A TEST FOR SPACE CLUSTERING AND ITS APPLICATION TO CONGENITAL LIMB DEFECTS IN CARDIFF

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Several methods are currently available for investigation of low intensity space-time clustering (Knox, 1963, 1964; Ederer, Myers, and Mantel, 1964; David and Barton, 1966; Mantel, 1967; Pike and Smith, 1968.) Its presence usually indicates one of two causes—either an infection or a causal factor which is local in both time and space and experienced by each individual in the cluster. There are, however, other situations in epidemiology where the effect of either time alone or space alone is localized. An annual cyclic trend is an example of the former; similarly, a condition localized only in space could exist without 'outbreaks' in the time period concerned. Admittedly if another time period in the same area were to be considered the spatial clusters might no longer exist, and in this sense we may still be considering the space-time problem. However, the main interest in this paper is a pattern in which the time component of clusters is so small that it becomes irrelevant to the analysis.

The study of spatial patterns of a disease in a given area necessarily involves the population at risk. The problem is trivial if the number of cases is large and the area already divided into well-defined sub-areas whose populations are known. Analysis and subsequent interpretation is difficult when the number of observed cases with the disease is relatively small, yet on visual inspection there appears to be spatial clustering. Notified limb defects (syndactyly, polydactyly, and reduction deformities) born in Cardiff between 1964 and 1966 exhibited these characteristics, and this paper presents the outcome of their analysis, primarily in respect of spatial clustering, but also with brief reference to time-clustering and space-time interaction.

SOURCES OF DATA

For the three years beginning 1 January 1964 information was collected on all infants born to women resident in two counties in South Wales (Glamorgan and Monmouthshire) and on all the congenital defects identified in that population. The notification of congenital defects was received from

four sources—birth notification cards, congenital defect notification forms received from various consultants, hospital diagnostic records, and still-birth and death registrations. More detailed descriptions of the method and the results of preliminary investigations can be found elsewhere (Richards and Lowe, 1971).

Although it would be unrealistic to consider all limb defects in isolation (because of their frequent coexistence with other malformations and skeletal deformities) there is a group of defects usually confined to the limbs which, although not necessarily of major clinical importance, is of considerable interest in the context of embryology and human physiology. This group consists of polydactyly, syndactyly, and reduction deformities. We decided to investigate all such defects born in Cardiff during the period of the survey (Table I). For clarity of analysis only the data from singleton births ($n = 14,451$) have been used. At the time of the survey Cardiff had a population of around 250,000 living within an area of approximately 36 square miles (93 km²).

RESULTS

DISTRIBUTION IN SPACE

The distribution of the population at risk within the study has to be considered before the observation of apparent spatial clustering on visual inspection alone can be interpreted. In the present study, for example, the population at risk (total births) was found to cluster in space because of variable

TABLE I
CATEGORIES OF LIMB DEFECTS (CARDIFF BIRTHS 1964-66) USED IN SPACE-CLUSTERING ANALYSIS

No. of singleton births 1964-66					14,451
No. of limb defects (singletons only)					
Syndactyly	..	..	..	..	35
Polydactyly	..	..	..	..	16
Reduction deformity	..	..	..	..	6
Total	..	..	..	..	57

TABLE II
FREQUENCY DISTRIBUTION OF ALL POSSIBLE PAIRS (LIMB DEFECTS AND RANDOM SAMPLES) BY DISTANCE

	Distance in 100 Metres (d)						Total
	$d < 1$	$1 \leq d < 2$	$2 \leq d < 3$	$3 \leq d < 4$	$4 \leq d < 10$	$d \geq 10$	
Limb cases	5	11	12	12	73	1,483	1,596
Random sample 1	6	4	4	12	97	1,473	1,596
Random sample 2	2	5	8	10	106	1,465	1,596
Random sample 3	5	7	8	6	115	1,455	1,596
Random sample 4	2	5	6	16	76	1,491	1,596
Random sample 5	0	5	4	11	117	1,459	1,596

population density and fertility. We overcame this problem by taking repeated sets of random samples from the pool of all singleton births in Cardiff for the same time period, the size of each sample being equal to that of the limb defects series (i.e., $n = 57$). X and Y coordinates were then estimated to the nearest 10 metres by the address of the mother for each limb defect case and each random sample subject. The distribution of distances for all possible pairs was then obtained for each set of cases as in Knox's method (Knox, 1963, 1964) and the number of pairs within various distance criteria for the limb defects was compared with the mean number of pairs satisfying the same criteria from the random samples. Significant values were calculated assuming that the null distribution is Poisson with this mean.

A difficulty at this stage was the absence of a basis on which to establish what critical values should be used for analysis. We decided to examine the distribution of distances for limb defects and five random samples by various intervals (Table II). For the intervals of 100 up to 200 m and 200 up to 300 m the number of pairs for limb defects is greater than any of the random samples, and the intervals either side of these suggest a somewhat diluted version of the same effect. This excess number of pairs of limb defects for 100 up to 300 m has been 'made up' in the interval of 400 up to 1,000 m by a deficiency of pairs for limb defects.

TABLE III
NUMBERS OF PAIRS BY CRITICAL DISTANCES AND SIGNIFICANCE VALUES (ASSUMING POISSON)

	Distance in 100 Metres (d)			
	$d < 2$	$d < 3$	$d < 4$	$d < 5$
Limb cases	16	28	40	48
Random sample 1	10	14	26	38
Random sample 2	7	15	25	45
Random sample 3	12	20	26	39
Random sample 4	7	13	29	36
Random sample 5	5	9	20	30
Mean of random samples	8.2	14.2	25.2	37.6
(Sample variance)	(6.2)	(12.6)	(8.6)	(23.4)
P	0.015	0.0001	0.0008	0.046

Table III gives the number of pairs less than specified distances derived from the figures in Table II. An attempt was made to give significance values to the observed number of limb defect pairs. A critical value of up to 300 metres gives the most significant result although other values in the table are also significant. The appropriateness of the Poisson distribution used here cannot be tested properly without further random samples to test the goodness of fit; this was not done in this study as the process of finding X and Y coordinates for a further series of addresses in Cardiff would have been too time-consuming without computerization. However, the sample variances give no evidence to suggest that the stated significance levels are unduly high as the variances are all smaller than the corresponding sample means.

DISTRIBUTION IN TIME

Knox (1964) has formulated a null distribution of time intervals for independent observation of pairs in a given time period. As all possible pairs cannot be considered as independent observations, a Monte Carlo procedure similar to the one used to determine the above spatial distribution was used, i.e., repeated sets of 57 dates were picked at random from the three-year period and the distribution of time intervals for all possible pairs of limb defects (by the date of last menstrual period) was compared with that of random samples in a similar manner to that for spatial distribution.

Table IV gives the distribution of time intervals of all possible pairs for limb defects and random samples. The numbers of pairs for various time intervals predicted by Knox's procedure (triangular distribution) are also given and they correspond very well to those predicted by the Monte Carlo procedure. The findings provide no evidence for clustering in time.

SPACE AND TIME INTERACTION

Finally, a brief analysis was made of space-time interaction using Knox's method to see if those pairs close in space were also close in time.

TABLE IV

FREQUENCY DISTRIBUTION OF ALL POSSIBLE PAIRS (LIMB DEFECTS AND RANDOM SAMPLES) BY TIME INTERVALS

	Time Interval (t) in Days						
	0-10	11-20	21-40	41-80	81-160	161-320	321+
Limb cases	34	21	41	106	211	374	809
Random sample 1 ..	33	26	51	120	199	320	847
Random sample 2 ..	27	28	45	123	220	402	751
Random sample 3 ..	35	23	54	104	211	362	807
Random sample 4 ..	36	25	62	114	213	405	741
Random sample 5 ..	23	24	56	118	218	413	744
Mean of random samples	30.8	25.2	53.6	115.8	212.2	380.4	778.0
Prediction by Knox's formula	30	29	57	110	207	364	799

TABLE V

FREQUENCY DISTRIBUTION OF ALL POSSIBLE PAIRS OF LIMB DEFECTS BY SPECIFIED TIME AND DISTANCE INTERVALS

Time in days	Distance in 100 Metres (d)				Total	% less than 500 metres
	$5 \leq d$	$5 < d \leq 10$	$10 < d \leq 20$	$d > 20$		
0-80	10*	7	24	161	202	5.0
81-160	8	8	32	163	211	3.8
161-320	12	16	58	288	374	3.2
321 and over	22	30	118	639	809	2.7
Total	52	61	232	1,251	1,596	3.3
% less than 80 days	19.2	11.5	10.3	12.9	12.7	

* Expected No. 6.6; $P = 0.1$
Finer intervals less than 80 days and 500 m were also considered, but it was decided to combine these intervals as the entries were so sparse.

Table V gives the distribution of all possible pairs of limb defects by specified time and distance intervals. Here again we have no prior knowledge of the critical values and it is necessary to look at various combinations of time and space intervals. The proportion of pairs less than 80 days for various distance intervals suggests an interaction, and so does the proportion of pairs less than 500 metres for various time intervals. By Knox's method, however, none of the combinations of critical values gave significant results—the smallest P value of 0.1 by permutational approach was obtained when $d = 500$ metres and $t = 80$ days. The P value for this combination obtained by Poisson distribution with the mean of 6.6 ($202 \times 50/1596$) was also approximately 0.1.

DISCUSSION

The cause of the spatial clustering observed in this study is not immediately obvious, and the test itself cannot distinguish between genetic and environmental causes of the phenomenon. Environmental factors related to socio-economic status (e.g., housing and income) are an unlikely explanation

of the observed distribution since although the controls were not matched for social class, there was no evidence of any association between social class and limb defects (Table VI).

It is said that polydactyly is common in Africans (Norman, 1963; Stevenson, Johnston, Stewart, and Golding, 1966). Polydactyly alone and syndactyly alone can occur in families, and in such cases the mode of inheritance is generally thought to be a simple dominant gene. But sporadic cases of both

TABLE VI
LIMB DEFECTS (CARDIFF 1964-66) BY SOCIAL CLASS

Social Class	Number Observed	Rates per 1,000 Births
I and II ..	9 (7)	4.8
III ..	29 (33)	3.5
IV and V ..	16 (14)	4.6
Unknown ..	3 (3)	3.6
Total	57	3.9

N.B. The numbers in parentheses are expected numbers, assuming there is no relationship by social class.

$$\chi^2_{[3]} = 1.34 \text{ NS}$$

(particularly the former) are not at all uncommon (Stevenson *et al.*, 1966) and in such cases the genetic contribution is unknown.

We traced 41 of the 57 notified cases and 21 (51%) reported a family history of limb defects. Eight mothers reported that the child's ethnic origin was non-European. It was also stated that five of the 16 cases of polydactyly came from one general practitioner's list. At the time of the study there were approximately 130 general practitioners in Cardiff and if we assume that their list sizes were the same the likelihood of this happening by chance alone is approximately 1 in 50,000. Although none of the five cases was born within 500 metres of each other, four out of the five reported a family history of limb defects. It therefore seems likely that the findings observed in this study are caused by ethnic factors, since families with similar genes, religions, and other common interests are more likely to live close to one another than those with no ethnic ties.

SUMMARY

Visual inspection of the distribution of place of residence of infants with limb defects born in Cardiff between 1964 and 1966 suggested spatial clustering. The problem of determining, in some systematic way, whether these apparent spatial clusters could have arisen by chance was approached as follows. Five sets of random samples of births were taken (each of the same size as the limb defects group) and the number of pairs less than 200 metres, 300 metres, 400 metres, and 500 metres apart were calculated for the limb defects group and for each of the random samples. A significant value was given to the observed number of pairs of limb defects satisfying each of the critical distances, assuming that its null distribution is Poisson with a mean estimated by the mean number of pairs of random samples satisfying the same critical distance. For all the values of critical distances the test was significant.

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