SPACE-TIME CLUSTERING IN INFECTIOUS MONONUCLEOSIS

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A good deal of work has been published in recent years on tests of space-time clustering applied to diseases of possible but unproved infectiousness. In particular, they have been used to test evidence suggestive of the infectivity of neoplastic conditions such as leukaemia and Burkitt's lymphoma. It seemed to us worth reporting the following rather unexpected results, obtained during a study of infectious mononucleosis in South London, in view of the apparently close immunological relationship of this disease to Burkitt's lymphoma, as demonstrated by the repeated appearance of Epstein Barr antibodies (Henle, Henle, and Diehl, 1968; Niederman, McCollum, Henle, and Henle, 1968). The aetiology of infectious mononucleosis is not known and, according to Pollock (1969) there are few well authenticated accounts of epidemic spread, but it would have been reasonable to expect space-time clustering of the kind reported for Burkitt's lymphoma by Williams, Spit, and Pike (1969) and Morrow *et al.* (1971) if there was any similarity in the epidemiology of the two diseases.

METHODS

An attempt was made to detect all cases of infectious mononucleosis occurring during a 15-month period within the catchment area of St. George's Hospital, London S.W.17. This area corresponds to 16 municipal wards of two Greater London boroughs; the population of the area at the 1966 10% sample census was 238,250. Cases of

infectious mononucleosis were detected in three ways—admission to hospital, notification by general practitioners, and requests to the hospital haematology laboratory for diagnostic blood tests. Between 3 November 1969 and 2 February 1971, 97 cases of infectious mononucleosis occurred within the catchment area. The clinical features were typical in every case and, with a single exception, all patients had positive Paul-Bunnell-Davidsohn tests. After the diagnosis had been established, each patient's home address was accurately pin-pointed on an Ordnance survey map of the area. Ninety-two patients were visited at home and the date of onset of illness was determined precisely: it was not possible to visit the remaining five patients, and in these instances the date of onset was known only approximately. The accuracy of this study depended to a large extent on the successful monitoring of all cases of infectious mononucleosis within the catchment area, and we cannot be absolutely confident that case detection was complete. However, the observed annual incidence, 3.2 cases per 10,000 population, is similar to that quoted for other areas of the United Kingdom (reviewed by Pollock, 1969) so it is unlikely that many cases reaching medical attention were missed.

RESULTS

The results of the study are summarized in the Table which shows the distribution of space and time intervals of all the 92 serologically and clinically confirmed cases. From the mean values in the

TABLE
DISTANCES AND TIME INTERVALS BETWEEN ALL PAIRS OF CASES

Distances (metres)	Time (days)											Mean Time Intervals
	< 35	35-69	70-104	105-139	140-174	175-209	210-244	245-279	280-314	315-349	> 350	
> 1800	462	429	404	360	324	308	230	206	120	111	163	148.6
1600-1800	27	24	17	12	20	11	19	7	6	6	10	150.1
1400-1600	20	15	22	15	11	14	12	15	10	9	11	170.6
1200-1400	22	19	22	22	20	10	14	8	6	11	8	155.0
1000-1200	21	11	15	15	15	18	14	7	5	9	12	170.2
800-1000	23	24	30	13	18	12	10	12	5	9	5	142.3
600-800	20	11	11	16	11	7	11	6	5	1	16	165.8
400-600	12	6	9	9	10	4	9	7	5	7	3	167.8
200-400	8	12	5	5	9	8	5	6	0	3	3	149.5
0-200	1	2	6	6	2	2	2	1	1	1	2	164.2
Same household	0	1	2	0	1	1	0	0	0	0	0	107.8
Mean distances	306.5	321.1	309.7	309.6	305.2	314.0	299.2	300.1	311.9	258.8	267.3	

margins it can be seen that there is a tendency for the distance between cases to decrease as the time interval between them increases and a corresponding tendency for neighbouring cases to occur further apart in time.

The statistical significance of the results can be conveniently assessed by Mantel's (1967) test which gives directly the mutual regression coefficients of the time and space distances and their standard errors, which are:

$$\left. \begin{array}{l} \text{Distance on time} \quad -0.043 \pm 0.019 \\ \text{Time on distance} \quad -0.096 \pm 0.043 \end{array} \right\} P \sim 0.04$$

(The national grid co-ordinates and Julian Days of occurrence of the cases can be obtained from the authors.)

DISCUSSION

The simplest explanation of the negative relation between time and distance is that it is a statistical artefact as tests of significance are likely to be misleading about 5% of the time. This possibility is supported by the fact that Barton, David and Merrington's (1965) test gave no statistically significant indication of departures from random association.

It appears nevertheless that there is no evidence at all for clustering such as might be expected in a disease which has almost certainly an infectious mode of transmission. Barton *et al.* (1965) have reported highly significant clustering in poliomyelitis, whose epidemiology has some points in common with mononucleosis, but these results were obtained during an epidemic period. An inter-epidemic or winter period would probably have given a better comparison. It would be of interest to try a cluster analysis on data of this kind to see whether the curiously inconsistent results of clustering techniques applied to leukaemia also occur in poliomyelitis and other diseases of established infectious origin but low contagiousness.

We have not been able to think of any plausible hypothesis which would explain the apparent 'negative' infectiousness of mononucleosis and would

regard this as an accident of sampling unless it is confirmed by subsequent investigation.

SUMMARY

Tests of space-time clustering applied to infectious mononucleosis showed no evidence of infectiousness but instead a statistically significant tendency for cases occurring near in time to be distant in space and vice versa.

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