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INCIDENCE OF LEUKAEMIA AFTER EXPOSURE TO DIAGNOSTIC RADIATION IN UTERO

BY

W. M. COURT BROWN, M.B., B.Sc., F.F.R.
Director of the Medical Research Council's General Effects of Radiation Research Unit, Western General Hospital, Edinburgh

R. DOLL, M.D., D.Sc., F.R.C.P.
Deputy Director of the Medical Research Council's Statistical Research Unit

AND

A. BRADFORD HILL, F.R.S.
Professor of Medical Statistics and Honorary Director of the Medical Research Council's Statistical Research Unit, London School of Hygiene and Tropical Medicine

With the co-operation of Drs. D. H. Cummack, Margaret S. King, Eric Samuel, and W. N. Thomson (Edinburgh), and R. E. Lawrence, F. Pygott, R. E. Steiner, and E. Rohan Williams (London)

Interest in the effects of small doses of ionizing radiations has focused attention on the possibility that doses of *x* rays such as are used in medical diagnostic radiology may on occasion be carcinogenic. Little direct evidence is available, since the effect (if it exists) is small, and to detect it very large numbers of subjects need to be studied. Mostly the evidence relates to the special case of the foetus irradiated during examination of the mother's abdomen or pelvis, and it has been obtained by retrospective inquiry into the history of her pregnancy after the child's death was known to have occurred.

The most extensive data are those published by Stewart and her colleagues at Oxford (Stewart, Webb, Giles, and Hewitt, 1956; Stewart, Webb, and Hewitt, 1958). In their study, histories were obtained from mothers whose children had died of malignant disease throughout England and Wales during the period 1953–6, and the results were compared with those obtained from a control group of mothers whose children were still alive. It was concluded that children who were exposed *in utero* to pelvimetry, or to another similar procedure, had approximately double the normal risk of dying from cancer before the age of 10 years.

In the present study, data have been obtained by a different technique. Women who were irradiated during pregnancy have been identified in the records of the radiological departments of selected hospitals and the subsequent deaths from leukaemia of the children of these pregnancies have then been discovered. The observed mortality from leukaemia has been compared with that expected on the basis of the national mortality rates. With the technique employed it was possible to study only leukaemia, and no evidence has been obtained about other types of cancer.

The Children Studied

Eight hospitals were selected, four of which served most of Edinburgh and four a compact area in North-west London. With the co-operation of the radiological departments, lists were compiled of all those women known to have been exposed, between 1945 and 1956, to diagnostic *x*-ray examination of the pelvis or abdomen during pregnancy. The great majority of these women were delivered in the same hospital, and information was obtained from the maternity department about the mother's address, the date of birth and sex of the child, and whether the child was born alive or dead. It was possible to obtain the same information for a small number of these women who (1) were found to have been delivered at another of the hospitals participating in the inquiry (or at another associated hospital), or (2) were delivered at home, but for whom out-patient records of delivery were readily available. Women whose maternity records were not thus available were excluded from the study. The great majority of these women were under the care of general practitioners or were private patients. The numbers in the various categories are shown in Table I.

TABLE I.—*Number of Women who Received Abdominal or Pelvic Irradiation During Pregnancy and Proportion for Whom Maternity Records were Available*

Maternity Records	Irradiated Women	
	No.	%
Available:		
Delivered in same hospital	38,114	87·1
,, ,, other hospital	351	0·8
,, at home	1,122	2·6
Not available	4,155	9·5
Total	43,742	100·0

In nearly all cases the information provided by the hospital enabled the registration of the child's birth to be identified in either the local or the central Register of Births. These registers then provided information about the first names of the child and the first names and the occupation of the father. The numbers of children for whom full records were obtained in this way are shown in Table II. No attempt was made to trace the

TABLE II.—*Number of Children Known to Have Been Irradiated in utero and Proportion for Whom Adequate Records were Obtained*

Records of Child	No. of Children			Total Children	
	Male	Female	Sex not Recorded	No.	%
Adequate records:					
Aborted	75	89	349	513	1·2
Stillborn	979	930	90	1,999	4·8
Liveborn	20,982	18,174	10	39,166	93·6
Inadequate records:					
Liveborn	76	70	2	148	0·4
Total ..	22,112	19,263	451	41,826	100·0

registration entries of stillborn children or of children who were known to have died in hospital, as in these cases the hospital records themselves provided all the necessary information.

The liveborn children whose sex was not recorded are known to have died in hospital in the neonatal period, so that further follow-up of these was not needed. The very few liveborn children for whom adequate records were not obtained may have been registered in districts other than those in which the hospital or the recorded address of the mother was situated, and their records could not be identified in the Central Register because, in many cases, there were too many entries that conceivably might have related to them. A few may have been missed because of a change of name at registration.

Information about the date and type of the mother's *x*-ray examination was obtained from the radiological records. All examinations directed at the mother's abdomen or pelvis were recorded if they had been made within nine calendar months of the date of delivery. On the basis of this information the women were classified into six categories according to the number and type of *x*-ray examinations to which they were exposed. The numbers of children born alive to women in each category, for whom full birth data were obtained, are shown in Table III.

TABLE III.—*Numbers of Liveborn Children Exposed to Various Types of Radiographic Examination in utero*

Exposure Category	No. of Liveborn Children		
	Male	Female	Total
A. Pelvimetry on one occasion only ..	7,864	6,900	14,768*
B. ,, ,, ,, plus additional exposure	2,487	2,072	4,561*
C. Simple abdominal radiography on one occasion only	8,921	7,659	16,584*
D. Simple abdominal radiography on one occasion plus additional exposure other than from pelvimetry	1,149	1,017	2,166
E. Intravenous pyelography	291	262	553
F. Miscellaneous	270	264	534
Total ..	20,982	18,174	39,166*

* For 10 children the sex was not recorded—4 each in categories A and C, and 2 in category B.

Identification of Leukaemia Deaths

The task of following up nearly 40,000 children until the age of 14 years to discover how many had died would have been extremely laborious. It was relatively simple, however, to discover how many had died of leukaemia, since we possessed copies of the death entries of all persons who had died of leukaemia in Great Britain from January 1, 1945, to December 31, 1958, which had been provided by the Registrars-General of England and Wales and of Scotland for the purposes of another inquiry. All that had to be done was to check the names of the children who had been irradiated against the names of the children who had died of leukaemia. If the child's first names and the first name of the father were alike on the two lists this was regarded as presumptive evidence that the irradiated child had died of leukaemia. The identity was, however, not considered to be established unless the occupation of the father was also alike and the addresses given at the time of birth and of death were the same. In all other circumstances—namely, of a lesser degree of similarity—inquiries were made from the hospital in which the child had died from leukaemia, or from the doctor who certified the death, about the date of birth of the child and the first names of the mother.

Calculation of the Expected Mortality

The mortality from leukaemia in childhood varies sharply with sex and age, and it also varied somewhat at each age during the period under investigation. We therefore had to estimate the number of children of each sex exposed to risk of death at each year of age during each of the years between 1945 and 1958. For this purpose children born in each calendar year were regarded as having been born at the mid-point of the year, and the numbers reaching each successive age were obtained by subtracting the numbers estimated to have been lost to the study during the course of the year. Since the identification of the children who died of leukaemia depended on the identification of the names of the child and of the parents given on the birth certificate, it is clear that adopted children would be liable to escape identification. All adopted children were therefore regarded as having been lost to the inquiry.

For children aged 0 years the loss rate was determined by adding the adoption rate to the infant mortality rate and the number of children of each sex lost to the study in the first year of life was then estimated by multiplying the number of entrants by this loss rate. For subsequent years the loss rate was obtained by adding the adoption rate to the corresponding age-specific death rate and the losses at each year of age were calculated by multiplying the loss rate by the average number of children estimated to have been alive throughout that year of life. For example, there were 916 living male children who were born in 1950 in the four London hospitals to mothers whose abdomen or pelvis was known to have been examined radiographically during the pregnancy. The male loss rate in the first year of life was 40.4 per 1,000 liveborn children (male infant mortality rate, 33.6, and male adoption rate at age 0–1 year, 6.8 per 1,000 liveborn children), so that the number of boys who reached the age of 1 year is calculated to be $916 - \frac{40.4}{1000} \times 916$—i.e., 879.0. The death rate and the adoption rate for boys aged 1–2 years in 1951 were 2.6 and 1.9 per 1,000 boys, so that the loss rate in the same group during this period was 4.5 per 1,000. Since the number of boys estimated at risk halfway through the year was 879.0 less half the number of losses, the total number of losses in the year (L) is $\frac{4.5}{1000}\left(879.0 - \frac{L}{2}\right)$, hence the number of losses was 3.9 and the number of boys who reached the age of 2 years is calculated to be 875.1.

Death rates from leukaemia for each sex and for each year of life were obtained for each calendar year between 1945 and 1958 by counting the number of the relevant death certificates in our possession and relating them to the published estimates of the corresponding populations. Finally, the numbers of deaths from leukaemia that could be expected to be found in our population of children irradiated *in utero* were calculated by multiplying the child-years at risk in each sex, age, and calendar year group by the corresponding leukaemia death rates. The total number of deaths from leukaemia was obtained by summing the results for all these subgroups. Throughout the calculations the data for London and for Edinburgh were treated separately. The loss rates from death and adoption for England and Wales were, however, used for both sets of data, as sufficiently detailed data were not available for Scotland.

Results

The number of children found to have died of leukaemia in the period 1945–58 was 9; the expected number was 10.5. Details of the 9 cases are given in Table IV. The numbers of deaths observed and expected among various groups of children are shown in Table V. In each group the observed and expected numbers are closely similar. It is perhaps particularly striking that there were 4 deaths from leukaemia among the 19,329 children exposed during pelvimetry, against 5.4 expected, and that there were 5 deaths among the 16,584 children exposed only in the course of one *x*-ray examination of the mother's abdomen, against 4.3 expected. All but one of the leukaemic children were exposed to radiation during the last four weeks of intrauterine life; the exception was exposed in the last month but one. An exact calculation of the expected numbers of deaths among children exposed at various periods of intrauterine life has not been made; but data obtained for a 1% sample show that 50% of the children were exposed only in the last four weeks, 38% were first exposed in the preceding two months, 10% were first exposed in the second trimester, and 2% were first exposed in the first trimester.

TABLE IV.—*Details of Irradiation in utero for Children Discovered to have Died of Leukaemia*

Date of Exposure	Category of Exposure*	Date of Birth	Interval between Exposure and Birth (Weeks)	Sex of Child	Age at Death (Years)	Type of Leukaemia
5/7/45	C	15/7/45	1	M	2	Acute lymphatic
11/7/45	C	27/7/45	2	F	9	,,
22/3/46	C	18/4/46	3	M	11	Unspecified
7/4/48	C	24/4/48	2	M	3	Aleukaemic
26/11/48	A	16/12/48	2	M	2	Acute lymphatic
18/8/49	C	10/10/49	7	F	1	Subacute
7/10/49	A	17/10/49	1	M	6	Acute lymphatic
22/8/52	A	31/8/52	1	M	4	,, myeloid
10/11/52	A	27/11/52	2	M	3	Lymphatic

* A=Pelvimetry on one occasion only.
C=Simple abdominal radiography on one occasion only.

TABLE V.—*Comparison Between Numbers of Deaths from Leukaemia Observed and Expected Divided by Age, Sex, Type of Irradiation, and Place of Residence*

Category of Children	No. of Deaths from Leukaemia	
	Observed	Expected
Boys	7	6·2
Girls	2	4·4
Age less than 5 years	6	7·5
,, 5–13 years	3	3·0
Exposure to irradiation during pelvimetry (radiation groups A and B)	4	5·4
Exposure only to one simple *x*-ray examination (radiation group C)	5	4·3
Irradiation in Edinburgh	5	5·7
,, ,, London	4	4·8
All children	9	10·5

It is clear from these data that the leukaemia mortality within the first 14 years of life was no greater among the group of children who were known to have been irradiated *in utero* than that for all children throughout the country who were born in the same years. Moreover, the leukaemia deaths were not disproportionately concentrated among those children who can be presumed to have received the heavier dose, nor among those children who were irradiated during the first part of intrauterine life. It should, however, be noted that few children were irradiated during the first three months, so that the inquiry provides little useful information about the extent of any possible risk in this period.

An incidental finding, which may be of some interest, is that the sex ratio among the irradiated children was substantially higher than normal. The sex ratio of liveborn children, shown in Table II, was 1.15 males to 1 female, whereas both for England and Wales and for Scotland the sex ratio for the years 1945 to 1956 was 1.06 to 1. An unusually high ratio was observed separately at each of the eight hospitals—the range being from 1.09 to 1 to 1.18 to 1—and in each of the years 1945 to 1956. The ratio was lower than average for the small number of children irradiated in 1956 who were born in 1957 (147 males to 144 females); but for the other 12 years the range was from 1.12 to 1 to 1.23 to 1. The reason for this high ratio is discussed elsewhere (Court Brown, Doll, and Hill, 1960). The most likely explanation would seem to be that the risk of a complicated delivery is higher for boys than for girls. Since the threat of a complicated delivery is one of the principal reasons for radiographic examination during pregnancy, this would result in a high male:female ratio among the children of irradiated mothers. There is no evident reason why the high proportion of boys in the series should have biased the results of the present inquiry.

Discussion

Before discussing the results of this investigation we must consider whether they could have been influenced by any of several factors. First, was the technique employed adequate to identify all the cases of leukaemia that actually occurred in the population studied? This we have tested in two ways: (*a*) The records of a random sample of 50 of the children were re-examined, to see if any errors had been made in recording the names of the children or of their parents; (*b*) A random sample of 50 deaths from leukaemia was selected (excluding those which referred to children born outside the period of the study) and the birth certificates of the children concerned were sought at the General Register Offices to see if the information recorded on these birth certificates would have enabled the child to be identified in the list of leukaemia deaths.

The first test revealed no inaccuracies in the data which had been extracted from the hospital records and the birth registers. The second test showed that in 46 instances the information given on the birth certificate

was identical with that available to us in the copy of the death entry. In two instances there were minor differences in spelling which would not have resulted in any difficulty in identifying the child, had he been one of those who were studied. In one instance there was a serious difference in spelling, and in one the previous birth entry could not be traced because the child had been adopted. As already pointed out, it had been realized that cases might be missed because of adoption, and this was allowed for in calculating the number of expected deaths. The one example of a serious difference in spelling might have resulted in a failure to recognize that one of the children in our records had subsequently developed leukaemia. A small number of deaths may also have been missed because the children had emigrated, but this can hardly be more than a few per cent. of the total for children under 15 years of age. It is possible, therefore, that the technique leads to an underestimate of the true incidence of leukaemia deaths by some 2 or 3%. But even if the deficiency were as much as 10% (which is very unlikely) the observed incidence of leukaemia among the irradiated children would still not exceed the national average.

Secondly, we may consider whether the results are distorted by the use of unsuitable data to calculate the expected mortality. Certainly it would have been preferable to compare the results with those obtained from a group of children born to unirradiated mothers from the same hospitals (although mothers who need to be *x*-rayed during pregnancy must differ from those who do not require such an examination and the comparison would not be ideal). Analysis of the leukaemia mortality for England and Wales and for Scotland has, however, shown that both the London and the Edinburgh leukaemia mortality rates are substantially above average for their respective countries (Hewitt, 1955; Court Brown, Doll, Spiers, Duffy, and McHugh, 1960); moreover, the Scottish mortality has been practically identical with that recorded in England and Wales. Unless, therefore, the children born at the hospitals included in this study were differentiated in some way which would have a major effect on their leukaemia mortality from all other children born in the same two cities, the method of comparison used in the study is more likely to have shown an excess among the irradiated children than the reverse.

Thirdly, it is possible that the dose of radiation received by the children in the present study may have been less than the average amount received from irradiation of the mother during pregnancy throughout the country. The eight hospitals which co-operated in the study were all metropolitan, and five of them were recognized for the teaching of obstetrics. The safety standards during radiological examination in these hospitals may therefore have been somewhat higher than average, and our results therefore not representative.

Fourthly, the number of cases of leukaemia that were observed is small and chance factors alone may have resulted in a fairly substantial risk being overlooked. If the effect of irradiation *in utero* were to raise the incidence of leukaemia by 50% above the national average the expected number of cases in our inquiry would have been $\frac{150}{100} \times 10.5$, or 15.8. In these circumstances it would not be unreasonable to attribute to chance the fact that only nine cases were observed ($P=0.04$); but it is unlikely that the effect of irradiation could be much more. Had the effect been to double the risk, the probability of obtaining only nine observed cases (or less) would have been less than 1 in 300.

The results of this investigation may therefore be regarded as evidence that radiographic examination of the mother's abdomen during pregnancy does not induce leukaemia in the foetus, or that, if it does, the additional risk induced by the methods used in eight metropolitan hospitals is likely to be less than half the general risk to which children aged under 15 years are normally exposed throughout the country. On the other hand, we may note that there was no excess of observed deaths in those children who had been exposed to procedures likely to produce the largest irradiation dose and that no cases of leukaemia occurred among children who had been exposed in the first two trimesters of pregnancy. These results weigh against the belief that a substantial excess mortality was not observed among the irradiated children merely through the operations of chance.

The results obtained in other studies have generally been somewhat different. The first and most important of these, in regard to both size and scope, was that reported by Stewart, Webb, and Hewitt (1958). They traced and arranged an interview with the mothers of (1) 677 of the 792 children under 10 years of age who had been certified as having died of leukaemia in England and Wales during the period 1953–5, and (2) 739 of the 902 children under 10 years of age who had been certified as dying in the same period from other forms of cancer. They also arranged an interview with a control group of mothers whose children were still alive and who were matched with respect to sex and place and date of birth with the children who had died. A small part of the data was eliminated because the matched pair of mothers were interviewed by different investigators or one child was adopted, and the published results relate to a total of 1,299 pairs (in 619 of which one child had died of leukaemia). The principal results relate in the history of maternal irradiation, and are shown in Table VI.

TABLE VI.—*Frequency of Previous Radiographic Examination: Mothers of 1,299 Children who had Died of Cancer Compared with Mothers of 1,299 Living Children (After Stewart et al., 1958)*

Period	*X*-ray Examination of					
	Abdomen			Other Part		
	No. of Mothers of Cancer Children	No. of Mothers of Control Children	Ratio	No. of Mothers of Cancer Children	No. of Mothers of Control Children	Ratio
Before marriage ..	44	26	1·69:1	335	275	1·22:1
Between marriage and relevant conception	109	121	0·90:1	213	184	1·16:1
During relevant pregnancy ..	178	93	1·91:1	117	100	1·17:1
Any period before birth of child ..	296	215	1·38:1	531	456	1·16:1

The most striking observation is that of a difference between the mothers of the children dying from cancer and the control mothers in respect of the frequency of abdominal *x*-ray examinations during the relevant pregnancy (178 to 93). The difference between the two

proportions (13.7% and 7.2%) is statistically highly significant, and it was from this difference that Stewart and her colleagues concluded that children exposed *in utero* to *x* rays were about twice as likely to die from cancer before the age of 10 years as other children.

The contrast depends, however, upon the controls being a representative sample of normal children, and it may be noted that about 40% of the children who were first chosen for this purpose could not be used, principally because they had moved away from the area in which they were born. It may well be that this has not influenced the findings, but the possibility cannot be entirely excluded. Secondly, the result might be influenced by a difference between the responses of mothers whose children were dead and of mothers whose children were still alive. That there is such a difference is suggested by the data in Table VI. In all categories of exposure, with the exception of abdominal *x*-ray exposures between marriage and the relevant conception, the mothers of children with cancer indicated more frequent radiation exposure than the control mothers. It is reasonable to suppose that the mothers of dead children, and perhaps particularly of children dead from cancer, may recall the events of pregnancy more completely than the mothers of children who are alive and well, so that the results may, to some extent, be biased by a relative under-reporting of radiation exposures by the control mothers. We should note, however, that there was some correlation between (1) the magnitude of the ratio between the numbers exposed to abdominal irradiation and the number of *x*-ray films reported to have been taken, and (2) that the ratio was highest for mothers exposed during the first few months of pregnancy. This period includes that of major foetal organogenesis, when the susceptibility to induced malformations is high. Maybe the susceptibility to leukaemia induction will also be high during the same period, although, so far as we know, this is unsupported by experimental evidence.

The results of other studies are summarized in Table VII. A survey of the radiation exposure histories of children whose deaths had been ascribed to acute leukaemia in the State of California during 1955 and 1956 was reported by Kaplan (1958). He studied also the exposure histories of the closest sib and of the child's habitual playmate, and the histories of the parents. His results were equivocal. He found that the mothers of the leukaemic children gave a history of irradiation more often while they were carrying the leukaemic child than while they were carrying the child's sib ; but there was less difference between the maternal radiation exposure when the leukaemic child was compared with his closest playmate.

Polhemus and Koch (1959) obtained evidence of increased frequency of post-natal radiation exposure in children developing leukaemia, but found little indication of an excessive frequency of antenatal *x* rays. They sent questionaries by post to the families of 317 children with leukaemia who had been seen at the Children's Hospital, Los Angeles, between January, 1950, and July, 1957, but obtained satisfactory data for only 251. For controls, the same number of children were chosen of a comparable social class, age, and birthplace who had attended the same hospital for other selected conditions. Of the leukaemic children 72 had been exposed *in utero*

TABLE VII.—*Frequency of Abdominal Irradiation During Pregnancy of Mothers of Cancer Children and Mothers of Control Children: Summary of Published Data**

Reference	Cancer Children		Control Children	
	Description of Group	Proportion of Mothers who Received Abdominal Irradiation During Pregnancy	Description of Group	Proportion of Mothers who Received Abdominal Irradiation During Pregnancy
Kjeldsberg (1957)	Children with leukaemia seen at Rikshospitalet, Oslo, 1946–56	5/55 (9·1%)	Healthy children	8/55 (14·5%)
Kaplan (1958)	Children dying of acute leukaemia in California, 1955–6	37/150 (24·7%) 34/125 (27·2%)	(a) Closest sib (b) Most habitual playmate	24/150 (16·0%) 27/125 (21·6%)
Polhemus and Koch (1959)	Children with leukaemia seen at the Children's Hospital, Los Angeles, 1950–7	72/251 (28·7%)	Children attending the Children's Hospital, Los Angeles, 1950–7 with other selected conditions	58/251 (23·1%)
Ford, *et al.* (1959)	Children dying of leukaemia under 10 years of age in Louisiana, 1951–5: (a) white (b) coloured	 20/70 (28·6%) 1/8 —	Children dying of causes other than cancer under 10 years of age in Louisiana, 1951–5: (a) white (b) coloured	 48/247 (19·4%) 8/59 —
Mac-Mahon (1958)	Children dying of cancer under 10 years of age in New York City, and born in a specified maternity hospital, 1947–57	8/114 (7·3%)	1% sample of children born in one of 11 specified maternity hospitals, 1947–57, residents of New York City only	173/2,520 (7·3%)

* Excluding data of Stewart *et al.* (1958), shown in Table VI, and the data of Murray, Heckel, and Hempelmann (1959), referred to in the text.

against 58 of the control children ; for exposure to pelvimetry the relevant figures were 65 and 58. In contrast, there were substantial differences in the frequency of post-natal irradiation, particularly irradiation to the thymus in infancy (reported for 11 of the leukaemic and 2 of the control children).

Ford, Paterson, and Treuting (1959) reported the results of a survey of the radiation histories of all children under the age of 10 years certified to have died from leukaemia or some other form of cancer in Louisiana between 1951 and 1955. In this study the information was obtained from the practitioners who attended the births of the children. Data were obtained for 78 children who had died from leukaemia (including 8 negro children), 74 children dying from other forms of cancer (including 13 negro children) and 306 control children who had died from other causes. The authors found that 21/78 leukaemic children (26.9%) and 21/74 children dying from some other form of cancer (28.4%) had been exposed *in utero* to *x*-rays, whereas 56/306 control children (18.3%) had been so exposed. The data for white children, which are more suitable for comparison with British data, show that exposure to radiation *in utero* was reported by 20/70 children with leukaemia (28.6%), 20/61 children with other forms of cancer (32.8%), and 48/247 control children (19.4%). The relative risk of developing cancer after exposure compared with the risk in the absence of exposure is 1.82 to 1 (that is, 40/91 : 48/199), which is close to the ratio of 2.06 to 1 obtained by Stewart and her

colleagues. It should be noted that the American investigators also found that the ratio between the cancer and control children was highest for those who were exposed during procedures involving four or more *x*-ray films (8/152 against 5/306 or 3.2:1). The similarity of these findings to those obtained by Stewart *et al.* (1958) is striking. The techniques used were, moreover, different in some important respects though they shared the characteristic that the data were obtained from persons who could have been influenced by knowledge of the subsequent fate of the child.

Kjeldsberg (1957) investigated the 68 children with leukaemia who had attended the children's clinic of Rikshospitalet in Oslo between 1946 and 1956. Data were obtained for 55 of them, and these were compared with the data for 55 living children of the same ages. The results showed a lower incidence of exposure *in utero* for the leukaemic children (9.1%) than for the control children (14.5%). The children in the control series were, however, born at a date later than the children with leukaemia, and radiographic examinations during pregnancy are likely to have changed in frequency with the passage of time.

Murray, Heckel, and Hempelmann (1959) interviewed the mothers of 65 out of the 75 residents of one county in New York State who died of leukaemia under the age of 20 years between 1940 and 1957. Three of the mothers (4.6%) said that they had received pelvic or abdominal irradiation during the relevant pregnancy which was identical with the corresponding figure for 65 residents, matched for race, sex, age, and time of death, who had died from other causes. The relevant figures for sibs of leukaemic and control children were respectively 7/93 (7.5%) and 2/82 (2.4%).

A different type of study has been reported by McMahon (1958). He examined a 1% sample of the records of all children born alive in 11 selected maternity hospitals in New York City between 1947 and 1954. Of the 2,520 selected children 160 were excluded as the parents were not permanently resident in New York City. The hospital records of the remaining children were searched for evidence of *x*-ray examination of the mother during her pregnancy, and it was found that 173 of the children (7.3%) had been exposed *in utero*. The death certificates were then reviewed of all the children who died under the age of 10 years in New York City during the period 1947–57 and whose deaths were attributed to leukaemia or some other form of cancer. These certificates include the date of birth, so that it was possible to trace the corresponding birth certificates. From these it was discovered that 114 of the children had been born in one or other of the 11 special maternity hospitals. Reference to the hospital records showed that eight of the children (7.3%) had been exposed *in utero*. The data therefore provide no evidence for a special risk associated with diagnostic *x*-ray exposure during prenatal life. The number of cancer cases, however, is small, and a slight risk might well not have been demonstrated. It is possible that the results might have been influenced by a differential migration out of New York City between children who had been exposed and children who had not. McMahon tested this by sending a questionary to a number of mothers whose radiation history was known. Replies were received equally, irrespective of whether the women had been irradiated, but it is notable that 10 out of 37 mothers who were known to have had an abdominal *x*-ray examination during a particular pregnancy stated that they had not been examined in this way. This may perhaps be regarded as confirming the suggestion that information sought direct from mothers is likely to be of variable accuracy and that it could be influenced by knowledge of the fate of the child.

It is clear, therefore, that the existing evidence of the effect of irradiation *in utero* is conflicting. This is not surprising, since the carcinogenic effect of the doses used in diagnostic radiography is certainly not great and, with the small numbers of cases recorded in some of the studies, chance factors alone could have been sufficient to prevent its recognition. During the early part of intrauterine life the risk may be relatively high, but there is little evidence relating to this period. In the present study some 750 women were irradiated in the first three months of their pregnancy and none of the children developed leukaemia during an average follow-up of over six years, which clearly suggests no major risk even at this stage of pregnancy. For the full duration of pregnancy the magnitude of any risk from irradiation in metropolitan hospitals is unlikely to be more than 50% of that normally incurred irrespective of radiographic examination. Even a small risk of this size would imply that the foetus was a great deal more susceptible to the induction of leukaemia than the adult. Estimates of the effect of radiation in the adult have suggested that a dose of 1 rad to the whole red marrow might produce about one case of leukaemia per million persons per annum for perhaps 10 years after the exposure. Since the amount of radiation received by the foetus from irradiation of the mother's abdomen is estimated to be of the order of 1 rad and the normal annual incidence of leukaemia in England and Wales under the age of 10 years is approximately 37 per million, it would follow, with a 50% increase, that the leukaemogenic effect of irradiation on the foetus would be about 20 times as great as on the adult irrespective of the relative sizes of the target tissue. If the difference in susceptibility was much less, the effect would in all probability escape recognition. In the light, however, of all the data it would seem that an increase of leukaemia among children due to radiographic examination of their mother's abdomen during the relevant pregnancy has not been established.

Summary

Evidence of the leukaemogenic effect on the foetus of exposure to ionizing radiations *in utero* has been sought by comparing the leukaemia mortality in a group of children whose mothers were known to have been irradiated during the relevant pregnancy with that expected from the corresponding sex-and-age specific national mortality rates. Pregnant women who received diagnostic irradiation directed towards their abdomen or pelvis between 1945 and 1956 were identified in the records of the radiological departments of eight hospitals in London and Edinburgh. Information about the date of birth and sex of the child was obtained from the corresponding maternity records. If the child left hospital alive, his full name and the first names of his father were obtained from the local register or, in a few instances, from the Central Register of Births. The children who had died of leukaemia were discovered

by comparing the children's names with the list of names of all the children who had died of leukaemia in Britain between 1945 and 1958.

Altogether information was obtained about 39,166 liveborn children whose mothers were known to have been subjected to abdominal or pelvic irradiation during their pregnancy. Among their children, nine were discovered to have died of leukaemia before the end of 1958. The expected number was estimated to be 10.5. There was no evidence of any disproportionate occurrence of leukaemia among the children who had been most heavily irradiated nor among the children who had been irradiated early in intrauterine life.

Published data on the leukaemogenic effect of irradiation *in utero* are conflicting. It is concluded that an increase of leukaemia among children due to radiographic examination of their mother's abdomen during the relevant pregnancy is not established.

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During the year under review the total sum committed to research by the Mental Health Research Fund was £31,477. By March 31 this year the Fund had awarded grants to research workers of £99,844 from money contributed directly to it, besides serving as an agency for funds amounting to £33,500: a total expenditure of £133,344. One of the largest grants (£3,320) was made for a study of family patterns of psychological illness as seen in general practice and the possible treatment of such illness by a combination of social worker and general practitioner; £2,100 went to the biochemistry department of Oxford University for fundamental research into the chemical structure of certain constituents of the urine in normals and schizophrenics, and another £2,510 was given for the study of chemical changes occurring in association with mood swings in manic-depressive patients. A grant of £3,000 was made towards elucidating the response of the endocrine system to stress, and £1,632 towards clarifying the nature of the intellectual changes occurring in senile dementia. (*Annual Report, 1959–60*, Mental Health Research Fund.)

LEUKAEMIA FOLLOWING RADIOIODINE TREATMENT OF THYROTOXICOSIS

BY

E. ERIC POCHIN, M.D., F.R.C.P.*

Director of the Medical Research Council Department of Clinical Research, University College Hospital Medical School, London

At least 60,000 patients have been treated for thyrotoxicosis with radioiodine during the last 20 years, and it is to be expected that leukaemia will have developed fortuitously in some of these patients, particularly since this treatment is most commonly given at ages at which the natural leukaemia incidence is high.

Reports have already been published of eight cases of leukaemia in patients previously treated with radioiodine for thyrotoxicosis (Pochin *et al.*, 1956; Abbatt *et al.*, 1956; Childs, 1956; Chapman, 1956; Werner *et al.*, 1957; Blomfield *et al.*, 1959; Vetter and Höfer, 1959; Kennedy and Fish, 1959), and 10 further unpublished cases are known to have occurred. It is obviously most important (1) to assess the number of cases that would be expected to have occurred purely on a chance basis, whether radioiodine treatment had been given or not; and (2) to establish the total number of cases that have in fact occurred.

In the present report an attempt is made to deal with the first of these problems as regards the United Kingdom, by determining the numbers of thyrotoxic patients that have been treated with radioiodine in this country, with estimates of their sex and age distribution and so of the leukaemia incidence to be expected since treatment on a purely chance basis. Preliminary estimates are given for certain other countries also.

The second problem is the more difficult, since the "follow-up" of these patients after treatment is unlikely to be complete and since a previous thyrotoxicosis, successfully treated with radioiodine, may presumably not always be recorded on the death certificate of a patient dying of leukaemia. It is hoped, however, that the evaluation and discussion of the first problem may in itself help to elicit information about further cases of leukaemia which may have occurred; and a study of the characteristics of such cases might give some evidence whether all could have arisen by chance or whether some may have been induced by the radioiodine treatment.

Survey in the United Kingdom

Letters were written to all physicians or hospitals in the United Kingdom that were believed to be using radioiodine in the treatment of thyrotoxicosis, a list having been prepared of all those authorized by the Medical Research Council (1948) to receive radioiodine for this purpose. This list was checked against one including all addresses to which any consignment of radioiodine greater than 10 mc. had been issued by the Radiochemical Centre, Amersham, during the previous year. The letters asked for information of any case of leukaemia known to have occurred since such treatment, the total numbers of patients treated, the numbers treated in each particular year, and the sex and age distribution of patients at the time of treatment.

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