this ratio is 1.73 for the younger children and 2.50 for the older children.

TABLE XI.—*Case/Control Ratio for Direct Foetal Irradiation. Comparison of Cases and Controls Defined by Age at the "Final Date"*

	Cases	Controls	Ratio
Deaths at ages 0 to 4	123	71	1·73
,, ,, 5 to 9	55	22	2·50
,, ,, 0 to 9	178	93	1·91

Estimates of Risk

The following estimates are based on the figures shown in Table II and necessarily represent a rough appraisal of the situation. In the case group 13.7% of the children were *x*-rayed before birth and 86.3% were not. The corresponding percentages for control children were 7.2 and 92.8. On this showing children who have been *x*-rayed *in utero* are $\frac{(13.7\times 92.8)}{(7.2\times 86.3)}$ times, or twice as likely to die of a malignant disease before their tenth birthday as other children. Since at the present time about one in every 1,200 children in Britain die in this way, it follows that less than one in a thousand of the pre-natal *x*-ray examinations performed in recent years have led to death from malignant disease before the age of 10 years. An alternative way of expressing this estimate is to say that abdominal *x*-ray examinations of pregnant women have in recent years been responsible for (13.7−7.2) % or between 6 and 7% of all deaths from malignant disease before the age of 10 years.

To sum up: there appears to be no doubt that there is a causal relationship between pre-natal exposure to *x* rays and the subsequent development of malignant disease, and there are indications that the risk is related both to the dose of *x* rays and to the date of exposure. There is nothing to suggest that irradiation *in utero* explains the early peak of leukaemia mortality (see Section IV for data on post-natal *x*-ray exposures) and it may even cause deaths from malignant disease after the age of 10 years. The rough estimates of risk which are given here apply only to one period of time and to the *x*-ray doses in use at that time. Evidently radiotherapy of pregnant women is an extremely rare event in this country, and contributed nothing to the cases we have considered.

[ADDENDUM.—After this report had been written we received the results of an independent study (Paterson, 1958) which had been designed specifically to test the conclusion announced in our preliminary communication. This study concerned children who had died under the age of 10 in the State of Louisiana during the years 1951–5. Although conducted on a rather small scale it had one important advantage over our own inquiry: all the information was obtained direct from professional sources, thus minimizing the risk from emotional bias or selective memory in the informants. The incidence of irradiation *in utero* discovered by Paterson was as follows: among 77 children who died of leukaemia, 27.3%; among 70 children who died of other cancers, 28.6%; and among 293 control children who died of other causes, 18.4%. These percentages are much higher than those found in England and Wales, but show two important resemblances: (1) the significantly higher incidence of foetal irradiation among children with malignant disease than among controls, and (2) similar figures obtained for children with leukaemia and those with other forms of malignant disease. Using Paterson's figures in the same way as our own to derive an estimate of the relative risk of malignant disease associated with irradiation *in utero*, we have $\frac{27.9}{18.4}\times\frac{81.6}{72.1}=1.72$, which is in reasonable agreement with our own estimate.]

SECTION III. MOTHERS' ILLNESSES

The mothers were asked whether they had ever had a serious illness or injury before the survey child was born. Although these events were actually recorded separately in the three periods (see Section II), only two periods are distinguished in the following analysis—namely, before and during the relevant pregnancy. Only information of a reasonably objective and definite type has been considered, and unless a common childhood infection—for example, measles—coincided with the relevant pregnancy it has been omitted from the following analyses. After omission of these items and such vague conditions as nervous breakdowns, influenza, anaemia, and injuries other than fractures, approximately half the mothers were left with no diseases before the birth of the survey child. The remaining records were classified according to the *International Classification of Diseases* (World Health Organization, 1949), and the results are shown in Table XII.

TABLE XII.—*Illnesses of Mothers Arising Before and During the Relevant Pregnancy*

International Classification Main Category	Arising Before Relevant Pregnancy		Arising During Relevant Pregnancy	
	Cases	Controls	Cases	Controls
I. Infective	86	82	13	1
II. Neoplasms	9	11	2	2
III. Allergic, etc. ..	24	22	1	3
VI. Nervous system ..	32	37	1	0
VII. Circulatory	53	44	0	4
VIII. Respiratory	219	207	12	13
IX. Digestive	74	91	12	4
X. Genito-urinary ..	62	44	0	0
XI. Pregnancy	32	32	113	77
XII. Skin	33	43	5	5
XIII. Bones and muscles ..	15	20	3	0
XIV. Congenital	5	7	—	—
XVII. Accidents	48	57	0	0
Total No. of illnesses	692	697	162	109
,, ,, women	565	554	155	104

Illnesses Originating Before the Relevant Pregnancy.—The total number of illnesses in this category was 1,389 (cases 692 and controls 697) and the number of mothers affected was 1,119 (cases 565 and controls 554). Unlike the series reported by Manning and Carroll (1957) there were no case/control differences for allergic conditions (category III), but compared with this American series the incidence of these conditions was low. The only group of illnesses with a substantial difference between cases and controls was category X (diseases of the genito-urinary system) with 62

records for cases and 44 for controls. The difference was confined to disease of the renal tract as such (49 cases and 30 controls), which represents a significant case excess (P approx. 0.04).

Illnesses Arising During the Relevant Pregnancy.—The total number of illnesses recorded in this period was 271 (162 cases, 109 controls) with 259 mothers affected (155 cases, 104 controls). Further analysis of the records showed that this case excess, which is statistically significant, was restricted to two categories—namely, infective disease (13 cases, 1 control) and direct complications of pregnancy (113 cases, 77 controls). The latter group (see Table XIII) is

TABLE XIII.—*Illnesses of Mothers Specifically Associated With the Relevant Pregnancy*

I.C.D. Numbers	Illness	Leukaemia		Other Cancers		Total	
		Cases	Controls	Cases	Controls	Cases	Controls
642	Toxaemias of pregnancy ..	29	31	38	26	67	57
640–641	Infections of genito-urinary tract during pregnancy ..	8	3	11	7	19	10
648·0	Threatened abortion ..	14	4	13	6	27	10
Total	.. ..	51	38	62	39	113	77

dominated by toxaemias of pregnancy (67 cases, 57 controls), but there were also 29 urinary infections (19 cases, 10 controls) and 37 threatened abortions (27 cases, 10 controls). The difference between cases and controls is not significant for toxaemia of pregnancy, and the difference for urinary infections is complicated by the fact that six of the mothers on the case side had also had an abdominal *x*-ray examination during the relevant pregnancy (mostly intravenous pyelograms). This leaves threatened abortions and infective diseases as the only ones with a significant and unambiguous excess on the case side. The infective disease group included 10 virus infections on the case side and one on the control side. These undated infections were associated with the childhood diseases shown in Table XIV.

TABLE XIV.—*Infections During the Relevant Pregnancy*

Maternal Infection	No. of Cases	Corresponding Children
Rubella	3	Congenital sarcoma of mediastinum Neuroblastoma at 12 months Lymphoblastoma at 15 months
Mumps	2	Congenital sarcoma of the meninges Leukaemia at 5 years
Herpes zoster ..	4	Healthy control Leukaemia at 7 years Leukaemia at 8 years Cerebral tumour at 6 years
Infective hepatitis ..	2	Leukaemia at 4 years Cerebral tumour at 6 years

To summarize: there is nothing in the illness records to suggest that the case mothers were, before the relevant pregnancy, less healthy than the control mothers. During the relevant pregnancy they appear to have suffered more from threatened abortions and virus infections than the control mothers, but the numbers involved are small.

SECTION IV. CHILDREN'S X-RAY HISTORIES

As already stated, the survey doctors had been told to record the illnesses of the children up to but not beyond the onset dates, these being defined as the dates on which the corresponding children first showed signs of the fatal disease. (In the following analyses the years before this date are referred to as the *pre-onset* period.) Since it was more likely that the mothers of the living children would mistakenly include events after this date than the mothers of dead children, we have in the following analyses discriminated carefully between accurately dated *x*-ray exposures and illnesses and those in which there was a margin of error. We will deal first with non-medical *x*-ray and then with medical *x*-ray exposures, but pedoscope exposures will be mentioned in both parts.

Non-Medical X-ray Exposure.—Three non-medical sources of ionizing radiations were considered—television sets, luminous clocks or toys, and pedoscopes. Only one fact relating to these (undated) exposures has been analysed—namely, whether the child was ever exposed during the pre-onset period. For each of the three sources there was a slight excess on the control side. In the case of television sets (278 cases and 301 controls) and luminous objects (328 cases and 333 controls) the differences were negligible, and even for pedoscopes (212 cases and 242 controls) they were not significant (P approximately 1 in 7). As, however, the exposures were undated, it is possible that the few extra cases in the control side represent exposures which occurred after the onset date. The possible effects of this type of mistake on the pedoscope records are considered again at the end of this section.

Medical X-ray Exposure.—Records of diagnostic and therapeutic *x*-ray exposures were comparatively uncommon, but a slight excess was shown on the case side (see Table XV). The excess was confined to 11 children having radiotherapy (8 cases, 3 controls) and 167 children who had been radiographed on more than one occasion (90/77). For single radiographic examinations there was a slight deficiency of cases (88/100).

TABLE XV.—*Numbers of Children With Post-natal Medical X-ray Exposure*

Type of Exposure	Leukaemia		Other Cancers		Total	
	Cases	Controls	Cases	Controls	Cases	Controls
Diagnostic:						
Once*	43	42	45	58	88	100
More than once	47	38	43	39	90	77
Therapeutic ..	5	1	3	2	8	3
Total ..	95	81	91	99	186	180

* Includes some children for whom the number of examinations was not ascertained.

Tissue Sensitivity.—When a child is *x*-rayed *in utero* it is safe to assume that the whole body has been exposed; but after birth this rarely happens. It was therefore appropriate to examine the records for an association between the parts of the body *x*-rayed after birth and subsequent developments. We have, however, searched the records in vain for any sign of this.

Estimate of Dose.—No attempt was made to discover the number of films taken at each *x*-ray examination or to check the doses used in radiotherapy. The latter were all of the type to treat minor skin conditions, and no examples of deep *x*-ray treatments of the kind recently followed up by Simpson and Hempelmann (1957) were recorded. The 11 children with histories of radiotherapy were all girls treated for naevi. The cases included five leukaemias, one glioma, one neuroblastoma, and one sarcoma of the umbilicus (not the site exposed to *x* rays). At least eight of these children (possibly nine) were treated before their first birthday, and two (both cases) had already been *x*-rayed *in utero*.

Time Relationship

In view of the evidence already presented that a foetus may be specially radiosensitive, the post-natal *x*-ray exposures (diagnostic and therapeutic combined) were analysed by age at first exposure (see Table XVI) to discover whether there were any time relationships. Included in this table are 67 children (27 cases, 40 controls) who have been classified as "age at first exposure unknown." These children were definitely *x*-rayed before the onset date, but the possible dates covered a period of more than 12 months. The remaining children included 128 where the month and year of the first *x*-ray exposure was known, and 171 where the date was given to within 12 months. In the latter group we have assumed that the actual date of exposure was midway between the two possible extremes and have placed the

TABLE XVI.—*Distribution of Children With Post-natal Medical X-ray Exposure According to Age at First X-ray Exposure*

Age at 1st Exposure	Leukaemia		Other Malignant		Total	
	Cases	Controls	Cases	Controls	Cases	Controls
0–	19	12	23	13	42	25
1–	21 } 57	10 } 31	12 } 50	15 } 43	33 } 107	25 } 74
2–	17	9	15	15	32	24
3–	6	4	10	13	16	17
4–	5	14	9	8	14	22
5–	5	9	5	6	10	15
6–	5 } 25	3 } 33	2 } 27	3 } 33	7 } 52	6 } 66
7–	3	2	1	3	4	5
8–	1	1	0	0	1	1
9–	0	0	0	0	0	0
Not known	13	17	14	23	27	40
Total ..	95	81	91	99	186	180

child accordingly. The last two columns of the table (where all cases and all controls are compared) show a significant excess on the case side of children exposed before their third birthdays. This excess is greater for the leukaemic children than for the children with other cancers. For first exposures between fourth and tenth birthdays the balance is on the control side, but the absolute and relative difference is small and may well be due to chance. In the interpretation of these figures much depends on the 67 children whose first exposures were inadequately dated. If the first exposure dates for these children were distributed in roughly the same way as in the dated series it would strengthen the impression of a genuine difference between early and later exposures, but if the distribution were markedly different it might have the opposite effect.

No such reservations need apply to the figures in Table XVII. Here the children have been placed according to their age in years at the onset date, and only three children have had to be relegated to the "age unknown" category. In three of the five age groups there were more cases than controls, and in two there were more controls than cases, but the most striking case/control difference relates to children who were aged between 2 and 3 years at the onset date (58 cases, 27 controls).

A similar arrangement by age at the final date (which was usually within a few weeks or months of the onset date) also picked out children who died between the second and fourth birthdays (51 cases, 24 controls), and again the difference was more marked for leukaemia than for other cancers. This is particularly interesting, since it is precisely this age group which has borne the brunt of the recent increase in childhood leukaemia mortality both in this country and in the U.S.A. (Hewitt, 1955).

TABLE XVII.—*Distribution of Children With Post-natal Medical X-ray Exposure According to Age of the Child at the Onset Date*

Age at Onset Date (Years)	Leukaemia		Other Malignant		Total	
	Cases	Controls	Cases	Controls	Cases	Controls
0, 1 ..	6	7	14	10	20	17
2, 3 ..	35	11	23	16	58	27
4, 5 ..	23	25	21	32	44	57
6, 7 ..	17	22	17	27	34	49
8, 9 ..	14	15	15	13	29	28
Not known	0	1	1	1	1	2
Total ..	95	81	91	99	186	180

* The onset date is defined as either the date of onset of the fatal illness (case children) or the date when the corresponding case developed its fatal illness (control children).

Thus far the evidence in favour of a link between childhood malignancies and post-natal *x*-ray exposure has depended on case/control comparisons of arguable validity. We have therefore attempted to assess the evidence by means of comparisons within the case and the control series, using the following argument. In a "normal" group of children, such as our own controls, the percentage who have ever been *x*-rayed should steadily increase with age, for each year adds to the number of children who are *x*-rayed for the first time. For the sake of simplicity we shall assume that the percentage of "first" *x*-ray exposures is normally the same in each of the first ten years of life. In order to test this assumption we have calculated for the control children the "expected" percentages of children ever *x*-rayed in each of the five age groups shown in Table XVII. In the first two columns of Table XVIII these expected figures are shown in italics together with the actual

TABLE XVIII.—*Distribution (by Age at Onset Date) of Children With Post-natal X-ray Exposure Compared With the Distribution Expected on the Basis of a Regular Increase with Age of the Percentage of Children Ever X-rayed Since Birth*

Age of Children at Onset Date (Years)	Controls		All Cases		Leukaemia		Other Cancers	
	Actual / *Expected*		Actual / *Expected*		Actual / *Expected*		Actual / *Expected*	
	%	No.	%	No.	%	No.	%	No.
0, 1	4·9 / *3·5*	17 / *12·28*	5·8 / *3·7*	20 / *12·76*	4·4 / *3·8*	6 / *5·25*	6·7 / *3·6*	14 / *7·43*
2, 3	7·2 / *10·6*	27 / *40·03*	15·4 / *11·0*	58 / *41·61*	17·9 / *11·4*	35 / *22·37*	12·7 / *10·7*	23 / *19·30*
4, 5	19·7 / *17·7*	57 / *51·15*	15·2 / *18·4*	44 / *53·16*	16·1 / *19·0*	23 / *27·20*	14·4 / *17·8*	21 / *25·95*
6, 7	25·9 / *24·8*	49 / *46·83*	18·0 / *25·8*	34 / *48·67*	18·3 / *26·6*	17 / *24·77*	17·7 / *24·9*	17 / *23·89*
8, 9	32·2 / *31·9*	28 / *27·71*	33·3 / *33·1*	29 / *28·80*	31·1 / *34·2*	14 / *15·41*	35·7 / *32·0*	15 / *13·44*
Total	13·8 / *13·8*	178 / *178·00*	*14·4* / *14·4*	185 / *185·00*	15·4 / *15·4*	95 / *95·00*	13·4 / *13·4*	90 / *90·01*
$\chi^2_{(4)}$ Value of P	7·622 >0·10		19·414 <0·001		12·478 <0·02		11·015 <0·05	

percentages and numbers. It will be seen that the correspondence between the two sets of figures is not exact but lies well within the limits of chance fluctuation (P>0.1). It follows that the original assumption is a reasonable one. Now, if the post-natal *x*-ray exposure had *not* influenced the risk of the children dying later of malignant diseases, the correspondence between the actual and expected figures for the case series should be much the same as in the control series. But the discrepancies are much greater in the case series than in the control. Subdivision of the cases into leukaemias and other cancers shows that in the second age group of the leukaemia series (which includes children who developed leukaemia between their second and fourth birthdays) the proportion of "*x*-rayed children" is actually higher than the proportion in the third age group, although for these children the period during which they had an opportunity to be *x*-rayed was half as long again. For children with other cancers the largest discrepancy is in the first age group, where the actual number of children *x*-rayed (14) is nearly twice the expected number (7.43).

In earlier parts of this paper (and again in Section IV) we discuss evidence which indicates that the decisive factor in some of the cases, particularly in the leukaemia series, dates back to a period well before birth. If this is so then there must be, in the newborn population, a number of children in what may be loosely called a "pre-malignant state." The present analysis of post-natal *x*-ray exposures suggests that if such children are *x*-rayed during infancy overt signs of the disease may appear relatively quickly.

This inference can be drawn from the tables already given, but is perhaps better illustrated by the distribution of cases and controls according to the interval between the first post-natal *x*-ray exposure and the final date. For children *x*-rayed in the first three years of life this was :

Interval, First Exposure to the Final Date	Cases	Controls
Up to 11 months	12	11
12 to 47 ,, ...	62	26
Longer intervals	33	37

This interpretation would also explain the deficiency on the case side of *x*-rayed children who developed the fatal disease between their fourth and eighth birthdays (see Table XVII). For, if irradiation in infancy hastens overt signs of the disease, then there must be some "vulnerable" children who survive a comparatively long time partly because they have not been *x*-rayed. If this is so, we would expect the percentage of *x*-rayed children in the older half of the case series to be below the level for healthy children.

Pedoscopes

We must now reconsider the records for shoe-shop *x*-ray exposures. The same rays are emitted from pedoscope machines as from diagnostic *x*-ray sets. If, therefore, the medical *x*-ray examinations have had an effect, one would expect the pedoscope records to show the same signs. A possible reason for there being no such excess has already been mentioned—namely, inclusion on the control side of children whose first pedoscopic examination was later than the onset date. Another reason should now be apparent. The data on medical *x*-ray examinations suggest a risk only when the first exposure takes place before the third birthday—that is to say, during a period when very few children will have had shoe-shop *x*-ray exposures. The relevant data cannot be analysed by age at first exposure, but if the cases with pedoscope exposures are examined in relation to the age at death some suggestive figures emerge. Only seven children dying before the age of 2 had been *x*-rayed in a shoe-shop, but six of them had leukaemia. The other pedoscope histories included 37 children who developed leukaemia between 2 and 4 years of age (18% of such cases), but only 17 (or 10%) of the children who developed other cancers between these ages. Thus there is no inconsistency between the figures for medical and shoe-shop *x*-ray exposures.

Comment

To sum up: there are two reasons for thinking that *x*-ray films taken shortly after birth influence the distribution of childhood deaths from malignant disease. In the first place, there is a significant case excess for *x*-ray exposures during infancy. Secondly, children who died of leukaemia at the age of 2 and 3 years were concentrated within the group of cases exposed to *x* rays in infancy. The effect of post-natal *x*-ray exposure appears to be more marked in respect of leukaemia than other cancers and to be much weaker than the effect of pre-natal *x*-ray exposure. It may in fact be restricted to speeding the date of death in children who are already predisposed to leukaemia.

The lack of any association between the parts of the body exposed to *x* rays and subsequent developments may be related to the fact that in infancy the reticulo-endothelial system is so widespread that it is likely to be involved in any exposure.

SECTION V. CHILDREN'S ILLNESSES AND THEIR TREATMENT

In this section we consider: (1) congenital defects, (2) acquired diseases during the pre-onset period, and (3) two classes of drugs—sulphonamides and antibiotics. Again we discriminate between accurately dated illnesses and ones which might have happened after the onset date.

Congenital Defects

These were mentioned in 75 of the case and 46 of the control records, but only two conditions, mongolism and naevi, were more common among the cases.

Mongols.—There were 17 mongols in the leukaemia series, one among the other malignant disease, and none in the control group, though one child placed first on a control selection list was said to be a mongol and to have been in an institution since infancy, and was for this reason not chosen (see Section I). Until two years ago only four cases of leukaemia associated with mongolism had been reported. Since then Krivit and Good (1956), Merrit and Harris (1956), Carter (1956), and Paterson (1958), have between them reported 13 cases. With the present series this makes a total of 34 reported cases. Since the incidence of mongolism in the present leukaemia series (2.6%) is nearly 20 times as high as the incidence of mongolism in 14,000 consecutive births (Malpas, 1937), the association is evidently not a fortuitous one. We have already shown that excessive maternal age at the time of the child's birth (which undoubtedly predisposes to mongolism) also predisposes to leukaemia (see Section I). It is therefore more likely that the two diseases are influenced by a common factor than that the antecedent condition, mongolism, predisposes to the later condition, leukaemia. If this is so then for some of the cases of leukaemia the decisive event must date back at least to the onset of the mongolism; that is to say, at the latest to the second month of gestation. A number of facts relating to the mongols in the survey are shown in Table XIX. The mongol who developed a glioma had been *x*-rayed 71 days before birth, but none of the mongols who died of leukaemia had been irradiated *in utero*. Four mothers had had previous abortions, but there were no threatened abortions in the relevant pregnancy and no previous stillbirths. One mother was married to a second cousin.

TABLE XIX.—*Features of the* 18 *Mongols Included in the Survey*

Cause of Death	Cell Type (Leukaemias)	Sex	Birth Rank	Age at Death	Age of Mother*
Cerebral glioma	—	M	4	3 years 5 months	40
Leukaemia	Myeloid	M	7	2 ,, 11 ,,	44
,,	,,	M	2	1 year 2 ,,	44
,,	Lymphatic	F	8	1 ,, 6 ,,	43
,,	,,	F	4	5 years 0 ,,	42
,,	Myeloid	M	5	2 ,, 1 ,,	40
,,	N/R	F	2	2 ,, 8 ,,	39
,,	Lymphatic	M	3	1 year 11 ,,	38
,,	,,	M	2	4 years 9 ,,	36
,,	Monocytic	M	2	5 ,, 11 ,,	34
,,	Lymphatic	F	1	2 ,, 0 ,,	34
,,	Myeloid	F	4	2 ,, 6 ,,	34
,,	Lymphatic	F	1	2 ,, 0 ,,	32
,,	,,	F	2	1 year 5 ,,	32
,,	Aleukaemic	F	3	8 years 4 ,,	29
,,	Lymphatic	M	1	6 ,, 5 ,,	26
,,	Monocytic	M	1	4 ,, 6 ,,	26
,,	Lymphatic	M	1	6 ,, 11 ,,	19

* Age at birth of survey child.

Naevi.—These were reported 34 times on the case side and 21 times on the control side. As previously stated, eight of the cases and three of the controls were treated with *x* rays. The overall difference between cases and controls is not statistically significant, and might be due to under-reporting on the control side of a condition which is only cosmetically important. For girls there were 18 cases and 14 controls, and for boys 16 cases and 7 controls.

The other congenital defects took various forms and were evenly distributed between the two series, with 25 records on the case side and 25 on the control side.

Other Diseases of Childhood

It was clearly important to exclude all illnesses which happened after the onset date. This raised two problems: what to do with an illness which appeared to coincide with the onset of the fatal disease; and what to do with an inaccurately dated event which might or might not have preceded this date. An illustration of the first problem is provided by a case record which stated: "Following measles the child was always ailing. The measles was complicated by pneumonia then . . ." In this case we should have placed the onset date immediately after the measles and excluded all subsequent events, even the so-called pneumonia.

The second problem arose when an illness was not more precisely dated than the year in which it happened or the age, in years, of the child at the time. In such cases we have assumed that the event occurred midway between the limiting dates. It follows that an illness dated, say,

"1953" would have been counted in the pre-onset period if the onset date was July 1 or later, but not otherwise. Similarly an illness occurring "at 4 years of age" would be counted in the pre-onset period if the onset date was 4 years and 6 months or over, but not otherwise.

It follows that, though some illness must have been wrongly placed, the errors in placing are likely to have cancelled out, leaving an approximately correct total in the two series; where there was possible confusion between a previous illness and an early but unrecognized manifestation of the fatal disease, the illness has not been included in the following analyses.

In Table XX the illnesses allocated to the pre-onset period have been classified as *recent* if within two years of the onset date, and *remote* if two or more years before this date. Events which could not be placed in one or other of these subgroups have been relegated to a separate column and are not included in the total of dated illnesses. The table deals with illnesses, not injuries, and is restricted to relatively acute episodes which could be more or less precisely dated. A number of chronic diseases, injuries, operations, and ill-defined conditions not included in the table are mentioned in the text.

The first part of Table XX deals with the six infectious diseases which comprise nearly 80% of all dated illnesses and of all illnesses in the *recent* period. The exclusion of

TABLE XX.—*Childhood Illnesses in* 1,299 *Pairs of Survey (M) and Control (C) Children*

	Illness Within 2 Years of Onset Date		Illness More than 2 Years Before Onset Date		Total of Dated Illnesses		Additional Illnesses of Uncertain Date	
	M	C	M	C	M	C	M	C
Measles	208	235	236	219	444	454	60	70
Chicken-pox	131	173	125	102	256	275	46	55
Whooping-cough	105	136	154	158	259	294	48	36
Mumps	57	61	45	38	102	99	10	22
Rubella	47	46	34	34	81	80	12	23
Scarlet fever	20	24	19	15	39	39	4	6
Total	568	675	613	566	1,181	1,241	180	212
Bronchitis	38	24	19	19	57	43	6	3
Bronchopneumonia	39	17	37	32	76	49	2	1
Total	77	41	56	51	133	92	8	4
Acute tonsillitis	30	22	14	12	44	34	1	4
Acute otitis media	20	25	15	9	35	34	0	2
Total	50	47	29	21	79	68	1	6
Other infections	88	54	65	47	153	101	12	9
Other illnesses	29	12	29	12	58	24	1	3
Total	117	66	94	59	211	125	13	12
Grand total	812	829	792	697	1,604	1,526	202	234

M=Survey children (all malignant diseases). C=Controls.

cases of uncertain date has still left an excess on the control side, but this is slight and confined to three diseases —measles, chicken-pox, and whooping-cough. As this comparison might have been affected by the deficit of first-born children in the control group, a rough standardization for birth rank was made. This had very little effect, particularly on the comparison between illnesses which happened within two years of the onset date, where the difference between cases and controls was mainly concentrated. Hence the popular idea that an infectious illness occasionally initiates a malignant process (or provokes a pre-malignant state) receives no support from the present survey. To argue the other way and say that the survey findings suggest an antagonism between exanthema and malignant diseases would also be wrong. Only in the *recent* period and for one disease (chicken-pox) was there a significant excess of controls, and for this disease there was a deficiency of control records in the *remote* period, which reduces the overall excess to a non-significant level.

The second part of Table XX shows that acute pulmonary infections were relatively uncommon, but for every three cases with such infections there were only two controls. In the *recent* period there were nearly twice as many records of acute bronchitis or pneumonia on the case side, and in the leukaemia series (not distinguished in the table) the case/control contrast was greater than in the other malignant series. Compared with all controls, the excess in the leukaemia series was highly significant ($P<0.001$) and indicates in this series an "extra" 24 cases of acute bronchitis or pneumonia in the two years before the onset date. If this is accepted as evidence of a causal relationship, then about 4% of leukaemia cases might be ascribed to a recent acute pulmonary infection. The corresponding figure (less than 2%) for other cancers was of borderline significance. Since there is no excess on the case side of acute pulmonary infections in the *remote* period, the recent infections are more likely to have accelerated overt signs of malignant diseases in vulnerable children than to have initiated the malignant process.

These estimates all relate to single acute episodes. A much smaller number of children were said to have recurrent attacks of bronchitis (often associated with teething), and these were also in the ratio of approximately three cases to two controls. Such reports are necessarily suspect and difficult to date, so the excess is less certainly a genuine finding. Nevertheless for three infections of the respiratory tract, which were suspect in the same way, there was an excess on the control side: these were "frequent colds" (242/295), "recurrent sore throat" (27/39), and "sinusitis" (10/21).

Clear-cut acute attacks of tonsillitis and otitis media are shown in the third part of Table XX. The slight excess of tonsillitis on the case side is confined to the *recent* period, and the figures for otitis media are roughly equal on the two sides. Not mentioned in the table are 35 case children and 29 controls who had their tonsils removed within two years of the onset date, also 10 cases and 19 controls with chronically discharging ears.

The fourth part of Table XX includes a number of illnesses which were either too rare or too vaguely described to be considered separately. In both periods there was a marked excess on the case side, but since the risk of "inflated reporting" by bereaved mothers is probably at a maximum with minor or ill-defined conditions (which form the bulk of this section), we prefer to draw no conclusions from these figures. Trivial conditions not included in the table are "feeding difficulties" (254 cases, 198 controls), allergic conditions (28 cases, 25 controls), worm infections (89 cases, 82 controls), and frequent colds (already mentioned). The even distribution of cases and controls for three of these four conditions does not suggest under-reporting on the control side; it is therefore possible that the figures in the fourth section of Table XX and the figures for recurrent attacks of bronchitis indicate a genuine excess on the case side.

Finally, some reference must be made to injuries and operations. A vast number of minor injuries, including bruises, were recorded, but only two types were regarded as important enough to merit analysis, and then only if they happened within two years of the onset date. In this period there were 44 fractures (26 cases, 18 controls) and 28 burns or scalds (16 cases, 12 controls). The case excess lay entirely within the leukaemia series, and for the two items combined these children produced 28 records, compared with 14 for the children with other cancers. For recent operations, other than tonsillectomy, the figures were 16 cases and 17 controls.

In summary: Neither in their lifetime as a whole, nor in the two years immediately preceding the fatal illness, did the children with leukaemia and other cancers have an excessive number of the common infectious diseases of childhood. If anything they experienced less chicken-pox and fewer throat and ear infections than usual. On the other hand, the children with leukaemia had a noticeable heavy incidence of acute pulmonary diseases and severe injuries during the two years before they showed signs of the fatal disease.

Sulphonamides and Antibiotics

There were three reasons why the interviewing doctors were specifically asked to record treatments with sulphonamides and antibiotics. In the first place, being new drugs, they might have contributed to the recent increase in leukaemia mortality. Secondly, intensive treatment with sulphonamides occasionally causes aplastic anaemia. Finally, it was thought that the mother would know, if not what exactly was given to the child, at least whether sulpha drugs or penicillin had been prescribed, and how these drugs had been administered.

In the following analyses we have omitted all local applications (drops, powders, and ointments) and made no distinction between oral and parenteral administrations. The conventions which were used to decide whether the drugs were actually given in the pre-onset period were the same as for the illnesses but, as Table XXI shows, there was a

TABLE XXI.—*Treatment of Children's Illnesses with Sulphonamides and Antibiotics*

Treatments	Leukaemia (619 Pairs)		Other Cancers (680 Pairs)		Total (1,299 Pairs)		Case/Control Ratios
	Cases	Controls	Cases	Controls	Cases	Controls	
Sulphonamides:							
Adequately dated ..	94	96	84	61	178	157	1·13
Not adequately dated	30	18	26	34	56	52	1·08
Total ..	124	114	110	95	234	209	1·12
Antibiotics:							
Adequately dated ..	109	83	95	77	204	160	1·28
Not adequately dated	36	36	29	41	65	77	0·84
Total ..	145	119	124	118	269	237	1·14

higher proportion of undated drugs than illnesses. This is due to the fact that in some of the records it was impossible to say which of the dated illnesses had been treated in this way. The table reveals an even distribution of adequately dated treatments with sulphonamides, but the corresponding figures for antibiotics show a small case excess. Since the high incidence of pulmonary infections on the case side was likely to have influenced these figures, Table XXII has been

TABLE XXII.—*Sulphonamide and Antibiotic Treatments, Distinguishing Children Who Had an Acute Pulmonary Infection Within Two Years of the Onset Date*

	All Cases		All Controls		Ratio*
	No.	%	No.	%	
Sulphonamide:					
Children who had acute pulmonary infection within 2 years of onset date ..	22/77	28·57	10/41	24·39	1·17
Remainder	156/1,222	12·77	147/1,258	11·69	1·09
Antibiotics:					
Children who had acute pulmonary infection within 2 years of onset date ..	36/77	46·75	13/41	31·71	1·48
Remainder	168/1,222	13·75	147/1,258	11·69	1·18

* Case/Control incidence ratio.

prepared in which the children who had such an illness in the two years before the onset date are shown separately. The effect of doing this is to reduce the case/control ratio for antibiotics from 1.28 (all treatments) to 1.18 (treatments other than those probably but not certainly related to a recent pulmonary infection). At this level it is within the conventional limits of chance fluctuation (P = approximately 1 in 15). The relatively high case/control ratio for both types of drugs in this table probably reflects the fact (not yet mentioned) that in the case series these infections were usually more severe, as well as more numerous, than in the control series, and for this reason were more likely to receive antibiotics or sulphonamides.

A record was also kept of treatments with ultraviolet light. These were reported for 50 cases and 40 controls. No conclusions can be drawn from these small numbers.

We conclude that there is no evidence for a direct relationship between childhood malignancies and the drugs considered here. There may, however, be an indirect relationship between antibiotics and leukaemia. In recent years antibiotics have revolutionized the prognosis for acute pulmonary infections and have undoubtedly kept alive children who would otherwise have died. If these infections occasionally provoke a latent leukaemic process, then, by increasing the number of children who survive, antibiotics may indirectly increase the prevalence of leukaemia.

SECTION VI. FEEDING HABITS AND HOME BACKGROUND OF THE SURVEY CHILD

Concern is often expressed about the widespread use of new chemicals, particularly food preservatives and detergents, on the ground that these may be carcinogenic. In the present survey no attempt was made to collect information about exposure to specific chemicals, but the mothers were asked a number of questions about their own habits and what they allowed their children to eat and drink.

Feeding Habits

The survey doctors were told to ask whether the children had been given certain foods and drinks every day, less than daily but at least one a week, less often, or never. They were also asked to state when these foodstuffs were first given; and what the mother thought the child had consumed in the way of coloured sweets. The completed records showed that a few control mothers had reported foods which were so unlikely to have been given during the pre-onset period—for example, fish and chips before the age of 1—that the analysis has been restricted to case/control pairs for whom the age at the onset date was not less than an arbitrarily chosen "qualifying age" for each foodstuff (see Table XXIII).

TABLE XXIII.—*Feeding Habits. Percentage of Cases and Controls Who Had Ever Taken Certain Foodstuffs*

Item	Qualifying Age	% of Children Who Had Ever Taken This Item		$\chi^2_{(1)}$	P Approx.
		Cases	Controls		
Dried milk	3 days	69·6	67·1	1·718	0·19
Fruit juice	1 month	90·6	90·7	0·002	0·96
Tinned sieved vegetables	4 months	61·1	58·2	1·976	0·16
Other tinned vegetables ..	12 ,,	55·1	60·6	6·797	0·009
Highly coloured cakes ..	12 ,,	33·5	33·7	<0·001	>0·98
Highly coloured fruit drinks	12 ,,	47·4	52·6	5·729	0·017
Coloured sweets * ..	12 ,,	32·6	33·0	0·018	0·90
Shop-fried fish and chips	12 ,,	43·2	43·9	0·066	0·79
Total ..				16·306	0·05>P>0·02

* For this item "ever" = more than ¼ lb. (113 g.) per week.

The figures shown in this table relate to children who had ever been given a food regardless of the reported frequency. In aggregate the case/control differences for the eight foodstuffs considered appear to be statistically significant (P<0.05), but only two foods—tinned vegetables and coloured drinks—showed a significant difference, and both were reported more often on the control than on the case side. For these two items the qualifying age may have been set too low, thus permitting some upward bias on the control side. If such bias exists the case/control ratios for other items may have been underestimated, but the reported percentages are so nearly level that it is unlikely that any important differences have been missed.

The foodstuffs listed on Table XXIII were also considered from the point of view of "dosage." Three of them showed a case excess in the highest consumption category:

Coloured Cakes.—Daily consumption of these was reported for 45 cases and 16 controls, but when this and the next-highest "dose" were combined the figures became 125 cases (11.3%) and 111 controls (10.0%).

Coloured Sweets.—At an estimated level of 12 oz. (340 g.) or more sweets per week there appeared to be an excess of cases (7.0%) over controls (4.4%), but this was balanced by an excess on the control side of children who usually ate between 3 and 12 oz. (85 and 340 g.) per week. As already shown, there was no deficiency of cases in the lowest consumption group.

Shop-fried Foods.—There was no difference in the proportion of cases and controls who had never had these foods, but consumption of fish and chips as often as once a week was reported by 191 cases and 140 controls. Once again the balance was made up by an excess of control children among those who occasionally had fish and chips.

In short, for none of the eight foodstuffs considered was there either a significant excess in the percentage of case children who had ever consumed them, or a consistent association between the amount consumed and subsequent events.

Other Factors

Contraception.—An attempt was made to discover whether there had been any attempt at family planning and if so what methods had been used. The proportion of completed records for contraception (89%) was lower than for most items, but the numbers of case and control mothers who gave satisfactory answers were similar (1,158 and 1,143). Chemical contraceptives were used by 124 case mothers (10.7% of those giving full information) and 107 control mothers (9.4%). The small difference arose principally in the leukaemia series, but these mothers did not differ significantly either from their own control pairs (P=approximately 0.21) or from the mothers of other cases (P= approximately 0.37).

Detergents.—The percentage of case mothers who stated that they used synthetic detergents was 61.3%—very similar to, but slightly below, the figure of 63.6% for mothers of controls.

Smoking.—Under this heading interviewers were asked to place the mother and father in one of the following categories: heavy, moderate, or light smokers, and non-smokers (the instructions gave quantitative definitions for these four categories). The figures quoted here relate only to "smokers" (at least one cigarette or pipe a day) and "non-smokers." The percentages of fathers and mothers in both series recorded as smokers were slightly higher than those recently reported for men and women of comparable age by Research Services Ltd. (Todd, 1957). For fathers of cases the proportion was 82.9% and for fathers of controls 80.9%, and for mothers 47.8% and 43.8% respectively. These percentages indicate a significant ($P \simeq 0.04$) excess among mothers of cases, but the difference is a small one (case/control ratio of 1.09), and we have not attempted to relate it to age, income, or number of children, as would be necessary before concluding that the mothers' smoking habits had affected their children. One factor which might well produce a genuine but irrelevant difference between mothers of cases and controls was, of course, the bereavement itself.

SECTION VII. FAMILY HISTORIES

Sibs—The records gave a complete tally of all the mothers' pregnancies up to the date of the interview, including those which ended with an abortion or stillbirth. As Table XXIV shows, there was no case/control difference in respect of stillbirths, but the case excess for abortions is at least suggestive, particularly as it is concentrated (like the case excess for threatened abortions during the "relevant" pregnancy) in the leukaemia series. The numbers of deaths among the liveborn sibs of the cases and controls were 132 and 129 respectively. This implies a very similar total mortality, since the numbers of liveborn sibs in the two series were almost equal (2,119 and 2,155) and the average number of years at risk was only slightly greater on the control side. Although most individual causes of death were equally common in the two series, deaths from malignant disease among the case sibs numbered eight as against only two for the controls. On the basis of the relatively high national mortality rates in 1953–5, and without allowing for reduction of the population at risk by other deaths, the expected number of deaths from malignant disease among the sibs of the cases is 2.15. It follows that the total of eight malignant deaths on the case side is significantly higher than expectation (P=0.001) (see Table XXV). Even five cancer deaths—that is, after the exclusion of three cases which were not certainly cancers—namely, the "acute anaemia," the "brain tumour," and the "growth in abdomen"—represent a significant case excess (P<0.05).

TABLE XXIV.—*Miscarriages and Stillbirths (Up to the Date of the Survey Child's Death)*

	Leukaemia		Other Cancers		Total	
	Cases	Controls	Cases	Controls	Cases	Controls
Mothers reporting abortions ..	129	93	119	118	248	211
Total No. of abortions ..	173	122	153	156	326	278
Mothers reporting stillbirths ..	26	23	27	23	53	46
Total No. of stillbirths.. ..	26	28	32	25	58	53

TABLE XXV.—*Siblings of Cases With Death Attributed to Malignant Disease*

Serial No.	Index Case			Sibling		
	Sex	Diagnosis	Age at Death (Years)	Sex	Diagnosis	Age at Death (Years)
122	F	Lymphosarcoma ..	6	M	"Acute anaemia"	1
289	F	Acute lymphatic leukaemia	1	F	Leukaemia ..	1
290	F	Acute reticular leukaemia	0	F	,, ..	0
347	M	Acute lymphatic leukaemia	5	M	Generalized lymphosarcoma	3
				M	Retroperitoneal sarcoma	2
476	F	,, ,,	5	M	"Brain tumour"	4
1293	F	Acute stem-cell" leukaemia	1	F	"Growth in abdomen"	2
1656	M	Neuroblastoma ..	1	M	Lymphatic leukaemia	5

Parents.—One reason for not obtaining the first name on a control selection list was death of the mother; therefore little meaning attaches to the excess of dead parents in the case series (20) as compared with the controls (5). Among nine dead parents in the leukaemia series two had died of leukaemia and one of lymphosarcoma. Among 11 dead parents in the other cancer series four had died of some form of malignant disease. One of the five deaths among parents of control children was attributed to leukaemia and two to other malignant diseases.

Grandparents.—A total of 4,508 deaths of grandparents were reported. Judged by the proportions of deaths for which the cause was unknown or attributed to "senility," mothers gave better information about their own than about their husbands' parents, but there was no difference between the standard of information supplied by case and control mothers. Overall mortality was almost identical in the two series, the number of surviving grandparents being 2,936 in the case and 2,948 on the control side. Among 53 specified causes of death the largest proportional discrepancies between cases and controls were war injuries (60/95) and renal conditions (32/54), the excess in each case being on the control side. For malignant diseases as a whole there was a proportionally smaller but significant excess on the case side, the totals being 387 for cases and 316 for controls. This excess ran uniformly through the records (Table XXVI). The proportion of case children with an affected grandparent varied very little between the main diagnoses in the case series. There was no detectable variation in the sex ratio of cases as between groups with an affected grandparent on the paternal or maternal side, nor when these relatives were subdivided into father's father, father's

TABLE XXVI.—*Reports of Malignant Disease in Grandparents of Cases and Controls*

	Cases	Controls	Ratio
Grandparents of leukaemia series	172	140	1·23
,, of other malignant series ..	215	176	1·22
All paternal grandparents	186	152	1·22
All maternal ,, ...	201	164	1·23

mother, etc. One tabulation which did appear to show some variation was that of the reported site of the cancer in the grandparents. For example, lung cancers in grandparents showed *no* excess of cases over controls (52/55), but a relatively high case/control ratio was observed for breast and genital cancers (cases 58, controls 37).

Uncles and Aunts.—The total number of uncles and aunts was much the same for cases and controls (9,578 for cases, 9,425 for controls). Only deaths attributed to malignant disease were coded for these relatives, the numbers being: uncles and aunts of cases, 77; of controls, 55. The case/control ratio of 1.20 is almost identical with that for grandparents. In the case series there was no significant variation between the diagnostic subgroups, but the cancers in the uncles and aunts seemed to parallel two features noted in the grandparents. Thus cancers of the respiratory system showed no case excess (8/13), while breast and genital cancers showed a relatively large case excess (18/8).

Remoter Relatives.—Rather more case mothers volunteered statements about cancer in relatives beyond the second degree than control mothers, and this revealed one interesting cancer pedigree. This concerned a boy who died at the age of 6 from "cancer of the liver and bowel" and had five relatives on the father's side who had also died of bowel cancer—the father himself, the grandfather, the great-grandfather, and two aunts.

Consanguinity.—The number of cousin marriages in the case series was not large either in relation to the controls or in relation to the frequency in the general hospital population (Bell, 1940). Of the 10 consanguineous matings reported in the case series, only 5 (0.4%) were between first cousins. To these should be added one case (not fully followed up and not included in the 1,299 pairs) in which a father–daughter mating resulted in the birth of a girl who died at the age of 5 months from Letterer–Siwe's disease.

Discussion

All scientific investigations are faced with the problem of eliminating unknown bias from test and control observations. Where, as in the present case, the findings are based on human data and involve comparisons between facts which have been obtained by different observers from inexpert witnesses the main sources of such bias are: (1) unequal recording of events by different observers; (2) unequal reporting of events by the individuals chosen to represent case and control groups; and (3) faulty selection of cases and/or controls.

The first source of error has been controlled by insisting on the same doctor seeing each member of a given case/control pair. By so doing, errors due to lack of skill in interviewing and recording should be equally represented on the case and control sides. The same device might be expected to control the second source of error; but here we were on less certain ground, and have therefore applied other tests of reliability. Thus for several items specified in the questionaries the proportions of completed records in the two samples have been calculated and found to be alike. To illustrate this point we have summarized the findings for six items in which a low response rate might, with some justification, have been expected (Table XXVII). By these criteria it would seem that the doctors were equally pertinacious when questioning the cases and controls, and the mothers were equally helpful when replying to the doctors' questions.

TABLE XXVII.—*Response of Case and Control Mothers to Certain Questions*

Items	Response Rate (i.e., Percentage of Complete Answers)	
	Cases	Controls
Family income	87	88
Contraception	88	89
Dated illnesses (children)	89	87
,, (antibiotics and sulpha drugs) (children) ..	76	71
,, post-natal *x*-ray exposure	85	78
Specific cause of death (grandparents)	82	81

Other safeguards include repeated demonstration that significant differences between cases and controls are not compatible with any *general* tendency on the part of control mothers to be unduly forgetful or uncooperative. For instance, the case excess for two maternal diseases which might have affected foetal development—virus infections, and threatened abortions in the relevant pregnancy—were not accompanied by a case excess for other maternal illnesses, either during this period or previously. Again, the case excess for pulmonary diseases in childhood must be viewed against a background of almost equal numbers of all childhood diseases in the two groups, and the case excess for *x*-ray exposure in infancy against almost equal numbers for post-natal *x*-ray exposure as a whole.

The third source of bias—namely, faulty selection of cases and controls—has been dealt with in the following ways. The cases were drawn from the total number of cases for a three-year period, and those actually included in the survey represent such a high proportion of this total that, however atypical the *lost cases* may be, the consequences would remain numerically unimportant. The controls were drawn from the general population of surviving children, thus avoiding some of the confusion which might have resulted from using more accessible children—for example, other hospital patients, children attending welfare clinics, or siblings of cases. The controls actually included in the survey have been shown to differ in two important respects (first-born children and twins) from the national population. But because the numbers in these classes can be calculated from official vital statistics, it has been possible to show that the deficiencies in the control group had a negligible effect on the main finding—namely, a large excess for direct foetal irradiation in the case series. We have also shown that this finding was not affected either by systematic checking of the mother's statements against hospital records, or by the publication of a preliminary report half-way through the survey. Finally, we already know that at least one independent observer has tested this main finding and used different methods to obtain virtually the same result.

We are therefore confident that the finding in respect of direct foetal irradiation is not an artifact. Nor have we any reason to doubt that there are genuine case/control differences in other respects—namely, maternal age at the time of conception, post-natal pulmonary infections, and *x*-ray exposure in infancy. All these factors appear to have a "causal" association with childhood malignancies, but we do not suggest that any one of them is either a necessary or a sufficient cause of the malignant changes. The special risks associated with these events may perhaps be compared with the well-known risk of being a male child. Thus boys are known to run a higher risk than girls of developing cancers, but no one ever cites the Y-chromosome as a "cause" of cancer. Nor do we claim that any of the associations are quantitatively important. The number of childhood malignancies which they might account for is small even in relation to the recent increase of these deaths reported during the last two decades—about 60% for children under 5 years (see McKenzie, Case, and Pearson, 1957).

Summary and Conclusions

The pre-natal and post-natal experiences of a large group of children who recently died of malignant diseases have been compared, point by point, with the experiences of a similar group of live children.

The frequency of three pre-natal events—namely, direct foetal irradiation, virus infections and threatened abortion—was significantly higher among the dead children than among the live children.

One other pre-natal influence—namely, excessive maternal age—appears to increase the risk of leukaemia in childhood and to be related to the fact that this disease and mongolism tend to occur together.

The frequency of three post-natal events—namely, *x*-ray exposures in infancy, acute pulmonary infections and severe injuries—was significantly higher for children who subsequently died of leukaemia than for other children. In the "pre-antibiotic era" some of these children might have died before showing signs of the leukaemia.

The health of the mothers and the home background of the children were not significantly different in the two groups, but there were minor points of difference in the family histories of cancer and leukaemia.

Our final conclusions are that foetal irradiation does not account for the recent increase in childhood malignancies, but the finding of a case excess for this event does underline the need to use minimum doses for essential medical *x*-ray examinations and treatments.

A survey on the scale achieved could never have been contemplated without the active co-operation of doctors and health visitors too numerous to mention by name. Principal medical officers of health of local authority areas assumed responsibility for the field work of the investigation and completed the whole of their arduous and self-imposed task in the short space of 18 months. The interviews were done either by principal or by assistant medical officers of health, and health visitors did invaluable work in tracing cases and controls. We record with gratitude the high standard of the work in all regions.

We are also indebted to the Lady Tata Memorial Trust, which defrayed all costs other than those borne by the Health Departments and Oxford University; to the General Register Office, which provided essential data; to the Medical Research Council Working Party on Leukaemia, who gave us constant encouragement and advice; and to the mothers of the dead children, who had the courage to reopen a painful topic and so often expressed the hope that by doing so they might be helping other children.

Finally, we thank two members of our own staff: Miss Dawn Giles, who, while holding the Mary Goodger Research Scholarship, helped with the organization of the survey and the coding of records, and W. E. C. Brooksbank, who was responsible for the machine sorting of the data.

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DIET AND ARTERIAL DISEASE IN A POPULATION SAMPLE

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It is a curious paradox that one of the most hopeful features of ischaemic heart disease is the apparent rise in its clinical incidence (Ryle and Russell, 1949; Morris, 1951); for it is this rise, especially as it affects the middle-aged, which suggests the importance of environmental factors rather than simple ageing. This raises the hope that if only the responsible change can be identified its reversal may possibly prevent or even cure the disease. Unfortunately, however, the search for the relevant change is impeded by the complexity of social development. For instance, the apparent fall in the mortality from ischaemic heart disease which Malmros (1950) observed in some Scandinavian countries during the last war, and which he attributed to the effects of food rationing, might have been due to some other of the many profound effects of war upon society.

Other attempts to correlate diet with the clinical or necropsy incidence of ischaemic heart disease in different populations are all open to similar criticism, since the various races that were studied differed in many ways besides diet (for example, Keys *et al.*, 1954a, 1954b; Bronte-Stewart *et al.*, 1955; see Yudkin, 1957). A more direct approach is to compare, within the same population group, those with and without the disease. This method has been used in comparing hospital cases with unaffected hospital patients, or else with healthy volunteers (for example, Gertler, White, *et al.*, 1954). Such studies are open to the serious objection that patients and controls come from different population groups. The proper control for a man in hospital with ischaemic heart disease is a man taken at random from the same population group; such ideal control is almost impossible of achievement.

An investigation requiring a completely acceptable control group is more suitably based upon the population at large. Such an approach is most laborious, for, in order to find a small number of people with the disease from among the general population, it is necessary to interview and examine a much larger number. In addition, those discovered may have only a limited desire to co-operate. In the present study these problems were simplified by making use of material which had been collected for a different purpose, but which was also very suitable for a controlled study of diet and arterial disease. Our purpose was to determine whether, within a defined section of the general population, the diet of those who had clinical ischaemic heart disease or intermittent claudication differed from those who had not.

Methods

In 1953–4 one of us collected data for a study on the inheritance of diabetes mellitus. The names and addresses were obtained of all first-degree relatives of (*a*) 550 diabetics