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EPIDEMIOLOGY OF ACUTE LEUKAEMIA OF CHILDHOOD IN THE LIVERPOOL AREA

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Aetiological factors known to influence the development of leukaemia in man include ionizing radiation and chromosomal abnormalities (Miller, 1964). Viral agents have been demonstrated in laboratory animals and although virus-like particles and mycoplasma have been found in affected marrow cells (Negroni, 1964; Grist and Fallon, 1964) attempts to show a direct causal relationship have so far been unsuccessful in man.

Epidemiological studies have become of increasing importance, and interest in the distribution has been stimulated by reports of clustering within various communities. The outbreak in one parish in Niles, Illinois, in which eight children developed the disease within 4 years, was thought to be due to an infectious cause, especially as there was an outbreak of a "rheumatic-like" illness during the same period (Heath and Hasterlik, 1963). Other reports of smaller clusterings (Wood, 1960; Pinkel and Nefzger, 1959) were more open to interpretation as being due to chance distribution, although infection could not be excluded as a contributory factor. Studies of variation in San Francisco (Mustacchi, 1965) supported the view that cases tend to occur in a non-random way referable to the presence of previous cases.

As the incidence of leukaemia in the population is very low, it is necessary to develop statistical techniques of suitable sensitivity and validity to detect clustering, if it exists, especially within communities where the overall incidence is not obviously different from that expected. Ideally the same method should be applied to as many sets of comparable data as possible. The procedure of Knox (1963), which was first used to study the epidemiology of childhood leukaemia in Northumberland and Durham (Knox, 1964) and later in Oregon (Meighan and Knox, 1965), has recently been assessed independently (David and Barton, 1966) and shown to be an effective method of revealing space-time interaction.

The object of the present study is to examine data from the large conurbation centred on the port of Liverpool where clustering was not apparent.

METHOD

The records of patients diagnosed and treated at Alder Hey Children's Hospital, Liverpool, during the period 1955–64 were examined. Records were also obtained from the Royal Liverpool Children's Hospital for all children seen there during the same period. It is unlikely that any other patients, with home addresses in any of the seven administrative areas listed in Table I, have been diagnosed without being referred to one of these children's hospitals. Examination of the annual mortality returns of the

TABLE I

INCIDENCE BY ADMINISTRATIVE AREA AND BY YEAR

Administrative Area	Total Number 1955–64	Number Diagnosed in Each Year									
		1955	1956	1957	1958	1959	1960	1961	1962	1963	1964
Liverpool C.B.	56	7	6	3	6	6	3	12	6	3	4
Bootle C.B.	3	—	—	1	1	—	—	1	—	—	—
Crosby M.B.	5	—	3	—	—	—	—	—	—	—	2
Huyton-with-Roby U.D.	3	—	—	—	—	1	1	—	—	—	1
Kirkby U.D.	4	—	2	1	—	—	—	—	—	—	1
Litherland U.D.	2	1	—	—	—	—	—	—	—	—	1
W. Lancs. R.D.	1	—	—	1	—	—	—	—	—	—	—
Total	74	8	11	6	7	7	4	13	6	3	9

Medical Officers of Health of the various Health Authorities provided some cross check, but any patient dying in either hospital would be included in Liverpool County Borough mortality figures, whereas the home address may lie outside the city boundaries. Ten patients who were still alive on December 31, 1964, are included in this survey.

The criteria for inclusion were as follows:

(1) The onset of acute leukaemia occurred before the 15th birthday.

(2) The home address was within the area comprising Liverpool C.B., Bootle C.B., Crosby M.B., Huyton-with-Roby U.D., Kirkby U.D., Litherland U.D., and that part of West Lancashire R.D. lying between Bootle and Kirkby.

(3) The patient was diagnosed between January 1, 1955, and December 31, 1964.

The area involved is approximately 161 sq. kilometres with a total population in 1962 of 1,091,890 (Registrar General's estimates). This year has been selected arbitrarily for all estimates of population, as the 1961 National Census figures were then available for more accurate computation. The population of Liverpool was 745,230, of whom 187,000 were estimated to be under 15 years of age. The population at risk in the whole area, if the proportion of children may be assumed to be constant throughout the area, would have been 273,900. From the whole area there were 74 cases, 56 of them living within the Liverpool city boundaries.

The date of onset has been taken as the date on which the first relevant symptom was noticed, as recorded in the case history at the time of admission. In about one-third, no accurate date could be remembered by the parent and the middle day of the month in which symptoms began has been arbitrarily chosen. One patient was not diagnosed during life but was found to have the disease at autopsy following a road traffic accident.

The geographical data were obtained by plotting the position of the patient's home on a street map of Liverpool and neighbouring authorities, scale 4″ : 1 mile. The position was taken as the middle of the block in which the house was known to be situated. National Grid references were then read, the least significant figure representing 0·1 km.

Results

During the 10-year period, 74 children were found to have had acute leukaemia. Taking the estimated population at risk as being 273,900, the mean annual incidence was 2·71 cases per 100,000 children over the whole area. In Liverpool, with 56 cases occurring in 187,700 children, the mean annual incidence was slightly higher, 2·98 per 100,000.

Table I gives the number of cases by year in each administrative area. Thirteen cases were diagnosed in 1961, of whom twelve lived in Liverpool, and in 1956, out of eleven cases, three lived in Crosby and two in Kirkby. In order to see whether this apparent concentration of cases in time and space was of significance, the dates of onset were first arranged seasonally, as in Table II.

Table II

Incidence by Month of Onset and Month of Diagnosis

Month	No. of Cases with Onset of Symptoms	Cases Diagnosed	Time Lag Between Onset and Diagnosis (days)			
			<30	30–60	60–90	>90
January	7	6	5	0	1	1
February	7	6	4	2	0	1
March	7	7	4	0	3	0
April	1	6*	1	0	0	0
May	8	9	5	2	1	0
June	8	7	6	0	1	1
July	7	3	0	2	3	2
August	8	4	4	2	1	1
September	5	9	4	1	0	0
October	3	9	1	1	0	1
November	2	5	2	0	0	0
December	11	3	5	2	0	4
Total	74	74	41	12	10	11

In the whole group there is no obvious evidence of seasonal variation, 39 cases beginning between May and October ("summer") and 35 cases between November and April ("winter"), although if the date of diagnosis were considered, one might form a false impression that more cases occur in the summer—43 cases were confirmed during the 6-months from May to October, and 33 between November and April.

The time lag between onset of symptoms and date of diagnosis has been tabulated in relation to the month of onset but there is no significant difference in the intervals seen in this series.

The cases were then divided by age, sex, and type of leukaemia. As exact typing of the more primitive leukaemias may be very difficult, all cases have been described as (*a*) myeloblastic, (*b*) lymphoblastic including undifferentiated blastic leukaemia and two cases of lymphosarcoma which underwent leukaemic transformation, or (*c*) monocytic. There was one case of erythroleukaemia. The diagnosis in each case was based upon clinical findings and full haematological investigation including bone marrow biopsy.

Table III (opposite) shows the distribution by age of the whole group, by sex and type of leukaemia. The well-recognized distribution pattern with preschool peak incidence is apparent, but the preponderance of males to females (63·6 per cent.:36·4 per cent).

is in excess of that obtained from the mortality figures for England and Wales (55·7 per cent.: 44·3 per cent. annual mean values for years 1959–63 for age groups 1–4 and 5–14).

TABLE III

AGE DISTRIBUTION, SEX, AND TYPE OF LEUKAEMIA

Age (yrs)	Total	Sex		Type of Leukaemia		
		Male	Female	Acute Lymphoblastic	Acute Myeloblastic	Other
<1	3	2	1	2	1	
1–2	5	3	2	3	1	1 Acute Monocytic
2–3	7	4	3	5	2	
3–4	4	3	1	3	1	
4–5	12	9	3	11	1	
5–6	6	3	3	2	3	1 Acute Monocytic
6–7	10	6	4	8	2	
7–8	3	2	1	2	1	
8–9	5	2	3	4	0	1 Acute Erythroleukaemia
9–10	2	1	1	1	1	
10–11	4	3	1	4	0	
11–12	5	3	2	3	1	1 Acute Monocytic
12–13	3	3	0	2	1	
13–14	1	0	1	0	1	
14–15	4	3	1	2	2	
Total	74	47	27	52	18	4

Table IV shows the seasonal occurrence of the various types of leukaemia for all ages, subdivided by age group into under 5 years and 5 years and over. The only apparent difference in this series is a small increase in the number of cases of acute lymphoblastic leukaemia with summer onsets in the younger age group. χ^2 testing gives $P > 0{\cdot}5$, however, and this impression is not statistically significant. The three cases of monocytic leukaemia all began in June, but no inference can be drawn from so few cases.

TABLE IV

SEASON OF ONSET, BY AGE AND TYPE OF LEUKAEMIA

Season	Type of Leukaemia	0–<15	0–<5	5–<15
Winter (November to April)	All Leukaemias	35	13	22
	A.B.L. + A.L.L.	23	9	14
	A.M.L.	11	4	7
	Acute Monocytic	0	0	0
	Acute Erythroleukaemia	1	0	1
Summer (May to October)	All Leukaemias	39	17	22
	A.B.L. + A.L.L.	28	12	16
	A.M.L.	8	4	4
	Acute Monocytic	3	1	2

In order to study the spatial distribution of cases and to determine whether certain areas contained excessive numbers of patients, the concentrations were calculated for each electoral ward of the city of Liverpool (Figure, overleaf). The estimated total populations in 1962 are listed in Table V, together with population density per acre (1 acre $= 4{\cdot}047 \times 10^{-3}$ sq. km.), the number of cases observed during the 10-year period, and the annual incidence per 100,000 total population (not population at risk, as these figures are not available). The overall annual incidence is 0·733 ±0·57 per 100,000 total population among the electoral wards. The expected incidence for each ward has been calculated on the basis of even distribution proportional to population. In six wards the number observed is more than double that expected, but χ^2 testing with 40 degrees of

TABLE V

DISTRIBUTION OF CASES OF CHILDHOOD LEUKAEMIA IN LIVERPOOL, BY ELECTORAL WARDS, 1955–64

Electoral Ward	Population*		No. of Cases		Incidence per 100,000 Population per Year
	Estimated Total (1962)	Density per Acre	Expected	Observed	
Abercromby	14,680	55·0	1·104	Nil	0
Aigburth	21,640	18·5	1·627	1	0·46
Allerton	15,910	9·9	1·196	Nil	0
Anfield	21,900	40·2	1·645	Nil	0
Arundel	19,860	39·3	1·492	Nil	0
Breckfield	17,170	98·1	1·294	1	0·58
Broadgreen	17,780	26·6	1·337	2	1·12
Central	10,740	17·3	0·807	Nil	0
Childwall	26,480	21·3	1·99	2	0·75
Church	21,280	26·7	1·599	2	0·94
Clubmoor	17,560	34·5	1·319	1	0·57
County	21,000	48·6	1·578	1	0·48
Croxteth	18,220	15·9	1·370	3	1·65
Dingle	19,030	53·7	1·43	1	0·53
Dovecot	22,420	23·6	1·685	1	0·45
Everton	15,350	70·4	1·153	1	0·65
Fairfield	21,150	34·9	1·59	1	0·47
Fazakerley	17,680	23·2	1·328	Nil	0
Gillmoss	24,980	13·7	1·877	5	2·02
Granby	17,600	92·1	1·322	Nil	0
Kensington	18,690	75·3	1·405	1	0·53
Low Hill	14,500	81·0	1·09	1	0·69
Melrose	14,550	78·6	1·092	1	0·68
Netherfield	12,040	90·5	0·894	1	0·47
Old Swan	22,980	43·2	1·727	2	0·93
Picton	21,570	57·4	1·621	1	0·46
Pirrie	25,730	20·6	1·933	2	0·78
Princes Park	20,190	69·6	1·517	2	0·99
St. Domingo	18,320	102·3	1·38	2	1·09
St. James	15,540	22·3	1·168	3	1·93
St. Mary's	17,040	14·0	1·28	Nil	0
St. Michael's	15,690	20·4	1·179	1	0·64
Smithdown	18,370	73·8	1·38	2	1·09
Speke	21,880	10·2	1·644	1	0·46
Sandhills	12,400	13·4	0·932	Nil	0
Tuebrook	19,690	45·6	1·48	4	2·03
Vauxhall	14,900	73·4	1·119	3	2·01
Warbreck	19,820	29·3	1·489	1	0·53
Westminster	11,370	80·6	0·854	4	3·52
Woolton	27,530	11·4	2·068	2	0·73
Total C.B.C. Liverpool	745,230	26·8	56	56	0·733

* The above population figures are derived from the figures in the Annual Report for 1962 of the Medical Officer of Health for Liverpool.

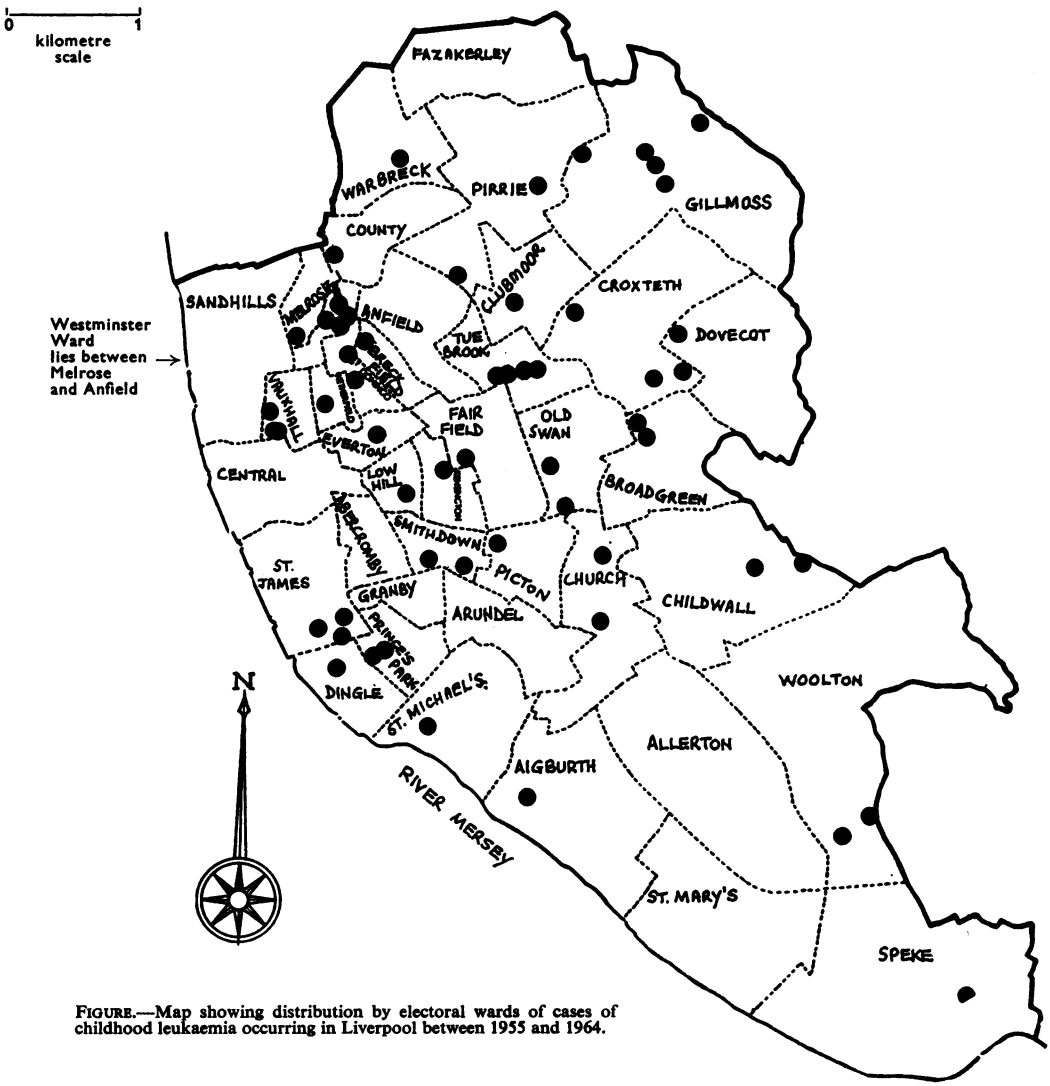

FIGURE.—Map showing distribution by electoral wards of cases of childhood leukaemia occurring in Liverpool between 1955 and 1964.

freedom does not give statistical confirmation of any significance as the numbers involved are small.

It is interesting that, of those wards with high incidence and low population density, Croxteth and Gillmoss are neighbouring wards consisting mainly of post-1920 housing development with comparatively large areas of open space—private parkland, playing fields, and a cemetery. St. James ward includes warehouses, docks, and other business premises which reduce the population density below the city mean, but the inhabitants tend to live in older terraced houses, many of which are overcrowded. Tuebrook, Vauxhall, and Westminster, the remaining wards with high incidence, are all areas in which most of the property is more than 50 years old and where overcrowding is common.

The data from all patients in the area were then analysed, using the computer technique first described by Knox in 1963, in order to investigate space-time relationships for possible clustering.

Dates of onset were converted to century day numbers. Six-figure grid references, as within square

SJ of the National Grid, with easterly and northerly components, of which the least significant figures represent 0·1 km., translated home addresses into numerical terms.

If all cases are compared with every other one 74 patients give 2,701 possible pairings. The time interval is obtained by subtraction of day numbers and distance apart by application of Pythagoras' theorem. In the first analysis, all cases were examined together, the allocation of pairs being seen in Table VIA. Cumulative frequencies are also shown in Table VIB, with + sign where a significant discrepancy (on the basis of χ^2 test which is not necessarily reliable) has been found between the observed cumulative frequency and that calculated in direct proportion to row and column totals. The excess number of pairs appearing in the upper left corner of Table VIA, *i.e.* those with short time intervals and living short distances apart, is confirmed by the appearance of significant discrepancies in columns to the right and rows below in Table VIB.

The data were then divided into two groups by age. By chance, 37 patients were aged under 6 years, and 37 were aged 6 years and over. 666 possible pairs were produced in each group and analysed in the same way. Division of the group by age did not make the clustering tendency any more apparent.

Discussion

The ascertainment of cases of acute leukaemia occurring in children under the age of 15 is probably complete, as patients were in no way selected before referral, but rather were sent to one of the two children's hospitals, which serve the whole area, for initial diagnosis. The number found in Liverpool and the neighbouring areas during the period 1955–64 compares very closely with those calculated from the Registrar General's mortality figures for England and Wales. The national death rates per million per year from all types of leukaemia in children aged 0–14 were as follows (Court Brown and Doll, 1961):

28 in 1945–49 32·5 in 1950–54 32·5 in 1955–59

and for the age group 0–5

42·9 in 1955–59

The corresponding Liverpool figures for *onsets* of leukaemia are:

29·8 (1955–64) per 1,000,000 aged 0–14
43·2 (1955–64) per 1,000,000 aged 0–4

Hence there is no evidence that the incidence of the disease is different in this part of the Merseyside conurbation from elsewhere in England and Wales.

The seasonal variation in onset detected by Lee (1962) and found elsewhere in Great Britain (Knox, 1964) is not definite in this series, but the slight increase seen in the number of cases of acute lymphatic leukaemia starting in the summer accords with Lee's later findings (1963) that this type of the disease is the one responsible for the summer peak.

In order to determine whether cases were tending to occur more frequently in some parts of the area than others, the data were examined in two ways:

(1) The distribution of cases in the city of Liverpool divided by electoral wards showed higher incidence in six of the more densely populated wards or parts of wards. The exact population of

TABLE VI (A AND B)

74 CASES OF ACUTE LEUKAEMIA IN LIVERPOOL

2,701 Possible Pairs	Time (days)	Distance (km.) 0–2	–3	–4	–5	–8	All Distances
(A) Times and Distances Apart	0–50	6	7	11	13	16	75
	–100	6	6	11	8	25	71
	–150	11	8	7	6	12	53
	–200	10	9	10	8	15	73
	–250	11	9	12	8	25	74
	–300	7	7	7	7	21	66
	–350	6	8	9	10	21	69
	–400	6	4	9	11	27	77
	–1,000	59	78	93	87	215	680
	All Times Apart	263	253	328	338	835	2,701
(B) Cumulative Frequencies	0–50	6	13	24	37	53	75
	–100	12	25	47	68	109	146
	–150	23	44	73	100	153	199
	–200	33	63	102	137	205	272
	–250	44	83+	134+	177+	270	346
	–300	51	97+	155+	209+	323	412
	–350	57	111+	178+	242+	377	481
	–400	63	121	197	272	434	558
	–1,000	122	258	427	589	976	1,238
	All Times Apart	263	516	844	1,182	2,017	2,701

children at risk in each ward is not known but, as the more densely populated areas of Liverpool tend to have higher birth rates, it is likely that the numbers actually at risk in these overcrowded parts are somewhat higher than proportions based on the figures for the whole city. Making allowance for this inaccuracy, there is still some suggestion that cases tended to occur preferentially in certain parts of the city although this is a difficult hypothesis to test and it did not prove possible to elicit positive significance tests.

(2) The data for the whole area were analysed by computer, as described previously, to detect any clustering in time and space. The results obtained show discrepancies from those to be expected if the cases had occurred at random. An excess number of pairs with short distances and short times apart was found in the analysis of the whole group. The highest levels of significance are centred on pairs with intervals less than 4 km. and 300 days. This pattern of clustering is comparable with that found by Meighan and Knox (1965) when 69 cases under 15 years in Portland, Oregon, during 1950–61 were analysed by this method. Knox (1964) found a space-time interaction affecting lymphoblastic leukaemia of young children in Northumberland, Durham, and Teeside during 1951–60, which was maximal for pairs with intervals less than 1 km. and less than 60 days. He also found a higher risk in children living in larger towns, the urban incidence being 47·1 per 1,000,000 child-years aged 0–5. This may represent a slightly lower overall incidence than in Merseyside children, where the incidence of 43·2 per 1,000,000 child-years refers to the higher risk age group 0–4.

These results support those found in previous studies in which the same technique has been applied. It is important that similar analytic tools should be used for data from as many different areas as possible in order that valid comparisons may be made.

SUMMARY

There were 74 cases of acute leukaemia in children under 15 years diagnosed between 1955 and 1964 in the Liverpool area. Seasonal variation was not found, but cases tended to occur in certain more densely populated areas. A clustering factor was detected by application of a computer technique, an excessive number of pairs separated by less than 4 km. and 300 days being found.

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