DETECTION OF LOW INTENSITY EPIDEMICITY
APPLICATION TO CLEFT LIP AND PALATE

BY

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The "Encyclopaedia Americana" defines an epidemic as a "sudden excessive prevalence of a disease in a population". This is a typical definition, and although suddenness is not always considered an essential feature of an epidemic, most would agree that it refers to disease, and that it denotes an increased prevalence. But there are two serious difficulties in this concept which limit its usefulness and unless they are recognized they may prove a serious hindrance to the detection of epidemic properties in several classes of disease.

The first is found when the occurrences are few in number, sparsely scattered in time, and widely separated in relationship to the frequency of any supposed fluctuations. This problem arises with uncommon illnesses such as congenital malformations when an apparent crop of cases poses the question how many cases can make an epidemic. The true difficulty seems to be the breakdown of the concept of prevalence upon which in turn the concept of an epidemic depends. The situation is analogous to the breakdown of the gas laws when very few molecules are involved and the inappropriateness there of the ordinary concept of pressure; or the breakdown of the theory of wave propagation in the study of low intensity radiation. Pressure, wave motion, prevalence, and epidemicity, are terms appropriate to the study of high concentrations and when we are compelled to deal with low intensities special methods of examination must be devised.

The second difficulty arises from the assumption implicit in the above definition, that an epidemic is recognized on a time base. However, it is clear that space must sometimes be taken into account as well as time. A feature of many epidemics is that the geographical region of maximum prevalence moves with change in time, or stated conversely, that the time of maximum prevalence changes with change of place. The result is that a disease which is manifestly epidemic on the time scale in each of a number of small regions, may over a sum of those areas show only equivocal evidence of epidemicity in the terms defined above. Conversely, a disease of which the incidence is geographically uneven during a short period may appear more evenly distributed when a longer period is considered.

These difficulties are not serious with a frequently occurring disease; either the time scale or the geographical area may be divided into sufficiently small classes to demonstrate variations of prevalence in terms of the other. But with uncommon diseases such as leukaemia or congenital malformations the procedure of subdivision leads back into the problems of small numbers. It may be impossible to examine either the space or the time variations in prevalence, without at the same time impairing the applicability of the concept of prevalence. This may not be for lack of large numbers of events for analysis, but because they occur sparsely over a large area and over a long period of time, and accumulation of further data may do little towards solving the problem. For these reasons, no doubt, most of the statements to date of low intensity space-time clustering in particular diseases have been based upon impressions and anecdotes rather than upon rigorous analysis.

A previous attempt (Knox, 1959) has been made to analyse low intensity data on time base alone and the present paper is an attempt to extend this to space and time jointly. The two purposes of the present study are to suggest a method of analysing this class of data in a more discriminating manner than has so far been employed and to employ the technique in the investigation of a particular problem.

METHOD

The problems of detecting epidemicity in any particular set of data are concerned with three distinct elements, a distribution in time, a distribution in
space, and any interactions between the two primary distributions. When events are scarce and the concept of prevalence is inappropriate, the exploration of each element is reduced to an examination of the distributions of interval lengths between pairs of events, measured in terms of time or distance or both. These distributions may form the basis of comparison with expectations based upon a null hypothesis.

There has been some recent attention to the distribution of time intervals between successive events and their evaluation (for example, Maguire, Pearson, and Wynn, 1952; Cox, 1955; Bartholomew, 1956). The recommended methods are chiefly based upon comparison between observed distributions and the negative exponential distribution expected if the events occurred randomly in time. However, tests of this kind are concerned with the form of the distribution rather than the order in which the longer and shorter intervals occur. A number of ad hoc tests, for example "runs tests" based on the median interval, can be devised in order to demonstrate particular patterns, but no single test based upon successive intervals only, seems capable of detecting all the epidemic patterns which can be envisaged.

The limitation of analysis to successive intervals has disadvantages also in the study of the space-time interaction, for here the examination resolves into a "salesman’s walk" type of problem. Quite apart from the intractable mathematics of such an approach it is likely to be effective only in detecting the simplest chains of events and inefficient in detecting forked or radiating series of events, or simultaneous independent sequences.

For the study of simple geographical distributions, the use of successive intervals becomes altogether meaningless.

For these reasons the approach proposed in the present context is the study of all possible pairs and not just of successive pairs. Its main advantage is that the time distribution and the geographical distribution, and therefore the space-time interaction, can be examined simultaneously in the same terms. In addition, a prior null hypothesis can be derived for the distribution of the time intervals and is indeed a simpler distribution than that for successive intervals only.

(A) The Time Intervals

A method of analysing all possible pairs was adopted in another study, an analysis of tracheo-oesophageal fistula (Knox, 1959). In a sufficiently long random series the distribution of intervals between all possible pairs is rectangular; each range of time interval from an index case carries the same risk as any other range of equal breadth. In the study referred to, indefinite length was achieved somewhat arbitrarily by joining the series end to end into a circle.

In circumstances in which it is inconvenient to consider the series circular, but rather a period of finite length with definite end-points, the distribution of intervals between all possible pairs of cases is triangular (see Figure, opposite), with a linear decrease of frequency with increasing interval length.

It follows by simple geometry that, for a series of events scattered at random within a period of time $T$, the proportion of intervals greater than $t$ in length will be $(T-t)^3/T^3$. Between $t_1$ and $t_2$ the proportions are $[(T-t_1)^3-(T-t_2)^3]/T^3$. The total number of intervals for $n$ events is $n(n-1)/2$, and the expected numbers in any interval range easily found.

Difficulties may occur in the practical application of this reasoning, because time is necessarily counted in units and any particular units used may result in inaccuracies. However, it can be shown that a continuity correction of 0·5 time units gives a very good approximation. The procedure is to record $t_1$ and $t_2$ as the means of the two units they separate. Thus the range (for example) 70 days to 79 days inclusive would be calculated from $t_1=69.5$ and $t_2=79.5$. When $t=0$ it is left uncorrected.

(B) Space-Time Interactions

The use of all possible pairs simplifies the formulation of the interaction concept. The question to be answered is whether pairs of cases which are relatively close in time are also relatively close in space. Pairs can be classified according to both criteria and a Contingency Table constructed and condensed as required.

The $2 \times 2$ condensation is the simplest and perhaps expresses the nature of the technique most clearly. Although dichotomy of the map intervals has no exact null expectations unless we use controls, and although the time interval dichotomy itself has some problems in this respect, the $2 \times 2$ Table has a third degree of freedom relating to interaction and this can be demonstrated even when no prior expectations for the two basic dimensions can be derived. Provided that a study area has not altered over the period of examination, it may not even be critical to the evaluation of a particular series of events that ascertainment has been incomplete, or that the margins of the geographical drainage area for ascertainment have been inexact. The $2 \times 2$ condensation also expresses clearly the three independent aspects of epidemicity, emphasizing that any particular epidemic disease or event may have its character manifest in any of the three manners or in any combination of the three.
The actual analysis of data in these terms is of course extremely laborious and inaccurate if done by hand on a map. Therefore, a programme was written for computer analysis of dates and map references and the analyses which follow were carried out by this means. The computer used was the Ferranti Pegasus.

**APPLICATION TO CLEFT LIP AND PALATE**

In the 10 years (3,652 days) 1949 to 1958, among a total of 404,124 live births in Northumberland and Durham, there were 574 children with clefts of lip or palate or both. Details of ascertainment have been published elsewhere (Knox and Braithwaite, 1963). Of 204 Northumberland cases and 370 Durham cases, 198 and 355 could be specified exactly in terms of the variety of lesion, whether cleft lip, cleft palate, or both, and in terms of the date of birth and the map reference of the address. The address used was usually that given at the time of first attendance at hospital, except in the few cases where a change had been recorded and the prior address was known. It is thought, however, that the great majority of addresses used would be the same as the address at the time of birth and in many cases no doubt at the time of conception. The map references used were taken from the National Grid which is in kilometre squares, the least significant figure of each component representing the nearest 0·1 km. For villages and other small areas, where the exact addresses could not be pin-pointed precisely but were within a restricted area, the reference was taken at some central point, usually the railway station or a prominent road junction. The great majority of references can be regarded as accurate to within less than 1 km.

(i) **Northumberland Data — 198 Cases**

A sample of the possible 19,503 pairs, consisting of all those separated by less than 800 days, is analysed in Table I both according to the time intervals, in 100-day bands, and according to distances apart in the ranges 0–2, 2–4, 4–8, 8–16, and over 16 km. There are 7,587 pairs in this sample, more than a third of the total.

<table>
<thead>
<tr>
<th>Time between Pairs (days)</th>
<th>Distance between Pairs (km.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0–2</td>
</tr>
<tr>
<td>0–99</td>
<td>74</td>
</tr>
<tr>
<td>199</td>
<td>61</td>
</tr>
<tr>
<td>299</td>
<td>52</td>
</tr>
<tr>
<td>399</td>
<td>46</td>
</tr>
<tr>
<td>499</td>
<td>43</td>
</tr>
<tr>
<td>599</td>
<td>49</td>
</tr>
<tr>
<td>699</td>
<td>51</td>
</tr>
<tr>
<td>799</td>
<td>52</td>
</tr>
<tr>
<td>Total</td>
<td>428</td>
</tr>
</tbody>
</table>

In Table II (overleaf) the results of a particular condensation of Table I are shown; this Table demonstrates a systematic fall and then a rise over a period of 800 days, of the proportion of pairs which were less than 4 km. apart. A $\chi^2$ value for interaction between the two distance ranges is also given and, if it were acceptable as a valid test in this context, would indicate a high level of statistical significance.
If the phenomenon were accorded a biological explanation, it would indicate local concentrations of malformations within radii of 4 km., subsiding in a period of about 6 months and recurring again in about 2 years. Comparison between observed numbers of pairs and the expected values, calculated on the basis of the time distribution formula already given, suggests that the interaction has more than one component, a fall and rise at distances 0-4 km., a complementary rise and fall at distances 4-8 km. and over 16 km., and a confused picture in the range 8-16 km. It could be interpreted as a geographical movement of high-risk areas at a rate of about 6 km. per year with a resulting reciprocal relationship between areas this far apart and a series of damping and augmenting interference patterns at other distances.

Table III shows the excesses of observed over expected values in each of the classes shown in Table I.

This initial analysis contained all forms of cleft, but by analysing separate components it is possible directly, or by difference, to tabulate the pattern for each of the six possible types of pairs between the three main varieties of malformation. The three main malformations are cleft lip (L), cleft palate (P), and cleft lip with palate (LP), and the six pair types are L-L, L-P, L-LP, P-P, P-LP, and LP-LP.

Fogh-Andersen (1942) and other authors have shown on the basis of sex ratios and genetic histories and by other methods (MacMahon and McKeown, 1953) that cleft palate (P) is in some respects distinctive, and in Table IV the pairs P-P, L-P, and P-LP are separated from the other pairs. The greater part of the cycle in proportions is seen to be associated with the non-P pairs. However there is possibly a discernible trace of the cycle in the P pairs and further analysis showed other anomalies. In particular, the LP-LP pairs showed no definite cycle, while the P-L pairs seemed to do so. Indeed, the most striking separation of cycled from non-cycled series of proportions seems to be on the basis of the presence of L in the pair, rather than the absence of P.

Table V (opposite) demonstrates this by comparing L-L, L-LP, L-P with LP-LP, P-P and P-LP.
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TABLE V
PROPORTIONS OF PAIRS CLOSER THAN 4 KM. BY TIME INTERVAL AND BY TYPE OF PAIR (L v. NON-L)
NORTHUMBERLAND, 1949-58

<table>
<thead>
<tr>
<th>Time Apart (days)</th>
<th>L-P-LP</th>
<th>P-P</th>
<th>L-P-L</th>
<th>L-P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Less than 4 km...</td>
<td>Total</td>
<td>Proportion...</td>
<td>Proportion...</td>
</tr>
<tr>
<td></td>
<td>69</td>
<td>418</td>
<td>0.16</td>
<td>1.26</td>
</tr>
<tr>
<td></td>
<td>56</td>
<td>416</td>
<td>0.13</td>
<td>0.14</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>435</td>
<td>0.14</td>
<td>0.14</td>
</tr>
<tr>
<td></td>
<td>58</td>
<td>411</td>
<td>0.14</td>
<td>0.14</td>
</tr>
<tr>
<td></td>
<td>67</td>
<td>426</td>
<td>0.16</td>
<td>0.16</td>
</tr>
<tr>
<td></td>
<td>57</td>
<td>398</td>
<td>0.16</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td>61</td>
<td>368</td>
<td>0.17</td>
<td>0.18</td>
</tr>
<tr>
<td></td>
<td>57</td>
<td>353</td>
<td>0.18</td>
<td>0.20</td>
</tr>
</tbody>
</table>

χ² for interaction between L and non-L pairs at a distance of less than 4 km. = 14.373; P < 0.05.

There seem to be two ways of interpreting this finding. It is possible to postulate that some epidemic agent may be capable of causing either of the three malformations in different proportions, say of the order L 0.5, LP 0.3, P 0.2, and that the relative frequency of short-time short-distance pairs of each class will depend upon binomial probabilities. Thus, for the above proportionate frequencies, L-L is 0.25, L-LP 0.30, L-P 0.20; by contrast P-P is 0.04, LP-LP 0.09, P-LP 0.12. This gives a total of 0.75 for the L pairs and 0.25 for the non-L pairs. Superimposition of these effects upon a background of malformations otherwise determined might well render the concentration detectable in the one group of pairs and not in the other. Alternatively it is possible that local space and time clusterings of epidemic cleft lip, designated Le, could react with a fortiuitously adjacent random clusters of mixed L, LP, and P, and could produce a group of short-distance short-time pairs of the varieties L-Le, L-LP, and L-P, as well as the more directly related L-P-Le pairs.

In either case the results suggest space-time interactions involving L, with or without a lesser effect upon the other groups of malformations.

(ii) Durham Data - 355 Cases

The results of an analysis similar to that for Northumberland in Table I, are given in Table VI. The interpretative problems seem to be of quite a different nature. First there is no suggestion of fluctuating proportions of short distances in terms of varying time and moreover the χ² values for individual columns of the Table are remarkably small. Similar analyses were carried out for different sub-groups of cases, and for L-L pairs, P-P pairs, non-L pairs, and non-P pairs the same feature of low χ² values, often significant at the high probability end of the scale, was found (Table VII). In case there should be some curious particular regional effect, for example a poly-phased circus-movement around a county whose population, in contrast with Northumberland, is centrifugally distributed, analysis was carried out separately for the elongated industrial area north of the grid line 560, an area corresponding approximately to the southern half of the Tyneside conurbation. The same sub-Poissonian variance was found.

It may be possible to construct biological hypotheses to explain reduced variances in a Table of this kind, based for example on fixed incubation periods.
However, this is highly speculative and for the time being it must be concluded that reduced variances may be a natural property of tables produced in this manner from non-epidemic data.

**DISCUSSION**

The main present difficulty with this method of analysis is the assessment of statistical significance of the results. Since pairs are not independent of each other, \( \chi^2 \) and similar tests are not necessarily applicable. For a particular type of interaction with a simple excess of short-time short-distance pairs, a large contingency table could supply enough cells to assess the variance of columns and rows on a parametric basis and thus to evaluate the significance of a specific cell. The present study has shown, however, that this approach may resolve itself into a more generalised wave form analysis, itself requiring further validation.

A question arising from the presented analysis is whether the low variances of the Durham data augment the validity of the \( \chi^2 \) probabilities estimated for Northumberland. This would be so if low variances are eventually shown to be a recurring characteristic in non-epidemic data. On the other hand an alternative augment can be advanced that the variances of the presentation may be unstable in either direction rather than systematically low, and that this tends to invalidate rather than support the apparent Northumbrian cycle. These questions must await further theoretical examination, perhaps further development of the method, as well as further experience of its application, but it is hoped that these first experiences with it may at least specify some of the questions which need to be answered.

Looking at the Northumbrian results on their own merits, it is of course disquieting that a similar interaction could not be confirmed in Durham, yet the nature of the hypothesis envisaged does not necessarily require that it should be so confirmed. We have found that cleft lip was distinctive in a number of features. It exhibited a significant variation between the different local areas of this region and it had a significant year-to-year variation over the area as a whole (Knox and Braithwaite, 1963). It was the only variety of cleft to vary significantly in incidence between this investigation and the only other large recent British study, undertaken in Birmingham by MacMahon and McKeown (1953). There is a good deal of circumstantial evidence from such other sources that the incidence of cleft lip in particular is labile. That the apparent cyclical interaction was evident only in Northumberland, within which the incidence varied geographically between two regional extremes and where the density of population likewise varies the most, could be because it is within this area that special problems of epidemiological stability are particularly important.

No directly comparable demonstration of space-time interactions in cleft lip and palate have been found in the literature, but there are some indications of time fluctuations in limited areas and of geographical variations over limited periods of time. Pleydell (1957) gained the impression that clefs of lip and palate as a whole in Northamptonshire did in fact occur in clusters. His presented results do not permit re-analysis in the manner described here but for the years 1944 to 1955 his data show some evidence of annual alternation, with 52 cases in the even years and with 31 cases in the odd years. This periodicity is comparable with the local fluctuations inferred in Northumberland. Annual data in Helsinki, again for all clefts together, are given by Gylling and Sovio (1962), and these too show significant variations between years.

There is very little to be found in the literature on local geographical variations. Fogh-Anderson (1942) looked at this carefully in Denmark and failed to find any special concentrations there. Rank and Thomson (1960), however, studying the malformation in Tasmania, remarked that the incidence was maximum in the North-east of the island, and scrutiny of their data suggests that the incidence may indeed have been significantly higher in the Northern parts of the island than in the Midland, South-eastern, Southern, and Western regions.

On the question of the basic methodology proposed in this paper, I have not been able to find any previous formulations of a similar nature. Pleydell (1957), presented groupings of malformations in the Northamptonshire area and on what was basically an intuitive basis thought he detected epidemiological associations in various groups of malformations but especially between the births of mongols. Kellett (1937) made similar inferences in the case of acute leukaemia and this disease has since been the basis of a number of statements of this kind. Methodologically, however, almost all have been simply intuitive.

Pinkel and Nefzger (1959) made a more sophisticated attempt to analyse leukaemia in New York State and they conducted a combinatorial analysis based upon a three-dimensional contingency block with the same dimensions as that used in the present analysis namely latitude, longitude and time. They overcame the problem of irregularities of geographical distribution in the population as a whole by using census tracts with approximately equal numbers in each; but they did not, so far as I interpret their presentation, separate the space-time concentration.
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they detected into its three separate components namely, space concentration, time concentration, and space-time interaction. A more recent study of tumours in children in New York State (Pinkel, Dowd, and Bross, 1962), uses a method more analogous to the present one, but uses a control series (traffic accidents in this case); full details of the method are not yet published, but it does not seem to specify explicitly the triple components of an epidemic.

SUMMARY

The concept of epidemicity is analysed and found to have three components, a time distribution, a space distribution, and a space-time interaction. It is found to depend in turn upon the concept of prevalence. Orthodox analysis for the detection of space-time interaction requires breakdown in terms either of geography or of time and results in a series of small subdivisions where the concept of prevalence may break down. A computer method of analysis is suggested which depends upon simultaneous measurement and classification of the time and distance intervals between all possible pairs of events.

This method is applied to clefts of lip and palate and the results and difficulties are described. Isolated cleft lip is interpreted as probably showing irregular epidemic properties in Northumberland in the period 1949 to 1958, but not in County Durham. The other clefts did not show any epidemic characters.

REFERENCES

Bartholomew, D. J. (1956). *Biometrika*, 43, 64.

APPENDIX

An empirical test of the utility of $\chi^2$ was made as follows. The group of 97 cases (all clefts) occurring in County Durham north of the grid line 560 was re-examined after detaching the map references from the dates, randomizing the order of the references, and re-attaching them to the dates. This was done by shuffling cards with the references marked upon them. Five different randomized lists were re-assembled and each was analysed. Pairs were classified on a 4-point distance scale (0–4, −8, −16, and $>16$ km.) and on a six-point time scale (0–99, −199, −299, −399, −499, −599 days). Components of $\chi^2$ were calculated for each cell, using the row and column totals to obtain the expected values. Summed values for each column of six time intervals, in each of the five tests, are given as values of $\chi^2(a)$ in Table A.

The results seem to confirm the supposition that low $\chi^2$ values are a usual characteristic of non-epidemic data analysed in this way, and that high values are rare and to be accorded somewhat greater significance than the probability values of the $\chi^2$ Table suggest. With this reasoning the analysis of results for County Durham can be regarded as showing no evidence of an interaction, while the (statistical) reality of the Northumberland reaction is enhanced.

<table>
<thead>
<tr>
<th>Test No.</th>
<th>Distance Apart (km.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0–4</td>
</tr>
<tr>
<td>1</td>
<td>4.431</td>
</tr>
<tr>
<td>2</td>
<td>7.599</td>
</tr>
<tr>
<td>3</td>
<td>2.757</td>
</tr>
<tr>
<td>4</td>
<td>3.324</td>
</tr>
<tr>
<td>5</td>
<td>5.588</td>
</tr>
<tr>
<td>Summed $\chi^2(a)$</td>
<td>23.699</td>
</tr>
</tbody>
</table>

* $P > 0.95$
† $P > 0.975$

The $\chi^2(a)$ value for $P = 0.05$ is 11.07, and for $P = 0.1$ it is 9.24.