MALFORMATIONS OF THE CENTRAL NERVOUS SYSTEM IN GLASGOW

AN EXAMINATION OF THE EVIDENCE FOR CLUSTERING IN SPACE AND TIME

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THE BACKGROUND

As long ago as 1859, Del-Vesco reported an apparent cluster of anencephalic births in Italy. An examination of the recent literature shows that clusters of births with lesions of the central nervous system are still being described (Polman, 1951; Pleydell, 1960; Boris, Blumberg, Feldman and Sellers, 1963; Spellman, 1969; Flynt, 1970) although the evidence never appears to have been subjected to statistical analysis.

It has frequently been noted that the incidence of anencephalus, spina bifida, and hydrocephalus varies not only with year (Leck and Rogers, 1967; Rogers, 1969; MacMahon and Yen, 1971, among many others) but also with month of conception (Record, 1961; Laurence, Carter, and David, 1968; Elwood and MacKenzie, 1971) and area of residence of the mother (Penrose, 1957; Edwards, 1958; Stevenson, Johnston Stewart, and Golding, 1966).

When the dates of birth of infants who were stillborn or who died soon after birth with a malformation of the central nervous system in the city of Glasgow were compared with the names and addresses of the mothers, it became apparent that there was some subjective evidence for clustering of cases in both space and time. For example, a case of spina bifida was born in January 1965 and exactly nine months later a further case was delivered to another woman residing in the same house, and in another house a case of hydrocephalus was born in October 1964 and one of anencephalus just one month later. In addition, there were examples of women living in adjacent houses on the same street having infants with defects of the central nervous system within a very short time of one another. It

was therefore decided to ascertain the statistical significance of this association.

THE DATA

The names and addresses of all mothers giving birth to infants with malformations of the central nervous system who were stillborn or who died soon after birth between 1 January 1964 and 31 December 1968 were coded according to the street in which the mother lived.

Similar details for a random sample of approximately 5% of all Glasgow births occurring in the same period were provided by the Registrar General for Scotland. These cases were also coded according to the street in which the mother lived. A map of Glasgow was then divided into 28 areas using natural boundaries (e.g., rivers, canals, railway lines, etc.) with as little bias as possible (Fig. 1). Each

— rivers and canals - - - railway lines major roads
FIG. 1.—Diagrammatic representation of the areas of Glasgow

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street was then allocated to its own area. In the unusual event of a particular street being in two different areas, it was generally possible to ascertain from the map which houses were in which area.

In addition, the father's occupation was obtained for each case in the sample; this was coded into the social class groupings employed by the Registrar General for England and Wales (1966).

DISTRIBUTION IN SPACE

The numbers of births with each malformation in the various areas of Fig. 1 are compared with the distribution of the random sample (Tables I to III). It can be seen that the estimated incidence (obtained

The incidence of all three lesions in the British Isles has been shown to be correlated with social class, the lower the social class the higher the incidence (Edwards, 1958; Butler and Alberman, 1969). One would therefore expect there to be lower incidences of each type of malformation in those areas with a high proportion of parents of social classes 1 and 2. In fact, although this trend is apparent for each lesion (Table IV), the variation in incidence is only significant for the anencephalics ($\chi^2 = 16$; D.F. = 1; $P < 0.0001$).

TABLE II
VARIATION IN ESTIMATED INCIDENCE OF
SPINA BIFIDA WITHIN THE CITY OF GLASGOW

Area	No. Spina Bifida	No. Random Sample	Estimated Incidence
NA1	18	312	2.88
NA2	12	343	1.75
NA3 + 4	11	426	1.29
NB1 + 2 + 3	11	462	1.19
NB4 + 5 + 6	17	608	1.40
NC1	13	279	2.33
NC2	11	276	1.99
NC3 + 4	6	389	0.77
SA1	7	259	1.35
SA2 + 3 + 4	18	536	1.68
SB1 + 2 + 3	7	296	1.18
SB4	9	259	1.74
SC1 + 2 + 3 + 4	6	206	1.46
SC5 + 6	9	250	1.80
Total	155	4,901	1.58

$\chi^2 = 15$; D.F. = 13; $P = 0.2$.

TABLE III
VARIATION IN ESTIMATED INCIDENCE OF
HYDROCEPHALUS WITHIN THE CITY OF GLASGOW

Area	No. Hydrocephalics	No. Random Sample	Estimated Incidence
NA1	7	312	1.12
NA2	6	343	0.87
NA3 + 4	6	426	0.70
NB1 + 2 + 3	12	462	1.30
NB4 + 5 + 6	10	608	0.82
NC1	4	279	0.72
NC2	6	276	1.09
NC3 + 4	3	389	0.39
SA1	2	259	0.39
SA2 + 3 + 4	13	536	1.21
SB1 + 2 + 3 + 4	10	555	0.90
SC1 - 6	7	456	0.77
Total	86	4,901	0.88

$\chi^2 = 8.2$; D.F. = 11; $P = 0.7$.

$\chi^2 = 16$; D.F. = 14; $P = 0.3$.

by taking the population at risk to be 20 times that of the random sample) appears to vary greatly from area to area. Using a chi-squared goodness of fit test, however, one is unable to reject the hypothesis that the distribution of the malformed infants and the random sample are the same. When the data are combined, however, the variation of the total malformations of the central nervous system within area is significantly different from that expected by chance ($\chi^2 = 19.8$; D.F. = 11; $P = 0.05$).

TABLE IV
INCIDENCE OF LESIONS OF CENTRAL NERVOUS SYSTEM IN AREAS OF HIGH (MORE THAN 12% IN SOCIAL CLASSES 1 AND 2) AND LOW (LESS THAN 12%) PARENTAL SOCIAL CLASS

	Areas of High Social Class		Areas of Low Social Class	
	No.	Incidence	No.	Incidence
Anencephalus	46	1.80	248	3.42
Spina bifida	36	1.41	119	1.64
Hydrocephalus	19	0.75	67	0.92
No. of births in the random sample	1,275		3,626	

VARIATION WITH TIME

Numbers of cases are shown in Fig. 2 according to the month and year of birth. In order to ascertain whether the overall variation in the number of cases born each month (disregarding any trends) was other

FIG. 2.—Number of cases occurring in each month of each year.

than random, the distribution was compared with that expected using a random Poisson process (Table V). There were no significant differences between the observed and expected numbers.

When the years are combined (Fig. 3) it can be seen that for each malformation the greatest number of births occurred in the first quarter of the year. This, though, is also true to a certain extent for the births in the control sample. When tested, the differences between the distributions of each lesion and the control sample failed to reach significance.

CLUSTERING IN TIME AND SPACE

Several methods for testing the clustering of cases

FIG. 3.—Total number of cases occurring each month.

in time and space have been developed. The data in the present series were analysed according to the well-defined areas with natural boundaries already described rather than the actual spatial coordinates of each house. This policy was adopted because it was felt that if one was testing for the effect of a contagious disease, a distance of say 200 yards along a street was not equivalent to a distance of 200 yards across a river. The method of David and Barton (1966) for detecting clustering has therefore not been used for this analysis.

The method developed by Ederer, Myers, and Mantel (1964) to examine the clustering of cases of leukaemia in Connecticut over the period 1945–59 has been adapted for the present series. Using this method, we consider the number of cases occurring in each year over the five-year period within each area.

Suppose within a given area the total numbers of

TABLE V
COMPARISON BETWEEN MONTHLY FREQUENCY OF BIRTHS WITH ANENCEPHALUS, SPINA BIFIDA OR HYDROCEPHALUS AND THAT EXPECTED BY CHANCE, ASSUMING A POISSON DISTRIBUTION

No. of Cases per Month	No. of Months					
	Anencephalus		Spina bifida		Hydrocephalus	
	Observed	Expected	Observed	Expected	Observed	Expected
0	1	0.5	9	4.5	14	14.4
1	4	2.4	10	11.6	21	20.4
2	5	5.6	11	14.8	13	14.5
3	14	9.0	14	12.7	9	6.8
4	5	10.7	7	8.2	3	} 3.9
5	8	10.3	5	4.2	0	
6	8	8.2	1	1.8	0	
7	6	5.6	2	0.7	0	
8	5	3.3	1	0.2	0	
9	2	1.8	0	0.1	0	
10+	2	1.4	0	0.1	0	
Poisson parameter	4.85		2.6		1.4	

cases occurring each year arranged in order of magnitude are

$(r_1, r_2, r_3, r_4, r_5)$ where $r_1 > r_2 > r_3 > r_4 > r_5$

and $\sum_{i=1}^5 r_i = r$. Then Feller (1957) showed that

$$P(r_1, r_2, r_3, r_4, r_5) = \frac{r!}{r_1! r_2! r_3! r_4! r_5!} \cdot \frac{5!}{n_0! \dots n_k!} \cdot \left(\frac{1}{5}\right)^r \dots \dots \dots (1)$$

where n_k is the number of years in which exactly k cases occur.

For example, given an area in which four cases occurred altogether, there would be the following possibilities: all four could occur in the same year (4, 0, 0, 0, 0), three cases could occur in one year and one in another (3, 1, 0, 0, 0); if two cases were noted in one year one could have either (2, 2, 0, 0, 0) or (2, 1, 1, 0, 0), and finally there could be one case in each of four years (1, 1, 1, 1, 0). The probability of each of these arrangements occurring is calculated from (1). Obviously if clustering is present one would obtain a greater number of areas with distributions (4, 0, 0, 0, 0) and (3, 1, 0, 0, 0) than one would expect. The test for this employs the total $m = \sum r_i$ for each r , together with the expected value $E(m)$ and variance $V(m)$ which were computed from the Table in Ederer *et al.* (1964). These values were then summed over all areas and, assuming asymptotic normality,

$$\chi^2_1 = \frac{[|\Sigma m - \Sigma E(m)| - 0.5]^2}{\Sigma V(m)}$$

The cases of hydrocephalus were analysed in this way and, as can be seen from Table VI, the result was highly significant ($P = 0.0002$).

Using the same method for the cases of spina bifida, the expected value of Σm was found to be 63 compared with an observed 69, the difference not

reaching statistical significance ($\chi^2 = 2.5$). For the cases of anencephalus the expected value (103.6) actually exceeded the observed value (100) of Σm . Thus, whereas the cases of hydrocephalus showed very highly significant evidence of clustering, the other malformations of the central nervous system did not seem to cluster at all. It was therefore decided to see whether the result could be repeated using a slightly more sophisticated method to take account of the overall secular and seasonal distributions.

The method of Knox (1964) has been adapted slightly to fit the present method of analysis. In his original paper, Knox took spatial coordinates of cases of leukaemia occurring in Northumberland and measured the distances in time and space between every possible pair of points. He then obtained the following table:

Time Apart $< t$ $t +$	Distance Apart $< J$ km J km +		Total
	n $A - n$	$B - n$ $N + n - A - B$	B $N - B$
Total	A	$N - A$	$r(r-1)/2 = N$

where r was the total number of cases observed, A the number of pairs observed to occur within J km of one another, B the number of pairs observed to occur within time t of one another, and n the number of pairs of cases observed to occur within both time t and distance J of one another. The probability of obtaining n or more pairs in a Poisson distribution of parameter $A.B/N$ was then calculated. This method has been shown to be justified by David and Barton (1966).

For the present analysis the pairs were considered according to whether they were in the same area and according to whether the members of the pair were delivered in the same or consecutive months. It can be seen from Table VII that whereas the evidence for clustering among cases with hydrocephalus was

TABLE VI
EXAMINATION OF HYPOTHESIS THAT THERE IS NO CLUSTERING IN TIME AND SPACE AMONG CASES OF HYDROCEPHALUS, USING THE METHOD OF EDERER *ET AL.* (1964)

r	$f(r)$	$E(r)$	$E(m)$	m	$V(m)$	$f(r) \cdot V(m)$
2	3	1.2	3.6	3	0.16	0.48
3	3	1.6	4.7	5	0.33	0.99
4	2	2.0	3.9	5	0.35	0.70
5	3	2.3	6.9	8	0.35	1.05
6	2	2.6	5.1	9	0.45	0.90
7	3	2.9	8.6	12	0.55	1.65
8	1	3.2	3.2	4	0.60	0.60
Total			36.0	46		6.37

$\chi^2 = 14$; D.F. = 1; $P = 0.0002$.

again very strong ($P < 0.004$), there was no such evidence for the cases of anencephalus or spina bifida.

DISCUSSION

The most striking point to emerge from the present analysis is the lack of evidence for clustering of spina bifida or anencephalus compared with the highly significant evidence among cases of hydrocephalus alone. This type of finding is assumed to indicate an infectious agent, but it could also suggest the presence of an environmental agent occurring in particular areas for relatively short periods of time—for example, a contaminated box of fruit sold only by one shop over a period of a few days. There are, however, certain qualifications that ought to be made before an agent of this sort is searched for.

For one thing, only stillbirths and early deaths have been included in the present series. It is possible that the picture would have been altered by the inclusion of those infants with spina bifida and hydrocephalus who survived the neonatal period. Secondly, since the type of clustering demonstrated above among the perinatal deaths with hydrocephalus has not been reported previously, it would probably be wise to await confirmation in a further series.

SUMMARY

All stillbirths and early deaths recorded as having malformations of the central nervous system delivered between 1 January 1964 and 31 December 1968 to women resident in Glasgow were compared

TABLE VII
EXAMINATION OF HYPOTHESIS THAT THERE IS NO CLUSTERING IN TIME AND SPACE AMONG EACH OF THE MALFORMATIONS OF THE CENTRAL NERVOUS SYSTEM, USING THE METHOD OF KNOX (1964)

Time Apart	Distance Apart		Total
	Same Area	Not Same Area	
Hydrocephalus			
≤ 1m.	18	157	175
2m. +	162	3,318	3,480
Total	180	3,475	3,655
Probability of obtaining 18 or more pairs = 0.0035			
Spina bifida			
≤ 1m.	36	617	653
2m. +	601	10,681	11,282
Total	637	11,298	11,935
Probability of obtaining 36 or more pairs ≥ 0.05			
Anencephalus			
≤ 1m.	103	1,957	2,060
2m. +	1,969	39,042	41,011
Total	2,072	40,999	43,071
Probability of obtaining 103 or more pairs ≥ 0.05			

with a random sample of 5% of all Glasgow births over the same period of time. Considerable geographical variation was demonstrated.

The methods of Knox and of Ederer, Myers, and Mantel were employed to demonstrate a clustering in space and time among the cases of hydrocephalus which was not evident for cases of spina bifida and anencephalus.

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