Leukaemia in Lewisham (1957-63)

S. P. LOCK,* M.A., M.B., M.R.C.P.; MAXINE MERRINGTON,† B.SC.

Brit. med. J., 1967, 3, 759-760

Several workers have reported that cases of leukaemia occur in clusters in place and time—for example, Kellett (1937), Heath and Hasterlick (1963), Knox (1964), Meighan and Knox (1965), and Mainwaring (1966). Conversely, it has also been reported that the disease does not occur in clusters (Clemmesen *et al.*, 1952; Ederer *et al.*, 1964; Barton *et al.*, 1965; Ager *et al.*, 1965; Lundin *et al.*, 1966). Until recently there have been no adequate statistical tests for detecting clustering; furthermore, the records of victims of leukaemia have not usually been available for the application of such statistical tests.

We here report our analysis of the incidence of leukaemia in a particular area—the former London borough of Lewisham—with special reference to the question of clustering. We have confidence that these records are largely complete and would expect to be able with these data to detect clustering if it occurred.

Materials and Methods

The patients studied had been diagnosed between 1 January 1957 and 30 December 1963 as having any type of leukaemia. At the time of diagnosis they were living in the London borough of Lewisham. Their names were obtained in a variety of ways: from case notes, with necropsy records from all the local hospitals, including Lewisham General Hospital, which provides a district haematological service for the area; from records of the South Metropolitan Cancer Registry, which are derived from the notifications from individual hospitals; and from the death certificates of all patients in the borough dying from leukaemia, kindly made available by Dr. W. M. Court Brown, of the Medical Research Council Clinical Effects of Radiation Research Unit in Edinburgh. The case notes of all the patients were obtained from the hospitals concerned.

In all, 115 patients were diagnosed as suffering from leukaemia; their ages ranged from 2 to 89 years. The clinical types were distributed as follows: 37 acute myeloid, 18 acute lymphatic, 4 myelomonoblastic, 21 chronic myeloid, 32 chronic lymphatic, and 3 erythroleukaemia. In almost every instance the diagnosis had been made from conventional haematological examinations, but one case of chronic lymphatic leukaemia had been diagnosed only at necropsy. The date of the first symptom, the date of diagnosis, and the date of death were all recorded. The addresses of the patients when they developed leukaemia were obtained. The location of each individual address was accurately determined by visiting it.

Statistical Analysis

Several statistical techniques are now available for determining whether a group of patients who develop a particular disease at about the same time also live near each other.

Two methods have been applied to the 115 cases of leukaemia in Lewisham. The first (David and Barton, 1966) is worked out on the basis of testing whether the spatial pattern is random within a group of cases in time. Initially all the

cases are written down chronologically. They are then divided into groups in time according to a rule, which must be decided on before the statistical analysis is calculated. Unless there is some particular reason for choosing a special interval it is usual to choose the groups with several different time intervals between them and to repeat the same statistical analysis for each interval. The next step is to find the distances between all cases. This may be done by taking the map readings of each patient's address from the National grid; with these as co-ordinates the distances are calculated. The David and Barton statistical test is the ratio of the variation within time groups to the variation of all the possible distances between the cases. If the cases are randomly distributed this ratio will be unity; the closer they are to each other within a time group the smaller the ratio will be. As a yardstick for deciding whether clustering exists we may subtract unity from this ratio and divide by the standard deviation. This is the David and Barton test criterion. If this measure is less than -2 it can be concluded that there is some clustering effect. The method of calculating the ratio and its standard deviation has been published (Barton *et al.*, 1965; David and Barton, 1966).

This test was calculated for each group of patients suffering from the different clinical types of leukaemia; it was also calculated for all 115 cases combined together. It was applied by using various time intervals between groups of patients. Finally, the patients were divided into adults and children (under 15 years old), and again the test was calculated. In none of these tests was the difference between the ratio and unity even as much as one and a half standard deviations. Therefore it must be concluded that among the cases of leukaemia in Lewisham during 1957 to 1963 there was no evidence of any clustering effect.

The second method used for detecting clustering is that devised by Knox (1964). All the cases are considered in pairs; their distance apart is calculated and their time apart is noted. If the number of cases with a short distance and a short time apart is larger than would be expected if they were randomly distributed then clustering must occur. Whatever specific distances and times were chosen for the test, there were no excessive numbers of pairs of cases close to each other in place and time. Thus this statistical test also provided no evidence of clustering.

Discussion

The difficulty with all statistical tests for space-time clustering is that the definition of what is "close" in time and what is "close" in distance will vary enormously. The results given by Knox (1964) for childhood leukaemia in Northumberland and Durham show that pairs of cases occurring within 60 days and within 1 km. of each other were unduly frequent. The conclusions reached by Meighan and Knox (1965) for childhood leukaemia in Portland, Oregon, showed that an excessive number of pairs of cases were closer than 250 days apart and closer than 4 km. apart. The results for acute leukaemia in childhood in the Liverpool area given by Mainwaring (1966) show an excessive number of pairs with short distances and short times apart, the highest levels of significance being for

* Lately Senior Registrar, Department of Pathology, Lewisham Hospital, London S.E.13.

† Department of Statistics, University College, London W.C.1.

pairs of cases with intervals less than 300 days and 4 km. Other investigators have drawn conclusions based on personal observations rather than on the results of any statistical tests. For example, Heath and Hasterlick (1963) reported eight cases of leukaemia among children living in Niles, Illinois, between 1957 and 1960. This was at a time when the population was expanding sharply (in 1950 the population was about 3,500 and in 1960 about 20,000). Wood (1960), describing leukaemia in Cornwall over a 12-year period, stated that there was a tendency to find tiny foci of victims living in close proximity but there was no significant predominance in any particular district. Dowsett (1966) reported similarly of cases in Kingston, Surrey. Heath and Manning (1964) described 14 cases in four communities in the United States.

The statistical test put forward by David and Barton (1966) has the advantage that it picks out non-randomness without the need for defining a "close" distance. The criterion is based on the overall average of all possible distances between all cases. A definition of shortness in time must be made. This test was carried out (Barton *et al.*, 1965) on cases of acute leukaemia in Northumberland and Durham, Liverpool, Birmingham, Bristol, Sheffield, and Cornwall. The results gave no evidence for the presence of clustering. Both this test and Knox's test were used by Pike *et al.* (1967) in analysing the incidence of Burkitt's tumour in the West Nile district of Uganda; both tests demonstrated significant space-time clustering.

In an investigation in Connecticut, Ederer *et al.* (1964, 1965), using a different statistical technique, analysed over 300 cases of leukaemia in children between 1945 and 1959 and found no evidence of "calendar-year clustering within towns," though, using their statistical technique, they did find evidence for clustering of poliomyelitis and hepatitis.

The 115 cases studied in Lewisham included several different clinical types of leukaemia (cytological and clinical), and the numbers of any one type were small. The data indicate that there is no evidence of clustering of leukaemia taken as a whole, nor do they provide evidence of clustering of one or other specific subtypes of leukaemia. It would appear that if cases of leukaemia are clustered at all the degrees

of clustering must be very slight, and quite unlike that found in poliomyelitis and infectious hepatitis.

Summary

Two statistical criteria for testing the association of cases of leukaemia in place and time were calculated for 115 patients in the London borough of Lewisham between 1957 and 1963. The analysis gives no evidence for any clustering of these cases.

We wish to acknowledge with thanks the help given by many doctors and medical records officers in hospitals in South-east London and elsewhere. Mr. P. M. Payne, Director of the South Metropolitan Cancer Registry, kindly gave us details of his registered cases of leukaemia in the district.

The calculations were carried out on the I.C.T. Atlas Computer at the University of London Institute of Computer Science. We wish to acknowledge gratefully the expert assistance given us by Mrs. Pat Hills, Miss Norma Pateman, and Miss Pat Williamott, of University College, London, in processing these data. Dr. Malcolm Pike, of the M.R.C. Statistical Research Unit at University College Hospital Medical School, London, kindly helped us concerning the calculations with the Knox test.

REFERENCES

- Ager, E. A., Schuman, L. M., Wallace, H. M., Rosenfield, A. B., and Gullen, W. H. (1965). *J. chron. Dis.*, **18**, 113.
 Barton, D. E., David, F. N., and Merrington, M. (1965). *Ann. hum. Genet.*, **29**, 97.
 Clemmesen, J., Busk, T., and Nielsen, A. (1952). *Acta radiol. Diagn.*, **37**, 223.
 David, F. N., and Barton, D. E. (1966). *Brit. J. prev. soc. Med.*, **20**, 44.
 Dowsett, E. G. (1966). *Brit. J. Cancer*, **20**, 16.
 Ederer, F., Myers, M. H., Eisenberg, H., and Campbell, P. C. (1965). *J. nat. Cancer Inst.*, **35**, 625.
 ——— and Mantel, N. (1964). *Biometrics*, **20**, 626.
 Heath C. W., and Hasterlick, R. J. (1963). *Amer. J. Med.*, **34**, 796.
 ——— and Manning, M. D. (1964). *Lancet*, **1**, 1394.
 Kellett, C. E. (1937). *Arch. Dis. Childh.*, **12**, 239.
 Knox, E. G. (1964). *Brit. J. prev. soc. Med.*, **18**, 17.
 Lundin, F. E., Fraumeni, J. F., Lloyd, J. W., and Smith, E. M. (1966). *J. nat. Cancer Inst.*, **37**, 123.
 Mainwaring, D. (1966). *Brit. J. prev. soc. Med.*, **20**, 189.
 Meighan, S. S., and Knox, E. G. (1965). *Cancer (Philad.)*, **18**, 811.
 Pike, M. C., Williams, E. H. and Wright B. (1967). *Brit. med. J.*, **2**, 395.
 Wood, E. E. (1960). *Ibid.*, **1**, 1760.

Transit Times of Food in Patients with Diverticulosis or Irritable Colon Syndrome and Normal Subjects

O. N. MANOUSOS,* M.B., D.PHIL.; S. C. TRUELOVE,* M.D., F.R.C.P.; K. LUMSDEN,† M.B., B.CHIR., D.M.R.E.

Brit. med. J., 1967, **3**, 760–762

The rate of passage of food residue through the alimentary canal of normal human subjects has been studied extensively, but there are no relevant data with regard to patients with diverticula of the colon.

Hurst (Hertz) (1907) administered bismuth carbonate mixed with food to normal subjects and followed the progress of the food residue by means of radiographs; he found that a proportion of the radio-opaque material was still in the large bowel three days after its administration. Alvarez and Freedlander (1924) studied the transit times by means of small glass beads taken with food and found that only 70% of the beads had been passed by the third day. Similar results were obtained by Burnett (1923), who used millet seeds as the tracer substance. Todd (1930) and Lönnerblad (1951) studied the transit time

of the small intestine by using barium sulphate mixed with water, but, as Cole (1914) suggested, unless the tracer substance is mixed with an ordinary meal the results are not representative of the actual progress of food residues through the gastrointestinal canal.

The figures of transit times given by Hurst (1919) for the normal are generally accepted (Barclay, 1933; Feldman, 1948). The food reaches the caecum in three to four hours, the hepatic flexure in six hours, the splenic flexure in 10 hours; between 18 and 24 hours the sigmoid is filled and some of the contents have been expelled; but, as was pointed out by Hurst himself, there is a wide variation in the normal transit. Indigestible material (roughage) increases the speed of food residue through the digestive tract, as has been shown by the comparative studies of McCance *et al.* (1953). They studied radiologically the transit time of white and brown bread administered with a small amount of barium sulphate to normal subjects. It was

* Nuffield Department of Clinical Medicine, the Radcliffe Infirmary, Oxford.

† Consultant Radiologist, United Oxford Hospitals, Oxford.