us to use their results. These are shown in Table XIII, together with those for the 259 non-neural, non-epithelial tumours included in the Children's Tumour Register and for the adult blood donors in Manchester.

TABLE XIII

	O	A	B	AB
Children (burns units)	49·5%	39%	7·8%	3·7%
Adult blood donors (Manchester)	48%	41%	8%	3%
Non-neural, non-epithelial tumours in Register	51·8%	38·9%	7·8%	1·3%

Distribution of Rh Groups

The only tumours in which the ratio rhesus positive: rhesus negative appears abnormal are the gliomas.

	Rh Positive	Rh Negative
Controls (Manchester)	8,445 ..	1,929
Gliomas	64 ..	7

P=0·07

The interpretation of this distribution of Rh groups among the children with gliomas is much more difficult than that of the ABO groups, not only because of the various subdivisions of the Rh factor, but also because their geographical variations have not been determined (A. C. Kopeć, 1959, personal communication).

Thus the blood-group distributions among children in the Register show the following pattern: (*a*) There is a very significant excess of group A over group O in children with gliomas and a less significant excess of group A over group O in children with epithelial tumours. Children with gliomas also show an excess of Rh positive which may be significant. (*b*) Possibly children with tumours of the sympathetic nervous system and retinoblastomas may have an abnormal O:A ratio. (*c*) Children with other tumours seem to have a normal ABO and Rh distribution.

Mayr, Diamond, Levine, and Mayr (1956) did not find any abnormal blood-group distributions in brain tumours except in pituitary adenomas. Their series was collected from various neurosurgical centres in Boston and New York and was not broken down according to age. The nature of the hospitals and the types of glioma suggest, however, that the number of children included was so small that any variation from normal would not be apparent. As a result of our finding an abnormal O:A ratio among children with gliomas in the Register, Yates and Pearce (1960) examined the blood-groups in patients of all ages with astrocytomas in Manchester, diagnosed between 1933 and 1958, and found an abnormal O:A ratio in those under 20 years old who were treated after 1945. However, their cases included those in the Register, so they could not be described as forming a completely independent series.

Summary and Conclusions

An analysis of cases included in the Manchester Children's Tumour Register has been made with two objects: (1) to give a picture of the problems involved in the treatment of children with tumours; and (2) to investigate certain aetiological and epidemiological problems.

Over one-third of the tumours were reticulo-endothelial, another third were derived from some part of the nervous system, and an eighth were connective tissues in origin. The high mortality rate (approximately 70%) is mainly due to the fact that most tumours in children by the time they can be diagnosed are already too far advanced to be cured by present therapeutic methods.

One family with retinoblastoma was included in the Register, but, apart from this, the survey did not demonstrate that tumours in children were familial. There was no evidence that social class and geographical location were significant aetiological factors. However, there was an abnormal blood-group distribution among children suffering from gliomas and possibly other tumours of neurectodermal origin.

This work could not have been done without the ready co-operation of the clinicians and pathologists of the Manchester Region who have allowed their cases to be included in the Register. Our thanks are also due to the panel of pathologists who have given their services to the project, and to Mrs. N. Rowe and Miss V. Maybury-Clare for secretarial and technical assistance. Dr. A. C. Kopeć, of the Nuffield Blood Group Centre, kindly supplied us with information about the distribution of blood groups in the Manchester Region.

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AETIOLOGY OF CHILDHOOD MALIGNANCIES

CONGENITALLY DETERMINED LEUKAEMIAS

BY

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The survey data which first suggested that prenatal *x*-ray exposure increases the risk of childhood malignancies showed that leukaemia is exceptionally common among mongols (Stewart, Webb, and Hewitt, 1958). They also indicated that " for some cases of leukaemia the decisive event must date back at least to the onset of the mongolism."

One objection to the idea that cancers and leukaemias are due to the inheritance of a cancer-producing gene is that, in such circumstances, there might be no chance of the foetus surviving. This objection would be removed if the gene produced, not malignant cells, but cells which are apt to become malignant if exposed to an unfavourable environment. This sequence of events is envisaged in the theory of cocarcinogenesis, which assumes that there are two stages in the development of cancers—" initiation " and " promotion " (Rous and Kidd, 1941; Salaman, 1958).

The Rous theory of cocarcinogenesis does not explicitly state that malignant diseases are due to gene mutations, but it does not exclude this possibility, nor the possibility that " initiators " cause mutations which convert normal cells and their offspring into pre-malignant cells. Later stresses or changes in the environment of these cells might then act as

"promoters" and thus provide the final links in the chain of cancer-producing events. In this way a "premalignant mutation" in a germinal cell might remain silent until the affected cell was successfully fertilized. Then one of four things should happen: (1) a miscarriage; (2) the development of cancer *in utero* or any time after birth; (3) the development of a premalignant disease—for example, intestinal polyposis; and (4) a normal phenotype associated with an abnormal genotype. According to this theory there are three phases in the development of cancers: (1) a *premalignant phase,* which may be absent or of infinitely long duration; (2) a *maturation phase* or incubation period; and (3) a *clinical phase.*

These possibilities, which are incorporated in the working hypothesis stated below, have already been envisaged for retinoblastomas. There is no doubt that an inherited form of this disease exists, though the pedigrees of index cases have some puzzling features (Hemmes, 1957). These might be explained if the suggestion of Weller (1941) is correct—namely, that familial retinoblastomas are due not to the inheritance of cancer but to the inheritance of a "lesion intermediate between a developmental disturbance and a true neoplasm."

Working Hypothesis

1. Malignant diseases are initiated by *x* rays and other mutagens before conception (prezygotic), during pregnancy (prenatal), or after birth (post-natal). The last two groups correspond to post-zygotic cancers and leukaemias.

2. In childhood the chief promoter of malignant diseases is the cell stress of embryogenesis. Consequently most childhood cancers and leukaemias are prezygotic.

3. At all ages the leucocyte stress provoked by infections is a promoter of leukaemias. By increasing susceptibility to infections mongolism acts as an indirect promoter of leukaemias. Because mongolism is an inherited condition (Lejeune, Gautier, and Turpin, 1959) it has more opportunity to affect prezygotic than post-zygotic leukaemias.

4. Prezygotic cancers and leukaemias are biased in favour of primitive cell types and may have a familial incidence. Post-zygotic cancers and leukaemias are biased in favour of mature cell types and have no familial incidence.

5. Individuals who develop prezygotic leukaemias have no normal leucocytes and therefore have an exceptionally low resistance to infections. The pedigrees of index cases have not been fully elucidated because the equivalent disease in relatives may take several forms—for example, leucopenia, anaemia, low resistance to infections, and leukaemia.

6. In childhood the maximum incidence of prezygotic leukaemias is earlier than the maximum incidence of prenatal leukaemias.

7. The recent increase in childhood leukaemias is a consequence of the falling death-rate for pneumonia and related diseases, and is due to prezygotic leukaemias.

Recent Changes in Incidence of Childhood Leukaemias

The recent increase in deaths from leukaemia has left children under 1 year almost untouched, and affected children between 1 and 5 years more than any other age-group below 70 years (see Fig. 1; also Hewitt, 1955). It has also brought the age distribution of childhood deaths from leukaemias more into line with the age distribution of childhood deaths from cancer of the eye (mainly retinoblastomas) and kidney (mainly nephroblastomas).

If the early peak of leukaemia mortality is due to prezygotic leukaemias it should consist mainly of stem-cell leukaemias which have taken between two and five years to produce symptoms. The maturation phase for leukaemias is not known for certain, but Polhemus and Koch (1959) have reported 11 cases of leukaemia which followed deep *x*-ray therapy administered before the age

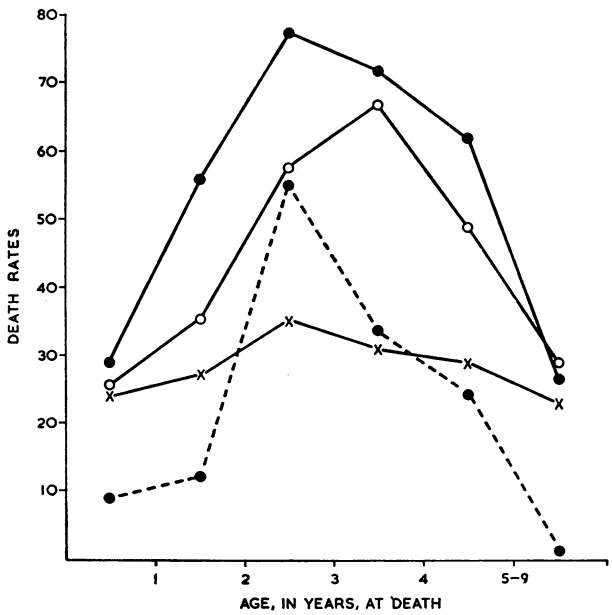

FIG. 1.—Mortality rates. Leukaemias, retinoblastomas, and renal tumours. O——O. Leukaemias (1950–7), rate per million, E. and W. ×——×, Leukaemias (1930–9), rate per million, E. and W. ●---●, Eye tumours (1950–7), rate per 10 million, U.S.A. ●——●, Renal tumours (1950–7), rate per million, E. and W.

of 6 months. In these cases the interval between exposure and the onset of symptoms ranged from 4½ to 9½ years, and averaged 7 years. From data provided by Court Brown and Doll (1957) the interval between exposure to deep *x* rays and death was calculated for men under and over 40 years of age. Excluding three cases where death occurred within a year of exposure, there were 20 men in the younger group with an average interval of 7 years (range 2–13 years), and 25 in the older group with an average interval of 5 years (range 2–11 years). Finally, the maximum incidence of leukaemia among survivors of the atomic explosions in Japan occurred 6 to 7 years after these events (J. Neel, 1960, personal communication); and Cobb, Miller, and Wald (1959) have calculated that 90% of radiation-induced leukaemias appear within 10 years of exposure.

These findings for irradiation leukaemias allow us to assume that if prezygotic leukaemias exist they will not as a rule become manifest until some time after birth. If more cases start maturing during embryogenesis than during any equally long period, the peak incidence of prezygotic leukaemias might be expected to occur some time between the second and fifth years of post-natal life—that is, during the years which show a peak of leukaemia mortality.

Survey Data

In order to test some of the epidemiological implications of the working hypothesis, the records of 1,638 children who recently died from either leukaemia (780) or cancer (858) and those of 1,638 live children were examined. The two groups (cases and controls) were matched for age, sex, and locality, and each control child was picked at random from an appropriate register of births. The dead children included 86% of all children who died of leukaemia or cancer before the age of 10 years in England, Scotland, and Wales during the three years 1953 to 1955, and all the children mentioned in the earlier report (Stewart *et al.*, 1958) are included in the new sample.

Diagnostic Criteria

The results of comparing death certificates with pathologists' reports are shown in Table 1. They show that stem-cell leukaemias are commoner and myeloid leukaemias rarer than one would expect from official statistics of mortality (Registrar-General, 1940–59). In several cases certified as myeloid leukaemias the original report stated that the marrow was packed with undifferentiated stem cells and that there were no granulocytes, or very few, in the circulating blood.

TABLE I.—*Survey Cases of Leukaemia. Comparison of Death Certificates and Pathological Reports*

Final Diagnosis	Death Certificates Only	Pathological Reports of Cases with the following Entries on Death Certificates:					All Cases with Pathological Reports	Total
		Lymphatic	Monocytic	Stem-Cell	Myeloid	Unspecified		
Lymphatic	156	154 (6)	—	—	22 (2)	73 (1)	249 (9)	405 (9)
Monocytic	7	5	7	—	2	7	21	28
Stem-cell	4	29 (4)	3 (1)	3	25 (2)	61 (3)	121 (10)	125 (10)
Myeloid ..	54	—	—	—	25	6	31	85
Unspecified	131	—	—	—	—	6	6	137
Total ..	352	188 (10)	10 (1)	3	74 (4)	153 (4)	428 (19)	780 (19)

Figures in parentheses indicate mongols.

TABLE II.—*Age and Sex Distribution of Survey Cases*

Sex	Age at Onset in Years	Diagnostic Groups (Mongols in Parentheses)						
		Leukaemias					Cancers	Total
		Lymphatic	Monocytic	Stem-Cell	Myeloid	Unspecified		
Boys ..	0	17 (1)	1	6	5	6	72 (1)	107
	1	32 (1)	2	9 (2)	5	7	73	128
	2	43	2	14 (1)	6	12	74	151
	3	36	3	6	2	6	65	118
	4	21	2	13 (2)	6	11	58	111
	5	27 (2)	2	7 (1)	5	5	53	99
	6	14 (2)	—	3	4	7	45	73
	7	22	2	4	3	7	25	63
	8	8	3	1	5	7	24	48
	9	10	1	1	2	4	10	28
	Total	230 (6)	18	64 (6)	43	72	499 (1)	926
Girls ..	0	15	2	11	4	7	67	106
	1	22 (1)	1	6 (1)	3	8	56	96
	2	29 (1)	—	14 (2)	2	14	46	105
	3	30	3	6	5	10	44	98
	4	26	2	6	6	8	42	90
	5	15 (1)	—	7	1	6	31	60
	6	10	1	5	10	4	33	63
	7	14	—	3	7	2	15	41
	8	10	—	2 (1)	3	5	21	41
	9	4	1	1	1	1	4	12
	Total	175 (3)	10	61 (4)	42	65	359	712
Average age (Years)		4·1	4·5	3·6	4·8	4·3	3·7	
Duration of Symptoms (Months)		5·2	5·4	5·3	5·4	5·2	9·3	

In the following account, pathologists' reports, available in over half the cases of leukaemia, will take precedence over death certificates. The survey group as a whole included the following subgroups:

Leukaemias (780)

Lymphatic	405	Non-granular	558
Stem-cell	125		
Monocytic	28		
Myeloid	85	Other and unspecified	222
Unspecified	137		

Cancers (858)

Cerebral tumours (mainly medulloblastomas) ..	254
Neuroblastomas	149
Renal cancers (mainly nephroblastomas)	149
Reticuloses (mainly lymphosarcomas)*	140
Cancers of other sites (mainly sarcomas)	166

* 10 cases classified as leukaemias were originally diagnosed as lymphosarcomas.

The age and sex distributions of the survey cases are shown in Table II, also the intervals between the onset of symptoms and death. The children with cancer were younger than those with leukaemia and were ill for longer periods. The duration of symptoms was the same for the four categories of leukaemia (five months), but the stem-cell leukaemias were approximately a year younger (3.6 years) than the myeloid leukaemias (4.8 years). In the large group of non-granular leukaemias there was a heavy concentration of cases between 1 and 4 years, particularly among boys (see Fig. 2), and there is little doubt that these cases are incorporated in the early peak of leukaemia mortality (see Fig. 1).

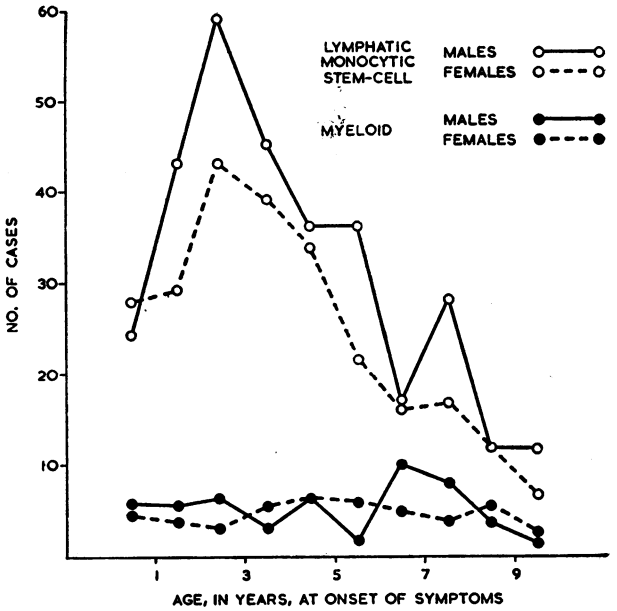

FIG. 2.—Age and sex distribution of leukaemias by cell type.

Pyogenic Infections

Most of the illnesses mentioned in the survey records were infectious diseases (measles, chicken-pox, whooping-cough, mumps, and rubella). Apart from rubella, none of these infections was reported more often by cases than by controls, and the average intervals between these illnesses and the end of the preclinical period was also the same for cases and controls.*

*The so-called preclinical periods were, by definition, the same for cases and controls, and corresponded to the intervals between birth and the onset of the fatal disease. Premalignant illnesses with no recognizable gap between recovery and the onset of the fatal disease are omitted from the following analyses. They included 67 infectious diseases (41 leukaemias, 26 cancers) and 22 respiratory infections (16 leukaemias, 6 cancers).

There were, however, several less common and more serious illnesses which were, collectively and separately, recorded more often by the children who subsequently died of leukaemia than by the other children, particularly towards the end of the premalignant period. These illnesses, which were regularly treated with sulphonamides and antibiotics, included pneumonia and acute bronchitis (264 cases), other serious pyogenic infections (44), burns (46), and fractures (96). These illnesses affected 396 children, who represented 16.9% of the leukaemia group, 10.7% of the cancer group, and 10.5% of controls. In the leukaemia series the case/control differences (see Table III) were greater for stem-cell leukaemias than for other leukaemias, greater for boys (89 leukaemias, 39 controls) than for girls (43/39), and mainly due to children who developed leukaemias before the age of 4 years (56/22). The rates for the leukaemia subgroups are given in Table IV.

TABLE III.—*Serious Infections and Injuries During the Premalignant Period: Leukaemia Cases and Matched Controls*

Diagnostic Groups by Age at Onset	Boys		Girls		Both Sexes	
	Cases	Controls	Cases	Controls	Cases	Controls
Lymphatic and Monocytic:						
Under 4 years	19	8	8	5	27	13
4–10 ,,	32	14	10	14	42	28
Total	51	22	18	19	69	41
Stem-Cell:						
Under 4 years	11	1	8	1	19	2
4–10 ,,	7	5	5	4	12	9
Total	18	6	13	5	31	11
Myeloid:						
Under 4 years	—	—	3	1	3	1
4–10 ,,	8	4	1	7	9	11
Total	8	4	4	8	12	12
Unspecified:						
Under 4 years	3	2	4	4	7	6
4–10 ,,	9	5	4	3	13	8
Total	12	7	8	7	20	14
All Children:						
Under 4 years	33	11	23	11	56	22
4–10 ,,	56	28	20	28	76	56
Total	89	39	43	39	132	78

TABLE IV

	All Serious Illnesses %	Pyogenic Infections %
Stem-cell leukaemias	24·2	20·8
Lymphatic and monocytic leukaemias	16·2	10·9
Myeloid leukaemias	14·1	11·8
Unspecified leukaemias	14·6	7·3
Matched controls	10·0	6·7

For 19 mongols with leukaemia and 96 children who were *x*-rayed *in utero* before developing leukaemia (see later) the corresponding rates for pyogenic infections were 58% and 10% respectively.

For the myeloid and unspecified leukaemias the average age at the onset of the fatal disease was the same for children with pyogenic infections as for other children; but children who had pyogenic infections, and later developed stem-cell or lymphatic leukaemias, were, on average, six months younger than all children with stem-cell and lymphatic leukaemias. This last finding is probably due to the fact that the serious illnesses hastened the onset of symptoms. This would also explain why the intervals between these illnesses and the onset of the fatal disease were shorter for children with leukaemia than for children with cancer. These so-called "preclinical intervals" were the same for children with cancer (average 34 months) and controls (35 months). For leukaemias under 4 years of age the corresponding interval was 16 months (matched controls 23 months) and for leukaemias over 4 years of age 39 months (matched controls 44 months).

The high incidence of fractures among the children with leukaemia is probably due to the fact that during the maturation phase of this disease it is quite common for a minor injury to cause a fracture.

Mongolism and Leukaemia

Minor congenital defects (mainly naevi) were reported with equal frequency by cases and controls. The commonest major defect was mongolism (19 leukaemias, 1 cancer); the next commonest defects were skeletal deformities (4 leukaemias, 4 cancers, 2 controls).

Only 4 of the 19 mongols with leukaemia could have been identified by means of death certificates, but from this source (England and Wales, 1945–59) 31 further cases were obtained (Table V).

TABLE V.—*Mongols with Leukaemia*

Death Certificates (England and Wales)	Boys	Girls
1945–7	1	1
1948–50	2	3
1951–3	1 (4)	6 (1)
1954–6	3 (6)	2 (4)
1957–9	8	8
Total	15 (10)	20 (5)

Numbers in parentheses are "extra" survey cases.

The age at death of these 50 mongols is shown in Fig. 3 and compared with the age at death of 37 children with retinoblastoma, obtained from the same source, and 125 with stem-cell leukaemia obtained from the survey sample. In all three groups there were more deaths between the ages of 2 and 3 years than in other years, and in all three groups deaths in the first year were rare.

The 50 mongols with leukaemia included 37 cases in which both the diagnosis given on the death certificate and the diagnosis stated by a pathologist were available.

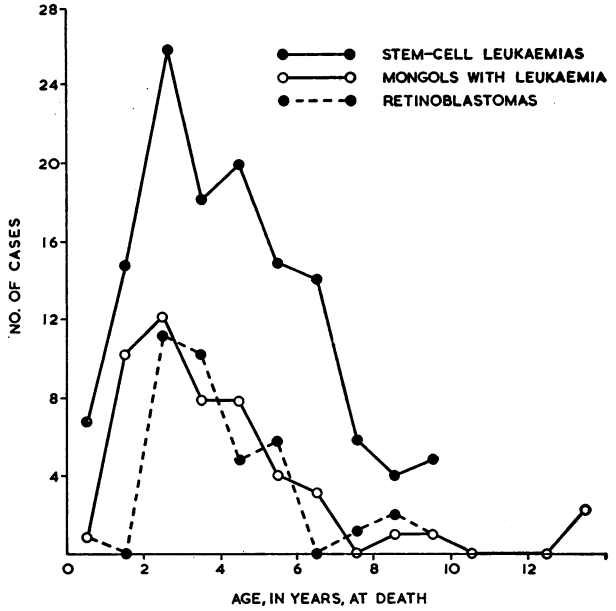

FIG. 3.—Age at death of 50 mongols with leukaemia, 37 patients with retinoblastoma, and 125 with stem-cell leukaemia.

According to the latter, there were 21 stem-cell and 16 acute lymphoblastic leukaemias. The corresponding death certificates recorded lymphatic (15), myeloid (7), monocytic (2), stem-cell (1), unspecified (12) leukaemia. In six cases the blood-group was stated on the pathologist's report (group A in five cases, group O in one case), and in two there were records of serum proteins:

	Total Protein	Albumin	Globulin
Case 1	4·2	2·0	2·2
,, 2	5·3	2·5	2·8

The much larger number of deaths from leukaemia among mongols between 1957 and 1959 than in previous three-year periods could be due to changing habits on the part of certifying doctors. But the literature suggests that there has been a genuine increase in these deaths in recent years. Before 1956 only four such deaths were recorded; by 1957 the number had increased to 16, and by the following year to 34 (Stewart *et al.*, 1958). The exceptionally high incidence of pyogenic infections among the survey mongols (58%) suggests that before the discovery of antibiotics there was little chance of a mongol who also had a congenitally deformed reticulo-endothelial system surviving long enough to develop leukaemia. A similar explanation would account for the inverse relationship between deaths from pneumonia and from leukaemia in childhood during the early years of the "antibiotic era" (see Fig. 4).

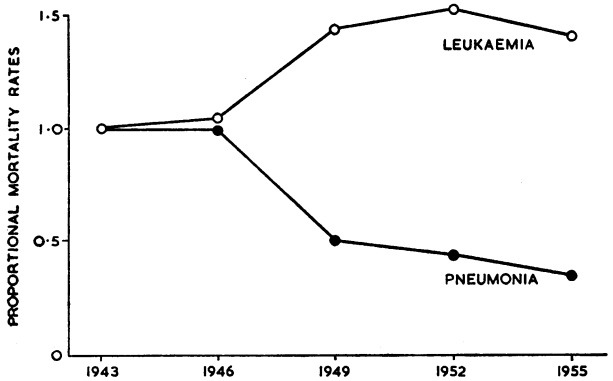

FIG. 4.—Proportional mortality rates; pneumonia and leukaemia (0–10 years).

From reading the pathologists' reports for the mongols who died of leukaemia it is clear that there is no easy way of deciding whether a cell is a malignant stem cell, a lymphoblast, or a monoblast. This raises the possibility that most if not all cases diagnosed as lymphatic or monocytic leukaemia before the age of 4 years are in fact stem-cell leukaemias. Recent work has shown that there are no lymph nodes in the foetal bone-marrow, though it contains more than four times as many cells resembling lymphocytes as the adult marrow (Yoffey, Thomas, and Russell, 1960). If this conclusion is correct, it means that the association between mongolism and leukaemia is virtually confined to one cell type, which is also the cell type one might expect to be due to premalignant germinal mutations.

Leukaemia and Cancer Fraternities

The survey records included data about relatives. They recorded the ages of children's parents, their illnesses and *x*-ray experiences; also miscarriages, stillbirths, and later deaths affecting the sibships of the survey children, together with a limited number of facts about more remote relatives. These data will be discussed in a later report. For the present, only sibs with cancer, leukaemia, and aplastic anaemia are considered. In addition to the cases discovered during the survey there were three which were discovered by checking the survey records (cases and controls) with death certificates (England and Wales, 1945–59). The "extra" cases all occurred after the survey was completed and were confined to the case series.

In the control group there were three sibships with a single case of malignant disease (one cancer, two leukaemias). In the case group there were, apart from the survey children, 11 sibships with a single case (including one aplastic anaemia) and three with two cases. In nine of these families the sib or sibs certainly had the same malignant disease as the survey child, in three they had different diseases, and in two there was a doubtful difference (leukaemia and lymphosarcoma, aplastic anaemia and reticulosis).

The relevant sibships are shown in Table VI. The "identical" pairs of trios included four sets of leukaemias (three sets specified as lymphatic or stem-cell), two sets of reticuloses, one of cerebellar medulloblastomas, one of neurofibromatoses, and one of retinoblastomas. In three families one or other parent probably had the same condition as the survey child; in four there were miscarriages or stillbirths; and in one family there were two sibs and a first cousin with leukaemia. The survey cases in these families included three children who also had a non-malignant congenital disease (mongolism, talipes, and ichthyosis).

Other instances of identical cancers in parents and more remote relatives will be reported later. The present findings confirm the existence of leukaemia and lymphadenoma "fraternities" and add to those already recorded in the literature (Jelke, 1940; Hornbaker, 1942; Videbaek, 1947; Riel, 1948; Anderson, 1951; Debré, Bernard, and Buhot, 1951; Reilly *et al.*, 1952; Guasch, 1954; Anderson and Hermann, 1955; Razis, Diamond, and Craver, 1959).

Prenatal X-ray Exposure

If both the chance of being *x*-rayed *in utero* and the interval between birth and the follow-up had been the same for all the survey children, the age distribution of the cases undergoing prenatal *x*-ray exposure would have indicated the age with the maximum number of "irradiation cases." But the children were born during a 13-year period (1943–55) when *x*-ray habits were changing, and died during a three-year period (1953–5). So there was less chance of observing the long-term effects of prenatal *x*-ray exposure in the younger children (who were more often *x*-rayed) than in the older children.

Several things happened during the years when the survey children were born, including the establishment of the National Health Service in 1948, a steady increase in the number of hospitals and clinics with *x*-ray departments, and an increasing use of *x*-ray by obstetricians. The effect of these changes is difficult to judge, but it has since been ascertained that in four maternity hospitals, serving large cities, the percentage of children who were *x*-rayed *in utero* more than doubled during the first seven years of the National Health Service.

In order, therefore, to discover the age distribution of the irradiated cases it was necessary to compare cases with controls. It has been suggested that mothers of live children are more likely to forget remote events

than mothers of dead children, but there were several pointers which suggested that this type of memory bias has not invalidated the survey records. For instance, the case/control differences for serious illnesses were greater for younger children than older children (see Table III). This was also true of *x*-ray films taken after birth (Stewart *et al.*, 1958) and of treatments with sulphonamides and antibiotics (unpublished data). Finally, a doubling of the percentage of control children exposed to prenatal *x*-ray between 1948 and 1955 would be expected if the mothers of controls were reporting accurately. In the four hospitals mentioned above, the percentage of *x*-rayed children increased from 16 in 1948 to 36 in 1955. In the control groups (see Table VII) the corresponding figures were 4 and 10%. It follows that it is probably safe to rely on case/control contrasts for judging the age distribution of cases of leukaemia and cancer due to prenatal *x*-ray exposure.

TABLE VI.—*Leukaemia and Cancer Sibships*

	Position in Sibship								Other Features
	1st	2nd	3rd	4th	5th	6th	7th	8th	
1	F. Dead. Lymphatic leukaemia. 1 year Pneumonia	M. Dead. Pyloric stenosis. 4 days	M. Dead. Pneumonia. 10 months	F. *Survey*. Lymphatic leukaemia. 5 years					One stillbirth
2	M. Alive. 22 years. Healthy	M. Alive. 19 years. "Not very fit"	M. Alive. 15 years. Healthy	F. Dead. Lymphatic leukaemia. 13 years	M. *Survey*. Mongol. Stem-cell leukaemia. 2 years				
3	M. Alive. 8 years. Healthy	F. Dead. Acute leukaemia. 8 months	F. *Survey*. Lymphatic leukaemia. 4 months. Bilateral talipes						Paternal first cousin with leukaemia
4	M. *Survey*. Lymphatic leukaemia. 7 years. Fracture	M. Dead. Lymphatic leukaemia. 4 years							Mother treated for anaemia during both pregnancies. Maternal grandparents first cousins
5	F. Alive. 8 years. Healthy	M. Alive. 7 years. Healthy	M. *Survey*. Cerebellar medullo-blastoma. 2 years	M. *Dead*. Cerebellar medullo-blastoma. 3 years	M. Alive. 4 years. Healthy				
6	M. Alive. 10 years. Neurofibro-matosis	F. *Survey*. 6 years. Neurofibro-matosis	M. Alive. 7 years. Healthy	M. Alive. 4 years. Neurofibro-matosis					Father also has neuro-fibromatosis (alive)
7	M. Dead. * Acute reticulosis. 3 months	F. Dead. * Acute reticulosis. 6 months	F. Alive. 5 years. "Blood dyscrasia"	M. *Survey*. 5 months. * Acute reticulosis					Both parents' blood investigated: mother normal; father "same as children"
8	M. Dead. Retino-blastoma. 5 years	F. *Survey*. Retino-blastoma. 5 years	M. Alive. 1 year. Healthy						Mother had left eye removed at 1 year
9	M. Alive. 21 years. Osteo-myelitis	M. Dead. Lympho-sarcoma. 2 years	M. Dead. Lympho-sarcoma. 2 years	M. *Survey*. Lymphatic leukaemia + lympho-sarcoma. 5 years					Two miscarriages. Paternal grandfather died of pneumonia at 27
10	M. Dead. Cerebral tumour. 4 years	F. *Survey*. Lympho-sarcoma + stem-cell leukaemia. 5 years	M. Alive. 6 years. Healthy	M. Alive. 6 months. Healthy					Mother had repeated ear infections
11	F. Dead. Lympho-sarcoma. 2 years	F. *Survey*. Stem-cell leukaemia. 4 years	F. Alive. 8 years. Healthy	M. Alive. 7 years. Healthy					Mother's sibship included several miscarriages and stillbirths
12	M. Alive. 15 years. Healthy	M. Dead. Lymphatic leukaemia. 5 years	M. Alive. 5 years. Healthy.	M. *Survey*. Neuro-blastoma. 18 months. Chronic otitis media					Paternal grandfather died of pneumonia at 29
13	M. Alive. 27 years. Healthy	F. Alive. 20 years. Healthy	F. Dead. Cerebral tumour. 13 years	F. Alive. 15 years. Healthy	F. Alive. 11 years. Healthy	F. Dead. Atelectasis. 2 days	F. Alive 8 years. Meningitis at 3 years	F. *Survey*. 3 years. Wilms's tumour	
14	M. Dead. Aplastic anaemia. 1 year	F. Alive. 11 years. Ichthyosis	F. *Survey*. Lipomel-anomatous reticulosis.† 6 years. Ichthyosis						One miscarriage. Father has psoriasis

* Haemophagocytic reticuloses of unusual type.
† High fever. Blood count: W.B.C., 3,000; 72% lymphocytes. Sternal puncture: marked granulocytic reaction and maturation delay at the metamyelocyte stage.

Division of the cases and controls into two-year age-groups (see Table VII) revealed a continuous rise in the case/control ratio for prenatal *x*-ray exposure from 1.38 for children under 2 years of age to 3.22 for children aged 6 and 7 years, followed by a slight fall to 3.00 for children aged 8 and 9 years. Division by year of birth produced comparable findings, but the difference between children born during 1946–8, who were between 4 and 9 years of age when they died (ratio 3.06), and children who were born earlier and were 7 to 10 years of age (ratio 1.29), was greater than the difference between the two oldest age-groups.

Ford, Paterson, and Treuting (1959) have since carried out a survey in which children who died of malignant diseases were compared with children who died from other causes. On this occasion the *x*-ray data were obtained from medical records and no reliance was placed on the mothers' memories. Again the case/control ratio for prenatal *x*-ray exposure was found to be greater for children between 5 and 10 years of age than for younger children.

TABLE VII.—*Prenatal X-ray Examinations. Age and Cohort Analyses*

	Cases				Controls		Case/Control Ratios
	Leukaemias		Cancers				
	No.	%	No.	%	No.	%	
Age at onset of symptoms							
<2 years	19	11·2	47	17·5	48	11·0	1·38
2–3 ,,	32	13·2	31	13·5	40	8·5	1·58
4–5 ,,	23	13·1	18	9·8	16	4·7	2·56
6–7 ,,	15	12·3	14	11·8	9	3·8	3·22
8–9 ,,	7	10·0	5	8·5	4	3·1	3·00
Year of Birth / Age at Death (Years)							
1943–5 7–10	6	9·5	3	4·3	7	5·3	1·29
1946–8 4– 9	23	10·8	26	11·5	16	3·6	3·06
1949–51 1– 6	41	13·6	41	14·2	46	7·8	1·78
1952–5 0– 3	26	12·8	45	16·5	48	10·1	1·43
Dating of *x*-ray:							
First half of pregnancy	7	0·9	18	2·1	2	0·1	12·50
Second ,, ,,	89	11·4	97	11·3	115	7·0	1·62
Totals ..	96	12·3	115	13·4	117	7·1	1·80
Numbers at risk ..	780		858		1,638		

Both surveys suggest that there are some cases of cancers and leukaemias due to prenatal *x*-ray exposure in every age-group between 0 and 10 years. But, in proportion to the number of children who are *x*-rayed, these cases are commoner between 5 and 10 years of age than between birth and 5 years of age. If this is so, it is safe to assume that prenatal *x*-ray exposures have contributed little or nothing to the early peak of leukaemia mortality, and are only numerically important after 5 years of age. The survey findings also suggest that the maturation period for leukaemias due to prenatal *x*-ray exposure is approximately the same as the maturation period for leukaemias due to neonatal *x*-ray exposure (Polhemus and Koch, 1959).

The precise risk attached to prenatal *x*-ray exposure is difficult to estimate, but it clearly depends on the date as well as the intensity of the exposure. Table VII shows the 27 children who were *x*-rayed in the first half of pregnancy. These included 2 controls, 7 with leukaemia, and 18 with cancer (including two retinoblastomas and three ovarian tumours). The numbers are small, but they suggest that children who are *x*-rayed early in pregnancy are more likely to develop cancer than leukaemia, and that the risk of both diseases is far greater than the risk attached to *x*-ray films taken shortly before birth.

In the leukaemia group there were four matched sets (cases and controls) which failed to show the usual excess of pre-natal *x*-ray exposures among cases (Table VIII).

In Table IX the leukaemias and cancers are divided into six diagnostic groups; in each of these subgroups the number of children exposed to prenatal *x*-rays is compared with the expected number, on the basis of the control children's experiences. According to this analysis neither stem-cell leukaemias nor monocytic leukaemias showed an excess of prenatal *x*-ray exposures, but the ratio of observed to expected numbers for all non-granular leukaemias (1.68) was not significantly different from the ratios for other and unspecified leukaemias (2.02) and for cancers (1.83).

TABLE VIII

	Prenatal X-ray Exposures		No. of Children	
	Leuk.	Cont.	Leuk.	Cont.
Boys with non-granular leukaemias ..	28	31	312	312
All children under 2 years	19	19	169	169
Children whose mothers were over 40 years	5	6	51	42
Mongols (case/control pairs) ..	0	2	19	19

TABLE IX.—*Prenatal X-ray Examinations. Diagnostic Groups*

Diagnostic Groups	Observed	Expected*	Ratio Observed to Expected
Leukaemias:			
Lymphatic	57	28·96	1·97
Stem-cell	9	8·88	1·01
Monocytic	1	1·96	0·51
Myeloid	10	5·13	1·95
Unspecified	19	9·25	2·05
All leukaemias	96	54·18	1·77
All cancers	115	62·82	1·83
Total ..	211	117	1·80

* Expectations based on all controls, in one-year age-groups, sexes combined.

Finally, the 96 children who were *x*-rayed *in utero* included five with fractures, 10 with serious pyogenic infections, and one child who had a distant relative (great-uncle) with leukaemia. There were no serious congenital defects; one child had nystagmus and three had naevi.

Discussion and Conclusions

Two distinct varieties of childhood leukaemias have been identified, only one of which is numerically important. The commoner variety is responsible for the early peak of leukaemia mortality and produces non-granular malignant cells. These cells are often called lymphoblasts or monoblasts, but they are probably derived from undifferentiated stem or blast cells. Children with this type of leukaemia, particularly boys, are especially prone to pneumonia and other pyogenic infections in infancy; they are often mongols, and occasionally a brother or sister has exactly the same type of leukaemia. It is suggested that these *prezygotic leukaemias* are due to the inheritance of a gene which produces premalignant changes in ancestral cells of the reticulo-endothelial system. During embryogenesis these abnormal cells are liable to undergo further changes which finally lead to the production of malignant cells. If the congenitally defective stem cells survive embryogenesis unchanged, they may become malignant at a later date if exposed to conditions of leucocyte stress—for example, bacterial infections—or remain indefinitely in a premalignant state.

The second variety of leukaemia is rare in childhood but may be caused by irradiation *in utero*. In these *prenatal leukaemias* the malignant cells may be myeloblasts, lymphoblasts, or stem cells; resistance to pyogenic infection is lower but not much lower than normal, and death before the age of 5 years is unusual. Prenatal leukaemias have not so far been found in association with mongolism nor with a second case of leukaemia in a near relative. It is suggested that they are due to changes in somatic cells which have premalignant and eventually malignant consequences. In these cases the unaffected leucocytes react normally to intercurrent infections.

According to this theory the relatively high incidence of cancers and leukaemias in early childhood is due to the fact that in this age-group there are, in addition to cases arising *in utero*, cases which are due to the inheritance of a cell-specific anomaly which has premalignant propensities. In these cases embryogenesis acts as a promoting factor and all cells of the specified type are abnormal. Hence the exceptionally low resistance to pyogenic infections in cases of prezygotic leukaemia.

Before the discovery of sulphonamides and antibiotics the commonest cause of death among children with a congenitally defective reticulo-endothelial system was probably pneumonia; nowadays it is possible for these children to survive these infections, only to die later of leukaemia. It is suggested that the advent of these remedies has produced three changes: a spectacular increase in the early peak of leukaemia mortality; an increase in the risk of death from leukaemia among mongols; and an increase in the number of sibships with more than one case of leukaemia or lymphosarcoma.

If these conclusions are correct, the leukaemia death-rate will eventually settle down to a level which will depend on how successful we are in preventing and curing bacterial infections. We shall also discover that some but not all children with stem-cell leukaemias have abnormal pedigrees. What exactly will be found in the relatives of these children will depend on several factors (including access to *x*-rays and antibiotics), but a systematic search for miscarriages, stillbirths, leucopenias, lethal infections, anaemias, and leukaemias is now indicated. Already Ardashnikov (1947) has noticed unusual lymphoid reactions to infections in the relations of leukaemia patients. De Vries, Peketh, and Joshua (1958) have found a case of lymphatic leukaemia in a family with hereditary leucopenia, and Cramblett, Friedman, and Najjar (1958) have discovered a mother and child with lymphatic leukaemia. This child was normal at birth and remained well for nine months, but, because the mother died during the puerperium, the child's blood was examined when it was a few days old. The differential white-cell count on this occasion revealed 65% of lymphocytes.

If, as has been suggested, there is a common link between mongolism, liability to pyogenic infections, and leukaemia, it should be possible to demonstrate this in other ways and discover whether the low serum proteins and poorly segmented polymorphs of mongols (Turpin and Bernyer, 1947; Mittwoch, 1957) are implicated.

Again, if diagnostic *x*-ray examinations are powerful enough to cause malignant or premalignant changes in foetal cells, they should also be capable of causing malignant or premalignant changes in germ cells. It is already on record that the mothers of the survey cases (leukaemias and cancers) had more abdominal *x*-ray examinations before marriage than the mothers of controls (Stewart *et al.*, 1958). This observation has been regarded as a weakness in the data (Cronkite, Moloney, and Bond, 1960), but it may prove to be an important finding.

The final conclusion is that the role of leucocytes in pyogenic infections, and the profound changes which have followed the discovery of antibiotics, have led to the discovery of a variety of leukaemia in which the first decisive event predates conception and produces a preleukaemic gene. The prezygotic leukaemias derived from these genes are responsible for the early peak of leukaemia mortality (2–4 years) and have their counterpart in other cancers. It is also suggested that in any population the numbers of preleukaemic genes and the numbers of prezygotic leukaemias are to a large extent controlled by the prevalence and mortality of pyogenic infections. In this country the pneumonia death-rate has been decreasing throughout the present century.

The findings as a whole suggest that malignant diseases are caused in the following ways.

In every case the *initial or predisposing event* is a gene mutation which may be caused by any mutagen, including *x* rays. These mutations may affect different loci and different alleles at the same locus; the loci determine the organ or system in which the cancer appears and the alleles determine the precise intermediate character of the cancer cells and the nature of the intermediate (premalignant) effects.

Thus leukaemias and lymphosarcomas are due to mutations in genes controlling the leucopoietic system. The resulting cancer cells may belong to the myeloid, lymphatic, stem-cell, or reticular series, depending on which alleles are affected, and the malignant phase of the disease may be preceded by aplastic anaemia, polycythaemia, leucopenia, impaired phagocytosis or reticulocytosis, thrombocytopenia, persistent foetal haemoglobin, or other signs of disturbance in the bone-marrow or lymph nodes.

If the original mutation occurs in a germ cell it produces no effects unless and until the affected cell is successfully fertilized. Should this happen the premalignant effects will be relatively conspicuous and may be transmitted to future generations as *a cell-specific congenital defect*. When the cancer supervenes the relevant tumours will consist mainly of embryological or "stem" cells and might be called *prezygotic or inherited cancers*.

If the original mutation occurs in a somatic cell, it will produce no effects unless and until the affected cell divides again. When this happens the premalignant effects may be inconspicuous or absent. When the cancer cells appear they will assume a relatively mature form which may differ from case to case. In these *post-zygotic or acquired* cancers there is no danger of a precancerous state being transmitted to future generations.

In all cases of prezygotic cancers, and in some cases of post-zygotic cancers, *secondary or precipitating events* may be needed to convert precancer cells into cancer cells. These events do not affect cancer sites or cell types but are apt to occur: (1) when the affected cells are immature or develop signs of senility, and (2) in the presence of coincidental conditions, which may be acute —for example, puberty, trauma, and acute infections—

or chronic—for example, mongolism, endocrine disorders, hyperchlorhydria, chronic mastitis, chronic bronchitis, etc.

In spite of their non-specificity all precipitating events have one thing in common: they represent conditions of "cell stress" and therefore tend to reveal latent defects in organs or systems derived from abnormal genes.

Prezygotic cancers fall into two groups, depending upon whether the original mutation has occurred in a parental germ cell (*first-generation cases*) or in a more remote ancestral cell (*pedigree cases*). In first-generation cases there will be no previous family history of the cell-specific cancer or congenital defect, but the descendants of these cases may be affected. In pedigree cases there may also be a previous familial incidence of the cell-specific congenital defect or cancer—for example, intestinal polyposis, von Recklinghausen's disease, hereditary leucopenia, or retinoblastoma.

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ADDENDUM

Since writing this paper three relevant investigations have been reported. A follow-up, in 1958, of 38,114 children who were born between 1945 and 1947 and were *x*-rayed *in utero* did not reveal an overall excess of deaths from leukaemia (Court Brown, Doll, and Hill, 1960). From unpublished data supplied by these authors it has since been ascertained that one-third of these children were born before 1950 and two-thirds during 1950–7. In the older group (aged 8–13 years at the time of the follow-up) there were 7 leukaemia deaths, or 70% more than the expected number; in the younger group (0–7 years) there were 2 leukaemia deaths, or only one-third of the expected numbers.

Doll (1960) has shown that international differences in leukaemia incidence are due mainly to lymphatic leukaemias in childhood and old age. These cases are relatively common in populations which have experienced a continuous decrease in the pneumonia death-rate since 1900—for example, Great Britain, Scandinavia, and the white population of the U.S.A.—and rare in populations which maintained a high pneumonia death-rate until 1945, when penicillin first became available—for example, Ceylon, Japan, and the coloured population of the U.S.A.

Finally, a case of lymphatic *cum* blast-cell leukaemia has been reported in a girl whose blood was found to contain 19% of foetal haemoglobin (Shuster, Jones, and Kilpatrick, 1960). A brother of this patient died in infancy of an unknown cause.

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CHRONIC DIFFUSE NON-SUPPURATIVE AMOEBIC HEPATITIS

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[WITH SPECIAL PLATE]

Amoebic hepatitis, well known in its acute form, is considered to be the early (pre-suppurative) stage of the solitary abscess or multiple abscesses of the liver (Lichtman, 1949; Seneca, 1956). Chronic lesions of the liver interstitium and parenchyma have been described as occurring in chronic abscess of the liver and in chronic amoebic colitis (Chatgidakis, 1953; Seneca, 1956). In the former condition fibrosis and thickening of the portal tracts have been observed. In the latter, fat degeneration or necrosis of the liver cells, hyperplasia of the connective tissue of the portal spaces with inflammatory infiltrations by lymphocytes and monocytes, as well as regeneration of the liver cells, have been reported (Lichtman, 1949; Seneca, 1956). These lesions are considered to be due to toxic substances produced by amoebae or other bacteria in chronic colitis (Lichtman, 1949).

Cases of chronic hepatitis due to the presence of amoebae in the liver without a localized abscess have not yet been published. The purpose of this paper is to present such a case.