

EPIDEMIOLOGY OF CHILDHOOD LEUKAEMIA IN NORTHUMBERLAND AND DURHAM

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Our understanding of the aetiology of leukaemia is progressing rapidly. Differentiation of chronic myeloid leukaemia through an abnormal chromosome 21, a high risk of acute leukaemia in mongols, again with anomalies of chromosome 21, a demonstrated association between the risk of leukaemia and the dose of radiation received, and between therapeutic irradiation and chromosomal anomalies, indicate the importance of chromosomal changes in many instances of the disease. At least one poison, benzene, is also known to have caused leukaemia in man. On the basis of animal experiments it is possible that other poisons may do the same.

Nevertheless the known specific effects have so far been shown to be responsible for only a small proportion of the leukaemias of childhood, and other known facts indicate the presence of unidentified causal factors. The disease seems to have been increasing in frequency, the risk to adults varies according to their occupation, an urban-rural differential of risk has been reported, a systematic variation in incidence from the North-West to the South-East of England has been demonstrated, a variation between states in the U.S.A. has been found, a seasonal variation of onset in children has been claimed, the multimodal curve of risk according to age suggests a number of separate and superimposed causes each operating maximally at different ages, and the historical development of the age pattern suggests that some of these causes have become important only in the last 30 years.

Leukaemia has also been stated, on several occasions, to occur in clusters in space and in time with undue frequency. Kellett (1937) was perhaps the first to point out this apparent feature, and more recently Pinkel and Nefzger (1960) in Buffalo, N.Y., and Wood (1960) in Cornwall, have made similar suggestions. If this could be substantiated, it would

clearly be a fact of the greatest importance, particularly although not exclusively with respect to theories of virus aetiology. I have tried elsewhere (Knox, 1963) to analyse the methodological and conceptual problems of the space-time cluster, particularly when we are dealing with a low intensity of events, as we are in leukaemia. Briefly, it is proposed that the examination of such events requires a separate examination for the three components of epidemicity: (a) concentrations in space, over the whole of the time of the study; (b) concentrations in time over the whole of the area of the study; (c) interactions between space and time concentrations. Examination for the last component amounts to a search for movements of high concentration areas and the method proposed is the examination of all possible pairs, or a selection of them, to see whether short geographical distances are positively correlated with short time intervals.

The present paper is an analysis, both in these terms and by more orthodox methods, of the space and time distribution of childhood leukaemia in the North of England over a period of 10 years.

MATERIAL AND METHODS

The cases of leukaemia accepted for analysis were those (a) with onset before the 15th birthday, (b) which occurred within the geographical limits of Northumberland, Durham, and that strip of the North Riding of Yorkshire between the Cleveland Hills and the River Tees, (c) with onset between January 1, 1951, and December 31, 1960, a total of 10 years.

The region covered measures approximately 90×45 miles, the area is approximately 3,100 square miles, the total population at the 1951 census was 2.48 millions, and the number of children at risk in 1956 approximately 599,500.

1961) and the rising incidence of adult life. The 3:2 male:female ratio is also a well-recognized feature of the disease.

Table I also gives separately the age distributions of lymphoblastic and myeloblastic leukaemias both in urban and in rural areas. For the purposes of this Table, "lymphoblastic" includes also undifferentiated acute leukaemias and those following upon an initial diagnosis of lymphosarcoma. "Myeloblastic" includes those considered to be monocytic. "Urban" means addresses within the Tyneside conurbation or within towns of at least 50,000 inhabitants: Darlington, Middlesbrough, Stockton, Sunderland, and West Hartlepool. "Rural" means the remainder, but it should be understood that, particularly in County Durham, much of the "rural" population lives in Municipal Boroughs and Urban Districts of 10,000 to 50,000 people and that such groupings account for about 620,000 of the total population of that county.

Table I shows different age distributions for the lymphoblastic and myeloblastic varieties. This is a well-recognized phenomenon. However, the apparent difference in age distributions of lymphoblastic leukaemias with urban and rural addresses has not been reported. The mean age at onset for the lymphoblastic leukaemias in the large towns was 5.82 years and in the other areas 4.50 years. The significance level is close to but slightly greater than 0.05 the F-ratio being 3.7. For myeloblastic leukaemias before the 15th birthday the mean age at onset was 7.70 years.

The different age distributions of urban and rural lymphoblastic leukaemias results in a changing urban:rural ratio with age and the change is most evident if we compare children aged 5 years or less with those aged 6 years or more. For the younger children there were 51 urban and 38 rural addresses at onset and for the older children 37 urban and 13 rural. The urban:rural ratio for lymphoblastic leukaemia with onset at 6 years or over is indistinguishable from that for the myeloblastic leukaemias at all ages under 15.

When related to the populations of children at risk, the rates by age and type of leukaemia are as in

Table II. The actual distribution between years of age differed in different years as the post-war birth-rate "bulge" moved up through the age groups considered, but as an approximation, over the whole period, the child population has been considered equally divided between years of age. The urban:rural distribution used is that for children aged 0-14 at the 1951 census and at that time 56.69 per cent. lived in urban areas as defined.

TABLE II
URBAN AND RURAL INCIDENCE
RATES PER MILLION CHILD-YEARS*

Cytology	Place	Age (yrs)	
		0-5	6-14
Lymphoblastic	Urban	37.5	18.1
	Rural	36.6	8.3
Myeloblastic	Urban	9.6	9.8
	Rural	4.8	5.1

* Populations at risk are estimated from a 1956 estimated population aged 0-14 years of 599,500, distributed equally between years of age and using the 1951 Census estimate of 56.69 per cent. of such children living in the urban areas, as defined in the text.

For leukaemias of all kinds up to age 14 the rate was significantly higher in the urban than in the rural areas, 35.6 against 24.7 cases per million child years, ($\chi^2_{(1)} = 6.7$). The lymphoblastic leukaemias under about 6 years seem to differ from the other groups in that risk is the same in both urban and rural areas, the overall urban:rural difference being concentrated in the other types. The age demarcation has been chosen arbitrarily here and the justification for division depends as we have seen upon a difference of mean ages of borderline significance but further evidence, to be presented, tends to justify this presentation.

In Table III the lymphoblastic and myeloblastic leukaemias are given according to the month of clinical onset. There is evidence here of a seasonal variation, maximized by comparing May to October with November to April. All cases together show 111 onsets in the summer against 74 in the winter and this is possibly concentrated in the lymphoblastic series with 84 summer and 55 winter onsets

TABLE III
TYPE OF LEUKAEMIA BY MONTH OF ONSET

Cytology	Month of Onset												Total
	1	2	3	4	5	6	7	8	9	10	11	12	
Lymphoblastic	12	10	8	7	13	23	10	10	14	14	8	10	139
Myeloblastic	4	3	3	4	3	4	3	5	5	7	1	4	46
Total	16	13	11	11	16	27	13	15	19	21	9	14	185

($\chi^2 = 6.05$) while the myeloblastic series has 27 and 19 respectively. The first ratio is significantly different from a 1:1 ratio, even if the χ^2 is allowed 2 degrees of freedom, the extra degree of freedom allowing for arbitrary choice of phase. The second ratio does not differ significantly; nor however, is the difference between the two ratios significant. Table IV shows the summer and winter onsets of lymphoblastic leukaemia by age at onset, the seasonal variation being discernible up to about the 6th birthday but not thereafter. Before the 6th birthday there were 59 summer and 30 winter onsets and at later ages there were 25 of each. Thus the difference is greatest at the age which also shows best the change in the urban:rural ratio.

The group of cases associated with the seasonal factor seems to be capable of greater resolution through the exclusion of children who on prior grounds may be suffering from leukaemias of aetiologies different from the remainder.

There were, in the whole group of 185 cases of leukaemia, nine children who were mongols and another in whom an exact diagnosis was not recorded but who was "slightly mongoloid", mentally defective with congenital heart disease, and whose mother was 42 years old at delivery. The ages at onset of these ten children were 11, 20, 22, 25, 25, 26, 41, 56, 56, and 66 months. Another child aged 63 months at onset suffered from Sturge-Weber's disease, a condition also sometimes stated to be associated with chromosomal anomalies (Patau, Therman, Smith, Inhorn, and Picken, 1961) and so rare that the presence of a single case in a series of this size may be significant. Since all of these children were under 6 years old, we may say that about 11 per cent. of affected children in this age group probably had abnormal karyotypes.

Three of these eleven cases of leukaemia were

classified as myeloblastic and two as lymphoblastic, and the remainder were not classified.

Further possible exclusions are eleven children with lymphoblastic leukaemia who had a history of irradiation either *in utero* or later. Omission both of these and of the group with abnormal karyotypes from the lymphoblastic leukaemias under 6 years of age leaves a group of 68 children with 48 summer and 20 winter onsets, a ratio of 2.4:1.

The seasonal factor seems to be independent of the urban concentrating factor on the grounds of the different groups affected by each. In addition, however, the above 68 children included 37 with urban and 31 with rural addresses and the respective summer:winter ratios were 24:13 and 24:7. Within the appropriate age group and cytological type the seasonal factor operates equally in both the town and the country.

Table V presents the frequencies of summer and winter onsets of lymphoblastic leukaemia in the above 68 children according to the year of onset. It shows that the seasonal variation has been present throughout the period examined, 8 of the 10 years showing the summer excess, and one of the remaining 2 years having equal numbers. Although total figures showed a rise compatible with the secular increase of the disease in recent years, it was not possible from our data to incriminate the seasonal or any other particular component. The children with abnormal karyotypes and those with a recorded exposure to irradiation belonged mainly to the second half of the period, but this was probably due to improved recognition of these associations.

SPACE-TIME INTERACTIONS

Enough has been said now to establish the existence in these data of concentrations of incidence both in space and in time. If space and time are considered

TABLE IV
LYMPHOBLASTIC LEUKAEMIA, BY AGE AT ONSET AND SEASON

Age at Onset (yrs)		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total
Season of Onset	May-October	9	8	12	16	6	8	5	3	4	3	3	2	1	1	3	84
	November-April	2	5	6	7	6	4	6	4	3	1	5	2	2	0	2	55
Summer:Winter Ratio		59:30 (5 yrs and Under)						25:25 (6 yrs and Over)									

TABLE V
SEASON AND YEAR OF ONSET IN CASES OF LYMPHOBLASTIC LEUKAEMIA UNDER AGE 6

Year of Onset		1951	'52	'53	'54	'55	'56	'57	'58	'59	1960	Total
Season of Onset	May-October	8	5	5	2	3	5	3	6	8	3	48
	November-April	3	1	3	3	3	1	0	3	1	2	20

jointly as a three-dimensional block of space-time with co-ordinates of time, latitude, and longitude, and if incidence (occurrences related to the population at risk) is represented within the volume of the block, it follows that there must be some unevenness. The presence of these concentrations in space-time follows inevitably from what has already been demonstrated, even though the two concentrating factors appear to be independent of each other and to operate upon different groups of cases.

The further question arises whether the space and time concentrations show any interactions, in other words whether spatial concentrations move about in the time dimension or, what amounts to the same thing, whether time concentrations exhibit out-of-phase patterns in different geographical areas. The apparent independence of the two factors so far demonstrated makes it unlikely that we shall find an interaction in cross-pairs from the groups separately affected by them, but there is still room for interactions within these groups.

First a computer analysis of the data for the total of 185 cases was carried out. There was no evidence of an interaction. However, this large number of pairs consists largely (approximately half) of non-informative cross-pairs between the two main groups already distinguished in terms of cytology, age, season, and address and it is quite possible that informative pairs could be difficult to distinguish against this background. We can use the language of communications and postulate an adversely affected signal:noise ratio. Separate analyses of different sub-groups were therefore carried out.

Negative results were obtained for the following groups of pairs:

(a) Pairs within the group of myeloblastic leukaemia, including monocytic, at all ages;

(b) Pairs within the group of lymphoblastic leukaemias, including undifferentiated leukaemia, of 6 years or older;

(c) Cross-pairs between the groups of lymphoblastic leukaemia over and under 6 years old.

By contrast, positive results were obtained from various groupings of children affected before the 6th birthday. This consisted of an excessive number of pairs showing short distances and short times. The excess was evident over a range of times and distances up to about 2 months and 2 km. but was more evident as the upper limits of time and distance were reduced. Table VI gives one of these tabulations showing an excess at distances less than 1 km. and less than 60 days. This Table does not represent too contrived a maximization. All but one of the ten children in the five close pairs had lymphoblastic

TABLE VI
96 CASES OF LEUKAEMIA UNDER 6 YEARS OLD, OF ANY CELL TYPE, ABNORMAL KARYOTYPES EXCLUDED

Distances Apart (km.)		0-1	Over 1	Total
Time Apart (days)	0- 59	5	147	152
	60-3651	20	4,388	4,408
Total	25	4,535	4,560

Expected < 1 km. and < 60 days = 0.79
Poisson probability of 5 or more, < 1/750

leukaemia, all were under 4 years old, all had summer onset, and none had been irradiated, thus affording scope for further maximization of the discrepancy through selection of the group examined and the upper limits accepted. Because of the differing mean distances between urban-urban, urban-rural, and rural-rural pairs, re-analysis of each kind of pair was carried out, but without challenging the general conclusion. The question of statistical significance is complex and has been discussed in general elsewhere (Knox, 1963), but at this level of asymmetry of tabulation the five independent (in fact) pairs can probably be regarded as a Poissonian variable and the result is then highly significant.

The actual times and distances between these five close pairs in the under-6 age group were 53 days and 0.2 km.; 43 days and 0.8 km.; 5 days and 0.7 km.; 18 days and 0.4 km.; 36 days and 0.2 km. The months of onset were respectively May-June; July-August; September-September; October-October; September-October. In no case did the members of a pair have the same general practitioner, and indeed the ten children had ten different doctors. These five pairs, although a very small proportion of all possible pairs, involved ten children, a substantial proportion of the 96 in the affected group. Since the end of this investigation we have seen another close pair, a time of less than a month, a distance of about 0.2 km., both in young children with lymphoblastic leukaemia and both with summer onset.

OTHER FACTORS

The whole group of leukaemias was examined with respect to other factors recorded, particularly with a view to finding any confirmatory differentiations between the leukaemia groups already separated, but little was found.

There was no clear differentiation in terms of the sex of affected children.

Maternal and paternal ages were respectively 27.9 and 30.9 at delivery for children under 6 years (excluding the mongols) and 26.2 and 28.8 for those over. These means differ neither between the groups nor from the population means.

Of 78 children under 6 (excluding mongols) with a record of birth rank, 29 (37.2 per cent.) were first children. Of the 51 children of 6 or over with a record of birth rank, 21 (41.2 per cent.) were first children. These proportions differ significantly neither from each other nor from the population proportions. More detailed analysis by finer age groups revealed nothing significant.

Children under 6 years had birth weights recorded in 71 instances and the mean was 7 lb. 6.5 oz. Children affected after the 6th birthday (41 recorded) weighted 7 lb. 11.2 oz. The difference is largely accounted for by the four twins in the first group and is probably not significant.

Birth dates were examined for a seasonal variation. This was recorded precisely in 166 cases. There was no suggestion of a regular cycle and the maximizing dichotomy was June–November:December–May with 70 and 96 respectively, not a difference which can be considered significant. Interactions between the month of birth and month of onset, and between the month of birth and age at onset were sought and not found.

Fathers' occupations, which were recorded sufficiently well for classification in 125 cases, followed a social class distribution not grossly different from the regional distribution. There was, however, some difference in detail between the "5 and under" and the "6 and over" age groups. Eight of the 56 older children (14 per cent.) and eighteen of the 73 younger ones (25 per cent.) had fathers who were miners or agricultural workers. This is probably a reflection of the different urban-rural distributions of the two groups.

DISCUSSION

The seasonal distribution demonstrated in this study corresponds well with the pattern demonstrated by Lee (1962). Lee's data were obtained from National Cancer Registrations, which achieve only a partial ascertainment, and the results were therefore suspect in that completeness might, for some reason, have varied with the season. The present data are largely independent of Lee's. Although some cases were registered under the Cancer Registration Scheme, local registrations of leukaemia were in fact very incomplete during the period of the study. As well as affording mutual confirmation of the cycle, the two sets of data agree remarkably in detail, with June the highest month in both distributions and July showing a concordant dip in the middle of the summer excess.

Steinberg (1960) gives recent figures for seasonal distributions of onset in New England, U.S.A. He

uses χ^2 with 11 degrees of freedom to assess significance and his negative conclusion is due partly to the statistical inefficiency of this method. Dichotomy of the year as in the present study (May–October: November–April) gives 242 and 207 cases respectively. This is not in itself significant, but the pattern is sufficiently like the present one, and like Lee's, to have made sub-division by cell type and age group of some interest.

A difference of the present study from Lee's analysis is that age as well as type of leukaemia, appears to be correlated with the presence of the cycle. In the northern data the cycle was evident up to about the 6th birthday and not beyond. Lee does not give a detailed breakdown by month and age, but quarterly percentages of onsets seem to indicate a more widespread age distribution of the cycle in the national data. The failure to demonstrate the pattern in our own older patients may be in part a question of small numbers, but variations of diagnostic criteria and their interaction with age may play some part.

Both the national and regional data agree in showing that the seasonal variation has been evident at least since 1951 in a fairly regular annual pattern.

Calculation of rates for the large towns of 50,000 population and over, together with those in the conurbation of Tyneside, showed an excess of cases compared with the other areas. Again this showed differences according to age and the type of leukaemia, and it was especially evident in those groups not subject, in our data, to the seasonal cycle.

An urban-rural difference has been noted before. Stewart, Webb, and Hewitt (1958) found it in England and Wales in the years 1953–55, although within this pattern the rates (deaths) in towns of 50,000 to 100,000 inhabitants were greater than in the very large towns and conurbations. Meadors (1956) found it in death rates in the U.S.A. in 1944–48. His result is of particular interest because, among the childhood cases, the urban-rural ratio of rates per million changed with age; in the successive age groups 0–4, 5–9, and 10–14, the ratios were 1.28, 1.44, and 1.59. This pattern is analogous with our own results and confirms differentiation in terms of geographical distribution between younger and older children. Stewart and others (1958) did not analyse their results in terms of age at death or at onset, and neither they nor Meadors analysed them according to the cytological type of leukaemia.

The search for interactions produced one positive result. In the children under 6 years old, those especially affected by lymphoblastic leukaemia and by the seasonal cycle, there were five very close pairs, closer than 60 days in their dates of onset and closer than 1 km. on the map. As the proportionate

expected value was 0.79 pairs, the observed figure which is seven times this may probably be considered statistically significant. Nine of the ten children had lymphoblastic leukaemia, they were all young children of 4 years or less, and all had summer onset. It is probable that the clustering factor is a genuine one and is due to a factor closely associated or identical with that responsible for the seasonal factor.

Pinkel and Nefzger (1959) also described space-time clusters in childhood leukaemia in Buffalo, N.Y., but did not separate space-clustering from time-clustering from space-time interactions. Their tests of significance were negative and it is doubtful whether their definition of a close pair as one within 2 years and one-third of a mile is accurately justified. In their paper they give positions on a map and serial numbers, although not dates. Some re-analysis has proved possible. A centimetre grid was placed over the map as published, references calculated on this basis, and a standardized form of dating achieved simply by successive labelling of the 95 cases in Buffalo as dates 1 to 95. The results are presented in Table VII; the main suggestive finding was the occurrence of eight time-adjacent pairs (*i.e.* a serial difference of one) closer than 1 cm. on the map (approximately two-thirds of a mile on the ground) against an expected value of 4.6. Sub-analysis of particular age groups and cell types would be worth while in this series.

Specific interpretation of the nature of the clustering is not yet possible. The seasonal factor, the clustering effect, the known virus aetiology of leukaemia in animals (*e.g.* see Syverton and Ross, 1960), and the production of leukaemia in mice by injection of filtered extracts of tissues and blood from leukaemic patients (Bergol'ts, 1959), together suggest very strongly that a virus infection may operate in the acute lymphoblastic leukaemias of the younger children. However, there are several other possible interpretations and there is no real suggestion from our results that leukaemia was transmitted from one case to another, only that two cases may sometimes have a common source. This could be interpreted variously as a toxic rather than an

infective agency, spread through atmospheric pollution, or contamination of food or water supplies, or as a result of direct contact with toxic weed killers, paints, solvents, and other poisonous materials, and so on. Moreover, the risk of exposure to many of these hypothetical factors might also be seasonal.

If the factor were an infective or toxic agent, effective following a short exposure, we must consider the likely length of the latent interval before the appearance of the first symptom. We can infer, because the seasonal variation is discernible in children of less than one year old, and certainly of less than 2 years, that the latent period may be less than one year. This is less than the latent period following large doses of radiation in adults, namely 3 to 5 years (Court-Brown and Doll, 1957). On the other hand, the nature of the disease makes a very short interval unlikely, and a possible range of, say, 6 to 18 months is perhaps as accurate a guess as is possible. The exact season of operation and therefore the nature of the seasonal factor are quite uncertain.

The effect could of course represent simply a seasonally correlated effect upon the rate of development of the pathological process in the pre-symptomatic phase, or even an artefact related to recognition or parental memory, rather than an event of aetiological significance. However, the interaction effect is less easily explained in this way and the suggestion that both the interaction and the seasonal variation are common manifestations of a single factor has a bearing on the interpretation of the latter. A seasonally distributed and clustered event of short duration, that is a trigger mechanism, seems a more likely explanation.

This point may be important in relation to either of two recently demonstrated features of childhood malignant disease. The first is the recently described geographical concentration of malignant lymphoma in African children and the suggestion that its distribution corresponds with that of the tsetse fly or some other biting arthropod, and therefore that the tumour may be infective in origin. The question of an insect vector in England is interesting, but would be

TABLE VII
ANALYSIS OF DATA OF 95 CASES IN BUFFALO, N.Y.
(Pinkel and Nefzger, 1959)

Map Distance (cm.)	<1	-2	-4	-8	>8	Total
Adjacent Cases	8 (4.6)	5	28	47	6	94
1 to 4 Intervening Cases	20 (18.1)	35	118	170	23	366
5 to 8 " "	14 (17.3)	34	101	182	19	350
All Possible Pairs	221	445	1,423	2,094	282	4,465

Expected numbers in parentheses.

1 cm. on map is approximately $\frac{1}{3}$ of a mile.

very difficult to investigate until we have some idea of the seasonal phasing of the supposed trigger event.

The second is the demonstration by Stewart and others (1958) that severe respiratory infections are unduly frequent in the 2 years preceding the onset of leukaemia, particularly those infections for which antibiotics were given. Stewart and her colleagues interpreted this association in an indirect manner, but the possibility of a direct effect of an infective organism, or of anoxia, or of the drugs used is not disproved.

The question of social class differences in the leukaemias of childhood is a vexed one and different studies have produced different results. Stewart and others (1958) found none. On the other hand, Pinkel and Nefzger (1959) found an interesting difference in the U.S.A. between the social groups of older and younger affected children. Our own data are inconclusive in terms of the overall social class distribution, but showed differences in detail between older and younger children analogous with the American data; both results could be secondary to different geographical distributions at different ages.

The maternal age effect reported by Stewart and others (1958) was not present in our data. A possible explanation of the difference might be under-reporting of mongolism in their series. Their reported incidence of sixteen mongols among 677 leukaemias is considerably less than our own—nine, or possibly ten, among 185.

SUMMARY

There were 185 clinical onsets of leukaemia in children under 15, in Northumberland, Durham, and on Tees-side, in the 10 years 1951 to 1960. Their distribution in space and time showed evidence of (a) a seasonal variation with a summer peak, and (b) a high risk in children living in the larger towns. These two factors appeared to affect different groups of cases and to be independent of each other, the seasonal variation affecting especially the lymphoblastic leukaemias in younger children, the large-town concentration being evident only in the myeloblastic leukaemias and in the lymphoblastic leukaemias of children over 6 years old. There was, in addition, evidence of a clustering factor, a space-time

interaction, affecting the lymphoblastic leukaemias of young children, such that pairs of cases occurring within 60 days and within 1 km. of each other were unduly frequent. The data suggest that the seasonal variation and the clustering effect may be common properties of a single factor.

The series showed a high incidence of leukaemia in mongols. There was a variation between the occupational groups of younger and older affected children which was probably secondary to the urban-rural distributions. Apart from the association with mongolism there was no evidence of maternal age or birth rank variations of risk.

The findings suggest further heterogeneity in the epidemiology and possibly the aetiology of childhood leukaemias, and particularly in the case of younger children suggest exposure to a seasonally variable factor which tends to be localized both in space and in time.

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APPENDIX

List of Hospitals

Bishop Auckland General Hospital.
Dryburn Hospital.
Fleming Memorial Hospital.
Ingham Infirmary.
Middlesbrough General Hospital.

Newcastle General Hospital.
Preston Hospital.
Queen Elizabeth Hospital.
Royal Victoria Infirmary.
Shotley Bridge General Hospital.

South Shields General Hospital.
Stockton Children's Hospital.
Sunderland Children's Hospital.
Walkergate Hospital.
West Hartlepool General Hospital.