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An investigation of space and space-time clustering in a large sample of infants with neural tube defects born in Cardiff

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Roberts, C. J., Laurence, K. M., and Lloyd, S. (1975). *British Journal of Preventive and Social Medicine*, **29**, 202-204. **An investigation of space, and space-time clustering in a large sample of infants with neural tube defects born in Cardiff.** Altogether 406 infants with neural tube defects born in Cardiff between 1956–71 were investigated for evidence of space-time clustering and 100 similarly affected infants, together with matched controls born in Cardiff between 1964–66 were investigated for evidence of spatial clustering. No evidence of excessive prevalence in either dimension was observed.

There have been several reports of subjective impressions of spatial clustering in small communities—in particular those of Polman (1951), Pleydell (1960), Boris *et al.* (1963), Laurence, Carter, and David (1968), and Flynt (1970). Recently Aylett, Roberts, and Lloyd (1974) reported statistically significant spatial clustering among 18 infants born over a five-year period in the small country town of Corsham, UK. The authors concluded that their findings implied the existence of some environmental influence over the spatial distribution of neural tube defects, but they did concede that their observations might just possibly have been the one in a thousand chance predicted by statistical analysis. An important piece of evidence in support of such an environmental influence would be the confirmation of this observation in a different population. To this end, we investigated space, and space-time clustering of neural tube defects using two substantial sources of data—the South Wales Malformation Study (Richards and Lowe, 1971), and the South Wales Neural Tube Defects Register which Laurence began in 1956.

Material and Methods

Cardiff has a population of about 250 000 who live within an area of approximately 93 square kilometres and have some 4500 births per annum.

In 1956 Laurence established a register of children with neural tube defects, and for the period 1956–71 406 infants thus afflicted were registered as domiciled in Cardiff at the time of their birth. The investigation of space-time epidemicity was based on these 406 cases. We were able to locate the house of each case and, with the use of 1 inch to 35 yards scale Ordnance Survey maps kindly provided by the Highways Office of the City Surveyors Department, Cardiff City Corporation, allocate to it an eight figure map reference. The distribution of all possible pairs of neural tube defects by specified time and distance intervals was then examined using Knox's method (1963).

For the years 1964–66 the South Wales Malformation Study collected information on all infants born to women resident in south Wales (including Cardiff) and on all congenital defects identified in that population. There were 14 451 births in Cardiff during this period of which 100 had neural tube defects. The investigation of spatial epidemicity was based on these 100 cases. For each, the following information was collected—birth date, place of birth, maternal age, parity, address at time of birth, and father's occupation. Five controls were then matched against each index case for maternal age, parity, social class, and time of birth. Eight figure map references were allocated (as above) to the house of each of these 100 children and to that of

each of their 500 matched controls. The distribution of all possible pairs of cases by specified distance criteria was calculated and this was compared with the mean number of pairs from the control samples satisfying the same distance criteria (Lloyd and Roberts, 1973).

Results

Table I shows the distribution of all possible pairs of neural tube defects by specified time and distance intervals. Since we had no prior knowledge of the critical values, it was necessary to look at various combinations of time and space intervals. For anencephalus, only one space-time interval (2000 m and 300 days) out of a possible 18, showed any evidence of a significant difference between observed and expected values and this was only at the 5% level. None of the intervals showed a significant difference for spina bifida; and for all central nervous system malformations only one interval (2000 m and 300 days) was significant, again at the 5% level. There is really no evidence that neural tube defects cluster together in space and time.

The number of pairs less than specified distances derived from the frequency of all possible pairs of neural tube defects, and from the mean of the matched control samples is shown in Table II. Significance values were calculated for the various distance criteria assuming that the null distribution was Poisson. For none of the specified distance did the number of pairs observed differ significantly from the expected number derived from the control samples. There is, therefore, no evidence of spatial clustering.

Discussion

This investigation failed to detect any evidence of space-time interaction as did the previous studies of Trichopoulos *et al.*, (1971), Fedrick and Wilson (1971), and Siemiatytki and McDonald (1972).

There would now appear to be a substantial body of evidence which suggests that neural tube defects do not behave in a manner normally associated with an infectious disease.

After the report of a significant spatial clustering of neural tube defects in Corsham (Aylett *et al.*, 1974), it was disappointing to find no evidence of similar behaviour amongst the Cardiff births. Re-examination of Aylett's original data, however,

Table I

FREQUENCY DISTRIBUTION OF ALL POSSIBLE PAIRS OF NEURAL TUBE DEFECTS BY SPECIFIED TIME AND DISTANCE INTERVALS
CARDIFF BIRTHS (1956–71)

d	t	No. of Pairs Observed		
		Anencephalus (n = 167)	Spina Bifida (n — 168)	All Neural Tube Defects (n — 406)
5	100	16	10	85
	200	24	24	161
	300	40	33	242
10	100	44	39	254
	200	76	67	463
	300	124	97	701
15	100	70	55	412
	200	136	103	804
	300	210	161	1203
20	100	95	80	587
	200	190	157	1179
	300	305*	244	1773†
25	100	129	112	810
	200	263	218	1615
	300	410	340	2452
30	100	174	150	1090
	200	352	286	2158
	300	548	447	3266

d = critical distance in 100 metres
t = critical time in days
* = expected number = 272 $P<0.05$ (assuming that the number
† = expected number = 1693 $P<0.05$ of pairs close in both space and time is normally distributed)
Based on data of last menstrual period

Table II

NUMBERS OF PAIRS BY CRITICAL DISTANCES FOR ALL NEURAL TUBE DEFECTS AND CONTROLS
CARDIFF BIRTHS 1964–66 (n = 100)

Distance (metres)	Control Samples						CNS Cases
	1	2	3	4	5	Mean	
Up to 200	43	27	30	27	36	32·6	33
200–399	87	78	66	75	86	78·4	58
400–599	92	89	80	88	102	90·2	83
600–799	104	99	124	94	115	107·2	90
800–999	127	104	102	101	136	114·0	115
1000–1999	628	705	584	749	760	685·2	651
2000–2999	902	960	841	922	1108	946·6	881
3000–3999	849	800	801	900	887	847·4	814
4000 and over ..	2118	2088	2322	1994	1720	2048·4	2225

revealed that one of his 18 cases was, in fact, the sib of a case already included in the study, and the claim that none of the study group was related was a mistaken one. The finding that two of the study subjects had the same address had important implications for the interpretation of any observed spatial clustering. The analysis was repeated using Aylett's original data but the sib of the index case was excluded. There was still significant clustering up to 100 m but the level of significance fell from 0·1% to 1%. The previous significant clustering observed at 250, and at 750 m had disappeared, but that at 1000 m remained, but at a reduced level (1% down to 5%). The observation reported by Aylett *et al.* (1974) could therefore have occurred by chance not once in a thousand but once in a hundred times.

The findings of the present investigation when considered with the revised calculations based on Aylett's original data suggest that the significant spatial clustering of neural tube defects observed by Aylett and his colleagues may well have been the one in a hundred chance predicted by statistical analysis. The optimism which that paper voiced concerning new evidence for an environmental influence on the spatial distribution of neural tube defects may, therefore, have been misplaced.

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